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REVIEW

Immune regulation of systemic hypertension, pulmonary arterial hypertension, and preeclampsia: shared disease mechanisms and translational opportunities

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Jafri S, Ormiston ML. Immune regulation of systemic hypertension, pulmonary arterial hypertension, and preeclampsia: shared disease mechanisms and translational opportunities. *Am J Physiol Regul Integr Comp Physiol* 313: R693–R705, 2017. First published October 4, 2017; doi:10.1152/ajpregu.00259.2017.— Systemic hypertension, preeclampsia, and pulmonary arterial hypertension (PAH) are diseases of high blood pressure in the systemic or pulmonary circulation. Beyond the well-defined contribution of more traditional pathophysiological mechanisms, such as changes in the renin–angiotensin–aldosterone system, to the development of these hypertensive disorders, there is substantial clinical evidence supporting an important role for inflammation and immunity in the pathogenesis of each of these three conditions. Over the last decade, work in small animal models, bearing targeted deficiencies in specific cytokines or immune cell subsets, has begun to clarify the immune-mediated mechanisms that drive changes in vascular structure and tone in hypertensive disease. By summarizing the clinical and experimental evidence supporting a contribution of the immune system to systemic hypertension, preeclampsia, and PAH, the current review highlights the cellular and molecular pathways that are common to all three hypertensive disorders. These mechanisms are centered on an imbalance in $CD4^+$ helper T cell populations, defined by excessive Th17 responses and impaired T_{reg} activity, as well as the excessive activation or impairment of additional immune cell types, including macrophages, dendritic cells, $CD8^+$ T cells, B cells, and natural killer cells. The identification of common immune mechanisms in systemic hypertension, preeclampsia, and PAH raises the possibility of new therapeutic strategies that target the immune component of hypertension across multiple disorders.

hypertension; immunity; inflammation; preeclampsia; pulmonary arterial hypertension

HYPERTENSION is broadly defined as an increase in blood pressure. Although most commonly considered in isolation in the context of essential systemic hypertension, hypertension can also present as a feature of multiple conditions, including during pregnancy as a component of preeclampsia (107) and in the pulmonary circulation in the form of pulmonary arterial hypertension (PAH) (138). These disparate hypertensive disorders are driven by a range of physiological changes, including increased arteriolar vascular tone and stiffness (79), as well as alterations in the balance between smooth muscle cell proliferation and apoptosis (45, 98), and can share common underlying molecular mechanisms, such as changes in the renin-angiotensin-aldosterone system (RAAS) (90, 125, 149) and elevations in other soluble vascular effectors like endothelin-1 (18, 43, 120, 127).

Beyond these well-defined, and thoroughly reviewed (90, 107, 117, 164) physiological changes that can drive the manifestation of hypertension, there is a wealth of research supporting an important role for immunity and inflammation in the pathogenesis of various forms of systemic hypertension, preeclampsia, and PAH. The current review will summarize the present understanding of the contribution of the immune system to each of these hypertensive disorders and highlight the common cellular and molecular pathways that are shared by these conditions. Clinical evidence supporting a role for altered immunity in each disorder will be presented, followed by a summary of the mechanistic studies, largely in animal models of disease, that have been used to identify the contribution of specific immune cell subsets to disease processes. Finally, we will examine how these recent advances are being translated into current and future therapies that target the immune component of hypertensive diseases.

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Clinical Evidence Supporting Immune Involvement in Hypertensive Disorders

Systemic hypertension. Systemic hypertension is defined clinically as a persistent raised blood pressure of 140/90 mmHg or greater in the systemic circulation (25). Essential hypertension, which presents in the absence of a known secondary cause, is a major risk factor for a variety of cardiovascular diseases, including myocardial infarction, stroke, congestive heart failure, and peripheral arterial disease (119). In addition to the well-defined link between established disease and RAAS signaling, salt-water balance, or activity of the sympathetic nervous system, various forms of systemic hypertension are also linked to persistent, low-level inflammation (141). This link is supported by multiple studies identifying increased inflammatory cytokines in the circulation of hypertensive individuals, including interleukin (IL)-6 (80, 182), tumor necrosis factor-α (TNF-α) (7, 100, 144), interferon (IFN)-γ (89), and IL-17a (87), as well as C-X-C chemokine receptor type 3 chemokines (57).

