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EXPRESSION OF SORCIN AND PROLIFEROTROPIC SIGNALING MOLECULES IN CARCINOMAS OF VARIOUS LOCALIZATIONS: ROLE AND IMPORTANCE IN THE ASSESSMENT OF THE PROGNOSIS OF NEOPLASMS

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INTRODUCTION

The study of the expression of various signaling molecules in tumors has theoretical and practical interest - it can expand the understanding of the patterns of tumor cell differentiation, as well as outline the principles of pathogenetic therapy for developing paraneoplastic disorders that cause certain metabolic disturbances in the body of a cancer patient.

Expression of signal molecules, occurring at early stages of tumor development, may be one of the first signs of a neoplasm, which is of great interest in the development of methods for the early diagnosis of malignant tumors. Signal molecules produced by a tumor may be the object of targeted therapeutic action, for example, it is possible to use antibodies to hormones as conductors of cytostatic drugs [34,102].

An analysis of literature data shows that most studies of tumor production of hormones and other biologically active molecules are based on radioimmunological or enzyme immunoassay determination of them in the blood serum of cancer patients or (much less frequently) on biochemical analysis of tumor tissue extracts [70,28,81]. However, a change in the level of any biologically active substance in the blood serum is not always a sign of secretion of this molecule by tumor cells.

Verification of signaling molecules in tumor tissue extracts is more reliable, however, these studies may yield negative results at low concentrations of the substance or reflect the possibility of adsorption and accumulation of molecules by the tumor from the blood, therefore, the production of biologically active molecules directly by tumor cells can only be judged on the basis of immunohistochemical studies with a positive reaction of tumor cells with specific antibodies to certain signaling molecules [21].

Studies have shown that the production of a wide range of signaling molecules by tumors is not an autonomous feature, but a genetically determined

process associated with the conditions of histogenesis and cell differentiation. Since this process is associated with the potential of cells to grow, divide, and subsequently differentiate, verification of signaling molecules produced by tumor cells and analysis of their biological properties may be important for assessing the prognosis of tumor development [80,107].

In addition, studies conducted in recent years have shown the involvement of signaling molecules produced by cells of the microenvironment of the prostate gland, stomach, thymus and other organs (especially fibroblasts) in the mechanisms of development of malignant neoplasms [108].

It has also been established that hyperexpression of the calcium-regulating protein sorcin in malignant neoplasms leads to the launch of a program of multiple drug resistance and contributes to the more accelerated development of organ hyperplastic processes [33].

The aim of the study is to investigate the expression of sorcinol and proliferotropic signaling molecules: melatonin, histamine, somatostatin , caldesmon and matrix metalloproteinase MMP-MT4 . to develop them as biomarkers in assessing the progression of malignant epithelial tumors (carcinomas) of the human stomach, prostate and lung .

To achieve this goal, the following tasks were set and consistently solved:

1. Study and compare expression sorcinol in human gastric, prostate, and lung carcinomas at various stages of tumor differentiation .
2. To evaluate and compare the expression of proliferotropic hormones – melatonin, histamine, somatostatin in human gastric, prostate, and lung carcinomas at various stages of tumor differentiation .
3. To evaluate and compare caldesmon expression in human gastric, prostate, and lung carcinomas at different stages of tumor differentiation.
4. To evaluate and compare the expression of matrix metalloproteinase MMP-MT4 in human gastric, prostate, and lung carcinomas at different stages of tumor differentiation.

5. To evaluate the possibility of using the studied signaling molecules as biomarkers for assessing tumor prognosis.
6. To develop a mathematical model for predicting carcinoma metastasis.

Scientific novelty

For the first time, the expression of signal molecules - sorcin , melatonin, histamine, somatostatin , caldesmon and MMP-4 - in human stomach, prostate and lung carcinomas has been verified. Correlations of the production of these signal molecules depending on the stages of tumor differentiation have been established.

It was shown for the first time that the area of sorcinol and histamine expression in human gastric, prostate and lung carcinomas of tumor differentiation stage G1 - G2 is significantly reduced compared to these indices in the corresponding tumors of tumor stages G3 - G4 . At the same time, the expression of melatonin and somatostatin in human gastric, prostate and lung carcinomas of tumor differentiation stage G1-G2 is significantly higher compared to these indices in the corresponding tumors of tumor stages G3-G4. It was established that the expression of caldesmon and MMP-4 in highly and moderately differentiated gastric, prostate and lung carcinomas (stages G1 - G2) is significantly lower than in poorly differentiated tumors (stages G3-G4).

Principles for the formation of risk groups for the development of distant metastases of carcinomas have been developed based on a mathematical model.

The established correlations between the expression of the studied signaling molecules and the degree of differentiation of carcinomas of different localizations allow them to be used as biomarkers for assessing tumor progression and sensitivity to chemotherapy.

Practical significance

The obtained results allowed us to conduct a comparative analysis of the

expression of sorcin and proliferotropic signaling molecules (melatonin, histamine, somatostatin , MMP-4) in malignant tumors (carcinomas) of the stomach, prostate gland, and human lungs at different stages of differentiation. The obtained data indicate that the study of the expression level of these signaling molecules can serve as a marker of tumor progression and the effectiveness of tumor chemotherapy.

Personal contribution of the applicant

The author has performed an analytical review of the literature, collected and systematized tumor samples, analyzed case histories, and defined the study design. The author analyzed microscopic images with automatic calculation of the area of expression of signaling molecules, performed mathematical and statistical processing of the obtained data, and interpreted the results.

Volume of dissertation work

The work consists of an introduction, a review of literature, materials and methods, a description of the results of own research, conclusions, findings and a reference list. The text of the dissertation is presented on 109 pages, illustrated with 20 figures and contains 15 tables. The list of references contains 125 sources, of which 16 are in Russian and 109 are in English.

The dissertation work was carried out in 2021-2023 at the Department of Pathology and at the scientific and educational base of St. Petersburg State University - Federal State Budgetary Institution "St. Petersburg Research Institute of Phthisiopulmonology " (Department of Translational Biomedicine) as part of a separate stage on the topic of State Assignment No. 056-00013-18-00 "Signaling Molecules as Biomarkers of Socially Significant Diseases of the Respiratory System". The research work on State Assignment No. 056-00013-18-00 was approved by the decision of the Ethics Committee of the Federal State Budgetary Institution "St. Petersburg Research Institute of Phthisiopulmonology" No. 93.1

dated November 23, 2022 (a copy of the decision is attached).

Main scientific results

During the dissertation research, a number of scientifically significant theoretical and practical results were obtained.

1. A comparative analysis of sirtuin concentrations in saliva in middle-aged and elderly individuals with coronary heart disease (CHD) and without cardiovascular pathology (CVP) showed that the study of Sirt1, Sirt6, Sirt7 concentrations in saliva in healthy middle-aged and elderly individuals can be used in a comprehensive assessment of biological age. For predictive diagnostics of CHD in middle-aged and elderly individuals, a promising method is the assessment of Sirt1, Sirt3, Sirt6, Sirt7 concentrations in saliva, see work [12 1], (personal contribution is not less than 80%)

2. The role of kisspeptins in the development of the body's immune response to viral infections in the cells of the ciliated epithelium of the upper respiratory tract has been shown; more and more data from modern studies demonstrate the involvement of kisspeptins and their participation in the regulation of the cell cycle, limiting cell metastasis and other processes, see work [122], (personal contribution is at least 80%).

3. Sorcinol has been found to promote metastasis by increasing chemoresistance of malignant cells and the development of drug resistance during tumor progression. Elevated sorcin levels observed in cells with multidrug resistance suggest its use as a potential biomarker for its prognosis in lung cancer, see [123] (personal contribution is at least 85%).

4. A study of caldesmon as a signaling molecule - a biomarker for predicting response to chemo- and radiotherapy has been conducted, see work [124], (personal contribution is at least 75%).

5. It was found that the relative expression of sorcinol , histamine and caldesmon is statistically significantly lower in tumors with a high degree of

differentiation (G1–G2) than in poorly differentiated tumors (G3–G4). However, the presence of metastases was registered only for tumors with a low degree of differentiation, see work [125], (personal contribution is not less than 85%).

6. carcinoma metastasis has been developed , see work [125] (personal contribution is at least 60%).

Provisions submitted for defense

1. Non-endocrine tumors of the stomach, prostate gland and lungs contain tumor neuroimmunoendocrine cells capable of producing biologically active signaling molecules.

2. In carcinomas of the stomach, prostate gland and lungs, the expression of sorcinol , melatonin , histamine, somatostatin , caldesmon , and matrix metalloproteinase MMP-MT4 was verified for the first time.

3. Tumor progression depends on the level of expression of signaling molecules in it.

4. Signaling molecules expressed by tumors may serve as biomarkers to assess tumor progression and sensitivity to chemotherapy.

5. The mathematical model allows to significantly increase the accuracy of the prognosis of carcinoma metastasis (up to 96%).

Chapter 1
LITERATURE REVIEW
THE ROLE OF SORCINOL AND PROLIFEROTROPIC SIGNALING MOLECULES IN THE PROGRESSION OF NEOPLASMS

The expression/production/secretion of signaling molecules in non-endocrine malignant tumors has been known for over half a century. Previously, in most cases, the so-called “ectopic secretion of hormones” was detected in tumors and was associated mainly with hypoglycemia and hypercalcemia [38], but the term “ectopic secretion of hormones” was first used in connection with Cushing's syndrome, caused by the secretion of adrenocorticotropic hormone (ACTH) by various tumors [22].

At present, the spectrum of ectopic hormone secretion has expanded considerably, which is associated with the acquisition of new knowledge and the improvement of sensitive research methods. However, the term "ectopic" used is not entirely accurate; previously, it was believed that any hormone is distinguished by strict tissue or organ specificity, that is, it is produced by certain cells of the tissue of a certain organ, but gonadotropic hormone is produced by intact gonads and intestines, thyrotropin - releasing hormone (TRH) and ACTH by the pancreas, and somatostatin by the kidneys and C-cells of the thyroid gland.

Thus, the term “ectopic hormone secretion” allows us to distinguish tumor-associated hormone production in a particular syndrome from increased secretion of the main specific hormone by truly endocrine tissues [22,38].

Ectopic hormone secretion is characteristic of a wide range of tumors. Although this property was initially attributed to primary lung carcinoma, carcinoids , thymomas , and fibrosarcomas, virtually all tumor types have the potential to secrete hormones. However, the frequency of ectopic hormone secretion by different tumor types is consistent. Ectopic hormone secretion is most

commonly found in small cell lung carcinomas, carcinoids , and pancreatic islet tumors . Carcinoid tumors are usually found in the lung or gastrointestinal tract [91].

The level of malignancy of a neoplasm is determined by the degree of differentiation of the cells. Highly differentiated cells are almost indistinguishable from the cells of the organ in which they were formed, and are still partially capable of performing their inherent tasks; the less differentiated they are, the less they resemble the original cells and the less functional they are. Undifferentiated cells are not at all similar to the original cells, and sometimes it is impossible to understand from which cells they originated (and they do not perform any functions).

Highly differentiated cells form tumors that grow slowly, rarely extend beyond the organ in which they formed, and metastasize much more slowly. Such forms of cancer (according to modern nomenclature – carcinomas) are non-invasive or minimally invasive forms. Moderately and poorly differentiated tumors are more malignant. Low- and undifferentiated carcinomas spread and metastasize much faster than all the above-mentioned forms of tumors [13].

Expression of signaling molecules is characteristic of both benign and malignant tumors. Despite the fact that a high level of cellular differentiation is normally required for molecular secretion , even incompletely differentiated tumors can secrete some signaling molecules [101].

Currently, the literature has accumulated extensive material on the verification of the synthesis and secretion of various signaling molecules in tumors, and this area of research has become key for the development of innovative personalized methods for the diagnosis, treatment and prevention of malignant neoplasms based on the fundamental knowledge obtained.

Within the framework of the topic of the dissertation, in this review we will consider the biological properties of a number of signaling molecules, the expression of which in malignant tumors (carcinomas) can significantly

determine their resistance to drug therapy and play an important role in the mechanisms of tumor progression and metastasis.

1.1. Sorcinol

A serious obstacle to successful cancer treatment remains tumor resistance to drugs, primarily multidrug resistance (MDR).

Pharmacokinetic aspects such as absorption, distribution, metabolism and excretion reduce the amount of chemotherapeutic agent that effectively reaches cancer cells. The development of drug resistance limits the effectiveness of chemotherapeutic treatment of cancer, with failure rates in metastatic tumors exceeding 90%.

In this regard, the search for molecular targets and mechanisms involved in the development of MDR in lung cancer is of great scientific and practical importance [15,94,95].

For several decades, researchers from different countries have confirmed that the development of cancer is associated with dysregulation of the metabolism of numerous signaling molecules that play a decisive role in the occurrence and progression of the disease. Such signaling molecules include Akt , ACLY, TNFα, Erk , IKK, NF- κB , STAT3 and others [84,96, 99]. Some of these molecules have high diagnostic and therapeutic value, since drugs targeting them have shown high therapeutic potential for various types of tumors.

sorcin has received increasing attention in lung cancer research because it has been found to be involved in the development of MDR.

Sorcinol is a soluble calcium-binding protein consisting of 198 amino acid residues and a molecular mass of 22 kDa . Sorcinol is a cytosolic protein that is associated with free ribosomes, rough endoplasmic reticulum , mitochondria , microfilaments , and perinuclear membranes [58,99].

This protein is encoded by the *SRI gene* with 9 exons, which is localized on

the seventh human chromosome (locus 7q21.12). Analysis of RNA sequencing of samples from patients with squamous cell lung cancer revealed that amplification of the *SRI gene* was detected in 4.11% of cases [99].

Sorcinol was first identified in the vincristine -resistant DC-3F/VCRd-5L Chinese hamster lung cell line and was shown to enhance drug efflux in MDR cells via a calcium (Ca2+)-dependent pathway [75].

At present, the actual role of sorcinol is not fully understood. However, it has been found that sorcinol plays an important role in the regulation of calcium (Ca2+) homeostasis in the human body. Sorcinol regulates calcium homeostasis in two ways: by influencing calcium channels or by directly binding calcium ions.

Hyperexpression Sorcinol induced by endoplasmic reticulum stress increases calcium concentration and accumulation, inducing cell resistance to apoptosis [72,99]. Sorcinol regulates calcium concentration in endoplasmic reticulum vesicles by activating SERCA (sarcoplasmic/endoplasmic reticulum Ca2+ -ATPase) and inhibiting RyR (ryanodine receptor). In addition to calcium homeostasis, sorcinol has been found to play a key role in the activation of mitosis and cytokinesis, and decreased sorcin levels result in disruption of mitosis and cytokinesis: an increase in the number of polynuclear round cells, cell cycle arrest in the G2/M phase, and cell entry into apoptosis [64,119].

Sorcinol is not normally expressed in terminally differentiated mature cells, but is overexpressed in most tumor tissues, making it a promising target for targeted diagnostics and treatment of cancer.

A shorter isoform of sorcin (18 kDa) found in mitochondria is a component of the quality control system controlled by the endoplasmic reticulum -associated protein 1 (TRAP1). TRAP1 is upregulated in human tumors and can modulate apoptosis. In TRAP1-negative cells, mitochondrial sorcin expression was found to be increased , protecting cancer cells from apoptosis following stress treatment , suggesting a post-transcriptional regulation of sorcin expression .

Sorcinol , by regulating calcium levels in the endoplasmic reticulum and

mitochondria , is involved in stress prevention and promotes protein response. Increased sorcin expression reduces apoptosis and stimulates proliferation of multidrug-resistant cancer cells [20,42].

Several mechanisms are known for the development of drug resistance to chemotherapeutic agents, including impaired drug uptake due to decreased expression and/or loss of drug influx transporters, increased drug efflux, alterations in plasma membrane lipid composition, inhibition of apoptosis, increased DNA damage repair, cell cycle alterations, drug compartmentalization away from the drug target, increased drug metabolism, drug inactivation, alteration of the drug target, and epithelial- mesenchymal transition in tissues.

Epithelial- mesenchymal transition, or transdifferentiation , is common in lung cancers and determines the clinical behavior of the tumor, in particular increasing its invasiveness , cancer cell survival, and causing immunosuppression [50].

Sorcinol has been shown to be directly involved in tumor progression by enhancing cell motility, invasion, migration, metastasis, epithelial- mesenchymal transition, and MDR.

In addition, it was found that sorcinol regulates the expression levels of proteins involved in the process of tumorigenesis , such as NF- κB , CTSZ , STAT3, Akt , ERK1/2, VEGF, MMP, caspase-3, -12 and others [40,43,66,109,113].

sorcin levels contribute to a decrease in the expression of proteins involved in angiogenesis, invasion and metastasis, and also lead to apoptosis and reversal of MDR cancer cells [41, 50].

Sorcinol inhibition may result in cancer cell membrane hyperpolarization and decreased mitochondrial calcium levels, which may promote drug- induced apoptosis in malignant cells.

It was found that overexpression Sorcinol also causes chemoresistance to a number of chemotherapeutic agents: 5-fluorouracil, cisplatin , doxorubicin ,

etoposide , homoharringtonine , paclitaxel , vincristine and others [41,87].

Doxorubicin is a chemotherapeutic drug used to treat various cancers, including lung cancer. Sorcinol has been shown to bind to doxorubicin , resulting in decreased intracellular drug concentrations and increased efflux via MDR1 [41,74].

Similarly, in MDR cells, chemoresistance to cisplatin is also associated with co-amplification sorcin [35]. It was found that overexpression sorcinol in K562 chronic myelogenous leukemia cells (pleural fluid) resulted in a 4.1–22.5-fold increase in drug resistance to various chemotherapeutic drugs such as doxorubicin , etoposide , homoharringtonine , and vincristine [120].

taxol- resistant non-small cell lung cancer cell line A549 was found to overexpress sorcin and demonstrates decreased calcium current through RyR receptors . These cells are characterized by impaired calcium homeostasis in the endoplasmic reticulum , increased calcium reuptake via SERCA, as well as increased calcium efflux through the sodium-calcium exchanger NCX and increased expression [83,116]. MDR1 K562 A549 RyR Bcl-2

Sorcinol has been shown to induce tumor invasion, migration and metastasis by modulating the levels of cathepsin Z (CTSZ), p-STAT3 and matrix metalloproteinases (MMP-2, -9) [52, 109].

Activation of STAT3 by sorcin promotes the development of chemoresistance and radioresistance in malignant cells through interaction with transcription factors, including the nuclear factor NF- κB [12].

Sorcinol regulates the progression of epithelial- mesenchymal transition of cancer stem cells by modulating the levels of E- cadherin , N- cadherin , fibronectin , α-SMA, vimentin , VEGF, and ERK signaling pathways [50,66]. Thus, it has been shown that increased expression of sorcin induces the activity of vimentin protein (mesenchymal marker), increases the level of p-ERK1/2, and decreases the activity of E- cadherin (epithelial marker) [106]. In addition, it has been found that overexpression of Sorcinol activates the PI3K/ Akt signaling

pathway , which plays an important role in migration, invasion and the change of the epithelial phenotype of cells to mesenchymal [65].

Sorcinol exerts its cytoprotective activity in cancer cells against chemotherapeutic agents by interacting with and stabilizing TRAP1 (TNF receptor-associated protein 1) to reduce mitochondrial apoptosis [106].

MDR is known to be mediated by various drug resistance genes such as MDR1, MRP1 and GST-π, which together form the classical signaling cascade of MDR development. ABCB1, MDR1 and MRP1 transporters are part of the ATP-dependent membrane transport proteins and play an important role in the efflux of chemotherapeutic drugs from the cell, promoting the development of the MDR phenotype of cells.

Sorcinol has been found to regulate MDR1 and MRP1 levels along with the expression of various other MDR genes such as GST-π, Livin , Src , survivin , Bcl-2, cyclin D1, c- myc , p21, and p53 [113]. Furthermore, overexpression of Sorcinol increases MDR1/P- gp levels by promoting CREB1 binding to cAMP mediators (CREs) present in the MDR1/P- gp promoter through increased phosphorylation and activation of CREB1 [115].

sorcin gene is located in the same chromosomal region (7q21.12) and in the same ABCB1 transporter amplicon in both the human and mouse genomes. Many studies have reported that genomic amplification of the ABCB1-containing chromosomal region 7q21.12 occurs in treatment-resistant cancers and that overexpression of genes in this region contributes to the development of MDR [41,59,114]. Amplification of the chromosomal region 7q21 containing ABCB1 and SRI (sorcin gene) has been described in lung tumor cells during the development of MDR [114].

Thus, the sorcin protein has a broad spectrum of action and is directly involved in such processes as angiogenesis, invasion and migration of tumor cells into lung tissue.

In addition, sorcin regulates the activity of key molecules that ensure

cellular metabolism, such as: NF- κB , CTSZ, STAT3, Akt , ERK1/2, VEGF, MMP, caspases . Sorcin is involved in signal transduction pathways, including the MAPK/ERK and PI3K/ Akt molecular cascades . Sorcin has also been found to induce metastasis, chemoresistance of malignant cells, and the development of drug resistance during tumor progression.

Elevated sorcin levels observed in MDR tumors suggest its potential use as a biomarker to predict chemotherapy response in different locations and types of carcinomas.

In this regard, the study of the role of sorcinol in the development of the MDR phenotype opens up prospects for its development as a new diagnostic and therapeutic marker for various types of tumors.

1.2. Melatonin

The discovery of the hormone melatonin in 1958 by a group of researchers led by the American dermatologist A. Lerner served as the start of the rapid development of at least two new fundamental directions in biomedicine – chronobiology and neuroimmunoendocrinology .

Despite the considerable time that has passed since the discovery of this hormone, the study of the mechanisms of its effect on the body continues actively.

Melatonin (N-acetyl-5-methoxytryptamine) was initially discovered in the pineal gland, but its synthesis was subsequently discovered in other organs and tissues [45,46,61].

The concentration of melatonin produced in the pineal gland changes in a circadian rhythm. The maximum concentration of melatonin is observed at night, the minimum - in the daytime. The concentration of extrapineal melatonin fluctuates in a much smaller range.

However, despite this, the importance of extrapineal sources of melatonin is not inferior in significance to pineal secretion, if only because the concentration of melatonin in the gastrointestinal tract is hundreds of times higher than that in

the pineal gland [46].

Melatonin has the following effects: regulation of circadian and seasonal rhythms; regulation of the psychoemotional and cognitive spheres; antioxidant, neuroprotective , geroprotective effects; immunomodulatory, vegetative-stabilizing , onco- and stress-protective effects [27,73].

The wide range of biological properties of melatonin is explained by the large number of targets on which this hormone acts. The most studied mechanism of melatonin action is its effect on the suprachiasmatic nucleus of the hypothalamus - the chronobiological action of melatonin, including sonotropic effects, is realized through the suprachiasmatic nucleus .

The biological effect of melatonin is mediated by two membrane receptors: MT_1 and MT_2. In humans, the concentration of MT_2 receptors in the suprachiasmatic nucleus is minimal, while outside the suprachiasmatic nucleus, a greater number of these receptors are found; they are localized in the duodenum, colon, cecum, appendix, gallbladder epithelium, parotid and pancreas glands, β-cells of the endocrine system, coronary and cerebral arteries, peripheral vascular network, and adipose tissue.

In addition to membrane receptors for melatonin, there are also nuclear receptors: RORα and RORβ . RORα is most abundant in T- and B-lymphocytes, neutrophils and monocytes. RORβ are found mainly in the brain, pineal gland, retina and spleen [118].

Changes in melatonin production are primarily observed with aging. At the same time, the nighttime concentration of melatonin may not change significantly, but the daytime concentration has a clear tendency to decrease with age [100].

oncostatic and antiproliferative properties of melatonin are of considerable interest to researchers .

Research conducted in the 1920s–40s (even before the discovery and isolation of the melatonin molecule) showed that removal of the pineal gland increases the possibility of growth of various tumors [56,79].

Also, in experimental oncology, the immunostimulating and immunomodulatory effects of melatonin are widely studied, which can have an indirect beneficial effect on the body by modulating a number of cytokines and autocoids [100].

Despite some publications on the inhibitory effect of melatonin on tumor development [85,98,118], the effectiveness of clinical use of melatonin remains unclear due to the lack of large-scale randomized studies.

The antitumor properties of melatonin are realized through several mechanisms: modulation of the cell cycle and induction of apoptosis [98], reduction of migration and invasiveness [118], inhibition of the development of tumor blood vessels [85].

Numerous experiments have been devoted to the study of the antitumor activity of melatonin . *vitro / in vivo* , which demonstrated the ability of melatonin to inhibit malignant growth and potentiate the action of cytostatics . This is achieved through various mechanisms of tumor growth inhibition: activation and reorientation of the immune response towards type 1 T-helpers and an increase in the production of a number of cytokines [57,76], a decrease in the expression of the VEGF receptor [54], activation of apoptosis in tumor cells [31,86,111, 112], and a decrease in telomerase activity [67].

A correlation has been observed between the antitumor effect of melatonin and the level of expression of MT_1 receptors in tumor cells [67].

The additional effects of the drug as an antioxidant may also contribute to the positive therapeutic effect of melatonin and provide additional justification for studying the drug as a component of antitumor therapy [14].

Since the early 1940s, studies have been conducted that have revealed that cancer patients exhibit morphological changes in the pineal gland. This is manifested by both hypertrophy [93] and atrophy of the pineal gland [105], the appearance of multiple cysts [44,104], and calcification of the pineal gland in patients with breast cancer [36,60].

