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Review Article

The role of certain neurotransmitters in the emergence and progression of malignant tumors, and the potential of using neurotransmitter antagonists to block the carcinogenic effect of the tumor stroma

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Abstract

Within the last ten years, there has been a growing body of data on the potential of neurotransmitter blockers as promising components of comprehensive cancer treatment. Neurotransmitters play an important role in the intercellular communication of the various tumor cells: malignant epithelial cells, myofibroblasts, tumor-associated macrophages, stromal cells, and endothelial cells of the tumor vasculature. In particular, they are responsible for the cells' resistance to chemotherapy.

The carcinogenic effect of n-cholinergic receptor stimulation is well known. Some data confirms that m-cholinomimetics can promote tumor growth, and in some non-clinical trials, blocking the m- and n-acetylcholine receptors improved chemotherapy outcomes. The pro-oncogenic effect of catecholamine neurotransmitters is also well known. Dopamine participates in the regulation of cancer cell migration and metastasis. Both dopamine agonists and antagonists show anticancer effects, and dopamine antagonists affect cancer stem cells, but do not interfere with the cells of the healthy tissues. Serotonin promotes tumor growth and also contributes to the malignant transformation of precancer cells, i.e. to cancer initiation.

This review article is a comprehensive summary of the current situation in this fairly new field of cancer therapy.

Keywords: Cancer, Neurotransmitters, Acetylcholine, Norepinephrine, Dopamine, Serotonin, Neurotransmitter agonists, Neurotransmitter antagonists

Basic Aspects of Malignant Tumor Histopathology

Malignant tumors consist of various cell types that constantly interact with one another. These interactions strongly modulate both disease progression and responses to therapy, support the very existence of the tumor and its progression and growth, and make it resistant to negative factors including cancer therapy. Tumor cells that are actually malignant are represented by abnormal cells at various stages of transformation, and include precancerous stem cells that can produce healthy, precancerous, and cancer stem cells. Cancer stem cells, in turn, produce additional cancer stem cells and cells of the tumor parenchyma. The next stage of malignant transformation is represented by invasive stem cells, and then metastatic cancer stem cells.

From the genetic point of view, metastatic cancer stem cells are identical to the stem cells of the primary tumor, which means that the difference between these types is epigenetic [1]. Stem cells are located in the so-called stromal niches. The stroma of the tumor includes various cells that constantly interact with the cancer cells [2-5]. Endothelial cells are involved in tumor angiogenesis. The important role of vasculature development in the very existence of the tumor is confirmed by the efficacy of angiogenesis inhibitors. Tumor stromal fibroblasts, also called cancer-associated fibroblasts, are partly derived from bone marrow, contain myosin, and are major components of the carcinoma

microenvironment [2-5]. Tumor- associated macrophages are somewhat like the tumor's immune system, and their chemokines can promote tumor growth and development [6].

The tumor stroma is amply innervated by sympathetic and parasympathetic nerves. These are a source of neurotrophic factors and neurotrasmitters that can induce cell growth and migration either directly or indirectly, through other cells of the stroma [7,8]. Neuroendocrine cells that can be present in the tumor stroma, and the neuropeptides or neurotransmitters they produce, can also stimulate the survival, growth, motility, and metastatic potential of carcinoma cells [9,10]. The extracellular matrix regulates tissue development and homeostasis. If secretory activity of the stromal cells is deregulated, the matrix can contribute to tumor progression and tumor cell differentiation and survival [11,12].

The Role of Neurotransmitters in The Functional Integrity of Tumors

Tumor integrity and therapy resistance are to a large extent based on the integrated communication network of various cytokines, chemokines, growth factors, and neurotrasmitters. Anti-inflammatory cytokines, and those produced by the myofibroblasts stimulate malignant transformation and trigger epigenetic changes that increase the malignant potential of the tumor cells [8]. Neurotransmitters strongly influence tumor development by regulating cytokine production via various cells [13], including myofibroblasts, stem cells in general, and cancer stem cells in particular [14,15]. Hence, they play a central role in orchestrating intracellular interactions and regulating the functioning of various cells, including those of cancer [16-18].

Existing reviews identify neurotransmitters as one of the potential targets of cancer therapy [19,20]. This review attempts to summarize the effects of various neurotransmitters and their inhibitors on carcinomas.

The cholinergic system of tumors

The paper includes studies of acetylcholine; muscarinic acetylcholine receptors (mAChRs) and nicotinic acetylcholine receptors (nAChRs) and their subgroups, which facilitate more specific effects on the controlled structures; choline acetyl transferase (ChAT), which participates in the synthesis of acetylcholine; vesicular acetylcholine transporter (VAChT); and cholinesterase, which cleaves acetylcholine. Acetylcholine is also synthesized in the cells of non-neural tissues. Non-neuronal acetylcholine is present in all organs, where it regulates intercellular interaction, the cell cycle, cell differentiation, and assembly of the intracellular filaments, including the cytoskeleton. Even picomolar to nanomolar concentrations of acetylcholine promote chronic inflammation. In epithelial tumors, the activity of the cholinergic system is increased [21]. Acetylcholine inhibits the release of other neurotransmitters, such as noradrenalin. Activity of the cholinergic system is suppressed by inhibitors of acetylcholine and of choline acetyl transferase [22]. Since acetylcholine inhibits other neurotransmitters, inhibiting the cholinergic system may increase the activity of other neurotransmitters that take its place in intercellular communication.

The role of acetylcholine and its agonists in cancer development: Nicotinic acetylcholine receptors of various types regulate cell proliferation, apoptosis, and epithelial-mesenchymal transition, and thus control carcinogenesis. It is well known that the use of tobacco, a source of nicotine and its derivatives, is an important cause of various types of cancer, including several lung cancers. During adenocarcinoma development, nicotine interacts with α7-nAChRs. As a result, the concentration of cyclic adenosine monophosphate (cAMP) increases in the target cells of the respiratory tract, promoting tumor development [23]. The risk of cancer is higher in people with a higher initial level of choline acetyltransferase (ChAT). Smoking allegedly also increases the risk of pancreatic cancer, through the suppression of the inhibitory neurotransmitter — gamma-amino-butyric acid (GABA) — which can downregulate cell growth and proliferation. Carcinogenic effects of nicotine and its derivatives were found in cases of stomach cancer, mesothelioma, breast cancer, and cancers in other locations [24-29]. In cancer cells, acetylcholine acts as an autocrine and paracrine growth factor that activates cell proliferation, including that of cancer stem cells [30,31]. This effect is neutralized by the antagonists of nAChRs, hexamethonium, and methyllycaconitine. Nicotine contributes to cancer cell survival through the PI3k/Akt pathway. Endothelial cell activation through the phosphorylation of calpains, acetylcholine, nicotine, and its metabolites induces neoangiogenesis and cancer metastasis. It is believed that nicotine and its agonists also promote cancer development by changing the intracellular calcium concentration [32]. For this reason, it has been proposed that nAChRs be included among the targets for antineoplastic medications [33].

