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

ABSTRACT

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 role to 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 invasive.

INTRODUCTION

Hypertension is defined as the persistent rise in both the systolic and diastolic blood pressure above 140mmHg and 90mmHg respectively. It is among the most prevalent of the chronic diseases, affecting about a third of the global adult population (James *et al*; 2014). The after effects of uncontrolled cases including cerebrovascular accidents, congestive cardiac failure as well as chronic kidney disease are associated with enormous morbidity and mortality. In spite substantial progress in many researches on hypertension, the ideal etiology of blood pressure rise are 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 bring about accumulation of inflammatory cells by encouraging increased extravasation of leukocytes (Muller *et al*; 2002). Subsequently, these mononuclear cells secret or induce many pro-hypertensive cytokines such as IL-6, IL–17 and TNF–α (Bautista *et al*; 2005, Ates*et al*; 2014). Recently, the roles of T-lymphocytes in promoting blood pressure increase in seminal adoptive studies were established (Guzik*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. 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 17β – 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. 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 (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 (Harrision; 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 Th^1, Th^2, Th^{17} or T-regulatory cell phenotypes based on local concentrations of specific cytokines.

- Th^1 commitment is triggered by IL – 2
- Th^2 commitment is induced by IL – 4
- Th^{17} differentiation requires IL – 6 and IL – 23
- T.reg with immunosuppressive activity is induced by TGF–β1 (Strom and Koumanda; 2009).

The Th^{17} 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). Bedsides IL–17a, other cytokines have been said to play part in the pathogenesis of hypertension.

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 substypes. 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). The 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^{-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^{-1-} mice received an adoptive transfer of T but not β-cells. 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 (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 Iand 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 angiotesim 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. A high salt diet may also play a role in the development of hypertension by two mechanisms;

a. Driving intravascular volume expansion
b. Favouring Th^{17} differentiation through inducible salt sensing kinase and GK1 (Kleinemietfeld *et al*; 2013, Wie *et al*; 2013).

THE ROLE OF CNS IN IMMUNE 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 organumvasculosum 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 (angiotensin II).

Various studies implicated the CNS in immune cell activation in hypertension. Lesions in the anteroventral third of cerebral ventricle (AV3V) preventangiotensin 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 ecSODin vascular smooth muscles lead to an increase in vascular reactive oxygen species but blood pressure and T-cell response were intact 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. 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-cells are 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 (Dhillion *et al*; 2012).

CLINICAL EVIDENCE SUPPORTING T-CELLS COMPONENT TO BLOOD PRESSURE CONTROL

Increased levels of cytokines in human blood have been reported in hypertensive 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) to male and female hypertensive patients with psoariasis 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-cellcounts 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 nucleotidepolymorphism 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 cytoxic 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 version host disease

(b) Transplant rejection
(c) Auto-immune diseases
(d) Type I DM (? clinical trial).

CONCLUSION

Many literatures support 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, such that specific mechanisms can be targeted therapeutically without distorting the natural immune defense is a great challenge. 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.

REFERENCES

Ashton N., Balment R.J (1991). Sexual Dimorphism in Renal Function and Hormonal Status of New Zealand Genetically Hypertensive Rats.*ActaEndocrinologica*. 124:91-97.

Ates I., Ozkayar N., Akyel F., Topcuoglu C., Akyel S., Barca A.N., Dede F (2014). The Relationship between Asymptomatic Organ Damage and Serum Soluble Tumor Factor-like Weak Inducer of Apoptosis (sTWEAK) and Interleukin-17A (IL-17A) Levels in Non-diabetic Hypertensive Patients.*BioMedCentral Nephrology*.15: 159.

Bautista L.E., Vera L.M., Arenas I.A., Gamarra G (2005). Independent Association between Inflammatory Markers (C-Reactive Protein, Interleukin-6, and TNF-alpha) and Essential Hypertension. *Journal of HumanHypertension*. 19:149-154.

Bhatia K., Zimmerman M.A., Sullivan J.C (2013). Sex Differences in Angiotensin Converting Enzyme Modulation of Ang (1-7) Levels in Normotensive WKY Rats.*American Journal of Hypertension*. 26:591-598.