Some studies have found conflicting data: increased melatonin levels in cancer patients regardless of the location of the tumor process [7] and, conversely, low melatonin levels in the urine of breast cancer patients [90], as well as a decrease in nocturnal peak concentrations in the blood in hormone-positive breast cancer [18].

Other studies have found that patients with tumors have normal or elevated melatonin levels, while patients undergoing chemotherapy have decreased melatonin levels [103].

However, further studies in this direction have clearly proven that patients with solid tumors have lower melatonin concentrations in the blood than healthy individuals. A decrease in daily melatonin concentrations in the urine of patients with gastric and rectal cancer has also been shown [5,71]. In addition, a decrease in melatonin concentration was found in patients with breast cancer, with the melatonin level being lower at a more severe stage of the disease [62]. It has also been shown that melatonin levels decrease only in patients with primary breast tumors, while normal melatonin values are observed in relapses of the disease [17,19].

Such conflicting information about the involvement of melatonin in carcinogenesis requires even closer attention to this hormone in terms of its oncological significance.

1.3. Histamine

Numerous researchers have proven that in oncology, the level of endogenous histamine increases in blood plasma, histamine-producing cells, and in the tumor tissue itself [55].

Histamine can control tumor growth through H_1-, H_2-receptors [92]. In this case, histamine can exhibit a bivalent effect: it acts as an immunosuppressant through its H_2-receptors and as a stimulator of immune reactions through H_1-

receptors [16].

Histamine is a determining factor in the bidirectional regulation between tumor structures and tumor-infiltrating immunocompetent cells [51].

A group of researchers showed that in histamine-sensitive C3N mice with methylcholanthrene -induced sarcoma, histamine injections slowed tumor growth until the appearance of acute hemorrhagic necrosis in its tissue [26].

In addition, clinical observations indicate that in patients after removal of solid tumors, stability of histamine levels can serve as a prognostically favorable sign [24].

It has been shown that a progressive decrease in the blood histamine level preceded clinical tumor relapse or detection of metastases. Histamine levels are also a parameter for monitoring the disease in neoplastic pathology of the mammary gland, malignant tumors of the lung and gastrointestinal tract in humans [39].

In mice deficient in mast cells (the main producers of histamine), the growth and metastasis rates of MC-B6-1 fibrosarcoma and Lewis lung carcinoma were more pronounced than in animals with normal levels of these cells [25]. The level of endogenous histamine was low against this background.

However, the addition of histamine to ascitic hepatoma tumor cells Zajdela increased tumor cell extravasation and metastatic diffusion in an experimental model [78].

Artificial creation of histamine deficiency in an experiment by excess inducible diamine oxidase or histaminase was accompanied by a decrease in tumor transplantability , a slowdown in their growth, and an oncolytic effect [77].

It was found that histamine at a concentration of 10^{-4} M is capable of inhibiting PHA-induced lymphocyte activation *in vitro* , but only at the early stage of blast transformation : during the transition of the cell from the G0 to G1 stage. Cells that have entered the G1 phase are not susceptible to histamine [110].

It was also found that in high concentrations histamine inhibits the

proliferative response of lymphocytes, in low concentrations it activates it, and the combined action of histamine with H1 $_{\text{and}}$ H2 $_{\text{blockers}}$ changed the cell reaction to the opposite [8].

Histaminergic suppression of lymphocyte adhesion was found to be mediated through stimulation of H2 $_{\text{receptors}}$, since histamine at concentrations of 10-4 $^{-10\text{-}5\ M}$ suppressed this test in patients with breast cancer, and the H2 $_{\text{blocker}}$ cimetidine abolished this inhibition [9]. These findings may prove useful in relation to cell-mediated tumor-immune system interactions.

Histamine has been shown to be a determining factor in bidirectional regulation between tumor cells and tumor-infiltrating immunocompetent cells [51].

In addition, histamine has the ability to suppress the formation of hydroperoxides and active forms of oxygen [4], i.e. to exhibit antioxidant action. It has been shown that histamine inhibits the growth of pancreatic cancer cells (in cell culture) through the activation of H2 $_{\text{receptors}}$, induces a delay in the transition of cells from the G0 to G1 phase and reduces the progression of the cell cycle, modulates the expression of Bcl-2 (apoptosis regulator) [32].

It should also be noted that histamine can be an angiogenic factor, exhibiting pro- or antiangiogenic properties depending on the receptors it binds to and the concentration of its endogenous level. It is assumed that the bivalent behavior of histamine in tumor growth angiogenesis may be partly due to the commonality of its metabolism with nitric oxide, which in turn is a powerful inducer of increased vascular wall permeability and blood flow velocity. Thus, elevated histamine levels in patients with allergies may lead to the risk of oncogenesis [48].

Summarizing the above information concerning the participation of histamine in oncogenesis, it is necessary to emphasize that its role in adenocarcinomas (glandular tumors) and hemocytoblastoses can be completely different. It is difficult to answer affirmatively the question of whether histamine

or its isoforms are markers of tumor growth.

However, in any case, histaminemia may accompany tumor growth and be pathogenetically conditioned. Stability of histamine levels in the blood within the limits close to the norm in patients after removal of solid tumors may serve as a prognostically favorable sign. Progressive decrease in histamine in the blood may precede clinical relapse of the tumor or detection of metastases.

1.4. Somatostatin

Somatostatin is a hypothalamic hormone, and its secretion is also found in the D- cells of the islets of Langerhans of the pancreas and in some other cells of the visceral organs.

According to its chemical structure, somatostatin is a peptide hormone and exists in two biologically active forms, differing in the length of the N-terminus: 14 and 28 amino acids.

Somatostatin suppresses the secretion of somatotropin -releasing hormone by the hypothalamus and the secretion of somatotropic and thyroid-stimulating hormones by the anterior pituitary gland.

In addition, it also suppresses the secretion of various peptide hormones and serotonin produced in the stomach, intestines, liver and pancreas - insulin, glucagon, gastrin, cholecystokinin, vasoactive intestinal peptide, insulin-like growth factor-1 [37].

It has been noted that with some tumors the level of somatostatin in the blood plasma increases; this has been recorded with a somatostatin -producing tumor (somatostatinoma), medullary thyroid cancer, pheochromocytoma and other types of neoplasms [23].

This peptide also has antiproliferative activity and suppresses tumor angiogenesis [23]. Somatostatin implements its biological activity through its specific receptors, of which 6 different subtypes have been verified (sst1, sst2A, sst2B, sst3, sst4, sst5). Moreover, receptors of the 2nd and 5th subtypes have the

highest affinity for the neuropeptide itself and its analogues.

Most well-differentiated carcinoid tumors and neuroendocrine tumors of the pancreas have increased expression of somatostatin receptors on the surface of their cells, which is widely and successfully used for diagnosis and treatment [63]. It is important to note that high expression of somatostatin receptors of the 2nd and 5th subtypes was shown by immunohistochemical studies of liver metastases associated with well-differentiated neuroendocrine tumors of the small intestine and pancreas [49].

Somatostatin has a very short half-life (1-4 min), therefore somatostatin analogues are of great importance – synthetic derivatives of the hormone that have similar pharmacological effects and a significantly longer duration of action (octreotide , genfastat , sandostatin , etc.) [89].

1.5. Caldesmon

According to the few data available in the literature, the expression of caldesmon (CaD) correlates with the increase in tumor cell migration mediated by the vascular endothelial growth factor signaling pathway.

CaD is also involved in the regulation of the assembly of intercellular tight junctions, morphogenesis of the endothelium of blood vessels, and the cellular response to increased nitric oxide concentrations.

In addition, data have been found that increased expression of the CaD protein activates the p53 and JAK/STAT signaling pathways, which are directly involved in cell division, death, and tumor formation [30,117].

Activation of the JAK/STAT pathway promotes cell proliferation and motility [68,69], increases microvascular permeability and thereby promotes extravasation and migration of tumor cells [47].

1.6. Matrix metalloproteinase MMP-MT4

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are involved in the degradation of various proteins in the extracellular matrix. Typically, MMPs have a propeptide sequence, a catalytic metalloproteinase domain with catalytic zinc, a hinge region or linker peptide, and a hemopexin domain [3,6].

MMPs have been proposed as biomarkers for numerous pathological conditions and are being studied as potential therapeutic targets in various cardiovascular and musculoskeletal diseases , as well as in oncological processes [11,53].

The ability to process molecules such as growth factors, receptors, adhesion molecules, other proteinases and proteinase inhibitors makes MMPs powerful regulators of physiological and pathological processes in the cellular microenvironment. Hyperactivation of MMPs is associated with numerous pathological conditions [10,82,88].

MT4MMP expression has been shown to induce lung metastasis development by destabilizing the vascular network, characterized by dilation of blood vessel lumens and pericyte detachment. Although no differences in the production of key angiogenic modulators (VEGF, PDGFR, FGF and their receptors) were detected, human thrombospondin2 (TSP2) expression was reduced in MT4MMP xenografts .

This result is consistent with the reduction of this antiangiogenic factor, which has been associated with impaired vascular integrity and permeability [29].

***

The data presented in the review demonstrate the feasibility of studying sorcinol and related biomolecules involved in the regulation of calcium metabolism – caldesmon and MMP-4, as well as such proliferotropic hormones as melatonin, histamine and somatostatin for their development as markers and

targets in new combination strategies in the treatment of oncological diseases.

Chapter 2
MATERIALS AND METHODS OF RESEARCH

2.1. Characteristics of the material under study

The study used tumor samples from the stomach ($n_1 = 32$), prostate gland ($n_2 = 32$) and human lungs ($n_3 = 34$). The samples for the study were obtained from the pathological departments of the Federal State Budgetary Institution " St. Petersburg Research Institute of Phthisiopulmonology " of the Ministry of Health of the Russian Federation and the St. Petersburg State Budgetary Healthcare Institution "City Hospital of the Holy Great Martyr George".

Further study of tissue samples was conducted in the Department of Translational Biomedicine of the Federal State Budgetary Institution “St. Petersburg Research Institute of Phthisiopulmonology ” of the Ministry of Health of the Russian Federation (scientific and educational base of St. Petersburg State University).

The age of patients ranged from 27 to 91 years (mean age was 65.2 years). The study included 61.9% men and 38.1% women. Well/moderately differentiated tumor subtypes accounted for 39.6%, poorly differentiated 51.9%, and subtypes with mixed histology 8.5%. 37.8% of patients had an early tumor stage (T1-T2), 62.2% - T3-T4. 25% of patients did not have lymph node metastases, 75% had lymph node metastases (N1-N3). 85.7% of patients did not have distant metastases, 14.3% had distant metastases (M1).

The studied material was divided into 6 groups based on the grading system [97], which determines the category of the degree of histological malignancy based on how atypical cells and tumor tissue as a whole appear under light microscopy.

In this system, the number of grades varies from 1 to 4 depending on the tumor type. If the malignantly transformed cells and the structural organization of

the tumor tissue are close to normal, the tumor is “well differentiated” (Grade 1). These tumors tend to grow and metastasize more slowly than “poorly differentiated” (Grade 2 and/or Grade 3) or “undifferentiated” (Grade 3 or 4). A higher Grade is associated with increased tumor aggressiveness and a worse prognosis.

Thus, Grade indicates the degree of activity and aggressiveness of the tumor, this feature is often referred to in the literature as the "degree of malignancy" of the tumor (Grade , G1-4). The degree of tumor malignancy is indicated as follows:

GX - the degree of tumor differentiation cannot be determined (few data);

G1 - highly differentiated tumor (non-aggressive);

G2 - moderately differentiated tumor (moderately aggressive);

G3 - poorly differentiated tumor (highly aggressive);

G4 - undifferentiated tumor (highly aggressive).

In other words, the higher the number, the more aggressive and active the tumor is. Recently, it has become common to combine G3 and G4 into G3-4.

Group 1 consisted of gastric carcinoma samples at the G1-G2 tumor differentiation stage (n=16) ;

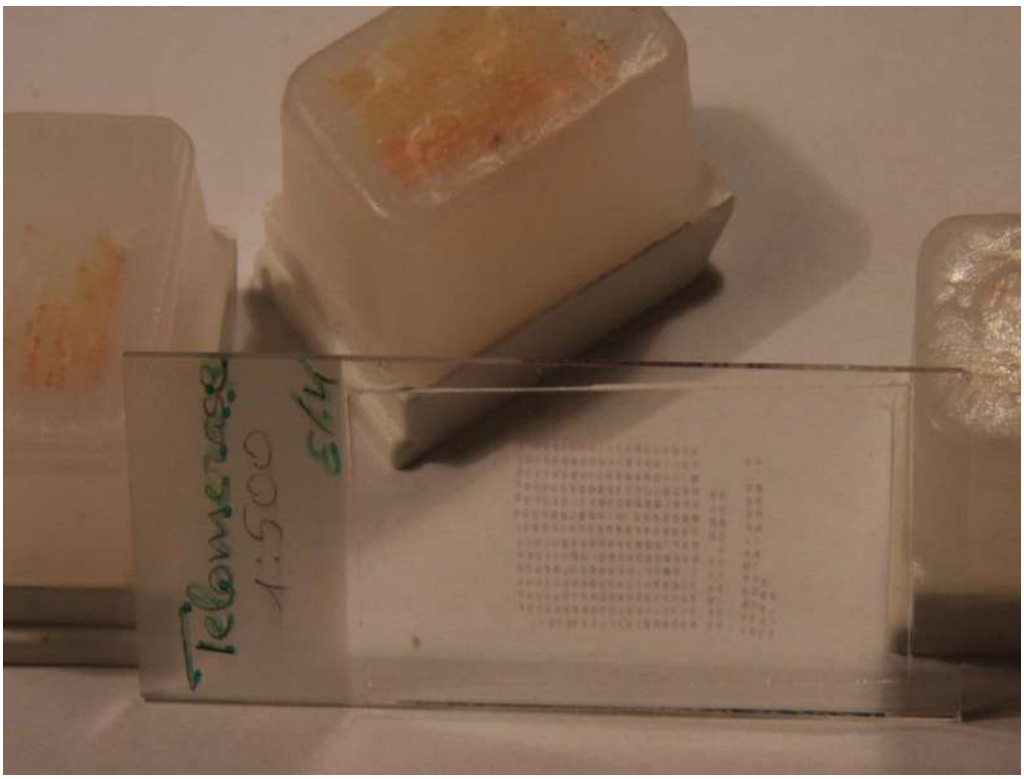
Group 2 – gastric carcinoma samples at G3-G4 stage of tumor differentiation (n=16);

Group 3 consisted of samples of prostate carcinoma at the G1-G2 stage of tumor differentiation (n=16);

Group 4 – samples of prostate carcinoma at G3-G4 stage of tumor differentiation (n=16) ;

Group 5 consisted of lung carcinoma samples at G 1- G 2 stages of tumor differentiation (n = 17);

6 – samples of lung carcinoma at G 3- G 4 stages of tumor differentiation (n = 17).



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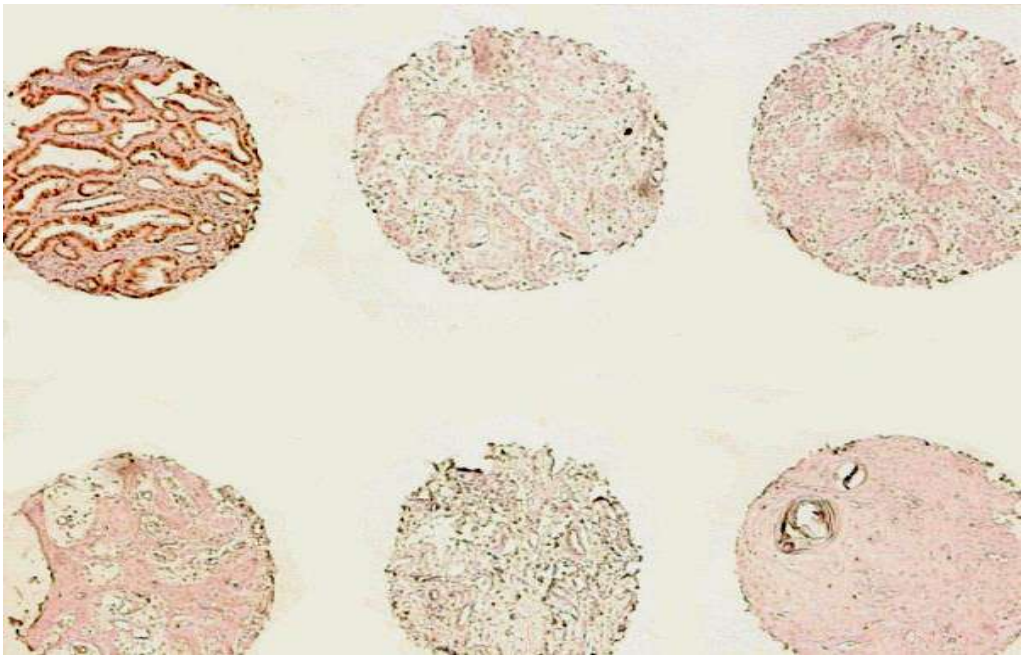


b

Figure 1. Sample of a glass slide with a tissue matrix (a) and sections of the tumor on it (b, x25).

sorcinol , melatonin, histamine, somatostatin , caldesmon and MMP-MT4 in tissues , as well as to assess the prognostic significance of hormones, classical

immunohistochemistry methods were used , as well as tissue matrix technologies (Fig. 1) and laser immunofluorescence scanning confocal microscopy (Fig. 2).

Figure 2. Laser immunofluorescence scanning confocal microscopy system

2.2. Immunohistochemical research method

2. 2 .1. Preparation of fabric samples for immunohistochemical reaction

Rehydration (dewaxing)

1. Place the glass in a thermostat (60 °) for 10 minutes.
2. Deparaffinize sections in xylene for 15 minutes.
3. Rehydrate them in a series of alcohols of descending concentration to distilled water.

Unmasking of tissue antigens must be performed after fixation of the sample in formalin and embedding in paraffin. This procedure is aimed at restoring the original structure of the protein.

One of the methods of "liberation" of antigens is carried out by heating, in which case an increase in the immunohistochemical reaction is noted on sections fixed in formalin. A water bath or microwave oven can be used to heat the sections. Sections are heated in citrate buffer at pH 6.0.

To prepare the citrate buffer: take 1 liter of distilled water, 2.94 g of citric sodium (sodium citrate) and stir in a flask on a magnetic stirrer. Using titration with citric acid, set the pH of the solution to 6.

4. Incubate sections in a pre-warmed citrate buffer solution for 20–40 min at 97 ^{0}C in a steamer.
5. Cool the container with the slices.

2.2.2. Conducting an immunohistochemical reaction

1. Prepare three containers of 200 ml each: distilled water, hydrogen peroxide (20 ml perhydrol + 180 ml distilled water) and sample washing buffer (WB).
2. Quickly transfer sections to WB and leave at room temperature for 10 min.
3. Rinse in distilled water.
4. Place in hydrogen peroxide H2O2 (15 %) for 10 minutes.
5. Transfer to WB for 10 min.
6. Remove excess moisture from the glass.
7. Before applying primary antibodies, outline the sections with a hydrophobic marker.
8. Apply primary antibodies at the required concentration Sorcin (1:100, ThermoFisherScientific), Melatonin (1:100, NovusBiologicals), Histamine (1:100, Sigma- Aldrich), Somatostatin (1:50, Abcam) to sections (20–40 µl per glass depending on the number of sections) and incubate in a humidified chamber (time and temperature are selected according to the manufacturer's recommendations). For LIF and CD 34 – 12 hours at 3 ^{o}C.

9. Rinse in distilled water.
10. Immerse the rack with sections in fresh WB for 10 min.
11. Remove excess moisture from the glass.
12. Apply secondary antibodies to sections (20–40 µl).
13. Incubate for 30 min at room temperature in a humid chamber.
14. Rinse in distilled water and repeat step 10.
15. Remove excess moisture from the glass.
16. Dilute the chromogen at a ratio of 1:50 and apply to the preparations.
17. Incubate for about 1 min (monitor the progress of the reaction under a microscope).
18. Place the tripod with glass slides in a container with distilled water.
19. Immerse the preparations in a container with hematoxylin for 1-2 minutes.
20. Develop the staining with hematoxylin for 10 minutes in running water. This dye stains basophilic cellular structures that contain nucleic acids (DNA and RNA) blue: the cell nucleus, ribosomes and RNA-rich areas of the cytoplasm.
21. Immerse the preparations in a container with fresh distilled water for 3 minutes.
22. Dry the sections in a thermostat at a temperature of 60 ° C.
23. Keep in xylene for 30 minutes to clear.
24. Before capturing, dip the sections in clean filter paper (to avoid the appearance of bubbles on the finished preparation).
25. Enclose in a mounting environment (UltraKitt , J. T. Baker) .

2.3. Immunofluorescence research method

2.3.1. Protocol for conducting immunofluorescence reaction

1. Cover the glass with paraformaldehyde (4%) and leave at room temperature for 15 minutes.
2. Rinse with sodium phosphate buffer for 10 min.
3. Cover with Triton X-100 (0.1%) and leave at room temperature for 15 min.
4. Rinse with sodium phosphate buffer for 10 min.
5. Apply Protein Block (Spring) to glass
6. Rinse with sodium phosphate buffer for 10 min.
7. Remove excess moisture from the glass.
8. Before applying primary antibodies, outline the sections with a hydrophobic marker.
9. Apply primary antibodies at the required concentration Sorcin (1:100, Thermo Fisher Scientific), Melatonin (1:100, Novus Biologicals), Histamine (1:100, Sigma- Aldrich), Somatostatin (1:50, Abcam) on sections (20-40 µl per glass depending on the number of sections) and incubate in a humidified chamber (time and temperature are selected according to the manufacturer's recommendations).
10. Rinse with sodium phosphate buffer for 10 min.
11. Remove excess moisture from the glass.
12. Apply secondary antibodies (Alexa 488, 594, 647 – depending on the species specificity of the antibodies) to the sections (20-40 µl).
13. Incubate for 30 min at room temperature in a humid chamber.
14. Rinse with sodium phosphate buffer for 10 min.
15. Dilute Hoechst33342 at a ratio of 1:100 and apply to the preparations. This dye stains basophilic cellular structures containing nucleic acids (DNA and

RNA) blue: the cell nucleus, ribosomes, and RNA-rich areas of the cytoplasm.

16. Incubate for about 1 min.
17. Rinse with sodium phosphate buffer for 10 min.
18. Dry the sections in a thermostat at a temperature of 37 ° C.
19. Before mounting, blot the sections with clean filter paper (to avoid bubbles appearing on the finished preparation).
20. Enclose in mounting medium (Dako , Fluorescence Mounting Medium).

2.4. Morphometry and computer analysis of microscopic images

The studied preparations, stained by the classical immunohistochemical method, were studied using the light microscopy method using a Nikon Eclipse E400 microscope (Japan).

Micrographs of human stomach, prostate and lung tumor preparations were obtained using laser scanning confocal microscopy using an OlympusIX 2- UCB microscope (Japan).

The analysis of the results of immunofluorescent staining was carried out in the ImageJ program , which is used to solve a wide range of applied and search problems in cytology, histology and many other fields.

For each preparation, 5 fields of vision were examined at x400. The results of immunohistochemical and immunofluorescent staining were assessed by the expression area index.

The expression area (*%*) was calculated as the ratio of the area occupied by immunopositive cells to the total area of the preparation in the field of view.

2.5. Statistical analysis of data

Statistical processing of the research results was carried out in the free software environment R. The data compliance with the normal distribution law was checked using the Shapiro - Wilk'sWtest .

If the data corresponded to the normal distribution law, the typical value was presented as the mean value and standard deviation (M±σ), and comparison of groups was performed using the Student's t-test.

In paired comparisons, the null hypothesis was rejected at a significance level of less than 0.05.

In multiple pairwise comparisons (three groups), the null hypothesis was rejected at a significance level of less than 0.01.

In solving the problem of predicting adenocarcinoma metastasis, discriminant analysis, the method of sequential analysis by A. Wald as modified by E.V. Gubler and a neural network model were used. In creating the neural network, a combined method of global optimization was used, which consisted of applying the methods of conjugate gradients, random search, inertial and genetic algorithms at various iterations.

The basis of the method of sequential analysis of A. Wald, modified by E.V. Gubler , is the formula of T. Bayes for independent features, the method of sequential analysis of A. Wald and the statistics of S. Kullback [2]. Its advantages are the simplicity of construction, independence from the type of features being studied (qualitative, quantitative, ordinal), the possibility of using the system both with the help of electronic computers and in a manual version.

Let us explain the basic logic of the method: let us denote the presence of metastasis as A, and its absence as B. In the probabilistic approach to the prognosis of metastasis, the doctor proceeds from the following considerations: a certain value of a feature is not always found in all cases of A and is absent in B. Often, the manifestation of a feature is observed in one or another part of cases

both with metastasis and in its absence. For example, if in A its value of the feature is large, and in B it is small, then we can conclude that the presence or absence of this feature is informative for the diagnosis of metastasis. If the feature is found equally often in both A and B, then it is obviously of little informative value for diagnosis.

