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Expression of the components of the renin-angiotensin system in oncological diseases

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Abstract

Analyzed the literature devoted to the changes in the expression of the RAS proteins of cancer cells. A brief review of protein expression dynamics PAC in malignant tumors and the possible role of epigenetic mechanisms in these processes. Through research epigenetic mechanisms state for cancer have been developed principally new techniques for their correction, based on the use of selective regulators systems covalent modification-histone proteins (for example, deacetylase inhibitor) and microRNA synthesis technologies. Literature data show promising pharmacological correction epigenetic modification of chromatin in the treatment of cancer.

Key words: oncology, ectopic RAS cancer cells, epigenetic stimulation PAC in oncology.

Introduction.

According to the literature, the components of the renin-angiotensin system (RAS) may participate in the processes of malignancy of tissues to stimulate the growth and metastasis of tumors (Regulska K. et al, 2013.;Gomez RA, Sequeira-Lopez MLS, 2016; Pinter

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M., Jain RK, 2017; Pinter M. et al., 2017). Earlier studies demonstrated the prognostic and diagnostic value of the components PAC expression analysis in oncology (Romer FK, 1981). Modern studies confirm the diagnostic value of expression analysis PAC component, their importance in compiling prognosis of disease and choosing a method of treatment of malignant tumors (Regulska K. et al, 2013.; Tawinwung S. et al, 2015.; Gomez RA, Sequeira-Lopez MLS, 2016). Stimulation of local production of angiotensin-II (A-2), increased receptor expression to A-2, the expression rebalancing angiotensin-I-converting enzyme (ACE-1 and ACE-2) and the level of product formation of reaction (A-2 and A -1-7 respectively) is regarded as the key pathogenic mechanisms of growth and metastasis of malignant tumors (Regulska K. et al, 2013.; Sobczuk P. et al, 2017.; Sun H. et al., 2017).Some object of attention of research is to study the degree of risk of carcinogenesis induction inhibitors PAC (Connolly S. et al, 2011; Azoulay L. et al, 2012; Yang Y. et al, 2015; Sobczuk P. et al., 2017). However, the pathogenic mechanisms of inducing increased expression of RAS components of proteins in cancer cells, their role in the growth and metastasis are poorly understood.

1. THE DIAGNOSTIC VALUE OF PROTEIN PAC COMPONENTS IN ONCOLOGY

1.1. Receptors for A-2.

A-2 exerts its effect through the AT1 and AT2 receptor populations. It is found that in cells astrocytoma human incidence of AT1 receptors in patients with the high grade of malignancy (grade III and IV) increases to 67% as against 10% in the low-grade, which positively correlated with the intensity of cell proliferation and density neoangiogenesis (Arrieta O . et al., 2008). In studies on experimental animals, inoculated culture colorectal cancer (CRC) cell, it has been found that A-2 through the AT1 and AT2 receptors stimulates the migration of malignant cells and their metastasis in the liver (Nguyen L. et al., 2016). It reported that cells of non-small cell lung cancer, exhibiting high expression levels of the AT1-receptor, have resistance to the effects of cytostatics (Cheng Q. et al., 2016). Clinical observation suggests that increased expression of AT1 receptor malignant cells indicates poor prognosis of the disease, caused by stimulation of neoangiogenesis, tumor growth and metastasis (Keizman D. et al, 2011;. Sun H. et al, 2017). It is emphasized that the activation of the AT1-dependent pleiotropic effects prooncogenic A-2 may involve including lymphocytes or tumor-associated macrophages, resulting in decreased anti-cancer immunity, modification and production of proinflammatory cytokines interleukin (Coulson R. et al, 2017;. Pinter M ., Jain RK, 2017). A