Stimulation of mAChRs also has carcinogenic effects [21,34,35]. For example, they play a specific role in breast carcinoma progression. There are five subtypes of mAChRs (M1-M5), which, when activated, increase the influx of Ca ions into the cell. As a result, nitric oxide synthase is activated and the concentration of nitrogen monoxide increases. The latter substance is one of the most important modulators of cell proliferation, including that of tumor cells. Brief stimulation with the nonselective agonist of mAChRs carbachol promotes murine mammary carcinoma cell growth *in vitro* [36]. Stimulation of M3 mAChR by acetylcholine upregulates the proliferation of gastric adenocarcinoma cells. This effect can be inhibited by the M3R antagonist darifenacin [37]. mAChR stimulation induces epithelial-mesenchymal transition, one of the first stages of tumorogenesis; however, this effect can be blocked by the selective M1 antagonist pirenzepin. M3-AChRs regulate cell proliferation in small-cell lung carcinoma [38]. Breast adenocarcinoma cells cause the production of IgG, which interacts with mAChRs of the tumor cells and mimics the action of a mACh agonist; it promotes cancer cell migration. This effect can be reduced by tropicamide, M3 and M4 inhibitor [39]. Proliferation of the gastric epithelium cells is stimulated by nerve growth factor (NGF); if its production is too high, the risk of cancer development increases. NGF production is upregulated by acetylcholine, so it has been proposed that anticholinergic agents be used to prevent and treat malignant tumors [40,41].

The role of choline acetyltransferase in the cholinergic system and cancer development: Choline acetyltransferase (ChAT) is responsible for the synthesis of acetylcholine [42]. When its activity is increased, it stimulates malignant cell growth in culture [43,44]. Inhibitors of ChAT are more efficient antiproliferation agents than m- and n-AChR antagonists [22].

The role of acetylcholinesterase in the cholinergic system and cancer development: Acetylcholinesterase (AchE) catalyzes

the breakdown of acetylcholine. Different forms of this enzyme prevail in different tissues and structures, such as synapses, erythroid tissues, and embryonic and tumor cells. Downexpression of AchE in tumor cells promotes their proliferation and tumor growth [44-46]. Acetylcholine degradation by AChE suppresses cell proliferation [47]. When AChE activity in cancerous gastric tissues is increased during adenovirus infection, cancer cell proliferation slows down [48]. AChE levels show a positive correlation with patient survival in some cancers [49]. Organophosphorous pesticides (inhibitors of AChE), when added to a mammary epithelial cancer cell culture, induced mutant p53 protein expression; in other words, the concentration of the normal tumor-suppressor protein p53 decreased. This effect was reversed by atropine [50]. The intracellular AChE level was upregulated by calcium ions in cytosol [51,52]. In some cancer cells, the AChE gene is amplified, and thus AChE activity increases. This amplification can be stimulated by parasitic invasion [53]. The direct relation between invasion and malignancies has not been established, although there is some data suggesting that helminthic invasions have an antitumor effect [53].

Some effects of AChE are not related to its cholinergic role. For example, an increased level of cholinesterases results in cell proliferation and tumor growth [55,56]. Human AChE enhances the proliferation and/or differentiation of glioma, neuroblastoma, osteosarcoma, and phaeochromocytoma cells in culture [57-59]. In the differentiated astrocytomas, AChE-S activity is increased, whereas in non-differentiated tumors, and especially in small round cells, it is higher. A high concentration of AChE-R causes the proliferation of glioblastoma cells. There is an insufficient understanding of the role AChE plays in tumorogenesis [60]. It has also been hypothesized that when acetylcholine accumulates in a cell where AchE is suppressed, it may inhibit the anti-carcinogenic effect of norepinephrine, the antagonist of acetylcholine [58,61].

Cholinergic denervation as a potential element of anti-cancer therapy: In a number of experiments on mice with gastric adenocarcinoma (induced by mutations, chemicals, or *Helicobacter pylori* infection), surgical denervation of the stomach (vagotomy) decreased the risk of cancer development, the size of the tumors, and the rate of cancer cell proliferation, as compared to the animals not operated on [62].

Another way to decrease the effect of acetylcholine on the tissue is by suppressing its secretion; this can be achieved using inhibitors of VAChT. In bronchoalveolar carcinoma cell culture, vesamicol, a VAChT inhibitor, induces potent apoptosis of cancer cells. Vesamicol (50 mg/kg) suppressed the growth of human cancer cell line A549 in nude mice models. Vesamicol showed a similar effect on the growth of murine prostatic cancer cells [63].

Similarly, acetylcholine secretion can be blocked by inactivating SNARE proteins that mediate the fusion of vesicles with the cell membrane [64]. After the proteins are cleaved by botulinum toxin, acetylcholine secretion stops and cancer progression slows. This effect was shown, for example, in prostate cancer and glioblastoma cells [65,66]. Binding the synaptic vesicle glycoprotein 2 using botulinum toxin suggests that it may become an element of some alternative cancer therapy [67]. In experiments on athymic nude mice with transplanted pancreatic cancer cells, it was shown that exposure to botulinum decreased the tumor size and increased the rate of cancer cell apoptosis [68]. Similar results were obtained with glioblastoma cells in immune- compromised mice [69].

The anti-cancer effect of acetylcholine antagonists

mAChRs antagonists: Activated muscarinic receptors regulate cell proliferation and angiogenesis through nitric oxide synthase activation [70]. Thus, it has been proposed that darifenacin, a muscarinic antagonist (patent U55096890, U56106864), be used to treat certain cancers [71]. The anti-muscarinic agent tiotropium bromide (Spiriva) decreases the number of lung fibroblasts and myofibrobrasts; these cells elevate the risk of malignant transformation of the lung epithelium [72].

Studies in the anti-cancer action of muscarinic receptor antagonists of various types showed that all anticholinergic agents can act as anti-cancer agents. In the cells of murine adenocarcinoma, inhibitors of M3 receptors suppress the production of nitric oxide (NO); inhibitors of M1 and M2 suppress neoangiogenesis [73].

In cell culture of murine neuroblastoma cells, activation of M1 receptors speed up proliferation in various ways: nitric oxide synthase activation increases NO production, and protein kinase C activationcytosolic calcium [74]. In prostate cancer cell culture, inhibition of M1 receptors with pirenzepine or dicyclomine 15-60 mcg/ml significantly slows cell proliferation [75].

