УДК: 616.12-008.331:611.1:615.224

СОВРЕМЕННЫЕ АСПЕКТЫ ИММУННЫХ МЕХАНИЗМОВ В ПАТОГЕНЕЗЕ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

Мухамедова М.М., Ганиева Ш.Ш.
Ташкентская Областная специализированная Соматическая Больница
Бухарский государственный медицинский институт

Резюме: В настоящем обзоре представлены данные современных научных исследований, свидетельствующие об участии иммунной системы в регуляции артериального давления, рассматриваются механизмы нейро-иммунной регуляции сосудистого тонуса, эндотелиальной дисфункции и модуляции цитокинового статуса в патогенезе артериальной гипертензии. Авторами сформулирован вывод о предикторах формирования артериальной гипертензии и причинно-следственной роли иммунных и воспалительных реакций организма.

Ключевые слова: артериальная гипертензия, иммунитет, цитокины, эндотелий, сердечно-сосудистые заболевания.

ARTERIAL GIPERTENZIYA PATOGENEZIDA IMMUN MEXANIZMLARNING ZAMONAVIY JIHATLARI

Muxamedova M.M, Ganiyeva Sh.Sh.
Toshkent Viloyati ixtissoslashtirilgan Somatika shifoxonasi
Buxoro davlat tibbiyot instituti

Xulosa: Tahliliy maqolada arterial gipertenziya patogenezida immun tizimining arterial qon bosimini boshqarishidagi o’rni, tomirlar tonusini boshqarishda neyro-immun tizimi va endotelial disfunksiyaning ahamiyati, hamda sitokinlar modulyatsiyasi haqida zamonaviy tadqiqotlar natijalari yoritilgan. Mualliflar tomonidan arterial gipertenziya shakllanishi prediktorlari, ularning organizmdagi immun va yallig’lanish reaksiyalariga ta’siri haqida xulosa berilgan.

Kalit so'zlar: arterial gipertenziya, immunitet, sitokinlar, endoteliy, yurak-qon-tomir kasalliklari.

MODERN ASPECTS OF IMMUNE MECHANISMS IN THE PATHOGENESIS OF ARTERIAL HYPERTENSION

Mukhamedova M.M., Ganiyeva Sh.Sh.
Tashkent Regional Specialized Somatic Hospital
Bukhara State Medical Institute

Resume: This review presents the data of modern scientific studies indicating the involvement of the immune system in the regulation of blood pressure, examines the mechanisms of neuro-immune regulation of vascular tone, endothelial dysfunction and modulation of cytokine status in the pathogenesis of hypertension. The authors have formulated a conclusion about the predictors of the formation of

arterial hypertension and the causal role of immune and inflammatory reactions of the body.

Key words: arterial hypertension, immunity, cytokines, endothelium, cardiovascular diseases.

In recent years, data have been accumulating indicating the role of the immune system in the regulation of blood pressure (BP) and cardiovascular risk associated with hypertension. The first line of defense of the immune system involves an innate reaction and occurs very quickly. The second line of defense, namely adaptive immunity, is characterized by a belated, but very purposeful reaction. From the point of view of the development of arterial hypertension (AH), the interaction between these two components of the immune system seems to be significant [8,30].

T-cell cytokines play a central role in the pathophysiology of cardiovascular diseases (CVD) and hypertension and contribute to damage to end organs [2;3]. One of the first identified and most well-characterized cytokines in relation to hypertension is interleukin (IL)-17. T-helper (Th) cells and their pro-inflammatory cytokine IL-17 play an essential role in hypertensive autoimmune diseases and endothelial dysfunction. In particular, CD4+ T cells of people with arterial hypertension produced a higher amount of IL-17A than the normotensive control CD8+ T cells produced a higher amount of interferon (IFN)-γ in patients with hypertension compared to the normotensive control [29].

