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THE ROLE OF THE RENIN-ANGIOTENSIN SYSTEM IN MALIGNANCY DEVELOPMENT IN THE LIGHT OF THE CONCEPT OF D. HANAHAN AND R. WEINBERG “THE HALLMARKS OF CANCER”

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Abstract. Due to the emergence of a large number of studies on the role of the renin-angiotensin system (RAS) in the mechanisms of the development of malignant tumors, it seems very relevant to structure these data within the framework of the integral concept of D. Hanahan and R. Weinberg “The Hallmarks of Cancer”. It turns out that the renin-angiotensin system plays a significant role in the genesis of almost all “The Hallmarks of Cancer” mainly through the activation of the ACE (angiotensin-converting enzyme) / Ang II (angiotensin II)/ATR1 (angiotensin II receptors type 1) axis and renin/prorenin receptors (PRRs), which increase tumor-associated inflammation. Activation of transcription factors NFκB and STAT-3 plays a primary role here. In addition, due to the presence of angiotensin II receptors on lymphocytes and macrophages, RAS may be directly involved in modulating of the immune response. Localization of intracellular RAS receptors on mitochondria allows this system to participate in changing the metabolism of tumor cells. The relationship of RAS with the mechanisms of cellular aging has also been revealed. It has been shown that RAS interacts with the microbiome. At the same time, the opinion about the unequivocal oncoprotection of the ACE 2 (angiotensin-converting enzyme 2) / Ang (1-7) (angiotensin 1-7) / MasR (Mas receptors) axis seems to be not fully justified. The complexity of the structure of the RAS, its relationship with the kallikrein-kinin system and the complement system, the dynamic nature of the tumor process, and the extremely high phenotypic plasticity of tumor cells can lead to ambiguous effects on this system, which is confirmed by contradictory clinical data. In the experiment, a number of very encouraging results have already been obtained from the use of angiotensin II receptor blockers and ACE inhibitors in hepatocellular carcinoma, myeloid leukemia, prostate cancer, lung cancer, ovarian cancer, glioblastoma, and other tumors. Further research of the role of RAS in the mechanisms of tumor development opens up new opportunities for the use of drugs that affect this system in oncological practice.

Keywords: renin-angiotensin system, hallmarks of cancer, malignancy, inflammation

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РОЛЬ РЕНИН-АНГИОТЕНЗИНОВОЙ СИСТЕМЫ В МЕХАНИЗМАХ РАЗВИТИЯ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ В СВЕТЕ КОНЦЕПЦИИ D. HANAHAN И R. WEINBERG «КЛЮЧЕВЫЕ ПРИЗНАКИ РАКА» («THE HALLMARKS OF CANCER»)

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Резюме. В связи с появлением большого количества исследований, посвященных роли ренин-ангиотензиновой системы (РАС) в механизмах развития злокачественных опухолей, весьма актуальным представляется структурирование этих данных в рамках интегральной концепции D. Hanahan и R. Weinberg «The Hallmarks of Cancer» («Ключевые признаки рака»). Выясняется, что ренин-ангиотензиновая система играет существенную роль в генезе практически всех «ключевых признаков рака» в основном за счет активации оси АПФ (ангиотензин-превращающий фермент) / Анг II (ангиотензин II)/ATR1 (рецепторы ангиотензина II 1-го типа) и рецепторов ренина/проренина (PRR), усиливающих ассоциированное с опухолью воспаление. Первостепенную роль здесь играет активация транскрипционных факторов NF-κB и STAT-3. Кроме этого, за счет наличия рецепторов ангиотензина II на лимфоцитах и макрофагах, РАС может непосредственно участвовать в модулировании иммунного ответа. Локализация рецепторов внутриклеточной РАС на митохондриях позволяет этой системе участвовать и в изменении метаболизма опухолевых клеток. Выявлены и взаимосвязи РАС с механизмами клеточного старения. Показано, что РАС взаимодействует с микробиомом. В то же время мнение об однозначной онкопротективности оси АПФ2 (ангиотензин-превращающий фермент 2) / Анг (1-7) (ангиотензин 1-7) / MasR (Mas рецепторы) представляется не вполне оправданным упрощением. Сложность устройства РАС, ее взаимосвязи с калликреин-кининовой системой и системой комплемента, динамический характер опухолевого процесса и чрезвычайно высокая фенотипическая пластичность опухолевых клеток могут приводить к неоднозначным эффектам при воздействии на эту систему, что и подтверждается противоречивыми клиническими данными. В эксперименте уже получен ряд весьма обнадеживающих результатов применения блокаторов рецепторов ангиотензина II и ингибиторов АПФ при гепатоцеллюлярной карциноме, миелоидном лейкозе, раке простаты, раке легкого, раке яичника, глиобластоме и других опухолях. Дальнейшее изучение роли РАС в механизмах развития опухолей открывает новые возможности для применения лекарственных препаратов, влияющих на эту систему, в онкологической практике.

Ключевые слова: ренин-ангиотензиновая система, ключевые признаки рака, злокачественные опухоли, воспаление

INTRODUCTION

The study of mechanisms of carcinogenesis and progression of malignant tumors is still a very relevant and complex task in the XXI century. On the one hand, this is due to the high prevalence of oncological pathology and the high mortality rate from a number of oncological diseases [1]. On the other hand, paradoxically, this is due to the progress of oncology, characterized by an exponential accumulation of a huge amount of clinical and experimental data addressing various aspects of the tumor process. In particular, according to the bibliometric analysis, in the last decade, many publications have appeared investigating the role of the RAS (renin-angiotensin system) and drugs that block and inhibit individual links of this system in the mechanisms of cancer development [2, 3]. These data should be analysed in accordance with an integral concept, which can evaluate the role of the RAS in the development of oncological process and its progression. In our opinion, "The Hallmarks of Cancer" [4–7] can be used as such a concept.

BASIC PRINCIPLES OF THE CONCEPT "THE HALLMARKS OF CANCER"

A classic figure in Russian experimental oncology, L.M. Shabad, noted back in the first half of the XX century that "tumors represent a biological problem" and emphasized the importance of "characterizing the problem of tumors as a whole" [8]. As if to confirm his words, in 2000, the journal Cell published an article by two biologists studying oncology, Douglas Hanahan and Robert Weinberg, entitled "The Hallmarks of Cancer" [5]. Despite the trivial title the article was a conceptual work summarizing ideas about fundamental properties of malignant tumors and mechanisms underlying the acquisition and manifestation of these properties. Having generated a wide response (more than 50,000 citations and 118,000 downloads, according to the journal Cell, www.cell.com), and apparently meeting the expectations of many scientists, this work was continued in the form of two publications in 2011 and 2022 with the corresponding titles: "Hallmarks of cancer: The Next Generation" and "Hallmarks of Cancer: New Dimensions" [6, 7]. These publications caused no less wide resonance, including among domestic oncologists [9, 10]. It became possible to talk about a full-fledged scientific research program (in the sense that the outstanding philosopher of science I. Lakatos gave to this term [11, 12]), opening up prospects for studying the mechanisms of the tumor process and identifying new targets for antitumor therapy. From the point of view of pathophysiology, "The Hallmarks of Cancer" is a synthesis of the most significant studies and theories that reveal various aspects and mechanisms of the tumor process, and allows not only oncologists, but also doctors of other specialties to obtain a more multifaceted and structured understanding of this typical pathological process. Let us briefly consider the main provisions of the concept of D. Hanahan and R. Weinberg.

"The Hallmarks Of Cancer" are considered as a set of properties that are acquired by human cells during neoplastic transformation and tumor progression and are the most significant and common to all types of malignant tumors. Based on the results of three publications, the following were added to the list of hallmarks of cancer:

1) self-sufficiency in growth signals, due to the production of growth factors by the tumor and its microenvironment, increased expression of growth factor receptors, and activation of intracellular signaling pathways;
2) evading growth suppressors;
3) resisting cell death;
4) enabling replicative immortality;
5) support of angiogenesis and providing the access to the vessels;
6) invasive growth and metastasis;
7) reprogramming of cell metabolism, including the Warburg effect;
8) avoidance of immune destruction;
9) phenotypic plasticity of tumor cells;
10) presence of senescent cells both in the tumor itself and in its microenvironment.

Authors identified four main mechanisms, causing the development of the above-mentioned hallmarks (Fig. 1):

1) genomic instability and mutations that ensure self-sustaining growth, blockade of apoptosis, unlimited replication and, in general, are an important mechanism of tumor evolution;
2) inflammation that enhacnes angiogenesis, production of growth factors, genomic instability, avoidance of immune destruction, invasive growth and other manifestations of the tumor process;
3) non-mutational epigenetic reprogramming that ensures phenotypic plasticity of the tumor, in particular, the epithelial-mesenchymal transition, which is extremely important for metastasis;
4) a polymorphic microbiome, present not only in the gastrointestinal tract, but also in other barrier tissues, affecting the immune response, proliferative potential, inflammation, genomic instability and other properties of the tumor.