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significant increase in the protein transformed cells AT1 occurs due to gene activation that increased expression of AT1 receptor malignant cells indicates poor prognosis of the disease, caused by stimulation of neoangiogenesis, tumor growth and metastasis (Keizman D. et al, 2011;. Sun H. et al, 2017.). It is emphasized that the activation of the AT1-dependent pleiotropic effects prooncogenic A-2 may involve including lymphocytes or tumor-associated macrophages, resulting in decreased anti-cancer immunity, modification and production of proinflammatory cytokines interleukin (Coulson R. et al, 2017;. Pinter M ., Jain RK, 2017). A significant increase in the protein transformed cells AT1 occurs due to gene activation that increased expression of AT1 receptor malignant cells indicates poor prognosis of the disease, caused by stimulation of neoangiogenesis, tumor growth and metastasis (Keizman D. et al, 2011;. Sun H. et al, 2017.). It is emphasized that the activation of the AT1-dependent pleiotropic effects prooncogenic A-2 may involve including lymphocytes or tumor-associated macrophages, resulting in decreased anti-cancer immunity, modification and production of proinflammatory cytokines interleukin (Coulson R. et al, 2017;. Pinter M ., Jain RK, 2017). A significant increase in the protein transformed cells AT1 occurs due to gene activation Activation of AT1-dependent pleiotropic effects prooncogenic A-2 may involve including lymphocytes or tumor-associated macrophages, resulting in decreased anti-cancer immunity, modification, and production of proinflammatory cytokines interleukin (Coulson R. et al, 2017;. Pinter M., Jain RK, 2017). A significant increase in the protein transformed cells AT1 occurs due to gene activation. Activation of AT1-dependent pleiotropic effects prooncogenic A-2 may involve including lymphocytes or tumor-associated macrophages, resulting in decreased anti-cancer immunity, modification, and production of proinflammatory cytokines interleukin (Coulson R. et al, 2017;. Pinter M., Jain RK, 2017). A significant increase in the protein transformed cells AT1 occurs due to gene activation AGTR1 (Coulson R. et al., 2017). Perhaps stimulation of neoangiogenesis sold through the AT1 receptor is a universal tumor progression pathogenetic mechanisms of various origins (Osumi H. et al, 2015.; Pinter M., Jain RK, 2017). The data on the synergistic effects of AT1 / A-2 systems and AT2 / A-2 in the stimulation of neoangiogenesis (Ager EI et al., 2011) and cell migration, inflammation and extracellular matrix formation via AT1 and AT2 receptor (Aydiner A. et al., 2015). It is shown that changes in the expression of AT1 and AT2 receptors acceptable regarded as markers of malignancy of gastric mucosa, induced Helicobacter pylori (Sugimoto M. et al., 2012), progression oral tongue squamous cell carcinoma (Itinteang T. et al, 2016), the progression of colorectal cancer risk assessment and its metastasis (Kuniyasu H., 2012;. Shimizu Y. et al, 2017), the diagnosis of lung cancer (Gallagher PE et al, 2011) and. breast (Vinson GP et al.,

2012). receptor expression levels A-2 is regarded as a prognostic criterion flow esophageal squamous cell carcinoma (Li S.-H. et al., 2016) and renal clear-cell carcinoma (Dolley-Hitze T. et al., 2010). Perhaps change the dynamics of expression AT1 and AT2 can be regarded as an integral indicator malignant tissue sensitivity to the effects of humoral inductors carcinogenesis (Rhodes DR et al, 2009.; Vinson GP et al, 2012.; Sugimoto M. et al, 2012.; Regulska K.et al, 2013.; Pinter M., Jain RK, 2017). A number of review articles are described in sufficient detail evaluation results of the study the expression characteristics of AT1 and AT2 receptors of the A-2 in various cancer diseases, their diagnostic and prognostic value. Arguments are presented in terms of their role in disease pathogenesis, progression and dissemination of tumors, as well as the prospect of clinical application of selective A-2 receptor antagonists in order to increase the effectiveness of chemotherapy, immunotherapy and neoangiogenesis inhibitors in oncology (Vinson GP et al, 2012.;Regulska K.et al, 2013.; Wegman-Ostrosky T. et al, 2015.; Sobczuk P. et al, 2017.; Pinter M., Jain RK, 2017).