The naive CD4+ T cell, depending on the cytokine medium, is polarized to the phenotypes Th1, Th2, Th17 or T-regulators (T-reg). The Th1 phenotype is generated in the medium of IL-12 and IFN-γ, mainly secretes IL-2, tumor necrosis factor (TNF)-α and IFN-γ. The Th2 phenotype is generated in the IL-4 medium and mainly secretes IL-4 and IL-10. The Th17 phenotype requires IL-6, IL-21, IL-23, transforming growth factor (TGF)-β and IL-1β; it is activated by aldosterone and secretes IL-17A, IL-17F, IL-21 and IL-22. The Treg phenotype is generated in the medium of TGF-β1 with a low concentration of IL-6, and its anti-inflammatory activity is manifested by the secretion of immunosuppressive immune factors, such as IL-9, IL-10, TGF-β and cytotoxic T-lymphocyte antigen 4 (CTLA-4) and direct intercellular contact. Finally, cytokines often have overlapping functions, which is a problem in studies targeting individual cytokines to assess their role in hypertension and tissue damage. All these circumstances are responsible for the variability in the improvement of hypertension due to the suppression of specific cytokines [36,37].

While pro-inflammatory cytokines such as IL-17, IFN-γ and TNF-α have a detrimental effect in the pathogenesis of hypertension, the role of anti-inflammatory IL-10 is protective. Adaptive immune responses mediated by both T-cells and B-cells play a key role in the development of hypertension and mediating damage to target organs. Activation of adaptive immunity, both T-cells and B-cells, is initiated at the early stages of the disease and makes a significant contribution to important pathogenetic changes due to the release of pro-inflammatory cytokines and antibodies. This leads to a change in the expression of the renal sodium transporter and vascular endothelium, as well as cardiac, renal and perivascular fibrosis. While these mechanisms have been well defined in animal models, there is less evidence available in humans. Undoubtedly, such a large amount of evidence justifies the

development of new antihypertensive strategies aimed at adaptive immunity of hypertensive mechanisms [25].

The immune system acts through the release of cytokines - small molecules that are involved in the transmission of cellular signals. Cytokines are the main regulatory mediators of immunity and are ideal mediators in communication between the nervous and immune systems, given that cytokines can cross the hemato-encephalic barrier, as can some neuropeptides. A number of studies have described the role of neuropeptides and substance P, as well as a number of cytokines in the modulation of CAD. Supporting the possible participation of these molecules in the occurrence and maintenance of the hypertensive state. The ubiquitous expression of cytokines and substance P in peripheral organs and blood, as well as their ability to cross the hemato-encephalic barrier, strongly indicate that these molecules act as messengers between the central nervous system (CNS), immune cells and the cardiovascular system, thereby contributing to blood pressure homeostasis [4].

The most intriguing innovation in the mosaic of mechanisms that have emerged in the last decade and contribute to the development of hypertension was the discovery that the components of innate and adaptive immunity are also involved in the development of hypertension [12].

Although in the past, angiotensin II - one of the main factors affecting blood pressure levels-has already been described as the main trigger of inflammation in the blood vessels and kidneys, only 10 years ago it became clear that the activation of immunity with angiotensin II is a pathogenetic mechanism involved in the occurrence of hypertension, and not just a random effect of damage to target organs. The nervous system and the immune system have a common ability to perform the role of a gatekeeper at the junctions between the internal and external environment [6; 32].

It is well known that immune organs are directly innervated by the autonomic nervous system. Abundant vegetative fibers, mainly sympathetic noradrenergic fibers, can be clearly recognized in both primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid organs. The available data confirm the idea that the sympathetic

the nervous system regulates immune and inflammatory responses, with some reports describing activating roles and others suggesting mitigating actions. A major breakthrough in this field of research occurred at the stage when the neurophysiological basis of the inflammatory reflex was discovered. In general, the above considerations have supported for many years the idea that this may become a new way of regulating immune and inflammatory reactions by fine-tuning sympathetic innervation directed at immune organs [33].

