Interaction of Various Cancer Tissue Components: Their Role in Tumor Development and Therapy Resistance

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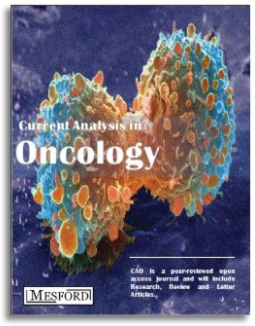

Abstract:

Cancer tumor development is the product of interactions between (1) genetically altered pre-cancerous epithelial stem cell and (2) its altered stromal microenvironment, including (a) bone marrow derived myofibroblasts (cancer associated fibroblasts), (b) tumor associated macrophages, and (c) some other altered stromal cells. Signals from the altered stromal cells promote epigenetical transformation of the pre-cancerous cell into a cancer cell, increase cancer cell invasive and metastatic capabilities, and promote neoangiogenesis. Together with the signals coming from the tumor cells, the stromal signals also trigger neoangiogenesis that is important for tumor existence and development. Stromal alterations that trigger pre-cancerous cell transformation may be a result of chronic inflammation. Inflammation also promotes migration of mast cells, mesenchymal stem cells and other neuroendocrine cells into the inflammation area. Neuroendocrine cells of the tumor and neurons that innervate the tumor secrete neurotransmitters. These neurotransmitters may increase cancer drug resistance and promote tumor growth and metastasis. This means that signaling molecules secreted by the neurons into the tumor matrix [alongside with some other molecules involved in cell communication e.g. cytokines and non-coding RNAs] support tumor integrity and stability. If the cell communication is interrupted, the tumor becomes less aggressive and more sensitive to the therapeutic agents. The use of neurotransmission antagonists as a potential novel therapeutic strategy against human cancer is worth exploring through clinical trials.

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1. TWOFOLD NATURE OF MALIGNANT TRANSFORMATION

Cancer tumor development is the product of interactions between altered epithelial stem cells and their altered stromal microenvironment. This hypothesis was proposed by Paget as early as 1889. He called it 'Seed and Soil' theory [1]. Subsequently, his insight was confirmed and developed in numerous papers. For details, please see our review [2] and reviews [3-7], which explain that genetic alteration in the epithelial stem cell is only a prerequisite for malignant transformation. A genetically altered stem cell has to go through multiple stages of malignant transformation: [1] a pre-cancerous stem cell that can either undergo further malignant transformation or develop into healthy cells; [2] a cancer stem cell that is no longer capable of normal development; [3] an invasive cancer stem cell, and [4] a metastatic cancer stem cell.

However, this transformation requires specific signals that stimulate proliferation and the altered behavior of the stem cell ('seed'). These signals come from the stromal cells ('soil'), which form the cell niche of the pre-cancerous stem cell. To various degrees, these stromal cells and their secretory activity differ from those in healthy tissue.

2. FUNCTIONAL UNITS OF THE TUMOR: CANCER STEM CELL NICHE AND CANCER TUMOR HISTION

The cancer stem cell niche includes stromal cells, myofibroblasts, capillary blood vessels and components of the extracellular matrix. It is the cancer stem cell microenvironment. The plasticity of the pre-cancerous stem cells is high enough that it can produce healthy daughter cells, if influenced by healthy stromal secretions, or produce cancer cells, if the stromal cells of the niche are altered [8]. This means that the stromal cells of the niche support stem cell homeostasis, but can also stimulate or inhibit differentiation and/or proliferation of the stem cells. Niche

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neovascularization depends on the circulating endothelial progenitors [9-11].

The cancer stem cell niche is an important component of the tumor. However, the elementary morpho-functional tissue unit of the tumor, as well as that of any other organ, is the histion [12]. The histion is a unit consisting of the parenchymal stem cell, connective tissue that surrounds the stem cell, and a capillary blood vessel. It also comprises various connective tissue cells and a neuron. Parenchymal cells are represented by epithelial cells of various degrees of differentiation and by neuroendocrine cells. Histion function is not limited to supplying nutrients to its parenchymal region and the removal of metabolic waste. Histions show a certain integrity and stability, because their cells exchange paracrine mediators. At the histion level, stroma and parenchyma demonstrate their structural and functional unity [12-14]. This idea was formulated 70 years ago by A.A. Zavarzin, who wrote that "epithelium cannot exist outside the epithelial-connective tissue system" [15]. The malignant tumor is a distinct and unusual system of the modified epithelial and connective tissues.

