Research Article

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Interleukin-17a: A New Therapeutic Target in Hypertension?

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ABSTRACT

Interleukin 17A (IL-17A) is a proinflammatory cytokine produced from the differentiation of TCD4 lymphocytes to Th17 lymphocytes as a defense response of the organism against stimuli received by pathogens; however, at present, this protein has It has gained great importance in the genesis of pathologies of cardiovascular origin, especially arterial hypertension (AHT) since various studies have shown that the plasmatic concentrations of this interleukin are increased in patients with mild or moderate arterial hypertension and that in those cases where For those who manage to establish an effective block of its action, a significant decrease is obtained in the value previously reported as a tension value due to direct action on the vascular wall and tubular transport.From this document we seek to review the pathophysiological and immunological mechanisms involved in the relationship IL-17A and HTA, as well as in the appearance of target organ damage with the aim of publicizing the feasibility of establishing a new therapeutic target for the effective management of the disease and the reduction of cases associated with morbidity and mortality.

KEYWORDS: Interleukin 17A, Proinflammatory, Differentiation, Genesis, HTA, Blockade

ABBREVATIONS: AHT: Arterial Hypertension; CRP: C-reactive protein; APCs: Antigen Presenting Cells; RAS: Renin-Angiotensin System; ROS: Reactive Oxygen Species; rAT1: Angiotensin Receptors; Ang-II: Angiotensin II; ACE: Angiotensin Converting Enzyme; SOD2: Superoxide Dismutase 2; NOS: Nitric Oxide Synthetase, NADPH: Nicotinamide Adenine Dinucleotide Phosphate; IL-17A: Interleukin 17A; AMI: Acute Myocardial Infarctions

INTRODUCTION

Arterial hypertension (AHT), as an important cause of morbidity and mortality in our society, is defined as the sustained elevation of blood pressure above normal limits, which may be apparently asymptomatic or cause damage to target organs at the cardiovascular, cerebral and kidney [1]. The etiology of the condition represents a

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clinical challenge because it has not been definitively established, which is why it is currently considered one of the main causes of death worldwide [2,3]. The cardiovascular risk factors described in the association of the condition are traditional and are mainly related to the presence of pathologies such as dyslipidemia, obesity or diabetes, as well as non-modifiable factors typical of the human being (angiotensin II levels, aldosterone, endothelin- 1, genetics) and lifestyles (salt intake, physical activity, balanced diet), however, through the development of various investigative processes, it has recently been possible to establish a direct relationship with the effects triggered by proinflammatory states and that these not only determine the development and/or progression of AHT but also lead to the damage of target organs through metabolic, chemical, mechanical and infectious aggressions [3,4].

Inflammation is defined as a non-specific response that a tissue suffers from the aggression produced by different factors, which has the purpose of suppressing the agent causing the damage as well as the recovery of the affected tissue [5], however, when the condition is maintained over a prolonged period of time, there is an increase in the concentrations of markers and inflammatory cells, including IL-6, which triggers a greater production of C-reactive protein (CRP) by the liver, as well as a reduction in vasodilation and an increase in blood flow. vascular damage (Figure 1); [2,6].