1.2. Angiotensin-I-converting enzyme (ACE-1).

Angiotensin-I-converting enzyme (ACE-1), carboxydipeptidase, one of the key factors in performing the conversion of angiotensin-I (A-1) a physiologically active angiotensin-II (A-2). However, in the pathology, including cancer, the role of the ACE-1 in the formation of A-2 can be varied by increasing the contribution of ACE-independent pathway of conversion of A-1 to A-2 in the presence of alpha-chymase and other peptidases forming resistance of tumor cells to modern methods of anticancer therapy (Xie G. et al, 2017; Sobczuk P. et al, 2017). Widely known is the fact that the ACE-1, possessing a relatively low substrate specificity may not only participate in the formation of A-2, but also the kinins as well as other physiologically active molecules potentially relevant to carcinogenesis, tumor growth and dissemination (Regulska K.et al, 2013.; Sobczuk P. et al., 2017). Attracted the attention of information that ACE-1, in addition to the peptidase activity, may be directly involved in the intracellular signaling of A-2, actually being the receptor octapeptide (de Alvarenga EC et al., 2016). According to the authors of the cited publication, the mechanism of ACE-dependent reception of the A-2 may play an important role in the management of migration and proliferation of cancer cells. Consequently, changes in topology and ACE expression levels in cancer may serve as a marker localization effects proonkogennyhA-2 and other humoral factors, the metabolism of which is associated with the functions of RAS components. For example, in cancer of the kidneys, a regular change in protein expression and activity of ACE topology (Errarte P. et al, 2017;. Sobczuk P. et al, 2017). Normally cortical epithelium tubule

of the nephron segments, in particular, epithelium proximal demonstrates high expression indicators ACE that is not in clear cell renal cell carcinoma (CCRCC) and is detected only in the tumor blood vessels (Errarte P. et al., 2017). The authors have shown that the protein expression level in the tumor and the magnitude of its enzymatic activity in blood plasma may be a marker CCRCC aggressiveness and overall survival of CCRCC patients. On the other hand, Shen J. et al., 2016). It is shown that microenvironment tumor cells from mice immunized colon cancer cells, by promoting the escape of anticancer immunity, formed by macrophages and cancer-associated fibroblasts (Nakamura K. et al., 2018). According to the authors, a sharp increase in the level of expression of ACE macrophages may indicate to increase local production of the intensity of immunosuppressive molecules, such as nitric oxide, TGF-b1, PGE2. Normally ACE expression is critical for the formation of a specific microenvironment in the processes in step cytodifferentiation embryonic organ development, or in some intensively proliferating adult tissues. However, excessively high level of expression is not only associated with impaired hematopoiesis but also considered as the effect of the ACE in neoplastic hematological diseases, Haznedaroglu IC, Malkan UY, 2016). A significant increase in expression of laryngeal cancer ACE indicates an unfavorable course of the disease and higher risk of tumor metastasis (Han C., Ge W., 2016). Therefore, change in the expression of ACE-1, along with the study of gene polymorphism ACE widely used in modern oncology as the severity of the disease marker and its prognosis (Regulska K. et al., 2013). However, the level of expression of the ACE-1 cells of malignant tumors is not always correlated with the intensity of the local production of A-2, because of the active chymase, regulating ACE-independent way of A-2 (Xie G. et al., 2017). In addition, be aware that the ACE is directly involved in the regulation of immune reactions of the body (Haznedaroglu IC, Malkan UY, 2016).

1.3. Angiotensin-I-converting enzyme-2 (ACE-2) and the axis of ACE2 / Ang- (1-7) / MAS1.

ACE-2 homolog of ACE-1 is responsible for metabolic clearance of A-2, the enzyme is used as a substrate for the synthesis of angiotensin-1-7 (A-1-7). In turn, A-1-7, exercising regulatory effect through MAS1-receptors has oppositional vasotonic action and proinflammatory prosclerotic effects A-2 (Clarke NE, Turner AJ, 2012). Reducing the level of expression of the ACE-2 breast cancer cells is considered as a marker of the severe form of the disease with a high risk of metastasis (Yu S. et al., 2016). According to the authors, the level of expression of ACE-2 represents the degree of influence of ACE2 / Ang- (1-7) / MAS1 axis to limit the transformation of calcium-dependent intracellular signaling pathways