Boynton R.E., Todd R.L (1947). Blood Pressure Readings of 75,258 University Students.*Archives of Internal Medicine*. 80:454-462

Brands M.W., Banes-Berceli A.K., Inscho E.W., Al-Azawi H., Allen A.J., Labazi H (2010). Interleukin-6 Knockout Prevents Angiotensin II Hypertension: Role of Renal Vasoconstriction and Janus Kinase 2/Signal Transducer and Activator of Transcription 3 Activation. *Hypertension*, 56:879-84.

Brinson K.N, Elmarakby A.A., Tipton A.J., Crislip G.R., Yamamoto T., Baban B., Sullivan J.C (2013). Female SHR have Greater Blood Pressure Sensitivity and Renal T-cell Infiltration Following Chronic NOS Inhibition than Males. *American Journal of Physiologic Regulation, Integrative and Comparative Physiology*. 305:R701-R710.

Brody M., Fink G., Buggy J., et al. (1979). Critical Role of the Anteroventral third Ventricle (AV3V) Region in Development and Maintenance of Experimental Hypertension.*Perspectives of Nephrology and Hypertension*. 6:76-84.

Cao X., Wang L.L., Luo X (2013).Expression of Regulatory T and Helper T-cells in Peripheral Blood of Patients with Pregnancy-induced Hypertension.*Clinical and Experimental Obstetrics and Gynecology*; 40:502-504.

Chatterjee P., Chiasson V.L., Kopriva S.E. et al. (2011). Interleukin-10 Deficiency Exacerbates Toll-like Receptor-3-induced Preeclampsia-like Symptoms in Mice. *Hypertension*, 58:489-96.

Chatterjee P., Kopriva S.E., Chiasson V.L. et al. (2013). Interleukin-4 Deficiency Induces Mild Preeclampsia in Mice. *Journal of Hypertension*; 31:1414-1423.

Chrysohoou C., Pitsavos C., Panagiotakos D.B., Skoumas J., Stefanadis C (2004). Association between Prehypertension Status and Inflammatory Markers Related to Atherosclerotic Disease: The ATTICA Study. *American Journal of Hypertension*. 17:568-573.

Cornelius D.C., Hogg J.P., Scott J., Wallace K, Herse F., Moseley J., Wallukat G., Dechend R., LaMarcaB (2013). Administration of Interleukin-17 Soluble Receptor-C Suppresses Thl7 Cells, Oxidative Stress and Hypertension in Response to Placental Ischemia during Pregnancy. *Hypertension*; 62:1068-1073.

Crowley S.D., Frey C.W., Gould S.K., Griffiths R., Ruiz P.,Burchette J.L., Howell D.N., Makhanova N., Yan M., Kim H-S, et al. (2008). Stimulation of Lymphocyte Responses by Angiotensin II Promotes Kidney Injury in Hypertension. *American Journal Physiology and Renal Physiology*; 295:F515-524.

Crowley S.D., Song Y.S., Lin E.E., Griffiths R., Kim H.S., Ruiz P (2010).Lymphocyte Responses Exacerbate Angiotensin II-dependent Hypertension.*American Journalof Physiologic Regulation, Integrative and Comparative Physiology*; 298: R1089-97.

Crowson C.S., Liao K.P., Davis J.M., 3rd, Solomon D.H., Matteson E.L., Knutson K.L., Hlatky M.A., Gabriel S.E (2013). Rheumatoid Arthritis and Cardiovascular Disease.*American Heart Journal*; 166:622-628 e621.

Dalpiaz P.L., Lamas A.Z., Caliman I.F., Medeiros A.R., Abreu G.R., Moyses M.R., Andrade T.U., AlvesM.F., Carmona A.K., Bissoli N.S (2013). The Chronic Blockade of Angiotensin I-Converting Enzyme Eliminates the Sex Differences of Serum Cytokine Levels of Spontaneously Hypertensive Rats. *Brazilian Journal Medicine and Biologic Research*;46:171-177.