Understanding the causal role of immune and inflammatory reactions in hypertension has led to questions about the relationship between hypertension and autoimmunity. The immune pathology in primary hypertension mimics several autoimmune mechanisms observed in the pathogenesis of systemic lupus erythematosus, psoriasis, systemic sclerosis, rheumatoid arthritis and periodontitis. More importantly, the prevalence of hypertension in patients with these autoimmune diseases increases significantly compared to control populations. Inflammation and oxidative stress are linked in a self-perpetuating cycle that contributes significantly to vascular dysfunction and kidney damage associated with hypertension. The

infiltration of T cells, B cells, macrophages and NK cells into these organs is important for this pathology. Effector cytokines, such as IFN-γ, TNF-α and IL-17, affect the exchange of Na+/H+ in the kidneys. In blood vessels, they lead to endothelial dysfunction and loss of bioavailability of nitric oxide, as well as cause vasoconstriction. Both renal and vascular effects are partially mediated by the induction of enzymes that produce reactive oxygen species, such as superoxide anions that generate NADPH oxidases, and the dysfunction of antioxidant systems. These mechanisms have recently become important therapeutic targets of new treatment methods aimed at purifying the oxidative (isoleplandin) modification of Neo-antigenic peptides [38].

This relationship is confirmed by numerous studies that have revealed an increased content of inflammatory cytokines in the bloodstream in individuals with hypertension, including IL-6, TNF-α, IFN-γ and IL-17a [22;45].

Inflammation makes an important contribution to the genesis of hypertension and associated damage to target organs. Inflammation is associated with increased vascular permeability and the release of powerful mediators, such as reactive oxygen species, NO, cytokines and metalloproteinases. Cytokines mediate the formation of Neo-intima (a new or thickened layer of arterial intima), thereby reducing the diameter of the lumen of resistant vessels (small arteries and arterioles, highly innervated by autonomic nerves and primary vessels involved in the regulation of blood pressure) and contributing to vascular fibrosis, leading to increased vascular resistance and stiffness. Cytokines also affect the function of the renal tubules, increasing the local synthesis of angiotensinogen and angiotensin II, as well as contributing to the retention of sodium and volume in hypertension.

Matrix metalloproteinases stimulate the degradation of the extracellular matrix, providing the infiltration of immune cells through the vessel wall into the interstitium of the affected organs, promoting apoptosis and enhancing collagen synthesis and matrix deposition, which leads to damage to target organs. While animal data clearly show a link between inflammation and hypertension, data in humans is limited. There are associations between C-reactive protein, TNF and various IL and AH, but there is no direct connection [15; 31].

The balance between the pro-inflammatory reactivity of T cells and the inflammatory suppression induced by T-reg cells determines the development of hypertension, which is demonstrated by the improvement of hypertension with adaptive transfer of T-regulatory cells in several animal models of hypertension. Disorders in both pro-inflammatory T cells and regulatory T cells are involved in hypertension-induced damage to target organs, since they regulate inflammatory processes in the kidneys and vascular system that underlie hypertension-induced kidney disease [31].

The degree of hypertension is closely related to the concentration of C-peptide and LDH in the blood. Therefore, the indicators of LDH and C-peptide can act as indicators of the prognosis of the severity of the severity of hypertension. In hypertension of the 2nd degree, the content of LDH in the blood determines the prognosis of the development of MS (prediabetes) and apoptosis of cells of internal organs, including the myocardium [28].

The vascular endothelium, which is known to have been inflamed, will experience the process of extravasation, i.e. the displacement of white blood cells into the endothelial tissue. In the case of interaction of white blood cells with the endothelium, neutrophils are the first cells that are activated by an inflammatory reaction that causes the neutrophil to stick to the inflamed endothelium. IL-17, produced by Th-1 cells, activates the elimination of neutrophils. Whereas Interferon-gamma, produced by Th-1 cells, activates macrophages and TNF, as well as chemokines, which are produced by T-lymphocytes and other cells, and participates in the excretion and activation of various types of white blood cells. Tissue damage occurs as a result of the production of lysosomal enzymes and pro-inflammatory cytokines [1].

Activation of the renin-angiotensin-aldosterone system (RAAS) is one of the important mechanisms contributing to the occurrence of endothelial dysfunction, vascular remodeling and hypertension. The frequency of remodeling associated with hypertrophy will cause an increase in the size of vascular smooth muscle cells and the accumulation of extracellular matrix proteins in smooth muscle, such as collagen, due to the activation of TGF-b [20].