characteristic of the process of malignant transformation of cells. It was shown that the expression level of ACE-2 is negatively correlated with the intensity of neoangiogenesis in non-small cell lung cancer and the sensitivity of tumor cells to cytostatics. ACE2 / Ang- (1-7) / MAS1 axis has VEGFa secretion inhibition effect, and matrix metalloproteinases MMP-2 and MMP-9, aids in limiting neoangiogenesis, increase the sensitivity of tumors to cytostatic drugs and reduce the risk metastasis (Feng Y. et al., 2011;. Cheng Q. et al., 2016.). A number of publications indicate that hypoxia is a hallmark of solid tumors and that hypoxia conditions contribute to strengthening the prooncogenic effect of ACE-1 / A-2 against the background of reducing the effects of ACE-2 / Ang- (1-7) / MAS1 axis (Fan L. et al., 2014). The authors of the cited publication it is shown that in vitro in cell culture Lewis lung carcinoma hypoxia reduces expression of ACE-2 in ACE-1 / A-2-dependent induction of VEGFa. Arguments in favor of promising clinical use of A-1-7, as a factor for cancer therapy breast tumor cells which do not express estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 (Luo Y. et al., 2015; Regulska K. et al., 2013). At the same time, it is emphasized that the nature of the influence ACE-2 / Ang- (1-7) / MAS1 axis on the cancer cells and the progression of the tumor may depend on the location of the tumor (Wegman-Ostrosky T. et al., 2015; Haznedaroglu IC, Malkan UY, 2016; Sobczuk P. et al., 2017). In particular, it shows the fact that A-1-7 stimulates cell migration renal cell carcinoma (RCC). upregulation of proinflammatory genes has a significant impact on RCC development and progression (Sobczuk P. et al., 2017). The authors are inclined to conclude that A-1-7 against RCC has rather a prooncogenic action.

1.4. Angiotensinogen.

Angiotensinogen (Agt) is the universal precursor of A-2 and A-1-7. Normally Agt, mainly synthesized in the liver. In cancer, typically the liver retains the main source of Agt (Vinson GP et al., 2012). However, of interest data on the diagnostic value of Agt local products as a marker of carcinogenesis. Also attracted the attention of particular metabolic Agt cancer cells. On the one hand, Agt regarded as one of the most informative markers of tumor neoangiogenesis activity (Choi J.-H. et al., 2014). On the other hand, according to the cited publications, a dominant Agt conversion product in the tumor tissues is A-2. Thus, the combined effect of HIF-1-alpha and A-2, against higher production Agt, considered as the basic pathogenetic mechanism of stimulation of growth factors (especially VEGFa) activating tumor neoangiogenesis. Indeed, the results of clinical studies have shown that, firstly, overexpression Agt gene in glioblastoma patients can be regarded as a marker of tumor

resistance to anti-cancer therapy based on the inhibition of tumor neoangiogenesis (Urup T. et al., 2016). Secondly, higher gene expression Agt tumor tissue accompanied by increased local production of A-2. However, the data given in the literature that Agt possesses the ability to inhibit neoangiogenesis (Wegman-Ostrosky T. et al., 2015). Discussing local products Agt, it is necessary to clarify that, according to some authors, the stimulation of the local expression of RAS components, including Agt, It is considered as a central inducer of intracellular cascade regulatory proteins that determine the processes of malignancy and metastatic cells (Sugimoto M. et al., 2012). Moreover, the reported results do not preclude the activation of intracellular metabolism and adjustment RAS components in cancer cells (Blanco L et al., 2014). Which is consistent with the opinion of universal pathogenetic role of the activation of the intracellular RAS also implicated and modulation of gene expression processes (Ellis B. et al, 2012; De Mello WC, 2015). However, tissue-specific expression patterns is emphasized Agt, as a marker of cancer risk. In particular, the risk of lung cancer associated with a reduction of protein production (Wang H. et., 2015). According to the authors, Epigenetic mechanisms of gene expression reducing Agt Agt and point mutations of the gene can be considered as factors that increase the risk of lung cancer diseases. Perhaps the dynamics of local production Agt and its plasma levels may be different form the prognosis metastatic colorectal cancer (Martin P. et al., 2014). The authors found, Increasing serum Agt levels were significantly associated with worse overall survival, and epithelial expression of Agt was significantly associated with improved progression-free survival. Another aspect of the diagnostic value of the local production Agt tumor tissues may be due to natural variation Agt gene expression as the disease (Vinson GP et al., 2012). increases the risk of cancer of lung diseases. Perhaps the dynamics of local production Agt and its plasma levels may be different form the prognosis metastatic colorectal cancer (Martin P. et al., 2014). The authors found, Increasing serum Agt levels were significantly associated with worse overall survival, and epithelial expression of Agt was significantly associated with improved progression-free survival. Another aspect of the diagnostic value of the local production Agt tumor tissues may be due to natural variation Agt gene expression as the disease (Vinson GP et al., 2012). increases the risk of cancer of lung diseases. Perhaps the dynamics of local production Agt and its plasma levels may be different form the prognosis metastatic colorectal cancer (Martin P. et al., 2014). The authors found, Increasing serum Agt levels were significantly associated with worse overall survival, and epithelial expression of Agt was significantly associated with improved progression-free survival. Another aspect of the diagnostic value of the local production Agt tumor tissues may be due to natural variation Agt gene expression as the

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1.5. (Pro) Renin.

