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About causes of early-stage asymptomatic prostate cancer

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Abstract

Background: The neurotransmitters (epinephrine and norepinephrine) of the sympathetic nervous system that perform numerous cellular and tissue functions contribute to tumor growth during the early stages of development. At the same time, these bioactive substances act as mediators of the descending antinociceptive system that cause inhibition of pain at the suprasegmental and segmental levels of the neurotransmission. Later studies point to the involvement of afferent sensory neurons in tumor process. The functionality of these structures can be changed due to the structural features caused by genetic disorders of myelin. In addition to that, tumor augmentation of sensory neurons endings leads to the involvement of myeloid-derived suppressor cells in the affected area and the creation of an immunosuppressive microenvironment. At the same time, in the secondary inflammatory process, various enzymes that change the cellular matrix and cause invasion and metastasis are released. In addition to sensitizing cytokines, immunocompetent cells – macrophages, neutrophils, lymphocytes – can also produce opioid peptides that target the desensitization of peripheral nociceptors. Opioid peptides inhibit the excitability of sensory nerves without central unwanted side effects such as depression of breathing, clouding of consciousness, or addiction. This peripheral antinociceptive system with ICC may allow the neoplasm to remain asymptomatic for a while. The changes in afferent impulses at the central level in oncopathology can also be associated with those in the functionality of Toll-like receptors.

Conclusions: Taking into account the aforementioned literature data about oncogenesis, it may be assumed the presence of a new complex pathogenetic pattern that ensures the asymptomatic evolution of prostate cancer. A better coverage of this data may facilitate further search for early markers of the disease.

Key words: prostate, cancer, asymptomatic.

Introduction

Prostate cancer (PCa) is the most common cancer type among the male population of Europe and it is on the third place in the structure of oncological diseases. In 2012, about 417,000 new cases of cancer were diagnosed, out of which PCa represents 12% of the total number of cases [1]. Castration-resistant prostate cancer (CRPC) is second among the main causes of death from malignant diseases in representatives of the stronger sex [2].

According to pathoanatomical studies, it was found that prostate cancer has a long period of asymptomatic growth. It sometimes takes several decades before the appearance of a clinically pronounced form. In the opinion of Sakr W. A. et al. [3], small foci of histological cancer were detected in 27% and 34% of 40 and 50-year-old men, respectively. According to Breslow N., et al. 1977, Barry M. J. 2001 [4-5] , prostate cancer appears in 60% - 80% of men older than 70 years and only in 0.1% of individuals aged under 50 years [6].

Despite such a high prevalence, the latent form of prostate cancer becomes clinically significant only in 10% of cases [7]. Most scientists share the view that late detection of prostate cancer is associated with a prolonged asymptomatic evolution of the disease. The study of the dynamics of cancerous tumours growth has shown that ¾ of time for their development falls on the preclinical period [8]. In the opinion of B. Ya. Alekseev et al., metastases are found in 60-80% of patients with primary prostate cancer [9].

Until the 1970s (pre-screening era), in Western countries, the late stage (metastatic prostate cancer) in primary diagnosis was observed in more than 50% of cases. In the present period, 10 to 20% of patients also have distant metastases at the time of diagnosis [10].

Authors who have studied the features of PCa with fatal outcome provide similar data. According to them, PCa metastases were identified in 56% of patients who died of prostate cancer [11]. The differential diagnosis of PCa is carried out with the other prostate diseases, previous ineffective drug therapy of LUTS [12].

Analyzing the scientific data on the tumour microenvironment and its interaction with various macroorganism systems, some features can be outlined, which may show that a tumour can remain asymptomatic for a long time.

Interaction of nerves and tumors

Experimental models have relatively recently shown the involvement of nerve fibres in the tumour tissue in prostate cancer [13]. Cancer cells can invade nerves surrounding the tumour by expression and secretion of nerve growth factor (NGF) [14]. The ability of NGF to regulate expression and production of neurotransmitters, as well as modulation of synaptic activity [15] were also detected. In their turn, antihyperalgesic and analgesic effects may be accompanied by changes in synaptic transmission [16-17].

