

THE PHYSIOLOGY OF T-CELL IN THE DEVELOPMENT OF HYPERTENSION: A REVIEW

ABSTRACT

T-cells have been shown to play a role in the development of hypertension but the subset of T-cells involved has not been fully elucidated. Also, there is a global rise in the incidence of hypertension mostly among the young populace. Majority of these cases are not secondary hypertension. This has posed concerns on the ideal aetiology of its development and progression. The place of immune deregulation has been scrutinized greatly. Current evidence has shown that inflammation and adaptive immunity play a role in the development of hypertension. Angiotensin II mediated hypertension has been shown to involve inflammatory mechanisms in the peripheral vessels, the kidneys and CNS. End organ lymphocyte infiltration is believed to be a part to the development of hypertension. Recent studies demonstrated the role of central nervous system and subfornical organs in the evolution and maintenance of angiotensin II-dependent hypertension which is associated with peripheral activation of lymphocytes and tissue inversion.

Key words: Hypertension, diastolic blood pressure, T-CELL

INTRODUCTION

“Hypertension is defined as the persistent rise in both the systolic and diastolic blood pressure above 140mmHg and 90mmHg respectively” (Obi et al; 2019, Nwafor et al; 2020). “It is among the most prevalent of chronic diseases, affecting about a third of the global adult population” (James *et al*; 2014, Obi et al; 2019, Nwafor et al; 2020). “The aftereffects of uncontrolled cases including cerebrovascular accidents, congestive cardiac failure as well as chronic kidney disease are associated with enormous morbidity and mortality. In spite of substantial progress in many research on hypertension, the ideal etiology of blood pressure rise is still unknown among many patients” (Zhang and Crowley; 2014).

“The dysfunction in the cardiovascular regulatory centers including the kidneys, vascular system and brain work in tandem to bring about sustained hypertension but the role of immune deregulation to induce hypertension has been greatly scrutinized in recent years. Macrophages and T-cells infiltrate the heart, vasculature and the kidneys during hypertension” (Wenzel *et al*; 2011, Muller *et al*; 2002). “The improved expression of adhesion molecules on the vascular beds of the above organs brings about accumulation of inflammatory cells by encouraging increased extravasation of leukocytes” (Muller *et al*; 2002). “Subsequently, these mononuclear cells secrete or induce many pro-hypertensive cytokines such as IL-6, IL-17 and TNF- α ” (Bautista *et al*;

2005, Ateset *et al*; 2014). “Recently, the roles of T-lymphocytes in promoting blood pressure increase in seminal adoptive studies were proposed” (Guziket *et al*; 2007).

“Evidence has shown that inflammation and adaptive immunity are important contributors to the development of hypertension” (Harrison *et al*; 2007, Lob *et al*; 2010). “Angiotensin II mediated hypertension has been shown to involve inflammatory mechanisms in the peripheral vessels, the kidneys and CNS” (Paton and Waki;2009, Zubcevic *et al*; 2011). “End organ lymphocyte infiltration is believed to be a part to the development of hypertension among males” (Paton and Waki;2009, Zubcevic *et al*; 2011). “Recent studies demonstrated the role of central nervous system and subfornical organs in the evolution and maintenance of angiotensin II – dependent hypertension which is associated with peripheral activation of lymphocytes and tissue invasive” (Harrison *et al*; 2011, Marvar *et al*; 2010). “Information regarding the role of immune system in the development of hypertension in females in limited but sex-specific differences in the emergence of hypertension are adequately documented” (Dubey *et al*; 2002, Sandberg and Ji; 2012, Lima *et al*; 2012).

“It has been suggested that 17 β – estradiol delays the onset of cardiovascular diseases (including hypertension) and may play a role in keeping women “cardiovascularly younger” than the men of the same age, as estradiol decreases the risk of cardiovascular diseases” (Goldman *et al*; 2009, Ji *et al*; 2007). “Similar observations were also made in experimental models of cardiovascular regulation and hypertension” (Goldman *et al*; 2009, Ji *et al*; 2007, Lindsey *et al*; 2011, Reckelhoff and Maric; 2010). “The major mechanism underlying the relative protection of females from hypertension involves multiple end organs and systems, this is because of the vast expression of estrogen receptors in the females compared to the men” (Maric *et al*; 2008, Xue *et al*; 2007).