Some AH recognition receptors trigger a distinct pro-inflammatory mechanism that involves the synthesis of cytosolic protein complexes called inflammasomes. After the synthesis of inflammasomes, caspase-1 is activated, which, in turn, processes pro-inflammatory cytokines of the IL-1β and IL-18 families from their inactive forms into active forms. Cell damage increases extracellular ATP, which, in turn, serves as a danger signal, which ultimately stimulates the release of IL-1[43].

The concept related to CAD and hypertension is immune aging. After thymus involution in early adulthood, naive T cells decrease, and memory cells, especially effector CD8+ memory T cells, increase. This is partly due to recurrent and / or persistent viral infections. After repeated divisions, these cells adopt an senile phenotype characterized by shortening of telomeres, loss of co-stimulating factors CD27 and CD28, and an increase in the surface marker CD57. Due to the lack of co-stimulating receptors, aging T cells are unable to activate classically. Nevertheless, these cells demonstrate a state of persistent pro-inflammatory activation, producing IFN-γ, IL-6 and TNF-α. Aging CD8+ T cells also produce a large amount of cytotoxic granzyme. Aging T cells were extracted from the atherosclerotic plaques of people with unstable angina, and rheumatoid arthritis was associated with premature aging of T cells and the accumulation of aging T cells in the synovial membrane. Recently, Younetal found that relatively young people with hypertension increase the number of circulating CD8+ T cells that are deficient in CD28 and produce excess IFN-γ, perforin and granzyme. The contribution of these cells to human hypertension has yet to be determined, but their cytokine production profile indicates that they may play a crucial role. There is substantial evidence that IL-6 contributes to the development of hypertension. IL-6 levels correlate with blood pressure in individuals with hypertension and decrease during treatment with angiotensin II receptor blockade. This direct effect of IL-6, together with its ability to shift T cells from the regulatory phenotype to IL-17-producing cells, is probably important in hypertension [23].

IL-1 enhances sympathetic activation, leading to systemic vasoconstriction, which worsens sodium natriuresis. Similarly, the infusion of exogenous IL-1 in the

systemic or pulmonary vascular system increases hypertensive reactions. Zhang and his colleagues found that IL-1R1 deficiency or its blockade blunts sodium retention in the large ascending intestine and thereby weakens angiotensin II-induced hypertension. Activation of IL-1R1 stimulates the maturation of myeloid cells, which inhibit sodium retention, producing NO [42; 46].

Future studies will need to investigate exactly how to disrupt these actions of IL-1 to weaken cardiovascular damage without increasing susceptibility to infection [41].

IFN is produced by T cells and macrophages, regulating and marking Th1 differentiation and activating myeloid cells and B lymphocytes, restricts natriuresis. However, blockade targeting the IFN 1 receptor (IFNGR1) did not reduce Ang II-dependent hypertensive reactions, suggesting that the IFN 2 receptor (IFNAR2) plays an important role in the regulation of sodium retention. Nevertheless, inhibition of IFN R1 does prevent the progression of tubulointerstitial inflammation in angiotensin-dependent hypertension [42; 7, 19, 35].

TGF-β is a key factor in renal fibrosis in RAAS-associated hypertension. TGF-β enhances renal fibrosis by inhibiting the activation of matrix metalloproteinases that increase deposition extracellular matrix. Infusion of exogenous TGF-β1 or TGF-β2 contributes to kidney fibrosis, albuminuria and increases blood pressure, possibly causing vascular dysfunction and / or increased sodium retention. Chronic infusion of AngII increases the level of TGF-β in the blood serum. Conversely, TGF-β generated by T-reg interacts with IL-10 to attenuate hypertensive reactions by suppressing the activation of T-effector lymphocytes. In hypertension, the exact effect of TGF-β on renal function may depend on the origin and concentration. Future studies will need to investigate exactly how to disrupt the signaling of TGF-β [36; 42].