In the human non-small-cell lung cancer (NSCLC) cell line, all five mAChR subtypes are expressed; these promote cancer cell growth though Akt phosphorylation. However, only methoctramine, an M2 mAChR antagonist, suppresses cell proliferation in this case. This agent also inhibits the growth of NSCLC xenografts *in vivo*; this effect is achieved through the suppression of Akt and epithelial-mesenchymal transition [34]. Other authors note that in NSCLC specimens taken from patients with this type of lung cancer, M3 receptor is the most prominent. Since it is effectively promoting cell proliferation and survival, these authors believe that it may be a promising therapeutic target [76,77]. It was shown that inhibition of M3 mAChRs in small-cell carcinoma cell cultures suppresses cancer cell growth [78,79].

Baclofen inhibits stomach cancer formation in rats treated with N-methyl-N'-nitro-nitrosoguanidine. This is achieved through M2 mAChR receptor activation [80]. Arecaidine, an M2 agonist, suppresses the proliferation and migration of bladder cancer cells [81]. M2 mAChR activation by arecaidine propargyl ester also suppresses the growth of glioblastoma cells *in vitro* and decreases their lifetime [82-84]. The combination of subthreshold concentrations of the M3 agonist carbochol with paclitaxel potentiates the death of breast cancer cells in culture [85].

Stimulation of M3 receptors promotes the proliferation of glioblastoma cells in culture [83]. In a cholangiocarcinoma cell culture, the M3 mAChR agonist pilocarpine substantially increased cancer cell migration, whereas the M3 mAChR antagonist atropine blocked this effect [86]. A nonselective muscarinic receptor antagonist (atropine), a selective M3R antagonist (p-fluorohexahydro-sila-difenidol hydrochloride), and a choline transport inhibitor (hemicholinum-3) all inhibited unstimulated colon cancer cell proliferation in culture [87].

It has been shown that the acetylcholine effect on M3R increases the activity and invasiveness of the cells in stomach cancer cell culture, because the M3R antagonist darifenacin inhibits cell activity [88].

In prostate cancer cell culture, carbachol increased DNA synthesis which, in turn, could be inhibited by the M3 mAChR antagonist diphenylpyralamine [89].

Experiments on six-week Apc(min/+) mice with high rates of intestinal cancer showed that eight-week scopolamine treatment decreased the number of intestine tumors by 22 percent (P = 0.027) and tumor volume by 36 percent (P = 0.004) as compared to the control group [90].

The muscarinic cholinergic system inhibitor 4-DAMP darifenacin suppresses the growth of small-cell cancer cells *in vitro* and *in vivo*. The synthetic specific inhibitor of M1 and M3 receptors (R2HBJJ, a derivative of hyosciamin), suppresses growth of NSCLC cells in culture [76].

Based on the research data, it is possible to assume that inhibition of mAChRs shows a positive effect on various types of cancer in various locations [91,92]. To a great extent, this effect is related to disruption of the links between cancer and stromal cells. The potential advantages of combining subthreshold concentrations of the cholinergic agonist with traditional paclitaxel therapy is very promising. The authors of this hypothesis point out that cancer cells are more susceptible to traditional chemotherapy when their proliferation is stimulated [85,93].

Inhibitors of nAChRs: It is well known that nicotine and tobacco-specific nitrosamines promote cancer development. Nitrosamines increase the levels of mRNAs, which participate in the synthesis of alpha 7-nicotine AchR, nuclear factor kappa B, 5-lipoxygenase (5-LOX), and cyklooxygenase-2 (COX-2). Bungarotoxin, an antagonist of alpha-7 nAChR, suppresses this effect, and thus slows cell proliferation [94]. The antagonists of nicotine, alpha-bungarotoxin and puromycin have a confirmed anti-cancer effect [95]. Cancer cell proliferation is suppressed, and the rate of apoptosis increases in the culture of pleural mesothelioma cells under the influence of the nicotine antagonists curare or alpha-cobratoxin [41,96]. Similar results were obtained in NSCLC xenografts in nude mice [97,98]. Alpha conotoxin, an nAChR antagonist, slows the progression of lung and breast cancers [99-102]. Snake-venom neurotoxins (including alpha-7 bungarotoxin) that show anticancer effects are the antagonists of alpha-7 nAChRs, their allosteric negative regulator [103].

N-benzylpiperedine derivatives that are antagonists of alpha-7 nAChRs are also their allosteric modulators. They suppress proliferation in the neuroblastoma cell culture and inhibit serotonin receptors [104]. These substances may be promising candidates for further research into their anti-cancer action.

3-alkylpyridinium polymers (poly-APSs), extracted from the sponge *Reniera sarai*, and their analog APS8, are the antagonists of alpha-7 nicotinic AchR. They are not toxic for normal lung cells, but suppress the growth of NSCLC cells [105]. Sinomenine, another alpha-7 nAChR antagonist, shows the same effect [106], as does QND7 [107].

Garcinol, a polyisoprenylated benzophenone isolated from the fruit *Garcinia indica*, acts as an efficient inhibitor of breast cancer cell proliferation through downregulation of alpha-9 nAChR and cyclin D3 expression [108]. It also suppresses growth of oral squamous cancer cells [109] and cells of human prostate cancer; this was shown in a xenograft mouse model [110,111]. Alkaloids from the shrub *Microcos paniculata* are antagonists of nAChR and have a cytostatic effect on colon cancer cells in culture [112].

Activators of cholinesterase: As has been discussed, the effect of acetylcholine on acetylcholine receptors can be suppressed by blocking the receptors. However, another approach is also possible: the availability of acetylcholine can be decreased by cholinesterase activation. In addition, acetylcholinesterase inhibits the transformation of fibroblasts to myofibroblasts that increase the viability of cancer cells [113]. In tumors, acetylcholinesterase activity is decreased, and this decrease shows a positive correlation with the aggressiveness of the tumor [47,114]. Thus, it may be possible to enhance the standard regimens with acetylcholinesterase activators to downregulate the protective effect of stroma on the cancer cells.

For example, in one study, oncolytic adenoviral vector LD55-AChE suppressed the proliferation of cancer cells including stem cells, increased the intensity of apoptosis, and slowed the growth of stomach cancer in mice, both *in vitro* and *in vivo* [47]. In another study [115], acupuncture stimulation of points GV20 and GV14 was used to increase serotonin, dopamine, and acetylcholinesterase levels; if this approach is successful, it may be used as a component of adjuvant cancer therapy. In experiments on non-small-cell lung cancer in nude mice, it was shown that acetylcholinesterase activity can be regulated with microRNA-212 [116]. It is well known that low or moderate physical activity increases the life expectancy of cancer patients [117,118]. Moderate exercise increases the activity of acetylcholinesterase [119], whereas excessive exertion substantially decreases it [120].

The acetylcholinesterase inhibitors eserine hemisulfate and bis-9-amino-1,2,3,4-tetrahydroacridine speed proliferation in colon cancer cell culture. Thus, the possibility of using certain inhibitors of acetylcholinesterase as anticancer medications [121] may need additional review and verification.