Dhillion P., Wallace K., Herse F., et al. (2012). IL-17-Mediated Oxidative Stress is an Important Stimulator of AT1-AA and Hypertension during Pregnancy. *American Journal of Physiologic Regulation, Integrative and Comparative Physiology*; 303:R353-8

Dubey R.K., Oparil S., Imthurn B., Jackson E.K. (2002).Sex Hormones and Hypertension.*Cardiovascular Research*; 53:688-708.

Ehret G.B., O'Connor A.A., Weder A., Cooper R.S., Chakravarti A (2009). Follow-up of a Major Linkage Peak on Chromosome 1 Reveals Suggestive QTLs Associated with Essential Hypertension: Gennet Study. *European Journal ofHuman Genetics*; 17:1650-1657.

Eid R.E., Rao D.A., Zhou J., et al. (2009). Interleukin-17 and Interferon-gamma are Produced Concomitantly by Human Coronary Artery-infiltrating T-cells and Act Synergistically on Vascular Smooth Muscle Cells. *Circulation*; 19:1424-32.

Factor S., Lo Y., Schoenbaum E., Klein R (2013).Incident Hypertension in Older Women and Men with or at Risk for HIV Infection.*HIV Medicine*; 14(6):337-46.

Felten D.L., Livnat S., Felten S.Y., Carlson S.L., Bellinger D.L., Yeh P (1984). Sympathetic Innervation of Lymph Nodes in Mice.*Brain Research Bulletin*;13:693-699.

Fijak M., Schneider E., Klug J., Bhushan S., Hackstein H., Schuler G., Wygrecka M., Gromoll J., Meinhardt A (2011). Testosterone Replacement Effectively Inhibits the Development of Experimental Autoimmune Orchitis in Rats: Evidence for a Direct Role of Testosterone on Regulatory T-cell Expansion. *Journal of Immunology*; 186:5162-5172.

Franco A., Touma R., Song Y., Shimizu C., Tremoulet A.H., Kanegaye J.T., Burns J.C., (2014).Specificity of Regulatory T-cells that Modulate Vascular Inflammation.*Autoimmunity*; 47:95-104.

Frauwirth K.A., Thompson C.B (2002). Activation and Inhibition of Lymphocytes by Co-stimulation.*Journal of Clinical Investigation*; 09:295-9.

Ganta C.K., Lu N., Helwig B.G., et al. (2005). Central Angiotensin Il-enhanced Splenic Cytokine Gene Expression is Mediated by the Sympathetic Nervous System. *American Journal of Physiologic Heart and Circulatory Physiology*;289:H 1683-1691.

Giachini F.R., Sullivan J.C., Lima V.V., Carneiro F.S., Fortes Z.B., Pollock D.M., Carvalho M.H., Webb R.C., Tostes R.C. (2010).Extracellular Signal-regulated Kinase 1/2 Activation via Down-regulation of Mitogen-activated Protein Kinase Phosphatase 1, Mediates Sex Differences in Deoxycorticosterone Acetate-salt Hypertension Vascular Reactivity.*Hypertension*; 55:172-I79.

Goldman R.K., Azar A.S., Mulvaney J.M., Hinojosa-Laborde C., Haywood J.R., Brooks V.L (2009).BaroreflexSensitivity Varies during the Rat Estrous Cycle: Role of Gonadal Steroids. *American Journal of Physiologic Regulation, Integrative and Comparative Physiology*; 296:R1419-1426.

Gross M.L., Adamczak M., Rabe T., Harbi N.A., Krtil J., Koch A., Hamar P., Amann K., Ritz E (2004). Beneficial Effects of Estrogens on Indices of Renal Damage in uninephrectomizedSHRsp Rats. *Journal of American Society of Nephrology*; 15:348-358.

Gu Q., Burt V.L., Paulose-Ram R., Dillon C.F (2008). Gender Differences in Hypertension Treatment, Drug Utilization Patterns and Blood Pressure Control among US Adults with Hypertension: Data from the National Health and Nutrition Examination Survey 1999-2004. *American Journal of Hypertension*; 2 1:789-798.