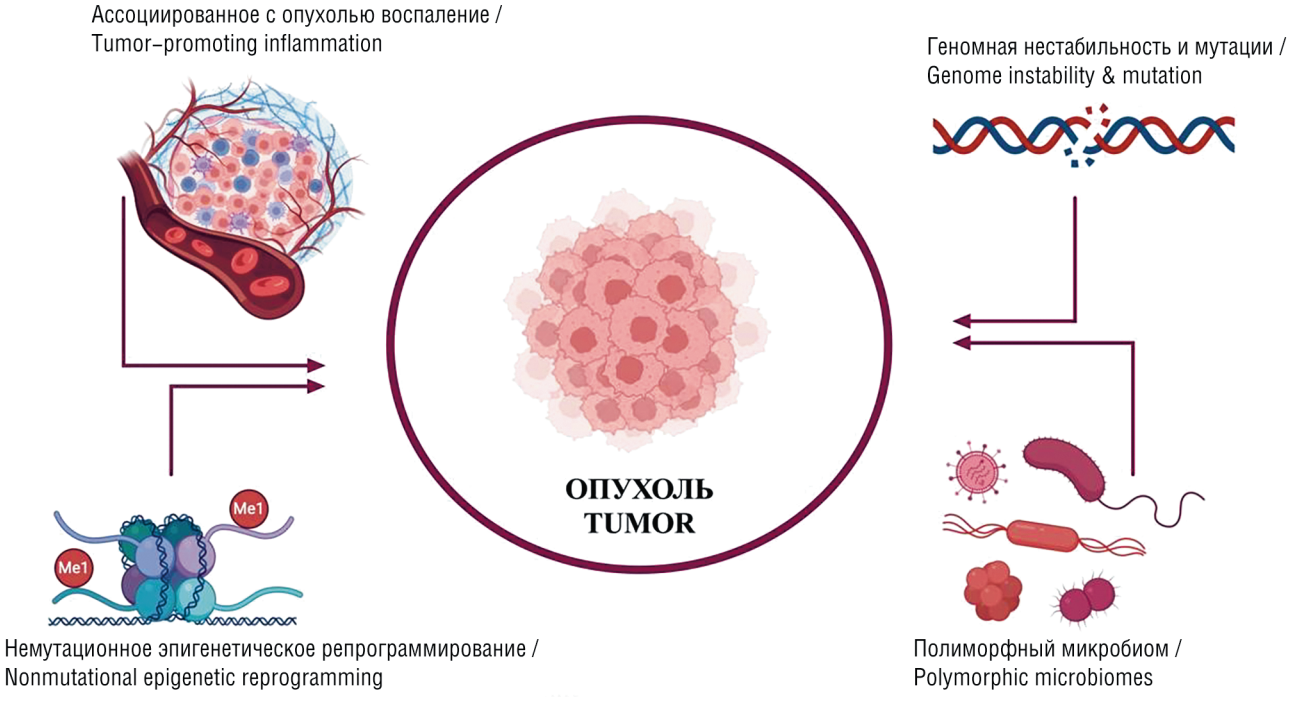

Fig. 1. The main mechanisms enabling the genesis of the hallmarks of cancer

Рис. 1. Основные механизмы, обусловливающие появление ключевых признаков рака

In contrast to reductionist ideas that view a tumor as a collection of relatively homogeneous cancer cells, according to the concept of D. Hanahan and R. Weinberg, a malignant tumor is viewed as a pathological organ [13], formed in the course of pathological evolution occurring inside the human body in tumor tissue and combining the principles of Darwinism and Lamarckism [14]. This organ conteins not only different cancer cells, showing very high phenotypic plasticity, but also cells of the so-called tumor microenvironment: tumor-associated fibroblasts, macrophages, immune cells, endothelium, pericytes, myeloid precursors, and senescent cells. A tumor reprograms tumor microenvironment cells, using them to increase proliferation, stimulate angiogenesis, avoid immune destruction, and facilitate invasive growth and metastasis [15]. Thus, the tumor behaves as a multicellular parasitic organ, using physiological regulatory mechanisms, such as epigenetic reprogramming, immune surveillance, aging, autophagy and a number of typical pathological processes, primarily chronic inflammation, especially its proliferative component, in its pathologically parasitic interests. The articles by D. Hanahan and R. Weinberg do not mention the RAS. However, a number of clinical and experimental data indicate a possible role of this system in the mechanisms of tumor growth and progression [16, 17]. It is appropriate to understand these data in light of the concept of “The Hallmarks of Cancer”.

BRIEF DESCRIPTION OF THE STRUCTURE AND FUNCTIONS OF THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system is a universal regulatory system of the body with both short-term and long-term, as well as systemic and local effects. Short-term systemic effects of RAS are associated with the regulation of Na^+ and water reabsorption in the kidneys, circulating blood volume and systemic arterial pressure, long-term effects are associated with changes in proliferative activity and apoptosis, angiogenesis, regulation of the immune response and inflammation. According to modern concepts, RAS is considered a multi-level and dual-axis system [18]. The synthesis of all its components is carried out both at the systemic level (renin in the juxtaglomerular apparatus of the kidneys, angiotensinogen in the liver, ACE (angiotensin-converting enzyme) in the vessels of the lungs) and at the local tissue level. A number of studies have shown that almost all components of RAS can be produced locally in various organs, including the heart, blood vessels, kidneys, liver, brain, pancreas, prostate, placenta, lungs, adipose tissue, eyes, etc. [19]. Some studies have also reported the presence of an intracellular RAS alongside the tissue RAS [20]. Intracellular synthesis and functional activity of AngII (angiotensin II), renin and other components of RAS were detected in a number of cells, including fibroblasts, vascular smooth

muscle cells, cardiomyocytes, kidney and adrenal cells, neurons [21–23]. Receptors such as ATR1 (angiotensin II receptors type 1), ATR2 (angiotensin II receptors type 2), MasR (angiotensin receptors (1–7)) are located not only on the plasma membrane of cells, but also intracellularly on the membrane of mitochondria, the cell nucleus, and in the sarcoplasmic reticulum [22, 24–26]. Thus, the structure of RAS can be described as following a fractal principle [27]. Tissue RAS regulates the blood supply to individual organs, are able to influence their structure, in particular, stimulate angiogenesis, fibroplasia, hypertrophy and hyperplasia processes, take an active part in the regulation of inflammation and modulate the activity of immune system cells, and influence the energy metabolism of cells [18, 20, 28]. Intracellular RAS plays a key role in regulating ion channels function, tissue (mitochondrial) respiration, mobilization of Ca from the sarcoplasmic reticulum, and secretion of extracellular matrix components [22]. While tissue RASs mainly work synergistically with circulatory RASs, intracellular RASs rather have buffering properties, counteracting excessive activation of one or another axis under physiological conditions [22].

Two axes are found in the RAS: the classical and alternative, which have opposite effects [19, 20, 21] (Fig.2). The classical axis is presented by well-known components: renin, which cleaves angiotensinogen to angiotensin I (Ang I); ACE, which converts Ang I to Ang II, and angiotensin

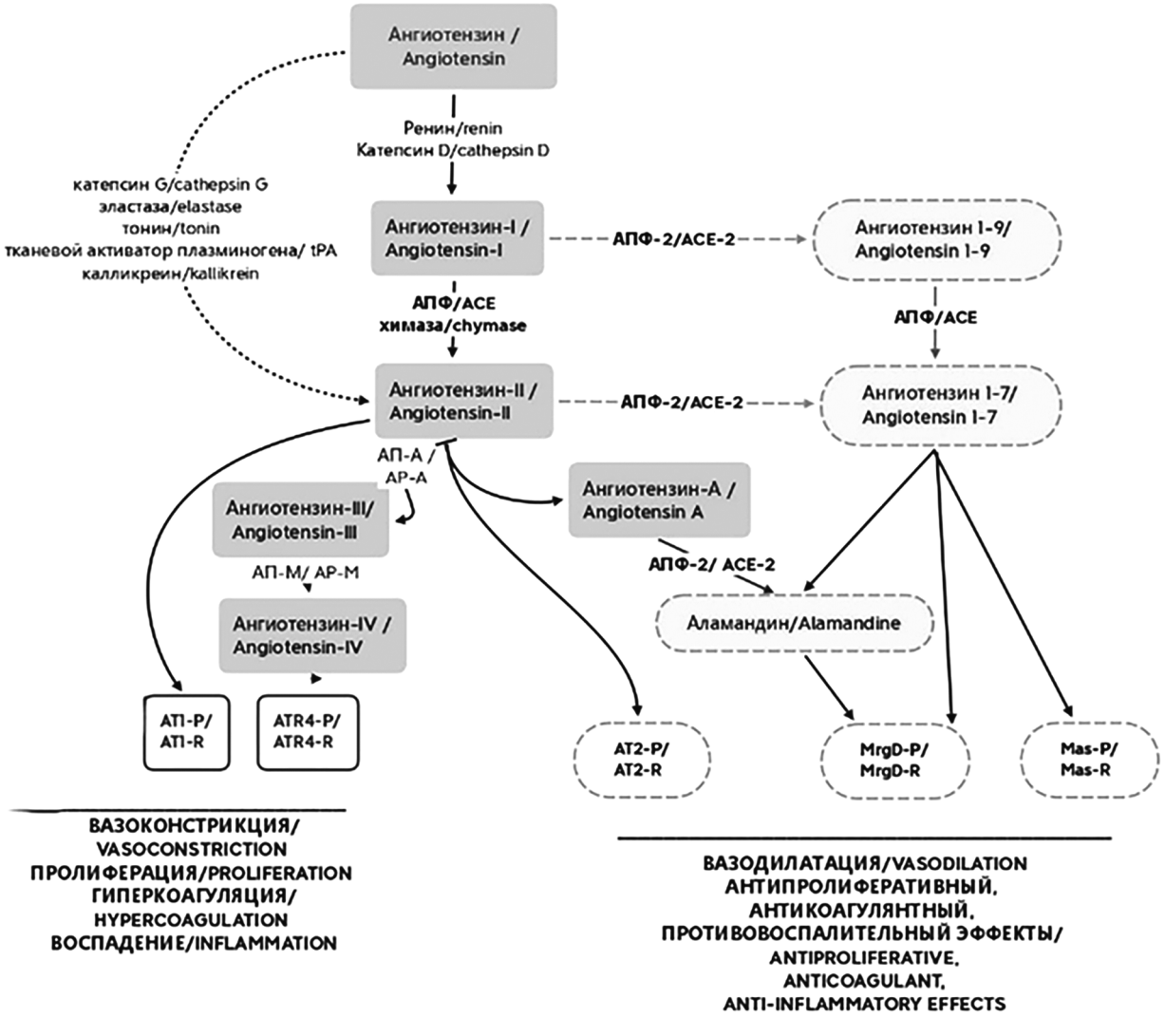

Fig. 2. **Diagram of the renin-angiotensin system: ACE, ACE-2 — angiotensin converting enzyme 2; AP-A — aminopeptidase A; AP-M — aminopeptidase-M; AT1,2,4 R — angiotensin receptors of the types 1,2,4 respectively; MasR — Mas-receptor; MrgdR — Mrgd-receptor**

Рис. 2. **Схема ренин-ангиотензиновой системы: АПФ, АПФ-2 — ангиотензин-превращающий фермент 2; АП-А — аминопептидаза А; АП-М — аминопептидаза М; AT1,2,4 Р — рецепторы к ангиотензину 1, 2 и 4-го типа соответственно; Mas-P — Mas-рецептор; Mrgd-P — Mrgd-рецептор**

II receptors (ATR1 and ATR2), which mediate opposite effects. It is important to note that in the adult body, ATR1 receptors predominate. Their activation causes vasoconstriction, Na retention, aldosterone secretion, increased sympathetic tone, cellular proliferation, inflammation, fibrosis, angiogenesis, and thrombosis. The classical axis also includes minor metabolites — Ang III and Ang IV. Ang III is formed from Ang II under the action of aminopeptidase A and has effects similar to those of Ang II mediated through the ATR1 and ATR2 receptors. Ang IV is formed from Ang III under the action of aminopeptidase M, binds to IRAP/ATR4 (insulin-regulated aminopeptidase receptor) and mediates pro-inflammatory effects (Fig. 2).

The key components of the alternative axis are ACE2 (angiotensin-converting enzyme 2), which converts Ang II into angiotensin (1-7) (Ang (1-7)). Ang-(1-7) interacts with MasR receptors, mediating effects such as: anti-inflammatory effects (due to decreased activity of the transcription factor NF-κB), vasodilation (due to increased NO production), reduced oxidative stress, decreased proliferative activity, reduced fibrosis, and antithrombotic effects [29, 30, 31]. Alamandine can be formed from Ang-(1-7), interacting with MrgD receptors, causing antiproliferative and vasodilating effects [32] (Fig. 2). In cardiology, the classical axis is conventionally considered cardiopathogenic, while the alternative axis is considered cardioprotective [18, 29, 32].