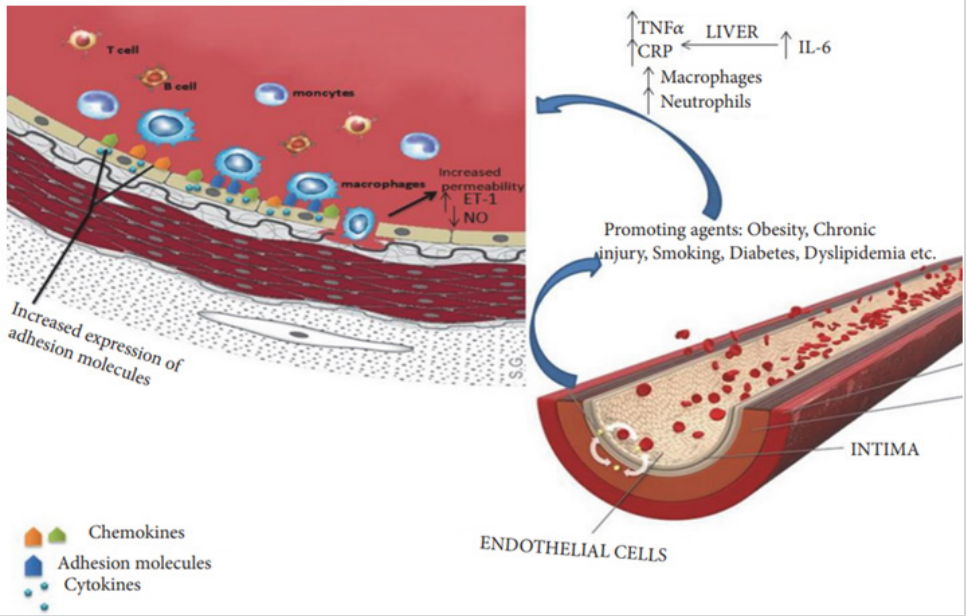

Figure 1: Etiology of the inflammatory process.

Chronic inflammation triggers increased concentrations of markers and inflammatory cells, leading to reduced vasodilation and increased vascular damage. The proinflammatory state associated with increased cardiovascular risk and the development of hypertension has been explained by different mechanisms, it being important to mention initially that hypertension is often related to hyperactivation of the sympathetic nervous system and the release of hormones known as catecholamines including norepinephrine and that it has been shown in in vitro studies that exposure of dermal microvascular endothelial cells with this substance followed by culture with antigen presenting cells (APCs), an antigen and sensitive T cells, induces a greater response of the adaptive immune system through the production of LTh17 [6,7] which have the capacity to alter processes related to the renin-angiotensin system (RAS),the regulation of reactive oxygen species (ROS), endothelial injury and the action of interleukins [8].

Regarding the relationship between the RAS, inflammation and hypertension, it should be known that T lymphocytes, dendritic cells and macrophages have the capacity to express type 1 angiotensin receptors (rAT1) through which the binding of the angiotensin II (Ang-II) determines the differentiation of immune cells, the production of proinflammatory cytokines, and increases leukocyte adhesion-migration through direct action on P-selectins. All of the above is related to the increase in the production of angiotensin converting enzyme (ACE) which contributes to the development and maintenance of hypertension [9,10].

Once the proinflammatory state has been established, excess ROS triggers the optimization of cellular processes related to differentiation and apoptosis while limiting vascular tone and endothelial function in the cell. This conditions the presence of oxidative stress at the mitochondrial level enhanced from the overproduction of mitochondrial superoxide and the reduction of the function of the enzyme superoxide dismutase 2 (SOD2) responsible for the elimination of ROS [11,12]. According to various studies, it is commented that ROS molecules that include xanthine oxidoreductase, nitric oxide synthetase (NOS), nicotinamide adenine dinucleotide phosphate (NADPH),

On the other hand, endothelial function contributes to a great extent to vascular and blood pressure homeostasis [13], which is why the arterial wall has the capacity to synthesize relaxing factors (prostacyclin nitric oxide, hydrogen sulfide) and constrictors (angiotensin II), endothelin 1) derived from the endothelium. These products present dysfunction after the establishment of the inflammatory state characteristic of chronic diseases, which leads to increased vascular permeability, cell apoptosis, and thrombosis. This is why endothelial dysfunction has been considered to be an early predictor of atherosclerosis and cardiovascular events associated with mortality in the general population [4,14].

Regarding the relationship between interleukins, inflammation and hypertension, it should be mentioned that interleukins are related to various cellular processes as they have the ability to induce

the recruitment and activation of immune cells through interaction with the inflammatory state [15] highlighting the power of IL-1, IL-6, IL-12, IL-18, IL-17 and IL-23, however, among the cytokines mainly involved in the genesis and progression of organ damage secondary to AHT the intervention of interleukin 17A (IL-17A), also known as effector cytokine of Th17 cells, is distinguished, which is currently recognized as one of the most promising therapeutic targets [16].

