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MODERN ASPECTS OF THE STUDY OF CYTOKINE STATUS IN HYPERTENSION

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Abstract:

This review presents the data of modern scientific research, indicating the involvement of the immune system in the regulation of blood pressure, discusses 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.

Keywords: Arterial Hypertension, Immunity, Cytokines, Endothelium, Cardiovascular Diseases.

In recent years, evidence has been accumulating indicating the role of the immune system in the regulation of blood pressure and cardiovascular risk associated with hypertension. The first line of defense of the immune system includes an innate reaction that proceeds fleetingly. Adaptive immunity, which is the second line of defense, has a late, but very accurate and targeted reaction. The effects between these two components of the immune system are significant in terms of the formation of arterial hypertension [8,13]

T-cell cytokines play an important role in the pathophysiology of cardiovascular diseases and hypertension, which have the ability to damage the end organs [3,6].

The effect of IL-17 on AH, which is one of the first identified cytokines, is deeply studied and described.

T helper cells 17 (Th 17) and their anti-inflammatory cytokine IL –17 play a significant role in the development of endothelial tissue dysfunction and hypertensive autoimmune pathologies. In particular, CD4+ T cells of people with arterial hypertension produced a higher amount of IL-17A than the normotensive control higher. In patients with arterial hypertension, the level of IFN – γ formation produced by CD 8+ T cells is significantly higher compared to the normotensive index [15]

According to the cytokine medium, CD 4+ T-cell is transformed into phenotypes of type Th1, Th2, Th17 or Thed. The phenotype of the Th1 group, secreting mainly IL-2, TNF -α and IFN-γ, is polarized in the medium of interferon-γ (IFN-γ) and IL-12. The secretion of IL-4 and IL-10 involves the phenotype Th2, which is formed in the IL-4 medium. The Th17 phenotype stimulated by aldosterone participates in the secretion of IL-17A, IL-17F, IL21, IL22 and depends on IL-6, IL-21, IL-23, IL-1ß, as well as on transforming growth factor (TGF)-β. The Thed phenotype, secreting such immunosuppressive immune factors as IL-9, IL-10, TGF-β and cytotoxic T-lymphocyte antigen 4 (CTLA-4), is formed in the medium of transforming growth factor (TGF)-β1 with a weak content of IL-6 and thereby showing anti-inflammatory activity. 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 [6,12].

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 Immune responses, among other things, are adaptive. By means of T- and B-cells, they play a primary role in the development of hypertension and damage to organs such as the heart, brain, blood vessels and kidneys (target organs). At the initial stages of the development of pathogenetic modifications, adaptive immunity is activated, which also has a significant effect on the severity of the disease, through a high level of cytokines that increase the inflammatory response in the body; as well as immunoglobulins. All these factors can provoke a violation of vascular endothelial proliferation and sodium transport in the kidneys. In addition, it can lead to perivascular fibrosis and severe complications such as fibrosis of the heart and kidneys.

While these mechanisms have been well defined in animal models, there is less evidence in humans. Undoubtedly, such a large amount of evidence justifies the development of new antihypertensive strategies aimed at adaptive immunity of hypertensive mechanisms [15,20].

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The most intriguing innovation in the mosaic of mechanisms that have emerged in the last decade and contribute to the development of GB was the discovery that the components of innate and adaptive immunity are also involved in the development of GB [11].

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 organ damage-targets. The nervous system and the immune system share the ability to act as a gatekeeper at the junctions between the internal and external environment [8].

Early evidence of the commonality of these two systems in hindsight led to the identification of some of their key components as the main players of the nervous system and immunity. In fact, different stimuli can activate both systems, which, in turn, recognize and integrate the corresponding reactions aimed at maintaining homeostasis. 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 addition, it has also been proven that activation of adrenergic neurons of the spleen, mediated by the vagus nerve, is associated with priming of a specific subset of T cells in the white pulp of the spleen, which produces acetylcholine. In turn, acetylcholine-producing T cells signal macrophages of the red pulp and marginal zone via Alpha-7-nicotine acetylcholine receptors (a7nAChR), in order to ultimately inhibit the production of TNF and other cytokines in the spleen. In general, the above considerations have supported for many years the idea that this could become a new way of regulating immune and inflammatory responses by fine-tuning sympathetic innervation directed at immune organs [1,3,10].