The original work on the interaction of malignant neoplasm and those involved in the pathological process of afferent (sensory) neurons was performed by the authors [18].

In the course of the study, they revealed that there is tumor augmentation of endings of sensory neurons leading to hyperproduction of chemokines by nerve cells of the dorsal root ganglia (DRG). According to scientists, the formed tumor-neuronal-immune axis promotes the involvement of myeloid-derived suppressor cells (MDSC) in the affected area and the creation of an immunosuppressive microenvironment.

According to Magnon C. et al. [13], the nerve fibres of the sympathetic nervous system "contribute" to prostate cancer in the early stages of development by producing the neurotransmitter "norepinephrine" (NE). Observations of scientists [19-20] point to the dominant role of norepinephrine locally secreted by nerve fibres in controlling beta-adrenergic effects on tumour development. On the other hand, NE is also a mediator of the descending antinociceptive system by activation of adrenergic receptors that causes inhibition of pain at the suprasegmental and segmental levels of the neurotransmission [21].

Abnormal architectonics of tumour tissue is reflected in the components of neurovascular structures. According to some researchers [13, 14, 22], differences between the growth of nerve cells in normal tissue and tumours can be detected. In a tumour, the axon lengthens, whereas in normal tissue the cell body of the neuron thickens. Moreover, some authors report the correlation between the density of nerve fibres within prostate carcinoma and the degree of its aggressive behavior [23, 14].

Studies on prediction of upgrading and disease upstaging in low-risk prostate cancer identify a panel of three genes which expression significantly affects the aggressive behavior of the disease [24]. One of these genes, PMP22, encodes glycoprotein contained in ~ 5% of the total myelin protein in the nervous system [25, 26], while genetic defects related to PMP22 are also associated with peripheral neuropathy [27]. The above features may affect the transaxonal transport. According to the author [28], the violation of the latter mechanism can lead to a decrease of mediator content in the presynaptic structures and create an analgesic effect. This principle – decrease of mediator content in presynaptic structures – underlies the action of anaesthetics.

Features of the metabolism of blastemal cells and nociception

The atypism of tumour tissue, as noted above, affects the morphology of the constituent nerve structures, a fact that may also change their functionality. Further, we will present some features of blastoma cells that may influence the intensity of pain impulses from the oncologic focus.

An increase in the proliferative activity of the cell in response to mitogenic stimulation is accompanied by a large-scale dynamic increase in the concentration of cytosolic calcium [29]. For example, the authors [30], examining the level of cytosolic calcium (Ca2+) oscillations in oesophageal squamous cell carcinoma (ESCC), have noted significantly higher indices of this parameter in blastemal cells in comparison to the control ones – 76% versus 26%, respectively.

The change in intracellular calcium concentration involves the inducing of a whole cascade of intracellular events, including the activation of transcriptional and apoptotic mechanisms [31, 32, 33].

The possibility to avoid the inclusion of the mechanisms of apoptosis provides one of the fundamental conditions of oncogenesis – the possibility of uncontrolled division. Tumour cells can avoid apoptosis by decreasing the cytosolic calcium concentration [34, 35]. The latter phenomenon can be achieved by changing the functionality of the membrane Ca2 + ion channels [36]. Some features of these structures have been revealed in the course of PCa [37, 38].

TRPM8 is one of the Ca2 + ion channel groups, and has been first identified in PCa cells, but it was found later that TRPM8 channels are also expressed in nociceptive neurons [39].

Some interesting features are noted by increasing the range of studies in terms of analyzing the consequences of disruption of the calcium channels. According to the feedback mechanism in the peripheral painful systems of Ca2 +, the ion channels are activated low and inactivated by a high concentration of cytosolic calcium [40]. According to the author [41], the suppression of calcium currents by 20-90% from the initial values (depending on the type) is one of the components of the local anaesthetic effect of tetracaine. Scientists [42, 43, 44, 45] provide similar data – blocking ion channels can ensure terminating the action potential (AP), with the establishment of local anesthesia. In this context, the authors' conclusions [46] that the decrease in the transmembrane Ca + transport facilitates the establishment of analgesia also enhances the effect of opioids.