The first cells identified as producing IL-17A were Th17 lymphocytes, driven by the differentiation of TCD4 lymphocytes, through which related substances such as IL-22, IL-26 and IL-23 are secreted that have the main function of defense against pathogens in infectious diseases, however, the existence of other types of IL-17A-producing cells, such as gamma delta (γδ) T cells, natural killer T cells (NK), macrophages, dendritic cells, neutrophils and mast cells [7,4,17]; (Figure 2). IL-17A was isolated for the first time in 1993 from a T-cell hybridoma where the presence of unstable sequences rich in adenylate-uridylate in the 3'UTR region was identified, conferring the property of interleukin. Finally, it is important to mention that the proinflammatory effects associated with the expression of IL-17A have been previously studied due to the existing relationship with the development of autoimmune diseases such as psoriasis through the proliferation of keratinocytes and Crohn's disease through of the promotion of intestinal inflammation, however, endothelial dysfunction associated with the activation of Rho-kinase as a promoter of cardiovascular disease has recently been explained [18-20].

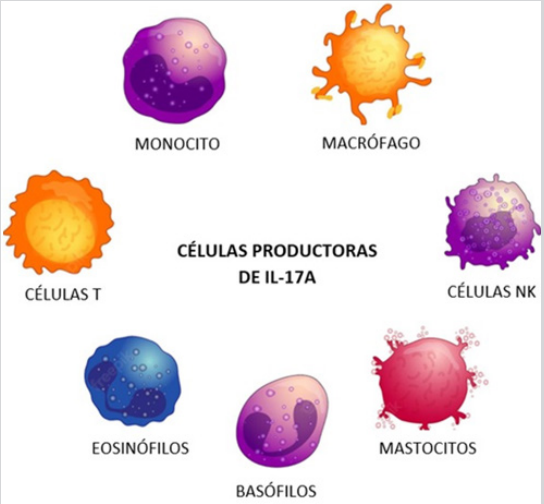

Figure 2: Interleukin 17A-producing cells.

METHODOLOGY

A bibliographic review was carried out through a systematic search in various data sources such as PubMed, Google Scholar, Scielo, Elsevier, Medline, among others. The selection of the article information was extracted from specialized indexed journals on the subject exposed in the English and Spanish languages between the years 2010 and 2022. Key search words such as "arterial hypertension", "interleukin 17-A" were used "immunity", "proinflammatory", "relationship" and "therapeutic" identifying a total of 60 original and review publications of which 31 articles met the requirements established as inclusion criteria for research, such as that the documents were within a time range of not less than 2010, that they were integral processes and that they reported on the relationship between IL-17A and the genesis of AHT. Documents that did not present complete information at the time of the review or that were not sufficiently clear on the subject in question were excluded.

RESULTS AND DISCUSSION

Hypertension is an important risk factor for cardiovascular diseases and a multifactorial condition that affects 40% of the entire population, causing approximately 7.5 million deaths annually worldwide. According to Tanase et al. [4] despite the different medical interventions, AHT causes 62% of cerebrovascular accidents (CVA) and 38% of heart diseases in developing countries. Additionally, according to Rodríguez et al. [7] despite providing the best therapeutic options, in up to 12% of all cases the blood pressure figures cannot be controlled.

The mechanisms that regulate blood pressure have been recognized as one of the main focuses of attention for the generation of investigations since they require the participation of various organs or systems. Authors such as Rodrígues et al. [2] have managed to satisfactorily demonstrate the existence of an important relationship between chronic inflammatory processes and the origin of diseases of the cardiovascular system, more specifically in the development and progression of AHT, with IL-17A being the main focus of attention since it has been established that during the infusion of Ang-II in an animal model, an increase in the level of circulating Th17 lymphocytes occurs in the body, as well as the production of the cytokine, which promotes the development of the condition [22-24]. Supporting this hypothesis, Tanase et al. [4] ensures that inflammation promotes endothelial dysfunction and atherosclerosis through ROS, which stimulate the secretion of proinflammatory cytokines, increasing the expression of IL-6 and decreasing the availability of nitric oxide NO while Rodrígues et al. [2]; Caillon [10]; Orejudo [11] comment that this has been evidenced through the intracellular RhoA/Rho-kinase (ROCK) signaling pathway through phosphorylation of the threonine residue 495 of endothelial nitric oxide synthase (eNOS) in mouse aorta. Additionally, Rodrígues et al. [2] mention that hypertensive patients have elevated serum levels of several proinflammatory cytokines, especially IL-17A, which suggests that innate immunity, both cellular and humoral, participate in the pathogenesis of the disease.