Acetylcholine stimulates the growth of cells, including cancer cells, through muscarinic and nicotinic receptors, nAChRs (primarily alpha-7 and alpha-9) and mAChRs (primarily M3). For this reason, antagonists of these receptors suppress cancer cell proliferation [30,41].

The adrenergic system of malignant tumors: Adrenergic nerve fibers belong to the sympathetic nervous system, are widely present in the stroma of tumors, and influence cancer cells. This influence is mediated by catecholamine neurotransmitters through alpha and beta adrenergic receptors. Their effect is similar to that of the catecholamines, which are produced by the adrenals. Their levels significantly increase in response to stress [121,123].

The role of stress and its mediators in cancer emergence and progression: It has long been known that stress, including post-operative stress, is associated with hypercatecholemia and high levels of adrenocortical hormones, and that this increase in hormone levels stimulates the growth and metastasis of cancer cells [124-126]. In experiments on mice, it was shown that stimulation of the autonomic nerve fibers in the tumorous prostate gland stimulates growth and metastasis of the tumor. This effect can be prevented by chemical or surgical denervation of the area. The same authors have studied specimens of prostate adenocarcinoma from forty-three patients. There is a positive correlation between the densities of sympathetic and parasympathetic nerve fibers in tumors and poor clinical outcomes [127].

In mice, when cold stress at an ambient temperature of 20-26°C is alleviated by housing at a comfortable temperature (30-31°C), a reduction in tumor formation, growth rate and metastasis is observed [128].

Agonists of the beta-2-adrenergic receptors increase cancer cell survival in ovarian carcinoma cell culture and in prostate carcinoma cell culture [129].

To study the role of stress in the growth of tumors, female mice of the BD2F1 strain weighing 18 to 20 grams were implanted with fragments of Lewis lung carcinoma. Stress was induced through spatial disorientation by spinning the cages at 45 rpm for 10 minutes every hour throughout the period of the experiment. To decrease the stress, a group of these mice was given guanethidine (which reduces the release of catecholamines, such as norepinephrine) at 60 milligrams per kilogram a day throughout the experiment. After twenty-one days, the tumors were weighed. In those mice that received anti-stress therapy, the tumors weighed significantly less that in the control group [130]. Another group of authors showed that sympathetic activation contributes to metastasis and invasion of the inoculated breast cancer cells in mice, and that this effect can be controlled by the beta blockers propranolol and ICI-118.551 [131,132]. These authors conclude that stress- or depression-related activation of the sympathetic nervous system promotes the progression and metastasis of tumors. Stress hormones stimulate the proliferation of cancer cells, increase their invasiveness, and speed tumor vascularization [133]. It was found that chronic stress increases norepinephrine levels in mice, and thus stimulates tumor growth. Sympathectomy of the prostate gland causes apoptosis of tumor cells and stops tumor growth; this effect is similar to that of beta blocker therapy. Similar results were obtained *in vitro* and *in vivo* in other tumors [134-137].

Activation of beta-adrenergic receptors stimulates tumors in various ways. When beta-adrenergic transmitters activate bone marrow cells, the number of bone marrow metastases increases [129,138].

When the intratumor norepinephrine level is increased, the circulating predecessors of the stromal cells (stem cells) are more actively included into the tumor, where they speed tumor vascularization and activate dormant metastatic cells [139,140]. The active role of epinephrine and norepinephrine in tumor angiogenesis has been widely discussed [141-144]. Suppression of the excessive angiogenesis is one of the anti-cancer therapy strategies.

Activation of the alpha-1B-adrenergic receptor, a member of the G-protein-coupled receptor family, results in fibroblast activation, and thus increases proliferation of the parenchymal cell [145,146]. Some evidence suggests that malignant transformation of cancer cells through beta-adrenergic stimulation is associated with increased expression of beta(3)-adrenoreceptor mRNA [147]. Some authors believe that since epinephrine and norepinephrine can induce DNA damage, they have a potential for inducing cellular transformation and/or tumor progression [148].

Adrenergic signal pathways promote cell transformation and tumor progression in various ways, one of them being increased cyclic adenosine monophosphate (cAMP) level. This substance, in turn, stimulates cell proliferation. In animal studies, beta blockers suppress this proliferation and thus slow tumor progression [149,150].

The efficacy of adrenergic antagonists in cancer therapy: In breast carcinoma cell culture, carvedilol significantly decreases the migration and invasion of breast cancer cells through blocking beta or alpha adrenergic receptor [151]. Proliferation of the cells of colorectal adenocarcinoma HT-29 in culture is effectively suppressed by propranolol beta blocker (50 mcmol), atenolol (the same concentration), carvedilol, and ICI-118,551 (5 mcmol) [152].

The anti-cancer effect of beta blockers: In experiments on nude mice, the development of lymph node metastases of PC-3 prostate carcinoma cells increased with the application of norepinephrine, while the betablocker propranolol inhibited this effect [153]. Beta-1 blockers suppress cancer cell invasion; beta-2 blockers slow tumor vascularization through the suppression of VEGF and cancer cell migration through the suppression of the metalloproteinases, and make cancer cells less viable by suppressing the release of prostaglandins [133,150,154,155].

Clinical observations have shown that in patients who have received beta blockers to treat hypertension for at least one year before the first signs of breast cancer, the risk of metastases decreases and life expectancy increases. Beta blockers also have a positive effect when used in the first stages of breast cancer: they slow tumor progression and decrease mortality [156-159]. In 3,561 patients with high-risk or metastatic prostate cancer, a combination of traditional methods (prostatectomy and radiotherapy) with beta blockers was associated with reduced mortality [160].

Beta blockers were helpful when used to treat melanoma in combination with the standard regimens [161]. Non-selective beta blockers significantly decreased the risk of hepatocellular carcinoma in patients with hepatic cirrhosis, although they did not decrease mortality in those who developed this complication [162]. Beta blockers inhibit the release of factors that contribute to cancer progression and metastasis, such as vascular endothelial growth factor, matrix metalloproteinases 2 and 9, and interleukins 6 and 8. The non-selective beta blocker propranolol inhibits the effect of the non-selective agonist of adrenoreceptors by 80 to 96 percent [163].

The beta-3 blocker SR59230A leads cancer cells to increase reactive oxygen species concentration, thus inducing cell death, and to decrease nitric oxide levels, thus inhibiting angiogenesis [164].

When added to the treatment regimen, beta blockers significantly increase progression-free survival [165,166].

The anti-cancer effect of alpha blockers: The alpha-adrenergic agonists clonidine and dexmedetomidine upregulate the growth of mouse mammary tumor cells [167], so it makes sense to hypothesize that their antagonists have the opposite effect [168]. In experiments on the androgen-independent prostate cancer cell lines PC-3 and DU145, the antagonist terazosin inhibited prostate cancer cell growth and colony- forming ability, which means that this substance may be a promising anti-cancer agent [169]. The quinazoline-based alpha-1 adrenoreceptor antagonists doxazosin and DZ-50 showed confirmed efficacy in the xenograft model of prostate cancer: they inhibited tumor growth and metastasis into the lungs. The authors believe that this effect is related to the inhibition of the tumor vascularization process [170,171].