IL-17A is produced by CD4+ T cells and plays an important role in infections and autoimmune diseases. IL-17A enhances the production of pro-inflammatory cytokines and chemokines that stimulate the cellular immune response [13; 16].

In patients with hypertension, the level of serum IL-17 is significantly increased compared to healthy people. Similarly, chronic angiotensin II infusion stimulates the production of IL-17 and increases the expression of IL-17 inside the vessel wall. Infusion of exogenous IL-17 increases hypertensive reactions and endothelial dysfunction. A deficiency or blockade aimed at IL-17A, but not IL-17F, reduces the increase in blood pressure and kidney inflammation in angiotensin II-dependent hypertension. However, non-specific inhibition of IL-17 causes a neutral or harmful effect on renal function in hypertension [35].

IL-10 is an anti-inflammatory cytokine and is produced by Th2-lymphocytes, T-reg, mast cells and monocytes. IL-10 weakens the production of pro-inflammatory cytokines and chemokines [5].

In rats, infusion of exogenous IL-10 weakens proteinuria, endothelial damage and increased blood pressure during pregnancy-induced hypertension. IL-10 deficiency exacerbates damage to the microvascular endothelium and an increase in blood pressure, stimulating NADPH oxidase signaling [14,21,39].

As an additional support for the role of CD8+ T cells in arterial hypertension, Sunetal. Recently, it was shown that these cells express the mineralocorticoid receptor (MR) and that this T-cell receptor plays an important role in systemic hypertension. It was found that MR, which is a nuclear protein, complexes with the nuclear factor

of activated T cells 1 (NFAT1) and with activating protein 1, stimulating the production of IFN-γ by CD8+ T cells, and that a specific deletion of the MR receptor in T cells causes a sharp decrease in blood pressure and damage to the kidneys and blood vessels, caused by angiotensin II. On the contrary, overexpression of MR in T cells worsened hypertension. Eplerenone, a widely used antagonist of MR receptors, prevented the production of IFN-γ by CD8+ T cells in hypertension [26].

Macrophages are immune cells that contribute to innate immunity. They activate the nuclear factor of activated B cells (NF-kB) of the signaling pathway, which leads to the release of cytokines such as IL-6 and TNF-α [3].

IL-6 leads to the formation of C-reactive protein, which is a biomarker of inflammation. The C-reactive protein, on the one hand, causes Th1 together with liposomes, and on the other hand, activates FcyRI and causes the differentiation of Th2 together with phosphatidylcholine. However, as the secretion of inflammatory factors (such as cytokines) increases in CVD, further differentiation of Th1 cells occurs, causing inflammation due to the production of pro-inflammatory cytokines and stimulation of immune cells [40; 44].

Conclusion

1. Sodium retention in the body, as the main link of arterial hypertension, is a cytokine-dependent mechanism and the study of the mediated chain effect of cytokines is paramount. Meanwhile, taking into account the recent results that sodium retention stimulates the production of pro-inflammatory cytokines by T-lymphocytes and macrophages, therapy that combines diuretics together with anti-inflammatory drugs reduces the risk of renal and cardiovascular damage in patients with hypertension.

2. Endothelial dysfunction as a predictor of metabolic syndrome and cardiovascular diseases develops with a deficiency of nitric oxide (NO) produced by macrophages. Pro-inflammatory macrophages, Th1 and Th17 cells increase kidney damage and hypertensive reactions, producing TNF-α, IL-17A, IL-1 and IFN, which in turn reduces sodium transport in the large ascending intestine and renal blood flow, thereby causing endothelial dysfunction.

3. The protective angioprotective function of IL-10 is to weaken the production of pro-inflammatory cytokines and chemokines, as well as the binding of TGF-β generated by T-reg, and thereby inhibit the profibrotic function leading to renal fibrosis. IL-10 deficiency exacerbates damage to the microvascular endothelium and an increase in blood pressure, stimulating the signaling of NADPH oxidase. However, the effect of IL-10 on systemic vascular resistance and / or renal sodium regulation is still not fully understood.