Recently molecule (pro) renin and its receptors are attracting increasing attention not only as a regulatory enzyme PAC but also as an important element of ontogenesis control mechanisms of wound healing and pathogenesis of several diseases (Gomez RA, Sequeira-Lopez MLS, 2016). Some reviews on the analysis of the pathogenetic role of RAS in cancer patients found important information about the impact of renin on the processes of malignancy cells and tumor progression (Vinson GP et al., 2012.; Sugimoto M. et al., 2012). In in vitro studies have shown that renin may have a stimulating effect on cell growth culture renal carcinoma cell (Hu J. et al., 2015). Expression of renin can be considered as a marker of normal maturation of blood cells or their precursors of malignancy (Haznedaroglu IC, Malkan UY, 2016). The authors of the cited survey emphasize that renin expression was detected from acute myeloid leukemia blast cells, in cells chronic myeloid leukemia and acute lymphoid leukemia. Reported that bone marrow progenitors, which express renin and become the source of lymphoblastic leukemia (Belyea BC et al., 2014). The data that the renin gene expression in normal and malignant hematopoiesis can be controlled by epigenetic mechanisms (Belyea BC et al., 2014.; Haznedaroglu IC, Malkan UY, 2016). In the context of the topic is relevant to recall that complex functioning, relatively little studied, receptor system to the (pro) renin is relevant not only to the PAC but also to the regulation of gene expression of proteins inductors processes of inflammation and tissue fibrosis (Nguyen G., 2011). Further studies confirmed the RAS-independent effects receptor system for (pro) renin, demonstrating their fundamental role in the regulation of cell homeostasis control mechanisms (Müller DN et al., 2012). It was also found that plasma levels (pro) renin receptor ((P) RR) in the cancer patient group were dramatically increased (Shibayama Y. et al., 2015). Based on the analysis of the dynamics expression (P) RR in cells at various stages

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of malignancy authors cited publication concludes, that (P) RR may be profoundly involved in ductal tumorigenesis in the pancreas. Results of studying in vitro expression of the PRR in cultured human glioma cell concludes that this receptor may be both a prognostic marker and a therapeutic target for glioma (Kouchi M. et al., 2017). The data that change expression (P) RR in the process of hematopoiesis may be regarded as a promising diagnostic marker promyelocytic leukemia (Haznedaroglu IC, Malkan UY, 2016).

2. EPIGENETIC MECHANISMS AS POSSIBLE REGULATORS EXPRESSION OF THE COMPONENTS PAC IN ONCOLOGY

The above summary of the expression of RAS components dynamics in tumor tissues indicates that, firstly, this figure can rise significantly in tissue, which normally does not have high levels of expression of RAS components (SugimotoM. et al., 2012.; Shibayama Y. et al., 2015.; Han C., Ge W., 2016; Itinteang T. et al., 2016.; Yue Z. et al., 2016). Conversely, under certain oncological diseases cells gradually lose their inherent ability to express normal RAS proteins (Errarte P. et al., 2017;.. Sobczuk P. et al., 2017). Secondly, there is a regular expression and topology change RAS proteins in tumor tissues, depending on the current stage and severity of the disease (Vinson GP et al., 2012;. Haznedaroglu IC, Malkan UY, 2016;. Kouchi M. et al., 2017). A number of publications are evidence leading role of epigenetic mechanisms in the change of the synthesis of proteins capable of stimulating the processes of malignancy, inflammation, fibrosis and metastasis (Tsai Y.-P., Wu K.-J., 2012;. Tan W. et al., 2014; Harb-De la Rosa A.et al., 2015;. Cheng Y. et al., 2016; Haznedaroglu IC, Malkan UY, 2016; Semenza GL, 2016). In this case, attention is paid to the restructuring epigenetic gene expression RAS components in the processes of malignancy and growth of cancer cells (Tsai Y.-P., Wu K.-J., 2012; Han C.-D., Ge W.-S., 2016; Haznedaroglu IC, Malkan UY, 2016; Xie G. et al., 2017). Epigenetic reorganization expression of RAS components - a relatively new and little-studied area in oncology. Normally, the impact on the dynamics of epigenetic mechanisms of gene expression of proteins PAC observed at early stages and histological organogenesis and in intensively proliferating tissues (Belyea BC et al., 2014;. Haznedaroglu IC, Malkan UY, 2016). It is reported that one of the universal inducers of gene expression of RAS components of proteins, the progression of malignant neoplasms, can be HIF-1alpha (Tsai Y.-P., Wu K.-J., 2012; Choi J.-H. et al, 2014;. Xie G. et al., 2017.). It is found that several factors related diabetes stream also affects the expression of