T-CELL SUBTYPES

“Studies have shown that T-cells play a role in the development of hypertension but have not defined the subset of T-cells involved” (Harrison; 2014). “Various subsets of T-lymphocytes alter blood pressure through their effects on the local cytokine milieu within the cardiovascular control organs. Naïve T-cells arise from hematopoietic stem cells in the bone marrow and mature in the thymus before they move to peripheral tissues” (Zhang and Crowley, 2014). “Based on the expression of major cell surface markers, T-lymphocytes can be grouped into different subsets with peculiar functions” (Zhu & Paul; 2008). Simply put, CD4 single positive T-cells are classified as T- helper cells (Th cells); CD8 single positive T-cells are called cytotoxic T-cells and CD1d positive T-cells are recognized as natural killer T-cells.

Once an antigen is presented in the context of a major histocompatibility complex (MHC) to the T-cell receptor (TCR) on the naive CD4⁺ T cells, the T-cell polarizes into Th¹, Th², Th¹⁷ or T-regulatory cell phenotypes based on local concentrations of specific cytokines. This process differentiates the T-cell to function in different specialized forms for different purposes as stated below.

- Th¹ commitment is triggered by IL – 2

- Th² commitment is induced by IL – 4
- Th¹⁷ differentiation requires IL – 6 and IL – 23
- T.reg with immunosuppressive activity is induced by TGF-β1 (Strom and Koumanda; 2009).

The Th¹⁷ cells are newly characterized and produce the cytokine IL – 17. Its role is shown in the following disease (Eid *et al*; 2009, Tesiner *et al*; 2008, Winer *et al*; 2009):

- Autoimmune diseases
- Obesity
- Cardiovascular disease

THE MECHANISM OF ACTIVATION OF T-CELLS

“To investigate the role of IL – 17 in the development of hypertension, a study was done on IL – 17a⁻¹⁻ mice and it was reported that angiotensin II caused an initial rise in the blood pressure of the animals but this was not sustained after a week” (Madhur *et al*; 2010). This was so because the angiotensin II-induced aortic T-cell infiltration as seen in wild type mice was deficient in IL – 17a⁻¹⁻ mice as were the increase in vascular oxidative stress and endothelia dysfunction. However, direct infusion of IL – 17a induced hypertension and endothelia dysfunction in mice (Nguyen *et al*; 2013) and the result of oxidative stress in the placenta of pregnant rats as a result of IL – 17, promote hypertension (Dhillion *et al*; 2012). Besides IL–17a, other cytokines have been said to play a part in the pathogenesis of hypertension, like TNF-α, IL-2,4,6 and 23.

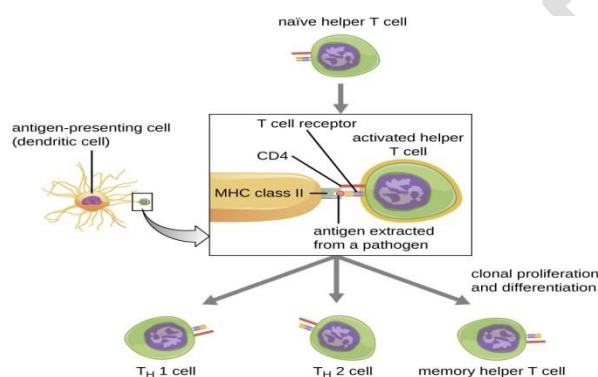


Figure 1: This illustration depicts the activation of a naïve (unactivated) helper T cell by an antigen-presenting cell and the subsequent proliferation and differentiation of the activated T cell into different subtypes.

“Etanercept (a TNF-α antagonist) is very functional in the prevention of hypertension” (Guzik *et al*; 2007, Tran *et al*; 2009, Venegas-Pont *et al*; 2010). “It should be noted that mice deficient in IL – 6 are protected in some models of hypertension” (Brands *et al*; 2010, Schrader *et al*; 2007). Interferon-γ is upregulated in the kidneys of hypertensive mice (Crowly *et al*; 2010) and the deletion of the interferon-γ receptor hinders angiotensin II-induced end organ damage (Marko *et al*; 2012). “The above facts suggest that hypertension is mediated by multiple pro-inflammatory T-cell subtypes. Therefore, T-regulatory cells which restrain pro-inflammatory T-cells increase hypertension induced end organ damage in mice” (Kvakan *et al*; 2009).