In addition, it is important to mention the presence of prorenin/renin receptors (PRR), expressed in the tissues of the cardiovascular system, brain, placenta, liver, kidneys, as well as on monocytes and T-lymphocytes. These receptors activate renin and mediating pro-inflammatory effects and proliferative signals by activating a number of signaling cascades (MAPK, ERK, Wnt) [33, 34].

The RAS is closely related to the kallikrein-kinin system and the complement system. ACE and ACE2 are both kininases that cleave bradykinin and des-Arg-bradykinin, respectively. Renin is capable of participating in the activation of the complement system. Thus, RAS is associated with the plasma sentinel polysystem, i.e. with plasma inflammatory mediators [35].

In pathological conditions, RAS imbalance is of great importance in the pathogenesis of arterial hypertension, heart failure, renal diseases, diabetes mellitus, obesity, and some infections, such as COVID-19 [19, 27, 36]. Drugs that inhibit RAS are among the most frequently prescribed in therapeutic, cardiological, and nephrological practice [37, 38].

THE ROLE OF RENIN-ANGIOTENSIN SYSTEM IN THE GENESIS OF "THE HALLMARKS OF CANCER"

According to the concept of D. Hanahan and R. Weinberg, one of the important driving mechanisms of malignant tumor growth is chronic inflammation. Rudolf Virchow, the founder of cellular pathology, was the first to note the possible relationship between inflammation and cancer [39, 40]. Subsequently, many researchers, including domestic ones [8, 41–43], studied this topic, revealing the ambiguity and complexity of the relationship between inflammation and tumor growth, noting that acute inflammation with pronounced alteration may rather play oncoprotective role, while chronic inflammation with a pronounced proliferative component can contribute to tumor progression.

The level of modern pathology allows us to evaluate molecular mechanisms of association between inflammation and tumor growth. S. Grivennikov et al. [44] highlight five aspects of the pathogenetic relationships between tumor growth and inflammation: 1) many inflammatory mediators and cytokines are growth and survival factors, stimulating the proliferation and survival of malignant cells; 2) inflammatory mediators, such as IL-1, activate oncogenic transcription factors NF-κB and STAT-3, while oncogenes such as Ras and Myc can, in turn, initiate an inflammatory response, enhancing the production of a number of cytokines, in particular IL-6; 3) tumor-associated inflammation can suppress the antitumor immune response and reprogram immune cells; 4) inflammation can induce angiogenesis; 5) inflammation can stimulate invasive growth and metastasis.

The imbalance of RAS in tumor tissue can be considered as one of the important mechanisms linking inflammation and tumor growth. The study of local expression of different RAS components, primaliry ATR1, has been carried out in more than 30 types of malignant tumors, including such common ones as colorectal cancer, gastric cancer, prostate cancer, breast cancer, ovarian cancer, and lung cancer [2]. It turned out that aberrant expression of RAS components, different from normal tissues, is characteristic of the vast majority of tumors studied. The imbalance of RAS components, detected both in tumor cells themselves and in tumor microenvironment cells (tumor-associated macrophages, fibroblasts, regulatory T-lymphocytes (Tregs), endothelial cells), usually leads to excessive activation of the ACE/Ang II/ATR1 axis and insufficient effects of the ACE2/Ang (1-7)/MasR axis [2, 17].

RAS receptors, such as ATR1, ATR2, MasR, and MrgD, belong to the family of G protein-coupled receptors (GPCRs). This is the largest family of signaling receptors, with about 900 types. GPCRs interact with various ligands: thrombin, endothelin, bombesin, gastrin, prostaglandin E2 (PGE2), thromboxane A2 (TxA2), Ang II and its derivatives, bradykinin, etc. [45]. Ligands of these receptors activate a number of intracellular signaling cascades, including mitogen-activated protein kinases (MAPKs). MAPKs regulate the activity of transcription factors and other regulatory proteins. This is accompanied by a change in the expression of the corresponding genes that regulate proliferative

activity, differentiation, migration, growth, apoptosis and cell survival both under physiological conditions and in various pathologies [46]. Activation of the ACE/Ang II/ATR1 axis stimulates some signaling pathways, leading to activation of transcription factors such as NF-κB and STAT-3 [17, 45, 47]. Moreover, stimulation of ATR1 leads to transactivation of epidermal growth factor receptors (EGFR) [16].

Activation of the transcription factor NF-κB leads to increased synthesis of angiogenesis stimulators — vascular endothelial growth factor (VEGF) and IL-8; growth factors — granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6; anti-apoptotic factors BCL-XL and c-FLIP; factors promoting invasive growth — MMP-2, MMP-7, MMP-9 (matrix metalloproteinases 2, 7 and 9, respectively), uPA (urokinase); inflammatory enzymes COX-2 (cyclooxygenase-2), LOX (lipoxygenase), iNOS (inducible nitric oxide synthase); chemokines CCL2, CCL20, IL-8; pro-inflammatory cytokines such as IL-1, IL-6, IL-23, TNFα, TGFβ (transforming growth factor β), EGF (epidermal growth factor); cell cycle regulators (cyclin D1, c-Myc); cell adhesion molecules (ICAM-1, ELAM-1, VCAM-17) [48]. NF-κB plays a key role in the mechanisms of inflammation and largely determines the pathogenetic links between inflammation and tumor growth. Its activation has been detected in more than 50% of all types of cancer [39, 44]. In an experimental model of hepatocellular carcinoma in mice induced by diethylnitrosamine, ATR1 inhibition suppressed tumor development by inactivating NF-κB [49].

At the same time, scientists also point to some antitumor effects of NF-κB, which are realized primarily in the cells of the immune system due to increased production of antitumor cytokines such as IL-12 and IFN-γ (interferon γ) [48]. In contrast to the ambivalent effects of NF-κB, activation of the transcription factor STAT-3, which can also be caused by stimulation of ATR1 receptors of the RAS [45], is considered to definitively enhance tumor growth, since in addition to stimulating the synthesis of cytokines, proangiogenic factors, growth factors and their receptors. It causes the expansion of Treg and Th17 (T-helper 17), thereby weakening the antitumor immune response [48].

Oxygen free radicals (OFR) and NO are important mediators of inflammation [50] and play a significant role in the pathogenetic relationships between inflammation and tumor growth. OFR and reactive nitrogen species produced by tumor cells and their microenvironment can damage DNA and disrupt its repair, increasing the genomic instability of tumor cells, modify oncoproteins, in particular p53, and inhibit apoptosis, cause epigenetic changes, suppress the immune response, and enhance angiogenesis and metastasis [48, 51, 52]. Ang II stimulates OFR production via ATR1 by activating NAD(P)H oxidases [53].

Thus, the RAS imbalance in tumor tissue and its microenvironment with the predominance of the effects of the Ang II/ATR1 axis enhacnes pathogenetically tumor-associated chronic inflammation. It results in tumor growth stimulation, decreased apoptosis, increased angiogenesis, reprogramming of the tumor microenvironment (immune cells, tumor-associated fibroblasts), increased collagen production, which causes hypoxia and activation of the transcription factor HIF (hypoxia-induced factor). This is important for both the inflammation progress and metabolism reprogramming of tumor cells, immune cells and increased angiogenesis.

Many researchers note the procarcinogenic role of ATR1 receptors and the oncoprotective role of ATR2, MasR, Mrgd, apparently largely using the analogy with their cardiopathogenic pro-inflammatory and cardioprotective anti-inflammatory properties, respectively [16, 17]. However, the first study demonstrating the involvement of GPCR in oncogenesis was published in 1986 and concerned the Mas oncogene (encoding MasR), the excessive activation of which caused tumor transformation in fibroblast cell culture and in “nude mice” [54, 55]. Although many modern researchers point to the oncoprotective role of the ACE2/Ang (1-7)/MasR axis, which reduces proliferation and enhacnes apoptosis [17], a number of publications indicate that activation of this and the related alamandin/MrgdR axis can enhance invasive growth and metastasis of renal cell carcinoma [56–58], non-small cell lung cancer [59, 60], and correlates with a poor prognosis in melanoma and breast cancer [61].

Prorenin/renin receptors (PRR) play a significant role in tumor development [17]. An increase in the expression of these receptors, correlating with the severity of tumor growth and progression, has been found in a number of tumors: pancreatic ductal adenocarcinoma [62], glioblastoma [63], breast cancer [64], colorectal cancer [65], endometrial cancer [66], and kidney tumors [67]. Stimulation of PRR is associated with activation of several intracellular signalling pathways (cascades), including PI3K/AKT/mTor and Wnt/β-catenin, which enhance tumor-associated inflammation and tumor cell proliferative activity [68]. Additionally, it was shown that intracellular PRR can enhance autophagy processes, which may be beneficial to the tumor as a protective mechanism against intracellular stress [67, 69]. In an *in vitro* experiment, the use of aliskiren resulted in a decrease in the proliferative activity of renal cell carcinoma cell lines [70].

A key feature of malignant tumors is the avoidance of immune destruction. The impact of RAS imbalance on the immune system can be both indirect and direct. The indirect effect is due to tumor-associated chronic inflammation, which contributes to a decrease in the activity of CTL (cytotoxic T lymphocyte) and NK (natural killer cells), the main weapon of antitumor defense, due to increased production of OFR, fibrosis (caused by increased production of TGF-β), hypoxia and acidosis [39, 71, 72]. The direct influence is

associated with the presence of ATR1 on T-lymphocytes and tumor-associated macrophages and fibroblasts and immunosuppressive effects carried out via the ACE/Ang II/ATR1 axis [73]. Activation of this axis also promotes the production of chemoattractants, in particular MCP-1 (monocyte chemoattractant), which promotes the recruitment of macrophages into the tumor microenvironment, enhancing tumor growth, angiogenesis and metastasis [2, 74, 75] and MDSCc (myeloid-derived suppressive cells), which suppress the antitumor immune response [52, 76]. In an experiment on mice, into which colorectal carcinoma cells with minimal expression of RAS components were transplanted, the administration of Ang II receptor blockers (ARBs) valsartan and candesartan increased the antitumor activity of T lymphocytes and reduced the immunosuppressive effects of MDSC, tumor-associated macrophages (TAM) and fibroblasts (CAF). The greatest effect was achieved by combination therapy of ARBs + PD-1/PD-L1 blockade (immune checkpoint blockade) [77].