genes of proteins PAC, increasing the risk of cancer (Yang X. et al., 2012;. Reddy MA et al., 2012;. Reddy MA, Natarajan R., 2015; Wegman-Ostrosky T. et al., 2015). Possibly, HIF-1alpha directly participates in the regulation of expression of angiotensinogen (Agt) (Choi J.-H. et al., 2014). In turn, Agt is importantly required for the increased production of A-2, stimulating tumor neovascularization and metastasis by AT1 receptors. It reported that AT1-receptor antagonist is olmesartan could upregulate miR-205 and inhibit VEGF-expression and cancer cells (Yue Z. et al., 2016). Consequently, A-2 may be considered as a regulator of the transcription process. Indeed, experimental studies have shown that the A-2 can enhance the production of proinflammatory cytokines (IFNγ, TNFα) and matrix metalloproteinases (MMP2, MMP9), stimulating cancer cell adhesion to endothelial cells, trans-endothelial migration and tumor cell migration across extracellular matrix (Rodrigues -Ferreira S., et al., 2012). Along with this, it is suggested the universality epigenetic adjustment expression RAS components in pathogenesis including cancer (Kemp JR et al., 2014;. Reddy MA, Natarajan R., 2015). On the other hand, provides information on the epigenetic effects of A-1-7, to limit the mobility of cancer cells and their ability to metastasize (de Oliveira da Silva B. et al., 2016). From this perspective, of particular importance acquire data on the ability of ACE-1 participate in intracellular signaling mechanisms of A-2 (de Alvarenga EC et al., 2016). No less relevant is the importance of information systems (pro) renin - (pro) renin receptor in the control of gene expression, regardless of the state PAC activity (Nguyen G., 2011; Müller DN et al., 2012.). The results further studies confirm the thesis that the system (pro) renin - (pro) renin receptor has an important function in pathogenesis and progression of cancer (Shibayama Y. et al., 2015; Wang C. et al, 2016; Kaneko K. et al., 2017). No less relevant is the importance of information systems (pro) renin - (pro) renin receptor in the control of gene expression, regardless of the state PAC activity (Nguyen G., 2011; Müller DN et al., 2012). The results further studies confirm the thesis that the system (pro) renin - (pro) renin receptor has an important function in pathogenesis and progression of cancer (Shibayama Y. et al., 2015; Wang C. et al., 2016; Kaneko K. et al., 2017). No less relevant is the importance of information systems (pro) renin - (pro) renin receptor in the control of gene expression, regardless of the state PAC activity (Nguyen G., 2011; Müller DN et al., 2012.). The results further studies confirm the thesis that the system (pro) renin - (pro) renin receptor has an important function in pathogenesis and progression of cancer (Shibayama Y. et al., 2015; Wang C. et al., 2016; Kaneko K. et al., 2017).