Furthermore, T-lymphocytes permeate several cardiovascular control organs during hypertension (including the kidneys and vasculature). **Aortic** adventitia is a major site of T-cell accumulation in hypertensive events. This process leads to exaggerated aortic stiffness and endothelial dysfunction which promotes collagen accumulation (Guzik *et al*; 2007). The renal blood vessels are also infiltrated during hypertension (Crowley *et al*; 2008). In this regard the protection of lymphocyte-deficient mice from hypertension as stated earlier is as a result of permission of pressure-induced sodium excretion through an eNOS- and COX-2-dependent pathway (Crowley *et al*; 2008). Another study also demonstrated that CD8-deficient mice are also resistant to acute sodium retention during prolonged angiotensin-II infusion (Trott *et al*; 2014).

THE ROLE OF T-LYMPHOCYTES IN HYPERTENSION

“Studies have shown the role of T-lymphocytes in the development of hypertension” (Guzik *et al*; 2007). “Mice lacking both T and β -lymphocytes [recombinase-activating gene -1 (RAG-1^{-/-}) deficient mice] were observed to have blunted hypertensive responses to angiotensin-II and increased salt levels. However, these animals did not show raised vascular superoxide production and endothelial dysfunction usually seen in hypertensive animals. **Hypertension and vascular dysfunctions were reversed when RAG-1^{-/-} mice received transfer of T-cells but no change or reversal when β -cells was transferred.** It is worthy of note that angiotensin-II increased circulating CD69⁺CCR5⁺ and CD44^{high} T-cells which are markers of effective memory T-cells” (Zhang and Crowley; 2014). “Further studies showed that mice with severe combined immune-suppression are protected against hypertension and showed reduction in albuminuria and renal damage” (Crowley *et al*; 2010). “Recently, another study attempted to delete the RAG-1 gene in salt-sensitive rat using zinc finger nuclease technology and this resulted in raised blood pressure, albuminuria and kidney damage, **confirming involvement of RAG-1 gene in immune modulation in the development of hypertension**” (Mattson *et al*; 2013).

“In contrast to the above evidence in support of the role of T-lymphocyte in experimental hypertension, the part played by T-cells to the development of human hypertension needs further proof although, testing causality in human studies becomes difficult, particularly given the heterogeneity of the diseases” (Harrison; 2014). “Studies have proved the infiltration of T-lymphocytes into the kidneys of patients with essential hypertension (Heptinstall; 1954) but in the circulation, hypertensive patients showed a raised fraction of immunosenescent CD8⁺ T-cells and better expression of the chemokine CXCR3 that recruits T-cells into damaged organs” (Youn *et al*; 2013). “Hypertensive patients also exhibit increased circulating levels of cytokines secreted by T-cells (TNF- α , IL-6, IL-4 and IFN- γ inducible protein)” (Stumpf *et al*; 2011, Chrysohoou *et al*; 2004). “Moreover, patients with autoimmune diseases but without renal impairment have higher frequency of hypertension compared with normal individuals, proving the role of inflammatory response in such patients in the promotion of hypertension” (Lozovoy *et al*; 2014).

“Conversely, hypertensive patients with autoimmune diseases who were given treatments to suppress lymphocyte infiltration showed improvements in blood pressure than normal individuals which shows that targeting the immune system may present a good step for antihypertensive therapy” (Herrera *et al*; 2006). “Large genome-wide association studies (GWAS) in humans have shown the links between hypertension and variants of genes expressed in T-lymphocytes. For instance, one GWA study identified a variant in CD247 that encodes the CD3C chain, which is associated with levels of blood pressure in more than 2000 African and European-American hypertensive subjects” (Ehret *et al*; 2009). “The global blood pressure genetics consortium analyzed GWAS data from more than 30,000 subjects of European origin and discovered that the immune-receptor signaling molecule SH2B3 (also called the lymphocyte-specific adapter protein), had a mis-sense SNP that separated with levels of diastolic blood pressure” (Newton Cheh *et al*; 2009). “The most recent GWAS report showed an association between hypertension and alleles of HLA-DQB1 and NFAT5 in a cohort of nearly 100,000 individuals” (Tragante *et al*; 2014).

ACTIVATION OF T-LYMPHOCYTES IN HYPERTENSION

The involvement of T-lymphocytes in hypertensive response shows that blood pressure is antigen-driven autoimmune process but the mechanism of T-cell activation in hypertension is an area of research.