Using the method of A. Wald as modified by E.V. Gubler , based on the frequency (probability) of the presence of factors (symptoms) in conditions A and B, it is possible to solve the inverse problem: based on a specific symptom complex of a patient, determine the probability of the occurrence of a disease:

$$DK_i = 5 * \lg \frac{P_j(A)}{P_j(B)} \quad (1)$$

where DKi is the diagnostic coefficient calculated for each question gradation, Pj (A) is the probability of the respondent falling into group A with the answer gradation Sj . Pj (B) is the probability of the respondent falling into group B with the answer gradation Sj .

This method is based on differences in the occurrence of features in two subgroups, and with similar values in groups A and B, the informativeness of the feature when dividing the population decreases.

To assess the informativeness of the feature, the S. Kullback criterion was used . The informativeness of the feature gradations was calculated, the so-called prognostic coefficient according to:

$$r(Xij) = 0.5[\_P2 - P1\_] \cdot 5\log(P2/P1), \quad (2)$$

where P2 is the probability of the state "absence of metastasis" P1 is the probability of the state "occurrence of metastasis". And then, the information content of the entire feature was calculated:

$$R(X_i) = \sum_{k=1}^{n} r(x_{ij}) \quad (3)$$

The decision to classify subjects into groups (“no risk of metastasis” or “increased risk of metastasis”) was made as follows: a card was filled out for each subject, the diagnostic coefficients for each specific respondent were summed up,

and the total diagnostic coefficients (TDC) were determined.

They were then compared with the theoretical threshold value of the SDC. To ensure theoretical thresholds of hyper- and hypodiagnosis for practical application, a threshold of 0 was chosen, i.e. if the calculated SDC value is less than 0, the respondent belonged to the group of "no risk of metastasis". If the SDC value is more than 0, the examined person belonged to the group of "increased risk of metastasis".

Chapter 3

RESULTS OF THE STUDY AND THEIR DISCUSSION

The study examined the relative expression area of sorcinol and associated signaling molecules in malignant tumors of the human stomach, prostate, and lungs (Table 1).

Table 1.

Relative area of expression of marker molecules
in carcinomas of various localizations

Relative expression area , %						
	Gastric carcinoma G1- G2	Gastric carcinoma G3- G4	Prostate carcinoma G1- G2	Prostate carcinoma G3- G4	Lung carcinoma G1- G2	Lung carcinoma G 3- G 4
Sorcin	2.64 ± 0.45	5.06 ± 1.48	1.65 ± 0.11	4.83 ± 1.33	2.14 ± 0.38	6.74 ± 1.22
Melatonin	10.16 ± 1.72	2.12 ± 0.21	12.34 ± 1.63	1.97 ± 0.17	12.86 ± 1.81	2.72 ± 0.19

Histamine	2.67 ± 0.31	9.54 ± 1.47	1.84 ± 0.12	8.65 ± 1.34	2.28 ± 0.10	10.12 ± 1.76
Somatosta - tin	7.82 ± 1.34	1.67 ± 0.07	8.43 ± 1.27	2.04 ± 0.16	8.62 ± 1.29	0.88 ± 0.04
Caldesmon	4.16 ± 0.27	8.24 ± 1.63	3.10 ± 0.22	5.78 ± 1.37	5.15 ± 1.62	9.31 ± 1.75
MMR-MT4	3.67 ± 0.12	7.27 ± 1.43	4.65 ± 0.90	9.32 ± 1.39	3.83 ± 0.42	8,11±1,23

G 1 according to the international classification of tumor differentiation means a well-differentiated tumor with a low degree of malignancy (Lowgrade); G stage 2 – moderately differentiated tumor with an intermediate degree of malignancy (Intermediategrade); G stage 3 – poorly differentiated tumor with a high degree of malignancy (Highgrade); G stage 4 – undifferentiated tumor with a high degree of malignancy (High grade).

3.1 Sorcinol expression in gastric, prostate and lung carcinomas

Sorcinol expression was detected in tissue samples of human gastric, prostate and lung tumors with varying degrees of differentiation (Fig. 3).

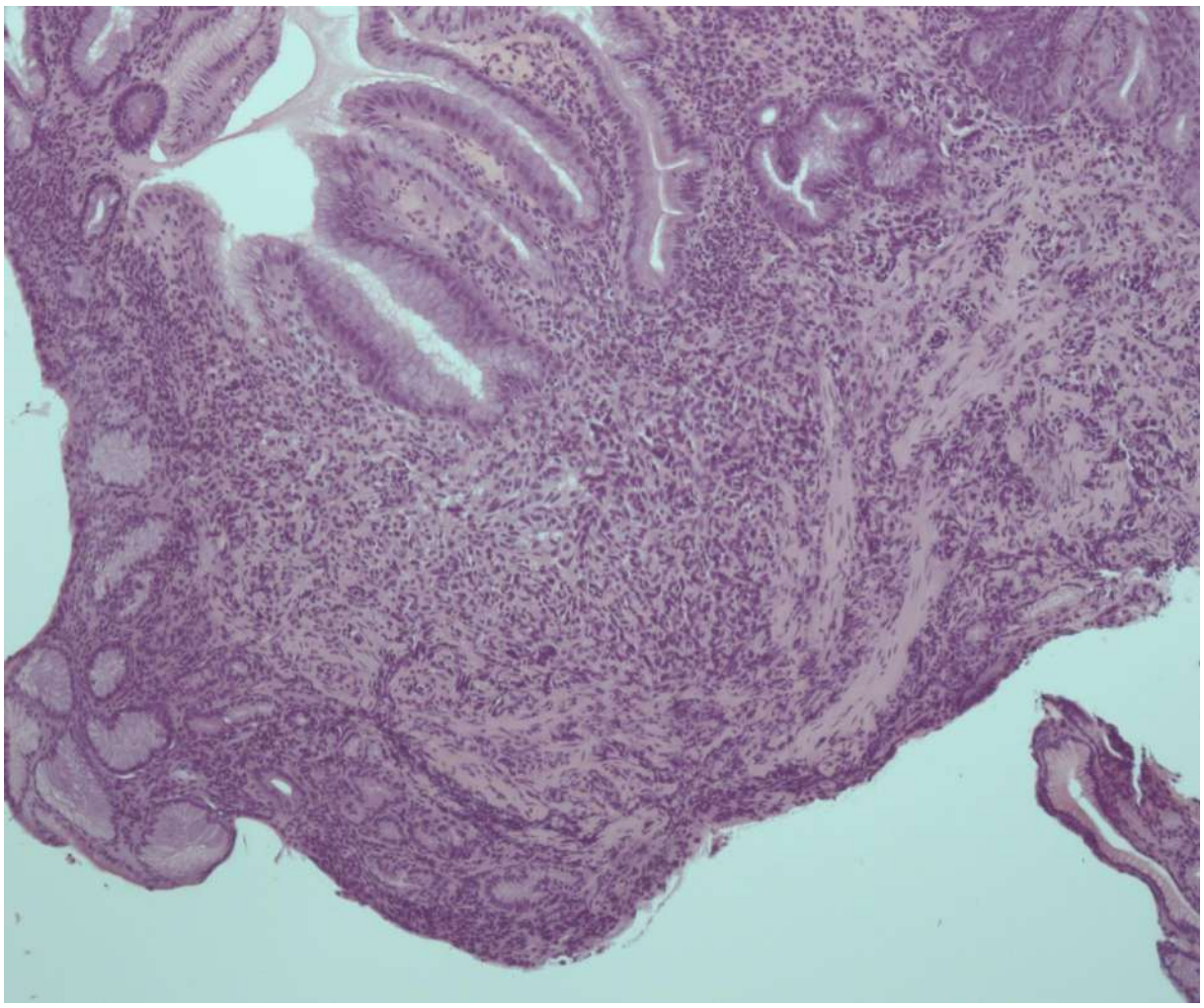


Fig . 3. Gastric carcinoma . Hematoxylin-eosin stain, x120.

The average value of the relative area of sorcin expression in gastric carcinoma G1-G2 was 2.64 ± 0.45% and was 1.92 times lower than in gastric carcinoma G3-G4 differentiation stage, where this indicator was 5.06 ± 1.48 %.

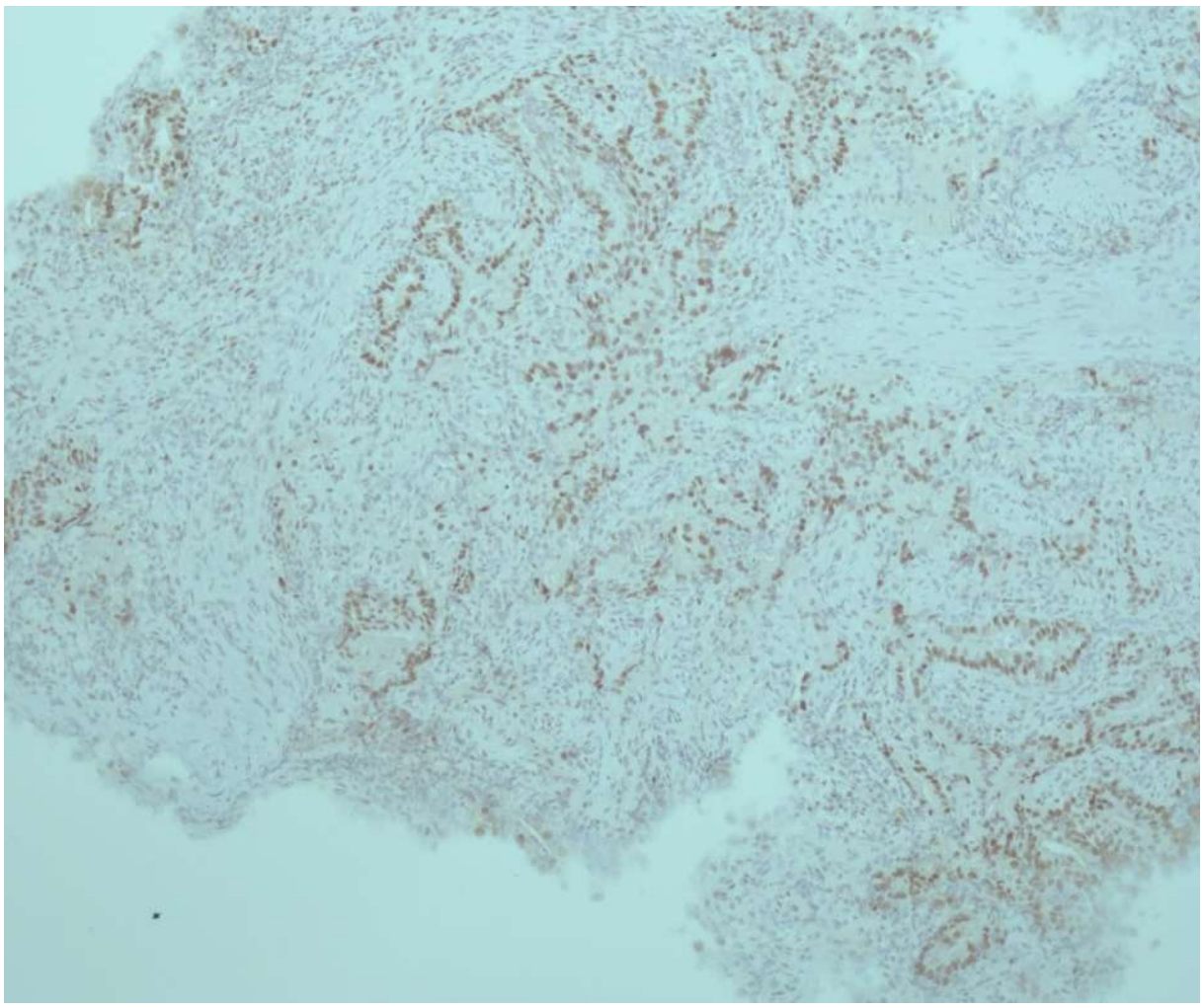
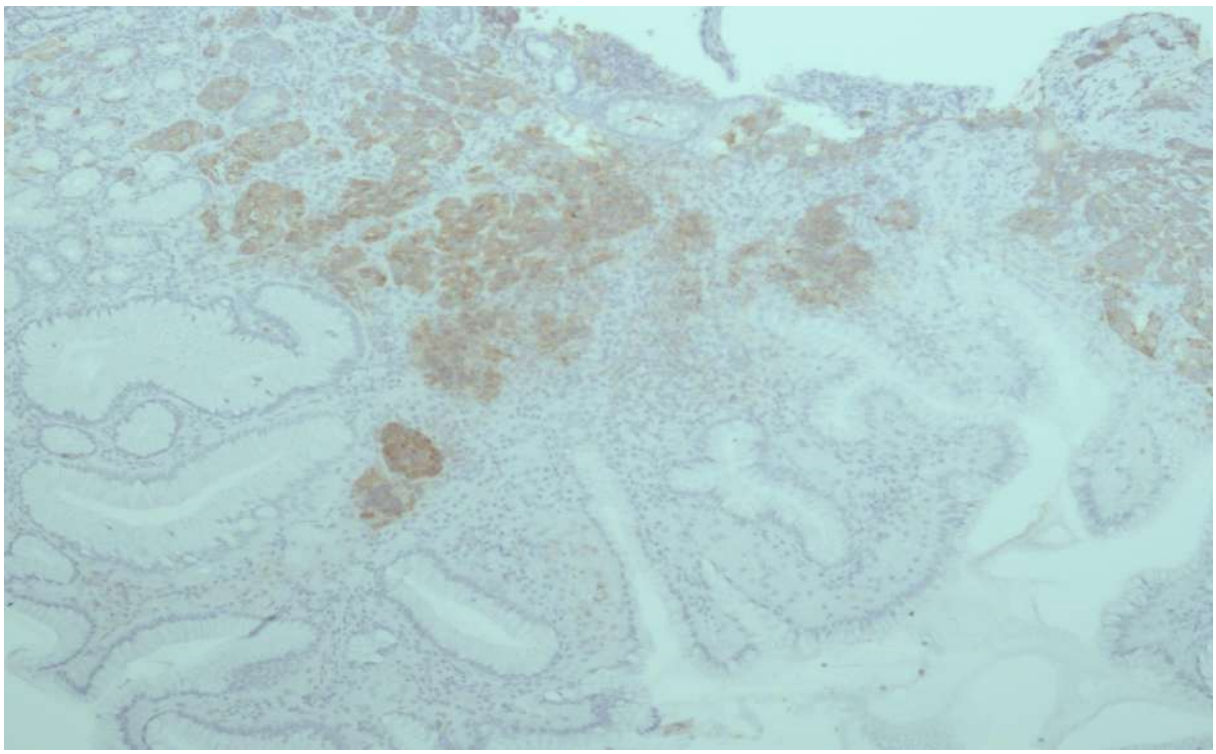


Figure 4. Sorcinol expression in prostate carcinoma (G1-G2). x120.

In turn, in prostate carcinoma G1-G2, the relative area of sorcin expression was 1.65 ± 0.11 % and was 2.93 times lower than in prostate carcinoma G3-G4 differentiation stage, where the average value was 4.83 ± 1.33 %.



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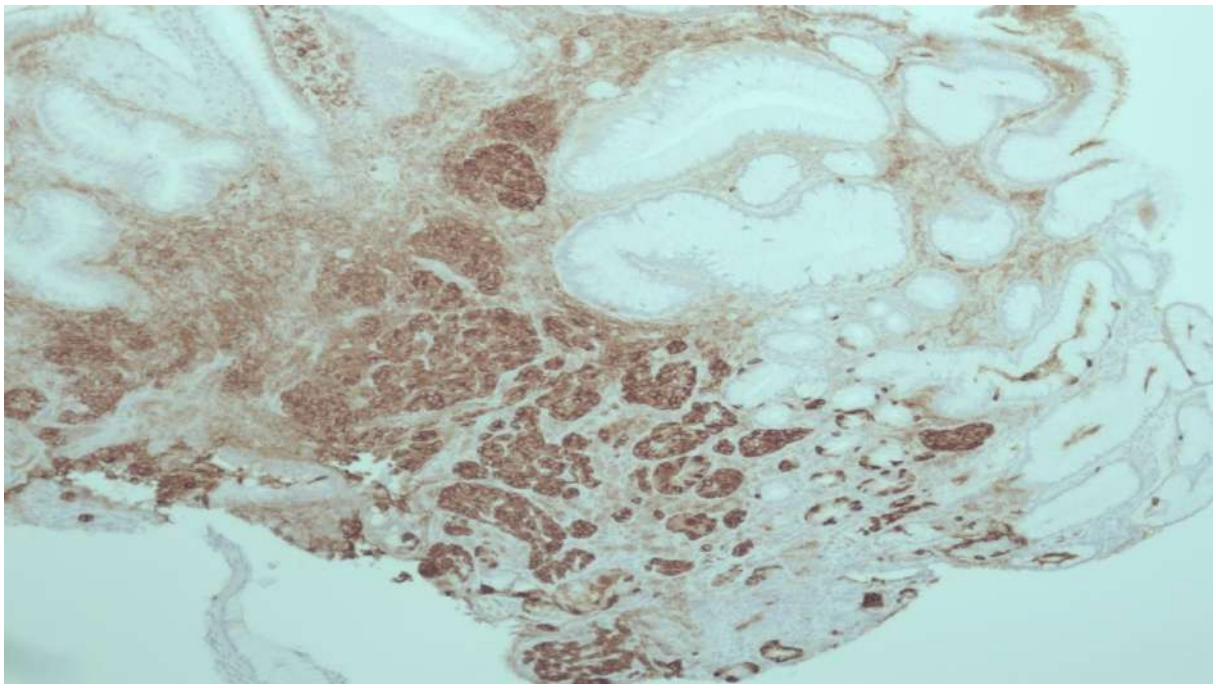
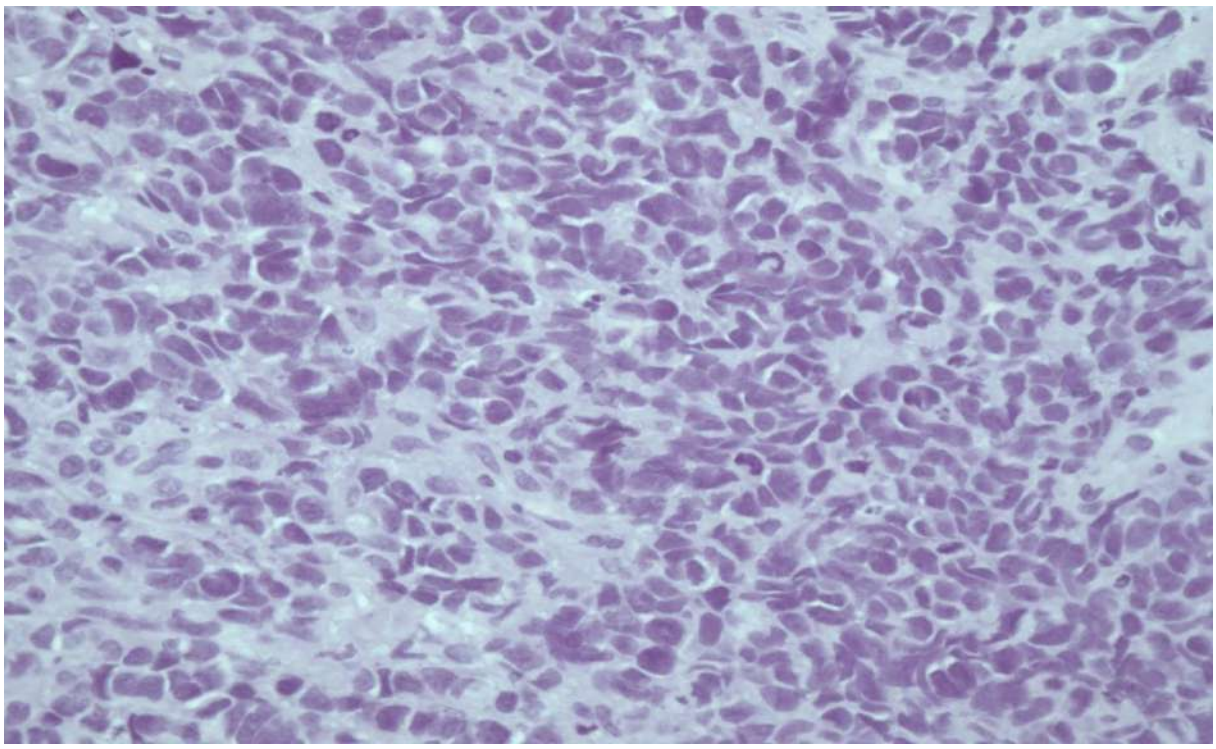


b

Figure 5. Expression of melatonin (a) and sorcin (b) in gastric carcinoma (G1-G2). x200.



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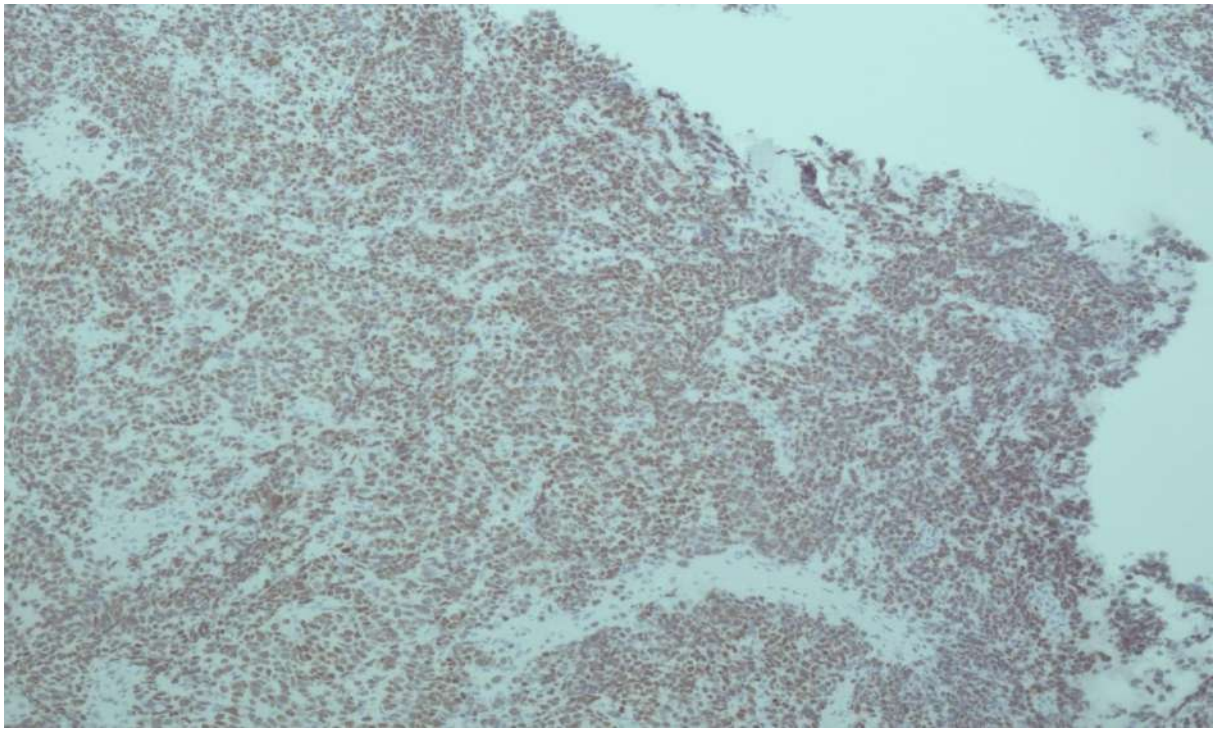


b

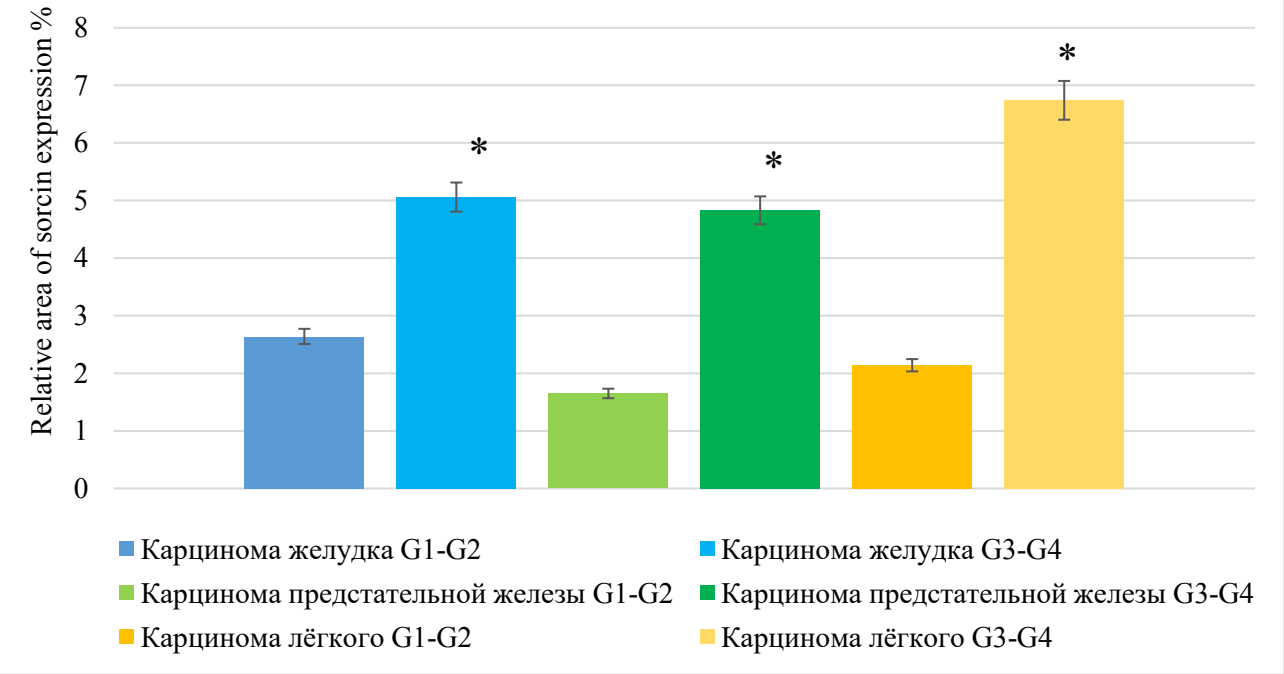
Figure 6. Lung carcinoma (G3-G4). Hematoxylin and eosin staining (a, x200); sorcin expression (b, x120).

