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Ecological aspect of molecular mechanism of epigenetic rearrangement of humoral system of the renal function regulation

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Abstract. Epigenetic transformation of chromatin is able to be induced by environmental factors and changes in the parameters of the state of metabolic processes in the body. Among them, the most common known factors are hypoxia (ischemia of the organ), hyperglycemia, heavy metals, endocrinopathies, infectious diseases.

The results of the review conclude that epigenetic mechanisms pay the very important contribution to the restructuring of humoral systems of renal regulation during renal failure sufficiently contributing to a progressive reduction of nephrons and directly preconditioning the unfavorable progress of the disease. In considering this potential etiologic factor, one must take into account several common triggers changing the epigenetic transformation of intrarenal synthesis and metabolism of physiologically active substances. Primary it is the formation of atypical foci of their products, which is most evident in the processes of restructuring of the RAS and nitric oxide systems. Secondary the renal coordinating humoral factors increasingly lose the control of regulation of homeostasis and switch on the pathophysiological way of progressive renal failure. Next are the epigenetic changes of proteins genes that perform key functions in the synthesis and metabolism of humoral factors in the regulation of renal functions. Uncontrolled synthesis of these peptides leads to a triggered enhancement of the process, again, involving epigenetic chromatin rearrangement.

The indicated regularity can be traced to unrestricted activation of RAAS and the renal system of TGF-beta. Other contributing factors occur as a result of unrestricted activation of RAAS and the TGF-beta system. On this background, there is a steady decline in the regulatory capabilities of the opposition control vector represented by the nitrogen oxide system, primarily by the constitutive isoforms eNOS and nNOS. The research of epigenetic processes during various nephropathies does not only enlightens theoretical basis for the pathogenesis of renal failure but also opens promising approaches for the development of new pharmacological corrects of renal function.

Key words: kidneys, renal failure, epigenetics, renin-angiotensin-aldosterone system, transforming growth factor beta, nitric oxide.

1. Introduction

Renal failure (chronic renal failure – CRF as well as acute renal failure – ARF) remains one of the major problems of medicine and is often a limiting factor in the treatment of certain diseases. Medical statistics show a steady growth in a number of nephrological patients who are suffering from lack of dialysis and kidney transplantation (Reddy & Natarajan, 2015; Uwaezuoke et al., 2016; Zununi, et al., 2016). The situation becomes much more complicated by the fact that this disorder is increasingly affecting children, including newborns (Uwaezuoke et al., 2016; Lee-Son & Jetton, 2016; Woroniecki, et al., 2014). Unlike many disease processes that have ample evidence available in order

to better manage the patient even coexisting up-to-date genetical approaches based on the laws of monogenic inheritance by G. Mendel do not fully enlighten the pathogenicity of renal failure. The to date research in the field of medical genetics is focused on identification of pathological alleles which are considered to be responsible for the risk of renal insufficiency and should be fulfilled by the research upon epigenetic mechanisms which are nowadays considered to be the predominant risk factors of renal damage (Lee-Son et al., 2016; Köttgen et al., 2010; Ma, 2016). Indeed, current reviews of experimental and clinical studies illustrate the requirement for the deeper scientific approaches based on the epigenetic mechanisms in the effort to determine causality of renal dysfunctions (Thomas, 2016; Witasp, 2017). At the same time, investigators should take into account the main feature of renal activity is that various segments of the nephron have significant differences between themselves due to their transport activities and due to the sum of humoral factors for regulating their activity matched with the physical and biochemical parameters of their microenvironment.

It has been reported the homeostatic functions of different parts of the nephron are coordinated by the complex system of humoral factors that determine the key physiological and pathophysiological mechanisms of the kidney response to the changes in the homeostatic parameters of the fluid balance and external adverse effects. Among these humoral factors, there are the renin-angiotensin-aldosterone system (RAAS) (Lee-Son & Jetton, 2016), nitric oxide (Shirodkar & Marsden, 2011), transforming growth factor-beta (Shi et al., 2011), etc. According to recent investigations, these humoral factors can control the development, growth and the basic homeostatic functions of the kidneys and obviously require more in-depth study since they are reported to be the mediators of structural and functional disorders of the renal parenchyma associated with epigenetic transformations of transcription and translation processes in acute and chronic renal failure.

From this point of view the importance of epigenetic approach should be emphasized due to the fact that changes in the expression of genes which control the biosynthesis of the intrarenal humoral factors of the renal homeostatic self-regulation can be reflected by dynamics of the concentration of certain peptides, which may appear to be useful laboratory criteria (Kobori et al., 2008). Therefore, determination of the epigenetic pathogenetic mechanisms of the renal dysfunctions creates the strategy for discovery of new pharmacological approaches, including those controlling the synthesis of various physiologically active molecules by the renal parenchyma (Reddy & Natarajan, 2015; Marumo et al., 2008).

Furthermore, the understanding of the epigenetic mechanisms of renal failure activation allows us to re-evaluate the spectrum of nephroprotective properties of already known and globally used drugs, which help in the correction of the intrarenal humoral systems monitoring the body's homeostatic functions (Hayashi al., 2015; Reddy et al., 2014).

Thus, we see our mission in the attempt to integrate the modern achievements in molecular biology and biochemistry and the already existing system of ideas about the role of intrarenal humoral mechanisms in the physiological and pathophysiological aspects of kidney functions.

Consequently, the aim of our research is to clarify few questions. First, what is the role of epigenetic mechanisms in breaking the metabolism of intrarenal humoral factors in the regulation of kidney function during the onset and progression of renal failure? Second, do these humoral factors take part in the processes of covalent modification of the components of the nucleoprotein chromatin complex?

2. General information about the epigenetic regulatory mechanisms

Epigenetics is the relatively modern science that studies the influence of environmental factors on the mechanisms of gene expression and its regulation. Epigenetic mechanisms have no effect on primary structure of nucleic acids (Beckerman et al., 2014), are provided by methylation and demethylation processes in the DNA molecule (Van der Wijst et al., 2015), RNA (Saletore et al., 2013) and posttranslational processing of histone proteins (Voon & Wong, 2016; Jamal et al., 2012). Epigenetics explains how the external environment can trigger the "on" and "off" activity of genes (Zama & Uzumcu, 2010). The most significant among the epigenetic mechanisms of regulation of gene expression is the process of DNA methylation. This process consists of the addition of methyl groups ($-CH_3$) to the one of the four types of nucleotides in the DNA by forming a covalent bond between them (Woroniecki et al., 2015; Lister et al., 2009). Attachment of methyl groups to nucleotides corresponds to one of four isoenzymes nuclear DNA methyltransferase (DNMT) named DNMT1, DNMT2, DNMT3a or DNMT3b (Reddy & Natarajan, 2015; Efimova et al., 2012). DNMT1 recognizes semi methylated DNA (each of its chains) during replication (Bechtel et al., 2010). DNMT3a and DNMT3b provide DNA methylation de novo, i.e. repeatedly in new sites. The function of DNMT2 is still a subject of discussion (Jamal et al., 2012). DNA methyltransferases have the ability to incorporate specific "labels" in the nucleic acid, leading to the shutdown of these genes (Van der Wijst et al., 2015). Labels in the DNA chain block the transcription process of more than two-thirds of the DNA strand (Ponnaluri et al., 2016). Thus, the somatic cells use a covalent modification of DNA to regulate the expression of genes by the so-called "on / off" principle (Quarta et al., 2016).