According to Rodrígues et al. [2]; Yao et al. [12] IL-17A has the ability to regulate some of the mechanisms identified as mediators in the development of arterial remodeling associated with AHT, such as inflammation, cell number and size, changes in cell phenotype, and changes in the composition of the extracellular matrix that trigger vascular fibrosis. The appearance of these structural and functional changes in the arteries are characterized by a reduction in the diameter of the lumen of the vessel or an increase in the relationship between the middle layer and the lumen, which leads to an increase in the pressure exerted by the blood on the wall. of the vessel as well as peripheral vascular resistance, finally triggering AHT (Figure 3); [18,25]. This is supported by different authors including Rodrígues et al. [2]. Who comment that systemically administering IL-17A in mice has caused an increase in blood pressure associated with inward hypertrophic vascular remodeling, as well as increased arterial stiffness. Yao et al. [12] also states that when a combined therapy of hydralazine and hydrochlorothiazide is performed when IL-17A has already induced an increase in blood pressure, blood pressure figures can be reduced but not reverse the changes in mechanical properties. and structural of the arteries, which demonstrates that the effects are direct and independent of the elevation of the vital sign [26]. After the establishment of the proinflammatory process, IL-17A potentiates the increase in vascular resistance which, in combination with the decrease in effective blood flow, leads to remodeling of the blood vessel through hypertrophy of the vascular smooth muscle cell.

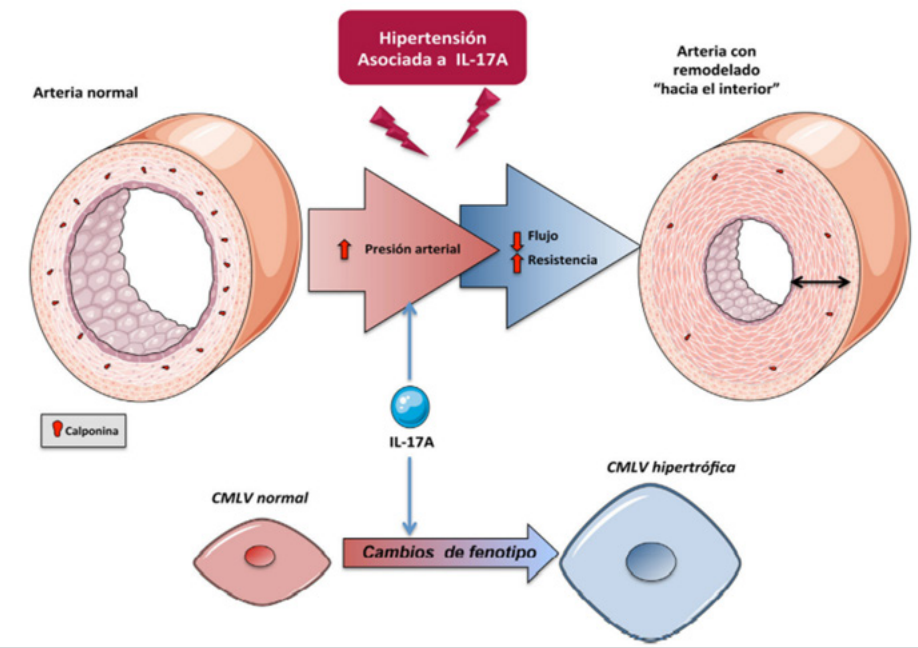

Figure 3: Effect of IL-17A on the regulation of arterial hypertension.

On the other hand, factors related to intestinal dysbiosis, which is defined as an alteration in the number of microorganisms recognized as beneficial for homeostasis, have emerged as possible modulators of the progression of hypertension. Davis et al. [5] comment that segmented filamentous bacteria have the ability to induce cell differentiation and promote the production of LTh17, causing interruptions in the activity of immune cells based on mechanisms that, although not precise, have been established by means of different reports where the presence of altered intestinal microbiota has been documented in addition to epithelial barrier dysfunction in patients with effectively diagnosed hypertension [19,27,28]. Additionally Higaki et al. [8].