The relative area of sorcin expression in G1-G2 lung carcinoma was 2.14 ±

0.38% and was 3.15 times lower than in G3-G4 lung carcinoma, where the area of sorcin expression was 6.74 ± 1.22% (Fig. 8).

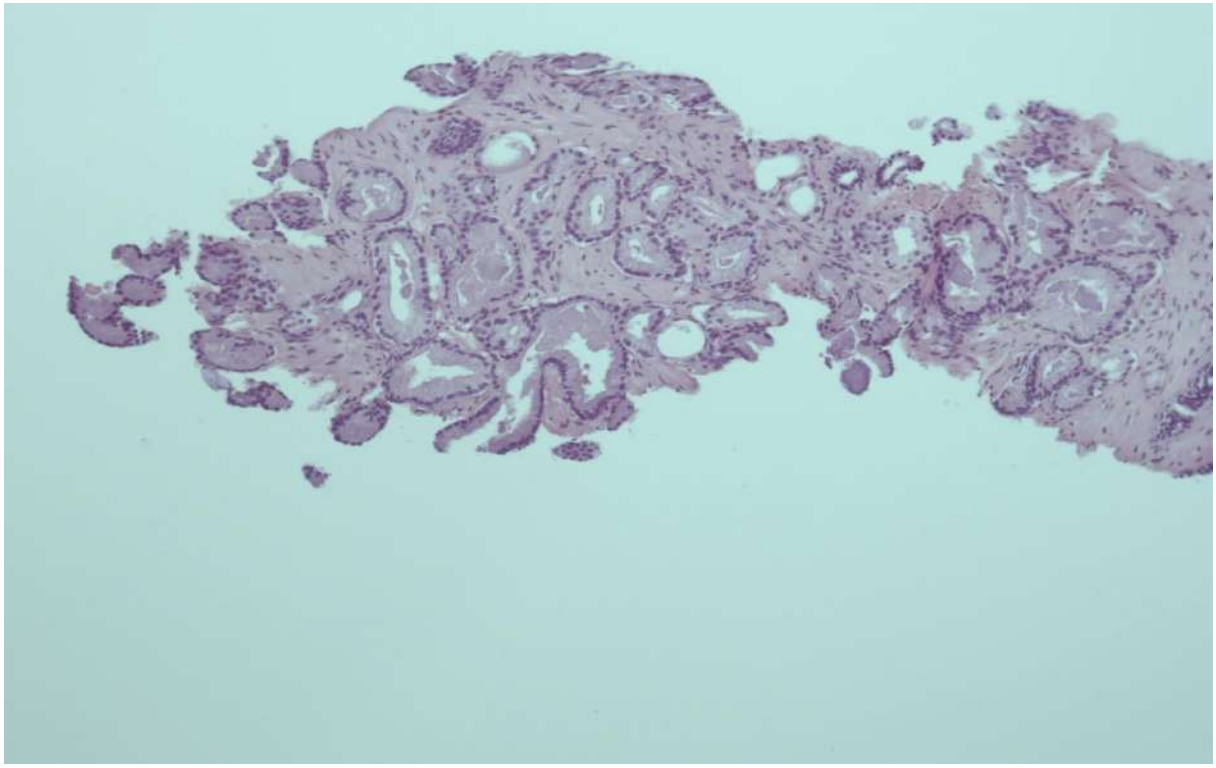
Thus, sorcin expression increases in tumors with a weak degree of differentiation (more malignant – G3-G4), since it is an activator of cell proliferation.

Sorcinol is also a marker of tumor cell resistance to drug chemotherapy and is also highly expressed in low-grade (more malignant) tumors.



Note: * $p < 0.05$ – compared with the corresponding indicator in tumor tissue with G1-G2 degree of differentiation.

Figure 7. The area of sorcin expression in gastric, prostate and lung carcinomas of varying degrees of differentiation.



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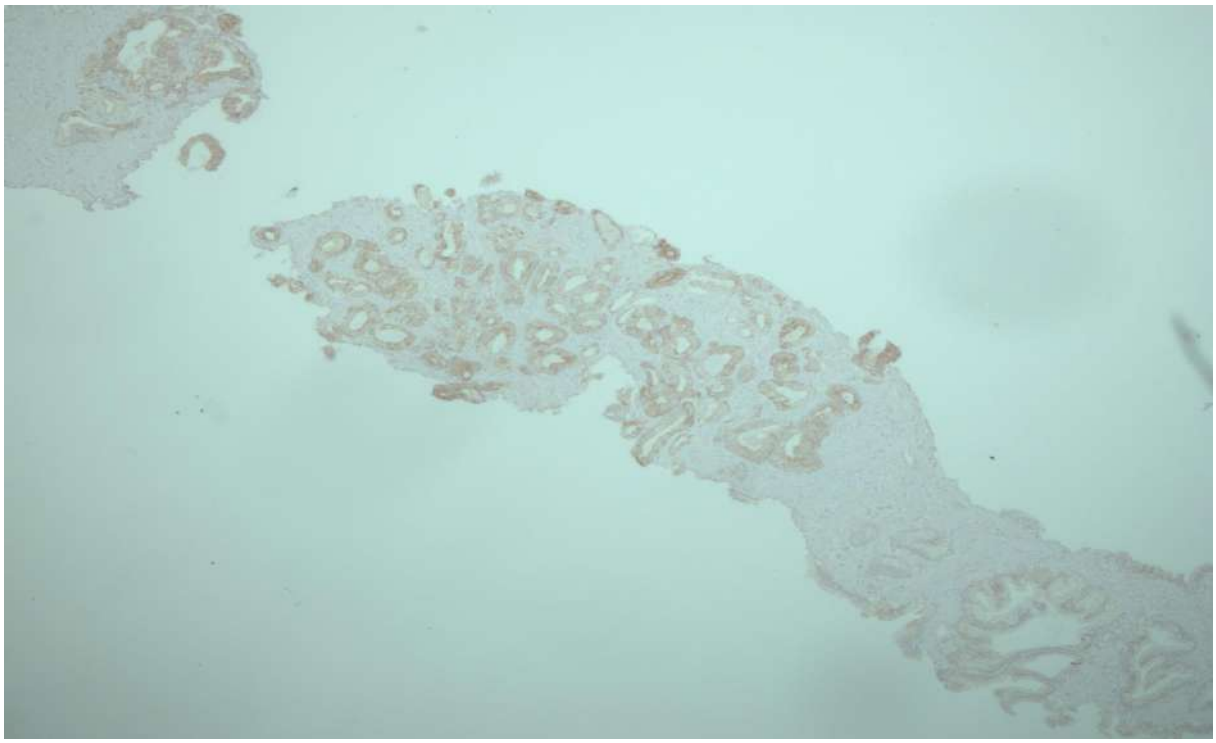

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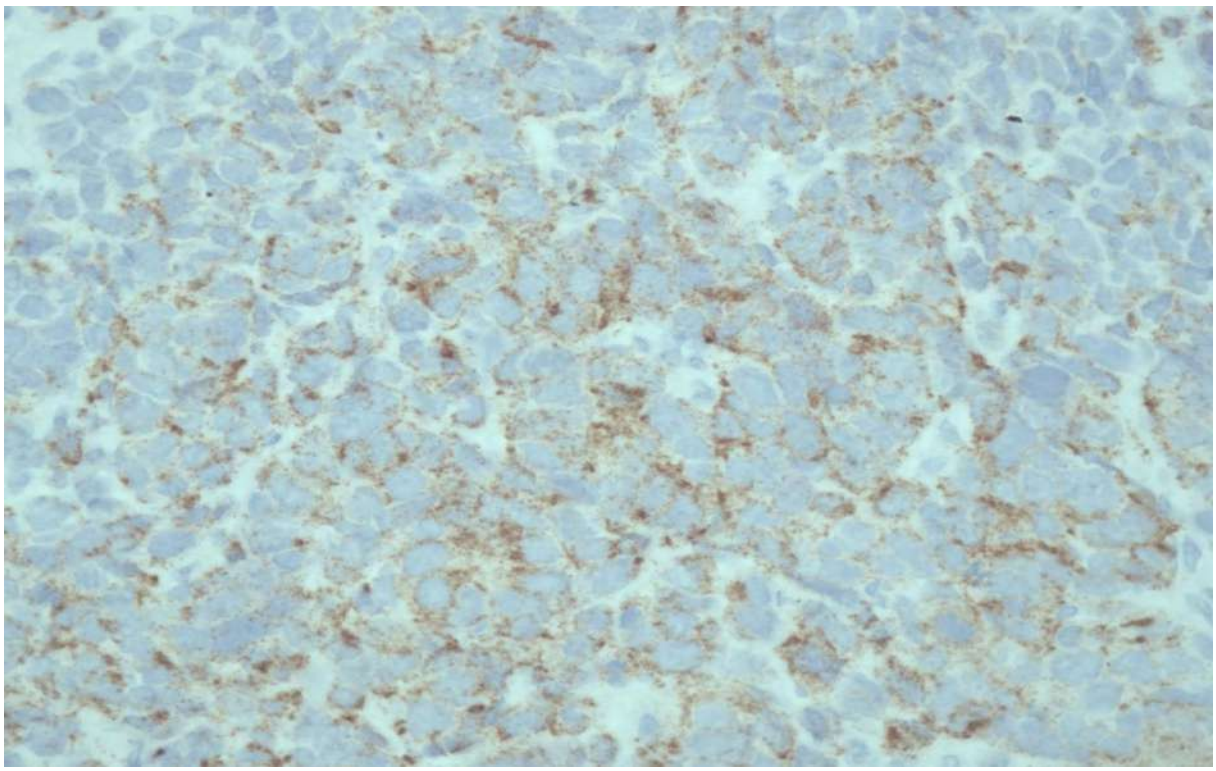
Figure 8. Lung carcinoma (G1-G2). Hematoxylin and eosin staining (a, x200); melatonin expression (b, x120).



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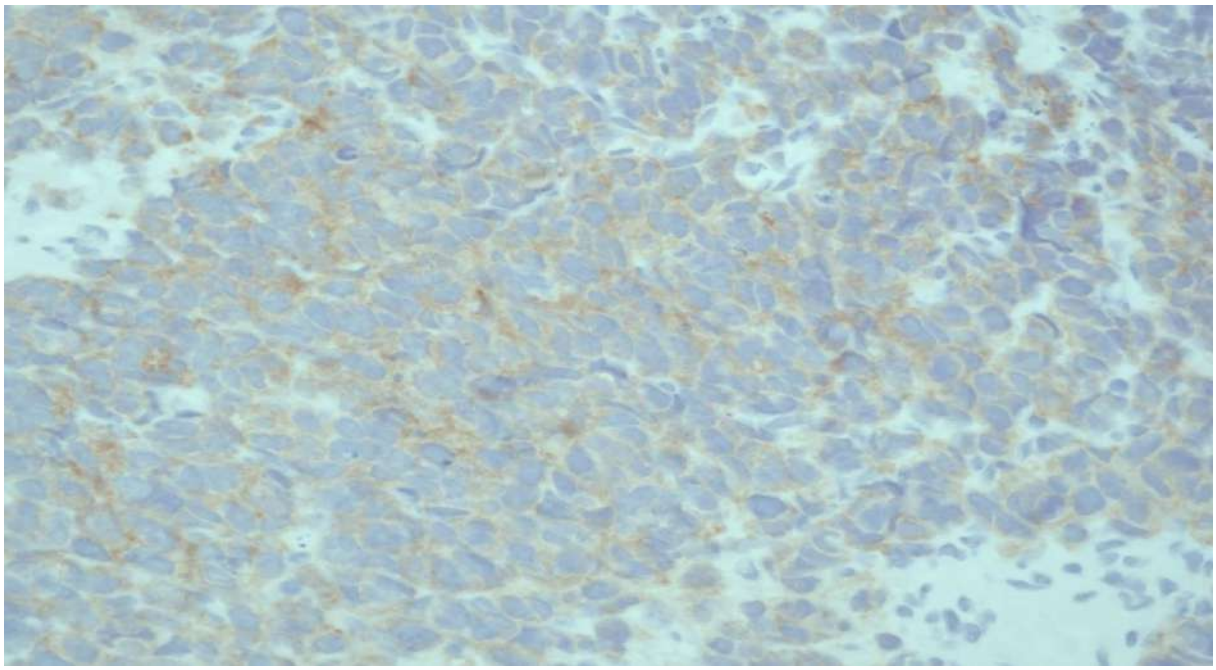


b

Figure 9. Melatonin expression in prostate carcinomas .

a – carcinoma (G1-G2); b – carcinoma (G3-G4). a, b - x200.

3.2. Melatonin expression in gastric, prostate and lung carcinomas

Melatonin expression was detected in tissue samples of human gastric, prostate, and lung tumors with varying degrees of differentiation (Fig. 10-11).

The average value of the relative area of melatonin expression in gastric carcinoma G1-G2 was 10.16 ± 1.72% and was 4.79 times higher than in gastric carcinoma of the G3-G4 differentiation stage, where this indicator was 2.12 ± 0.21 %.

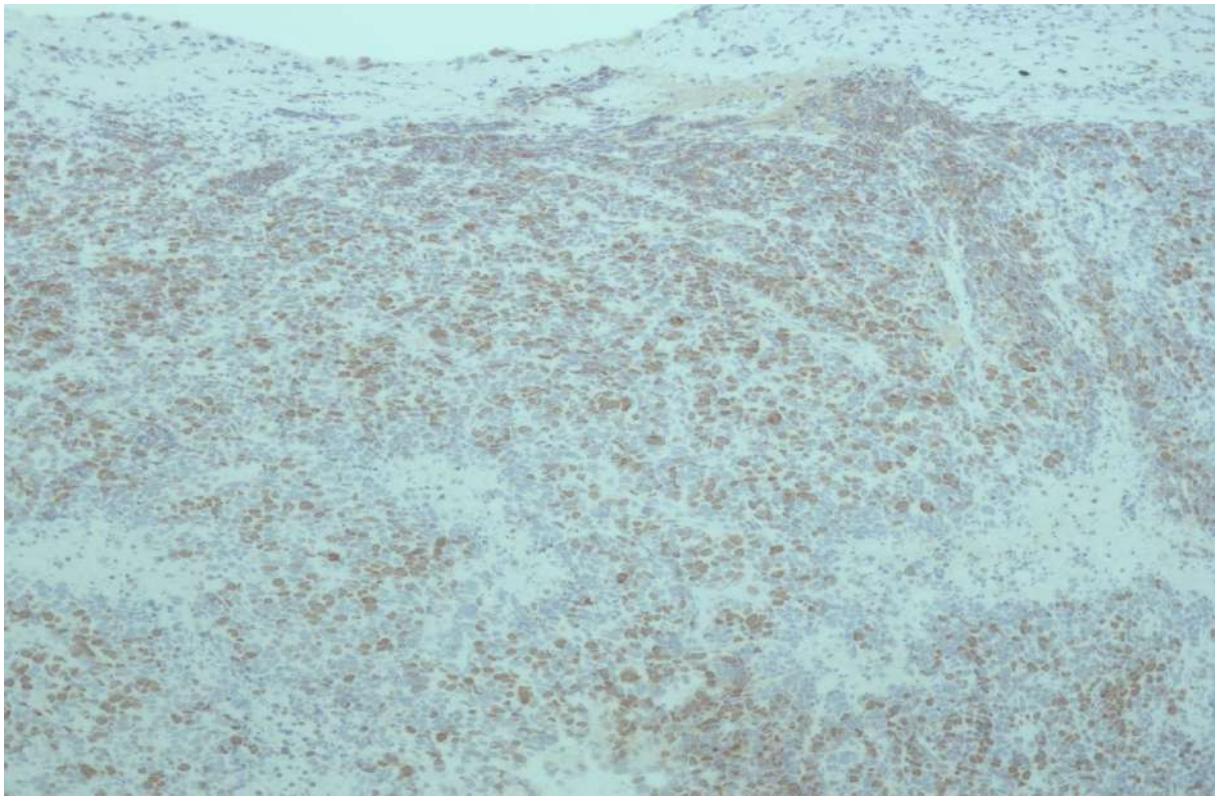


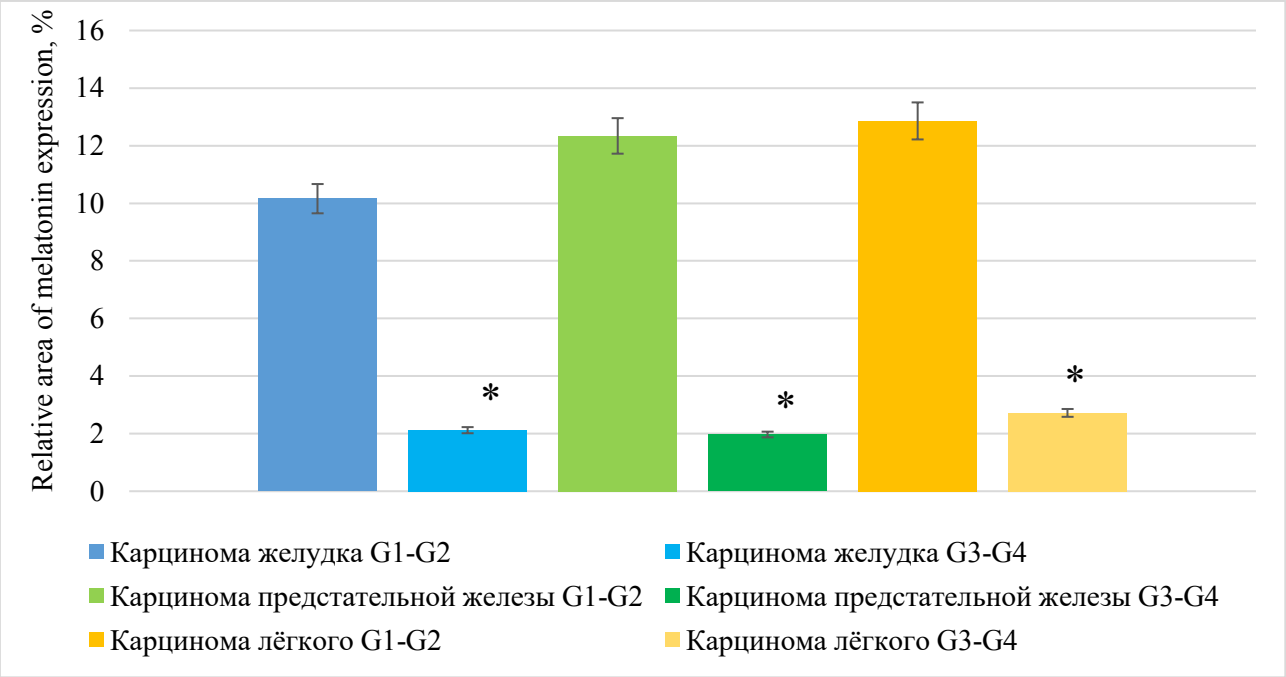
Figure 10. Melatonin expression in prostate carcinoma (G1-G2). x200.

In turn, in prostate carcinoma G1-G2, the relative area of melatonin expression was 12.34 ± 1.63 % and was 6.26 times higher than in prostate carcinoma G3-G4 differentiation stage, where the average value was 1.97 ± 0.17 %.

The relative area of melatonin expression in G1-G2 lung carcinoma was 12.86 ± 1.81% and was 4.73 times lower than in G3-G4 lung carcinoma of differentiation stage, where the area of melatonin expression was 2.72 ± 0.19%

(Fig. 11).

Thus, melatonin expression is reduced in tumors with a weak degree of differentiation (more malignant G3-G4), since melatonin has a cytostatic effect .



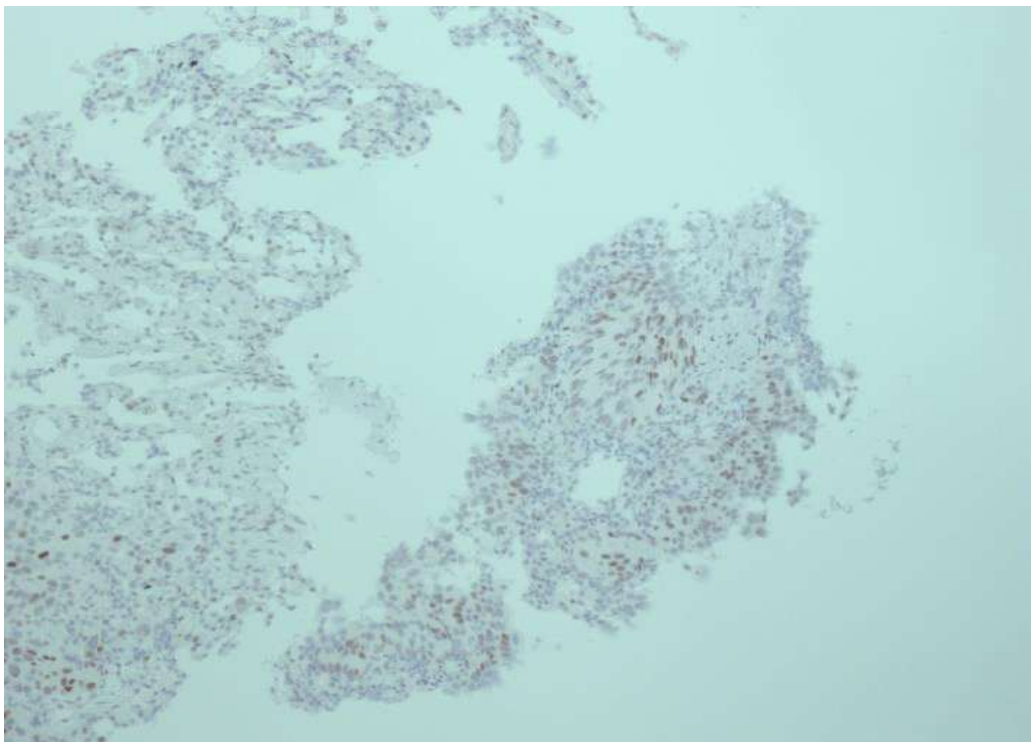
Note: * $p < 0.05$ – compared with the corresponding indicator in tumor tissue with G1-G2 degree of differentiation.

Figure 11. The area of melatonin expression in gastric, prostate and lung carcinomas of varying degrees of differentiation.

3.3. Histamine expression in gastric, prostate and lung carcinomas

Histamine expression was detected in tissue samples of human gastric, prostate and lung tumors with varying degrees of differentiation (Fig. 12, 13).

The average value of the relative area of histamine expression in gastric carcinoma G1-G2 was 2.67 ± 0.31% and was 3.57 times lower than in gastric carcinoma of the G3-G4 differentiation stage, where this indicator was 9.54 ± 1.47 %.