DNA methylation in most cases occurs on the cytosine nitrogen base (C), paired with guanine (G), on the so-called CpG sites or CpG clusters (Dwivedi et al., 2011). In the human body about 70-80% of CpG-dinucleotides are stored in the methylated state (Ziller et al., 2013). Sections of the DNA chain where the density of CpG clusters are particularly high are called CpG islands (Zhang et al., 2009). However, the DNA methylation process is carried out at the sites with a reduced density of CpG dinucleotides (Ziller et al., 2013). Along with the process of DNA methylation the process of demethylation has great importance in the epigenetic regulation of gene expression (Van der Wijst et al., 2015; Efimova et al. 2012). DNA demethylation is the process of DNA release from methyl groups, which is carried out with the help of special enzymes demethylases (Auclair & Weber, 2012). In addition, post-translational modifications of histones are also referred to epigenetic mechanisms. These modifications result in changing the amino acid residues of the N-terminal end of histones (lysine, serine, arginine, etc.) as a result of the processes of acetylation, deacetylation, phosphorylation, ubiquitination (Araki & Mimura, 2017; Ganai et al., 2016), etc. The processes of acetylation and deacetylation are made possible due to a number of specific enzymes – histone acetylases (acetyltransferases, HAT) and histone deacetylases (HDAC) (Gong et al., 2016). Phosphorylation occurs due to kinase enzymes (phosphotransferases) (Araki & Mimura, 2017; Nathan et al., 2006). Histone modifications tend to weaken the relationship between the nucleosome and DNA, which facilitates the activation of the transcription process (Rossetto et al., 2012).

Thus, the acetylation of lysine at position 27 of histone H3 (H3K27ac) leads to an increase in gene expression. The combination of acetylated lysine 14 (H3K14ac) and phosphorylated serine 10 of histone H3 (H3S10ph) also indicates increased gene expression (Chen & Chen, 2017). Other modifications are the acetylation of lysine H2AK5, H2BK20, H3K14, H4K5, etc. And the threonine phosphorylation of H3T3 and serine H3S28 and H4S1 similarly lead to activation of the genes (Araki & Mimura, 2017; Rossetto et al., 2012; Wang et al., 2008). Deacetylation of histones, on the other hand, is accompanied by inactivation of the genes since DNA condensation and the impossibility of transcription occur (Ganai et al., 2016). Posttranscriptional expression of genes is regulated by such an epigenetic mechanism as RNA interference. RNA interference is the process of suppressing the activity of genes by the help of microRNA at the stage of transcription, translation, degradation or de-adenylation (Nabzdyk et al., 2017). In this case, the microRNA posses an effect on the intensity with which mRNA is translated into a protein (Dwivedi et al., 2011; Cui et al., 2017). Actually, the process of suppression of gene expression is called silencing (Cui et al., 2017). MicroRNA (miRNA) is a class of short single-stranded non-coding RNAs of 21-24 nucleotides in length (Dwivedi et al., 2011; Zhang et al., 2009). Endogenous non-coding genes are responsible for the production of microRNAs. MicroRNA is capable of "jamming" genes in the transcription stage by methylation of DNA sequences of promoters (Dwivedi et al., 2011). All microRNAs' actions are strictly limited, which allows them to participate directly in the processes of apoptosis, proliferation, and differentiation of cells. The epigenetic effect of microRNA is manifested in the regulation of adipocyte differentiation and insulin secretion, the immune response, and so on (Dwivedi et al., 2011). Summarizing the following epigenetics highlights a new approach in the study of hereditary mechanisms illustrating how the environment regulates the gene expression.

Recent studies have reported that epigenetic mechanisms seem to be the important element of adaptation at the populational level that coordinate the expression of genes accordingly to environmental factors. The term "epigenetic mechanisms" is frequently associated with the phenomenon of fetal programming. Meanwhile, epigenetic activities are intensively taking place in the postnatal period of ontogenesis. It is difficult to say where is hidden the imperfection of this form of adaptive response, however, its violation is often associated with the activation of pathogenetic mechanisms inside various organs and systems.

3. Renin-angiotensin system (RAS)

In order to describe the main results of the epigenetic reorganization of the local intrarenal RAS, we shall allow ourselves to mention in brief the well-known scheme of its functions. It was assumed that inside the kidney the specialized juxtaglomerular cells (JGC) are the main site for the synthesis of renin. The substrate of renin is angiotensinogen which is produced by the liver. The main regulatory effects of angiotensin II are formed as a result of the progressive conversion of angiotensinogen into angiotensin-I with the involvement of renin, and then in angiotensin II by the action of angiotensin-converting enzyme-1 (ACE-1) which is concentrated at the proximal segment of the nephron and enters in the bloodstream of kidney vessels mainly via the AT1-receptor population. Due to its effects, angiotensin II monitors blood pressure, controls blood circulating volume, regulates parameters of the water-salt balance of the body and participates in autoregulation of renal blood flow. Some authors assume that physiologically angiotensinogen could be also synthesized in small amounts by nephrocytes of the proximal nephron (Kobori et al., 2013). However, the results of experimental studies indicate that the main source of angiotensinogen for the non-affected kidneys is the liver (Matsusaka et al., 2012). In addition to ACE-1, the kidney contains quite high lev-

els of the ACE-2 activity responsible for the synthesis of angiotensin-1-7 which is responsible for negative response mechanisms to angiotensin II, although strictly speaking, angiotensin-1-7 is not the antagonist of octapeptide.

It should be noted that according to some authors, angiotensin-II should be considered as one of the main factors contributing to the progression of renal failure by deteriorating visceral hemodynamics, stimulating fibrosis, activating the pro-inflammatory factors that limit cell cycle in tubular epithelium and provoke metabolic disorders in the nephrocytes (Kobori et al., 2013). It indicates that during the progression of renal failure angiotensin-II concentrations in kidney tissues can be significantly increased followed by the octapeptide minor level changes in the systemic circulation (Kobori et al., 2013; Matsusaka et al., 2012). One draws attention to the fact that a substantial increase of intrarenal production of angiotensin-II on a background of progression of renal failure is accompanied by a distinct increase in the biosynthesis of components of RAS proteins: angiotensinogen, prorenin, ACE-1 and AT1 receptors of angiotensin-II (main population of receptors responsible for most of the physiological and pathophysiological effects of angiotensin-II), not only in the proximal nephrocytes, but in abnormal foci of RAS activity which is the epithelium distal nephron (Kobori et al., 2013). The authors of the cited publication do not discuss in detail the possible role of epigenetic mechanisms in the restructuring of the intrarenal RAS during the pathological processes in the renal parenchyma. Nevertheless, the very logic of the presented facts leads to the discussion of this question. We will try to find out how justified this assumption is.

Indeed, further studies have shown that the expression of RAS components can be controlled by epigenetic mechanisms at the different stages of ontogenesis (Tain et al, 2017; Tain & Hsu, 2017; Witasp et al., 2017). Moreover, epigenetic modulation of the RAS components expression is considered as one of the leading pathogenetic mechanisms in a number of severe diseases (Tain et al., 2017). In particular, it has been shown that epigenetic changes are critically important for understanding the transition of acute renal failure to a chronic form (Rodríguez-Romo et al., 2015). In the available data, we found evidence that experimental model of fetal programming is confirmed by the participation of epigenetic factors in the regulation of angiotensin-II AT1 receptor expression levels (Bogdarina et al, 2007; Wu et al, 2016).