Similar studies have also identified links between essential hypertension and altered cellular immunity, including a rise in the proportion of immunosenescent $CD8^+$ effector T cells in the circulation (181) and the presence of immune cell infiltrates, consisting of macrophages and T cells, in the kidneys and vasculature of hypertensive patients (20, 128). Hypertension is also associated with increased serum immunoglobulins, with IgG levels positively correlating to blood pressure (37, 55, 71). These findings, coupled with the identification of autoantibodies, including antinuclear antibodies (72, 176), in the serum of hypertensive subjects and the increased prevalence of hypertension in patients with systemic lupus erythematosus (SLE) (14), implicate an important role for enhanced B cell activation in the pathogenesis of disease.

Preeclampsia. Preeclampsia is a disease of systemic hypertension that occurs in the maternal circulation selectively during pregnancy and is typically accompanied with proteinuria. Preeclampsia affects 3–5% of pregnancies and is a leading cause of premature birth and maternal mortality, particularly in developing countries (8). The precise mechanism leading to preeclampsia is not well understood nor is it universal. However, the syndrome is believed to occur following improper placental implantation and development. Although disease does not typically manifest until the second and third trimesters of pregnancy, the onset of preeclampsia has been linked to abnormal trophoblast invasion and an inadequate demuscularization of the spiral arteries of the uterus during the first trimester of development. This inadequate vascular remodelling causes diminished placental perfusion, leading to the excessive production of reactive oxygen species (ROS), increased oxidative stress, and the elevated production of factors that promote systemic hypertension, including antiangiogenic, soluble forms of Endoglin (sEng), and the vascular endothelial growth factor (VEGF) receptor fms-like tyrosine kinase-1 (sFlt-1) (115).

Relative to other hypertensive conditions, the relationship between preeclampsia and immunity is more implicit, as placental implantation by its very nature necessitates the development of maternal immune tolerance for alloantigens from the developing fetus. This tolerance is mediated by a variety of immune subsets within the pregnant uterus, including macrophages, dendritic cells (DCs), T cells, and a specialized subset of uterine natural killer (uNK) cells (174). Genetic studies examining the contribution of these uNKs to placental vascular remodelling have identified a link between polymorphisms in maternal NK receptors, known as killer immunoglobulin-like receptors (KIRs), the KIR ligand HLA-C on fetal trophoblast cells, and a mother's risk of developing preeclampsia (53, 54), providing some of the most compelling evidence to date of a role for the immune system in the development of disease.

Beyond these genetic studies, preeclamptic mothers have also been shown to exhibit increased levels of activated circulating $CD4^+$ and $CD8^+$ T cells (32), elevated inflammatory cytokines, including IL-6, IL-8, TNF-α, and IL-17 (73, 97, 156), reduced levels of anti-inflammatory cytokines, such as IL-10 (50), enhanced infiltration of $CD4^+$ T cells in the placenta (167), and an increased prevalence of inflammatory mononuclear cell lesions within the vascular walls of the decidua (126). The prevalence of a proinflammatory state in disease is further supported by studies examining the phenotype of macrophages within the uterus of healthy and preeclamptic mothers. Although recent studies have shown that activated macrophages can adopt a spectrum of unique phenotypes (180), these phenotypes are more classically categorized as M1 macrophages, which produce IL-12, IL-23, and TNF-α and skew T cells toward proinflammatory; Th1-type immune responses, or M2 macrophages, which produce TGFβ and IL-10 and promote Th2-type, antibody mediated and fibrotic immunity. Healthy pregnancy is associated with an influx of macrophages into the decidua, which transition from a predominantly M1 phenotype at the time of implantation to a dominance of M2 macrophages during fetal development (12, 28). This balance, which has been shown to contribute to early implantation, spiral artery remodelling, and fetal tolerance, shifts in preeclampsia toward an overrepresentation of M1 macrophages (94, 134), marking an alteration in the maternal inflammatory state that can persist in a mother for weeks or years postpartum of a preeclamptic pregnancy (74, 165).

As with essential hypertension, B cell activation is also implicated in disease pathogenesis. The prevalence of preeclampsia is increased to over 20% of pregnancies in women with SLE (108). Autoreactive antibodies directed toward the angiotensin receptor AT1 have also been identified at elevated levels in preeclamptic mothers (169).