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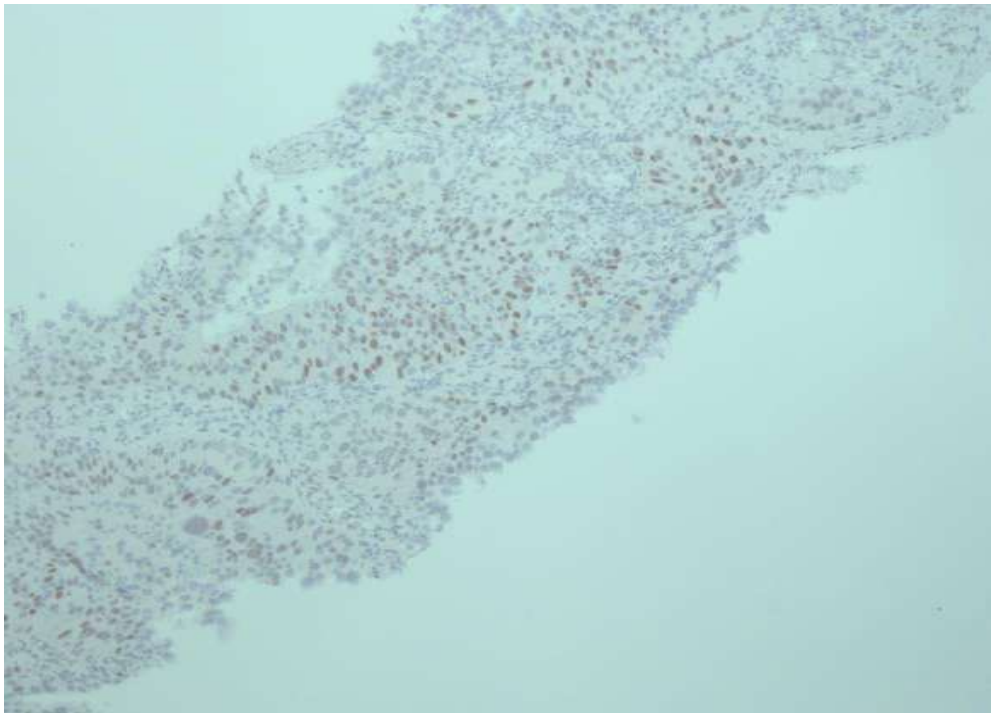


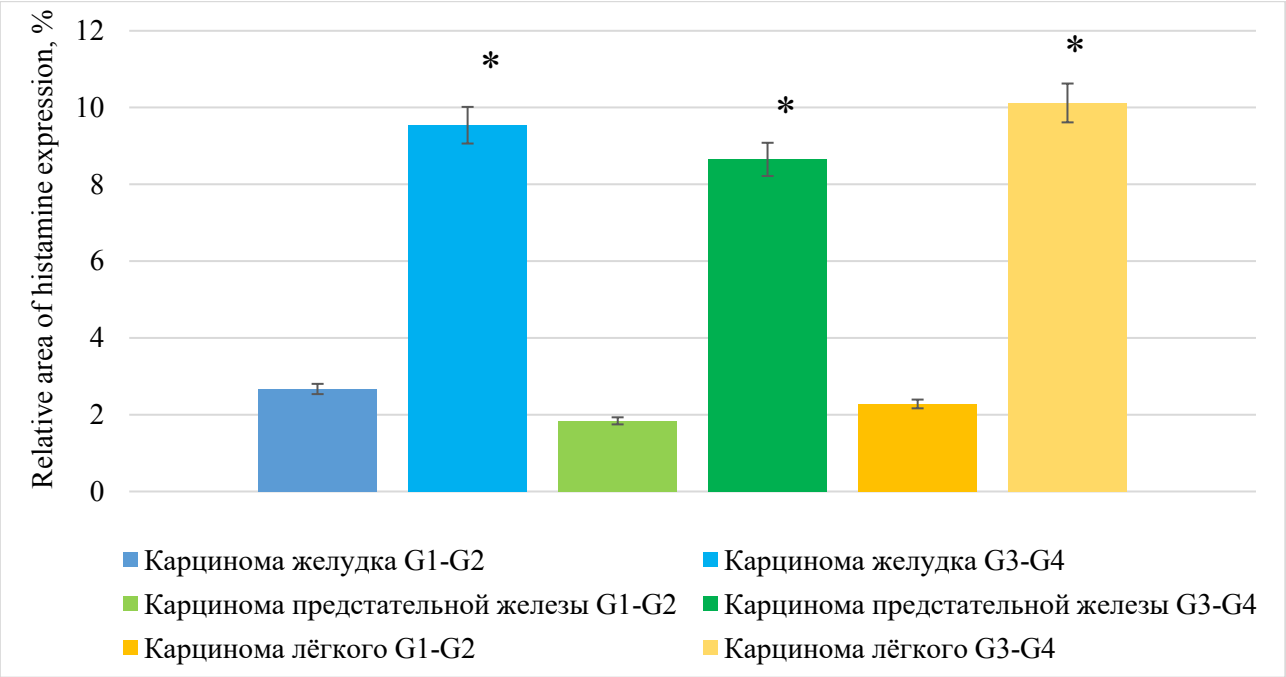
b

Figure 12. Histamine expression in gastric carcinomas (G3-G4, a) and light (G3-G4 , b). a, b – x120.

In turn, in prostate carcinoma G1-G2, the relative area of histamine

expression was 1.84 ± 0.12 % and was 4.70 times lower than in prostate carcinoma G3-G4 differentiation stage, where the average value was 8.65 ± 1.34 %.

The relative area of histamine expression in G1-G2 lung carcinoma was 2.28 ± 0.10% and was 4.44 times lower than in G3-G4 lung carcinoma of differentiation stage, where the area of histamine expression was 10.12 ± 1.76% (Fig. 13).



Note: * $p < 0.05$ – compared with the corresponding indicator in tumor tissue with G1-G2 degree of differentiation.

Figure 13. The area of histamine expression in gastric, prostate and lung carcinomas of varying degrees of differentiation.

Thus, histamine expression increases in tumors with a weak degree of differentiation (more malignant – G3-G4), since it is an activator of cell proliferation.

3.4. Somatostatin expression in gastric, prostate and lung carcinomas

Somatostatin expression was detected in tissue samples of human gastric, prostate, and lung tumors with varying degrees of differentiation (Fig. 14-15).

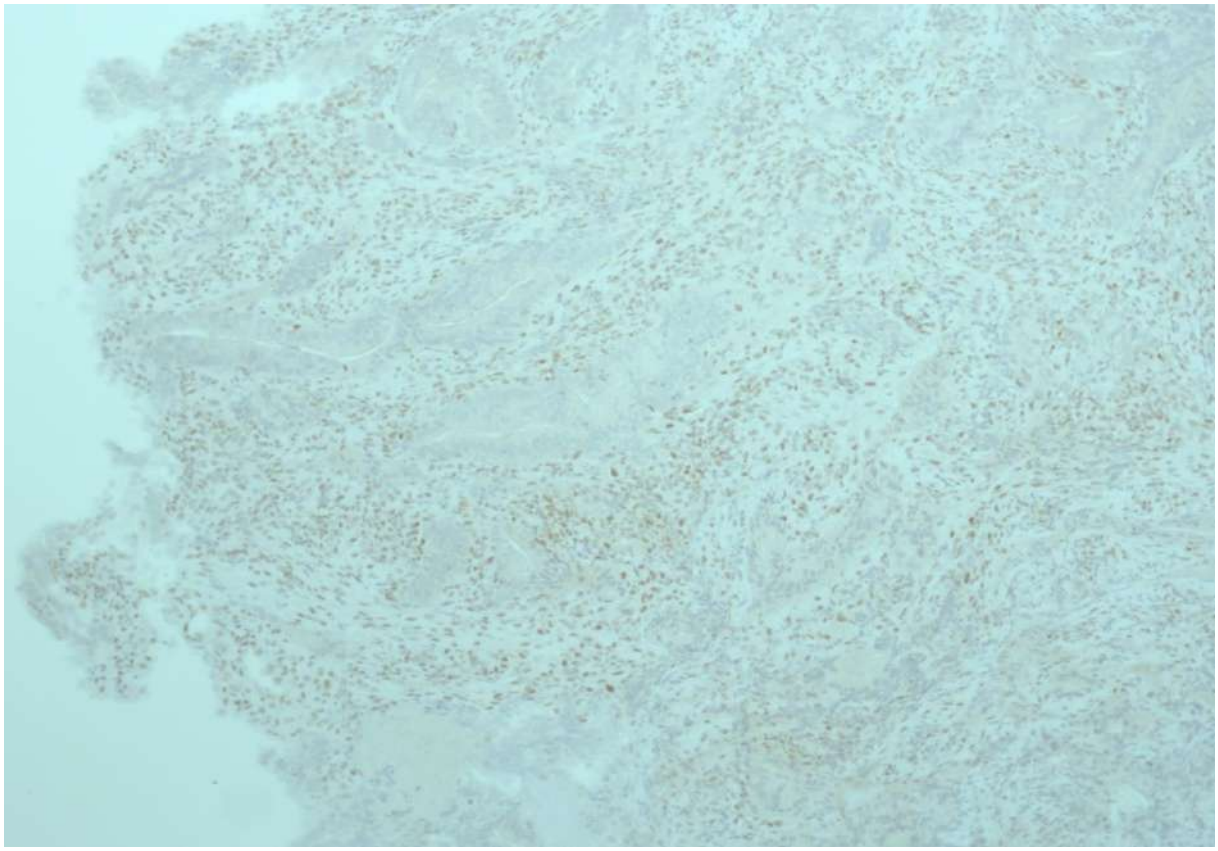


Figure 14. Somatostatin expression in lung carcinoma (G1-G2). x120.

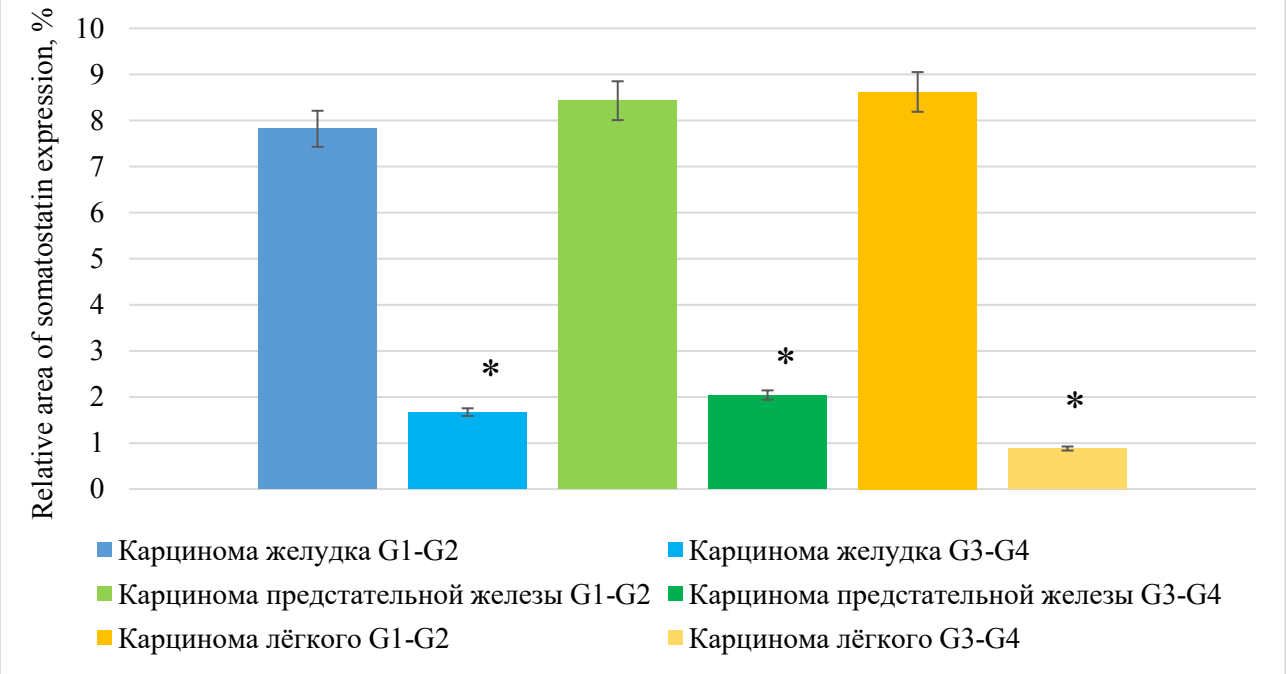
The average value of the relative area of somatostatin expression in gastric carcinoma G1-G2 was 7.82 ± 1.34% and was 4.68 times higher than in gastric carcinoma of the G3-G4 differentiation stage, where this indicator was 1.67 ± 0.07 %.

In turn, in prostate carcinoma G1-G2, the relative area of somatostatin expression was 8.43 ± 1.27 % and was 4.13 times higher than in prostate carcinoma G3-G4 differentiation stage, where the average value was 2.04 ± 0.16 %.

The relative area of somatostatin expression in G1-G2 lung carcinoma was 8.62 ± 1.29% and was 9.80 times higher than in G3-G4 lung carcinoma of

differentiation stage , where the area of somatostatin expression was 0.88 ± 0.04% (Fig. 15).

Thus, somatostatin expression is reduced in tumors with a weak degree of differentiation (more malignant G3-G4), since somatostatin has a cytostatic effect.



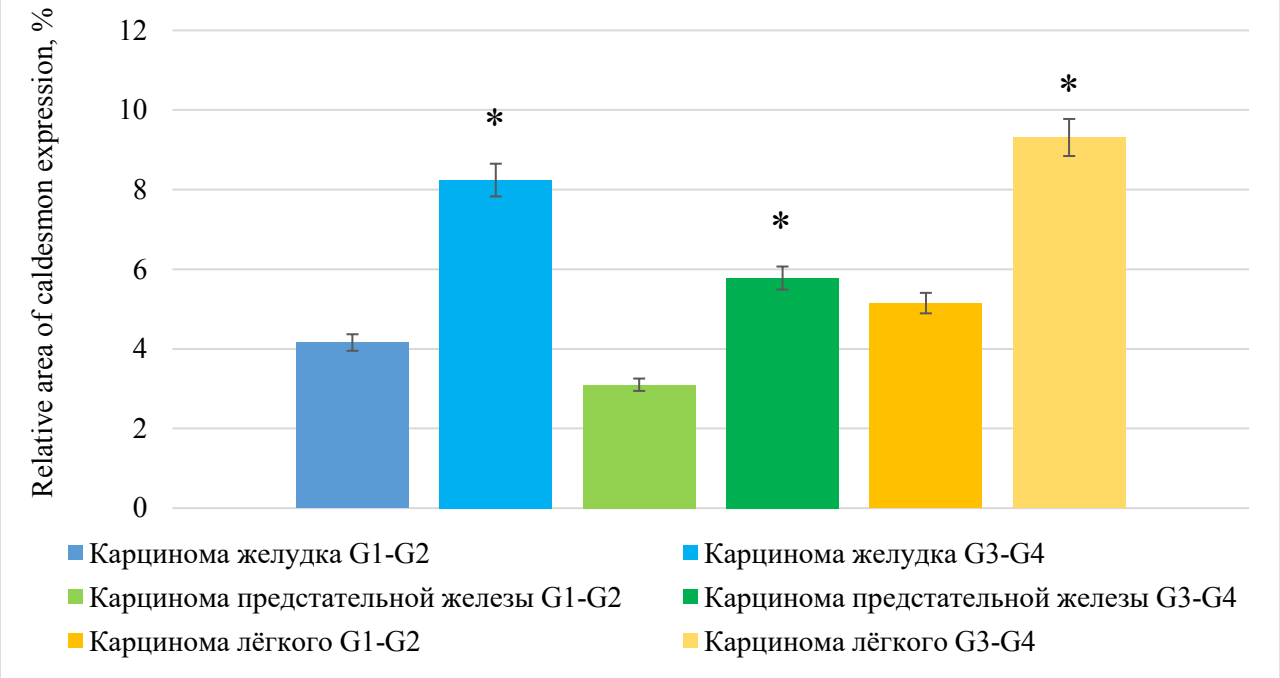
Note: * $p < 0.05$ – compared with the corresponding indicator in tumor tissue with G1-G2 degree of differentiation.

Figure 15. The area of somatostatin expression in gastric, prostate and lung carcinomas of varying degrees of differentiation.

3.5. Caldesmon expression in gastric, prostate and lung carcinomas

When studying the expression indices of caldesmon in various tumors, an increase in its production was shown in parallel with a decrease in tumor differentiation. For example, the relative expression area of caldesmon in lung

carcinoma G1-G2 was 5.15 ± 1.62 and was significantly lower than in lung carcinoma G3-G4 differentiation stage, where the expression area of caldesmon was 9.31 ± 1.75 (Fig. 16). A similar picture was observed in relation to all studied tumor localizations.



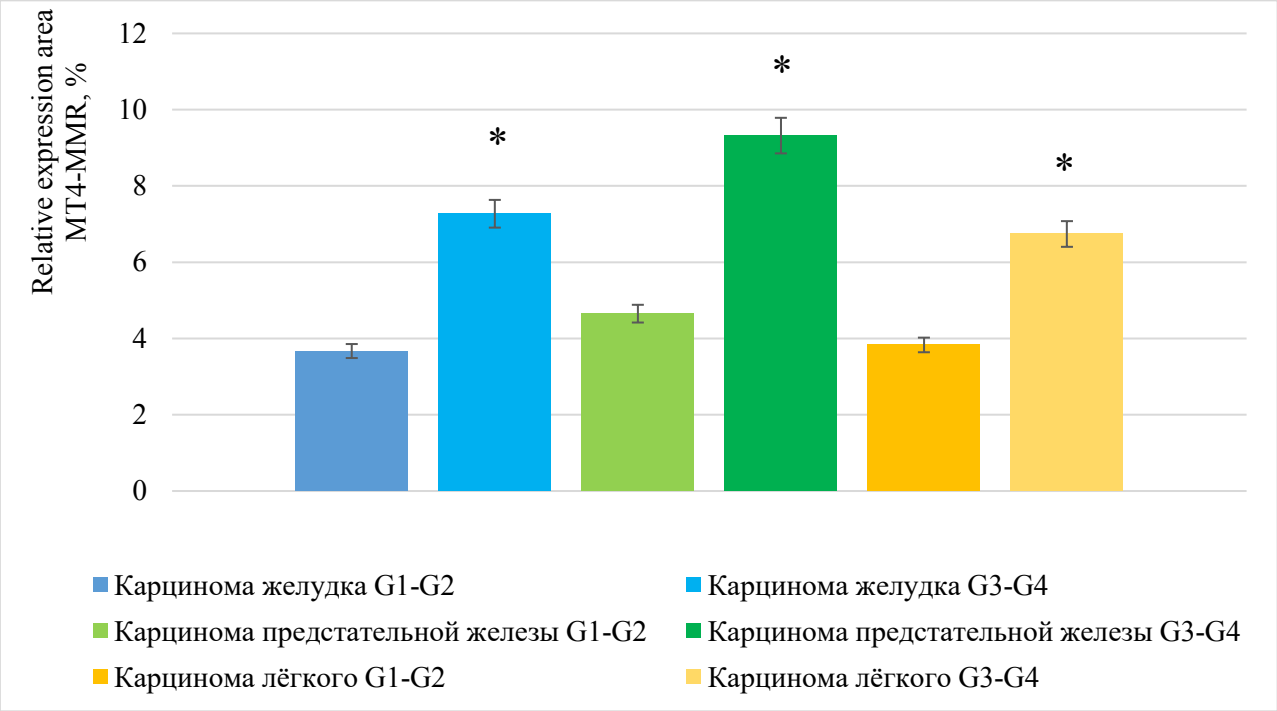
Note: * $p < 0.05$ – compared with the corresponding indicator in tumor tissue with G1-G2 degree of differentiation.

Figure 16. Area of caldesmon expression in gastric carcinomas, prostate gland and lung of varying degrees of differentiation.

3.6. MT4-MMP expression in gastric, prostate and lung carcinomas

When studying the expression indices of MT4-MMP in various tumors, an increase in its production was shown in parallel with a decrease in tumor differentiation. For example, the relative expression area of MT4-MMP in lung

carcinoma G1-G2 was 3.83 ± 0.42 and was significantly lower than in lung carcinoma G3-G4 differentiation stage, where the expression area of MT4-MMP was 8.11 ± 1.23 (Fig. 17). A similar picture was observed in relation to all studied tumor localizations.



Note: * $p < 0.05$ – compared with the corresponding indicator in tumor tissue with G1-G2 degree of differentiation.

Figure 17. The area of MT4-MMP expression in gastric, prostate and lung carcinomas of varying degrees of differentiation.

3.7. Use of signaling molecules as biomarkers to assess the prognosis of tumors

The study found that the relative expression of sorcinol , histamine and caldesmon was statistically significantly lower in highly differentiated tumors (G1-G2) than in poorly differentiated tumors (G3-G4).

Thus, for sorcin, when localized in the stomach - 2.64+0.45 versus

5.06+1.48, in the prostate gland - 1.65+0.11 versus 4.83+1.33, and in the lung - 2.14+0.38 versus 6.74+1.22, respectively.

For histamine localized in the stomach - 2.64 ± 0.31 versus 9.54 ± 1.47, in the prostate gland 1.84 ± 0.12 versus 8.65 ± 1.34, in the lung - 2.28 ± 0.10 versus 10.12 ± 1.76, respectively.

For caldesmon localized in the stomach - 4.16 ± 0.27 versus 8.24 ± 1.63 , in the prostate gland 3.10 ± 0.22 versus 5.78 ± 1.37 , in the lung - 5.15 ± 1.62 versus 9.31 ± 1.75 .

For matrix metalloproteinases when localized in the stomach - 3.67 ± 0.12 versus 7.27 ± 1.43 , in the prostate gland 4.65 ± 0.90 versus 9.32 ± 1.39 , in the lung - 3.83 ± 0.42 versus 9.31 ± 1.75 .

In addition, it was revealed that the presence of distant metastasis was characteristic only of a low degree of tumor differentiation.

The relationship between the relative expression area of immunohistochemical markers and tumor differentiation is presented in Table 2.

Table 2

Correlation coefficients characterizing the relationship between the indicators of the relative area of expression of immunohistochemical markers and the degree of tumor differentiation, regardless of its location.

Immunohistochemical marker	Spearman's correlation coefficient
Sorcinol	0.8*

Melatonin	-0.9*
Histamine	0.9*
Somatostatin	-0.9*
Caldesmon	0.7*
MMP	0.9*
* The significance level of the Spearman coefficient is $p<0.05$	

As can be seen from the table, the relative expression area of all immunohistochemical markers considered in the study is closely related to the degree of tumor differentiation.

The relationship between the relative expression area of immunohistochemical markers and distant metastases of gastric carcinoma is presented in Table 3.

Table 3

Correlation coefficients characterizing the relationship between the indicators of the relative area of expression of immunohistochemical markers with distant metastases of gastric carcinoma.

Immunohistochemical marker	Spearman's correlation coefficient
Sorcinol	0,1
Melatonin	-0.6*
Histamine	0.5*

Somatostatin	-0.4*
Caldesmon	0.5*
MMP	0.4*
* The significance level of the Spearman coefficient is $p<0.05$	

As can be seen from the table, a moderate-strength relationship was established between the relative expression area of melatonin, histamine, somatostatin , caldesmon , and MPP with distant metastases of gastric carcinoma.

The relationship between the relative expression area of immunohistochemical markers and distant metastases of prostate carcinoma is presented in Table 4.

Table 4

Correlation coefficients characterizing the relationship between the indicators of the relative area of expression of immunohistochemical markers with distant metastases of prostate carcinoma.

Immunohistochemical marker	Spearman's correlation coefficient
Sorcinol	0,1
Melatonin	-0.4*

Histamine	0.4*
Somatostatin	-0.1
Caldesmon	0.4*
MMP	0.3
* The significance level of the Spearman coefficient is $p<0.05$	

As can be seen from the table, a moderate-strength relationship was established between the relative area of expression of melatonin, histamine, and caldesmon with distant metastases of prostate carcinoma.

The relationship between the relative expression area of immunohistochemical markers and distant metastases of lung carcinoma is presented in Table 5.

Table 5

Correlation coefficients characterizing the relationship between the indicators of the relative area of expression of immunohistochemical markers with distant metastases of lung carcinoma.

Immunohistochemical marker	Spearman's correlation coefficient
Sorcinol	0,1

Melatonin	-0.3
Histamine	0.4*
Somatostatin	-0.4*
Caldesmon	0.4*
MMP	0.4*
* The significance level of the Spearman coefficient is $p<0.05$	

As can be seen from the table, a moderate-strength relationship was established between the relative expression area of histamine, somatostatin , caldesmon , and MPP with distant metastases of lung carcinoma.

The relationship between the relative expression area of immunohistochemical markers and distant metastases of carcinomas, regardless of their location, is presented in Table 6.

As can be seen from the table, a medium-strength relationship was established between the relative expression area of melatonin, histamine, somatostatin , caldesmon , and MPP with distant metastases of carcinomas, regardless of their location.

Further study of the relationship between the expression area indicators of immunohistochemical markers, regardless of the localization of the tumor with distant metastasis, made it possible to establish a strong connection between melatonin and somatostatin (R = 0.8) and melatonin and caldesmon (R = 0.9).

Table 6

Correlation coefficients characterizing the relationship between the indicators of the relative area of expression of immunohistochemical markers of carcinomas regardless of their location.

Immunohistochemical marker	Spearman's correlation coefficient
Sorcinol	0,1

Melatonin	-0.4*
Histamine	0.4*
Somatostatin	-0.3*
Caldesmon	0.4*
MMP	0.3*
* The significance level of the Spearman coefficient is $p<0.05$	

area of expression of sorcin , histamine, caldesmon and matrix metalloproteinases, which differ in the presence of metastasis, revealed during the study , allowed us to assume the existence of factors that contribute to the prognosis of metastasis.

To predict the metastasis of the tumor process, the corresponding entire population of those examined using random number tables were divided into training groups and control groups in a ratio of 2/3 and 1/3: three groups (patients with carcinomas of the stomach, prostate gland and lungs) and three control groups. The informativeness of the signs was assessed using the Kullback coefficient .

The diagnostic coefficients for predicting metastasis of gastric carcinoma, which form the basis of the diagnostic table of gastric carcinoma, are presented in Table 7.

Table 7.

Diagnostic coefficients for predicting the occurrence of metastasis of gastric carcinoma (fragment of the diagnostic table)

Kullback coefficient R	Questions of the diagnostic table	Diagnostic coefficients
0,1	Differentiation of tumor by grade : 1) low 2) moderate and high	1)0.5; 2)-0.7

0.6	Relative area of sorcin expression (%): 1) Less than 4; 2) 4 or more	1)-1.9; 2)0
0.7	Relative area of melatonin expression (%): 1) Less than 4; 2) 4 or more	1)0; 2)-2.2
0.6	Relative area of histamine expression (%): 1) Less than 7; 2) 7 or more	1)-1.9; 2)0
1,1	Relative area of somatostatin expression (%): 1) Less than 3; 2) 3 or more	1)0; 2)-2.9
0.5	Relative area of caldesmon expression (%): 1) Less than 7; 2) 7 or more	1)1.1; 2)-2.2
0,1	Relative area of MMP expression (%): 1) Less than 7; 2) 7 or more	1)0.5; 2)-0.7

As can be seen from the table, the most informative features that allow predicting metastasis of gastric carcinoma were: the relative area of expression of somatostatin (R=1.3) and melatonin (R =0.7).