Great importance has the fact that epigenetic mechanisms due to increasing the synthesis of RAS components create the preconditions for activation of intracellular (autocrine) effects of angiotensin-II and that, according to some authors, is the basic pathogenetic mechanism of RAS-dependent tissue damage (De Mello, 2015). The proof of that statement that can be provided by the data that acetylation of histone 3 (H3Ac), as well as methylation (H3K4me3) and demethylation (H3K9me2), may contribute to the release of ACE-1 gene promoter in renal parenchyma which activates protein biosynthesis (Liang et al., 2013). On the one hand, according to the classical view of the activity of the RAS, ACE-1 in our body is present in excess amounts and doesn't appear to be limiting factor for the formation of angiotensin II. But if we evaluate the above-mentioned fact from the standpoint of the formation of a fully functioning intracellular RAS, it acquires a completely different meaning (Abadir et al., 2012; Ellis et al., 2012). Indeed, according to some reviews, an increased expression of the ACE-1 gene in the kidney tissues is a marker of the adverse course of diabetic nephropathy (Thomas, 2016). In addition to the above, can result in message groups of researchers have revealed in the conditions of diabetic nephropathy gain intracellular production of angiotensinogen in the proximal nephrocytes due to acetylation of histone 3 (H3K9) and trimethylation (H3K4me3) (Marumo et al., 2015). According to the authors, the detected effect can indicate how to increase active functional loading on the segment of the nephron, and reveal the pathophysiological mechanisms which induce damage to the population of tubular epithelial cells. The idea that increased expression of angiotensinogen in the proximal nephrocytes possesses a leading role in the progression of renal failure, state, and other authors (O'Leary et al., 2016; Bourgeois et al., 2017).

Some researchers are complementing data about the mechanisms of the phenomenon that the processes of epigenetic control of angiotensinogen synthesis in proximal nephrocytes may be affected by interferon-gamma (Satou et al., 2013), IL-6 (O'Leary R. et al., 2016) and sex steroid hormones (Bourgeois et al., 2017).

In addition, angiotensin II also has the ability to modulate the state of protein expression in the renal tissues by stimulating an increased expression of AT1 receptors and transforming growth factor-beta1 while suppressing ACE-2 (Macconi et al., 2014). Epigenetic mechanisms initiated at the stage of acute renal insufficiency can be considered as a factor creating the prerequisites for the progression of renal failure contributing into unfavorable prognosis of the disease progress (Beckerman et al., 2014; Tang & Zhuang, 2015; Lee-Son & Jetton, 2016).

In the discussion context of this topic, it is worth recalling that the pharmacological inhibitors of RAS (ACE-1 inhibitors, AT1 antagonists, and renin inhibitors) have been widely and successfully prescribed to solve the problem of progressive renal failure. This group of drugs contributes to the decrease of proteinuria, prevents damage of the tubular epithelium, diminishes inflammation and renal fibrosis (Macconi et al., 2014). Therefore, the question of the possible involvement of RAS blockers in normalizing the changes induced by epigenetic chromatin rearrangements appears to be quite logical. It has been established that during acute toxic renal insufficiency the renoprotective

properties of the antagonist of AT1 receptors (Losartan) are the result of the epigenetic suppression of the mechanisms that induce desquamation of podocytes and stimulate proteinuria (Hayashi et al., 2015). In particular, the authors found that losartan affects the state of methylation of the nephrin protein gene promotor. According to some data concerning the experimental model of diabetic nephropathy, losartan can demonstrate a moderately beneficial effect on the epigenetic mechanisms (Reddy et al., 2013). On the previously applied experimental model the authors showed that losartan effectively blocked epigenetic mechanisms (through the regulation of H3K9 / 14Ac acetylation processes) of the expression of genes responsible for stimulating the synthesis of the inhibitor of the plasminogen-1 activator (PAI-1) and monocyte chemoattractant protein-1 (MCP-1), which are the important mediators of renal tissue damage (Reddy et al., 2014). Based on the obtained data the authors of the cited publication conclude that the most effective pharmacological therapy for renal failure should be based on the combined use of RAS inhibitors and specific modulators of epigenetic mechanisms.

A similar point of view is expressed by other authors, suggesting that the combination of an ACE-1 inhibitor and an HDACI inhibitor (Zhong Y. et al., 2013) may lead to the most favorable therapeutic outcome. Recognizing the efficacy of losartan in limiting methylation of histones (Harshman & Zepeda-Orozco, 2016) authors see the promising clinical use of drugs belonging to the HDACI inhibitor group in nephrological practice. In addition, an opinion is expressed on the role of micro-RNA in epigenetic mechanisms of activation of local renal RAS in chronic renal failure (Witasp et al., 2017).

It should be emphasized that the study of epigenetic mechanisms of functioning of intracellular RAS is a fundamental direction of modern medical science, designed to solve the most urgent practical problems in the field of nephrology and diseases of the cardiovascular system (De Mello, 2017). Thus, the analysis of literature data has shown that the epigenetic aspects of restructuring of the intrarenal RAS have fundamental importance for understanding the pathophysiological mechanisms of renal impairments induced by angiotensin II. Primary epigenetic modification of the chromatin complex leads to the appearance of new atypical foci of intensive angiotensin II production in the tubular epithelium of the proximal and distal tubule of the nephron. Moreover, the self-sufficient (containing all the main components) intracellular RAS of the tubular epithelium switches on autocrine and paracrine mechanisms and this, on the one hand, weakens its role in the regulation of the homeostatic functions of the kidneys. But on the other hand, activation of intracellular RAS is increasingly aimed at enhancing tissue damage through abnormal energy metabolism of the cell (De Mello, 2017). In addition, the genes activated by the epigenetic mechanisms of the RAS protein components, through the increase in angiotensin II production, trigger a new cascade of covalent amplification of the covalent chromatin modification, where, angiotensin II itself as an inducer of epigenetic transformations acts directly or indirectly. This is convincingly evidenced by the results of the use of RAS blockers. In the reviews available to us there are individual indirect data that allows us to judge how effectively pharmacological inhibitors of RAS penetrate into cells (including the tubule epithelium) (Foster et al., 2009). At the same time, we can only assume the source of their possible therapeutic effect on intracellular RAS. Therefore this line of research contributes to the development of completely new pharmacological agents that contribute to the effective solution of practical problems not only in nephrology but also in controlling diseases of the cardiovascular system and in the field of oncology.

4. Mineralocorticoids

It should be noted that the analysis of pharmacological methods for controlling the metabolism of mineralocorticoids is involved in a rather wide range of problems, far beyond the study of the pathogenesis of renal dysfunctions (Zhang et al., 2009; Welch et al., 2016; Bavishi et al., 2016; Kawarazaki & Fujita, 2016; Azzam et al., 2017). However, the role of aldosterone in the pathogenesis of renal dysfunction still occupies a central position (Currie et al., 2016). Strictly speaking, aldosterone is synthesized out of the kidney. In spite of this, we consider it is possible to mention the epigenetic effects associated with its metabolism since its physiological, pathophysiological and pharmacological aspects are closely related to the functions of local and intrarenal RAS (Feraille & Dizin, 2016; Kawarazaki & Fujita, 2016; Nehme & Zibara, 2017). Perhaps such a consolidation of two topics may have more valid arguments, however, this problem requires further investigation (De Mello, 2017). Nevertheless, already known facts are widely used in practical medicine (Bavishi et al., 2016, Currie et al., 2016) and that can give us the right to supplement the mentioned above arguments with the information about the role of epigenetic mechanisms in the pathophysiology of aldosterone and RAAS.

Let us afford to make one more brief remark. In the process of phylogenesis, the primary production of mineralocorticoids in amniotes occurred relatively recently in connection with the accommodation of vertebrates on land. While in the lower vertebrates (anamniums), the function of mineral corticoids was performed by cortisol (Dolomatov et al., 2012). This is probably why we can observe interferent effects of glucocorticoids and aldosterone on sodium reabsorption processes in the distal part of the human nephron (Feraille & Dizin, 2016; Nehme & Zibara,

2017). Due to these facts, the mentioned role of glucocorticoids should be considered as an attempt for the better understanding of the discussed processes. Perhaps the consideration of the role of epigenetic modulation mechanisms of aldosterone regulatory effects must begin with the most important stimuli of intensity of its secretion by the adrenal cortex which are the increased concentration of potassium ions in the extracellular (intravascular) fluid and angiotensin-II which is formed in a local (intraorgan) RAS of suprarenal glands and kidneys (Feraille & Dizin, 2016; Kawarazaki & Fujita, 2016; Nehme & Zibara, 2017). Since angiotensin-II stimulating effect on aldosterone secretion is passing through the AT1-receptor population, it is appropriate to recall the previously established role of epigenetic mechanisms of the AT1 receptors expression control including those in the adrenal cortex (Bogdarina et al., 2007; Liang et al., 2013).

