Autoimmunity and Hypertension

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Abstract- The blood circulatory system is intimately linked to the lymphocyte circulatory system and thus, plays an important role in the bodily homeostasis. Strong immunological reaction, such as allergic reactions (e.g. anaphylaxis) will cause imminent effect on the blood pressure and in some cases lead to a fatal event. Less is known how ongoing immune reaction as those manifested in autoimmune reactions can effect blood pressure. In here we review part of this field and suggest some possible mechanisms, with special emphasis on Angiotensin II, hsp and recently discovered immune-reactive apoB peptide epitopes on the Low Density Lipoprotein, expressed only on oxidized or modified LDL. These neoantigen formations can be new pathway to lead hypertension disease since there are clinical evidence that support the participations of autoimmunity in blood pressure control.

Keywords: Lymphocytes, Autoimmunity, Hypertension, Inflammation

I. INTRODUCTION

Hypertension is the major driving force in cardiopathy and includes stroke myocardial infarction and as a secondary event impairment of renal function. World-wide hypertension affects approximately one-third of the population. The alarming increase in obesity in the society, regardless of degree of Human development index (e.g. HDI), combined with subsequent impact on this important risk factor motivates a more in-depth knowledge of what leads to hypertension, what mechanisms/factors are involved and how they can be manipulated [1].

The sympathetic nervous system control blood pressure via hormones produced by adrenal glands. Growing evidence suggests that the sympathetic nervous system via various vasoactive hormones contribute to the pathogenesis of hypertension [2]. Most interestingly adrenal glands may also regulate of lymphoid organs by neuroendocrine pathway [3]. The lymphatic system participates in the recirculation of lymphocytes and is connected to the blood circulatory system. Beside its importance for the exchange of cells and serum components between the lymphatic and red blood cell circulatory system it is also the mechanism by which the arterial/venous pressure by virtue of maintenance of the liquid balance and osmotic pressure (i.e. turgor) [4]. Strong immune reactions such as allergic reaction, initiating an anaphylactic reaction will rapidly cause a vasodilation/contraction with severe consequences if not reverted. However it is highly likely that in various degrees, immune reactions as those seen in adjacent or distal autoimmune foci’s may cause similar events. For obvious reasons these will be less perturbing however these may cause if chronic cause local damage with distal or systemic consequences. In this case the response can act direct by local tissue damage by cellular or humoral components or indirectly by virtue of cytokines. Antigen-driven cytokines/lymphokines such as interleukin 1-β (IL-1 β), IL-4 and TNF-α with a capacity cause capillary damage or induce SMC.
growth and reduction of arterial/capillary morphology are important targets for further studies [4].

II. IMMUNE CELLS AND HYPERTENSION

Inflammation plays an important component in the pathogenesis of hypertension [7]. However, most interestingly studies observed the infiltration of T lymphocytes (T-cells) in the kidney and arteries can , in part, be responsible for changes in blood pressure levels [5,6]. The infiltration and accumulation of immune cells in the kidneys, central nervous system and arteries are commonly observed in experimental models of hypertension [2,3,6]. Spontaneously hypertensive rats (SHR) exhibit an infiltration of immune cells prior to hypertension, and the animals with larger infiltrates of macrophages and CD4 T-cells associate with degree of hypertension, suggesting that way the cause-effect with inflammatory process [8-10]. However, whether T cells accumulation in these target organs as result of antigen-induced immune response is still unclear. In the arterial wall where the accumulation of macrophages and T cells is evident [11] Modified LDL and their degradation products (e.g. apoB peptides) is a major contributing factor in the various events in the atheroma and plaque formation [12-14].

It has been shown that heat shock protein 70 (HSP-70), implied in atherosclerosis induced autoimmune responses leads to the chronic inflammation in kidney and subsequent hypertension [15]. However others proteins and peptide can be associated with elevated blood pressure and their regulation.

Inflammation in hypertension disease can be modulating by angiotensin II with action in distinct regions to control blood pressure. In experimental studies lymphocytes infiltration has been showed in the perivascular aortic tissue in angiotensin II-induced hypertension, desoxycorticosterone acetate (DOCA)-salt hypertension [16] and aldosterone-induced hypertension [17]. In perivascular tissue is showed primarily lymphocytes CD4+ and less CD8+ [16]. The higher arterial blood pressure can occur by angiotensin II central actions in circumventricular regions to lead in perivascular regions activation and infiltration of CD4+ T cells [18]. Perivascular immune cells infiltration promote reduction of nitric oxide (NO) viability by increase of oxidative stress leading to higher artery resistance and endothelial dysfunction [19]. Moreover, endothelial permeability are enhanced by oxidative injury, which increases entry of lipoproteins into the subendothelial space, where they are oxidized. This will cause recruitment of inflammatory cells, T cells reacting to and activated by angiotensin II promote changes in endothelial morphology that lead to hypertension by increase of artery resistance [20].