The diagnostic coefficients were summed up to obtain the resulting diagnostic coefficient. A negative value predicted a high risk of metastasis of gastric carcinoma, while a positive value predicted a low risk of metastasis. The resulting decision rule was applied to the validation group, showing the correct result in 60% of cases. The validation results are presented in Table 8.

Table 8.

Results of testing the diagnostic table for predicting metastasis of gastric carcinoma in the testing group

Indicator	Verification group	
	Relative values, %	Number of people
Sensitivity	100,0	2
Specificity	50.0	4

False negative response	100,0	
False positive response	33.3	

The diagnostic coefficients for predicting metastasis of prostate carcinoma, which form the basis of the diagnostic table for gastric carcinoma, are presented in Table 9.

As can be seen from the table, the most informative features that allow predicting prostate carcinoma metastasis were: the relative area of expression of melatonin and caldesmon (both with R = 0.5).

By summing up the diagnostic coefficients, we obtained the resulting diagnostic coefficient. A negative value predicted a high risk of prostate gland metastasis , while a positive value predicted a low risk of metastasis.

Table 9.

Diagnostic coefficients for predicting the occurrence of metastasis of prostate carcinoma (fragment of the diagnostic table)

Kullback coefficient R	Questions of the diagnostic table	Diagnostic coefficients
0,1	Differentiation of tumor by grade : 1) low 2) moderate and high	1)0.5; 2)-0.7
0.4	Relative area of sorcin expression (%): 1) Less than 4; 2) 4 or more	1)-1.7; 2)0
0.5	Relative area of melatonin expression (%): 1) Less than 4; 2) 4 or more	1)0; 2)-1.8
0.4	Relative area of histamine expression (%): 1) Less than 7; 2) 7 or more	1)-1.7; 2)0

0,0	Relative area of somatostatin expression (%): 1) Less than 3; 2) 3 or more	1)0; 2)0
0.5	Relative area of caldesmon expression (%): 1) Less than 7; 2) 7 or more	1)0; 2)-1.8
0,1	Relative area of MMP expression (%): 1) Less than 7; 2) 7 or more	1)0.5; 2)-0.7

The resulting decision rule was applied to the test group, showing the correct result in 80% of cases. The test results are presented in Table 10.

Table 10.

Results of testing the diagnostic table for predicting metastasis of prostate carcinoma in the testing group

Indicator	Verification group	
	Relative values, %	Number of people
Sensitivity	100,0	2
Specificity	75.0	6
False negative response	100,0	
False positive response	50.0	

The diagnostic coefficients for predicting metastasis of lung carcinoma, which form the basis of the diagnostic table, of gastric carcinoma are presented in Table 11.

Table 11.

Diagnostic coefficients for predicting the occurrence of metastasis of lung carcinoma (fragment of the diagnostic table)

Coeff . Kullback R	Questions of the diagnostic table	Diagnostic coefficients
0.5	Differentiation of tumor by grade : 1) low 2) moderate and high	1)0; 2)-1.7
0.2	Relative area of sorcin expression (%): 1) Less than 4; 2) 4 or more	1) -0.8; 2) 1.1
0.2	Relative area of melatonin expression (%): 1) Less than 4; 2) 4 or more	1)1.1; 2)-0.8
0.2	Relative area of histamine expression (%): 1) Less than 7; 2) 7 or more	1) -0.8; 2) 1.1
0.2	Relative area of somatostatin expression (%): 1) Less than 3; 2) 3 or more	1)1.1; 2)-0.8
0.7	Relative area of caldesmon expression (%): 1) Less than 7; 2) 7 or more	1)0; 2)-2.2
0.5	Relative area of MMP expression (%): 1) Less than 7; 2) 7 or more	1)0; 2)-1.7

As can be seen from the table, the most informative features that allow predicting metastasis of lung carcinoma were: the relative area of caldesmon expression (R=0.7) and MM P (R=0.5).

By summing up the diagnostic coefficients, we obtained the resulting diagnostic coefficient. A negative value predicted a high risk of metastasis, while a positive value predicted a low risk of metastasis. The resulting decision rule was applied to the validation group, showing the correct result in 70% of cases. The validation results are presented in Table 12.

Table 12.

Results of testing the diagnostic table for predicting lung carcinoma metastasis in the testing group

Indicator	Verification group	
	Relative values, %	Number of people
Sensitivity	100,0	2
Specificity	62.5	5
False negative response	100,0	
False positive response	40.0	

When predicting metastasis, regardless of location, the entire study population (98 people) was divided into two subgroups: training – 68.6% (70 people), and verification – 31.4% (28 people).

To predict distant metastasis, discriminant analysis was used, which allowed the development of discriminant functions (1,2).

$$P\,1 = 0.6\,S - 0.3\,G + 1\,K - 3.3 \quad (4)$$

$$P2 = -1{,}8 \cdot S + 1G + 1{,}9K - 1{,}9 \quad (5)$$

where P 1 and P 2 are discriminant functions that allow one to predict the absence (P 1) or presence (P 2) of metastasis, S is the area of sorcin expression , in %, G is the area of histamine expression, in %, K is the area of caldesmon expression , in %, The evaluation of the obtained discriminant model showed the correctness of the prediction in 91% of cases.

The practical determination of the risk of metastasis is carried out as follows: the numerical values of the expression area of sorcin , histamine and caldesmon are substituted into both functions . After calculating the numerical values according to the proposed functions, the one with the greater numerical

value is retained (i.e., predicting the presence or absence of the risk of metastasis).

The results of the discriminant function analysis are presented in Table 13.

Table 13

Results of the discriminant function analysis

Marker	Wilkes	Private	F- except	p- level .	Tolerance .	1- tolerant.
Sorcinol	0.773542	0.707243	38,08267	<0.001	0.230746	0.769254
Histamine	0.729447	0.749995	30,66746	<0.001	0.228339	0.771662
Caldesmon	0.603939	0.905856	9,56145	0.00263	0.519054	0.480946

As can be seen from the table, statistically significant difference from zero of sorcin , histamine and caldesmon allows their use in the model of metastasis prognosis. Higher results of prognosis on the discriminant model compared to the method of sequential Wald procedure are obtained, apparently, due to finding more accurate discrimination functions.

A feature of the constructed models of A. Wald in the modification of E.V. Gubler and discriminant analysis is the assumption of the linearity of the interaction of factors within the model. This feature can significantly reduce the accuracy of the forecast, therefore, to eliminate these shortcomings, a neural network model was chosen, and the input parameters previously used in the A. Wald model were used for its construction and training. The structure of the neural network included an input layer of 3 neurons, a hidden layer of 6 neurons, and an output layer of one neuron (Fig. 18).

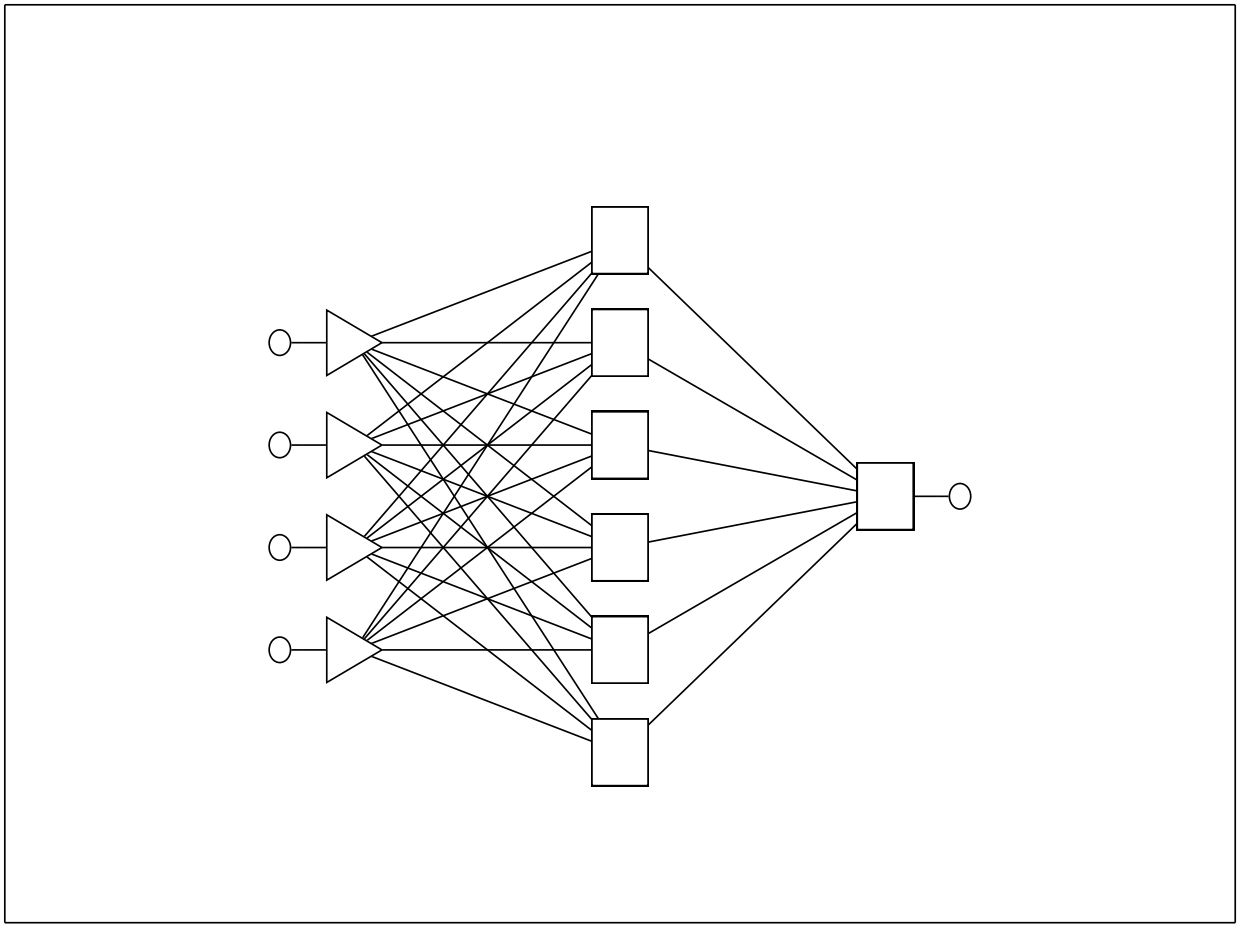


Figure 18. Structure of the neural network predicting metastasis

The neural network was trained using the methods of backpropagation of errors and conjugate gradients. Three groups were formed from the entire population, two of which were directly involved in the training: the training group (48 people) and the control group (25 people), as well as the testing (verification) group - 25 people. The correct result in the training group was 98%, control 96% and testing - 96%.

The results of testing the neural network on the testing group are presented in Table 14.

Table 14.

Results of testing the neural network for predicting metastasis on the test group

Indicator	Testing group	
	Relative values, %	Number of people
Sensitivity	90.0	9
Specificity	100,0	15
False negative response	93.8	
False positive response	100,0	

The sensitivity of the neural network was 96%, the specificity was 100%. The sensitivity of individual variables in the neural network model was determined as the ratio of the neural network errors in the testing group without the factorial feature of interest to the network errors with the factorial feature of interest. The higher the sensitivity, the greater the significance of the predictor under study, the smaller the neural network forecast error.

The information value of the factors included in the neural network is presented in Table 15.

Table 15.

Results of sensitivity analysis of predictor factors of neural network

Factor	Sensitivity	Rank
Histamine	3.9	1
Caldesmon	3.5	2
Sorcinol	2.0	3
MMP	1.7	4

In predicting metastasis using a neural network, the most informative factor was the relative area of histamine and caldesmon expression .

The study found that the linear model of discriminant analysis, sequential analysis by A. Wald in the modification by E.V. Gubler allows to correctly predict cases of metastasis up to 80%, and discriminant analysis - 91% of cases. At the same time, taking into account the nonlinearity of the relationship between the relative area of histamine and caldesmon allowed to increase the accuracy of the metastasis prediction to 96%. In addition, taking into account the nonlinearity of the relationship between the relative area of expression of histamine and caldesmon in the neural network model in the tumor process allowed to increase the accuracy of the metastasis prediction.

Thus, the study showed that high expression rates of sorcin , histamine and caldesmon indicate low differentiation of adenocarcinomas in the stomach, prostate gland and lungs. Expression of the studied molecular markers can be used to predict distant metastases when choosing further tactics of targeted tumor treatment.

***

Since, as shown in this study, carcinomas can produce various peptide hormones and biogenic amines, which should also be considered as hormones, when discussing the results obtained, we should focus on the analysis of the phenomenon that is still often referred to in many oncology manuals and textbooks as “ectopic tumor production of hormones” and is understood to mean the ability of neoplasms of non-endocrine origin to produce certain hormones .

The study of this problem is of theoretical and practical interest, since, on the one hand, it can expand and clarify ideas about the patterns of differentiation of tumor cells, and on the other hand, outline the principles of pathogenetic therapy for developing hormonal disorders that cause certain metabolic shifts in the body.

In addition, arising at the early stages of tumor development , hormone production may be one of the first signs of a neoplasm, which is of particular

interest in the search for methods of early diagnosis of malignant tumors. Hormones produced by a tumor may be the object of targeted therapeutic action: it is fundamentally possible to use antibodies to hormones as conductors of cytostatic drugs .

Despite the large amount of literary data on the study of the secretion of ACTH, STH, MSH, antidiuretic hormone (ADH), parathyroid hormone, TSH, insulin, gastrin and other products by non-endocrine tumors, only a few hormonal syndromes in malignant non-endocrine neoplasms associated with the production of these substances have been described .

The mechanism of the so-called "ectopic" tumor production of hormones has also not been studied sufficiently. It is noteworthy that in most cases non-endocrine tumors produce peptide hormones and biogenic amines. In this regard, it is of interest to study the "ectopic" tumor production of hormones from the point of view of the existence of the APUD system in the body, for the cells of which the main function is precisely the synthesis of peptide hormones and biogenic amines.

An analysis of literature data shows that most studies on "ectopic" tumor production of hormones are based on radioimmunological determination of hormones in the blood serum of cancer patients or (much less frequently) on biochemical analysis of tumor tissue extracts . It should be noted that an increase in the level of any hormone in the blood serum is not always a sign of "ectopic" secretion.

Hyperproduction of one or another hormone during tumor growth may be a secondary reaction of the corresponding apudocytes to the tumor process and thus determine the occurrence of some paraneoplastic syndromes.

Determination of hormones in tumor tissue extracts is more reliable when studying “ectopic” secretion, however, conducting these studies can give negative results at low concentrations of the substance or reflect the possibility of adsorption and accumulation of hormones by the tumor from the bloodstream.

the non-endocrine tumor itself only on the basis of immunohistochemical and electron microscopic studies with a positive reaction of tumor cells with a specific antiserum to a particular hormone and the detection of endocrine secretory granules in them .

There is a significant amount of work on the possibility of hormonal secretion in non-endocrine tumors. Thus, in cancerous tumors of the liver, lungs, and adrenal glands, the production of chorionic gonadotropin was observed; in neoplasms of the mammary gland, ovaries, lungs, kidneys, and other organs, the secretion of parathyroid hormone was noted.

"Ectopic" secretion of calcitonin has been described in lung cancer. Ovarian and breast cancer tissue may contain elevated concentrations of immunoreactive STH, with the highest concentration found in metastases. There is evidence of ACTH production by malignant tumors of various organs.

Most often, "ectopic" secretion of ACTH occurs in lung cancer, kidney tumors, less often - gastrointestinal tract, thyroid cancer . In some cases, MSH was extracted from tumors simultaneously with ACTH .

In our study, tumor apudocytes producing various hormones were detected in 30% of observations . In these studies, certain correlations were established between the type of hormone produced and the histological type of tumor (see study results).

Studies have shown that, as a rule, the nature of the histological structure of the tumor, reflecting the level of its differentiation , to a certain extent correlates with the biological properties of the hormones they produce .

Thus, in more differentiated tumors, tumor apudocytes are more often present , synthesizing melatonin and somatostatin - a substance with an inhibitory effect on the processes of cell proliferation . In less differentiated cancer tumors , tumor apudocytes are usually found synthesizing histamine - a hormone that is an activator of cell division.

At present, there is no consensus on the mechanism of "ectopic" formation

and secretion of hormones. Some authors believe that the tumor adsorbs the hormone from the blood through special "ectopic" receptors. A number of studies associate "ectopic" production with the expression of certain genes in non-endocrine cells during malignancy , which entails endocrine secretion that is not characteristic of the normal cells from which the tumor arose.

Three possible mechanisms underlying the “ectopic” secretion of hormones have been described: the return of tumor cells to an embryonic state, pluripotent in the production of peptides with hormonal activity; an anomaly in protein synthesis associated with abnormal DNA in the tumor cell; hybridization of malignant non-endocrine cells with normal endocrine cells under the influence of an oncogenic virus.

As our studies have shown, the production of hormones by non-endocrine epithelial tumors is associated with the presence of tumor endocrine cells (apudocytes) in them and their production of peptide hormones and/or biogenic amines . The mechanism of the appearance of tumor endocrine cells in non-endocrine neoplasms can be explained as follows.

Tumor cells have ultrastructural organo- and tissue specificity , due to the preservation of their ability to undergo specific differentiation. The direction of differentiation depends on the level of differentiation of cells (stem, partially committed , progenitor cells) that have undergone malignancy, which subsequently determines the formation of one or more types of cells in the tumor and is associated with the pluri- or monopotency of the transforming cells.

It has been shown that apudocytes of certain organs develop from a common source with the corresponding parenchymatous cells. This is evidenced by the discovery of chimera cells in various organs and tumors , combining ultrastructural features of diverse differentiation. The fact that certain apudocytes can have a single histogenetic source with parenchymatous epithelial cells is evidenced by the presence of a single stem cell for all four types of intestinal epithelial cells: enterocytes , goblet cells,

Paneth cells , and endocrine cells.

Based on the above, we have proposed a scheme of apudocytes from a common source with epithelial cells – a pluripotent stem cell. Based on the idea of the ability of tumor cells to differentiate in various directions depending on the degree of differentiation of the cells that have undergone malignancy, and taking into account this scheme, we can assume three options for the appearance of endocrine tumor cells in neoplasms: 1) if malignancy occurred at the level of a pluripotent stem cell, then the neoplasm can be represented by tumor epithelial cells and tumor apudocytes in a variety of combinations; 2) if malignancy occurred at the level of a pluripotent or partially committed epithelioblast or apudoblast , then the tumor can be represented by epithelial or endocrine cells of several types; 3) if malignancy occurred at the level of a monopotent precursor cell of the epithelium of a certain type, then in this case cancer of the corresponding histological type or monomorphic apudoma (apudoblastoma) can occur.

Consequently, "ectopic" tumor production of hormones occurs in the first variant of cell malignancy and is caused by the presence of tumor apudocytes in the neoplasm that synthesize certain hormones. Since the endocrine function of the tumor is genetically determined by the presence of tumor apudocytes of the same type as in the organ under normal conditions, it is inappropriate to talk about "ectopic" production of hormones in this situation, and even more so about paraneoplastic syndrome, since the endocrine function is associated with the activity of the tumor itself, and not of the cells of the APUD system outside the neoplasm. Thus, we are talking about primary, not secondary apudopathy . For this phenomenon, the term "endocrine function of non-endocrine tumors" is more appropriate.

It is obvious that the production of hormones by non-endocrine tumors is based on the peculiarities of the histogenesis of neoplasms associated with the presence of corresponding hormones in normal organs . apudocytes ,

developing from common with the parenchymatous cells of a given organ pluripotent (stem) elements, and the level of differentiation of cells that have undergone malignancy. During malignancy, the precursor cells of apudocytes , which have monopotent differentiation , form apudomas ; during malignancy, precursor cells of epithelial elements (also monopotent) - cancer without the presence of endocrine cells; in case of malignancy at the level of a pluripotent stem cell , differentiation can proceed both in the direction of the formation of tumor cells of the parenchymatous and endocrine types , which leads to the emergence of neoplasms with the presence of endocrine-type tumor cells in them . It is the latter that determine the production of hormones in tumors built mainly from non-endocrine (epithelial) elements.

The conducted studies have shown that the phenomenon of endocrine secretion in non-endocrine tumors is not an autonomous feature, but a genetically determined process associated with the conditions of histogenesis and cell differentiation.

Increased expression of MT4- MMP has been identified in some breast cancer cell lines, and this metalloproteinase enhances tumor growth and stimulates the development of lung metastases. Ultrastructural analysis of tumor vessel pericytes expressing MT4- MMP in large quantities showed that the pericytes have an irregular shape, increased cytoplasmic volume, and poor connection with endothelial cells. Thus, it is assumed that MT4- MMP can affect angiogenesis. It is noted that MT4- MMP activates pro-MMP-2. The level of expression of the gene encoding MT4- MMP is increased in cartilage tissue in osteoarthritis. A certain role, together with other proteases , MT4- MMP plays in the protease cascade of ovulation, which was demonstrated in a mouse model [101] .

MMP transcript has also been detected in other cancers. The contribution of MT4- MMP to tumor development has been studied in gastric cancer, colon cancer, head and neck cancer, breast cancer, and lung cancer.

Wang et al. examined the expression of MT4- MMP transcripts and proteins in 42 cases, including gastric cancer and normal tissues and 40 cases of atrophic gastritis. The results showed that there was no difference in the expression of MT4- MMP between normal tissues and cases of atrophic gastritis. However, its expression was higher in patients with gastric cancer than in normal tissues and in atrophic gastritis. The authors concluded that there was a relationship between MT4- MMP expression and the depth of tumor invasion, lymph node metastasis, and serous cell involvement in the pathological process in patients with gastric cancer [42] .

MT4- MMP is expressed in lipid rafts highly metastatic HM-7 cell line but not in the parental low metastatic LS174T cell line, suggesting a role for MT4-MMP in the metastatic distribution of colon cancer [20] . In contrast, caveolin-1 is not expressed at all in HM-7 cells and is weakly expressed in the cytosolic fraction of LS174T cells. Restoration of caveolin-1 expression in HM-7 inhibits MT4- MMP expression in lipid rafts , suppressing the metastatic phenotype of colon cancer cells. Although a role for caveolin-1 in MT4- MMP trafficking has been excluded [64] , the effect of caveolin-1 on MT4 - MMP expression could be explained by other mechanisms, including regulation of MT4- MMP transcription or translation , or release of MT4- MMP from the membrane by proteases or phospholipases, each of which may be regulated by caveolin-1 activity [20] .

In their study, Hieronimus et al. analyzed different lines human tumor cells and tissue homogenates were analyzed for MT4- MMP expression by Western blotting and quantitative PCR . SK-Mel-28 cell organelles were separated using continuous iodixanol gradients . SK-Mel-28 protein glycosylation was studied using glucosidases and site-directed mutagenesis of MT4- MMP cDNA before transfection. The scientists found that MT4 - MMP is highly expressed in human melanoma cell lines, as well as in melanoma skin and tissue samples. Three forms of MT4-MMP with molecular weights of 45 kDa , 58 kDa and 69 kDa were detected . In addition, they demonstrated that the 58 kDa form is the mature

protein in the cell membrane and the 69 kDa form is its precursor found in intracellular compartments. The 69 kDa forms are cleaved by furin in the Golgi apparatus. In addition, they also identified Asn318 as the only N-glycosylation site of MT4- MMP . Moreover, the authors propose to use metastatic melanoma cells as a model to study MT4- MMP , its expression, different forms, intracellular localization, precursor/product ratio [50] .

Alejandra et al. investigated the expression of MT4-MMP in MDA-MB-231 cells and the mRNA expression profile modulated by metalloproteinase using mRNA microarrays . Results showed that MT4 - MMP overexpression in breast cancer cells induced modulation of 65 mRNAs that were associated with alteration of p53, TGF-β, MAPK, ErbB , and Wnt -dependent pathways , as well as processes such as cell cycle, apoptosis, and focal adhesion. Some of the upregulated mRNAs were associated with worse prognosis in patients. Thus, the authors conclude that in breast cancer cells, MT4- MMP overexpression modulates the expression of mRNAs involved in several biological processes associated with tumor formation and progression and having clinical relevance. Host et al. found evidence for MT4- MMP -mediated proangiogenic and prometastatic effects. In contrast, MT4- MMP has mitogenic effects on triple-negative breast cancer cells that are independent of its proteolytic activity. Indeed, MT4- MMP stimulates cell proliferation by interacting with EGFR and enhancing its activation in response to its ligands , epidermal growth factor (EGF) and tumor growth factor (TGF) [119] . MT4- MMP expression was recently identified as a biomarker of triple-negative breast cancer patient responses to chemotherapy and to anti-EGFR combination drugs that participate in the cell cycle. These recent data highlight the clinical relevance of using the MT4- MMP /EGFR axis to select patients who may benefit from specific combinations of targeted therapies [40] .

MMP has been shown to be overexpressed in some breast cancer cell lines, and this metalloproteinase enhances tumor growth and stimulates the development of lung metastases. MT4 - MMP is also detected in human

eosinophils, lymphocytes, monocytes, and macrophages, suggesting a role for this protease in inflammation. MT4-MMP contributes to comorbidities such as arthritis and atherosclerosis, as well as thoracic aortic aneurysms with potential for dissection, suggesting its involvement in inflammation and angiogenesis [101] . The latter processes may be optionally involved in the formation of lung tumors.