Pulmonary arterial hypertension. Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) of $\geq$25 mmHg at rest. PH can manifest secondary to a broad range of diverse conditions that are divided into five groups based on the current World Health Organization classification of pulmonary hypertensive disorders (138). Group 1 PH, or pulmonary arterial hypertension (PAH), arises as a result of the excessive muscularization of the pulmonary arteries and the formation of occlusive cellular lesions at the level of the precapillary pulmonary arterioles, which occurs in the absence of other causes of PH, including left heart failure, interstitial lung disease, or chronic pulmonary thromboembolism. PAH is strongly associated with immune dysfunction, both in the setting of viral infection and autoimmune diseases, such as scleroderma (101) and SLE (116). In the case of HIV infection, the prevalence of PAH is over 300-fold higher in the HIV patient population (0.46%) than in the general population, where the estimated prevalence is roughly 15 patients per

million (60, 139). PAH patients with no associated immune conditions also exhibit signs of chronic inflammation, which is most clearly illustrated by increased circulating cytokines including interleukins −1β, −2, −4, −6, −8, −10, −12p70, −18, TNF-α, and the chemokines CCL2 (monocyte chemoattractant protein-1, MCP-1), CXC3L1 (fractalkine), and CCL5 (RANTES) (6, 58, 112, 129, 142). Of these factors, IL-6, −8, −10, and −12p70 have been found to predict the survival of PAH patients in a manner that is superior to traditional prognostic markers, including cardiopulmonary hemodynamics and 6-min walk distance (142).

As with other hypertensive disorders, the infiltration of a variety of immune cell subsets, including $CD4^+$ and $CD8^+$ T cells, B cells, monocytes, macrophages, mast cells, and DCs within the pulmonary vascular lesions of PAH patients is a major pathological feature of disease (131, 159). In addition to this localized vascular accumulation, T and B lymphocyte changes in PAH are evident through the ectopic formation of tertiary lymphoid structures in the lungs (111) and heightened autoantibody levels in PAH patient serum (62, 122, 150, 154). More recently, reductions in NK cell number and function, linked to the decreased expression of specific KIR receptors, have also been identified in PAH patients (105).

Contribution of Cellular Immunity to Hypertensive Disorders: Mechanistic Insights

Animal models of hypertensive disorders. Despite the extensive clinical evidence supporting a role for immunity in the pathogenesis of systemic hypertension, preeclampsia, and PAH, these patient studies are primarily correlative and do little to address whether immune processes actively contribute to disease progression or are simply a secondary effect of established disease. Instead, the majority of insights into the contribution of specific immune cell subsets to the structure and tone of the uterine, systemic, and pulmonary circulation have been drawn from mechanistic studies using rodent models of disease.

Historically, rats have been the primary choice for models of systemic hypertension, PAH, and preeclampsia. The most frequently used rat models of systemic hypertension include the angiotensin II infusion model, the DOCA-salt model, which involves the administration of deoxycorticosterone acetate (DOCA) and sodium chloride to uninephrectomised rats (136), or the use of spontaneously hypertensive rats (SHR) (103), which have been bred to develop hypertension from 5 wk of age. In preeclampsia, the partial ligation of both the abdominal aorta and the uterine arteries on *day 14* of gestation, known as the reduced uterine perfusion pressure (RUPP) model (2, 24), mimics the reduced uterine blood flow and increased oxidative stress that is observed in preeclamptic women (135). In PAH, disease in rats is initiated either through the delivery of monocrotaline, a plant alkaloid that causes selective and irreversible damage to the pulmonary vasculature (175), or through exposure to chronic hypoxia, with or without the induction of endothelial cell apoptosis through administration of the VEGF receptor blocker SU5416 (Sugen) (152). More recently, several groups have shifted toward mouse models of these hypertensive conditions to capitalize on the mechanistic insights to be gained from genetically modified mouse strains lacking specific cytokines, cytokine receptors, or immune cell subsets.

Despite the fact that mechanistic studies in systemic hypertension, preeclampsia, and PAH make use of unique animal models that develop disease in response to discrete initiating stimuli, these works have begun to converge on common immune mechanisms of disease that are shared across all three hypertensive conditions. These mechanisms, which involve a variety of immune cell subsets, including T, B, and NK lymphocytes, as well as monocytic cell types, such as macrophages and DCs, are detailed below and summarized by the schematic diagram in Fig. 1.