3. ONCOLOGICAL ASPECTS OF EXPRESSION OF THE COMPONENTS PAC AND LOCAL RENIN-ANGIOTENSIN SYSTEM

The concept of "local races" was formed as an idea of the element inorganic humoral complex homeostatic control of body functions. In the example local renal PAC this point can be illustrated by the following example. Normally, an adequate stimulus activation intrarenal PAC has two distinct mechanisms: a renal baroreceptor and sodium chloride delivery to the macula densa. As a result, it increases the secretion of cell juxta-glomerular apparatus PAC regulatory enzyme - renin and increased production of A-2. Basic renotropic physiological effects of A-2 implemented mainly on the parameters of renal hemodynamics and filtration processes at proximal nephron. Including initiation effects through controlling transcription regulatory proteins and transport in the proximal nephrocytes (Li XC et al., 2012;. Satou R., Gonzalez-Villalobos RA, 2012). Under physiological conditions, the induction of the secretion of renin (Sparks MA et al., 2014) and stimulation of the A-2 transcription transport proteins tubular epithelium (Shao W. et al., 2013) adequate to the current state of the water-salt balance of the body. For example, a diet-induced hyponatrium physiological stimulation of RAS are not reflected by increased urinary Agt or the development of renal injury (Shao W. et al., 2013). Consequently, the end result of a complex set of activities humoral regulators intrarenal homeostatic control system is to maintain a stable blood pressure parameters, ion homeostasis, acid-base equilibrium constant volume of extracellular body fluids (Satou R., Gonzalez-Villalobos RA, 2012; Zhuo JL et al., 2013; Sparks MA et al., 2014;. Ferrão FM et al., 2014).. induction renin secretion (Sparks MA et al., 2014) and stimulation of the A-2 transcription transport proteins tubular epithelium (Shao W. et al., 2013) adequate to the current state of the water-salt balance of the body. For example, a diet-induced hyponatrium physiological stimulation of RAS are not reflected by increased urinary Agt or the development of renal injury (Shao W. et al., 2013). Consequently, the end result of a complex set of activities humoral regulators intrarenal homeostatic control system is to maintain a stable blood pressure parameters, ion homeostasis, acid-base equilibrium constant volume of extracellular body fluids (Satou R., Gonzalez-Villalobos RA, 2012; Zhuo JL et al., 2013; Sparks MA et al., 2014;. Ferrão FM et al., 2014).. induction renin secretion (Sparks MA et al., 2014) and stimulation of the A-2 transcription transport proteins tubular epithelium (Shao W. et al., 2013) adequate to the current state of the water-salt balance of the body. For example, a diet-induced hyponatrium physiological stimulation of RAS are not reflected by increased urinary Agt or the development of renal injury (Shao W. et al., 2013). Consequently, the end

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On the other hand, hypoxia, oxidative stress, high blood glucose levels and other adverse factors capable of inducing epigenetic mechanisms of activation of inflammation and fibrosis Renal parenchyma, including topology change RAS components through gene expression control mechanisms (Macconi D.et al., 2014; Reddy MA, Natarajan R., 2015, Nangaku M. et al., 2017). An important result of these events is a strengthening renin secretion in the parenchyma cerebral kidney layer (Zhuo JL, 2011), arteriolar smooth muscle cells, mesangial cells and interstitial cells by epigenetic gene expression control mechanisms (Sparks MA et al., 2014;. De Mello WC 2015). Renin - regulatory enzyme PAC-determining the intensity of the further production of A-2. On accumulation of reactive oxygen species (ROS) in tissue enhances renal excretion of Agt in urine, reinforcing feedback loop between ROS activation and subsequent activation of ROS synthesis Agt(Nguyen MTX et al., 2015). It is shown that the infusion of an animal A-2 is essential to activate the biosynthesisAgt proximal nephrocytes, Leading to a further increase in tubular products A-2 and enhance its pathogenic influence (Ramkumar N. et al., 2016). In general, accumulation of RAS components in proximal nephrocytes, increased intracellular production of A-2 and its effects on the transcription process, mitochondrial function, amplification productsROS - one of the basic pathogenetic mechanisms homeostatic disturbances of kidney function (Navar LG et al., 2011;. Ellis B. et al., 2012;. Li XC, Zhuo JL, 2016). The recommended use of the renal excretion of angiotensinogen (Kobori H.et al, 2002; Navar LG et al., 2011; Alge JL et al., 2013). As a diagnostic criterion for the pathological transformation of intrarenal RAS.

Thus, pathological intrarenal PAC transformation is carried out:

1. Under the control of epigenetic mechanisms that alter transcription processes, including protein components PAC.

2. The advent of ectopic foci biosynthesis of key components RAS proteins.

3. Strengthening of intracellular production of A-2 and increased its influence on the transcription of proteins.

4. Weakening the expression of ACE-2, decreased the production of A-1-7, the effects of which are the oppositional character in relation to the A-2.

As a result, in contrast to physiological conditions, pathological change in topology and level of expression PAC components leads to:

1. The emergence of ectopic foci and increased intracellular PAC tubular epithelium.

2. The formation of ectopic foci PAC (Renin, angiotensinogen) facilitates the escape of triggers activation of RAS in respect of regulatory stimuli settings water-salt balance of the body and hemodynamics.