Furthermore, it was shown that the mechanisms of fetal programming accompanied even by the short-lived increase of cortisol in the blood of the mother can enhance the expression of their receptors in the fetus (Liang et al., 2013; Tain & Hsu, 2017). In the opinion of authors of the cited publications, such a mechanism can contribute to the inadequate stimulation of sodium reabsorption in adulthood, leading to systemic disturbances in hemodynamic parameters. Moreover, the authors note that the activation of sodium reabsorption in the distal nephron may occur due to trimethylation of H3K36, accompanied by the gene suppression of 11β-hydroxysteroid dehydrogenase-2 which is responsible for metabolic clearance of glucocorticoids. It should be emphasized that the pathophysiological mechanisms of aldosterone in the kidneys are directly related to the stimulation of fibrogenesis in the visceral tissues, damage of podocytes and the increase in proteinuria (Kawarazaki & Fujita, 2016).

In the modern reports, we have noticed the great increase of interest in epigenetic mechanisms of renal rearrangement associated with the changes in the expression of transport systems of sodium, potassium, and chlorine in various segments of the nephron (Tain & Hsu, 2017). One of the central targets of research is the epithelial sodium channel (ENaC) of the distal nephron (Duarte et al., 2012; Kone, 2013; Yu et al., 2013). In the cited sources it was reported that aldosterone stimulates gene transcription of the alpha subunit protein EnaC (αENaC) via activation of serum- and glucocorticoid-induced kinase-1 Sgk1, suppresses Dot1a activity (histone methyltransferase H3K79 – a disrupter of telomeric silencing) and transcription factor and Af9 deacetylase Sirt1 along with the changing the activity of the Dot1 / Af9 complex. In addition, there is evidence that the aldosterone-induced chromatin modification can enhance the expression of the endothelin-1 gene in the connecting tubes of the internal renal medulla (Welch et al., 2016).

Since mineralocorticoid receptors play an important role in the transmission of epigenetic effects of aldosterone, some interest could be shown by the data enlightening the role of this receptor population in the regulation of the expression of genes sensitive to aldosterone (Ueda et al., 2014). Our attention is also attracted to statements that epigenetic changes in the RAAS system can fundamentally disrupt the mechanisms of stimulation of aldosterone secretion in the adrenal cortex diminishing the regulatory role of the intraorganic RAS of the kidneys and adrenal glands and by the same time affecting quite different factors (for example, leptin) which are not directly associated with the renal functions and are not tied to the parameters of water-salt metabolism (Kawarazaki & Fujita, 2016). Thus, the analysis of data has shown that epigenetic mechanisms of aldosterone metabolism rearrangement are the important factors in the pathogenesis of renal dysfunctions and pathological disorders of systemic hemodynamics. It is established that epigenetic mechanisms affect the system of regulation of non-sexual steroids metabolism, aldosterone-controlled mechanisms of expression of transport proteins in the distal nephron and the secretion of physiologically active peptides in the distal nephron. In addition, there is a reason to believe that aldosterone secretion supervision processes can also undergo epigenetic changes, leading to inadequate stimulation of hormone production.

Perhaps the combination of the revealed patterns can allow some authors to assert that unrestricted activation of RAAS and the mutual enhancement of the pathophysiological effects of angiotensin II and aldosterone caused by epigenetic chromatin rearrangement appears to be one of the fundamental pathogenetic mechanisms of chronic renal and cardiovascular diseases (De Mello, 2017).

5. Transforming factor of growth-beta1

The transforming growth factor-beta1 (TGF-beta1) belongs to the superfamily of cytokines, which, in addition to TGF-beta, contains a large number of proteins, for example, BMP, which are normally important for cytodifferentiation of tissues and wound healing processes (Shi et al., 2011). Angiotensin II plays an important role in the AT1 receptor population in stimulating the intrapartum synthesis of TGF-beta (Reddy et al., 2014). Meanwhile, the authors of the quoted source note that antagonists of AT1 receptors and ACE-1 blockers possess a moderately beneficial effect on the processes of organ fibrosis in chronic renal insufficiency since there are PAC-independent ways of inducing TGF-beta1. It is known that TGF-beta1 and TGF-beta3 are the key factors in stimulating the fibrogenesis of kidney tissue in chronic renal failure (Wing et al., 2013). It was found that pathological renal impairment under conditions of experimental models of acute renal failure

is accompanied by a rather rapid increase in the production of TGF-beta1 in the tissues of the kidney through the activation of epigenetic mechanisms (Zager et al., 2011), disrupting the normal course of reparative processes in the kidney (Bonventre & Yang, 2011). During experimental acute renal failure in vivo and in modeling acute toxic effects on cultured proximal nephrocytes, it was established that stimulation of H3 (H3K4me3) methylation precedes a sharp increase in the level of TGF-beta1 mRNA in tissue (Zager & Johnson, 2010). The results of experimental studies confirm that epigenetic activation of the TGF-beta1 gene occurs during acute renal failure leading to the chronic kidney disease (Sun et al., 2014).

Since TGF-beta1 can participate in the metastasis of malignant tumors, it is one of the main inducers of renal, hepatic, pulmonary, skin fibrosis. The problem of the clinical use of anti-TGF-beta in therapy on epigenetic mechanisms is the most promising direction in the treatment of a number of dangerous diseases (Zeisberg & Zeisberg, 2015). In particular, the effectiveness is assumed for inhibiting pathogenetic TGF-beta1-dependent mechanisms through the selective inhibition of the cytokine II-type receptor population (Doi et al., 2011), application of the TGF-beta1 protein antigens (Zeisberg & Zeisberg, 2015), the involvement of selective blockers of histone deacetylase (HDAC) activity (Guo et al., 2009). Although, in the opinion of some authors, the HDAC of class I which is critically important for stimulating TGF-beta1-dependent renal fibrosis (Liu et al., 2013) it should be considered as the main target of such specific blockers. It is also suggested to apply the pharmacological correction of histone acetyl transferases (HATs) and histone deacetylases (HDACs) activity balance (Yuan et al., 2013).

It should be noted that in the literature there are represented reviews, containing sufficient depth and comprehensive analysis of possible systemic therapeutic effects of inhibitors of enzymatic activity of HDACs, aimed at preventing fibrosis of internal organs, including kidneys and other modulators of epigenetic changes in renal parenchyma (Van Beneden et al., 2013; Tang & Zhuang, 2015). Arguments are given in favor of the therapeutic efficacy of methylation inhibitors in the development of TGF-beta1-dependent fibrogenesis of the kidney (Bechtel et al., 2010). At the same time methyltransferase 7/9 (SET7 / 9), which carries out monomethylation of lysine 4 of histone H3 (H3K4me1) (Sasaki et al., 2016) is proposed as the most actual target of promising drugs. On the basic postulate that some types of miRNAs (in particular, miR-29b) has the ability to suppress some profibrotic effects of TGF-beta1, it is assumed this direction can also potentially be applied to inhibit progressive renal failure (Wing et al., 2013). It has been established that some miRNAs (miR-21 and miR-192) are inducers of TGF-beta1-dependent tubulointerstitial fibrosis and glomerulosclerosis (Liu et al., 2015). Stimulated by TGF-beta1 increase of transcription miR-192 is confirmed in experiments in vitro in cell culture (human and mouse) mesangium, podocytes, endothelial and tubular epithelium (Kato et al., 2013). The authors also found that stimulation of the TGF-beta1 transcription of miR-192 depends on the acetylation of histone H3 (H3K9, H3K14, and H3K27). Moreover, the authors of this publication suggest that miR-192 plays a special role in the cascade amplification of profibrotic effects of TGF-beta1 through activation of the transcription miR-200b and miR-200c by enhancing the expression of genes 1alfa2 collagen (Col1a2), collagen-4alfa1 (Col4a1) and the TGF-beta1 (TGF-β1) itself. On the other hand, it is known that TGF-beta1 through Smad3-protein stimulates the formation of miR-21, activating in turn gene expression of collagen I and fibronectin, as well as contributing to improving the α-SMA levels in the kidney (Wing et al., 2013). It was shown that TGF-beta1 by activating H3K4-methyltransferase SET7 / 9, increases the expression of genes that trigger processes fibrogenesis in kidney, in contrast, the suppression of SET7 / 9 inhibits the expression of TGF-beta1-induced fibrosis gene (Reddy & Natarajan, 2015; Dressler & Patel, 2015; Hilliard & El-Dahr, 2016). Perhaps the mediators of the effect of TGF-beta1 in relation to SET7 / 9 activity are reaction products catalyzed by the enzyme 12/15-Lipoxygenase (Yuan et al., 2016). Along with this, it is reported that TGF-beta1-dependent activation of fibrogenesis is carried out through the system of intracellular signal transmission by Smad proteins (Reddy & Natarajan, 2015). The authors indicate that for example Smad2 protein is involved in stimulating the acetylation of the histone H3 molecule (H3K9 / 14Ac).