Although matrix metalloproteinases are involved in the remodeling of various vascular types, their immune regulatory roles in atherosclerosis are still limited. Clemente et al. showed that MT4- MMP- deficient mice exhibit increased macrophage adhesion to the inflamed peritoneum, as well as larger lipid deposits and macrophage infiltration in atherosclerotic plaques. They also demonstrated that in these mice, impaired MT4 - MMP activity results in a higher number of patrolling monocytes, free and attached to the inflamed endothelium. The absence of MT4-MMP in patrolling monocytes results in the accumulation of Mafb $^{+}$ AIM $^{+}$ macrophages in nascent atherosclerotic plaques. MT4-MMP-nullMafb $^{+}$ AIM $^{+}$ peritoneal macrophages express higher AIM and the scavenger receptor CD36. They are more resistant to apoptosis and actively bind acLDL , which promotes the development of atherosclerosis. Conversely, CCR5 inhibition reduces these effects by preventing the enhanced recruitment of MT4-MMP-null patrolling monocytes to early atherosclerotic lesions, thereby blocking the accumulation of Mafb+AIM + macrophages and the acceleration of atherosclerosis. These results by Clemente et al. suggest that correction of MT4-MMP expression may represent a novel strategy to enhance monocyte patrolling activity in early inflammation [66] .

On the other hand, Vincent et al. studied the mechanism by which MT4-MMP , expressed by breast tumor cells, promotes metastatic spread to the lungs. The researchers applied experimental (intravenous) and spontaneous (subcutaneous) models of lung metastasis using MDA-MB-231 human breast adenocarcinoma cells overexpressing or not MT4- MMP . As a result, it was found that MT4- MMP does not affect lymph node colonization or cell extravasation

from the bloodstream, but increases the intravasation step leading to metastasis. Ultrastructural and fluorescence microscopic observations revealed that MT4-MMP induces changes in tumor blood vessel architecture and also induces an angiogenic switch to a catalytic-dependent pathway. MT4-MMP also stimulates tumor cell proliferation by enhancing EGFR signaling, which does not require metalloproteinase activity. Based on this, the authors suggest that MT4 - MMP promotes lung metastasis by disrupting tumor vascular integrity and thereby facilitating tumor cell intravasation [40] .

Data from various studies have shown important roles for other MMP subgroups in the formation and progression of lung cancer. For example, Masaaki et al. isolated a novel, 3.3 kbp related gene MT-MMP from a mouse lung cDNA library using human MT1-MMP cDNA as a probe. The deduced protein sequence showed 87% homology with human MT2-MMP and 52, 50, and 29% with MT1-MMP, MT3-MMP, and MT4-MMP, respectively. Therefore, this gene is considered to be the mouse homolog of human MT2-MMP. A monoclonal antibody raised against a synthetic peptide recognized mouse MT2-MMP as a 70 kDa protein . Like MT1- and MT3-MMP, mouse MT2-MMP induced progelatinase A activation when cotransfected into COS-1 cells [109] .

Li et al. determined cell migration and invasion potential *in in vitro* in a lung cancer model in 4–6-week-old female mice using Transwell chambers . Based on the data obtained, the authors postulated that microRNA-21 promotes the proliferation of lung cancer cells by suppressing the apoptosis of these cells via the AKT/P-AKT/cleaved caspase 3/MMP-2/MMP-9 signaling pathway [43] .

Among the diverse family of MMPs, MT4-MMP is currently of great interest as a promising molecular marker of tumor progression.

Further expansion of research in this direction opens up new prospects for a detailed elucidation of the role of MMPs as possible tumor markers and targets for targeted therapy. antitumor therapy.

Since there is a fairly large number of malignant tumors that are resistant

to drug therapy, the question of co-expression of hormones and sorcin , responsible for tumor chemo-resistance in the same neoplasms, has become relevant.

Sorcinol plays a critical role in the regulation of calcium homeostasis, apoptosis, vesicle trafficking, cancer development and multidrug resistance.

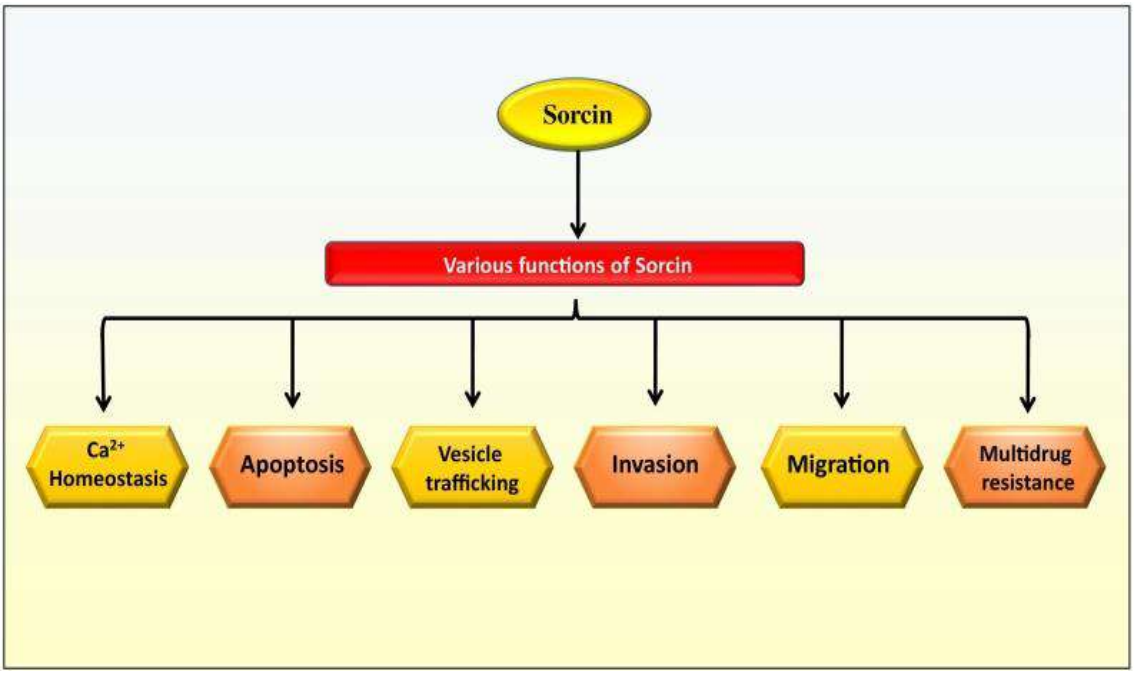


Figure 19. Functions of sorcinol [75].

Overexpression has been reported Sorcinol has been linked to various types of cancer such as breast cancer, colorectal cancer, gastric cancer, leukemia, lung cancer, nasopharyngeal cancer, ovarian cancer, etc. In fact, sorcinol expression has been found to be increased in cancer cells compared to normal cells, indicating that it plays an important role in cancer development.

Moreover, sorcinol has been found to be a regulator of various proteins that are associated with carcinogenesis, including NF- κB , STAT3, Akt , ERK1/2, VEGF, MMP, caspases , etc. This also leads to an increase in the levels of pro-apoptotic genes and the induction of the mitochondrial apoptotic pathway in cancer.

Interestingly, mutations in the sorcin gene were strongly associated with poor overall survival in bladder cancer, low-grade glioma, glioblastoma , multiforme glioblastoma , clear cell renal cell carcinoma and gastric adenocarcinoma.

In addition, it was found that overexpression Sorcinol causes resistance to various chemotherapeutic drugs.

All these data indicate the importance of sorcinol in the development of cancer and tumor drug resistance.

Analysis of the expression pattern of sorcinol showed that it is expressed in most human tissues, such as bone, heart, brain, kidney, breast, skin, B lymphocytes, T lymphocytes and monocytes. In addition, it was found that overexpression sorcina is overexpressed in various forms of cancer, including breast cancer, colorectal cancer, gastric cancer, leukemia, lung cancer, nasopharyngeal cancer, and ovarian cancer.

It has also been shown that sorcin is not normally expressed in terminally differentiated mature tissues, but is highly expressed in most tumor tissues, making it a potent target for cancer diagnosis and treatment.

Many studies show that sorcin may play an important role in cancer progression by enhancing various cancer hallmarks such as cell motility, invasion, migration, metastasis, and epithelial-to-mesenchymal transition.

In addition, sorcinol has been found to modulate the levels of important cellular proteins that are involved in the process of tumorigenesis such as NF- κB , CTSZ, STAT3, Akt , ERK1/2, VEGF, MMP, caspases , etc. [96,119,42,20,50]. Suppression of this protein leads to apoptosis and reversal of MDR cancer cells, and furthermore, sorcinol depletion reduces the levels of various proteins involved in angiogenesis, invasion, and metastasis [42,50].

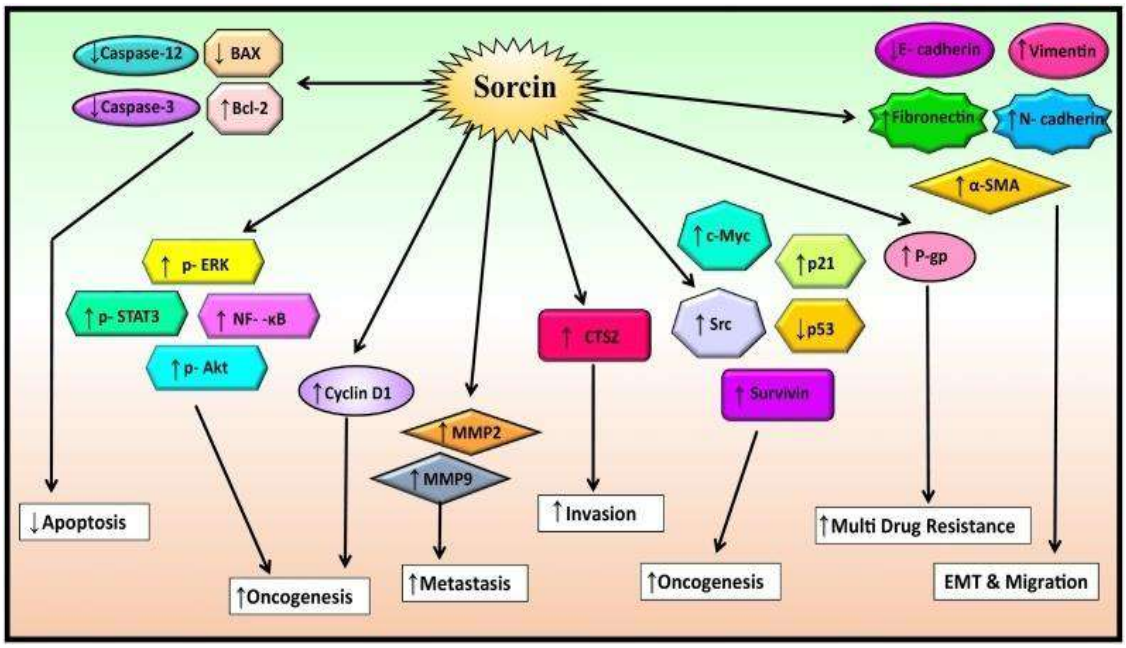


Figure 20. Sorcinol activates a gene involved in cell migration, invasion, tumorigenesis, and metastasis, and suppresses a gene involved in in apoptosis [75].

It is noteworthy that overexpression Sorcinol also induces chemoresistance to a number of chemotherapeutic agents including 5-fluorouracil, cisplatin , doxorubicin , etoposide , homoharringtonine , paclitaxel , vincristine , etc. [95].

Thus, it is evident that sorcin does play a key role in cancer development. However, the exact mechanism(s) of sorcin action in the initiation and progression of many cancers remains unclear. A number of studies are currently underway to investigate the actual cellular functions of sorcin and its involvement in tumorigenesis and drug resistance . Therefore, the current review discusses the collective role and associated molecular mechanisms of this calcium (Ca2+) binding protein in cancer and MDR, summarizing the available literature.

Sorcinol also shows a differential expression pattern in malignant and multidrug-resistant cancer cells. It is known to be closely associated with ribosomes, endoplasmic reticulum , mitochondria , and nuclear membranes.

In the past few years, sorcin has emerged as one of the most effective means of calcium homeostasis in cells. However, the expression level of sorcin is much

lower than that of the protein calmodulin (calcium-binding protein). Several reports suggest that in addition to regulating calcium ions, sorcin may also be involved in maintaining the size of ER vesicles, regulating cell cycle progression through the activation of mitosis and cytokinesis, and regulating the activity of Ca2+-dependent kinases .

In addition, sorcin has been found to regulate angiogenesis, invasion and migration of various tumor cells by regulating various key molecules involved in the processes such as NF- κB , CTSZ, STAT3, Akt , ERK1/2, VEGF, MMPs , caspases and signaling pathways including ERK, MAPK/ERK and PI3K/ Akt .

Sorcinol has also been found to stimulate metastasis and chemoresistance in malignant cells. In addition, calcium homeostasis, a major function of sorcinol , is an important cellular response to stress conditions that contributes to drug resistance during tumor progression.

sorcin overexpression is associated with worse prognosis. Upregulation of sorcin in malignant cells significantly induces cell proliferation, migration, and invasion, while knockdown of the same reduces cancer cell proliferation, migration, and invasion, demonstrating the importance of sorcin in cancer development and progression.

In addition to its cancer-promoting effects , sorcin has been shown to induce MDR against various chemotherapeutic agents through modulation of MDR1, MRP1, NF- κB , apoptotic , anti-apoptotic prosurvival proteins. Sorcin downregulation can lead to membrane hyperpolarization and decreased mitochondrial calcium , which may further promote drug-induced apoptosis in malignant cells.

The TCGA data analysis also showed that the sorcin gene alteration status was significantly associated with cancer patient survival, indicating the prognostic value of this protein. Furthermore, the elevated sorcin levels observed in various multidrug-resistant cells suggest its use as a potential biomarker for predicting drug resistance in various cancers.

So far, most of the research on sorcin has focused on the relationship between sorcin and diseases, but the regulation of sorcin by various chemotherapeutic drugs has rarely been discussed.

Furthermore, there is an urgent need for new therapeutic strategies targeting sorcin to better treat various types of multidrug-resistant cancers.

However, further studies are needed to uncover the actual role of sorcin in cancer development and multidrug resistance phenotype, and to identify sorcin as a new diagnostic and therapeutic marker for various cancers.

In this regard, the study of co-expression of sorcin and signaling molecules produced in malignant tumors may prove to be a new promising direction for the development of cancer chemotherapy methods.

CONCLUSION

Numerous data from the literature convincingly indicate that the production of hormones and other signaling molecules by non-endocrine tumors is based on the features of the histogenesis of neoplasms associated with the presence in normal organs of corresponding neuroendocrine cells (apudocytes) developing from pluripotent (stem) elements common with the parenchymatous cells of a given organ , and the level of differentiation of cells that have undergone malignancy.

precursor cells of apudocytes , which have monopotent differentiation , apudomas are formed ; in the case of malignancy of the precursor cells of epithelial elements (also monopotent) , carcinoma arises without the presence of endocrine cells; in the case of malignancy at the level of a pluripotent stem cell, differentiation can proceed both in the direction of the formation of tumor cells of the parenchymatous and endocrine types , which leads to the emergence of neoplasms with the presence of tumor neuroendocrine cells in them. It is the latter that are the source of hormone expression in carcinomas , built mainly from non-endocrine (epithelial) elements.

Thus, it can be assumed that the expression of hormones and other signaling molecules in carcinomas of various localizations is not an autonomous feature, but a genetically determined process associated with the conditions of histogenesis and cell differentiation.

Since this process is associated with the potential of cells to grow, divide and subsequently differentiate , determining the type of hormone produced by tumor cells and analyzing its biological properties may be important for assessing tumor progression .

CONCLUSIONS

1. In non-endocrine epithelial tumors (carcinomas) of the stomach, prostate gland and lungs, the expression of signaling molecules – sorcinol , melatonin, histamine and somatostatin – has been verified .

2. The degree of expression of sorcinol , melatonin, histamine and somatostatin in carcinomas of the indicated localization correlates with the aggressiveness and malignancy of the tumor (according to the Grading system : G 1- G 4).

3. Sorcinol expression (in terms of relative expression area) in highly and moderately differentiated carcinomas of the stomach, prostate and lungs (stages G 1- G 2) is 2, 3, and 3 times lower, respectively, than in poorly differentiated tumors (stages G3-G4).

4. Melatonin expression in highly and moderately differentiated gastric, prostate and lung carcinomas (stages G 1- G 2) is 5, 6 and 5 times higher, respectively, than in poorly differentiated tumors (stages G3-G4).

5. Histamine expression in highly and moderately differentiated carcinomas of the stomach, prostate and lungs (stages G 1- G 2) is 4, 5, 4 times lower, respectively, than in poorly differentiated tumors (stages G3-G4).

6. The expression of somatostatin in highly and moderately differentiated carcinomas of the stomach, prostate and lungs (stages G 1- G 2) is 5 and 4.9 times higher, respectively, than in poorly differentiated tumors (stages G3-G4).

7. Caldesmon expression in highly and moderately differentiated carcinomas of the stomach, prostate and lung (stages G 1- G 2) is 2 times lower than in poorly differentiated tumors (stages G3-G4).

8. MMP expression in highly and moderately differentiated carcinomas of the stomach, prostate and lungs (stages G 1- G 2) is 2 times lower than in poorly differentiated tumors (stages G3-G4).

9. The established correlations between the expression of the studied signaling molecules and the degree of differentiation of carcinomas of different localizations allow them to be used as biomarkers for assessing tumor progression and sensitivity to chemotherapy.

10. Taking into account the nonlinearity of the relationship between the relative area of expression of histamine and caldesmon in a neural network model during the tumor process made it possible to increase the accuracy of the metastasis prediction to 96%.

PRACTICAL RECOMMENDATIONS

1. The obtained results allow us to propose an algorithm for using the expression indicators of sorcinol and associated signaling molecules (caldesmon and MMP4) in lung carcinomas as markers of malignant tumor progression.

2. The algorithm is as follows: during the morphological examination of all types of malignant epithelial lung tumors, in addition to the standard staining of preparations with hematoxylin-eosin , an immunohistochemical study of the expression of sorcinol and associated signaling molecules (caldesmon and MMP4) in the tumor tissue is carried out. With positive immunostaining for the above biomarkers In addition to making a histological diagnosis, a pathologist indicates a possible development of the process based on the assessment of the expression indicators of kisspeptin1, caldesmon , and MMP4.

LIST OF SYMBOLS AND SYMBOLS

ACTH – adrenocorticotropic hormone

MDR – multiple drug resistance

TRH – thyrotropin - releasing hormone

ABCB1 is a glycoprotein from the ABC transporter family.

ACLY – ATP- citrate synthase

Akt – alpha serine /threonine protein kinase

Bcl -2 – apoptosis regulator

STAT 3 – transcription factor

SERCA – Ca2+- ATPase of the sarcoplasmic/endoplasmic reticulum

CTSZ – gene encoding cathepsin Z

Erk is an extracellular signal-regulated kinase

IKK – kinase complex

MDR 1 – multidrug resistance protein 1

MMP-MT4 – matrix metalloproteinase

NCX – sodium-calcium exchanger

NF - κB – transcription factor

MTNR1 α – melatonin nuclear receptor α

MTNR1 β – melatonin nuclear receptor β

RyR – ryanodine -sensitive channel

SRI is a gene encoding the protein sorcinol

TNF α /TNF – tumor necrosis factor α

TRAP1 – 75 kDa heat shock protein

VEGF – vascular endothelial growth factor

LIST OF USED SOURCES

1. Gmurman V.E. Probability Theory and Mathematical Statistics. Moscow: Higher School , 2004. 479 p.

2. Gubler E.V. Informatics in pathology, clinical medicine and pediatrics / E.V. Gubler . - Leningrad: Medicine: Leningrad department , 1990. - 175s.

3. Zubareva, T.S. et al. Matrix metalloproteinase membrane type 4 (MT4 MMP): role and significance in the pathogenesis of tumor growth // Medical Alliance. 2022 Vol. 10. No. 2. P. 5867.

4. Iskusnykh A.Yu., Basharina O.V., Artyukhov V.G., Alabovsky V.V. The influence of histamine on the functional properties of neutrophils and the intensity of the lipid peroxidation process in the blood of donors. VSU Bulletin, series: Chemistry. Biology. Pharmacy. 2008, No. 1, pp. 93-96.

5. Kvetnoy I., Levin I. Daily excretion of melatonin in patients with stomach and colon cancer. Vopr . Oncol ., 1997, No. 33, pp. 23-32.

6. Klisho , E.V. Kondakova, I.V. Choynzonov , E.L. Matrix metalloproteinases in oncogenesis // Siberian oncological journal. 2003 No. 2. P. 6270.

7. Raikhlin N., Kvetnoy I., Tyurin E. Melatonin in the blood serum of cancer patients. Klin. Med., 1980.№ 58. P. 77-79.

8. Speransky V.V., Alekhine E.K., Petrova I.V., Alekhine V.E. On the role of histamine and antihistamines in oncogenesis. Medical Bulletin of Bashkortostan, 2010, No. 4, pp. 1-7.

9. Kharkevich D.D., Polevaya E.V. Histamine receptor sensitivity of blood lymphocytes in patients with breast cancer in the early and late stages. Experimental oncology, 1988, Vol. 10, No. 1. P. 27-33.

10. Shadrina, A.S. et al. Classification, regulation of activity, genetic

polymorphism of matrix metalloproteinases in norm and pathology // Almanac of Clinical Medicine. 2017 Vol.45. No.4. P.266279.

11. Yarmolinskaya , M.I. Molotkov, A.S. Denisova, V.M. Matrix metalloproteinases and inhibitors: classification, mechanism of action // Journal of obstetrics and women's diseases. 2012 Vol.61. No.1. P.113125.

12. Aggarwal B.B., Kunnumakkara A.B., Harikumar K.B., Gupta S.R., Tharakan S.T., Koca C., Dey S., Sung B. Signal transducer and activator of transcription-3, inflammation, and cancer: how intimate is the relationship? Ann N Y Acad Sci., 2009, Vol. 1171, pp. 59-76.

13. Aldea M., Orillard E., Mansi L., Marabelle A., Scotte F., Lambotte O., Michot J.M. How to manage patients with corticosteroids in oncology in the era of immunotherapy? Eur J Cancer., 2020, Vol. 141, pp. 239-251. doi:10.1016/j.ejca.2020.09.032.

14. Anisimov V.N., Popovich I.G., Zabezhinski M.A. Melatonin as antioxidant, geroprotector and anticarcinogen. Biochim Biophys Acta., 2006,Vol.1757, pp.573-589.

15. Bade B.C., Dela Cruz C.S. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clin Chest Med., 2020, Vol. 41(1), pp. 1-24. doi: 10.1016/j.ccm.2019.10.001.

16. BartholeynsJ.,Bouclier M. Involvement of histamine in growth of mouse and rat tumors: Antitumoral properties of monofluoromethylhistidine, an enzyme-activated irreversible inhibitor of histidine decarboxylase. Cancer Res., 1984, Vol. 44, pp. 639-645.

17. Bartsch C., Bartsch H., Fuchs U. Stage-dependent depression of melatonin in patients with primary breast cancer: Correlation with prolactin, thyroid stimulating hormone and steroid receptors. Cancer, 1989,Vol. 64, pp. 426-433.

18. Bartsch C., Bartsch H., Jain A. Urinary melatonin levels in human breast cancer patients. J. Neural Transm.,1981.Vol.52. pp. 281-294.

19. Bartsch S., Bartsch H., Bellmann O. Depression of Serum Melatonin in Patients with Primary Breast Cancer Is Not Due to an Increased Peripheral Metabolism. Cancer, 1991,Vol.67, pp. 1681-1684.

20. Battista T., Fiorillo A., Chiarini V., Genovese I., Ilari A., Colotti G. Roles of Sorcin in Drug Resistance in Cancer: One Protein, Many Mechanisms, for a Novel Potential Anticancer Drug Target. Cancers (Basel), 2020, Vol. 12(4), pp. 887. doi:10.3390/cancers12040887.

21. Bodmer A., Castiglione-Gertsch M. Role of hormonal manipulations in patients with hormone-sensitive metastatic breast cancer. Eur J Cancer., 2011, Vol. 47, Suppl 3, pp. 28-37. doi:10.1016/S0959-8049(11)70144-7.

22. Boto A.N., Hui P. Hormone producing gynecological tumors: pathologic entities and clinical significance. Expert Rev Endocrinol Metab., 2018,Vol. 13(1), pp. 9-24. doi:10.1080/17446651.2018.1411799.

23. Breeman W.A.P., de Jong M., Kwekkeboom D.J. Somatostatin receptor-mediated imaging and therapy: basic science, current knowledge, limitations and future perspectives. Eur. J. Nucl. Med., 2001,Vol. 28,pp. 1421-1429.

24. Burtin C., Noirot C., Paupe J., Scheinmann P. Decreased blood histamine levels in patients with solid malignant tumours. Brit. J. Cancer., 1983, Vol. 47, № 3, pp. 367-372.

25. Burtin C., Ponvert C., Fray A.J. Inverse correlation between tumor incidence and tissue histamine levels in W/WV, WV/+, and +/+ mice Nat. Cancer Inst., 1985, Vol. 74, № 3, pp.671-674.