Patients with the early stages of benign or malignant tumors of the prostate showed improved urine passage when treated with an antagonist of alpha-1 adrenergic receptors (tamusulosin 0.2

mg once daily for three months); in patients with prostate cancer, the level of prostate-specific antigen increased [172]. However, naftopidil and silodosin (selective antagonists of alpha-1 adrenergic receptors) inhibited the growth of prostate cancer by increasing the rate of apoptosis. In addition, naftopidil slowed tumor growth by inhibiting the proliferation of cancer stroma fibroblasts. In other words, it efficiently inhibits the stromal support of the cancer cells [173]. Silodosin, in addition to its effect on prostate cancer cells, potentiates the cytotoxic effect of gemcitabine [174].

The anti-cancer effect of norepinephrine agonists: In experiments on nude mice with tumor xenografts, it was shown that epinephrine speeds up proliferation of the cancer cells. Further addition of isoprenaline and salbutamol reduced tumor growth [175]. Pancreatic cancer cells showed migratory activity *in vitro* when treated with norepinephrine [176]. Norepinephrine (10 mcmol) also decreases the expression of CXCR4 in breast cancer cell culture, and explains the decreased migratory activity of the tumor cells [177].

Combinations of adrenoreceptor antagonists with other anti-cancer medications: Adrenergic antagonists are more efficient in combination with standard treatment methods: radical surgery, radiation, and chemotherapies. Such combinations lengthen remission and increase the survival rate [178-180]. For example, the beta blocker carvedilol in combination with denosumab (a monoclonal antibody for the treatment of osteoporosis) suppresses the metastasis of breast cancer cells and thus increases life expectancy. The beta blocker ICI-118551 in combination with gemcitabine significantly decreases the proliferation of prostate and pancreatic cancer cells. In addition, the beta blocker propranolol inhibits the effect of VEGF and thus slows angiogenesis through the inhibition of endothelial cell proliferation, which is required for cancer progression. Beta blockers also decrease the quantity of metalloproteinases 2 and 9, which promote cell migration, in cancer cell culture. COX-2 levels are increased in many tumors; medications that decrease this level slow tumor growth and can even cause the regression of human esophageal adenocarcinoma xenografts in nude mice. These medications decrease the invasiveness and migratory activity of the tumor cells and inhibit angiogenesis. When the beta blocker propranolol is used in combination with the COX-2 inhibitor etodolac (an NSAID) in mice during the postoperative period, recurrence-free survival increases [181,182].

Clinical observations show that in patients with hypertension who are treated with propranolol and have breast cancer, survival is longer than in those who do not receive this treatment [183,184]. Some authors explain this effect by the ability of propranolol to inhibit the adhesion of cancer cells to the endothelial cells [185]. It has been observed that beta blockers such as propranolol suppress the growth of melanoma [186].

Active migration of cancer cells is required for metastasis, and is stimulated by catecholamines such as norepinephrine, dopamine, and substance P. Cell migration is suppressed by the traditional antagonists of these receptors that are widely used to treat other conditions: beta-2 blockers, inhibitors of D2 dopamine receptors, and neurokinin-1 receptors of substance P. These neurotransmitters activate cAMP response element binding protein (CREBP) and thus induce migration of the cancer cell, which gives rise to metastases [17].

The dopamine system and cancer: Dopamine is a neurotransmitter that facilitates intercellular communication in dopaminergic cells. Dysfunction of this system leads to a number of neurological and mental disorders, but the function of dopamine is not limited to the nervous system. It facilitates communication between cells in various tissues of all organisms, including plants [187]. In the central nervous system, dopamine is released by neurons [188]. It is also released by the adrenals (like other catecholamines), intestines (both by the intestinal cells and the gut microbiota) [189,190], and renal proximal tubule [191,192]. These may not be the only organs where dopamine is synthesized. Five subtypes of dopamine receptors have so far been identified. They are members of two receptor families: the D1-like family (receptors D1 and D5) and the D2-like family (D2, D3, and D4). The level of dopamine receptors in a tissue to a great extent determines the importance of dopaminergic regulation of the tissue cells.

Dopamine participates in the regulation of cancer cell activity in all locations. For example, migration of cancer cells, and thus the process of metastasis, are regulated by dopamine along with other neurotransmitters. Dopamine receptors play an important role in the development of various human tumors [17].

The anti-cancer effect of dopamine and its agonists: One of the most important anti-cancer effects of dopamine and its agonists is their ability to slow angiogenesis by activation of D2 receptors in the tumor and its metastases through the inhibition of vascular endothelial growth factor [193-199].

Disorders of the dopaminergic system play an important role in the development of certain conditions, including malignant tumors. This is because DR1 activation results in increased cAMP levels by stimulating protein kinase A. This enzyme, in turn, interacts with glutamate receptors, GABA receptors, and ion channels, and increases the phosphorylation of DARPP-32 protein, which has a pro-carcinogenic effect [200,201].

The direct effect of dopamine on cells, including cancer cells, includes suppression of DNA synthesis and the slowing of cancer cell proliferation [202]. In addition, it stimulates apoptosis in various cells, including cancer cells [203]. When the D2 receptor is stimulated, it inhibits growth of gastric carcinoma cells in culture and decreases their invasiveness and migratory activity [204]. The authors of that article recommend studying the clinical potential of DRD2 agonists. DRD2 also promoted BrCa cells' sensitivity to paclitaxel and apoptosis in vitro and in vivo [205]. D2DR activation by dopamine or its agonist quinpirole in the cancer cells of non-small-cell lung carcinoma, whether *in vitro* (cell cultures) or *in vivo* (xenotransplants of human NSCLC cells in nude mice), significantly downregulated their proliferation and invasiveness, especially if these substances were combined with standard chemo- and/or radiation therapy [206].

Aripiprazole, a partial dopamine D2 agonist, inhibits the growth of cancer cells in culture, decreases their resistance to chemotherapy, and increases the level of their differentiation [207,208].

Apomorphine, another dopamine agonist, slows the proliferation of human breast cancer (MCF-7) cells and suppresses the growth of leukemic cells in intraperitoneally inoculated mice, which have a longer survival rate [209]. In addition, dopamine, apomorphine, and phenylethylamine reduce to zero the level of phosphorilated insulin receptor substrate 1 — a major intracellular substrate of the insulin-like growth factor (IGF)-1 receptor [210]. The anti-

cancer effect of apomorphine was demonstrated in experiments on choriocarcinoma cell culture. This included a decrease in the proliferation rate and ATP synthesis, and a higher apoptotic rate. The authors also observed mitochondrial depolarization and changes in the endoplasmic reticulum [211].