Along with the previously mentioned epigenetic changes it is noted that methylation of histone H3 (H3K9me2 and H3K9me3) appears to be an important mechanism in regulating the expression of collagen-1alph1 (Col1α1) and plasminogen activator inhibitor (PAI-1) (Reddy et al., 2013; Sun et al., 2014). One of the basic pathogenetic mechanisms of tubulointerstitial lesions of the tubular nephron department is the epithelial-mesenchymal transition which intensity marker is detected by α-smooth muscle actin (αSMA) expression. In this connection, it is interesting to report that TGF-β1 had no significant effect on the state of H3K9Ac in proximal nephrocytes and myofibroblasts under the experimental model of unilateral ureteric obstruction in mice. In addition, the cytokine resulted in a redistribution of the H3K9Me3 label in the chromatin of the fibroblast nucleus, which correlated with an increase in αSMA expression (Hewitson et al., 2017). Thus, the literature data review showed that the epigenetic effects of TGF-β1 exert a very significant influence on the processes of fibrogenesis in the renal tissues, affecting, in fact, all the known mechanisms of imprinting: methylation and acetylation of histone proteins, as well as re-

arrangement of the expression of microRNA. It should be noted that the epigenetic mechanisms initiated by TGF-β1 in the renal parenchyma do not only directly participate in the realization of the sclerosing effect of the cytokine, but also sharply increase the TGF-β1-dependent pathogenetic mechanisms of remodeling of the renal parenchyma. At the same time, inhibition of TGF-β1-dependent modification of chromatin helps to slow down pathological changes in kidney metabolism.

That one side proves the leading pathogenetic role of TGF-β1 in the chronic and progressing of renal failure. On the other hand, this opens up new promising approaches for the use of selective modulators of epigenetic processes in practical medicine as it was evidenced by data on their readiness for preclinical trials (Van Beneden et al., 2013).

6. Nitric oxide molecules (NO)

According to available data epigenetic mechanisms perform the very important function in the regulation of the arginine-dependent pathway of NO synthesis in the system of isoforms of NO synthases: endothelial (nNOS-NOS-1), inducible (iNOS-NOS-2), and neural (eNOS – NOS-3). Some authors consider another isoform – mitochondrial mtNOS. There is evidence that hypoxia as one of the most potent activators of epigenetic modification of chromatin promotes a change in the expression of the genes controlling one or another isoform of the NOS enzyme (Shirodkar & Marsden, 2011). According to the cited review ischemia may be accompanied by repression of the eNOS gene in endotheliocytes, against the background of activation of transcription of all three NOS isoforms in neointima, including transcription of the eNOS gene in the muscle fibers of the blood vessel wall. The authors note that the addition to the cultured vascular smooth muscle cell inhibitor of methyltransferase DNA (5-azacytidine), as well as the inhibitor of HDAC (Trichostatin A), stimulated the transcription of the eNOS gene in these cells, also promoting an increase in eNOS mRNA. In vitro studies on the culture of proangiogenic cells (early EPCs) and mesoangioblasts found that the addition of only 3-deazaneplanocin A (DZNep), an inhibitor of trimethylation of H3K27, did not significantly affect the expression of the eNOS gene, whereas in the combined effect on the cells DZNep and the histone deacetylase inhibitor Trichostatin A (TSA) increases eNOS expression (Ohtani et al., 2011). The results of clinical observations, confirming the role of histone methylation and acetylation in the regulation of the expression of the eNOS gene, also are focused on DNA methylation processes (Kheirandish-Gozal et al., 2013). Perhaps the analysis of the process of the promoter of the eNOS gene methylation could be interesting for making a prognosis of pathological disturbances risk of some parameters of human mineral metabolism (Harvey et al., 2012). Epigenetic mechanisms controlling the expression of eNOS in the endothelium of the blood vessels of the kidney are critical in the process of organogenesis, as well as during adaptation of the kidney to hypoxia and changes in hemodynamic parameters (Jamal et al., 2012). According to the source, endotheliocytes are not sensitive to the action of cytokines that stimulate iNOS expression, since the promoter of this gene is abundantly methylated.

Normally, nNOS (NOS-1) is present mainly in the macula densa region, as well as eNOS (NOS-3) is found in endotheliocytes and tubular epithelium of renal tissues. It is known that NO participates in the regulation of renal hemodynamics, tubular sodium transport, and regulation of the glomerular filtration rate. It is an important controlling factor of tubuloglomerular response, the regulator of the blood density and inflammatory processes. However, the dynamics of changes in the intracellular production of NO does not always coincide with the level of expression of NO-synthase genes. Since the intensity of intracellular NO synthesis as renal failure progresses may decrease as a result of vascular lesions, fibrosis of the cortical layer of the kidney, changes in substrate metabolism (L-Arginine), increase in the concentration of the endogenous NO-synthase blocker (ADMA) and NOS Co-factor availability. It is established that the progression of renal failure is accompanied by a decrease in the intrarenal production of NO, which correlates with the intensity of fibrogenesis in the kidney (Schmidt Dellamea et al., 2014). At the same time, the authors note the role of some biologically active substances (insulin, tumor necrosis factor-alpha, angiotensin-II) in the regulation of expression of NO synthase genes. Perhaps the insulin-stimulated overexpression of the eNOS gene (NOS-3) is one of the most important pathogenetic mechanisms of the progression of diabetic nephropathy, since the experimental model of administration of Vorinostat (non-selectively inhibits the actions of class I (HDACs 1 to 3 and 8) and class II (HDACs 4 to 7, 9, and 10) lowered the expression of this gene, which contributed to the restriction of proteinuria on the accumulation of extracellular matrix proteins by mesangial cells (Advani et al., 2011). It is reported that primary under experimental kidney pathology excessive production of NO is the important pathogenic factor of glomerulopathy development. Secondly, Trichostatin A (TSA) is an HDAC inhibitor can help to normalize excess NO production, both endogenous NO in mesangial cells and inducible iNOS, activated by certain cytokines (eg, IL -1β) (Van Beneden et al., 2013). It is possible that HDAC inhibitors should be considered as a promising group of pharmacological agents that can contain a number of NO-dependent pathogenetic mechanisms of renal failure progression. Inflammatory and sclerosing components of tubulo-interstitial lesions block the activation of kidney fibroblasts and apoptosis of the tubular epi-

thelium (Jamal et al., 2012). In addition, HDAC inhibitors promote the restoration of kidney function by restriction of α-SMA, collagen I, fibronectin, TGFβ-1, apoptosis in diabetic nephropathy reducing the expression of iNOS and eNOS genes in the kidney (Khan & Jena, 2014).