T cells. The importance of T cells to disease pathogenesis is most clearly demonstrated through the examination of disease severity in T cell-deficient rodents. In hypertension, several studies have pointed to a pathological role for T cells in disease progression. Athymic nude mice, which lack mature T cell populations, and severe combined immunodeficiency (SCID) mice, which are also largely deficient in lymphocyte populations, develop significantly milder hypertension than wild-type mice in response to the DOCA-salt and angiotensin II infusion models, respectively (27, 148). $RAG1^{-/-}$ mice, which lack both B cells and T cells, are similarly resistant to developing hypertension in response to both angiotensin II and the DOCA-salt models (44). This protection in $RAG1^{-/-}$ animals is reversed by the adoptive transfer of T cells but is unaffected by B cell transfer, further highlighting the essential role for T cells in disease development (44, 158). Transplant studies have demonstrated a similar role for T cells in disease pathology in the SHR, which exhibits a significant delay in disease onset following transplantation of thymus from younger rats (5). Moreover, the Dahl salt-sensitive rat model, which develops systemic hypertension in response to a high-salt diet, exhibits renal damage and fibrosis that is accompanied by the infiltration of a variety of immune cell types, including T cells, into the kidneys (124). This infiltration and the associated hypertension is blocked in salt-sensitive rats bearing targeted mutations in either RAG1 or the gene encoding the CD247 T cell receptor (93, 124).

As in models of systemic hypertension, athymic nude rats are protected from disease in the RUPP model of preeclampsia (102). Moreover, transfer of $CD4^+$ T cells from pregnant rats exposed to the RUPP model is sufficient to induce preeclampsia in normal pregnant rats through a mechanism that is dependent on endothelin-1 (167, 168). In contrast, the contribution of T cells to the pathogenesis of PAH is more uncertain. $RAG1^{-/-}$ mice have been shown to exhibit protection from monocrotaline-induced disease, which is lost upon the reconstitution of $CD4^+$ T cell populations by adoptive transfer (29). However, athymic rats develop exaggerated pulmonary hypertension in response to either monocrotaline (96) or Sugen (151, 153). This discrepancy between PAH models, as well as between PAH and other models of systemic hypertension and preeclampsia, can be explained by more detailed studies examining the contribution of specific $CD4^+$ helper T cell subsets to disease pathology.

$CD4^+$ T cell subsets. Helper T cells can be classified into Th1, Th2, Th17, or regulatory (T_{reg}) subsets based on the expression of specific transcription factors and the secretion of distinct cytokine profiles (Fig. 2). These cytokines direct immune responses through the selective activation of a variety of