The D1R agonists fenoldopam and 1-stepholidine decrease the viability of triple-negative MDA-MB-231, MDA-MB-468, and SUM 149 breast carcinoma cells in culture. The combination of dopamine agonists with sunitinib (protein tyrosine kinase inhibitor) allowed a reduced dose of chemotherapy and limited its side effects. The combination of axitinib (tyrosine kinase inhibitor) with the D1R agonist fenoldopam suppressed the invasiveness of MDA-MB-231 and BT-20 breast cancer cells by 70 percent, and increased the apoptotic rate in cancer cells [200].

The D2 agonist bromocriptine suppressed cell proliferation and increased the apoptotic rate in MCF-7 breast cancer cell cultures [212]. Cabergoline (DRD2 agonist) showed the same effect on MCF-7 and SKBR-3 cancer cell cultures [213].

Combinations of dopamine or its agonist with the traditional chemotherapies had a more pronounced therapeutic effect, represented by cell growth and proliferation suppression. In experiments on MDA-MB-231, MDA-MB-468, SUM149, BT-20 breast cancer cell cultures and on the xenograft model of breast cancer, fenoldopam, another dopamine agonist, in combination with tyrosine kinase inhibitors or temozolomide, showed a strong anti-cancer effect. In xenograft models, it was shown that N-arilpiperazine (D1R agonist) in combination with sunitinib suppressed proliferation of SW1990 and PANK-1 pancreatic cancer cells in culture [200,214]. Aripiprasole alone or in combination with chemotherapies stimulated cancer cell differentiation in culture [207]. *Mucuna pruriens* (L) preparation, which is widely used in Indian ethnomedicine and as a treatment for Parkinson's disease because of its high L-DOPA content, decreased the resistance of MCF-7 breast cancer cells to cisplatin [215].

Others obtained similar results in experiments on cancer cell cultures and xenografts of human tumors in mice, when combinations of dopamine or its agonists with traditional chemotherapies were used [216-219].

The effect of DARPP-32 and t-DARPP: Dopamine, alongside cAMP and calcium, regulates the activity of DARPP-32 and t-DARPP proteins. These participate in the regulation of signaling through the cytotransmitters serotonin, glutamate, gamma-aminobutyric acid, and adenosine. In the cells of some cancers, the number of genes encoding DARPP-32 and t-DARPP is higher than normal. When activated, these proteins increase the malignancy of cancer cells, speed their proliferation, increase their invasiveness, and decrease the apoptotic rate. In addition, cells become more resistant to radiation therapy and chemotherapy [220,221].

Histological and immunohistochemical study of 533 stomach specimens showed increased levels of DARPP-32 after the transformation of intestinal metaplasia cells into adenocarcinoma. These results confirm the mutagenic potential of this protein [222]. High levels of t-DARPP increase AKT phosphorylation through a PI 3-kinase-dependent mechanism, and this increase stimulates MCF-7 breast cancer cell proliferation in culture [223]. DARPP-32 increases the invasiveness of MKN-45 gastric carcinoma cells in culture [224]. In experiments on DMS-53 and H1048 strains of human small-cell lung cancer cells, it was shown that t-DARPP stimulates growth and proliferation of these cells and inhibits their apoptosis [225]. Analysis of 513 human lung adenocarcinomas confirmed these results [226]. t-DARPP is also responsible for the increased tolerance of breast cancer cells to trastuzumab (Herceptin); this was shown in experiments on BT474, SK-BR-3 cell cultures and in analysis of the survival of breast cancer patients treated with trastuzumab [227-229]. Study of 141 specimens of human primary esophageal adenocarcinoma also showed the relation between the overexpression of t-DARPP and higher resistance of the cancer cells to trastuzumab [230]. Thus, overexpression of DARPP-32 and t-DARPP increases the tolerance of various cancers to standard chemotherapy, and increases cancer cell migration and proliferation through AKT overactivation. This phenomenon is discussed in detail in a large-scale review, based on papers describing clinical observations and mouse studies, including studies on xenograft models [231].

The anti-cancer effect of dopamine antagonists: Results reviewed in this section were obtained through the same methods as in the case of dopamine agonists, using cell culture and xenograft models.

Anti-cancer therapies include suppression of angiogenesis in the tumor and its microenvironment. In *in vivo* and *in vitro* experiments on various tumors, penfluridol, an inhibitor of D2 dopamine receptors and calcium channels, demonstrated a pronounced anti-cancer activity: it blocks angiogenesis through inhibition of VEGF and its signaling pathways, which play an important role in the regulation of angiogenesis [232,233].

Pimozide is an antagonist of DR D2, D3, D4, and 5HT7 receptors, and K^+ ion channels. It inhibits the migration and invasion of various cancer cells, suppresses proliferation of cancer stem cells, and blocks epithelial-to-mesenchymal transition. It is considered to be a potential therapy for non-small-cell lung carcinoma and prostate carcinoma, and for the prevention of metastasis [234-237].

Another DRD2 agonist, thioridazine, is a candidate for targeted cancer therapy: it affects cancer stem cells of various tumors, including lung and breast cancers, but has no effect on healthy stem cells. It also decreases acquired cancer cell tolerance to traditional chemotherapies [238]. Other dopamine antagonists have a similar profile: olanzapine successfully overcomes multidrug chemoresistance, as shown in experiments on lung and pancreatic cell cultures. Trifluoperazine is an efficient treatment for colorectal cancer. Pimozide and sulpiride, DRD2 antagonists, inhibit prostate and breast cancers [91,239-249].

The following antagonists of DRD3 have not been approved for clinical practice: PG01037, NGB2904, SB277011A, and U99194, but in non-toxic concentrations can bind certain substances that stimulate multidrug resistance in cancer cells. This might present new opportunities in the chemotherapy of cancers [250].

The D4 antagonist nemonapride (approved in Japan for schizophrenia treatment) and antagonist L745,870 (still under investigation) suppress the growth of glioblastoma cells, especially when used in combination with the traditional chemotherapy medication temozolomide [251,252].

In a xenograft model study of the combined therapy of murine glioblastoma (trifluoperazine or guetiapine (antagonist of receptors D1,2,3,4,5), atorvastatin, and radiation therapy) antagonists

lengthened survival [253,254]. Study of the therapy with the DRD2 antagonist chlorpromazine in combination with the traditional chemotherapy temozolomide [255] has been proposed. A new DRD2 antagonist (lab code ONC201) is currently being studied; this antagonist affects both the bulk of tumor cells and cancer stem cells, cancer-associated fibroblasts, and immune cells in the tumor microenvironment. In experiments on subcutaneous xenografts of temozolomide-resistant glioblastoma, this new antagonist was highly effective. Nonclinical *in vitro* studies in cell cultures showed that ONC201 may be an effective treatment for human colorectal carcinoma cells and human non-small-cell lung cancer [256-258].