Classically, T-cells require two signals for activation.

- (a) **Signal I:** This involves the interaction of T-cell receptor (TCR) with an antigen presented in the context of a major histocompatibility complex.
- (b) **Signal II:** This involves the stimulation of co-stimulatory molecules on the T-cells by ligands on the antigen presenting cell.

“The major co-stimulatory molecule on T-cells is the CD28 which is bound by the B7 ligand, CD80 and CD86 of the antigen presenting cells (APC). Ligation of the TCR in the absence of co-stimulation leads to T-cells apoptosis” (Frauwirth and Thompson; 2002). “CTLA4 -1g (a pharmacologic agent) inhibits Co-stimulation by binding to B7 ligands on APC and this action blunts blood pressure T-cell activation and vascular infiltration in both angiotensin-II and deoxycorticosterone acetate salt-induced hypertension” (Vinh *et al*; 2010). This shows that signals **I and II** in T-cell activation are necessary for the development of hypertension.

“Initial increases in blood pressure seem to be an initiating factor in T-cell activation. This is because the induction of hypertension pushes inflammatory cells into the kidneys which promote salt sensitivity even when the hypertensive stimulus is withdrawn” (Lombardi *et al*; 1999). “Recent research showed that prevention of hypertension in angiotensin II-infused mice via blockage of sympathetic outflow from the CNS or by treatment with hydralazine also abrogated T-cells activation and pre-vascular infiltration” (Marvar *et al*; 2010).

“The activation of T-cells requires the stimulation of TCR by APC (most potent of which is the dendritic cells). The oxidative stress induction in dendritic cells augments susceptibility to hypertension upon adaptive transfer due to the influence of highly reactive gamma

ketoaldehydes” (Kirabo *et al*; 2014). The above discovery shows that the neo-antigen that drives the adaptive immune response in hypertension may be an isoketal (Ketoaldehyde)- modified self-antigen.

THE ROLE OF CNS IN THE IMMUNE SYSTEM MEDIATED HYPERTENSION

“The human vasculature, kidneys and central nervous system (CNS) all play a part in the pathogenesis of hypertension. The secondary lymphoid tissues (including the lymph nodes and spleen) are highly innervated” (Felten *et al*; 1984). “Studies have shown that intracerebroventricular angiotensin II raises splenic efferent nerve firing and splenic mRNA expression of multiple cytokines” (Ganta *et al*; 2005). The circumventricular organs of the brain, including the subfornical organ (SFO), the organum vasculosum of the lateral terminalis, the median eminence and the area postrema have an incomplete blood-brain-barrier and as such are influenced by circulating hormones **such as angiotensin II**.

“Various studies implicated the CNS in immune cell activation in hypertension. Lesions in the anteroventral third of cerebral ventricle (AV3V) prevent angiotensin II-induced hypertension” (Brody *et al*; 1979, Marvar *et al*; 2010). “This was possible because AV3V lesion protected against T-cell activation and aortic infiltration of T-cells in response to angiotensin II” (Marvar *et al*; 2010). **Furthermore**, sympathetic drive with the release of nor-epinephrine mediates T-cell activation and hypertension since angiotensin II-induced T-cell activation is not due to direct action of angiotensin II on T-cells but due to central signals” (Harrison; 2014).

“Superoxide in the SFO also promotes hypertension. The SFO sends and receives signals from other cardiovascular centre of the brain. Mice with Loxp sites housing extracellular superoxide dismutase (ecSOD) coding region were used in an experiment for ICV injection of an adenovirus encoding Cre-recombinase, deleting ecSOD in the SFO. The effect of this included” (Lob *et al*; 2010):

- Increased reactive oxygen species (ROS) levels in SFO
- Increased sympathetic outflow with variable ratio of low to high heart rate
- Elevation in blood pressure

In a separate study, specific deletion of ecSOD in vascular smooth muscles lead to an increase in vascular reactive oxygen species but blood pressure and T-cell response **produced no change** compared with control group (Lob *et al*; 2011). The above findings showed the crucial role of the CNS in mediating T-cell response in hypertension.