References:

1. Agita A., Alsagaff M.T. Inflammation, Immunity, and Hypertension. Acta MedIndones. 2017 Apr; 49(2):158-165. PMID: 28790231.
2. Amador C.A., Barrientos V., Pena J., et al. Spironolactone decreases DOCA-salt-induced organ damage by blocking the activation of T helper 17 and the down regulation of regulatory T lymphocytes. //Hypertension. 2014;63(4):797–803. [PubMed] [GoogleScholar].
3. Baghai T. C., Varallo-Bedarida G., Born C., Ндfner S., Schьle C., Eser D., et al. (2018). Classical risk factors and inflammatory biomarkers: One of the missing biological links

between cardiovascular disease and major depressive disorder. //International Journal of Molecular Sciences, 19(6), 1740.
4. Calvillo L, Gironacci MM, Crotti L, Meroni PL, Parati G. Neuroimmune crosstalk in the pathophysiology of hypertension.// NatRevCardiol. 2019 Aug;16(8):476-490. doi: 10.1038/s41569-019-0178-1. PMID: 30894678.
5. Chatterjee P., Chiasson V.L., Seerangan G., Tobin R.P., Kopriva S.E., Newell-Rogers M.K., Mitchell B.M.: Cotreatment with interleukin 4 and interleukin 10 modulates immune cells and prevents hypertension in pregnant mice. //Am J Hypertens 28: 135–142, 2015 [PubMed] [Google Scholar]
6. Chavan S.S., Pavlov V.A., Tracey K.J. //Mechanisms and therapeutic relevance of neuro-immune communication. Immunity. 2017;46(6):927–42. https://doi.org/10.1016/j.immuni.2017.06. 008.
7. Chen K., Kolls J.K. (2017) Interluekin-17A (IL17A).// Gene 614:8–14
8. Drummond G.R., Vinh A., Guzik T.J., Sobey C.G. Immune mechanisms of hypertension. Nat Rev Immunol. 2019. **State-of-the-art review of innate and adaptive immunity mechanisms of hypertension.**
9. Edwards, N., Langford-Smith, A. W., Wilkinson, F. L., &Alexander, M. Y. (2018). Endothelial progenitor cells: New targets for therapeutics for inflammatory conditions with high cardiovascular risk. FrontiersinMedicine, 5, 200.
10. Godo S., Shimokawa H. Endothelial Functions.// ArteriosclerThrombVasc Biol. 2017 Sep;37(9):e108-e114. doi: 10.1161/ATVBAHA.117.309813. PMID: 28835487.
11. Guan X., Wang L., Liu Z., Guo X., Jiang Y., Lu Y., et al. (2016). miR-106a promotes cardiac hypertrophy by targeting mitofusin // Journal of Molecular and Cellular Cardiology, 99, 207–217.
12. Guzik T.J., Skiba D.S., Touyz R.M., Harrison D.G. The role of infiltrating immune cells in dysfunctional adipose tissue. Cardiovasc Res. 2017;113(9):1009–23. https://doi.org/10.1093/cvr/cvx108.
13. Han L., Dai L., Zhao Y.-F. Li, H.-Y., Liu O., Lan F., et al. (2018). CD40L promotes development of acute aortic dissection via induction of inflammation and impairment of endothelial cell function. Aging (Albany NY), 10(3), 371.
14. Harmon A, Cornelius D, Amaral L, Paige A, Herse F, Ibrahim T et al (2015) IL-10 supplementation increases Tregs and decreases hypertension in the RUPP rat model of preeclampsia. Hypertens Pregnancy 34:291–306
15. Harrison D.G. & Bernstein K.E. Inflammation and Immunity in Hypertension. Hypertension: A Companion to Braunwald's Heart Disease 60–69 (2018). doi:10.1016/b978-0-323-42973-3.00007-x
16. Haybar H., & Zayeri, Z. D. (2017). The value of using polymorphisms in anti-platelet therapy. Frontiers in Biology, 12(5), 349–356.
17. Incalza M.A., D'Oria R., Natalicchio A., Perrini S., Laviola L., Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascul Pharmacol. 2018 Jan;100:1-19. doi: 10.1016/j.vph.2017.05.005. Epub 2017 Jun 1. PMID: 28579545.
18. Jensen, H. A., & Mehta, J. L. (2016). Endothelial cell dysfunction as a novel therapeutic target in atherosclerosis . Expert Review of Cardiovascular Therapy, 14(9), 1021–1033.
19. Kim B.S., Park Y.J., Chung Y. (2016) Targeting IL-17 in autoimmunity and inflammation. ArchPharmRes 39:1537–1547
20. Lilly L.S. Braunwald's heart disease: A textbook of cardiovascular medicine. Elsevier. 2015;10:935–53.
21. LimaV.V., Zemse S.M., Chiao C.W., Bomfim G.F.,Tostes R.C., Clinton R., Giachini F.R. (2016) Interleukin-10 limits increased blood pressure and vascular RhoA/Rho-kinase signaling in angiotensin IIinfused mice. LifeSci. 145:137–143