It has been established that hypoxia is one of the most potent factors regulating the expression of the NOS3 gene of endothelial NO synthase of endotheliocytes through reduced acetylation and lysine 4 (histone H3) methylation (Fish et al., 2010). It is suggested that the hypoxia-induced enhancement of the expression of inducible iNOS can also have a nephroprotective effect in reperfusion injuries of the organ (Bonventre & Yang, 2012). Nevertheless, prolonged stimulation of iNOS expression in toxic kidney damage is considered as the unfavorable factor aggravating the course of the disease (Sattarinezhad et al., 2017). It should be recognized that the problem of epigenetic rearrangement of the intracellular nitric oxide system is rather multifaceted, in particular, the literature on the analysis of changes in the balance of some humoral regulators of kidney activity (NO, angiotensin II, arachidonic acid derivatives) under fetal programming conditions (Tain & Joles, 2016). The issues under discussion are evidenced by review publications containing information on the fundamental epigenetic mechanisms of the regulation of the nitric oxide system (Vasudevan et al., 2016; Socco et al., 2017). However, it is impossible to exclude the possibility of organ-specific mechanisms including renal parenchyma for controlling the expression of various NOS isoforms, in particular, iNOS and eNOS (Cerkezkayabekir et al., 2017).

Summarizing the facts, we can conclude that the epigenetic transformation of the system of nitric oxide is the important part of pathogenetic mechanisms of disorders of the kidneys. Available data facts indicate that the triggering of this pathway, for example, by tissue hypoxia or under the influence of hormones and cytokines may be carried out at the early stages of kidney disease. In addition, renal NOS system undergoes a radical modification during progression of renal failure, which is manifested in the reduction of nNOS expression in the cortical substance of the kidneys, the steady decrease in the expression of eNOS in endothelial cells and the occurrence of atypical localization of eNOS in the muscular layer of the vascular wall and stimulation of the iNOS expression. On the one hand, it is known that renal NOS (mainly nNOS) is involved in regulating the activity of renal RAS, and the molecule NO is one of the main antagonists inotropic effects of angiotensin II on the vascular and tubular level (Chappell, 2012; Thoonen et al., 2013). Consequently, the decrease of NO regulatory effects may be one of the reasons for the unlimited activation of the intrarenal RAS and TGF-beta during renal failure progression (Macconi et al., 2014). Moreover, according to some authors, the activation of mitochondrial NOS is possible to consider as a trigger for the basic pathogenic mechanisms of epigenetic activation of intracellular RAS (De Mello, 2017). On the other hand, we have inadequate activation of the expression of NOS (eNOS and iNOS) at the certain stages of the disease, because of the specific physicochemical properties of the final product – the molecules of nitrogen oxide and of the functioning of the NO-synthase complexes can serve as a source of active forms of oxygen and nitrogen, making this a significant contribution to the exacerbation of pathological processes (Advani et al., 2011; Sattarinezhad et al., 2017; Tain et al., 2017).

In addition, the discussion of epigenetic alterations the arginine dependent pathway of NO formation does not exhaust all the topics of the metabolism of nitric oxide in the kidneys both normal and pathological. It is known that there is a mechanism of NO-molecule resynthesis which uses chemically stable oxidation products of NO (nitrites, nitrates, etc.) as a substrate and controlled by such proteins as hemoglobin or cytochrome P450. In contemporary reports, we find no mention of arginine, independent of NO synthesis in connection with epigenetic modulation system of nitric oxide (Vasudevan et al., 2016; Socco et al., 2017). However, these mechanisms have a certain specificity typical for the metabolic and transport processes occurring in the renal tissues.

7. Factors inducting epigenetic changes of kidney functions

Epigenetic transformation of chromatin is able to be triggered by environmental factors and changes in the parameters of the state of metabolic processes in the body. Among them, the most common known factors are:

1. Hypoxia (ischemia of the organ).
2. Hyperglycemia.
3. Heavy metals.
4. Endocrinopathies.
5. Infectious diseases.

Hypoxia. Let us emphasize that hypoxia of the renal parenchyma of various genesis is considered as one of the basic inducers of epigenetic mechanisms of transformation of humoral systems controlling the renal functions (Clarke, 2012). It is known that stimulated by hypoxia HIF-1alpha is a potent activator of epigenetic mechanisms (Perez-Perri et al., 2011). Being an important element in the system of kidney adaptation to hypoxia HIF-1alpha is directly involved in pathogenetic mechanisms of chronic and progressive renal failure (Shoji et al., 2014). It has been established that the inhibition of methylation of histones (H3K9me3 and H3K27me3) accompanies the progression of renal failure (Nangaku et al., 2017). It is reported that epigenetic mechanisms of activation of the renin-angiotensin system can play a key role in the chroniciza-

tion and progression of renal failure (Chou et al., 2017). It was shown that the HIF-1alpha at the transcription level changes the balance of expression of the components of the RAS in the direction of stimulation of the biosynthesis of the components of this axis: Angiotensin-I-converting enzyme (ACE) / Angiotensin-2 / AT1 receptors stand against the inhibition of the opposite response loop PAC ACE-2 / Angiotensin- 1-7 / MASS1 receptors (Macconi et al., 2014; Clarke, 2012). In addition to the fact that HIF-1alpha increases the expression of AT1 receptors and ACE, acute activation of the ACE-independent pathway of the formation of angiotensin-I in the presence of hypoxia-induced lactate-chymase-dependent mechanism is observed under conditions of hypoxia in the kidney (Xie et al. 2017). Together, the hypoxia-induced shift in balance in favor of the axis of the Angiotensin-I-converting enzyme (ACE) / Angiotensin-2 / AT1 receptors against the inhibition of the opposite response loop of RAS ACE-2 / Angiotensin-1-7 / MASS1 promotes the inflammation, violates cell cycle of the renal parenchyma and energy metabolism of nephrocytes, activates epithelial-to-mesenchymal transition (Macconi et al., 2014, Chou, 2017). Epigenetic mechanisms play an important role in the chronicization and progression of renal failure, inducing a disturbance in the function of podocytes (Lin & Lee, 2014) and mesangium (Lu et al., 2017). According to a number of researchers, the key link in this process is the induced RAS lesion of the proximal nephron (Marumo et al., 2008). Along with this, arguments are given that the epigenetic processes stimulated by the family of HIF proteins can be the promising object of pharmacological methods of restraining the progressive renal failure (Matsusaka et al., 2012).

Hyperglycemia. In the vast majority of cases, hyperglycemia is considered as a symptom related to a duration of diabetes. However, consistently elevated levels of glucose in the extracellular fluid acts as an independent pathogenic factor of renal dysfunction (Dounousi et al., 2015) and are capable of initiating further progression of kidney failure due to the covalent transformation of the chromatin (Ruiz-Hernandez et al., 2015). When discussing the role of hyperglycemia in mechanisms of epigenetic adjustment of the kidney function it should be noted that the symptoms of II type diabetes are accompanied by changes in insulin secretion, metabolic disturbances, increased production of reactive oxygen species, disturbance of the parameters of systemic and organ hemodynamics, increased levels of HIF-1 (Macconi et al., 2014). According to the cited authors, HIF-1 was shown to induce the expression of several epigenetic regulators such as histone demethylases. It has been suggested that hyperglycemia is largely responsible for a number of typical changes in signaling mechanisms in kidney cells including tubular epithelial cells, fibroblasts, endothelial cells, mesangial cells and podocytes (Macconi et al., 2014). The review indicates that the stimulation of fibrosis of the renal tissues may increase TGF-β induced enrichment of active epigenetic marks on miR-29, H3K9/14Ac, H3K9Ac, H3K4me1 and H3K4me3, and decreased levels of repressive marks such as H3K9me3. These changes may be accompanied by increased expression of Agt gene (angiotensinogen) in the proximal kidney cells causes significant release caused by inhibition of DNMT and increase of HDAC.

