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ROLE OF THE AGT GENE IN THE DEVELOPMENT OF CHRONIC KIDNEY DISEASE

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Tayanch so‘zlar: AGT geni, angiotenzinogen, surunkali buyrak kasalligi, renin–angiotenzin tizimi, genetik polimorfizm, buyrak fibrozi, arterial gipertenziya.
Ключевые слова: ген AGT, ангиотензиноген, хроническая болезнь почек, ренин–ангиотензиновая система, генетический полиморфизм, почечный фиброз, артериальная гипертензия.

Chronic kidney disease (CKD) is a progressive disorder characterized by gradual loss of renal function and structural damage to kidney tissue. Genetic and environmental factors both contribute to CKD development and progression. Among genetic determinants, the angiotensinogen (AGT) gene plays a critical role in regulating the renin–angiotensin–aldosterone system (RAAS), which is essential for maintaining blood pressure, fluid balance, and renal hemodynamics. Variations in the AGT gene, particularly the M235T polymorphism, have been associated with increased angiotensinogen levels and enhanced RAAS activation, contributing to hypertension, glomerular hyperfiltration, and progressive renal damage. Overactivation of RAAS leads to increased intraglomerular pressure, inflammation, oxidative stress, and fibrosis, ultimately accelerating CKD progression. Additionally, angiotensin II stimulates transforming growth factor-β (TGF-β) expression, promoting extracellular matrix accumulation and renal fibrosis. Understanding the molecular mechanisms linking AGT gene polymorphisms to CKD pathogenesis may provide new insights into personalized therapeutic approaches and early risk assessment. This review summarizes current knowledge on the biological role of the AGT gene, its polymorphisms, and their contribution to the development and progression of chronic kidney disease.

SURUNKALI BUYRAK KASALLIGI RIVOJLANISHIDA AGT GENINING ROLI

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Surunkali buyrak kasalligi (SBK) buyrak funksiyasining asta-sekin pasayishi va buyrak to‘qimasining strukturaviy shikastlanishi bilan tavsiflanadigan progressiv kasallikdir. SBK rivojlanishi va uning progressiyasida genetik hamda atrof-muhit omillari muhim rol o‘ynaydi. Genetik determinantlar orasida angiotenzinogen geni (AGT) renin–angiotenzin–aldosteron tizimini (RAAT) boshqarishda muhim ahamiyatga ega bo‘lib, u arterial qon bosimi, suyuqlik muvozanati va buyrak gemodinamikasini saqlashda asosiy rol o‘ynaydi. AGT genidagi variatsiyalar, xususan M235T polimorfizmi, angiotenzinogen darajasining oshishi va RAAT tizimining kuchli faollashuvi bilan bog‘liq bo‘lib, bu arterial gipertenziya, glomerulyar giperfiltratsiya va buyrakning progressiv shikastlanishiga olib kelishi mumkin. RAAT tizimining ortiqcha faollashuvi intraglomerulyar bosimning oshishi, yallig‘lanish, oksidativ stress va fibroz rivojlanishiga sabab bo‘ladi hamda natijada SBK progressiyasini tezlashtiradi. Bundan tashqari, angiotenzin II transforming growth factor-β (TGF-β) ekspressiyasini rag‘batlantiradi, bu esa ekstrasellyulyar matriks to‘planishini kuchaytirib, buyrak fibrozining rivojlanishiga olib keladi. AGT geni polimorfizmlarining SBK patogeneziga ta’sirini tushunish shaxsga yo‘naltirilgan davolash usullarini ishlab chiqish hamda kasallik xavfini erta baholash uchun yangi ilmiy yondashuvlarni taqdim etishi mumkin. Ushbu sharhda AGT genining biologik roli, uning polimorfizmlari hamda ularning surunkali buyrak kasalligining rivojlanishi va progressiyasidagi o‘rni bo‘yicha mavjud ilmiy ma’lumotlar umumlashtirilgan.