22. Marko L,, Kvakan H., Park J.K., Qadri F., Spallek B. Binger K.J. et al. (2012) Interferon-gamma signaling inhibition ameliorates angiotensin II-induced cardiac damage. Hypertension 60:1430–1436.
23. McMaster W.G, Kirabo A., Madhur M.S., Harrison D.G. Inflammation, immunity, and hypertensive end-organ damage. CircRes. 2015 Mar 13; 116(6):1022-33. doi: 10.1161/CIRCRESAHA.116.303697. PMID: 25767287; PMCID: PMC4535695.
24. Meza C.A., La Favor J.D., Kim D.H., Hickner R.C. Endothelial Dysfunction: Is There a Hyperglycemia-Induced Imbalance of NOX and NOS? Int J Mol Sci. 2019 Aug 2; 20(15):3775. doi: 10.3390/ijms20153775. PMID: 31382355; PMCID: PMC6696313.
25. Mikolajczyk T.P., Guzik T.J. Adaptive Immunity in Hypertension. CurrHypertens Rep. 2019 Jul 18; 21(9):68. doi: 10.1007/s11906-019-0971-6. PMID: 31321561; PMCID: PMC6647517.
26. Miller L. E. (2018). Methylsulfonylmethane decreases inflammatory response to tumor necrosis factor-α in cardiac cells.// American Journal of Cardiovascular Disease, 8(3), 31.
27. Morris G., Puri B.K., Olive L., Carvalho A., Berk M., Walder K., Gustad L.T., Maes M. Endothelial dysfunction in neuroprogressive disorders-causes and suggested treatments. BMCMed. 2020 Oct 19; 18(1):305. doi: 10.1186/s12916-020-01749-w. PMID: 33070778; PMCID: PMC7570030.
28. Navruzova Sh.I., Shodmonova N.K., Soliev A.U. (2021) The significance of markers of immune inflammation and indicators of metabolic syndrome in the prognosis of complications of arterial hypertension. NEW DAY IN MEDICINE, 3 (35), P. 166-171.
29. Nguyen H., Chiasson V.L., Chatterjee P., Kopriva S.E., Young K.J., Mitchell B.M. Interleukin-17 causes Rho-kinase-mediated endothelial dysfunction and hypertension. Cardiovasc Res. 2013;97(4):696–704. [PMCfree article] [PubMed] [Google Scholar].
30. Norlander A.E., Madhur M.S., Harrison D.G. The immunology of hypertension. J.Exp.Med. 2018;215(1):21–33. [PMCfree rticle] [PubMed] [Google Scholar].
31. Oparil S., Acelajado M.C., Bakris G.L., Berlowitz D.R., Cífková R., Dominiczak A.F., Grassi G., Jordan J., Poulter N.R., Rodgers A., Whelton P.K. Hypertension. Nat Rev Dis Primers. 2018 Mar 22; 4:18014. doi: 10.1038/nrdp.2018.14. PMID: 29565029; PMCID: PMC6477925.
32. Ordovas-Montanes J., Rakoff-Nahoum S., Huang S., Riol-Blanco L., Barreiro O., von Andrian U.H. The regulation of immunological processes by peripheral neurons in homeostasis and disease. //Trends Immunol. 2015;36(10):578–604. https://doi.org/10.1016/j.it.2015.08.007.
33. Perrotta M., Lembo G., Carnevale D. The Interactions of the Immune System and the Brain in Hypertension. CurrHypertensRep. 2018 Feb 24;20(1):7. doi: 10.1007/s11906-018-0808-8. PMID: 29478153.
34. Popa M., Tahir S., Elrod J., Kim S. H., Leuschner F., Kessler T., et al. (2018). Role of CD40 and ADAMTS13 in von Willebrand factor-mediated endothelial cell–platelet–monocyte interaction. Proceedings of the National Academy of Sciences of the United States of America, 115, E5556–E5565.
35. Ridker P.M., Everett B.M., Thuren T., MacFadyen J.G., Chang W.H., Ballantyne C. et al. (2017) Anti inflammatory therapy with canakinumab for atherosclerotic disease. N. Engl. J. Med. 377:1119–1131
36. Rodriguez-Iturbe B, Pons H, Johnson RJ (2017) Role of the immune system in hypertension. Physiol. Rev. 97:1127–1164.
37. Rodriguez-Iturbe B, Pons H, Johnson RJ (2017) Role of the immune system in hypertension. Physiol. Rev. 97:1127–1164.
38. Small H.Y., Migliarino S., Czesnikiewicz-Guzik M., Guzik T.J. Hypertension: Focus on autoimmunity and oxidative stress. Free Radic Biol Med. 2018 Sep; 125:104-115. doi: 10.1016/j.freeradbiomed.2018.05.085. Epub 2018 May 30. PMID: 29857140.