Another of the mechanisms studied in the control of blood pressure by means of IL-17A is related to the kidney since, from the physiological point of view, it has been shown that various cytokines modulate the water and salt balance by altering the tone sympathetic generating endothelial dysfunction with repercussions at the level of renal blood flow or in the modulation of sodium transport in the nephron [21,29]. Rodrigues et al. [2] states that IL-17A increases sodium reabsorption through the sodium-proton exchanger type 3 (NHE-3) in the proximal tubule and the thiazide-sensitive sodium-chlorine cotransporter (NCC). in the distal convoluted tubule thus contributing to the development of AHT. Prat et al. [14] also comment that the decrease in natriuretic capacity during the development of AHT is associated with the appearance of leukocyte infiltrates in the tubulointerstitial space that lead to oxidative stress, reduced bioavailability of renal NO, depleted flow renal medullary blood and decreased urinary sodium excretion. The above agrees with Tanase et al. [4] who express that IL-17A deficiency suppresses the activation of the distal tubule transporters, decreasing the kidney damage induced by Ang II, while the administration of Ang II in mice produced AHT and reduced the ability to excrete. salt overload, a situation that was categorized as limited in specimens deficient in the protein. Davis et al. [5] ensure that the effects of IL-17A on the expression of NHE-3 and NCC depend on the kinase 1 regulated by serum and glucocorticoids known as SGK1 (serine/threonine-protein kinase) which inhibits the degradation of the distal convoluted tubule transporters by improving their expression on the cell surface.

Regarding outcomes, Simundic et al. [15] demonstrated that IL-17A levels are higher in patients with hypertension and asymptomatic target organ damage compared to those without damage. Additionally, Davis et al. [5] state that the protein is capable of generating ventricular hypertrophy, which reduces overall survival while Rodrígues et al. [2] ensures that the rates related to the occurrence of cardiac events such as acute myocardial infarctions (AMI) are higher in patients with elevated levels of IL-17A. Taking the above into account, currently the potential clinical use of cytokine

inhibitors has acquired significant value in research processes since, for example, Davis et al. [5] comment that after hypertension induced by Ang-II infusion for 4 weeks in rodents, neutralizing antibodies against IL-17A or against the IL-17RA receptor subunit (administered in the last 2 weeks of the initial infusion) achieved an effective reduction of approximately 30 mmHg in blood pressure, as well as markers of inflammation, fibrosis, and glomerular lesion progression established from albuminuria quantification. Contrary to this, Markó et al. [16] state that they failed to demonstrate an effective action of the neutralizing antibody against IL-17A on blood pressure or albuminuria; however, various authors state that this is explained by differences in the doses of Ang-II administered, the frequency in the administration of antibodies and the duration of the study in question, which was stopped after only 14 days. External and internal hypertensive stimuli trigger a slight initial rise in blood pressure by stimulating the sympathetic nervous system, causing mild tissue damage and activation of innate immunity from Toll-like receptors on macrophages, dendritic cells, and B cells. The proinflammatory process contributes to the establishment of oxidative stress and the activation of adaptive immunity by inducing the action of interleukins and autoantibodies that perpetuate the action of T cells. All of the above triggers vascular and renal injury by combined action, which leads to maintenance of the proinflammatory state (Figure 4).