Thus, cancer may be considered an outcome of histion disease, of both the epithelial and stromal cells. This disease also involves the extracellular matrix that serves as a cell communication medium [16, 17]. An equally important role in disease progression is played by other histion elements e.g. tumor blood vessels. It has been shown that tumor growth depends on tumor angiogenesis [18, 19].

The way the tumor emerges and develops is also influenced by chronic inflammation of the affected organ. Malignant transformation and tumor development are provoked by inflammation agents and inflammatory response cells. Both these agents and cells damage the basal membrane between epithelium and stroma and stimulate substitution of fibroblasts with myofibroblasts (also called 'cancer-associated fibroblasts') [20]. Myofibroblasts are the major cell component of tumor stroma. It was shown that bone marrow myofibroblasts are one of the key factors of the malignant transformation process [21-25].

It is worthwhile to note that certain forms of stromal differentiation (e.g. mucinous or scirrhous) make cancer more resistant to the effect of antitumor drugs [26, 27]. It has also been shown that stromal fibrosis can make histopathologic signs of cancer less clear [28].

For a tumor to develop, both tumor components are required: altered epithelial cells and altered stromal cells. Changes in stromal cells (e.g. in response to inflammation) may precede the emergence of altered epithelial cells, or develop after the pre-cancerous cells emerge [29]. On the other hand, the progressing cancer is a system of interacting cells [30].

2.1. Cell Components of the Histion

As has been noted, bone marrow-derived myofibroblasts of stroma are a key factor in the malignant transformation process. However, other tumor cells also support and regulate cancer cell functioning.

Immune cells, including T- and B-lymphocytes, natural killer cells (NK), macrophages, mast cells, and neutrophils constitute the greater part of tumor cells [31].

Tumor-associated macrophages (TAM) release vascular endothelial growth factor (VEGF) that stimulates tumor angiogenesis and facilitates metastatic spread. They also increase tumor resistance to chemotherapy and radiation therapy [32].

It has been emphasized that macrophages acquire these capabilities through synergistic cross-talk with cancer cells [33, 34], in addition to tumor tissue hypoxia and the presence of dead cells [35]. Expansion of myeloid-derived cells into the tumor microenvironment increases the ability of the extracellular matrix to support the viability of the cells it surrounds [36], and to induce stem-like properties in differentiated cells (cancer cell stemness) [37].

Migration of mast cells into the tumor and their further degranulation (release of various mediators) stimulates growth and metastatic spread of the cancer cells [38]. Chronic inflammation of any organ is associated with the invasion of inflammation-related cells, such as neutrophils. These inflammation-related cells play an important role in the development of aggressive tumor cells, and thus participate in cancer initiation and progression [39].

Migration of mesenchymal cells into the tumor stroma is also important for cancer initiation, because of their pro-tumorigenic influence on pre-cancerous cell transformation [40].

Natural killers (NK) are large, granular lymphocytes which are toxic to cancer cells. However, certain stromal cells [41] and stress [42] may impair this NK function.

Some features of adipose tissue are also associated with cancer. First, obese adipose tissue hypoxia establishes a highly proinflammatory microenvironment, which is likely to breed tumors. Second, adipose cells secrete various cytokines, chemokines, and hormone-like substances capable of initiating cancer growth [43-45].

As has been mentioned, tumor angiogenesis, which is important for tumor growth and existence, depends on the circulating endothelial cells. These cells release angiocrine factors that stimulate tumor growth, make it more invasive, and thus contribute to tumor metastasis [46, 47].

Tumor angiogenesis is regulated by the cells of the tumor microenvironment through cues released by these cells [48]. An important role in angiogenesis stimulation is played by pericytes and the growth factors they secrete into the extracellular matrix [49, 50].