РОЛЬ ГЕНА AGT В РАЗВИТИИ ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК

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Хроническая болезнь почек (ХБП) является прогрессирующим заболеванием, характеризующимся постепенным снижением функции почек и структурным повреждением почечной ткани. Как генетические, так и факторы окружающей среды способствуют развитию и прогрессированию ХБП. Среди генетических детерминант ген ангиотензиногена (AGT) играет важную роль в регуляции ренин–ангиотензин–альдостероновой системы (РААС), которая имеет ключевое значение для поддержания артериального давления, водно-электролитного баланса и почечной гемодинамики. Вариации гена AGT, в частности полиморфизм M235T, связаны с повышением уровня ангиотензиногена и усиленной активацией РААС, что способствует развитию артериальной гипертензии, клубочковой гиперфильтрации и прогрессирующего повреждения почек. Чрезмерная активация РААС приводит к повышению внутриклубочкового давления, воспалению, оксидативному стрессу и фиброзу, что в конечном итоге ускоряет прогрессирование ХБП. Кроме того, ангиотензин II стимулирует экспрессию трансформирующего фактора роста-β (TGF-β), способствуя накоплению внеклеточного матрикса и развитию почечного фиброза. Понимание молекулярных механизмов, связывающих полиморфизмы гена AGT с патогенезом ХБП, может дать новые представления для разработки персонализированных терапевтических подходов и ранней оценки риска заболевания. В данном обзоре обобщены современные данные о биологической роли гена AGT, его полиморфизмах и их вкладе в развитие и прогрессирование хронической болезни почек.

Introduction. Chronic kidney disease (CKD) represents a major global public health problem, affecting approximately 10–15% of the world's population. The disease is characterized by progressive nephron loss, reduced glomerular filtration rate (GFR), and structural remodeling of kidney tissue. CKD frequently progresses to end-stage kidney disease (ESKD), requiring renal replacement therapy such as dialysis or kidney transplantation (Bikbov et al., 2020).

The development of CKD is influenced by a complex interaction between environmental and genetic factors. While diabetes mellitus, hypertension, and aging are well-known risk factors, genetic susceptibility also plays a significant role in determining disease onset and progression. Among the genes involved in renal pathophysiology, the angiotensinogen (AGT) gene has attracted considerable attention due to its central role in the renin–angiotensin–aldosterone system (RAAS) (Kim et al., 2015).

The RAAS system regulates blood pressure, sodium balance, and renal perfusion. Dysregulation of this system contributes to hypertension, inflammation, oxidative stress, and fibrosis—key mechanisms involved in CKD progression. Angiotensinogen, the precursor of angiotensin peptides, is encoded by the AGT gene and represents a rate-limiting component of RAAS activation. Genetic variations in the AGT gene can increase angiotensinogen production, resulting in excessive formation of angiotensin II and subsequent renal injury.

Understanding the role of the AGT gene and its polymorphisms in CKD development is essential for identifying individuals at increased risk and developing targeted therapeutic strategies.

Molecular Biology of the AGT Gene

Gene Structure and Expression

The angiotensinogen (AGT) gene is located on chromosome 1q42–q43 and encodes a glycoprotein consisting of approximately 485 amino acids. Angiotensinogen is primarily synthesized in the liver, although it is also expressed in several other tissues, including the kidneys, adipose tissue, brain, and vascular endothelium.

Angiotensinogen serves as the precursor molecule for angiotensin peptides. Renin, a proteolytic enzyme released from the juxtaglomerular cells of the kidney, cleaves angiotensinogen to form angiotensin I. This inactive decapeptide is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE), primarily in the pulmonary endothelium.

Angiotensin II is the main effector peptide of the RAAS system and exerts multiple physiological effects, including vasoconstriction, aldosterone secretion, sodium retention, and stimulation of sympathetic nervous activity. These actions play an essential role in maintaining systemic blood pressure and extracellular fluid balance.

However, excessive RAAS activation may lead to pathological consequences, particularly in the cardiovascular and renal systems.

AGT Gene Polymorphisms

Several polymorphisms of the AGT gene have been identified, but the most widely studied variant is the M235T polymorphism, which involves substitution of methionine (M) with threonine (T) at position 235 of the protein.

This polymorphism has been associated with increased plasma angiotensinogen levels and enhanced RAAS activity. Individuals carrying the TT genotype often exhibit higher circulating levels of angiotensinogen compared with those carrying the MM genotype.

Elevated angiotensinogen levels result in increased production of angiotensin II, which can lead to:

- systemic hypertension
- increased glomerular capillary pressure
- endothelial dysfunction
- inflammatory activation
- renal fibrosis

Numerous epidemiological studies have demonstrated an association between the AGT M235T polymorphism and increased susceptibility to hypertension and kidney disease.