IMMUNE SYSTEM AND PRE-ECLAMPSIA

“Pre-eclampsia is the onset of hypertension in pregnancy associated with proteinuria” (Obi *et al*; 2019, Nwafor *et al*; 2020). This condition is associated with the formation of auto-antibodies that stimulate angiotensin II receptor (Wallukat *et al*; 1999) and when these antibodies are infused in mice, pre-eclampsia-like symptoms developed (Zhou *et al*; 2008). “A specific subset of β -cell **is** said to produce these antibodies” (Jensen *et al*; 2012). “Rituximab (an anti CD20 antibody) can deplete the β -cells and blunt the blood pressure response in reduced intrauterine

perfusion pressure rat model of pre-eclampsia” (Lamarca *et al*; 2011). “Subsequently, adoptive transfer of CD4⁺ T-cells from reduced intrauterine perfusion pressure rats to normal pregnant rats increased blood pressure in the control group” (Novotny *et al*; 2012). “Also supporting the role of T-cells in pre-eclampsia, mice deficient in IL-4 or IL-10 developed pre-eclampsia-like symptoms when pregnant” (Chatterjee *et al*; 2011, Chatterjee *et al*; 2013). IL-17 mediates placental oxidative stress and raises blood pressure in pregnant rats (Dhillon *et al*; 2012).

CLINICAL EVIDENCE SUPPORTING T-CELLS COMPONENT TO BLOOD PRESSURE CONTROL

Increased levels of cytokines in human blood have been reported in hypertension and individuals at risk of hypertension. It has been shown that;

- a. Serum levels of IL-17 are greater in diabetic patients with hypertension compared with normotensive subjects (Modhur *et al*; 2010).
- b. Plasma levels of inflammatory cytokines such as C-reactive protein, IL-6 and TNF- α are positively correlated with blood pressure in humans (Bautista *et al*; 2005). In a cross-sectional survey of inflammatory biomarkers among men and women in Switzerland, serum levels of IL-6, TNF- α and C-reactive protein were positively correlated with blood pressure in both sexes but the association between these cytokines and blood pressure tend to be stronger in women (Pruijim *et al*; 2013).

Lymphocytes have also been shown to play a part in blood pressure control in human hypertension. Administration of MMF (an immunosuppressant drug) to male and female hypertensive patients with psoriasis or rheumatoid arthritis significantly decreased the blood pressure over 3 months of treatment (Herrera *et al*; 2006) but this returned to pre-treatment level following the withdrawal of MMF. HIV positive patients have reduced T-cell counts and lower incidence of hypertension than healthy individuals; however, the risk of developing hypertension in these patients is positively related to increased T-cell level following treatment (Ho *et al*; 2012, Factor *et al*; 2013). Also, a single nucleotide polymorphism in CD247 (a key protein in the T-cell receptor complex) is associated with blood pressure in hypertensive individuals (Ehret *et al*; 2009). Hypertensive patients exhibit higher number of cytotoxic CD8⁺ T-cells when compared to normotensive individuals (Youn *et al*; 2013) while T_{regs} are reduced in women with pregnancy induced hypertensive compared to normal pregnant women (Cao *et al*; 2013).

THERAPEUTIC APPLICATIONS OF TARGETING T-CELLS IN HUMAN HYPERTENSION

T_{regs} offer protection against hypertensive and hypertension-induced end organ damage, hence making T_{regs} an attractive therapeutic target to improve blood pressure control rates. Intravenous immunoglobulin therapy (IVIG) is often used in the treatment of autoimmune disease and recently, IVIG acts partly by driving the expansion of T_{regs} in children with Kawasaki disease (Franco *et al*; 2014).

Autologous T_{regs} are now being used clinically to treat;

- (a) Graft versus host disease
- (b) Transplant rejection
- (c) Auto-immune diseases

(d) Type I DM (? clinical trial).

CONCLUSION

Much literature supports the causal role of T-cells to hypertension with associated end organ damage. However, understanding the molecular mechanisms through which the immune system controls blood pressure and the modalities of interactions of the various components of the immune system is important. This will help to elucidate specific mechanisms that can be targeted therapeutically without distorting the natural immune defense. Generally, the central actions of hypertensive stimuli increase sympathetic outflow, leading to an initial rise in blood pressure which is consistent with clinical “prehypertension” resulting in protein modifications. These are processed and presented by dendritic cells, leading to T-cell activation. The activated T-cells infiltrate the kidneys and vasculature to give rise to cytokines. This promotes renal salt and water retention as well as vascular constrictions and remodeling. These alterations lead to overt hypertension.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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