Neuroendocrine cells are another cancer tumor component; they release neuropeptides that facilitate tumor growth, angiogenesis, and metastasis [51, 52].

Some tumors are innervated by the ingrown nerve endings of the autonomic nervous system. These tumor-innervating nerve cells may release neurotransmitters that provide proliferative signals to the tumor cells [53, 54]. The effect of adrenergic and

cholinergic nerves on stromal and cancer cells has been discussed in a number of papers [55-57]. For example, the overall nerve densities are higher in high-risk prostate tumors relative to low-risk ones. Nerves also can serve as a route for cancer spreading through the process of perineural invasion. Perineural invasion is often associated with poor prognosis. Tumors can be innervated by sensory fibers in addition to the nerve endings of the autonomic nervous system. The possible involvement of sensory fibers in tumor progression and metastasis cannot be excluded [58]. In tumors, nerves are a source of neurotransmitters and neurotrophic factors, including various growth factors [59]. The nerve cells and neuroendocrine cells of the tumor may regulate the cancer genome [60]. Thus, the tumor nerve cells help preserve and support its integrity and development, and protect the tumor against damage [61].

2.2. Extracellular Matrix

The extracellular matrix is another active component of the tumor microenvironment [62]. The extracellular matrix of a tumor differs from that of a healthy tissue [63]. It promotes proliferation and tumor growth and has a pro-survival effect, in particular, through changes in the collagen matrix. Altered extracellular matrix is associated with chronic inflammation [64] and facilitates malignant transformation of the precancerous cells, if they are present. In addition, senescent fibroblasts release into the matrix cues that can drive the progression of precancerous cells into cancer cells [65]. Biologically active substances released by various cells, in particular, stromal cells, are transported into cancer cells through the cancer cell-derived extracellular matrix [66]. The cancer cell-derived extracellular matrix supports cancer cell proliferation, whereas the extracellular matrix of healthy tissues inhibits their proliferation [67]. Various tumor growth-promoting signaling molecules have been found in the extracellular matrix of tumors, among them, Vascular Endothelial Growth Factor and Epidermal Growth Factor. Upon binding to their receptors, they initiate various signaling pathways, for example, Ras/MARK, AKT/PKB, STAT-3 [Signal Transducer and Activator of Transcription] and others that inhibit apoptosis and stimulate proliferation and neoangiogenesis. Metastatic cancer cells migrate to the extracellular matrix, where the stromal cells release metalloproteinases, collagenases, gelatinases and other substances that are required for this process [68, 69].

The extracellular matrix, which belongs to the cancer cell microenvironment, is formed by the cells of the altered stroma [70, 71]. At the same time, cancer cells release various substances that initiate and maintain the myofibroblast population, which promotes cancer cell progression [72].

Substances contained in the extracellular matrix cause pro-malignant epigenetic alterations in cancer cells [73]. Another potential mechanism of malignant progression involves regulation of cancer cell behavior [invasiveness, migration, and ability to form metastases] through physical and chemical gradients within the matrix. In the metastatic process, specific roles are played by tissue hypoxia, changes in tissue pH and Na+ and Cl- concentrations, and by the disruptive effect these conditions have on the steadiness of the naturally occurring electrical fields within the matrix. For example, galvanotaxis promotes metastatic development of prostate cancer, breast cancers, lung cancer, and glioblastomas [74].

In addition, the authors hypothesize that tumor cell behavior may also be regulated by haptotactic, alignotactic, and durotactic gradients within the extracellular matrix. Haptotaxis is a type of chemotaxis in the non-liquid environment. It is a migration of cells along the gradients of substrate-bound cues within the extracellular matrix e.g. along the gradient of a specific glycoprotein. Alignotaxis is the tumor cell migration promoted by reorganization of collagen into straight-aligned fibers. Durotaxis is cell migration fostered by endogenous stiffness gradients [75, 76].

Thus, the extracellular matrix is the location and immediate regulator of the cancer development process.