Guzik T.J., Hoch N.E., Brown K.A., McCann L.A., Rahman A., Dikalov S., Goronzy J., Weyand C., Harrison D.G (2007). Role of the T-cell in the Genesis of Angiotensin II-induced Hypertension and Vascular Dysfunction.*Journal of Experimental Medicine*; 204:2449-2460.

Harrison D.G., Guzik T.J., Lob H.E., Madhur M.S., Marvar P.J., Thabet SR, Vinh A., Weyand C.M (2011). Inflammation, Immunity and Hypertension. *Hypertension*; 57:132 -140.

Hermida R.C., Ayala D.E., Mojon A., Fontao M.J., Chayan L., Fernandez JR. (2013). Differences between Men and Women in Ambulatory Blood Pressure Thresholds for Diagnosis of Hypertension Based on Cardiovascular Outcomes.*Chronobiology International*; 30:221-232.

Heptinstall R.H (1954). Renal Biopsies in Hypertension.*British Heart Journal*; 1954; 16: 133-141.

Herrera J., Ferrebuz A., MacGregor E.G., Rodriguez-Iturbe B (2006).MycophenolateMofetil TreatmentImproves Hypertension in Patients with Psoriasis and Rheumatoid Arthritis. *Journal of American Society of Nephrology*;17:S218-225.

Ho J.E., Scherzer R., Hecht F.M., Maka K., Selby V., Martin J.N., Ganz P., Deeks S.G., Hsue P.Y (2012). The Association of $CD4^+$ T-cell Counts and Cardiovascular Risks in Treated HIV Disease.*AIDS*; 26:1115-1120.

James P.A., Oparil S., Carter B.L., Cushman W.C., Dennison-Himmelfarb C., Handler J., Lackland D.T., LeFevre M.L., MacKenzie T.D., Ogedegbe O., et al. (2014). Evidence-based Guideline for the Management of High Blood Pressure in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8).*Journal of American Medical Association*; 31 1:507-520.

Jensen F., Wallukat G., Horse F., et al. (2012). $CD19^+$ $CD5^+$ Cells as Indicators of Preeclampsia.*Hypertension*; 59:861 – 8.

Ji H., Zheng W., Li X., Liu J., Wu X., Zhang M.A., Umans J.G., Hay M., Speth R.C., Dunn S.E., Sandberg K (2014). Sex-specific T-cell Regulation of Angiotensin II-dependent Hypertension.*Hypertension*; 2014 Epub Ahead of Print.

Ji H., Zheng W., Menini S., Pesce C., Kim J., Wu X., Mulroney S.E., Sandberg K (2007). Female Protection in Progressive Renal Disease is Associated with Estradiol Attenuation of Superoxide Production. *Gender Medicine*; 4: 56-71.

Ji H., Pesce C., Zheng W., Kim J., Zhang Y., Menini S., Haywood J.R., Sandberg K (2005). Sex Differences in Renal Injury and Nitric Oxide Production in Renal Wrap Hypertension.*American Journal of Physiologic Heart and Circulatory Physiology*; 288:H43-47.

Kirabo A., Fontana V., de Faria A.P., Loperena R., Galindo C.L., Wu J., Bikineyeva A.T., Dikalov S., Xiao L., Chen W., et al. (2014). DCIsoketal-modified Proteins Activate T-cells and Promote Hypertension.*Journal of Clinical Investigation*; 124:4642-4656.

Kleinewietfeld M., Manzel A., Titze J., Kvakan H.,Yosef N., Linker R.A., Muller D.N., Hafler D.A(2013). Sodium Chloride Drives Autoimmune Diseases by the Induction of Pathogenic TH^{17} Cells. *Nature*;496:518-522.

Kvakan H., Kleinewietfeld M., Qadri F., et al. (2009). Regulatory T-cells Ameliorate Angiotensin II-induced Cardiac Damage. *Circulation*; 11 9: 2904-2912.

Kyurkchiev D., Ivanova-Todorova E., Hayrabedyan S., AltankovaL.,Kyurkchiev S (2007). Female Sex Steroid Hormones Modify some Regulatory Properties of Monocyte-derived Dendritic Cells. *American Journal of Reproductive Immunology*; 58:425-433.