Reduction of the axon excitability and nerve endings in some neurons has also been observed in the hyperfunction of calcium-activated chloride channels (CaCCs). These structures are expressed in excitable and epithelial cells, ensuring stabilization of the resting membrane potential and cell volume regulation. The number of functioning nerve endings is regulated by modulating conductivity of chlorine. For example, the activation of CACCs reduces the normal excitability and facilitates the establishment of a block for carrying out the action potential in the branch node [47, 48].

Investigating the impact of neuroendocrine differentiation in PCa cells on the characteristics of the volume-regulated chloride channels, Lazarenko R. N. [49] has revealed a 2-fold excess of this parameter in comparison to the control level.

Some of the above theoretical considerations have been practically confirmed in various experiments on animals. It was found that modulation of both central and peripheral ion channels could significantly change the pain sensitivity threshold. Researchers [51, 52, 53] have established signs of a decrease in pain sensitivity in experimental rodents with impaired permeability of calcium channels. An interesting fact is that the increased Ca2+ influx is considered critical for the transmission of persistent but not short-term pain

impulses [54]. The noted features can be manifested in cancer patients because of local ionic disorders.

An atypical metabolism with a predominance of glycolysis is one of the main logos of carcinogenesis. During rapid replication of tumour cells, it is necessary to have a huge amount of biomaterial for the synthesis of cellular structures, which to some extent can be provided by anaerobic glycolysis [55]. At the same time, this feature of the exchange is ineffective in terms of ATP production [56]. The production of ATP is only 50% of the total level in the mitochondria of malignant cells, whereas in conventional cells this figure reaches 90% [57]. The latter feature may possibly affect the level of this substrate in blastemal cells, followed by a violation of purinergic signal transmission between neurons in the tumour environment and its microenvironment [58]. According to Fields R.D., et al., the release of neurotransmitters in the peripheral nervous system (PNS) occurs with the assistance of ATP and adenosine [59], and also processing of sensory information [60] is provided by means of these mediators by purinergic receptors.

Perversion of metabolic processes characteristic to cancer cell degeneration is accompanied by a decreased activity or the absence of certain specialized enzymes inherent in normal tissues (arhipase, catalase, cytochrome oxidase, cytochrome c, esterase, etc.) [61]. For example, researchers [62, 63] indicate a decreased expression of Na +, K + -ATPase in some carcinomas. Na+ /K+ -ATPase is a necessary enzyme to maintain sufficient activity of the Na+/K+) pump – one of the key processes of vital activity involved in the regulation of cellular metabolism, water-salt metabolism, as well as to generate excitation. The activity of Na / K-ATPase is dependent on the ATP content in the cell [64]. A decrease in Na+, K+-ATPase activity leads to slower nerve impulses and may be accompanied by a loss of pain sensitivity [65].

Another mechanism that contributes to the reduction of nociception in the early stages of cancer is probably related to a change in the functionality of the cyclase systems. In particular, some solid tumours show a deficiency of adenylate cyclase in the intermembrane space [61]. The authors [66, 67] have noted the direct inhibitory effect of calcium ions on isoforms 5, 6 of adenylate cyclase. In the light of the above data on the increase of cytosolic calcium level in blast cells, remarks of the authors [68] who report a marked decrease in acute and chronic pain intensity via blocking adenylate cyclase activity in animal models are very interesting.