2.3. Matrix Exosomes

Tumor and stromal cells interact through gap junctions and exosomes. Another communication channel is represented by microvesicles, plasma membrane-derived particles that are released into the extracellular environment by the outward budding of the plasma membrane. Cell communication is the most important role of exosomes and microvesicles. Their membranes protect signaling molecules against lytic enzymes and help transport them to the target cells. Targeted delivery of the signals also depends on the structure of exosome and microvesicle membranes. This targeted microvesicle binding is important when it comes to the creation of artificial exosomes capable of delivering therapeutic active cargo into the target cells [77-82].

2.4. Biologically Active Molecules of the Extracellular Matrix Involved in Cell Communications

The extracellular matrix is a medium of interaction between the connective tissue and epithelial cells, including cancer cells. Collagen is the major component of the extracellular matrix. Collagen, fibrin, elastin and hyaluronic acid are responsible for the structural function of the extracellular matrix. However, this is not its only function. The matrix is also a place where biologically active molecules released by stromal and epithelial cells are located. These substances are responsible for integrating the cells, tissues, and tumor into one complex system. The altered extracellular matrix may substantially increase tumor cell survival and decrease their response to chemo- and radiation therapy.

Stromal alterations of this sort are associated with desmoplastic changes, increased numbers of cancer-associated fibroblasts (bone marrow-derived myofibroblasts), accumulation of beta-1 integrin and PI 3-kinase activator, as well as collagen VI [83-85]. Detachment of cells from the matrix integrins may lead to cell death [86]. Decorin ensures the integrity of the connective tissue in various organs, but also plays an important role in regulating cancer cell proliferation [87]. Its derivative, Leucine Rich Repeat 5 (LRR5), inhibits angiogenesis through suppressing the vascular endothelial growth factor (VEGF) and slowing down endothelial cell migration [88].

Periostin is also important for tumor progression [89-91]. Clusterin is a widespread protein which participates in intracellular communication and regulates growth, invasiveness, and metastatic spread of cancer cells. It also helps these cells recover after damage and contribute to their resistance to chemo- and radiation therapy. It is released by both stromal and cancer cells. In the healing of wounds, connective tissue cells also release this cancer-stimulating protein [92].

Bone marrow-derived mesenchymal stromal cells that colonize the tumor produce chemerin. This protein increases the migration of mesenchymal stem cells into the tumor and their transformation into cancer-associated myofibroblasts. These myofibroblasts, in turn, promote cancer cell progression. Chemerin synthesis suppression may slow down cancer progression [93].

Bone marrow-derived myofibroblasts release matrix metalloproteinase 13, which also affects cancer cell invasiveness [94].

The family of AKT kinases plays a crucial role in oncogenesis [95]. Metastases develop after the epithelial-mesenchymal transition of cancer cells in situ; the PI3K/AKT signaling pathway [96] plays an important role in this process. In tumors, increased AKT activity is associated with the activity of stromal fibroblasts (CAFs, or myofibroblasts [97]).

CAFs also produce hydrogen peroxide which leads to the malignant transformation of epithelial cells and the progression of those cancer cells that have been transformed [98].

3. OTHER NON-ENDOCRINE CELL-DERIVED MOLECULES THAT ENSURE HISTION INTEGRITY, AND CONTROL THE FUNCTION OF OTHER CELLS

3.1. Role of Cytokines in Cell Communication

Cytokines are produced by both stromal and tumor cells. Many of them promote tumor progression and tumor resistance to chemo- and radiation therapy. For example, the levels of stromal cell-derived factor-1 are increased in tumors. This factor increases the proliferation, migration and invasiveness of cancer cells [99, 100].

Stromal cell-derived factor-1 (CXCL 12) binds chemokine receptor CXCR4. If this receptor is blocked by antibodies, the metastatic potential of the cancer cells decreases [101-106].

Blocking chemokine receptors [107] and ligands [108] is a promising line of research in anti-cancer therapy.

Other ligands and their receptors (e.g. CXCL16 and CXCR6) can also promote cancer cell proliferation [109].