LaMarca B., Wallace K., Herse F., et al. (2011). Hypertension in Response to Placental Ischemia during Pregnancy: Role of B-lymphocytes. *Hypertension*; 57:865 – 871.

Laresgoiti-Servitje E.A(2013). Leading Role for the Immune System in the Pathophysiology of Preeclampsia.*Journal of Leukocyte Biology*; 94:247-257.

Lee D.L., Sturgis L.C., Labazi H., et al. (2006). Angiotensin II Hypertension is Attenuated in Interleukin-6 Knockout Mice. *American Journal of Physiologic Heart and Circulatory Physiology*; 290:H935.

Lima R., Wofford M., Reckelhoff J.F (2012).Hypertension in Postmenopausal Women.*Current Hypertension and Reproduction*; 14:254-260.

Lindsey S.H., YamaieyevaL.M.,Brosnihan K.B., Gallagher P.E., Chappeil M.C (2011). Estrogen Receptor GPRSO Reduces Oxidative Stress and Proteinuria in the Salt-sensitive Female Lewis Rat.*Hypertension*; 58:665-671.

Lob H.E., Marvar P.J., Guzik T.J., et al (2010).Induction of Hypertension and Peripheral Inflammation by Reduction of Extracellular Superoxide Dismutase in the Central Nervous System.*Hypertension*;55:276-283.

Lob H.E., Vinh A., Li L., Blinder Y., Offermanns S., Harrison D.G. (2011). Role of Vascular Extracellular Superoxide Dismutase in Hypertension.*Hypertension*; 58:232-9.

Lombard D., Gordon K.L., Polinsky P., Suga S., Schwartz S.M, Johnson R.J (1999).Salt-sensitiveHypertension Develops after Short-term Exposure to Angiotensin II. *Hypertension*; 33:1013-1019.

Lozovoy M.A., Simao A.N., Morimoto H.K., Iryioda T.M., Panis C., Reiche E.M, Borelli S.D., Oliveira SR., Cecchini R., Dichi I (2014). Hypertension is Associated with Serologically Active Disease in Patients with Systemic Lupus Erythromatosus: Role of Increased Th^{l}/Th^{2} Ratio and Oxidative Stress. *ScandivanJournal of Rheumatology*; 43:59-62.

Madhur M.S., Lob H.E., McCann L.A., Iwakura Y., Blinder Y., Guzik T.J., Harrison D.G (2010). Interleukin-17 Promotes Angiotensin Il-induced Hypertension and Vascular Dysfunction. *Hypertension*; 55:500-507.

Maranon R., Reckelhoff J.F (2013).Sex and Gender Differences in Control of Blood Pressure.*Clinical Science*;125:311-318.

Maric C., Xu Q., Sandberg K., Hinojosa-Laborde C. (2008).Age-related Renal Disease in Female Dahl Salt-sensitive Rats is Attenuated with 17-beta-estradiol Supplementation by Modulating Nitric Oxide Synthase Expression. *Gender Medicine*; 5: 147-1 59.

Marko L., Kvakan H., Park J.K., et al. (2012). Interferon-gamma Signaling Inhibition Ameliorates Angiotensin II-induced Cardiac Damage. *Hypertension*;60:1430-6.

Marvar P.J., Thabet S.R., Guzik T.J., Lob H.E., McCann L.A., Weyand C., Gordon F.J., Harrison D.G (2010). Central and Peripheral Mechanisms of T-Lymphocyte Activation and Vascular Inflammation Produced by Angiotensin Il-Induced Hypertension. *Circulation Research*; 107:263-270.

Mattson D.L., Lund H, Guo C., Rudemiller N., Geurts A.M., Jacob H (2013). Genetic Mutation of Recombinant Activating Gene 1 in Dahl Salt-sensitive Rats Attenuates Hypertension and Renal Damage. *American Journal of Physiologic Regulation, Integrative and Comparative Physiology*; 304: ar407-14.