Others mechanisms associated with hypertension are immune cells infiltration in kidney, studies using mycophenolate mofetil to block T cells kidney infiltration showed that preventing renal lymphocytes infiltration can reduced or prevent hypertension in animal models [21,22]. These effects of mycophenolate mofetil is supported by studies that show hypertension in angiotensin II-infused mice was suppressed in the recombination activating gene 1 (Rag1+/-) which lacks T lymphocytes, and that angiotensin resistance was lost by adoptive transfer of T cell [16].

In addition to subsets CD4+ already mentioned other T cell with function of maintenance self-tolerance has a contrary role to induce hypertension. The T regulatory cells (Tregs) are characterized by expression of the fokhead transcription factor FoxP3+ and surface expression of CD25. Studies have showed that adoptative transfer of Treg cells has a protective effect in hypertensive response to angiotensin II by upregulation of T-cell infiltration into the kidney with reduction in inflammatory signaling [23-24]. The IL-10 derivate the Treg cells has an important effect to preventive endothelial dysfunction, by reduction of superoxide production derivate of angiotensin II stimulate, this pathway is crucial for preventive hypertension [25].

In a clinical study patients received immunosuppressant tacrolimus showed hypertension with reduced numbers of Treg cells concomitant less levels of FK506 binding protein 12 (FKBP12) and TGF-β receptor, resulting in decrease of FoxP3+ cells, and elevation in Th17 cells showed the balance between lymphocytes Th17 and FoxP3+ cells might determine whether hypertension develops in these models [26].

The clinical evidences of the role of T lymphocytes in hypertension was observed by Seaberg et al., that patients HIV-infected with low CD4+ counts showed reduced prevalence of hypertension compared with antiretroviral treating patients with
Hypertensive patients show increase numbers of CD8+ cytotoxic T cells with increase marker CD57 and lost CD28 showing immunosenesence cellular [28] suggesting that inflammation in target organs could be responsible for increase of neoantigens (see explanation below) that repeated bouts of stimulation would lead to long-term CD28 loss in hypertensive patients [29].

III. CYTOKINE AND HYPERTENSION

Activated T cell produce cytokines such as IL-17 by Th17 cell, a subset of CD4+ cell distinct of Th1 and Th2, and by this can contribute to maintenance of angiotensin II-induced hypertension [30]. Studies in mice lacking isoform IL-17 A (IL-17c) develop blunted hypertension after angiotensin II infusion and that increase in superoxide production and promote endothelial dysfunction showed in hypertensive wild-type mice does not occur in animals knock out for IL-17 [31]. The IL17 likely contributes to vascular pathology in hypertension not only by direct effects, but also recruiting immune cells, active the NADPH oxidase, stimulates chemokines release and promotes chemotaxis [32].

The source of IL-17 is IL-6, acts to polarize both CD4+ and CD8+ cells toward IL-17 release. IL-6 stimulates the liver to produce inflammatory acute phase proteins (C-reactive protein and serum amyloid A) to enhance inflammatory milieu. Clinical and experimental studies have shown strong correlations between IL-6 and presence of hypertension [33]. However, production of IL-6 can derive of angiotensin II stimulate by smooth muscle cells via a pathway relationship AT1 receptor, increased intracellular calcium, tyrosine kinase and MAP-kinase stimulation to release IL-6 [34]. In humans showed that angiotensin II infusion increases IL-6 levels and aldosterone block by spironolactone prevent hypertension with no changes in IL-6 levels [35]. The mechanism of cytokines interact remains unclear, by IL-6-derive of kidney and smooth cells induce T cells to release IL-17 leading to hypertension. These inflammatory pathways need further investigations about future pharmacological interventions.

IV. AUTOIMMUNITY RESPONSE AND HYPERTENSION

The formation of new antigens by secondary modifications such as glycosylation, chemical modifications or proteolytic cleavage creating neoantigens can be targets of autoimmune responses in hypertension as proposed above. The neoantigens formations can be new pathway to lead hypertension disease since clinical evidence that there is a causal link between autoimmune manifestations and impaired blood pressure control. Studies suggest the autoimmunity response to HSP-peptide fragments expressed in kidney, CNS and arteries is associated with elevation in oxidative stress, sympathetic stimulation, and stress associated in animals with hypertension [36-37] In clinical studies essential hypertension is associated with elevated autoantibodies anti-HSP70 [38].

The association of humoral immunity and hypertension was postulated by Kristensen, reported an increase in IgG and IgM autoantibodies in patients with essential hypertension [39-41].