On the other hand, it should be given the role of diabetes-related changes of hemodynamic parameters on epigenetic processes (Kuo et al., 2013). It is known that a sustained increase in blood pressure may contribute to the increased expression of the ACE gene (angiotensin converting enzyme) including kidney via increases in activation marks (H3KAc and H3K4me) and decreases in repressive mark (H3K9me2) (Liang et al., 2013; Macconi et al., 2014). Epigenetic mechanisms of pathogenesis and progression of hypertension considered in a number of review publications (Friso et al., 2015; Wise & Charchar, 2016). The authors of the cited papers mentioned a number of genes the expression of which is closely associated with hypertension, including genes of renin, ACE, angiotensin-receptor-2 and endothelial NO-synthase. Epigenetic alteration of gene expression of NO-synthases can be induced by hypoxia (Fish et al., 2010) and hyperglycemia (Advani et al., 2011). It is shown that histone deacetylases inhibitor Vorinostat decreased albuminuria, mesangial collagen type IV deposition, and oxidative-nitrosative stress in experimental models of diabetes type I (Advani et al., 2011).

Heavy metals. Heavy metals are widely known for their nephrotoxic action of heavy metals. But the modern data review contains the small amount of information about their epigenetic effects (Ruiz-Hernandez et al., 2015). In particular, the authors have noted increased DNA methylation due to elevated cadmium exposure where a general trend towards hypomethylation with increasing blood lead levels was observed. The most informative data about mercury effects were obtained from the experimental studies. They reveal the evidence that mercury can change DNA methylation patterns. In rat embryonic neural stem cells and prenatally exposed adult rats methylmercury reduced neural cell proliferation and was associated with global DNA hypomethylation. Also, the authors of the cited publications have reported that the induction mechanisms of heavy metals in the epigenetic restructuring of the DNA remained almost unstudied. Because the highly toxic heavy metals (mercury, cadmium, and lead) are present in human body usually in trace amounts without causing acute toxic effects, it would be rather interesting to analyze their influence on the change of metabolic processes in the body, the endocrine functions of the pancreas, in the pathogenesis of tissue resistance to insulin and induction of excess body weight (Kuo et al., 2013).

Endocrinopathies. The progress of endocrinopathies is related to the fact that several factors can influence the state of epigenetic mechanisms simultaneously. The example of such combined effect we have already discussed by analyzing the epigenetic effects of hyperglycemia. At the same time, the factor of inadequate secretion of insulin is not secondary in the line of triggering factors and can participate in epigenetic mechanisms of the renal regulations (Shiels et al., 2017). The participation of insulin in the regulation of the expression of mouse and human genes through the DNA methylation system has been experimentally confirmed (Kuroda et al., 2009). It is also known that aldosterone can directly regulate the expression of the α-subunit gene of the epithelial sodium channel of the distal nephron part – αENaC through the histone methylation system (Kone, 2013), as well as endothelin-1 (Welch et al., 2016). It is suggested that understanding these epigenetic mechanisms of aldosterone can be useful during treatment of hypertension and in the overweight control (Kawarazaki & Fujita, 2016). Hormones of the thyroid gland can be mentioned as a potential inducer of the epigenetic transformation of humoral systems controlling of homeostatic functions of the kidneys. In the literature, there are indications of the effect of thyroid hormone as a naturally occurring histone acetylase inhibitor (Re et al., 2016). It has also been established that epigenetic effects of histone deacetylase 5 (HDAC5) by thyroxin can be realized via the signaling pathway through integrin αvβ3 / PKD / HDAC5 (120). In the recent reviews, there is also presented data that in terms of hypothyroidism a subsequent change in the expression of some genes through the imprinting mechanism an be also observed (Hu et al., 2014; Leow, 2016). Consequently, both hypo- and hyperthyroidism can be considered as potential inducers of epigenetic rearrangement of humoral systems for controlling kidney functioning. Since it is widely known that the violation of the thyroid status of the body increases the risk of kidney disease through the activation of RAS (Kobori et al., 1999).

Infectious diseases. Inflammatory reactions of human kidney tissues in response to infectious and non-infectious diseases are analyzed by taking into account their populational characteristics from the standpoint of modern views on the phylogeny of the excretory system and the principles of anthropogenesis (Chevalier, 2017). The role of epigenetic mechanisms is emphasized in the evolutionary aspects of the formation of adaptive responses of the immune system and kidney tissues. Based on the results of population studies, the possible role of the microflora of the human body was analyzed in the epigenetic rearrangement of immune reactions associated with the risk of kidney disease (Uy et al., 2015). Further studies have shown that the state of the microflora of the body can influence the risk of kidney disease via epigenetic mechanisms of the restructuring of the intrarenal RAS (Marques et al., 2017). The relevance of the RAS epigenetic induction and viral invasion was illustrated (Chandel et al., 2013).

8. Discussion

The results of the review allow us to conclude that epigenetic mechanisms provide a very important contribution to the reconstruction of humoral regulation systems of the kidneys in conditions of renal failure, largely contributing to a progressive reduction of active nephrons and directly raising the risk of the mortality.

In this case, we can identify several common trends typical for the epigenetic transformation of intrarenal synthesis and metabolism of physiologically active substances. Primary we should consider the formation of atypical foci of their synthesis, which is most evident in the processes of restructuring of the RAS and nitric oxide systems. Secondly, the humoral factors that coordinate the physiological control systems of the homeostatic activity of the kidneys during the epigenetic changes increasingly disturb the functions of regulation of homeostasis and switch on the pathophysiology of renal dysfunctions and progressive renal failure. The next triggering factor is the epigenetic changes affecting genes of proteins and peptides that perform key functions in the synthesis and metabolism of humoral factors regulating renal functions. Uncontrolled synthesis of these peptides leads to a triggered enhancement of the pathological process again involving epigenetic chromatin rearrangement. Consequently, on the one hand, the genes controlling the expression of humoral factors in the regulation of kidney functions are the subject of imprinting. On the other hand, stimulation by imprinting modulation of the humoral synthesis on a subsequent coil turn promotes the further progress of epigenetic modification of chromatin and the further increase of humoral synthesis. The clearest evidence can be traced in the unrestricted activation of RAAS and the system of TGF-beta. It can be concluded that by imprinting an enormous increase in the vasotonic, fibrotic and pro-inflammatory inducers is observed as a result of imbalanced of RAAS and the TGF-beta system. Against this background, there is a steady decrease in the regulatory capabilities of the opposition control vector, represented, in particular, by the nitrogen oxide system, primarily by the constitutive isoforms eNOS and nNOS. And finally the disclosure of epigenetic processes in the formation and progression of nephropathies of different genesis do not only contribute to the creation of a more reliable theoretical basis to understand the pathogenesis of renal failure but opens the way to the development of fundamentally new promising pharmacological methods for therapy of renal injury. Unfortunately, the format of this manuscript does not allow us to pay as much attention to this topic as it certainly deserves. Meanwhile, one should

take into account the results of a studies describing the role of epigenetic mechanisms in the modulation of arginine-vasopressin systems (Murgatroyd, 2014, Lesse et al., 2017), pore-forming proteins of aquaporins (Park & Kwon, 2015, MacManes, 2017) and the atrial natriuretic peptide (Sergeeva et al., 2014; Sergeeva et al., 2016). The products of the metabolism of arachidonic acid (Yuan et al., 2016) and thyroxine (Liu et al., 2014; Re et al., 2016) may be directly related to the issues under discussion equally to the renotropic epigenetic effects of insulin (Kumar et al., 2016; Shiels et al., 2017), Hypoxia Inducible Factors (HIFs family) (Perez-Perri et al., 2011; Liu et al., 2017).