26. Burtin C., Scheinmann P., Salomon J.C. The influence of intraperitoneal injections of histamine on tumour growth in fibrosarcoma-bearing mice. Cancer letters, 1981, Vol. 12, №3, pp. 195-201.

27. Campos C.I., Nogueira C.H., Fernandes L. Aging, circadian rhythms and depressive disorders: A review. Am J Neurodegener Dis., 2013, Vol.

2, pp. 228-246.

28. Ceresoli G.L., De Vincenzo F., Sauta M.G., Bonomi M., Zucali P.A. Role of chemotherapy in combination with hormonal therapy in first-line treatment of metastatic hormone-sensitive prostate cancer. Q J Nucl Med Mol Imaging., 2015, Vol. 59(4), pp. 374-380.

29. Chabottaux, V. et al. Membrane type 4 matrix metalloproteinase (MT4 MMP) induces lung metastasis by alteration of primary breast tumour vascular architecture // Journal of cellular and molecular medicine.
2009 V.13. No9b. P.40024013.

30. Cheng Q, Tang A, Wang Z, et al. CALD1 modulates gliomas progression via facilitating tumor angiogenesis. Cancers. 2021;13(11):2705. https://doi.org/10.3390/cancers13112705

31. Chuffa L., Alves M., Martinez M. Apoptosis is triggered by melatonin in an in vivo model of ovarian carcinoma. Endocr. Relat. Cancer.,2015, ERC-15-0463.

32. Crisso G., Matrin G., Meina V. Histamine inhibits cell proliferation and modulates the expression of Bcl-2 Family proteins via the H2 receptor in human pancreatic cells. Anticancer Res., 2006, Vol. 26, № 6, pp. 4443-4450.

33. Czarnecka A.M., Niedzwiedzka M., Porta C., Szczylik C. Hormone signaling pathways as treatment targets in renal cell cancer (Review). Int J Oncol., 2016, Vol. 48(6), pp. 2221-2235. doi:10.3892/ijo.2016.3460.

34. Deli T., Orosz M., Jakab A. Hormone Replacement Therapy in Cancer Survivors - Review of the Literature. Pathol Oncol Res., 2020, Vol. 26(1), pp. 63-78. doi:10.1007/s12253-018-00569-x.

35. Demidova N.S., Ilyinskaya G.V., Shiryaeva O.A., Chernova O.B., Goncharova S.A., Kopnin B.P. Decreased sensitivity of multidrug-resistant tumor cells to cisplatin is correlated with sorcin gene co-amplification. Neoplasma, 1995, Vol. 42(4), pp. 195-201.

36. Drexler J., Meaney T., McCormack L. The calcified pineal body and

carcinoma. Clew. Clin. Q., 1957, Vol.24, pp. 242-247.

37. Eychenne R., Bouvry C., Bourgeois M., Loyer P., Benoist E., Lepareur N. Overview of Radiolabeled Somatostatin Analogs for Cancer Imaging and Therapy. Molecules, 2020, Vol. 25(17), pp. 4012. doi:10.3390/molecules25174012.

38. [PubMed] Fairchild A, Tirumani SH, Rosenthal MH, Howard SA, Krajewski KM, Nishino M, Shinagare AB, Jagannathan JP, Ramaiya NH Hormonal therapy in oncology: a primer for the radiologist. AJR Am J Roentgenol . 204(6) , pp 620-630. doi:10.2214/JR.14.13604.

39. Faverio F., Guzzetti A., Mereghetti A., Jemoli R. Hyperhistaminemia in the neoplasms from the breast . Surgery Italian , 1982, Vol. 34(5), pp . 727-734.

40. Gao Y., Li W., Liu X., Gao F., Zhao X. Reversing effect and mechanism of soluble resistance-related calcium-binding protein on multidrug resistance in human lung cancer A549/DDP cells. Mol Med Rep. 2015, Vol. 11(3), pp. 2118-2124. doi:10.3892/mmr.2014.2936.

41. Genovese I., Fiorillo A., Ilari A., Masciarelli S., Fazi F., Colotti G. Binding of doxorubicin to sorcin impairs cell death and increases drug resistance in cancer cells. Cell Death Dis., 2017, Vol. 8(7), e2950.

42. Genovese I., Ilari A., Assaraf Y.G., Fazi F., Colotti G. Not only P-glycoprotein: Amplification of the ABCB1-containing chromosome region 7q21 confers multidrug resistance upon cancer cells by coordinated overexpression of an assortment of resistance-related proteins. Drug Resist Updat., 2017,Vol. 32,pp. 23-46. doi:10.1016/j.drup.2017.10.003.

43. Gupta K., Sirohi V.K., Kumari S., Shukla V., Manohar M., Popli P., Dwivedi A. Sorcin is involved during embryo implantation via activating VEGF/PI3K/Akt pathway in mice. J Mol Endocrinol., 2018, Vol. 60(2), 119-132. doi:10.1530/JME-17-0153.

44. Hajdu S., Porro R., Lieberman P., Foote F. Degeneration of the

pineal gland in patients with cancer. Cancer, 1972, Vol.29, pp. 706-709.

45. Hardeland R. Melatonin, hormone of darkness and more—occurrence, control mechanisms, actions and bioactive metabolites. Cellular and Molecular Life Sciences. 2008, Vol. 65(13), pp. 2001-2018. doi:10.1007/s00018-008-8001-x 3.

46. Hardeland R., Cardinali D.P., Srinivasan V., Spence D.W., Brown G.M., Pandi-Perumal S.R. Melatonin — apleiotropic, orchestrating regulator molecule. Progress in Neurobiology. 2011, Vol. 93(3), pp. 350-384. doi:10.1016/j.pneurobio.2010.12.004.

47. Helfman DM, Levy ET, Berthier C, et al. Caldesmon inhibits nonmuscle cell contractility and interferes with the formation of focal adhesions. Molecular Biology of the Cell. 1999;10(10):3097-3112. https://doi.org/10.1091/mbc.10.10.3097

48. Hirst D.G.,Flitney F.W. The physiological importance and therapeutic potencial of nitric oxide in the tumorassociated vasculature. In: Tumor angiogenesis (Eds. R. Bicknell, C.E. Lewis, N. Ferrar) Oxford Univ. Press, N.-Y. 1997,pp. 153-167.

49. HoL.J., Lamberts S.W. Somatostatin receptor subtype expression in human tumors. Ann. Oncol., 2001, Vol. 12 (Suppl. 2), pp. 31-36.

50. Hu Y., Li S., Yang M., Yan C., Fan D., Zhou Y., Zhang Y., Yague E., Xiong D. Sorcin silencing inhibits epithelial-to-mesenchymal transition and suppresses breast cancer metastasis in vivo. Breast Cancer Res Treat., 2014,Vol. 143(2), pp. 287-299.

51. Huang Z., Guo B.-J., Xiang J.-J. Zhongguo Bingli Shengli zazhi (KHP). Clin . J. Pathphysiol ., 2003, Vol . 19, № 7,pp. 1000-1010.

52. Ilari A., Fiorillo A., Poser E., Lalioti VS, Sundell GN, Ivarsson Y., Genovese I., Colotti G. Structural basis of Sorcin -mediated calcium-dependent signal transduction. Sci Rep ., 2015, Vol . 5, pp . 16828. doi:10.1038/srep16828.

53. Itoh, Y. et al. Membrane type 4 matrix metalloproteinase (MT4-MMP, MMP17) is a glycosylphosphatidylinositolanchored proteinase // Journal of Biological Chemistry.1999 V.274. No48. P.3426034266.

54. Jardim-Perassi B., Ali S. Arbab, Ferreira L. Effect of Melatonin on Tumor Growth and Angiogenesis in Xenograft Model of Breast Cancer. PLoS One, 2014, Vol. 9(1), e85311.

55. Johansson S.,Landstrom M., Henriksson R. Alterations of tumor cells, stroma and apoptosis in rat prostatic adenocarcinoma following treatment with histamine, interleukin-2 and irradiation. Anticancer Res., 1999, Vol. 19, pp. 1961-1970.

56. Katagiri E. Studies on the pineal gland; tumor proliferation and the pineal gland. Osaka Igakkai Zasshi., 1944, Vol. 43, pp. 315-320.

57. Kidd P. Th1/th2 balance: The hypothesis, its limitations, and implications for health and disease. Altern Med Rev., 2003, Vol.8, pp. 223-246.

58. Kim S.I., Lee H.J., Kim S.S., Kwon Y.S., Chun W. Sequestration of sorcin by aberrant forms of tau results in the defective calcium homeostasis. Korean J Physiol Pharmacol., 2016, Vol. 20(4),pp. 387-397.

59. Kitada K., Yamasaki T. The MDR1/ABCB1 regional amplification in large inverted repeats with asymmetric sequences and microhomologies at the junction sites. Cancer Genet Cytogenet., 2007, Vol. 178(2), pp. 120-127.

60. Kutcherenko B. On the changes in cases of malignant neoformations. Probl. Endokrinol. (Mosk), 1941, Vol.1, pp.131-135.

61. Kvetnoy I. Extrapineal melatonin: location and role within diffuse neuroendocrine system. Histochem J., 1999, Vol. 31(1), pp. 1-12.

62. Kvetnoy I., Levin I., The daily excretion of melatonin in patients with gastric cancer and colon cancer. Probl. In Oncol., 1997, Vol.33, P. 23-32.

63. Kwekkeboom D.J., Krenning E.P. Somatostatin receptor imaging. Seminars in nuclear medicine,2002, Vol. 32, № 2, pp. 84-91.

64. Lalioti V.S., Ilari A., O'Connell D.J., Poser E., Sandoval I.V.,

Colotti G. Sorcin links calcium signaling to vesicle trafficking, regulates Polo-like kinase 1 and is necessary for mitosis. PLoS One, 2014, Vol. 9(1), e85438.

65. Landriscina M., Laudiero G., Maddalena F., Amoroso M.R., Piscazzi A., Cozzolino F., Monti M., Garbi C., Fersini A., Pucci P. Mitochondrial chaperone Trap1 and the calcium binding protein Sorcin interact and protect cells against apoptosis induced by antiblastic agents. Cancer Res., 2010, Vol. 70(16), pp. 6577-6586.

66. Lei X., Liang Y., Chen J., Xiao S., Lei J., Li J., Duanmu J., Jiang Q., Liu D., Tang C. Sorcin predicts poor prognosis and promotes metastasis by facilitating epithelial-mesenchymal transition in hepatocellular carcinoma. Sci Rep., 2017, Vol. 7(1), pp. 10049.

67. Leon Blanco M., Guerrero J., Reiter R. Melatonin inhibits telomerase activity in the MCF-7 tumor cell line both in vivo and in vitro. J. Pineal Res., 2003, Vol.35, pp. 204-211.

68. Li C, Yang F, Wang R, et al. CALD1 promotes the expression of PD-L1 in bladder cancer via the JAK/stat signaling pathway. Annals of Translational Medicine. 2021;9(18):1441-1441. https://doi.org/10.21037/atm-21-4192

69. Li Y, Shan Z, Liu C, et al. MicroRNA-294 promotes cellular proliferation and motility through the PI3K/akt and JAK/STAT pathways by upregulation of NRAS in bladder cancer. Biochemistry (Moscow). 2017;82(4):474-482.https://doi.org/10.1134/s0006297917040095

70. Liaw B.C., Shevach J., Oh W.K. Systemic therapy for the treatment of hormone-sensitive metastatic prostate cancer: from intermittent androgen deprivation therapy to chemotherapy. Curr Urol Rep., 2015, 16(3), pp. 13. doi:10.1007/s11934-015-0486-x.

71. Lissoni P., Bastone A., Sala R. The clinical significance of melatonin serum determination in oncological patients and its correlations with GH and PRL blood levels. Eur. J. Cancer Clin. Oncol., 1987, Vol.23(7), pp. 949-

957.

72. Mao J., Ling F., Gislaine Pires Sanches J., Yu X., Wei Y., Zhang J. The potential mechanism of action of Sorcin and its interacting proteins. Clin Chim Acta. 2020, Vol. 510, pp. 741-745. doi:10.1016/j.cca.2020.09.011.

73. Marks I.E. Cure and care of neurosis. NY.: J.V. Scott Med. Found. 2001, 429, 11.

74. Matsumoto T., Hisamatsu Y., Ohkusa T., Inoue N., Sato T., Suzuki S., Ikeda Y., Matsuzaki M. Sorcin interacts with sarcoplasmic reticulum Ca(2+)-ATPase and modulates excitation-contraction coupling in the heart. Basic Res Cardiol., 2005, Vol. 100(3), pp. 250-262. doi:10.1007/s00395-005-0518-7.

75. Meyers M.B., Biedler J.L. Increased synthesis of a low molecular weight protein in vincristine-resistant cells. Biochem Biophys Res Commun., 1981, Vol.99(1), pp.228-235.

76. Miller S.C., Pandi-Perumal S.R., Esquifino A.I. The role of melatonin in immuno-enhancement: Potential application in cancer. Int J Exp Pathol.,2006, Vol.87, pp. 81-87.

77. Möse JR, Moser M., Fischer G. The effect of a experimental generated Histamine deficiency on growth and attack rate of model tumors . Arch . Gosehwulstforsch ., 1980, Vol. 50(1), pp . 58-65.

78. Mouton Y.,Demaille A. Mesentery capillary barrier in rats injected intravascularly with ascetic Zajdela hepatoma. Effect of serotonin and histamine on the extravasation of the tumor. Comp. rend. séances Soc.biol. et filial., 1975, Vol. 169, № 4. pp. 974-978.

79. Nakatani M., Ohara Y., Katagiri E., Nakano K. Studies on the thermoregulation system weeblichen weissen rattan .Nippon Byori Gakkai Kaishi ., 1940, Vol . 30, pp . 232-236.

80. Neschadim A., Summerlee A.J., Silvertown J.D. Targeting the relaxin hormonal pathway in prostate cancer. Int J Cancer., 2015, Vol. 137(10), 2287-2295. doi:10.1002/ijc.29079.

81. Nualart F., Los Angeles García M., Medina R.A., Owen G.I. Glucose transporters in sex steroid hormone related cancer. Curr Vasc Pharmacol. 2009, Vol. 7(4), pp. 534-548. doi:10.2174/157016109789043928.

82. Ou, Y-
X. Bi, R. Metaanalysis on the relationship between the SNP of MMP21306 C> T and susceptibility to breast cancer // European Review for Medical Pharmacological Sciences.2020 V.24. No3.

83. Padar S., van Breemen C., Thomas D.W., Uchizono J.A., Livesey J.C., Rahimian R. Differential regulation of calcium homeostasis in adenocarcinoma cell line A549 and its Taxol-resistant subclone. Br. J. Pharmacol., 2004, Vol. 142, pp. 305-316. doi:10.1038/sj.bjp.0705755.

84. Padmavathi G., Banik K., Monisha J., Bordoloi D., Shabnam B., Arfuso F., Sethi G., Fan L., Kunnumakkara AB Novel tumor necrosis factor-alpha induced protein eight (TNFAIP8/TIPE) family: functions and downstream targets involved in cancer progression. Cancer Lett ., 2018, Vol . 432,pp. 260-2

85. Park S.Y., Jang W.J., Yi E.Y., Jang J.Y., Jung Y., Jeong J.W., Kim Y.J. Melatonin suppresses tumor angiogenesis by inhibiting HIF-1alpha stabilization under hypoxia. J Pineal Res. 2010, Vol. 48, pp. 178-184. doi:10.1111/j.1600-079x.2009.00742.x

86. Paroni R., Terraneo L., Bonomini F. Antitumor activity of melatonin in a mouse model of human prostate cancer: relationship with hypoxia signaling. J. Pineal Res., 2014, Vol.57, pp. 43-52.

87. Qu Y., Yang Y., Liu B., Xiao W. Comparative proteomic profiling identified sorcin being associated with gemcitabine resistance in non-small cell lung cancer. Med Oncol., 2010,Vol. 27(4), pp. 1303-1308. doi:10.1007/s12032-009-9379-5.

88. Radunovic, M. et al. The MMP2 and MMP9 promoter polymorphisms and susceptibility to salivary gland cancer // BUON. 2016 V.21. No3. P.597602.

89. Rai U., Thrimawithana T.R., Valery C., Young S.A. Therapeutic uses of somatostatin and its analogues: Current view and potential applications. Pharmacol Ther., 2015, Vol. 152, pp. 98-110. doi:10.1016/j.pharmthera.2015.05.007.

90. Reichlin N., Kvetnoy I., Tyurin E. Melatonin in serum of cancer patients. Clin. Med., 1980, Vol.58,pp. 77-79.

91. Reznikov A. Hormonal impact on tumor growth and progression. Exp Oncol., 2015, Vol. 37(3), pp. 162-172.

92. Rivera E.S., Davio C.A., Venturino A. Histamine receptors in an experimental mammary carcinoma. Biomed. Pharmacother., 1994, Vol. 48,pp. 399-340.

93. Rodin A., Overall J. Statistical relationships of weight of the human pineal gland to age and malignancy. Cancer, 1967, Vol.20, pp. 1203-1214.

94. Rodriguez-Canales J., Parra-Cuentas E., Wistuba I.I. Diagnosis and Molecular Classification of Lung Cancer. Cancer Treat Res., 2016, Vol.170, pp.25-46. doi:10.1007/978-3-319-40389-2_2.

95. Romaszko A.M., Doboszyńska A. Multiple primary lung cancer: A literature review. Adv Clin Exp Med., 2018, Vol. 27(5), pp. 725-730. doi:10.17219/acem/68631.

96. Roy NK, Bordoloi D, Monisha J, Padmavathi G, Kotoky J, Golla R, Kunnumakkara AB Specific targeting of Akt kinase isoforms: taking the precise path for prevention and treatment of cancer. Curr Drugs Targets ., 2017,Vol. 18(4), 421-4

97. Saeger W., Schnabel P.A., Komminoth P. Grading neuroendokriner Tumoren. Pathologe, 2016, Vol. 37, pp. 304-313.doi:10.1007/s00292-016-0186-4.

98. Sanchez-Hidalgo M., Lee M., de la Lastra C.A., Guerrero J.M., Packham G. Melatonin inhibits cell proliferation and induces caspase activation and apoptosis in human malignant lymphoid cell lines. J Pineal Res. 2012, Vol.

53, pp. 366-373. doi:10.1111/j.1600-079x.2012.01006.x22.

99. Shabnam B., Padmavathi G., Banik K., Girisa S., Monisha J., Sethi G., Fan L., Wang L., Mao X., Kunnumakkara AB Sorcin a Potential Molecular Target for Cancer Therapy. Transl Oncol ., 2018, Vol . 11(6) , pp 1379-1 doi:10.1016/j.tranon.2018.08.015 .

100. Srinivasan V., Pandi-Perumal S.R., Brzezinski A., Bhatnagar K.P., Cardinali D.P. Melatonin, immune function and cancer. Recent Pat Endocr Metab Immune Drug Discov. 2011, Vol. 5, pp. 109-123. doi:10.2174/187221411799015408.

101. Stecklein S.R., Sharma P. Last but not least: antibody-drug conjugates in hormone receptor-positive metastatic breast cancer. Ann Oncol., 2020, Vol. 31(12), pp. 1594-1596. doi:10.1016/j.annonc.2020.10.001.

102. Subramani R., Nandy S.B., Pedroza D.A., Lakshmanaswamy R. Role of Growth Hormone in Breast Cancer. Endocrinology, 2017, Vol. 158(6), pp. 1543-1555. doi:10.1210/en.2016-1928.

103. Tamarkin L., Danforth D., Lichter A. Decreased nocturnal plasma melatonin peak in patients with estrogen receptor positive breast cancer. Science, 1982, Vol.216, pp. 1003-1005.

104. Tapp E. The human pineal gland in malignancy. J. Neural Transm., 1980, Vol.48,pp. 119-129.

105. Tapp E., Blumfield M. The weight of the pineal gland in malignancy. Br. J. Cancer, 1970,Vol. 24, pp. 67-70.

106. Tong W., Sun D., Wang Q., Suo J. Sorcin enhances metastasis and promotes epithelial-to-mesenchymal transition of colorectal cancer. Cell Biochem Biophys., 2015, Vol. 72(2), pp. 453-459.

107. Truong T.H., Lange C.A. Deciphering Steroid Receptor Crosstalk in Hormone-Driven Cancers. Endocrinology, 2018, Vol. 159(12), pp. 3897-3907. doi:10.1210/en.2018-00831.

108. Tucci M., Leone G., Buttigliero C., Zichi C., DI Stefano RF,

Pignataro D., Vignani F., Scagliotti GV, DI Maio M. Hormonal treatment and quality of life of prostate cancer patients: new evidence. Minerva Urol Nephrol ., 2018, Vol . 70(2), pp . 144-151. doi:10.23736/S0393-2249.17.03066-1.

109. Tuo H., Shu F., She S., Yang M., Zou X.Q., Huang J., Hu H.D., Hu P., Ren H., Peng S.F. Sorcin induces gastric cancer cell migration and invasion contributing to STAT3 activation. Oncotarget, 2017, Vol. 8(61), pp. 104258-104271.

110. Volk HD, Grunow R., Jahn S., Eckert R. Histamine receptor-bearing Lymphocytes V1 Influence of histamine on the G0-G1 transition of activated lymphocytes . Allergy and Immunol . (Leipz), 1986, Vol . 32(2), pp . 103-110.

111. Wang J., Xiao X., Zhang Y. Simultaneous modulation of COX-2, p300, Akt, and Apaf-1 signaling by melatonin to inhibit proliferation and induce apoptosis in breast cancer cells. J. Pineal Res., 2012. Vol.53(1), pp. 77-90.

112. Xi S.C., Siu S.W., Fong S.W., Shiu S.Y. Inhibition of androgen-sensitive LNCaP prostate cancer growth in vivo by melatonin: association of antiproliferative action of the pineal hormone with mt1 receptor protein expression. Prostate, 2001,Vol.46(1), pp. 52-61.

113. Xu P., Jiang Y.F., Wang J.H. shRNA-mediated silencing of sorcin increases drug chemosensitivity in myeloma KM3/DDP and U266/ADM cell lines. Int J Clin Exp Pathol., 2015,Vol. 8(3),pp. 2300-2310.

114. Yabuki N, Sakata K, Yamasaki T, Terashima H, Mio T, Miyazaki Y, Fujii T, Kitada K. Gene amplification and expression in lung cancer cells with acquired paclitaxel resistance. Cancer Genet Cytogenet ., 2007, Vol . 173(1) , pp 1-9 doi:10.1016/cancercencyto.2006.07.020 .

115. Yamagishi N., Nakao R., Kondo R., Nishitsuji M., Saito Y., Kuga T., Hatayama T., Nakayama Y. Increased expression of sorcin is associated with multidrug resistance in leukemia cells via up-regulation of MDR1 expression through cAMP response element-binding protein. Biochem Biophys Res

Commun., 2014, Vol. 448(4), pp. 430-436.

116. Zheng B.B., Zhang P., Jia W.W., Yu L.G., Guo X.L. Sorcin, a potential therapeutic target for reversing multidrug resistance in cancer. J Physiol Biochem., 2012,Vol. 68(2), pp. 281-287. doi:10.1007/s13105-011-0140-0.

117. Zheng P-P, Hop WC, SillevisSmitt PAE, et al. Low-molecular weight caldesmon as a potential serum marker for glioma. Clinical Cancer Research. 2005;11(12):4388-4392. https://doi.org/10.1158/1078-0432.ccr-04-2512

118. Zhou Q., Gui S., Wang Y. Melatonin Inhibits the migration of human lung adenocarcinoma A549 cell lines involving JNK/MAPK pathway. PLoS One, 2014, Vol. 9, pp. 101-132. doi:10.1371/journal.pone.0101132 23.

119. Zhou X., Wu X., Chen B. Sorcin: a novel potential target in therapies of cancers. Cancer Manag Res., 2019,Vol. 11, pp. 7327-7336. doi:10.2147/CMAR.S208677.

120. Zhou Y., Xu Y., Tan Y., Qi J., Xiao Y., Yang C., Zhu Z., Xiong D. Sorcin , an important gene associated with multidrug-resistance in human leukemia cells. Leuk Res., 2006, Vol . 30(4), pp . 469-476.

121. Linkova N.S. et al. Concentration of sirtuins in saliva: prospects for use in the diagnosis of coronary heart disease and the rate of aging of the body // Molecular Medicine. - 2021 - Vol. 19. - No. 6. - P. 37-42.

122. Pal'tsev M.A. et al. Kisceptins : molecular mechanisms of respiratory system pathology / / Molecular Medicine.-2022- V.20.-No.4.-P.3-8.

123. Mironova E.S. et al. Sorcinol as a potential target in molecular diagnostics and targeted therapy of lung cancer / / Molecular Medicine.-2021-T19.-No3.-P.3-7.

124. Pal'tsev M.A. et al. Caldesmon and tumor growth: prospects for optimization of diagnostics and targeted therapy // Archives of Pathology. - 2023 - Vol. 85. - No. 2. - P. 53-59.

125. Novak - Bobarikina U.A., Dokhov M.A., Krylova Yu.S., Kvetnaya

T.V., Pal'tsev M.A. Prognostic significance of expression of signaling molecules for assessing metastasis of carcinomas of various localizations // Molecular Medicine.- 2024-V.22.-No.3.- P.28-33.