According to D. Hanahan and R. Weinberg, an important driving mechanism of tumor growth is the polymorphic microbiome. In particular, it is known that *Helicobacter pylori* plays an important role in the development of gastric cancer, although the pathogenetic mechanisms of this influence are not entirely clear [78]. A number of studies have shown that *Helicobacter pylori* infection enhacnes the expression of tissue RAS components (Ang I, Ang II and its receptors, ACE) in the gastric mucosa in humans and experimentally in Mongolian gerbils, which leads to increased tumor growth and progression through the mechanisms described above [78, 79]. RAS imbalance with hyperactivation of the Ang II/ATR1 axis, in turn, can lead to changes in the gut microbiota, which affects the immune response and inflammation [80–83]. Thus, we can talk about a complex mutual influence of RAS and the microbiome [80].

One of the key features of cancer is the reprogramming of cellular metabolism. Intracellular RAS, due to the presence of ATR1 and ATR2 receptors on mitochondria, regulation of Ca release from the cytoplasmic reticulum, activation of oxidases and production of SCR, can play a significant role in the genesis of this feature [22, 25].

Cellular senescence, previously considered rather an oncoprotective mechanism, is now recognized as one of the key signs of cancer [7, 84]. The presence of senescent cells in a tumor and its microenvironment enhacnes tumor growth. An imbalance of RAS, increasing the production of SCR, reprogramming the work of mitochondria, can also participate in the genesis of this characteristic sign of tumors [53].

CONCLUSION

Thus, the RAS plays a significant role in pathogenesis of malignant tumors, directly or indirectly influencing the occurrence and development of almost all “hallmarks of cancer”. It appears that the most significant contribution to the mechanisms of tumor growth and progression is made by the pathogenetic relationship between RAS imbalance and tumor-associated chronic inflammation. At the same time, we need to take into account that inflammation is a typical pathological process and has the property of equifinality [50, 85], i.e. duplicated by the action of a whole complex of mediators, among which the components of RAS play an important, but not exclusive, role.

The use of pharmacological drugs that affect the RAS (ACE inhibitors, ARBs, prorenin receptor inhibitors) may prove effective in the complex therapy of tumors. A number of very encouraging results have already been obtained experimentally from the use of ARBs and ACE inhibitors in hepatocellular carcinoma [49], myeloid leukemia [86], prostate cancer [87], lung cancer [88], ovarian cancer [89], glioblastoma [90] and other tumors. However, data from clinical studies on the use of these drugs remain contradictory [2, 61, 91–96]. The complexity of the RAS structure: the presence of different receptors with multidirectional and often antagonistic effects, multi-level organisation (including the intracellular level); relationships with the kallikrein-kinin system and the complement system, and a number of other factors, including genetic features of the RAS and the tumor process in a particular patient, can lead to unexpected results when influencing this system. The concepts of the unambiguous oncogenicity and unambiguous oncoprotectiveness of the ACE/Ang II/ATR1 and ACE2/Ang-(1-7)/MasR axes, respectively, promoted by a number of researchers [17], also seem to be an oversimplification [36, 97, 98].

Further research in this area is needed to develop algorithms for the effective use of drugs that modulate RAS function in the context of personalized combination therapy for cancer patients.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования

и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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REFERENCES

1. Bray F., Ferlay J., Soerjomataram I., Siegel R.L., Torre L.A., Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424. DOI: 10.3322/caac.21492.
2. Jiang H., Tai Z., Chen Z., Zhu Q., Bao L. Clinical applicability of renin-angiotensin system inhibitors in cancer treatment. Am J Cancer Res. 2021;11(2):318–336.
3. Sipahi I., Debanne S.M., Rowland D.Y., Simon D.I., Fang J.C. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol. 2010;11:627–636. DOI: 10.1016/S1470-2045(10)70106-6.
4. Wegman-Ostrosky T., Soto-Reyes E., Vidal-Millán S., Sánchez-Corona J. The renin-angiotensin system meets the hallmarks of cancer. J Renin Angiotensin Aldosterone Syst. 2015;16(2):227–33. DOI: 10.1177/1470320313496858.
5. Hanahan D., Weinberg R.A. The hallmarks of cancer. Cell. 2000;100(1):57–70. DOI: 10.1016/s0092-8674(00)81683-9.
6. Hanahan D., Weinberg R.A. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74. DOI: 10.1016/j.cell.2011.02.013.
7. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022;12(1):31–46. DOI: 10.1158/2159-8290.CD-21-1059.
8. Shabad L.M. Essays on Experimental Oncology. Pod obshchey redaktsiey akademika A.I. Abrikosova. Izdatel'stvo Akademii Meditsinskikh Nauk SSSR; Moscow; 1947. (In Russian).
9. Imyanitov E.N. Fundamental Oncology in 2011: A Review of the Most Interesting Discoveries. Prakticheskaya onkologiya. 2012; 13(1):1–8. (In Russian).
10. Kiselev F.L. On the molecular mechanisms of tumor formation. Priroda. 2014;4:12–22. (In Russian).
11. Lakatos I. Falsification and methodology of research programs. Moscow: Academic project; 1995. (In Russian).
12. Yankina O.P. The concept of research programs in the philosophy of science of I. Lakatos. Vestnik PGGPU. Seriya № 3. Gumanitarnye i obshchestvennye nauki. 2022;2. Available at: https://cyberleninka.ru/article/n/kontseptsiya-nauchno-issledovatelskih-programm-v-filosofii-nauki-i-lakatosa (accessed: 22.05.2025). (In Russian).
13. Egeblad M. Nakasone E.S., Werb Z. Tumors as organs: complex tissues that interface with the entire organism. Dev. Cell. 2010;18:884–901.
14. Huang S. Tumor progression: Chance and necessity in Darwinian and Lamarckian somatic (mutationless) evolution. Progress in Biophysics and Molecular Biology. 2012;110(1):69–86. DOI: 10.1016/j.pbiomolbio.2012.05.001.
15. Polyak K., Haviv I., Campbell I.G. Co-evolution of tumor cells and their microenvironment. Trends Genet. 2009;25:30–38.
16. George A., Thomas W. & Hannan R. The renin-angiotensin system and cancer: old dog, new tricks. Nat Rev Cancer. 2010;10:745–759. DOI: 10.1038/nrc2945.
17. Hassani B., Attar Z., Firouzabadi N. The renin-angiotensin-aldosterone system (RAAS) signaling pathways and cancer: foes versus allies. Cancer Cell Int. 2023;23(1):254. DOI: 10.1186/s12935-023-03080-9.
18. Santos RAS., Oudit G.Y., Verano-Braga T., Canta G., Steckelings U.M., Bader M. The renin-angiotensin system: going beyond the classical paradigms. Am J Physiol Heart Circ Physiol. 2019;316(5):H958–H970. DOI: 10.1152/ajpheart.00723.2018.
19. Shestakova M.V. The role of the tissue renin-angiotensin-aldosterone system in the development of metabolic syndrome, diabetes mellitus and its vascular complications. Sakharnyy diabet. 2010;13(3):14–19. (In Russian). DOI: 10.14341/2072-0351-5481.
20. Fyhrquist F., Saijonmaa O. Renin-angiotensin system revisited. J Intern Med. 2008;264(3):224–36. DOI: 10.1111/j.1365-2796.2008.01981.x.
21. Kumar R., Thomas C.M., Yong Q.C., Chen W., Baker K.M. The intracrine renin-angiotensin system. Clin. Sci. 2012;123:273–284. DOI: 10.1042/CS20120089.
22. Labandeira-Garcia J.L., Valenzuela R., Costa-Besada M.A., Villar-Cheda B., Rodriguez-Perez A.I. The intracellular renin-angiotensin system: Friend or foe. Some light from the dopaminergic neurons. Prog Neurobiol. 2021;199:101919. DOI: 10.1016/j.pneurobio.2020.101919.
23. Re R.N. Role of intracellular angiotensin II. Am. J. Physiol. Heart Circ. Physiol. 2018;314:H766–H771. DOI: 10.1152/ajpheart.00632.2017.
24. Abadir P.M., Foster D.B., Crow M., Cooke C.A., Rucker J.J., Jain A., Smith B.J., Burks T.N., Cohn R.D., Fedarko N.S., Carey R.M., O'Rourke B., Walston J.D. Identification and characterization of a functional mitochondrial angiotensin system. Proc. Natl. Acad. Sci. U. S. A. 2011;108:14849–14854. DOI: 10.1073/pnas.1101507108.
25. Escobales N., Nunez R.E., Javadov S. Mitochondrial angiotensin receptors and cardioprotective pathways. Am. J. Physiol. Heart Circ. Physiol. 2019;316:H1426–H1438. DOI: 10.1152/ajpheart.00772.2018.
26. Li X.C., Zhu D., Zheng X., Zhang J., Zhuo J.L. Intratubular and intracellular renin-angiotensin system in the kidney: a unifying perspective in blood pressure control. Clin. Sci. 2018;132:1383–1401. DOI: 10.1042/CS20180121.
27. Zabezhinskiy M.M., Semenova A.A. The role of the renin-angiotensin-aldosterone system in the development of cardiovascular complications in Covid-19. Pediatr. 2023;14(1):99–118. (In Russian). DOI: 10.17816/PED14199-118.
28. Bader M., Ganten D. Update on tissue renin-angiotensin systems. J Mol Med (Berl). 2008;86(6):615–21. DOI: 10.1007/s00109-008-0336-0.