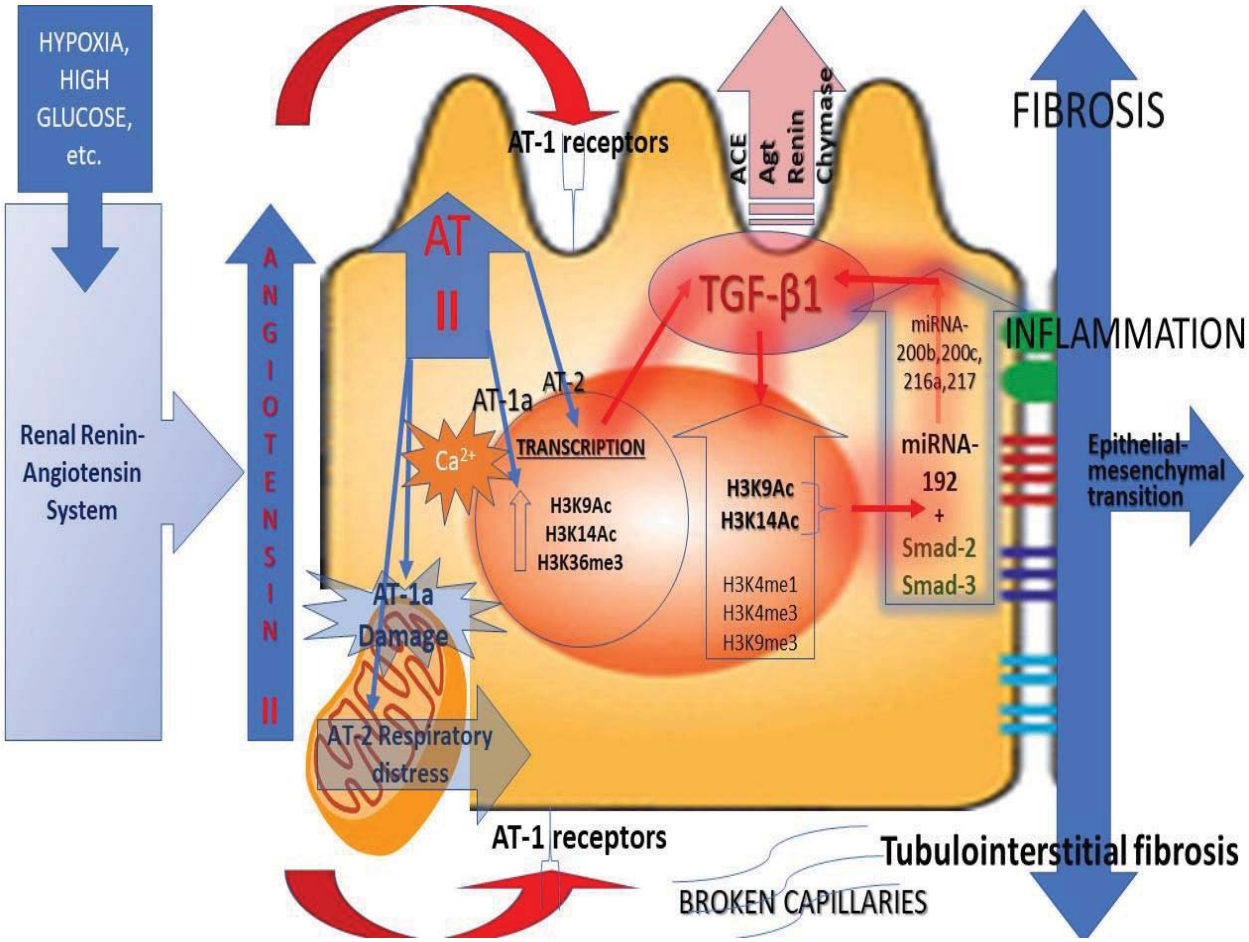

Figure 1. The damage of the proximal nephron parts is considered as one of the universal pathogenetic mechanisms of chronic and progressive renal failure. The figure shows the possible pathogenetic effects of enhancing the intracellular RAS activity and increasing synthesis of TGF-beta1 in the epithelium of the proximal nephron, inducing epigenetic rearrangement of the hereditary apparatus. Inductors (High glucose, HIF-1 et al.) of intracellular Ang-II (angiotensin) production induce the stable high activity of the intrarenal RAS (Abadir et al., 2012; Ellis et al., 2012; Macconi & Remuzzi, 2014). Elevated concentration of Ang-II in the kidneys helps destroy the peritubular network of capillaries and increase the internalization of Ang-II by proximal nephrocytes through the apical and basolateral poles of the cell. The growth of intracellular concentration of Ang-II occurs as a result of absorption of extracellular Ang-II by nephrocytes and enhancement of its intracellular production. The intracellular effects of Ang-II occur due to the interaction of this peptide with the AT1a and AT2 receptors of the nucleus and mitochondria (Ellis et al., 2012; Gwathmey et al., 2012). Via AT1 receptors, mitochondria Ang-II can induce damage and a reduction in the number of these organelles. Through AT2 receptors, NO-dependent respiratory depression (inhibition of cytochrome C) is carried out (Ellis et al., 2012; Gwathmey et al., 2012). Interaction with ATA-receptors of the nucleus is accompanied by an increase in the concentration of calcium ions Ca^{2+}. AT1a and AT2 receptor receptors mediate hormone regulation of protein biosynthesis at the transcription level (Ellis et al., 2012). Via AT1a nuclear receptors the Ang-II can directly regulate the covalent modification of some histones (Reddy, M.A. et al., 2014). In turn, the increase in H3K9Ac and H3K14As stimulates the biosynthesis of RAS components in the cell. The cytosolic content of

RAS components increases the levels of angiotensinogen (Agt), angiotensin-converting enzyme (ACE), renin, AT1a receptor and chymase on the background of the ACE-2 synthesis repression (Ellis et al., 2012; Gwathmey et al., 2012). These changes enhance the effects of ang-2 through AT1a receptors, including the ACE-independent pathway for the formation of an octapeptide in the presence of chymase. At the same time, the production of TGF-beta1 stimulated by Ang-II and Ang-II -independent mechanisms is increasing (Ellis et al., 2012; Macconi & Remuzzi, 2014; Gwathmey et al., 2012). TGF-beta1 is also an inducer of epigenetic mechanisms, stimulating the covalent modification of a wide range of histones and the formation of a number of miRNA molecules (Macconi & Remuzzi, 2014; Reddy et al., 2013; Kato et al., 2013). Perhaps the key role in the chain of activated TGF-beta1 synthesis of miRNA belongs to miRNA-192 (Kato et al., 2013). The authors demonstrated that miRNA-192 stimulated miRNA-200b and miRNA-200c synthesis and in addition activated the biosynthesis of TGF-beta1. Thus, epigenetic processes are involved not only in stimulating the activity of intracellular production of Ang-II and TGF-beta1 but are directly involved in the pathophysiological mechanisms of cascade gene enhancement of the of Ang-II and TGF-beta1 expression. In turn, this activates fibrosis and hypertrophy of cells, stimulates inflammation, oxidative stress, activation of the epithelial-mesenchymal transition and progression of tubulo-interstitial fibrosis.

9. Conclusions

The following conclusions can be drawn from the results of the review and discussion presented in this paper:

1. It has been established that epigenetic modifications of chromatin greatly contribute to disbalance of intrarenal metabolism of biologically active substances in the renal regulations.

2. The mechanisms of imprinting largely determine the progression of renal failure.

3. Changing the processes of the synthesis of humoral factors under the influence of epigenetic mechanisms exerts the further impact on the covalent modification of chromatin, enhancing the pathophysiological mechanisms of renal parenchyma damage.

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