Immune system and sensory influences

One of the most significant milestones of modern immunology is the formation of a scientifically based concept of innate and adaptive immunity. From an evolutionary point of view, innate immunity is an earlier protective mechanism inherent in virtually all multicellular organisms. Being hereditary, this structure provides protection of the individual from various microorganisms and endogenous derivatives of tissue disintegration, activating for several minutes or hours. All components of innate immunity are invariably inherited and are not genetically modified throughout life. Functioning of this protective system is provided by numerous cellular elements (eosinophils, mast cells, macrophages, neutrophils, basophils, NK cells), microglial cells – resident macrophages of the central nervous system (CNS) and humoral factors (lysozyme, cytokines, complement, acute-phase proteins (APPs), cationic antimicrobial peptides, etc.) [69]. C. Janeway formulated the principle of innate immunity at the end of the 20th century by introducing the concept of pathogen-associated molecular patterns (PAMPs), which are encoded in the genomes of bacteria and absent in the genome of macroorganisms. The most studied PAMPs are DNA and RNA viruses and bacteria, flagellin, bacterial wall lipopolysaccharides (LPS), glycolipids, lipoteichoic acid (LTA), lipoproteins, zymosan fungi [70, 71]. It has also been found that many macroorganism-derived compounds formed during cytolysis can act as PAMPs (fibrinogen, heat shock proteins, fibronectin, etc.) – damage-associated molecular patterns (DAMPs) [72, 73, 74]. Identification of antigens by the cells of the innate immune system is carried out by receptor formations that distinguish the pattern of pathogens (pattern recognition receptors – PRRs). Pattern-recognition receptors (PRRs) are divided into three classes according to their function: signaling, endocytic and secreted. Signaling PRRs contribute to the transmission of the signal into the cell nucleus to activate the genes of adaptive immunity. Endocytic PRRs mediate the damage of the pathological agent in the lysosomes of macroorganism cells. Secreted PRRs act as opsonins, "marking" antigenic structures and contributing to the process of phagocytosis [75]. One of the most significant elements of the class of PRRs are Toll-like receptors (TLRs) [76]. These structures were first discovered in 1997 in mammals [77]. Receptors of this class are widely represented in various cells of organs and body systems (monocytes, leukocytes, fibroblasts, endothelium, epithelium, cardiomyocytes, B cells [78], mast cells [79], natural killer cells (NK cells) [80]. TLRs are common in various cell populations of the central nervous system (CNS): dendritic cells (DCs) [81], neurons [82], astrocytes [83] and oligodendrocytes [84], and glia [85]. This feature provides a significant link between the innate immune system and the CNS. The abundance of TLRs in pain responsive regions makes them a critical potential component of pain signaling.

Glia is a collection of accessory cells of the neural tissue, accounting for more than 70% of all cells found within the brain and spinal cord [86]. Glial cells have been recognized as key mediators of the innate immune responses in the CNS and play a major role in the clearance of cellular detritus and immune surveillance [86, 87]. It should be noted that complementary glial cells are important modulators of pain. According to scientists Piccinini AM. et al. [89]; Scholz Z., et al. [90], damage-associated molecular patterns (DAMPs) can activate glial cells through TLR receptors, which have a well-established role in pathological pain. On the other hand, it has been proven that some tricyclic compounds that are commonly used for clinical neuropathic

pain treatment possess significant TLR4 inhibitory activity and can reduce sensitivity (Hutchinson MR, et al.,) [91]. In preclinical experiments, the study of pain mechanisms revealed interesting features of expression of TLRs [92]. After the induction of peripheral inflammation (plantar administration of Complete Freund's Adjuvant (CFA) in laboratory rats), the transcriptional level of mRNA TLR4 significantly increased within a short period of time (4 hours) in various regions of the central nervous system. This indicator has remained high for 14 days, and persisted even when the emerging signs of experimental allodynia disappeared. In this context, I would like to mention the remarks of researchers [93], who noted the activation of microglial cells as a result of peripheral nerve damage (peripheral neuropathy). The authors noted an interesting feature of glia – once activated microglial cells can remain in a "sensitized" state. Similar changes in the properties of glial cells were noted not only as a result of peripheral nerve damage, but also as a result of stress factors [94]. According to Ferraz CC. et al. [95], Diogenes A. et al. [96], the functionality of TLR4 depends on the amount of intracellular calcium and the level of sensitization of TRPV1.Given the above information about the ability of tumor cells to suppress the functionality of membrane calcium channels [37], we can assume a local (tumor) inhibitory effect on TLR systems. Perhaps this phenomenon ultimately operates systemically, inducing a special "hyposensitized" state of glia. Probably the indirect confirmation of this assumption is the observations of scientists Tashiro M, et al. [97], who studied the brain of 19 patients with various types of cancer (except for brain cancer) using positron emission tomography. The results of the study were compared with images of 17 patients with benign diseases. The authors noted a decrease in regional cerebral glucose metabolism in separate areas of the CNS – limbic system, thalamus, hippocampus, basal ganglia, etc. According to them, the psychological deficit in cancer patients is associated with abnormalities of regional brain metabolism in the limbic system. Given the specifics of our research, we consider it worthwhile first of all to note the reduction of regional cerebral glucose metabolism in the thalamus. This structure not only retransmits all sensory and motor information from the sense organs, but also performs primary processing and thus filters the incoming sensory information before transferring it to the cortex of the large hemispheres [98]. The given changes in such an important area of the central nervous system as the thalamus most likely have a negative impact on its functionality and lead to sensory disorders.