39. Sun B., Wang H., Zhang L., Yang X., Zhang M., Zhu X., Ji X., and Wang H.. 2017a Role of interleukin 17 in TGF-β signaling-mediated renal interstitial fibrosis. Cytokine. 10.1016/j.cyto.2017.10.015 [PubMed] [CrossRef] [GoogleScholar]
40. Trial J., Cieslik K. A., &Entman, M. L. (2016). Phosphocholine containing ligands direct CRP induction of M2 macrophage polarization independent of T cell polarization: Implication for chronic inflammatory states. Immunity, Inflammation and Disease, 4(3), 274–288.
41. Wei L.H., Huang X.R., Zhang Y., Li Y.Q., Chen H.Y., Heuchel R. et al. (2013) Deficiency of Smad7 enhances cardiac remodeling induced by angiotensin II infusion in a mouse model of hypertension. PLoS ONE 8:e70195
42. Wen Y, Crowley SD. Renal Effects of Cytokines in Hypertension. Adv Exp Med Biol. 2019; 1165:443-454. doi: 10.1007/978-981-13-8871-2_21. PMID: 31399978.
43. Wenzel U., Turner J.E., Krebs C., Kurts C., Harrison D.G., Ehmke H. Immune Mechanisms in Arterial Hypertension. //J. Am.Soc.Nephrol. 2016;27(3):677-686. doi:10.1681/ASN.2015050562
44. Yin J., Xia W., Zhang Y., Ding G., Chen L., Yang G., et al. (2018). Role of dihydroartemisinin in regulating prostaglandin E2 synthesis cascade and inflammation in endothelial cells.// Heart and Vessels, 33(11), 1411–1422.
45. Zhang C., Li Y., Wang C., Wu Y., Cui W., Miwa T., Sato S., Li H., Song W.C., Du J.: Complement 5a receptor mediates angiotensin II-induced cardiac inflammation and remodeling.// ArteriosclerThrombVasc Biol 34: 1240–1248, 2014 [PubMed] [Google Scholar
46. Zhang C., Li Y., Wang C., Wu Y., Du J.: Antagonist of C5aR prevents cardiac remodeling in angiotensin II-induced hypertension. //AmJHypertens 27: 857–864, 2014 [PubMed] [GoogleScholar]