Transforming growth factor beta 1 (TGF beta 1) also facilitates stromal and cancer cell communication. It induces transformation of fibroblasts into myofibroblasts and mobilization of bone marrow stromal stem cells into the tumor, with their further transformation into myofibroblasts that promote the growth of cancer cells and increase their invasiveness [110-113].

Tumor growth factor beta 1 (TGF beta 1) is produced by both cancer cells and myofibroblasts [114, 115]. Blocking TGF beta 1 can have a therapeutic effect on malignant neoplasms [116, 117].

Bone marrow-derived myofibroblasts promote tumorigenesis and tumor growth through activating pro-inflammatory cytokines IL-1 and IL-6. Adipocytes and cells that are involved in chronic inflammation also produce these cytokines [118-120]. Cyclo-oxygenase-2 (COX-2) is controlled by various growth factors and cytokines IL-1, IL-6, and TNF alpha [121]. COX-2 inhibition decreases the level of IL-6 [122] and slows down cancer progression [123].

3.2. Role of Non-coding RNA in Cell Communication

MicroRNAs (miRNAs) of the extracellular matrix are another group of signaling molecules which participate in the interaction of stromal and cancer cells [124, 125]. It is believed that all types of non-coding RNAs (i.e. both long non-coding RNAs and microRNAs) can be regulatory messengers between stroma and cancer cells [126]. Their action is allegedly related to the epigenetic effect on the genome of epithelial cells [127, 128]. Based on this hypothesis, it is supposed that non-coding RNAs participate in intratumor cell communications and may contribute to the resistance of cancer cells to anti-cancer therapy [129].

3.3. Neurotransmitters as cell-Signaling Molecules of Tumors

Acetylcholine was one of the first neurotransmitters—chemical messengers that transmit signals across chemical synapses—to be discovered. Acetylcholine is synthesized by choline acetyltransferase in the pre-synaptic neural cell, whereas acetylcholinesterase degrades free acetylcholine in the synaptic cleft. Nicotinic (nAChR) and muscarinic (mAChRs) receptors are two main types of cholinergic receptors. Muscarinic receptors are so named because they are more sensitive to muscarine than to nicotine, whereas nicotinic receptors are more sensitive to nicotine. When bound to acetylcholine, mAChRs activate G-protein. This activation results, in turn, in the activation of certain ion channels. A number of nAChR subunits have been identified, and there are five types of mAChRs (M1, M2, M3, M4, M5) [130].

Acetylcholine also occurs in non-nerve tissues [131]. In these tissues, it controls many vital cell functions, such as gene expression, proliferation, differentiation, cytoskeletal anchoring and clustering, migration, secretion, and absorption. It also plays an important role in various pathological processes, such as inflammation and cancer [132]. Different non-nerve cells have different combinations of choline receptor subtypes. Certain endogenic substances can induce specific types of choline receptors. For example, choline induces synthesis of alpha 9 subtype, whereas bile acids induce M3 receptors. Cholinergic non-nerve cell communication does not correlate with the cholinergic or adrenergic type of tissue innervation. Acetylcholine can change signals from other cells through its effect on ion channels [133]. Acetylcholine promotes fibroblast proliferation and regulates synthesis of cytokines and extracellular matrix [134]. The cholinergic signaling system also

promotes mesenchymal stem cell migration into damaged tissues if it is required for tissue regeneration [135].

Neurotransmitters regulate embriogenesis at the early stages, even before nerve system development begins. Already at these early stages, embryo cells synthesize several transmitters that are present both on the cell membranes and inside the cells. Antagonists of neurotransmitters can block cell communication in sea urchin embryos at the very early stages of their development [136]. In chicken embryos, some cholinolytics impair embryonic development [137].