The above data confirms that both dopamine agonists and antagonists have anti-cancer activity. There is no reliable explanation for these findings. Most likely, cell growth and proliferation require a certain dopamine level in the tissues, and when this deviates from the optimal concentration, the process becomes deregulated. This situation may be similar to that of therapy for emotional disorders [259].

Serotonin and cancer

The role of serotonin in cancer manifestations: Serotonin is a cytotransmitter. Blood serotonin accumulates in platelets and mast cells, and is transported by the vesicular monoamine transporter when needed. On the cell surface, it is bound by the selective serotonin transporter (SERT). As a result, the intracellular level of cAMP decreases and Ca^{2+} concentration increases. Inside the cell, serotonin is degraded by monooxidase. In non-nervous tissues, it stimulates tissue regeneration, and in epithelial tissues it acts as a local regulator of cell functioning [260]. In cancers, it stimulates the growth and progression of tumor tissue. Serotonin receptor antagonists and inhibitors of serotonin synthesis and transport slow cancer cell proliferation [261].

Serotonin also causes the activation of certain proto-oncogenes [262-264]; in other words, it may be able to promote cancer initiation. In a significant review, Witz [265] stresses the important role of the abnormal tumor environment in tumorigenesis, and tumor progression and resistance to therapy. Similarly, other authors have discussed the role of myofibroblasts of the microenvironment in pre-cancer cell transformation [2,266]. It has been found that cells of the cancer microenvironment, primarily myofibroblasts and cells of the tumor blood vessels, release substances other than those released by fibroblasts and endothelial cells of healthy tissues (cytoguardin (5-MTP) and melatonin). In the presence of cancer, they release serotonin, a substance that has a similar structure, but a completely different function [267,268] and strong carcinogenic potential. After cancer cells appear, the level of serotonin rapidly increases, because the tumor cells produce it and thus ensure their own support and protection against chemotherapy [269].

The prognostic role of serotonin: After it was found that serotonin has carcinogenic potential and plays an important role in supporting cancer development, it became obvious that its level can have prognostic value. Indeed, the overall survival of patients with cancer or carcinoid tumors is related to serotonin level [270-272].

The therapeutic potential of serotonin inhibitors

Prevention of chemotherapy-associated nausea and vomiting: Antagonists of 5-HT3 receptors are well known and effective antiemetics, widely used in chemotherapy patients [273-278]. The mechanism of action of 5-HT3 receptor antagonists is based on their ability to close ion channels (ligand-gated ion channels) [279].

Suppression of tumor angiogenesis: In addition to tumor growth and metastasis, serotonin stimulates angiogenesis, which also contributes to disease progression. This occurs through the activation of 5-HT1A, 5-HT2B, and 5-HT3 receptors in the endothelial cells [280,281]. Serotonin also increases the level of PI3K/AKT, eNOS, and VEGF, which in turn stimulates angiogenesis [282,283]. The lower the density of the tumor vascular network, the lower is the risk of metastases and tumor growth [284]. Anti-angiogenic therapy decreases tumor resistance to anti-cancer medications, but its effect becomes observable only if combination therapy is used [285,286]. However, anti-angiogenic therapy has to be part of the chemotherapy regimen [287].

A deficit of serotonin decreases the tumor's vascular density, and thus limits its growth rate [288]. Pimavanserin, an inhibitor of the serotonin receptor 5-HT(2A), also inhibits Akt, and effectively downregulates cancer cell proliferation and increases the apoptotic rate in pancreatic cancer xenografts in mice [289]. Inhibiting 5-HTR(2B) with its antagonist SB204741 decreased tumor growth and the density of the tumor vascular network in mice with lung cancer or melanoma [290].

Serotonin inhibitors in the treatment of chronic inflammation, a predecessor of cancer: Signals from inflamed tissue are the universal drivers of cancer cell progression. They affect stem and progenitor cells, including cancer cells, and stimulate migration and metastasis of the latter [291,292]. Such a signal can be transmitted through epithelial cells. It is also transmitted by serotonin through the 5-HT(1p) receptors, and becomes even stronger if 5-HT(4) receptors are activated [293]. For example, patients with inflammatory bowel disease (IBD) often develop colitis-associated cancer (CAC). This happens because the levels of serotonin and its receptors, primarily 5-HT(3) receptor, are high in patients with IBD. Tropisetron, an antagonist of the 5-HT(3) receptor, significantly decreases the risk of azoxymethane/dextran sodium sulfate-induced CAC in BALB/c mice [294]. The potential of tolfenamic acid (an NSAID) as an anti-cancer agent for the treatment of children and adults is currently being studied [295]. Its effect is based on noncompetitive suppression of serotonin accumulation [296]. Antagonists of the 5-HT(3) receptor can treat bowel inflammation [297].

Ways to decrease serotonin levels, and the anti-cancer effect of this treatment: In mice with spontaneous mouse mammary adenocarcinoma, limited tryptophan intake resulted in a significant decrease in tumor weight [298]. Since low tryptophan intake decreases the serotonin level in rats [299], it makes sense to assume that low tumor weight is related to serotonin insufficiency.

Low intracellular tryptophan level can be achieved by limiting the intake of its predecessor, tryptophan. For example, tryptophan intake can be blocked by trametinib, an inhibitor of mitogen-activated extracellular signal-regulated kinase (MEK). MEK decreases tryptophan intake into the cells and thus brings down intracellular serotonin levels. It has been shown that this substance slows the progression of azoxymethane-induced colorectal cancer [300].

Serotonin depletion can also be achieved by inhibition of its synthesis, for example, by p-chlorophenylalanine (pCPA, or fenclonine), an inhibitor of tryptophan hydroxylase (TPH1).

In experiments in nude mice inoculated with Mz-ChA-1 biliary adenocarcinoma cell culture, pCPA slowed the proliferation rate [301]. Telotristat ethyl is another efficient and safe inhibitor of TPH1 and can be used to treat patients with carcinoid syndrome [302,303]. Its anti-cancer activity has been observed in patients with neuroendocrine tumors [304,305].