Recent studies indicate the probability of synthesis and secretion of identical regulatory peptides (substance P (SP), VIP, enkephalins, cholecystokinin, somatostatin, beta-endorphin, lipotropins, angiotensin, calcitonin) by cells of various organs and tissues. The affinity of these compounds to the receptors has been discovered, and it looks common in many body systems. Considering the latter, substitution of the concept of nervous, immune, endocrine and humoral modulation by the term "regulatory continuum" has been proposed [99].

According to the postulates of integrative medicine, the conjugated interaction of nociception and immunity now occurs both at all levels of the nervous system, and in all organs and components of the immune system. In the last process, almost all known hormones, neurotransmitters and cytokines are involved. Thus, the receptors of neurotransmitters involved in the occurrence and conduct of pain impulses also affect the functionality of immune cells. At the same time, a number of hormones, cytokines and other bioactive compounds secreted by lymphoid cells, changes the excitability of nerve fibres [100].

Early studies on the role of the immune system in the development of cancer indicate a circular infiltration of immune cells by tumours [101, 102, 103]. The authors have convincingly demonstrated tumour stimulation by immune system cells and neoplastic progression [104, 105]. Stimulation of these structures occurs as a means of adrenergic influences of macroorganism and cytokines produced by a cancerous tumour [106, 107]. The suppressor effect in prostate cancer on the population of T-killers [108] was also proven. In the inflammatory process, the release of proangiogenic factors and enzymes that change the cellular matrix and promote invasion and metastasis occurs in infiltration of the tumour microenvironment by immunocompetent cells [109].

On the other hand, besides these sensitizing cytokines, immunocompetent cells (ICC) – macrophaghes, neutrophils, lymphocytes – can also produce opioid peptides that provide desensitization of peripheral nociceptors [110, 111, 112, 113].

Inflammation of peripheral tissues leads to increased synthesis and axonal transport of opiate receptors in dorsal root ganglion neurons, which causes an enhanced analgesic efficacy of peripherally active opioids. Once secreted, opioid peptides activate peripheral opiate receptors and produce analgesia by inhibiting the excitability of sensory nerves. These effects occur without central untoward side effects such as depression of breathing, clouding of consciousness, or addiction [114, 115]. This peripheral antinociceptive system with ICC may allow the neoplasm to remain asymptomatic for a while. In this context, we consider interesting the observations of the authors [116] who have noted that Mycobacterium tuberculosis activates formyl peptide receptor (FPR) on neutrophils, resulting in tonic secretion of opioid peptides from neutrophils and in a decreased inflammatory pain.

Earlier it was suggested that malignant tumour formation is analogous to a certain "killer organ" [117, 118]. Successful progression of this process is provided with clearly outlined strategies. Some of the most well-known strategies are changes in the microenvironment by isolating specific metabolites and tumour secretion of growth factors, growth of malignant blastemal cells during the deterioration of medium conditions, immune-suppression by developing an

antigenic simplification, divergence and antigenic reversion [119]. As is known, a long asymptomatic flowing provides oncogenesis with a "special" effect and perhaps outlines an additional strategy.

Conclusions

Taking into account the aforementioned literature data about oncogenesis, it may be assumed the presence of a new complex pathogenetic pattern that ensures the asymptomatic evolution of PCa. A better coverage of this data may facilitate further search for early markers of the disease.

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