29. Santos R.A.S., Sampaio W.O., Alzamora A.C., Motta-Santos D., Alenina N., Bader M., Campagnole-Santos M.J. The ACE2/Angiotensin-(1-7)/MAS Axis of the renin-angiotensin system: focus on angiotensin-(1-7) Physiol. Rev. 2018;98:505–553. DOI: 10.1152/physrev.00023.2016.
30. Kostenis E., Milligan G., Christopoulos A., Sanchez-Ferrer C.F., Heringer-Walther S., Sexton P.M., Gembardt F., Kellett E., Martini L., Vanderheyden P., Schultheiss H.P., Walther T. G-protein-coupled receptor Mas is a physiological antagonist of the angiotensin II type 1 receptor. Circulation. 2005;111:1806–1813. DOI: 10.1161/01.CIR.0000160867.23556.7D.
31. Molaei A., Molaei E., Hayes A.W., Karimi G. Mas receptor: a potential strategy in the management of ischemic cardiovascular diseases. Cell Cycle. 2023;22(13):1654–1674. DOI: 10.1080/15384101.2023.2228089.
32. Hrenak J., Paulis L., Simko F. Angiotensin A/Alamandine/MrgD Axis: Another Clue to Understanding Cardiovascular Pathophysiology. Int J Mol Sci. 2016;17(7):1098. DOI: 10.3390/ijms17071098.
33. Nguyen G., Burcklé C.A., Sraer J.D. Renin/prorenin-receptor biochemistry and functional significance. Curr Hypertens Rep. 2004;6(2):129–32. DOI: 10.1007/s11906-004-0088-3.
34. Nguyen G. Renin/prorenin receptors. Kidney Int. 2006;69(9):1503–6. DOI: 10.1038/sj.ki.5000265.
35. Bekassy Z., Lopatko Fagerström I., Bader M., Karpman D. Crosstalk between the renin-angiotensin, complement and kallikrein-kinin systems in inflammation. Nat Rev Immunol. 2022;22(7):411–428. DOI: 10.1038/s41577-021-00634-8.
36. Smith G.R. Angiotensin and systems thinking: wrapping your mind around the big picture. Ochsner J. 2013;13(1):11–25.
37. Maksimov M.L. Modern rational combination therapy in the treatment of patients with arterial hypertension. RMZh. 2014;6:423. (In Russian).
38. Mancia G., Kreutz R., Brunström M., Burnier M., Grassi G., Januszewicz A., Muiesan M.L. et al. 2023 ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). Journal of Hypertension. 2023;41(12):1874–2071. DOI: 10.1097/HJH.0000000000003480.
39. Grivennikov S.I., Greten F.R., Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883–99. DOI: 10.1016/j.cell.2010.01.025.
40. Virchow R. Die Krankhaften Geschwülste. Vols. I-III, [all published]. Berlin: August Hirschwald, 1863–1867.
41. Garshin V.G. Inflammatory growths of the epithelium, their biological significance and relation to the problem of cancer. Medgiz; 1939. (In Russian).
42. Zabezhinskiy M.A. Effect of nonspecific tissue damage on carcinogenesis (experimental morphological study). PhD thesis. Leningrad; 1987. (In Russian).
43. Monastyrskaya B.I. On the role of inflammation in the genesis of experimental skin cancer. MD dissertation. Leningrad. 1945. (In Russian).
44. Grivennikov S.I., Karin M. Inflammation and oncogenesis: a vicious connection. Curr Opin Genet Dev. 2010;20(1):65–71. DOI: 10.1016/j.gde.2009.11.004.
45. Chaudhary P.K., Kim S. An Insight into GPCR and G-Proteins as Cancer Drivers. Cells. 2021;10(12):3288. DOI: 10.3390/cells10123288.
46. Shurygina I.A., Shurygin M.G., Zelenin N.V., Granina G.B. The role of map kinase mechanisms in the regulation of cell growth (literature review). BMZh. 2009;6. Available at: https://cyberleninka.ru/article/n/rol-map-kinaznyh-mehanizmov-v-regulyatsii-kletochnogo-rosta-obzor-literatury (accessed: 29.01.2025). (In Russian).
47. Imai N., Hashimoto T., Kihara M. et al. Roles for host and tumor angiotensin II type 1 receptor in tumor growth and tumor-associated angiogenesis. Lab Invest. 2007;87:189–198.
48. Multhoff G., Molls M., Radons J. Chronic inflammation in cancer development. Front Immunol. 2012;2:98. DOI: 10.3389/fimmu.2011.00098.
49. Saber S., Mahmoud AAA., Goda R., Helal N.S., El-Ahwany E., Abdelghany R.H. Perindopril, fosinopril and losartan inhibited the progression of diethylnitrosamine-induced hepatocellular carcinoma in mice via the inactivation of nuclear transcription factor kappa-B. Toxicol Lett. 2018;295:32–40. DOI: 10.1016/j.toxlet.2018.05.036.
50. Vasiliev A.V., Vlasov T.D., Galagudza M.M., red. Pathophysiology. Typical pathological processes and conditions. Uchebnik dlya studentov meditsinskikh vuzov. Saint Petersburg: SPbGPMU; 2023. (In Russian).
51. Tyrtova L.V., Skobeleva K.V., Il'chenko M.S., Holopova M.S. Adrenocortical adenoma as a cause of hyperandrogenism syndrome in girls: a path to diagnosis. Medicine: Theory and Practice. 2024;9(2):79–88. (In Russian). DOI: 10.56871/MTP.2024.37.58.009.
52. Colotta F., Allavena P., Sica A., Garlanda C., Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009;30:1073–1081. DOI: 10.1093/carcin/bgp127.
53. de Cavanagh E.M., Piotrkowski B., Fraga C.G. Concerted action of the renin-angiotensin system, mitochondria, and antioxidant defenses in aging. Mol Aspects Med. 2004;25(1-2):27–36. DOI: 10.1016/j.mam.2004.02.006.
54. Arang N., Gutkind J.S. G Protein-Coupled receptors and heterotrimeric G proteins as cancer drivers. FEBS Lett. 2020;594(24):4201–4232. DOI: 10.1002/1873-3468.14017.
55. Young D., Waitches G., Birchmeier C., Fasano O., Wigler M. Isolation and characterization of a new cellular oncogene encoding a protein with multiple potential transmembrane domains. Cell. 1986;45(5):711–9. DOI: 10.1016/0092-8674(86)90785-3.
56. Kogan M.I., Akhokhov Z.M., Chernogubova E.A., Gusev A.A., Oytova Z.Kh. Renin-angiotensin system: role in the development and progression of renal cell carcinoma (literature review). Onkourologiya. 2019;15(3):143–149. (In Russian). DOI: 10.17650/1726-9776-2019-15-3-143-149.
57. Larrinaga G., Valdivia A., Arrieta-Aguirre I., Solano-Iturri J.D., Ugalde-Olano A., Loizaga-Iriarte A., Santos-Martín A., Pérez-Fernández A., Angulo J.C., López J.I. The Expression of Alamandine Receptor MrgD in Clear Cell Renal Cell Carcinoma Is Associated with a Worse Prognosis and Unfavorable Response to Antiangiogenic Therapy. Int J Mol Sci. 2024;25(3):1499. DOI: 10.3390/ijms25031499.

58. Zheng S., Yang Y., Song R., Yang X., Liu H., Ma Q., Yang L., Meng R., Tao T., Wang S., He J. Ang-(1-7) promotes the migration and invasion of human renal cell carcinoma cells via Mas-mediated AKT signaling pathway. Biochem Biophys Res Commun. 2015;460(2):333–40. DOI: 10.1016/j.bbrc.2015.03.035.
59. Li Z., Xie Y., Zhong T., Zhang X., Dang Y., Gan T., Chen G. Expression and clinical contribution of MRGD mRNA in non-small cell lung cancers. J. BUON. 2015;20:1101–1106.
60. Nishimura S., Uno M., Kaneta Y., Fukuchi K., Nishigohri H., Hasegawa J., Komori H., Takeda S., Enomoto K., Nara F. et al. MRGD, a MAS-related G-protein coupled receptor, promotes tumorigenesis and is highly expressed in lung cancer. PLoS ONE. 2012;7:e38618. DOI: 10.1371/journal.pone.0038618.
61. Yang J., Yang X., Gao L., Zhang J., Yi C., Huang Y. The role of the renin-angiotensin system inhibitors in malignancy: a review. Am J Cancer Res. 2021;11(3):884–897.
62. Shibayama Y., Fujimori T., Nguyen G., Hirose T., Totsune K., Ichihara A., Kitada K., Nakano D., Kobori H., Kohno M. et al. (Pro)renin receptor is crucial for Wnt/β-catenin-dependent genesis of pancreatic ductal adenocarcinoma. Sci. Rep. 2015;5:8854. DOI: 10.1038/srep08854.
63. Kouchi M., Shibayama Y., Ogawa D., Miyake K., Nishiyama A., Tamiya T. (Pro)renin receptor is crucial for glioma development via the Wnt/beta-catenin signaling pathway. J. Neurosurg. 2017;127:819–828. DOI: 10.3171/2016.9.JNS16431.
64. Ohba K., Suzuki T., Nishiyama H., Kaneko K., Hirose T., Totsune K., Sasano H., Takahashi K. Expression of (pro)renin receptor in breast cancers and its effect on cancer cell proliferation. Biomed. Res. 2014;35:117–126. DOI: 10.2220/biomedres.35.117.
65. Wang J., Shibayama Y., Zhang A., Ohsaki H., Asano E., Suzuki Y., Kushida Y., Kobara H., Masaki T., Wang Z. et al. (Pro)renin receptor promotes colorectal cancer through the Wnt/beta-catenin signalling pathway despite constitutive pathway component mutations. Br. J. Cancer. 2019;120:229–237. DOI: 10.1038/s41416-018-0350-0.
66. Delforce S.J., Lumbers E.R., De Meaultsart C.C., Wang Y., Proietto A., Otton G., Scurry J., Verrills N.M., Scott R.J., Pringle K.G. Expression of rennin-angiotensin system (RAS) components in endometrial cancer. Endocr. Connect. 2017;6:9–19. DOI: 10.1530/EC-16-0082.
67. Solano-Iturri J.D., Echevarría E., Unda M., Loizaga-Iriarte A., Pérez-Fernández A., Angulo J.C., López J.I., Larrinaga G. Clinical Implications of (Pro)renin Receptor (PRR) Expression in Renal Tumours. Diagnostics (Basel). 2021;11(2):272. DOI: 10.3390/diagnostics11020272.
68. Wang J., Nishiyama A., Matsuyama M., Wang Z., Yuan Y. The (pro)renin receptor: a novel biomarker and potential therapeutic target for various cancers. Cell Commun. Signal. 2020;18:1–13. DOI: 10.1186/s12964-020-0531-3.
69. Ohba K., Endo M., Sato S., Kashio-Yokota Y., Hirose T., Takahashi K. (Pro)renin receptor/ATP6AP2 is required for autophagy and regulates proliferation in lung adenocarcinoma cells. Genes Cells. 2020;25:782–795. DOI: 10.1111/gtc.12812.
70. Hu J., Zhang L.-C., Song X., Lu J.-R., Jin Z. KRT6 interacting with notch1 contributes to progression of renal cell carcinoma, and aliskiren inhibits renal carcinoma cell lines proliferation in vitro. Int. J. Clin. Exp. Pathol. 2015;8:9182–9188.
71. Dementieva E.A., Gurina O.P. Immunological changes accompanying the development of the experimental neoplastic process. Pediatr. 2015;6(2):96–108. (In Russian).
72. Vallejo-Ardila D.L., Fifis T., Burrell L.M., Walsh K., Christophi C. Renin-angiotensin inhibitors reprogram tumor immune microenvironment: A comprehensive view of the influences on anti-tumor immunity. Oncotarget. 2018;9(84):35500–35511. DOI: 10.18632/oncotarget.26174.
73. Crowley S.D., Rudemiller N.P. Immunologic Effects of the Renin-Angiotensin System. J Am Soc Nephrol. 2017;28(5):1350–1361. DOI: 10.1681/ASN.2016101066.
74. Condeelis J., Pollard J.W. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell. 2006;124:263–266. DOI: 10.1016/j.cell.2006.01.007.
75. Cortez-Retamozo V., Etzrodt M., Newton A. et al. Angiotensin II drives the production of tumor-promoting macrophages. Immunity. 2013;38:296–308.
76. Malekov D.A., Pozdnyakov A.V., Sotnikova E.A., Kanina L.Ya., Malekova D.V., Zvereva E.A. Disseminated lymphangiomatosis. A clinical case. Visualization in Medicine. 2021;3(1):41–50. (In Russian).
77. Nakamura K., Yaguchi T., Ohmura G., Kobayashi A., Kawamura N., Iwata T., Kiniwa Y., Okuyama R., Kawakami Y. Involvement of local renin-angiotensin system in immunosuppression of tumor microenvironment. Cancer Sci. 2018;109(1):54–64. DOI: 10.1111/cas.13423.
78. Sugimoto M., Yamaoka Y., Shirai N., Furuta T. Role of renin-angiotensin system in gastric oncogenesis. J Gastroenterol Hepatol. 2012;27(3):442–51. DOI: 10.1111/j.1440-1746.2011.06964.x.
79. Kinoshita J., Fushida S., Harada S., Yagi Y., Fujita H., Kinami S., Ninomiya I., Fujimura T., Kayahara M., Yashiro M., Hirakawa K., Ohta T. Local angiotensin II-generation in human gastric cancer: correlation with tumor progression through the activation of ERK1/2, NF-kappaB and survivin. Int J Oncol. 2009;34(6):1573–82. DOI: 10.3892/ijo_00000287.
80. Jaworska K., Koper M., Ufnal M. Gut microbiota and renin-angiotensin system: a complex interplay at local and systemic levels. Am J Physiol Gastrointest Liver Physiol. 2021;321(4):G355-G366. DOI: 10.1152/ajpgi.00099.2021.
81. Santisteban M.M., Qi Y., Zubcevic J. et al. Hypertension-linked pathophysiological alterations in the gut. Circ Res. 2017;120(2):312–323. DOI: 10.1161/circresaha.116.309006.
82. Yan D., Sun Y., Zhou X., Si W., Liu J., Li M., Wu M. Regulatory effect of gut microbes on blood pressure. Animal Model Exp Med. 2022;5(6):513–531. DOI: 10.1002/ame2.12233.
83. Yang T., Santisteban M.M., Rodriguez V. et al. Gut dysbiosis is linked to hypertension. Hypertension. 2015;65(6):1331–1340. DOI: 10.1161/hypertensionaha.115.05315.
84. Domen A., Deben C., Verswyvel J., Flieswasser T., Prenen H., Peeters M., Lardon F., Wouters A. Cellular senescence in cancer: clinical detection and prognostic implications. J Exp Clin Cancer Res. 2022;41(1):360. DOI: 10.1186/s13046-022-02555-3.