Miller V.M., Reckelhoff J.F., Sieck G.C (2014). Physiology's Impact: Stop Ignoring the Obvious Sex Matters! *Physiology*; 29:4-5.

Muller D.N., Shagdarsuren E., Park J.K., Dechend R., Mervaala E., Hampich F., Fiebeler A., Ju X., Finckenberg P., Theuer J., et al. (2002). Immunosuppressive Treatment Protects against Angiotensin II-induced Renal Damage. *American Journal of Pathology*; 161:1679-1693.

Newton-Cheh C., Johnson T., Gateva V., Tobin M.D., Bochud M., Coin L., Najjar S.S., Zhao J.H., Heath S.C., Eyheramendy S., et al. (2009). Genome-wide Association Study Identifies Eight Loci Associated with Blood Pressure. *Nature and Genetics*; 41:666-676.

Nguyen H., Chiasson V.L., Chatterjee P.,Kopriva S.E., Young K.J., Mitchell B.M (2013).Interleukin-17 Causes Rho-kinase-mediated Endothelial Dysfunction and Hypertension.*Cardiovascular Research*; 97:696-704.

Novotny S.R., Wallace K., Health J., et al (2012).Activating Auto-antibodies to the Angiotensin II Type I Receptor Play an Important Role in Mediating Hypertension in Response to Adoptive Transfer of CD4+ T-lymphocytes from Placental Ischemic Rats.*American Journal of Physiologic Regulation, Integrative and Comparative Physiology*; 302: R 1197-R1201.

Page S.T., Plymate S.R., Bremner W.J., Matsumoto A.M., Hess D.L., Lin D.W., Amory J.K., Nelson P.S., Wu J.D (2006). Effects of Medical Castration on $CD4^+$ $CD25^+$ T-cells, $CD8^+$ T-cell, IFN-γ Expression and NK Cells: A Physiological Role for Testosterone and/or its Metabolites. *American Journal of Physiology, Endocrinology and Metabolism*;290:E856-863.

Pendergrass K.D., Pirro N.T., Westwood B.M., Ferrario C.M., Brosnihan K.B., Chappell M.C (2008). Sex Differences in Circulating and Renal Angiotensins of Hypertensive Men (2).Lewis but not Normotensive Lewis Rats.*American Journal of Physiologic Heart and Circulatory Physiology*; 295:H10-H20.

Perez-Sepulveda A., Torres M.J., Khoury M., Illanes S.E (2009).Innate Immune System and Preeclampsia.*Frontiers of Immunology*; X5:244.

Pettersson U.S., Walden T.B., Carlsson P.O., Jansson L., Phillipson M (2012). Female Mice are Protectedagainst High-fat Diet Induced Metabolic Syndrome and Increase the Regulatory T-cell Population in Adipose Tissue. *PLoS One*; 7:e46057.

Pollow D.P., Uhrlaub J., Romero-Aleshire M.J., Sandberg K., Nikolich-Zugich J., Brooks H.L., Hay M (2014).Sex Differences in T-Lymphocyte Tissue Infiltration and Development of Angiotensin II Hypertension.*Hypertension*; 2014 Epub Ahead of Print.

Pruijm M., Vollenweider P., Mooser V., Paccaud F., Preisig M., Waeber G., Marques- Vidal P., BurnierM., Bochud M (2013). Inflammatory Markers and Blood Pressure: Sex Differences and the Effect of Fat Mass in the COLAUS Study. *Journal of Human Hypertension*; 27:169-175.

Reckelhoff J.F., Zhang H., Srivastava K (2000). Gender Differences in Development of Hypertension in Spontaneously Hypertensive Rats: Role of the Renin-angiotensin System.*Hypertension*; 35:480-483.

Reckelhoff JF, Marie C(2010). Sex and Gender Differences in Cardiovascular-renal Physiology and Pathophysiology.*Steroids*; 75:745-746.

Roberts J., Maurer K (1977). Blood Pressure Levels of Persons 6-74 Years. United States, 1971-1974 Vital and Health Statistics; Series 11, Data from the National Health Survey i-v. 1-103.