3. Interaction of ectopic foci PAC remains, but this interaction is not directed at maintaining homeostasis, it further provides unlimited induction of expression of RAS components and other regulatory proteins that promote fibrosis, inflammation and hypertrophy of the renal parenchyma cells.

4. There is a transformation of intracellular signal transduction systems (Satou R., Gonzalez-Villalobos RA, 2012) and the balance of regulatory action A-2 and A-1-7 in the direction of enhancing the activity of ACE-1 and alpha-chymase on lower ACE expression -2 (Sparks MA et al., 2014).

Note that these changes occur as a result of adjustment components PAC expression in cells PLNokachestvennyh tumors, inducing cell malignancy, fibrosis and tissue inflammation, neoangiogenesis, metastasis and immunosuppression (Regulska K.et al., 2013.; Pinter M., Jain RK, 2017; Sobczuk P. et al., 2017).

As well as in the pathogenesis and the progression of renal failure, the components of the RAS cancer cells are not involved in the implementation of the homeostatic functions. Therefore, we believe that the local ASD are not.

From the point of view of practical medicine interests, it comes to expediency of utilization of RAS blockers in the treatment of cancer. In our opinion, some aspects can be distinguished in this respect. On the one hand, enhancement of expression of ectopic foci of cancer cells, PAC, at first glance, gives reason to expect performance using ACE inhibitors and A-2 receptor antagonists in the treatment of cancer. Indeed, monotherapy RAS blockers cancer may exhibit relatively moderate therapeutic result. It reported on how to enhance the anticancer effects of RAS inhibitors in combination with chemotherapy and immunotherapy activities (Pinter M., Jain RK, 2017). Along with this, it indicates the potential risks

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associated with the use of certain RAS blockers in the treatment of specific cancers (Sobczuk P. et al., 2017), up to complete their use inappropriate (Sørensen GV et al., 2013; Chae YK et al., 2014; Nakai Y. et al., 2016).. On the other hand, are assumed to be qualitatively different methods for their pharmacological correction based on epigenetic mechanisms modulating suppress ectopic activity PAC (Zhong Y. et al., 2013.; Reddy MA et al., 2014.) Based on the analysis of the nature of the expression of ectopic foci PAC. The opinion of the universal role of epigenetic mechanisms in the pathogenesis of ectopic formation of PAC in oncological and non-oncological diseases (Kemp JR et al., 2014;. Tang J., Zhuang S., 2015; Reddy MA, Natarajan R., 2015). Analyzed advantageous methods for treating cancer, completely based on the management epigenetic mechanisms using synthetic microRNA (Tan W. et al., 2014;. Felipe AV et al., 2014.). New prospects for the use of selective modulators of epigenetic processes in the practice of medicine, and of interest for oncology, confirming information about the readiness of application of this group of pharmacological agents (deacetylase inhibitors) in preclinical trials (Van Beneden K. et al., 2013).

CONCLUSION

A review of the literature showed that the variation of expression of RAS components closely related to the pathogenesis of neoplastic transformation of cells progression of cancer, as well as stimulation of the processes of metastasis. Information about the state of expression of protein components PAC components contributes to the understanding of mechanisms of carcinogenesis and dissemination of tumor cells. These data allow the use of qualitative and quantitative expression parameters PAC component as the severity of cancer markers. Tight engagement components PAC in carcinogenesis was the basis for using the RAS inhibitor (ACE inhibitor-1 receptor antagonists and A-2) in the therapy of cancer. However, analysis of causes of changes in the expression of RAS protein in tumor cells has revealed that very significant function belongs epigenetic mechanisms of regulation of gene expression in these processes. Through research status of epigenetic mechanisms in cancer have been developed principally new techniques for their correction, based on the use of selective regulators systems covalent modification-histone proteins (for example, deacetylase inhibitor) and synthesis technology microRNA. The published data on the pharmacological properties of these drugs suggest their prospects for effective treatment of cancer.

Abbreviations:

PAC - renin-angiotensin system

A-2 - angiotensin-II

ACE-1 - angiotensin-I-converting enzyme 1

ACE-2 - angiotensin-I-converting enzyme 2

AT1 - subpopulation-1 angiotensin-II receptor

AT2 - subpopulation 2-angiotensin-II receptor

ROS - active oxygen forms

Agt - angiotensinogen

TGF-b1 - transforming growth factor-beta1

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