85. Churilov L.P. General pathophysiology (with the basics of immunopathology). Uchebnik dlya studentov medvuzov. 5-e Izd. Saint Petersburg: ELBI-SPb; 2015. (In Russian).
86. Ghasemi M., Okay M., Turk S., Naeemaee R., Guver E., Malkan U.Y., Aksu S., Sayinalp N., Haznedaroglu I.C. The impact of At1r inhibition via losartan on the anti-leukaemic effects of doxorubicin in acute myeloid leukaemia. J Renin Angiotensin Aldosterone Syst. 2019;20(2):1470320319851310. DOI: 10.1177/1470320319851310.
87. Uemura H., Ishiguro H., Nakaigawa N., Nagashima Y., Miyoshi Y., Fujinami K., Sakaguchi A., Kubota Y. Angiotensin II receptor blocker shows antiproliferative activity in prostate cancer cells: a possibility of tyrosine kinase inhibitor of growth factor. Mol Cancer Ther. 2003;2(11):1139–47.
88. Kawabata A., Baoum A., Ohta N., Jacquez S., Seo G.M., Berkland C., Tamura M. Intratracheal administration of a nanoparticle-based therapy with the angiotensin II type 2 receptor gene attenuates lung cancer growth. Cancer Res. 2012;72(8):2057–67. DOI: 10.1158/0008-5472.CAN-11-3634.
89. Zhao Y. et al. Losartan treatment enhances chemotherapy efficacy and reduces ascites in ovarian cancer models by normalizing the tumor stroma. Proceedings of the National Academy of Sciences, 2019;116(6): 210–2219.
90. Chang Y.L., Chou C.H., Li Y.F. et al. Antiproliferative and apoptotic effects of telmisartan in human glioma cells. Cancer Cell Int. 2023;23:111. DOI: 10.1186/s12935-023-02963-1.
91. Baranova E.I. Antihypertensive therapy with angiotensin II receptor antagonists and the risk of developing malignant neoplasms. Arterial'naya gipertenziya. 2012;18(5):375–384. (In Russian).
92. Isobe A., Takeda T., Sakata M., Miyake A., Yamamoto T., Minekawa R., Nishimoto F., Oskamoto Y., Walker C.L., Kimura T. Dual repressive effect of angiotensin II-type 1 receptor blocker telmisartan on angiotensin II-induced and estradiol-induced uterine leiomyoma cell proliferation. Hum Reprod. 2008;23(2):440–6. DOI: 10.1093/humrep/dem247.
93. Khoshghamat N., Jafari N., Toloue-Pouya V., Azami S., Mirnourbakhsh S.H., Khazaei M., Ferns G.A., Rajabian M., Avan A. The therapeutic potential of renin-angiotensin system inhibitors in the treatment of pancreatic cancer. Life Sci. 2021;270:119118. DOI: 10.1016/j.lfs.2021.119118.
94. Morris Z.S., Saha S., Magnuson W.J., Morris B.A., Borkenhagen J.F., Ching A., Hirose G., McMurry V., Francis D.M., Harari P.M., Chappell R., Tsuji S., Ritter M.A. Increased tumor response to neoadjuvant therapy among rectal cancer patients taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Cancer. 2016;122:2487–2495. DOI: 10.1002/cncr.30079.
95. Perdomo-Pantoja A., Mejía-Pérez S.I., Gómez-Flores-Ramos L. et al. Renin angiotensin system and its role in biomarkers and treatment in gliomas. J Neurooncol. 2018;138:1–15. DOI: 10.1007/s11060-018-2789-5.
96. Zhang R., Yin H., Yang M., Liu J., Zhen D., Zhang Z. Advanced progress of the relationship between renin-angiotensin-aldosterone system inhibitors and cancers. J Hypertens. 2024;42(11):1862–1873. DOI: 10.1097/HJH.0000000000003836.
97. Sobczuk P., Szczylik C., Porta C., Czarnecka A.M. Renin angiotensin system deregulation as renal cancer risk factor. Oncol Lett. 2017;14(5):5059–5068. DOI: 10.3892/ol.2017.6826.
98. Xu J., Fan J., Wu F., Huang Q., Guo M., Lv Z., Han J., Duan L., Hu G., Chen L., Liao T., Ma W., Tao X., Jin Y.. The ACE2/Angiotensin-(1-7)/Mas Receptor Axis: Pleiotropic Roles in Cancer. Front Physiol. 2017;8:276. DOI: 10.3389/fphys.2017.00276.

ЛИТЕРАТУРА

1. Bray F., Ferlay J., Soerjomataram I., Siegel R.L., Torre L.A., Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424. DOI: 10.3322/caac.21492.
2. Jiang H., Tai Z., Chen Z., Zhu Q., Bao L. Clinical applicability of renin-angiotensin system inhibitors in cancer treatment. Am J Cancer Res. 2021;11(2):318–336.
3. Sipahi I., Debanne S.M., Rowland D.Y., Simon D.I., Fang J.C. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol. 2010;11:627–636. DOI: 10.1016/S1470-2045(10)70106-6.
4. Wegman-Ostrosky T., Soto-Reyes E., Vidal-Millán S., Sánchez-Corona J. The renin-angiotensin system meets the hallmarks of cancer. J Renin Angiotensin Aldosterone Syst. 2015;16(2):227–33. DOI: 10.1177/1470320313496858.
5. Hanahan D., Weinberg R.A. The hallmarks of cancer. Cell. 2000;100(1):57–70. DOI: 10.1016/s0092-8674(00)81683-9.
6. Hanahan D., Weinberg R.A. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74. DOI: 10.1016/j.cell.2011.02.013.
7. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022;12(1):31–46. DOI: 10.1158/2159-8290.CD-21-1059.
8. Шабад Л.М. Очерки экспериментальной онкологии. Под общей редакцией академика А.И. Абрикосова. Издательство Академии Медицинских Наук СССР. М.; 1947.
9. Имянитов Е.Н. Фундаментальная онкология в 2011 году. Обзор наиболее интересных открытий. Практическая онкология. 2012; 13(1):1–8.
10. Киселев Ф.Л. О молекулярных механизмах возникновения опухолей. Природа. 2014;4:12–22.
11. Лакатос И. Фальсификация и методология научно-исследовательских программ. М.: Академический проект; 1995.
12. Янкина О.П. Концепция научно-исследовательских программ в философии науки И. Лакатоса. Вестник ПГГПУ. Серия № 3. Гуманитарные и общественные науки. 2022;2. Доступно по: https://cyberleninka.ru/article/n/kontseptsiya-nauchno-issledovatelskih-programm-v-filosofii-nauki-i-lakatosa (дата обращения: 22.05.2025).
13. Egeblad M. Nakasone E.S., Werb Z. Tumors as organs: complex tissues that interface with the entire organism. Dev Cell. 2010;18: 884–901.
14. Huang S. Tumor progression: Chance and necessity in Darwinian and Lamarckian somatic (mutationless) evolution. Progress in Biophysics and Molecular Biology. 2012;110(1):69–86. DOI: 10.1016/j.pbiomolbio.2012.05.001.