In addition to neuron signal transduction, neuropeptides and neurotransmitters are involved in various cell interactions. For example, enzymes responsible for the synthesis of neuropeptides, acetylcholine, catecholamines, glutamates, and their receptors have been found in keratinocyte cell culture. All these neurotransmitters are involved in the processes of cell proliferation, migration, angiogenesis, and regeneration [138].

nAChR, mAChRs, and serotoninergic receptors regulate the activity of natural killer cells [139]. Cytotoxicity and migration of NK cells and T-lymphocytes is regulated by endorphin, histamine, substance P, and a number of hormones, such as cortisone, testosterone and estradiol [140]. T-lymphocyte function is regulated by cytokines, but also by a number of peptides, neuropeptides, and neurotransmitters, such as somatostatin, calcitonin gene-related peptide, substance P, and dopamine. Neurotransmitters can effectively alter the cytokine-dependent activity of T-lymphocytes [141]. For example, purinergic signaling mechanisms associated with T-lymphocyte regulation were found in tissues affected by inflammatory bowel disease [142].

Macrophages are an important element of the immune system. Their cytostatic or cytotoxic activity is supported by the production of nitric oxide (NO), a neurotransmitter, which is synthesized by the NO synthases of the macrophages [143]. NO also stimulates synthesis of metalloproteinase-regulating mRNA; these enzymes are required for cell migration [144].

It has been shown that in adenocarcinomas of the mammaries, lungs, pancreas, and colon, synthesis of arachidonic acid [which regulates cancer cell growth] is controlled by beta-adrenergic cues [145].

Cannabinoid neurotransmitters inhibit the growth of colon cancer cells through the destruction of one of the microRNAs [146]. Neurotransmitters belong to the complex target cell-regulating network of signaling pathways [147]. It is also worth noting that only some beta-adrenergic antagonists can block the pathogenic effect of beta-adrenergic agonists [148]; effective antagonists must be selected by trial and error. Synthesis of neurotransmitters is regulated by nucleic acids, microRNAs in particular [149, 150].

Cytokine-mediated cancer parenchyma and stromal cell interactions lead to tumor progression. Cytokine-blocking therapy slows this process down. Cytokines are regulated by neurotransmitters. Moreover, neurotransmitters, such as the catecholamines dopamine, norepinephrine and epinephrine, as well as nicotine, their agonist, promote cancer cell migration and enhance their metastatic potential. Norepinephrine and epinephrine are typical stress hormones. Their beta-blockers can inhibit migration of cancer cells. Gamma-aminobutyric acid also inhibits norepinephrine's pro-migratory effect. Inflammation-associated neurotransmitters, such as histamine, bradykinin, and substance P, exert a tumor-progressive effect [151-155].

Nicotine increases cancer cell migration through PI3K/AKT signaling pathway activation [156].

Beta-adrenergic blocking agents may reduce cancer cell migration and thus improve treatment outcomes. This hypothesis was confirmed in a mid size clinical trial, where beta-blocker treated patients showed a significant reduction in metastasis development, tumor recurrence, and longer disease free interval [157].

4. SUMMARY

Interactions of the tumor parenchyma cells and stromal cells are a continuous, mutually supportive process. These cells form an aberrant histion, a complex ecological system [158] that supports its own stability, viability, and resistance to therapies. Cells that constitute this system interact through secretion of cytokines, miRNAs, and neurotransmitters—in this context, it may be better to call them cytotransmitters. To some extent, neurotransmitters control the synthesis of cytokines and nucleic acids.

Cancer development requires both damage to the epithelial stem cell genome to transform it into a precancerous cell, and altered secretory activity of the stromal cells, primarily of the bone marrow-derived myofibroblasts. Altered stromal signals transform precancerous stem cells into cancer stem cells. Stromal and cancer cells communicate through regulatory pathways that include various ligands produced by the stromal cells, and their receptors located on or in target cells. It is very likely that if the main pathway is blocked, then other pathways get activated. These alternative pathways use different ligands and receptors. Thus, it is possible to speak of a regulatory network that integrates different regulatory pathways. This means that the effective blocking of target cell interactions can only be achieved through switching off as many elements of the regulatory network as possible.

The above considerations allow us to assume that research into neurotransmitters, their agonists and antagonists may be a promising line of inquiry and may help develop methods for cancer histion integrity disruption. Such methods could be a helpful addition to chemo- and radiotherapy and may improve therapy outcomes. It should also be mentioned that neurotransmitters, their agonists and antagonists are readily available substances, thus the development of neurotransmitter-based therapeutic agents may be a relatively easy task.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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