Role of the AGT Gene in CKD Pathogenesis

Hemodynamic Effects

One of the primary mechanisms through which the AGT gene contributes to CKD development is through hemodynamic changes in the kidney.

Excessive angiotensin II production leads to constriction of efferent arterioles within the

glomerulus. This increases intraglomerular pressure and initially enhances glomerular filtration. However, prolonged exposure to elevated pressure results in glomerular injury and structural damage.

Persistent glomerular hypertension contributes to:

glomerulosclerosis

proteinuria

progressive nephron loss

These processes ultimately accelerate CKD progression.

Inflammatory and Oxidative Mechanisms

Angiotensin II also acts as a potent pro-inflammatory mediator. It stimulates the production of inflammatory cytokines such as:

interleukin-6 (IL-6)

tumor necrosis factor-α (TNF-α)

monocyte chemoattractant protein-1 (MCP-1)

These cytokines promote infiltration of immune cells, including macrophages and lymphocytes, into renal tissue.

Furthermore, angiotensin II increases the generation of reactive oxygen species (ROS) through activation of NADPH oxidase. Oxidative stress damages renal cells and further amplifies inflammatory signaling pathways.

Fibrosis and Extracellular Matrix Accumulation

Another important mechanism linking AGT gene activity to CKD progression is stimulation of renal fibrosis.

Angiotensin II induces expression of profibrotic cytokines such as transforming growth factor-β (TGF-β). TGF-β promotes the synthesis of extracellular matrix components, including collagen and fibronectin, leading to progressive accumulation of fibrotic tissue.

Excessive ECM deposition results in:

glomerulosclerosis

tubulointerstitial fibrosis

tubular atrophy

These pathological changes gradually replace functional nephrons with fibrotic tissue.

Interaction Between AGT and Other Genetic Factors

CKD is a multifactorial disease involving interactions between multiple genes. In addition to AGT, several other genes contribute to RAAS regulation and renal injury.

These include:

ACE gene

AT1 receptor gene (AGTR1)

TGF-β1 gene

Gene–gene interactions may influence the severity and progression of CKD. For example, combined polymorphisms in AGT and ACE genes may significantly increase RAAS activity and accelerate renal damage.

Clinical Significance of AGT Gene Variations

Identification of AGT gene polymorphisms may have important clinical implications.

First, genetic screening could help identify individuals who are genetically predisposed to CKD or hypertension. Early detection may allow implementation of preventive strategies such as lifestyle modification and strict blood pressure control.

Second, genetic information may guide personalized treatment approaches. Patients with increased RAAS activity due to AGT polymorphisms may benefit particularly from RAAS-blocking medications, including:

ACE inhibitors

angiotensin receptor blockers (ARBs)

direct renin inhibitors

These therapies reduce angiotensin II activity and slow the progression of renal damage.

Therapeutic Implications

Targeting the RAAS system remains one of the most effective strategies for slowing CKD progression.

ACE inhibitors and ARBs have been shown to reduce proteinuria, decrease intraglomerular

pressure, and limit renal fibrosis. In addition to these established treatments, novel therapeutic approaches are being investigated.

These include:

RNA-based therapies targeting AGT gene expression

gene-editing technologies

novel RAAS pathway inhibitors

Such approaches may provide new opportunities for precision medicine in CKD management.

Conclusion. The AGT gene plays a central role in the regulation of the renin–angiotensin–aldosterone system and contributes significantly to the pathogenesis of chronic kidney disease. Genetic polymorphisms in the AGT gene, particularly the M235T variant, are associated with increased angiotensinogen levels, enhanced RAAS activation, and increased susceptibility to hypertension and renal injury.

Through hemodynamic, inflammatory, oxidative, and fibrotic mechanisms, excessive RAAS activation accelerates renal damage and promotes CKD progression. Understanding the genetic basis of CKD provides valuable insights into disease mechanisms and may facilitate the development of personalized therapeutic strategies aimed at preventing or slowing kidney disease progression.

Future research should focus on clarifying gene–environment interactions and developing targeted therapies that specifically modulate AGT-mediated signaling pathways.

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