Serotonin is transported by the serotonin transporter SERT. If it is blocked, cancer and other cells increase their tryptophan uptake, and tumor progression accelerates. However, sertraline, a selective serotonin reuptake inhibitor (SSRI), shows anti-cancer activity [300]. The same is true for other SSRIs, including sertraline, fluoxetine, and paroxetine. Even though they increase the cell uptake of serotonin [280], they have an anti-cancer activity, because they affect tumor-initiating cells [306]. In experiments on immune-compromised mice, sertraline in combination with the chemotherapy drug docetaxel (Taxotere) caused shrinking of the breast cancer xenograft [307]. Similar results were obtained in experiments with another SSRI, vilazodone [308]. Another, mirtazapine, suppressed tumor growth in colon-carcinoma-bearing mice by influencing the tumor microenvironment [309]. Various inhibitors of the serotonin reuptake transporter, as well as inhibitors of the reuptake of dopamine and norepinephrine, increase the survival of patients with lung cancer [310]. The anti-cancer effect of the SSRIs fluoxetine and paroxetine is more pronounced if they are used in combination with a prosurvival pathway blocker, such as an inhibitor of Akt, MAPK(MEK)/ERK or inverse agonists 5-HT(1A) receptor — spiperone or buspirone [311]. The anti-cancer activity of SSRIs also affects tumor-initiating cells. However, their mechanism of action is not related to decreased levels of serotonin. Oncotoxic activity is achieved through secondary mechanisms, in particular through blocking 5HTR 1B, 1D, 2A, 2B, 2C, 5A, 6, blocking receptor tyrosine kinases [306,312], or the influence on the metabolism of the biologically active one-carbon amino acids [313-316]. The anti-cancer effect of fluoxetine is achieved through the activation of the AMPA-type glutamate receptor [317] and stimulation of anti-tumor immunity [318]. Those SSRIs with no such secondary activity showed no anti-cancer properties [319,320].

The role of serotonin receptors in cancer progression, and the anti-cancer effect of their inhibitors: Many *in vitro* studies on cell cultures of various origins show the anti-cancer effect of inhibitors of serotonin receptors [305]. This effect has also been confirmed by *in vivo* experiments. Mouse mammary carcinoma and xenografts of human breast cancer shrank in immunocompromised mice if treated by antagonists of 5-HTRs [306]. An inhibitor of serotonin receptor 5-HT(1A) alone or in combination with traditional anti-cancer agents was efficient against carcinoid syndrome cells and prostate cancer [321,322]. These inhibitors include spiperone and buspirone [311]. Selective inhibitors of 5HT2A and 3A, such as pimavanserin (Nuplazid) also slow cancer cell proliferation [289,323]. SB204741, an inhibitor of 5-HT2B, suppresses the growth of pancreatic ductal adenocarcinoma cells in culture and in xenograft in mice [324]. SB-699551, an inhibitor of 5-HT5A, slows the growth of breast-tumor-initiating cells in culture. The authors believe that this substance is a promising candidate for breast cancer chemotherapy in combination with cytotoxic agents [325]. The level of 5-HT7 serotonin receptor is increased in non-small-cell lung cancer cells. Its activation by serotonin increases their proliferation, migration, and invasiveness [326]. Similarly, a high content of 5-HT7 was found in prostate cancer cells. Suppression of cell proliferation and stimulation of apoptosis in prostate cancer cell culture PC-3 can be induced by SB-269970, an inhibitor of 5-HT7 receptor [327].

Methiothepin, a universal inhibitor of serotonin receptors, stimulates apoptosis, suppresses proliferation, and has a cytotoxic effect on melanoma cells in culture, especially if combined with traditional chemotherapy [328]. This latter combination is effective against ovarian cancer cells in culture [329]. Sulforaphane suppresses a number of serotonin receptors. In colon adenocarcinoma cell culture, it reduces the density of serotonin receptors. It has potential as an anti-cancer agent [280,330].

Effect of monoaminoxidase (MAO) on cancer cells: Currently, two types of monoaminoxidase are known: MAO A, which catalyzes the breakdown of norepinephrine and histamine, and MAO B, which breaks down dopamine. MAO-catalyzed breakdown of monoamines results in the formation of free radicals (reactive oxygen species), which are required for the interaction of serotonin with its receptors. The balance of amine oxidases and antioxidant enzymes appears to be a crucial point for cancer inhibition or progression [331]. The serotonin signal pathway supports cancer cells. Thus, it would be logical to assume that high MAO activity should decrease the malignancy of cancer cells, whereas inhibition of MAO should result in increased malignancy [306]. However, experiments on hepatocellular carcinoma cell cultures and clinical observation of 254 patients demonstrate the opposite correlation between MAO A expression and cancer cell malignancy [332]. Other studies show that clorgyline, an MAO A inhibitor, slows the growth of prostate cancer and glioma cells in culture and in a xenograft animal model [333]. A combination of clorgyline with the traditional chemotherapy temozolomide improves treatment results in xenografts of human glioblastoma in nude mice [334]. Increased MAO A activity is required for tumor sphere formation in human breast cancer cell culture [335]. In mice, it has been shown that if chemotherapy is enhanced by MAO A, it decreases metastasis and increases survival [336,337]. Phenelzine, an inhibitor of MAO A, is not toxic to humans; a clinical study of this regimen is under way [338].

To switch off the serotonin signal, M- and H-cholinergic signals have to be blocked as well [104,339,340].

Summary

These neurotransmitters and their agonists, antagonists, and receptors are the elements of intercellular communication. They play a role in the malignant transformation and further development of precancerous cells. There are many more signal pathways, but the above mechanisms are the most important and well studied. This makes various combinations of antagonists and blockers a promising element of adjuvant anti-cancer therapy.

N-cholinomimetics, such as nicotine, have a significant carcinogenic effect. Activation of m-cholinoreceptors stimulates the growth of breast cancer. Blocking the cholinoreceptors slows the growth of various cancers, especially if combined with a traditional chemotherapy.

The role of stress in cancer initiation and development, and of the adrenergic system as a mediator of stress, is well known. In mice, antistress agents from the beta-blockers group slow tumor growth and metastasis and increase apoptosis. In clinical experience, treatment with beta-blockers combined with chemotherapy resulted in a decreased number of metastases and longer life expectancy.

Antagonists of alpha-adrenoreceptors in combination with chemotherapy have shown proven efficacy in xenograft models of prostate cancer, and in patients with breast cancer and melanoma.

The dopamine system is active in cancers of any localization. Its role is ambiguous: on the one hand it has an anticancer effect, and on the other, through the activation of DARPP-32 and t-DARPP, it stimulates the progression of cancer cell malignancy and increases the cells' resistance to chemotherapy. Dopamine antagonists have an anticancer effect, as shown by experiments in cell tissue and xenograft models. They inhibit neoangionesis, and limit cancer cell migration and invasion, as well as blocking epithelial-to-mesenchymal transition. These antagonists also suppress cancer stem cells in non-small-cell lung carcinoma, breast cancer, and prostate cancer.

The serotonin system stimulates cancer growth and the progression of malignancy. Serotonin receptor antagonists and inhibitors of serotonin synthesis or of serotonin transporters, slow the cancer cells' growth. One specific effect of serotonin is its ability to stimulate the transition of precancerous stem cells to cancer cells; in other words, it promotes cancer initiation. Cells of healthy stroma produce cytoguardin and melatonin. On the other hand, the altered stroma produces their precursor serotonin, which initiates cancer. The efficacy of serotonin inhibitors is potentiated by simultaneous inhibition of n- and m-cholinergic receptors.

Recent studies show that the antagonists of neurotransmitters may be a promising component of chemotherapy.

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