Ryan M.J (2009). The Pathophysiology of Hypertension in Systemic Lupus Erythromatosus.*American Journal of Physiologic Regulation, Integrative and Comparative Physiology*; 296:R1258-R1267.

Sainz J., Osuna A., Wangensteen R., de Dios LunaJ., Rodriguez-Gomez I., Duarte J., Moreno J.M., Vargas F (2004).Role of Sex Gonadectomy and Sex Hormones in the Development of Nitric Oxide Inhibition-induced Hypertension.*Experimental Physiology*; 89:155-162.

Sampson A.K., Jennings G.L., Chin-Dusting J.P (2012).Why are Males so Difficult to Understand?: A Case whereX" does not Mark the Spot. *Hypertension*; 59:525-531.

Sandberg K., Ji H (2012). Sex Differences in Primary Hypertension.*Biology of Sex Differences*; 3:7.

Saraiva M., O' Garra A (2010).The Regulation of IL–10 Production by Immune Cells.*Natures Review in Immunology*; 10: 170 – 181.

Schrader L.I., Kinzenbaw D.A., Johnson A.W., Faraci F.M., Didion S.P (2007). IL-6 Deficiency Protects against Angiotensin II-induced Endothelial Dysfunction and Hypertrophy. *Arteriosclerosis, Thrombosis and Vascular Biology*;27:2576-81.

Sinicato N.A., da Silva Cardoso P.A., Appenzeller S (2013). Risk Factors in Cardiovascular Disease in Systemic Lupus Erythromatosus. *Current Cardiology Review*; 9:15-19.

Strom T.B.,Koulmanda M (2009). Recently Discovered T-cell Subsets Cannot Keep their Commitments. *Journal of AmericanSociety of Nephrology*; 20: 1677-1680.

Stumpf C., Auer C., Yilmaz A., Lewczuk P., Klinghammer L., Schneider M., Daniel W.G., Schmieder R.E., Garlichs C.D (2011).Serum Levels of the Th[l] Chemo-attractant Interferon-gamma-inducible Protein (IP)-10 are Elevated in Patients with Essential Hypertension. *Hypertension Research*; 34:484-488

Sullivan J.C (2008). Sex and the Renin-angiotensin System: Inequality between the Sexes in Response to RAS Stimulation and Inhibition. *American Journal of Physiologic Regulation, Integrative and Comparative Physiology*; 294:R1220-1226.

Sullivan J.C., Bhatia K., Yamamoto T., Elmarakby A.A (2010).Angiotensin (1-7) Receptor Antagonism Equalizes Angiotensin II-induced Hypertension in Male and Female Spontaneously Hypertensive Rats.*Hypertension*; 56:658-666.

Sullivan J.C., Pardieck J.L., Doran D., Zhang Y., She J.X., Pollock J.S (2009). Greater FractalkineExpression in Mesenteric Arteries of Female Spontaneously Hypertensive Rats Compared with Males. *American Journal of Physiology*; 296:H1080-H1088.

Sullivan J.C., Semprun-PrietoL., BoesenE.I., Pollock D.M., Pollock J.S (2007). Sex and Sex Hormones Influence the Development of Albuminuria and Renal Macrophage Infiltration in Spontaneously Hypertensive Rats. *American Journal of Physiologic Regulation, Integrative and Comparative Physiology*; 293:R1573-R1579.

Tai P., Wang J., Jin H., Song X., Van J., Rang Y., Zhao L., An X., Du X., Chen X., Wang S., Xia G., Wang B (2008).Induction of Regulatory T-cells by Physiological Level Estrogen.*Journal of Cellular Physiology*; 214:456-464.

Tesmer L.A., Lundy S.K., Sarkar S., Fox D.A (2008).Th^{l7}-cells in Human Disease.*Immunology Review*; 223:87-113.

Tipton A.J., Baban B., Sullivan J.C (2012). Female Spontaneously Hypertensive Rats have Greater Renal Anti-inflammatory T-Lymphocyte Infiltration than Males. *American Journal of Physiologic Regulation, Integrative and Comparative Physiology*;303:R359-367.