According to recent decades, changes in the immune system play a significant role in the pathogenesis of hypertension. Immune damage with inflammation of the vascular wall can lead to an imbalance between factors synthesized by endotheliocytes. The components of the immune system damage and activate endothelial cells. The resulting structural and functional changes in the vessels contribute to the formation and progression of hypertension [5,17].

For many decades, it has been recognized that immune mechanisms play an important role in the pathogenesis of hypertension, vascular diseases and kidney damage in humans and animals. Modern advances in experiments have allowed a deeper understanding of the mechanisms by which inflammation and immunity are involved in cardiovascular diseases, and numerous observations have demonstrated a strong correlation between discoveries made in animals and discoveries made in patients with hypertension. It should be noted that a striking phenotypic similarity was observed in the infiltration of immune cells in the kidneys and the development of damage to end organs in patients and animal models with sodium-sensitive hypertension. The available data suggest that the initial increase in perfusion pressure in the kidneys caused by salt, which probably does not depend on immune mechanisms, induces infiltration of immune cells into the kidney. The mechanisms mediating the infiltration of immune cells in the kidneys are not well understood, but probably include tissue damage, the direct effect of salt on stimulating the activation of immune cells, stimulation of sympathetic nerves, or other factors. Infiltrating cells then release cytokines, free radicals and other factors that contribute to kidney damage, as well as increased sodium and water retention and vascular resistance, which leads to the further development of hypertension [2,7].

Understanding the causal role of immune and inflammatory reactions in hypertension has led to questions about the relationship between hypertension and autoimmunity. 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. Clinical and epidemiological data are considered, as well as possible mechanisms linking hypertension and autoimmunity. Inflammation and oxidative stress are linked in a self-perpetuating cycle that contributes

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significantly to vascular dysfunction and kidney damage associated with hypertension. 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 Na+/H+ metabolism in the kidneys. In blood vessels, they lead to endothelial dysfunction and loss of bioavailability of nitric oxide, and also cause vasoconstriction. Both renal and vascular effects are partially mediated by induction of enzymes producing reactive oxygen species, such as superoxide anions generating NADPH oxidases, and dysfunction of antioxidant systems. These mechanisms have recently become important therapeutic targets of new treatment methods aimed at purification of oxidative (isoleplandin) modification of Neo-antigenic peptides [4,14].

IL-10 is an anti-inflammatory cytokine and is produced by Th2 lymphocytes, Tregs, mast cells and monocytes. IL-10 weakens the production of proinflammatory cytokines and chemokines [18].

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 increases blood pressure by stimulating NADPH oxidase signaling [3.19].

Thus, the actions of Il-10 in protecting vascular function are consistent, but future studies will need to investigate the effect of Il-10 on systemic vascular resistance and/or renal sodium regulation. Guyton and his colleagues demonstrated that increased sodium and water retention is the basis for an increase in blood pressure. Thus, understanding the action of inflammatory cytokines in the modulation of kidney function is crucial for understanding the role of the immune system in the pathogenesis of hypertension. Sympathetic tone and activation of renal nerves, endothelial dysfunction dependent on renal blood flow, and sodium transport in the large ascending intestine are the main targets for inflammatory cytokines. The effect of TGF-β on renal function and hypertension is complex due to pro-fibrotic and immunosuppressive functions. As a rule, polarized inflammatory cells alter sodium retention in the blood and increase blood pressure due to the secretion of individual cytokines. [1,2,7].

Conclusion. Thus, understanding the exact renal effects of cytokines in hypertension is of paramount importance to prevent cytokine-dependent sodium retention. Pro-inflammatory macrophages M1, Th1 and Th17 cells increase kidney damage and hypertensive reactions, producing TNF, Il-17A, IL-1 and IFN. On the contrary, Treg-derived IL-10 inhibits the increase in blood pressure and damage to target organs. Derived by macrophages, nitric oxide (NO) has an antihypertensive effect, facilitating natriuresis. Meanwhile, given recent results that sodium retention stimulates pro-inflammatory polarizations of T-lymphocytes and macrophages, therapy that combines diuretics together with anti-inflammatory drugs offers the potential to weaken renal and cardiovascular damage in patients with hypertension.

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