Several examples exist where the antigen is known; an example is HSP have been found to be overexpressed in target organs in animal models of hypertension. Angiotensin-II, ROS, sympathetic activation can induce expression of HSPs in different tissue (kidney, blood vessels and brain) [42-43]. HSP derivate-peptides can stimulate acquired and innate immunity involves the CD91, CD40 and LOX-1 in antigen-present cells [44]. Determination of overexpression HSP-70, for example, might have antigenic properties initiation immune response to alter blood pressure in animal models salt-sensitive hypertension [45]. HSP 70 fragments can induces T-cell response derived IL-10 to blocked the development of salt-sensitive hypertension with reduction of renal inflammation and increases expression of IL-10 in the kidney [46] suggesting a new possibility of immunotherapy target HSP-70 expression for hypertension control.

We previous studies [47,48] have showed the oxLDL induces differentiation in T cells with increase expression of HSP-60, higher autoantibodies, and elevation pro-inflammatory status, suggesting that endothelial dysfunction can promote oxidation of LDL particle with possibility the increase HSP expression to lead elevation in autoimmune response to trigger hypertension disease [47-49].
Patients in the early stages of hypertension have shown IgG and IgM antibodies against endothelial cells, revealing a possible role of the humoral response in the pathophysiology of hypertension [50]. The endothelial cells the processes of apoptosis release microparticles that can be recognized by the humoral response, especially IgM antibodies with greater affinity for oxidized lipid of membranes that are abundant in senescent cells [51]. The endothelial microparticles are implicated with chronic elevation of blood pressure and endothelial cell senescence to occur hypertension disease [52].

Humoral immunity can recognize oxidized LDL particles similarly to apoptotic cells as discussed above, initiating a response by anti-oxLDL antibodies IgG and IgM isotype, more specifically against epitopes formed during the oxidation process have been associated to the degree of hypertension degree [53]. We have showed that reducing blood pressure can modulate humoral IgG anti-oxLDL [54] and that metabolic factors associated with obesity can also modify the immune response of patients with hypertension [55].

Several pathological condition driving atherosclerosis and hypertension such as acute inflammation, chronic inflammation modify low density lipoprotein particle. These modification leads to the expression of neoantigens and the immune response against these newly formed antigens have been implied in the pathogenesis of atherosclerosis. Our group has demonstrated that humoral response to apoB peptide-derived (apoBD) a peptide fragment derived from an integral part of the apoB protein, is associated with blood pressure levels [48] and that the peptide itself can cause endothelial dysfunction [56]. This peptide neoantigen is generated from the apoB part component of LDL particle. The apoBD epitope is not expressed on the native, “normal”, but in particle fragment by degradation. These peptide fragments can be involved with modulate of humoral immunity in hypertension and atherosclerosis process [57,58]. In a prospective study we have shown that HIV infected patients undergoing antiretroviral therapy (ART) demonstrate an inverse correlation between anti-apoBD autoantibodies levels and carotid artery intimal-media thickness with subsequent decreased arterial caliber [59].

Yet, our group recently findings other peptide (ApoBDS-1) with immunogenic properties with potential to atherosclerosis contribution, by differentiation T cells to Th1 phenotype with increase inflammatory cytokines. Interestingly, ApoBDS-1 peptide has a specific Ca\(^{2+}\) receptor to signaling IL-8 expression and increase burst oxidative in inflammatory cells. They ApoBDS-1 peptide can be associated with atherosclerosis process as well as hypertension diseases by inflammatory and oxidative stress increase [60].

Other evidences show that presence of antagonistic antibodies to α-adrenergic receptor, angiotensin type 1 (AT-1) receptor, and β-1 adrenergic receptor are involved with hypertension [61] and the removal of α1-adrenergic receptor antibodies in patients with hypertension was shown to reduce blood pressure revealing the clinical relevance of antibodies in higher blood pressure [62].

T-cells subsets have important roles in the development of autoimmune diseases by activation of B cell to production of autoantibodies, however special subset Th2 cells are implicated in humoral-mediated immunity and Th17 to release IL-17, which can also increase TNF-α production. These immunity responses are present in different autoimmune disease, example of Systemic Lupus Erythematosus (SLE), in which patients showed prevalence of hypertension when compared health patients controls [63].

In summary, evidences suggest that cellular and humoral autoimmunity responses may have a pivotal role in the pathogenesis of hypertension. Various subsets of T lymphocytes can participate as well as antibodies. Some of the have been identified (e.g. angiotensin II and apoBD) Today we know some candidate antigens and epitopes. The further characterization of the underlying mechanisms behind this response as well as new potential neoantigens can be important new strategies for the understanding of hypertension as well as strategies for new therapy modalities.

CONFLICT OF INTEREST STATEMENT

Magnus Gidlund is inventor of apoB peptides (apoBD) for application as biomarkers, immunotherapy and vaccine in cardiovascular diseases.

References