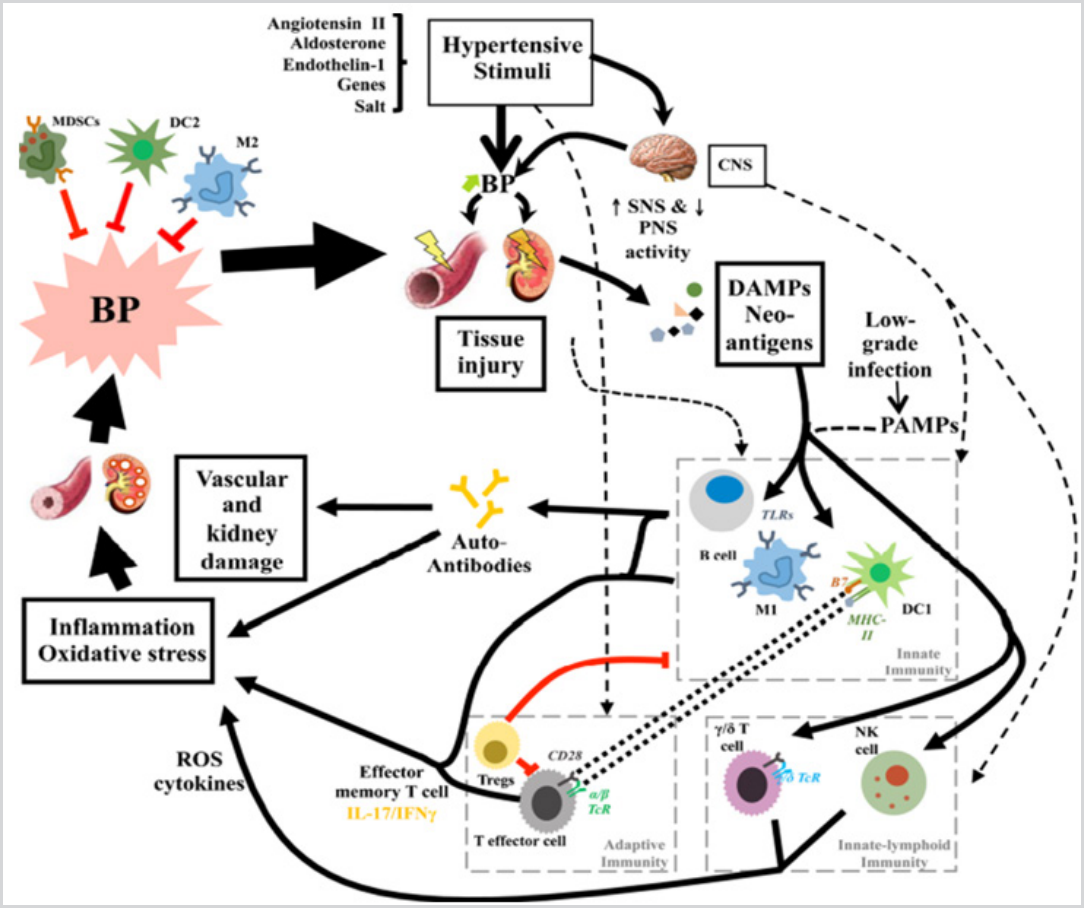

Figure 4: Action of immune cells during inflammation in hypertension.

Statins are another of the drugs studied in the relationship between IL-17A and HBP, since it has been shown that they have the ability to negatively regulate Ang-II receptors, increasing the production of NO and that of proinflammatory cytokines. van der Meij et al. [18] comment that patients treated with statins have dose-dependent anti-inflammatory effects while Rizzo et al. [19] ensures that the effect depends on the severity of the disease, being more evident in patients with higher blood pressure values in whom an effective reduction of approximately 5 mmHg has been achieved; however, Sepehri et al. [20] found that this type of medication does not have any antihypertensive effect. Finally, drugs targeting the renin-angiotensin-aldosterone system (angiotensin-converting enzyme inhibitors and aldosterone blockers) and calcium channel blockers, in addition to their known antihypertensive effect, have shown some anti-inflammatory benefits, but are still under investigation.

CONCLUSION

This document has reviewed updated data that directly implicates IL-17A as a relevant cytokine in the pathogenesis of AHT, as well as in renal and cardiovascular damage. Additionally, various periclinical studies were able to effectively demonstrate that this protein can be considered as an effector of tissue damage related to AHT, so it could be considered as a potential effective therapeutic target to control the clinical repercussions associated with the pathology. At the moment, several clinical trials are under development that aim to block the action of IL-17A, which have had promising results as they provide novel insight into the complex interaction of the immune system and tissue damage. Therefore, it is expected that once its clinical safety is demonstrated, there is the possibility of evaluating the routine administration of these drugs in the management of AHT and the prevention of target organ damage related to the disease.

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