15. Polyak K., Haviv I., Campbell I.G. Co-evolution of tumor cells and their microenvironment. Trends Genet. 2009;25:30–38.
16. George A., Thomas W. & Hannan R. The renin–angiotensin system and cancer: old dog, new tricks. Nat Rev Cancer. 2010;10:745–759. DOI: 10.1038/nrc2945.
17. Hassani B., Attar Z., Firouzabadi N. The renin-angiotensin-aldosterone system (RAAS) signaling pathways and cancer: foes versus allies. Cancer Cell Int. 2023;23(1):254. DOI: 10.1186/s12935-023-03080-9.
18. Santos RAS., Oudit G.Y., Verano-Braga T., Canta G., Steckelings U.M., Bader M. The renin-angiotensin system: going beyond the classical paradigms. Am J Physiol Heart Circ Physiol. 2019;316(5):H958–H970. DOI: 10.1152/ajpheart.00723.2018.
19. Шестакова М.В. Роль тканевой ренин-ангиотензин-альдостероновой системы в развитии метаболического синдрома, сахарного диабета и его сосудистых осложнений. Сахарный диабет. 2010;13(3):14–19. DOI: 10.14341/2072-0351-5481.
20. Fyhrquist F., Saijonmaa O. Renin-angiotensin system revisited. J Intern Med. 2008;264(3):224–36. DOI: 10.1111/j.1365-2796.2008.01981.x.
21. Kumar R., Thomas C.M., Yong Q.C., Chen W., Baker K.M. The intracrine renin-angiotensin system. Clin. Sci. 2012;123:273–284. DOI: 10.1042/CS20120089.
22. Labandeira-Garcia J.L., Valenzuela R., Costa-Besada M.A., Villar-Cheda B., Rodriguez-Perez A.I. The intracellular renin-angiotensin system: Friend or foe. Some light from the dopaminergic neurons. Prog Neurobiol. 2021;199:101919. DOI: 10.1016/j.pneurobio.2020.101919.
23. Re R.N. Role of intracellular angiotensin II. Am. J. Physiol. Heart Circ. Physiol. 2018;314:H766–H771. DOI: 10.1152/ajpheart.00632.2017.
24. Abadir P.M., Foster D.B., Crow M., Cooke C.A., Rucker J.J., Jain A., Smith B.J., Burks T.N., Cohn R.D., Fedarko N.S., Carey R.M., O'Rourke B., Walston J.D. Identification and characterization of a functional mitochondrial angiotensin system. Proc. Natl. Acad. Sci. U. S. A. 2011;108:14849–14854. DOI: 10.1073/pnas.1101507108.
25. Escobales N., Nunez R.E., Javadov S. Mitochondrial angiotensin receptors and cardioprotective pathways. Am J Physiol Heart Circ Physiol. 2019;316:H1426–H1438. DOI: 10.1152/ajpheart.00772.2018.
26. Li X.C., Zhu D., Zheng X., Zhang J., Zhuo J.L. Intratubular and intracellular renin-angiotensin system in the kidney: a unifying perspective in blood pressure control. Clin. Sci. 2018;132:1383–1401. DOI: 10.1042/CS20180121.
27. Забежинский М.М., Семенова А.А. Роль ренин-ангиотензин-альдостероновой системы в развитии сердечно-сосудистых осложнений при Covid-19. Педиатр. 2023;14(1):99–118. DOI: 10.17816/PED14199-118.
28. Bader M., Ganten D. Update on tissue renin-angiotensin systems. J Mol Med (Berl). 2008;86(6):615–21. DOI: 10.1007/s00109-008-0336-0.
29. Santos R.A.S., Sampaio W.O., Alzamora A.C., Motta-Santos D., Alenina N., Bader M., Campagnole-Santos M.J. The ACE2/Angiotensin-(1-7)/MAS Axis of the renin-angiotensin system: focus on angiotensin-(1-7) Physiol. Rev. 2018;98:505–553. DOI: 10.1152/physrev.00023.2016.
30. Kostenis E., Milligan G., Christopoulos A., Sanchez-Ferrer C.F., Heringer-Walther S., Sexton P.M., Gembardt F., Kellett E., Martini L., Vanderheyden P., Schultheiss H.P., Walther T. G-protein-coupled receptor Mas is a physiological antagonist of the angiotensin II type 1 receptor. Circulation. 2005;111:1806–1813. DOI: 10.1161/01.CIR.0000160867.23556.7D.
31. Molaei A., Molaei E., Hayes A.W., Karimi G. Mas receptor: a potential strategy in the management of ischemic cardiovascular diseases. Cell Cycle. 2023;22(13):1654–1674. DOI: 10.1080/15384101.2023.2228089.
32. Hrenak J., Paulis L., Simko F. Angiotensin A/Alamandine/MrgD Axis: Another Clue to Understanding Cardiovascular Pathophysiology. Int J Mol Sci. 2016;17(7):1098. DOI: 10.3390/ijms17071098.
33. Nguyen G., Burcklé C.A., Sraer J.D. Renin/prorenin-receptor biochemistry and functional significance. Curr Hypertens Rep. 2004;6(2):129–32. DOI: 10.1007/s11906-004-0088-3.
34. Nguyen G. Renin/prorenin receptors. Kidney Int. 2006;69(9):1503–6. DOI: 10.1038/sj.ki.5000265.
35. Bekassy Z., Lopatko Fagerström I., Bader M., Karpman D. Crosstalk between the renin-angiotensin, complement and kallikrein-kinin systems in inflammation. Nat Rev Immunol. 2022;22(7):411–428. DOI: 10.1038/s41577-021-00634-8.
36. Smith G.R. Angiotensin and systems thinking: wrapping your mind around the big picture. Ochsner J. 2013;13(1):11–25.
37. Максимов М.Л. Современная рациональная комбинированная терапия в лечении пациентов с артериальной гипертензией. РМЖ. 2014;6:423.
38. Mancia G., Kreutz R., Brunström M., Burnier M., Grassi G., Januszewicz A., Muiesan M.L. et al. 2023 ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). Journal of Hypertension. 2023;41(12):1874–2071. DOI: 10.1097/HJH.0000000000003480.
39. Grivennikov S.I., Greten F.R., Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883–99. DOI: 10.1016/j.cell.2010.01.025.
40. Virchow R. Die Krankhaften Geschwülste. Vols. I-III, [all published]. Berlin: August Hirschwald, 1863–1867.
41. Гаршин В.Г., Воспалительные разрастания эпителия, их биологическое значение и отношение к проблеме рака. Медгиз.1939.
42. Забежинский М.А., Влияние неспецифического повреждения тканей на канцерогенез (экспериментально-морфологическое исследование). Автореф. дис. … д-ра мед. наук. Ленинград; 1987.
43. Монастырская Б.И. О роли воспаления в генезе экспериментального рака кожи. Дис. … д-ра мед. наук. Л.; 1945.
44. Grivennikov S.I., Karin M. Inflammation and oncogenesis: a vicious connection. Curr Opin Genet Dev. 2010;20(1):65–71. DOI: 10.1016/j.gde.2009.11.004.
45. Chaudhary P.K., Kim S. An Insight into GPCR and G-Proteins as Cancer Drivers. Cells. 2021;10(12):3288. DOI: 10.3390/cells10123288.
46. Шурыгина И.А., Шурыгин М.Г., Зеленин Н.В., Гранина Г.Б. Роль мар-киназных механизмов в регуляции клеточного роста (обзор литературы). БМЖ. 2009;6. Доступно по: https://cyberleninka.ru/

article/n/rol-map-kinaznyh-mehanizmov-v-regulyatsii-kletochnogo-rosta-obzor-literatury (дата обращения: 29.01.2025).
47. Imai N., Hashimoto T., Kihara M. et al. Roles for host and tumor angiotensin II type 1 receptor in tumor growth and tumor-associated angiogenesis. Lab Invest. 2007;87:189–198.
48. Multhoff G., Molls M., Radons J. Chronic inflammation in cancer development. Front Immunol. 2012;2:98. DOI: 10.3389/fimmu.2011.00098.
49. Saber S., Mahmoud AAA., Goda R., Helal N.S., El-Ahwany E., Abdelghany R.H. Perindopril, fosinopril and losartan inhibited the progression of diethylnitrosamine-induced hepatocellular carcinoma in mice via the inactivation of nuclear transcription factor kappa-B. Toxicol Lett. 2018;295:32–40. DOI: 10.1016/j.toxlet.2018.05.036.
50. Васильев А.В., Власов Т.Д., Галагудза М.М., ред. Патофизиология. Типовые патологические процессы и состояния. Учебник для студентов медицинских вузов. СПб.: СПбГПМУ; 2023.
51. Тыртова Л.В., Скобелева К.В., Ильченко М.С., Холопова М.С. Адренокортикальная аденома как причина синдрома гиперандрогении у девочки: путь к диагнозу. Медицина: теория и практика. 2024;9(2):79–88. DOI: 10.56871/MTP.2024.37.58.009.
52. Colotta F., Allavena P., Sica A., Garlanda C., Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009;30:1073–1081. DOI: 10.1093/carcin/bgp127.
53. de Cavanagh E.M., Piotrkowski B., Fraga C.G. Concerted action of the renin-angiotensin system, mitochondria, and antioxidant defenses in aging. Mol Aspects Med. 2004;25(1-2):27–36. DOI: 10.1016/j.mam.2004.02.006.
54. Arang N., Gutkind J.S. G Protein-Coupled receptors and heterotrimeric G proteins as cancer drivers. FEBS Lett. 2020;594(24):4201–4232. DOI: 10.1002/1873-3468.14017.
55. Young D., Waitches G., Birchmeier C., Fasano O., Wigler M. Isolation and characterization of a new cellular oncogene encoding a protein with multiple potential transmembrane domains. Cell. 1986;45(5):711–9. DOI: 10.1016/0092-8674(86)90785-3.
56. Коган М.И., Ахохов З.М., Черногубова Е.А., Гусев А.А., Ойтова З.Х. Ренин-ангиотензиновая система: роль в развитии и прогрессии почечно-клеточного рака (обзор литературы). Онкоурология. 2019;15(3):143-149. DOI: 10.17650/1726-9776-2019-15-3-143-149.
57. Larrinaga G., Valdivia A., Arrieta-Aguirre I., Solano-Iturri J.D., Ugalde-Olano A., Loizaga-Iriarte A., Santos-Martín A., Pérez-Fernández A., Angulo J.C., López J.I. The Expression of Alamandine Receptor MrgD in Clear Cell Renal Cell Carcinoma Is Associated with a Worse Prognosis and Unfavorable Response to Antiangiogenic Therapy. Int J Mol Sci. 2024;25(3):1499. DOI: 10.3390/ijms25031499.
58. Zheng S., Yang Y., Song R., Yang X., Liu H., Ma Q., Yang L., Meng R., Tao T., Wang S., He J. Ang-(1-7) promotes the migration and invasion of human renal cell carcinoma cells via Mas-mediated AKT signaling pathway. Biochem Biophys Res Commun. 2015;460(2):333–40. DOI: 10.1016/j.bbrc.2015.03.035.
59. Li Z., Xie Y., Zhong T., Zhang X., Dang Y., Gan T., Chen G. Expression and clinical contribution of MRGD mRNA in non-small cell lung cancers. J. BUON. 2015;20:1101–1106.
60. Nishimura S., Uno M., Kaneta Y., Fukuchi K., Nishigohri H., Hasegawa J., Komori H., Takeda S., Enomoto K., Nara F. et al. MRGD, a MAS-related G-protein coupled receptor, promotes tumorigenesis and is highly expressed in lung cancer. PLoS ONE. 2012;7:e38618. DOI: 10.1371/journal.pone.0038618.
61. Yang J., Yang X., Gao L., Zhang J., Yi C., Huang Y. The role of the renin-angiotensin system inhibitors in malignancy: a review. Am J Cancer Res. 2021;11(3):884–897.
62. Shibayama Y., Fujimori T., Nguyen G., Hirose T., Totsune K., Ichihara A., Kitada K., Nakano D., Kobori H., Kohno M. et al. (Pro)renin receptor is crucial for Wnt/β-catenin-dependent genesis of pancreatic ductal adenocarcinoma. Sci. Rep. 2015;5:8854. DOI: 10.1038/srep08854.
63. Kouchi M., Shibayama Y., Ogawa D., Miyake K., Nishiyama A., Tamiya T. (Pro)renin receptor is crucial for glioma development via the Wnt/beta-catenin signaling pathway. J. Neurosurg. 2017;127:819–828. DOI: 10.3171/2016.9.JNS16431.
64. Ohba K., Suzuki T., Nishiyama H., Kaneko K., Hirose T., Totsune K., Sasano H., Takahashi K. Expression of (pro)renin receptor in breast cancers and its effect on cancer cell proliferation. Biomed. Res. 2014;35:117–126. DOI: 10.2220/biomedres.35.117.
65. Wang J., Shibayama Y., Zhang A., Ohsaki H., Asano E., Suzuki Y., Kushida Y., Kobara H., Masaki T., Wang Z. et al. (Pro)renin receptor promotes colorectal cancer through the Wnt/beta-catenin signalling pathway despite constitutive pathway component mutations. Br. J. Cancer. 2019;120:229–237. DOI: 10.1038/s41416-018-0350-0.
66. Delforce S.J., Lumbers E.R., De Meaultsart C.C., Wang Y., Proietto A., Otton G., Scurry J., Verrills N.M., Scott R.J., Pringle K.G. Expression of rennin-angiotensin system (RAS) components in endometrial cancer. Endocr Connect. 2017;6:9–19. DOI: 10.1530/EC-16-0082.
67. Solano-Iturri J.D., Echevarría E., Unda M., Loizaga-Iriarte A., Pérez-Fernández A., Angulo J.C., López J.I., Larrinaga G. Clinical Implications of (Pro)renin Receptor (PRR) Expression in Renal Tumours. Diagnostics (Basel). 2021;11(2):272. DOI: 10.3390/diagnostics11020272.
68. Wang J., Nishiyama A., Matsuyama M., Wang Z., Yuan Y. The (pro)renin receptor: a novel biomarker and potential therapeutic target for various cancers. Cell Commun. Signal. 2020;18:1–13. DOI: 10.1186/s12964-020-0531-3.
69. Ohba K., Endo M., Sato S., Kashio-Yokota Y., Hirose T., Takahashi K. (Pro)renin receptor/ATP6AP2 is required for autophagy and regulates proliferation in lung adenocarcinoma cells. Genes Cells. 2020;25:782–795. DOI: 10.1111/gtc.12812.
70. Hu J., Zhang L.-C., Song X., Lu J.-R., Jin Z. KRT6 interacting with notch1 contributes to progression of renal cell carcinoma, and aliskiren inhibits renal carcinoma cell lines proliferation in vitro. Int. J. Clin. Exp. Pathol. 2015;8:9182–9188.
71. Дементьева Е.А., Гурина О.П. Иммунологические изменения, сопровождающие развитие экспериментального неопластического процесса. Педиатр. 2015;6(2):96–108.
72. Vallejo-Ardila D.L., Fifis T., Burrell L.M., Walsh K., Christophi C. Renin-angiotensin inhibitors reprogram tumor immune microenvironment: A comprehensive view of the influences on anti-tumor immunity. Oncotarget. 2018;9(84):35500–35511. DOI: 10.18632/oncotarget.26174.