Tipton A.J., Baban B., Sullivan J.C (2014). Female Spontaneously Hypertensive Rats have a Compensatory Increase in Renal Regulatory T-cells in Response to Elevations in Blood Pressure. *Hypertension*; 2014 Epub Ahead of Print.

Tragante V., Barnes M.R., Ganesh S.K., Lanktree M.B., Guo W., Franceschini N., Smith E.N., Johnson T., Holmes M.V., Padmanabhan S., et al. (2014).Gene-centric Meta-analysis in 87,736 Individuals of European Ancestry Identifies Multiple Blood Pressure Related Loci.*American Journal of Human Genetics*; 94:349-360.

Tran L.T., MacLeod K.M., McNeill J.H (2009). Chronic Etanercept Treatment Prevents the Development ofHypertension in Fructose-fed Rats. *Molecular and Cell Biochemistry*; 330:219-28.

Trott D.W., Thabet S.R., Kirabo A., Saleh M.A., Itani H., Norlander A.E., Wu J., Goldstein A., Arendshorst W.J., Madhur M.S., et al. (2014). Oligoclonal CD8^{+} Cells Play a Critical Role in the Development of Hypertension. *Hypertension*. 64(5):1108-1115.

Venegas-Pont M., Manigrasso M.B., Grifoni S.C., et al. (2010).Tumor Necrosis Factor-alpha Antagonist Etanercept Decreases Blood Pressure and Protects the Kidney in a Mouse Model of Systemic LupusErythromatosus. *Hypertension*; 56:643-9.

Vinh A., Chen W., Blinder Y., et al. (2010). Inhibition and Genetic Ablation of the B7/CD28 T-cell Co-stimulation Axis Prevents Experimental Hypertension.*Circulation*; 122:2529-2537.

Wallukat G., Homuth V., Fischer T., et al. (1999). Patients with Pre-eclampsia Develop Agonistic Auto-antibodies against the Angiotensin AT$_{I}$ Receptor.*Journal of Clinical Investigation*; 103:945 –952.

Wenzel P., Knorr M., Kossmann S., Stratmann J.,Hausding M., Schuhmacher S., Karbach S.H., SchwenkM., Yogev N., Schulz E., et al. (2011). Lysozyme M-positive Monocytes Mediate Angiotensin II-induced Arterial Hypertension and Vascular Dysfunction.*Circulation*; 124:1370-1381.

Whitacre C.C (2001). Sex Differences in Autoimmune Diseases.*Nature Immunology*; 2:777-780.

Winer S., Paltser G., Chan Y., et al. (2009).Obesity Predisposes to Th^{17} Bias. *European Journal of Immunology*; 39:2629.

Wu C., Yosef N., Thalhamer T., Zhu C., Xiao S., Kishi Y., Regev A., Kuchroo V.K (2013). Induction of Pathogenic Th^{17} Cells by Inducible Salt-sensing Kinase SGK1.*Nature*; 496:513-517.

Xue B., Pamidimukkala J., Lubahn D.B., Hay M (2007). Estrogen Receptor-alpha Mediates Estrogen Protection from Angiotensin II-induced Hypertension in Conscious Female Mice. *American Journal of Physiologic Heart and Circulatory Physiology*; 292:H1770-1776.

Youn J.C., Yu H.T., Lim B.J., Koh M.J., Lee J., Chang D.Y., Choi Y.S., Lee S.H., Kang S.M., Jang Y., YooO.J., Shin E.C., Park S (2013). Immunosenescent $CD8^+$ T-cells and c-x-c Chemokine Receptor Type 3 Chemokinases Increased in Human Hypertension.*Hypertension*; 62:126-133.

Zhu J., Paul W.E (2008). CD4 T-cells: Fates, Functions and Faults. *Blood*; 12:1557-1569.

Zhuo C.C., Zhang Y., Irani R.A., et al (2008). Angiotensin Receptor Agonistic Auto-antibodies Induce Pre-eclampsia in Pregnant Mice. *Nature Medicine*.14:855 – 862.

Zimmerman M.A., Sullivan J.C. (2013). Hypertension: What's Sex got to do with it? *Physiology*; 28:234-244.