73. Crowley S.D., Rudemiller N.P. Immunologic Effects of the Renin-Angiotensin System. J Am Soc Nephrol. 2017;28(5):1350–1361. DOI: 10.1681/ASN.2016101066.
74. Condeelis J., Pollard J.W. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell. 2006;124:263–266. DOI: 10.1016/j.cell.2006.01.007.
75. Cortez-Retamozo V., Etzrodt M., Newton A. et al. Angiotensin II drives the production of tumor-promoting macrophages. Immunity. 2013;38:296–308.
76. Малеков Д.А., Поздняков А.В., Сотникова Е.А., Канина Л.Я., Малекова Д.В., Зверева Е.А. Диссеминированный лимфангиоматоз. Клинический случай. Визуализация в медицине. 2021;3(1):41–50.
77. Nakamura K., Yaguchi T., Ohmura G., Kobayashi A., Kawamura N., Iwata T., Kiniwa Y., Okuyama R., Kawakami Y. Involvement of local renin-angiotensin system in immunosuppression of tumor microenvironment. Cancer Sci. 2018;109(1):54–64. DOI: 10.1111/cas.13423.
78. Sugimoto M., Yamaoka Y., Shirai N., Furuta T. Role of renin-angiotensin system in gastric oncogenesis. J Gastroenterol Hepatol. 2012;27(3):442–51. DOI: 10.1111/j.1440-1746.2011.06964.x.
79. Kinoshita J., Fushida S., Harada S., Yagi Y., Fujita H., Kinami S., Ninomiya I., Fujimura T., Kayahara M., Yashiro M., Hirakawa K., Ohta T. Local angiotensin II-generation in human gastric cancer: correlation with tumor progression through the activation of ERK1/2, NF-kappaB and survivin. Int J Oncol. 2009;34(6):1573–82. DOI: 10.3892/ijo_00000287.
80. Jaworska K., Koper M., Ufnal M. Gut microbiota and renin-angiotensin system: a complex interplay at local and systemic levels. Am J Physiol Gastrointest Liver Physiol. 2021;321(4):G355-G366. DOI: 10.1152/ajpgi.00099.2021.
81. Santisteban M.M., Qi Y., Zubcevic J. et al. Hypertension-linked pathophysiological alterations in the gut. Circ Res. 2017;120(2):312–323. DOI: 10.1161/circresaha.116.309006.
82. Yan D., Sun Y., Zhou X., Si W., Liu J., Li M., Wu M. Regulatory effect of gut microbes on blood pressure. Animal Model Exp Med. 2022;5(6):513–531. DOI: 10.1002/ame2.12233.
83. Yang T., Santisteban M.M., Rodriguez V. et al. Gut dysbiosis is linked to hypertension. Hypertension. 2015;65(6):1331–1340. DOI: 10.1161/hypertensionaha.115.05315.
84. Domen A., Deben C., Verswyvel J., Flieswasser T., Prenen H., Peeters M., Lardon F., Wouters A. Cellular senescence in cancer: clinical detection and prognostic implications. J Exp Clin Cancer Res. 2022;41(1):360. DOI: 10.1186/s13046-022-02555-3.
85. Чурилов Л.П. Общая патофизиология (с основами иммунопатологии). Учебник для студентов медвузов. 5-е изд. СПб.: ЭЛБИ-СПб; 2015.
86. Ghasemi M., Okay M., Turk S., Naeemaee R., Guver E., Malkan U.Y., Aksu S., Sayinalp N., Haznedaroglu I.C. The impact of At1r inhibition via losartan on the anti-leukaemic effects of doxorubicin in acute myeloid leukaemia. J Renin Angiotensin Aldosterone Syst. 2019;20(2):1470320319851310. DOI: 10.1177/1470320319851310.
87. Uemura H., Ishiguro H., Nakaigawa N., Nagashima Y., Miyoshi Y., Fujinami K., Sakaguchi A., Kubota Y. Angiotensin II receptor blocker shows antiproliferative activity in prostate cancer cells: a possibility of tyrosine kinase inhibitor of growth factor. Mol Cancer Ther. 2003;2(11):1139–47.
88. Kawabata A., Baoum A., Ohta N., Jacquez S., Seo G.M., Berkland C., Tamura M. Intratracheal administration of a nanoparticle-based therapy with the angiotensin II type 2 receptor gene attenuates lung cancer growth. Cancer Res. 2012;72(8):2057–67. DOI: 10.1158/0008-5472.CAN-11-3634.
89. Zhao Y. et al. Losartan treatment enhances chemotherapy efficacy and reduces ascites in ovarian cancer models by normalizing the tumor stroma. Proceedings of the National Academy of Sciences, 2019;116(6): 210–2219.
90. Chang Y.L., Chou C.H., Li Y.F. et al. Antiproliferative and apoptotic effects of telmisartan in human glioma cells. Cancer Cell Int. 2023;23:111. DOI: 10.1186/s12935-023-02963-1.
91. Баранова Е.И. Антигипертензивная терапия антагонистами рецепторов ангиотензина II и риск развития злокачественных новообразований. Артериальная гипертензия. 2012;18(5):375–384.
92. Isobe A., Takeda T., Sakata M., Miyake A., Yamamoto T., Minekawa R., Nishimoto F., Oskamoto Y., Walker C.L., Kimura T. Dual repressive effect of angiotensin II-type 1 receptor blocker telmisartan on angiotensin II-induced and estradiol-induced uterine leiomyoma cell proliferation. Hum Reprod. 2008;23(2):440–6. DOI: 10.1093/humrep/dem247.
93. Khoshghamat N., Jafari N., Toloue-Pouya V., Azami S., Mirnourbakhsh S.H., Khazaei M., Ferns G.A., Rajabian M., Avan A. The therapeutic potential of renin-angiotensin system inhibitors in the treatment of pancreatic cancer. Life Sci. 2021;270:119118. DOI: 10.1016/j.lfs.2021.119118.
94. Morris Z.S., Saha S., Magnuson W.J., Morris B.A., Borkenhagen J.F., Ching A., Hirose G., McMurry V., Francis D.M., Harari P.M., Chappell R., Tsuji S., Ritter M.A. Increased tumor response to neoadjuvant therapy among rectal cancer patients taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Cancer. 2016;122:2487–2495. DOI: 10.1002/cncr.30079.
95. Perdomo-Pantoja A., Mejía-Pérez S.I., Gómez-Flores-Ramos L. et al. Renin angiotensin system and its role in biomarkers and treatment in gliomas. J Neurooncol. 2018;138:1–15. DOI: 10.1007/s11060-018-2789-5.
96. Zhang R., Yin H., Yang M., Liu J., Zhen D., Zhang Z. Advanced progress of the relationship between renin-angiotensin-aldosterone system inhibitors and cancers. J Hypertens. 2024;42(11):1862–1873. DOI: 10.1097/HJH.0000000000003836.
97. Sobczuk P., Szczylik C., Porta C., Czarnecka A.M. Renin angiotensin system deregulation as renal cancer risk factor. Oncol Lett. 2017;14(5):5059–5068. DOI: 10.3892/ol.2017.6826.
98. Xu J., Fan J., Wu F., Huang Q., Guo M., Lv Z., Han J., Duan L., Hu G., Chen L., Liao T., Ma W., Tao X., Jin Y.. The ACE2/Angiotensin-(1-7)/Mas Receptor Axis: Pleiotropic Roles in Cancer. Front Physiol. 2017;8:276. DOI: 10.3389/fphys.2017.00276.