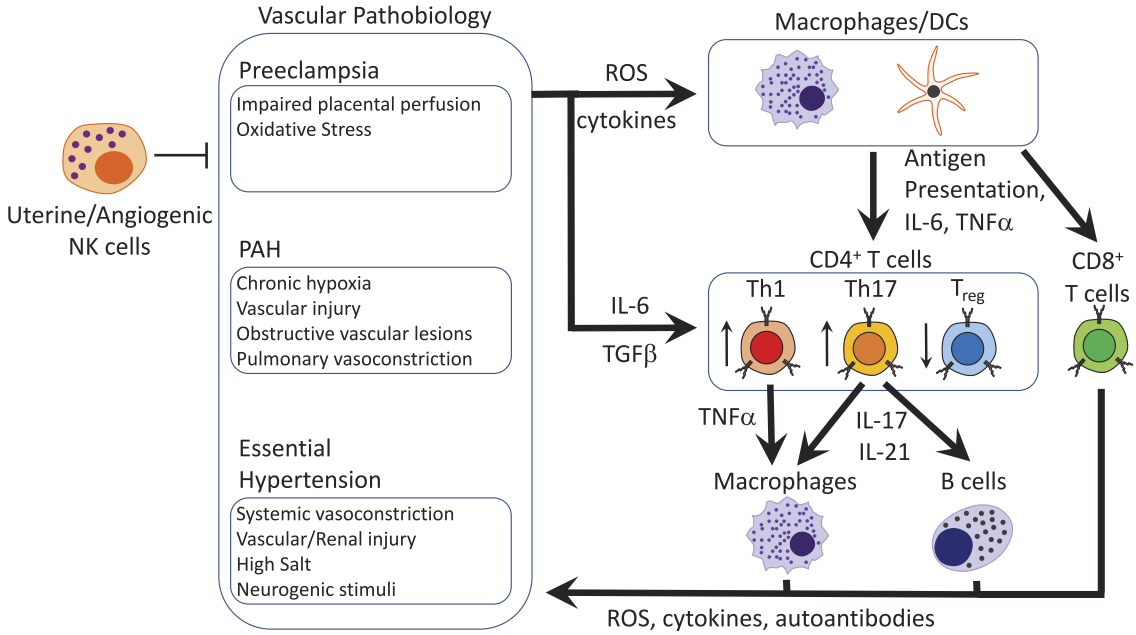

Fig. 1. Schematic diagram illustrating a proposed common immune-mediated mechanism in systemic hypertension, preeclampsia, and PAH by which the actions of specific immune cell subsets can perpetuate vascular pathology. Initial vascular triggers can drive macrophage-mediated inflammation and an imbalance in $CD4^+$ T cell responses, which subsequently perpetuate inflammatory and autoimmune responses by macrophages and B cells. PAH, pulmonary arterial hypertension; TNF-α, tumor necrosis factor-α; IL, interleukin; ROS, reactive oxygen species; NK, natural killer; DCs, dendritic cells; TGF-β, transforming growth factor-β.

cell types, including B cells, neutrophils, macrophages, and cytotoxic T cells. The prevalence of the classical Th1 cytokine TNF-α in clinical cases and animal models of essential hypertension, preeclampsia, and PAH suggests an important role for Th1 responses in these conditions. Infusion of TNF-α into pregnant rats is sufficient to induce hypertension (1). The blockade of TNF-α signaling using the TNF-α ligand trap Etanercept has also been shown to improve disease in animal models of PAH, preeclampsia, and systemic hypertension (44, 61, 77, 147). Studies examining pathological pulmonary vascular remodelling in response to repeated antigenic airway challenge (30) or infestation with the parasitic flatworm *Schistosoma hematobium* have also suggested a potential role for the Th2 cytokines IL-4 and IL-13 in certain forms of PAH (26). However, in the case of the airway antigen challenge model, it is important to note that the vascular remodelling observed was not accompanied by increased pulmonary arterial pressures (30).

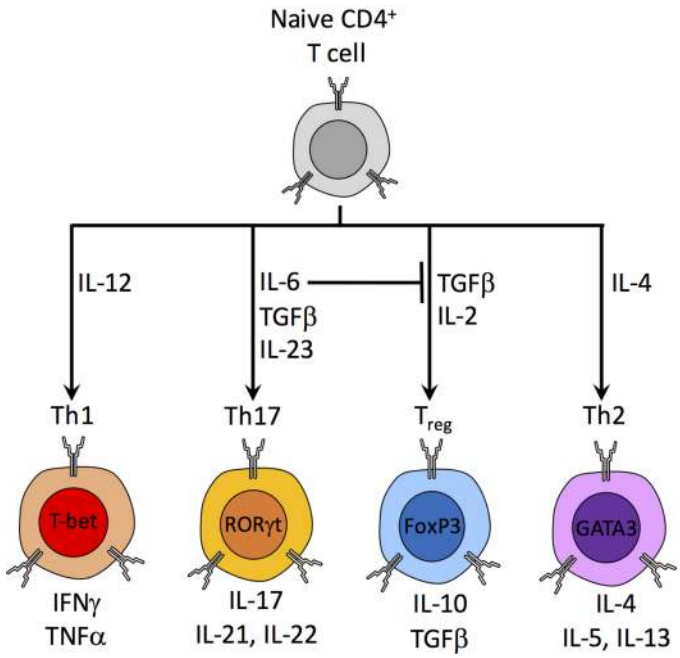

Fig. 2. $CD4^+$ helper T cell differentiation. Specific cytokines can drive the differentiation of naïve $CD4^+$ T cells toward a Th1, Th2, Th17, and T_{reg} fate defined by specific transcription factors and cytokine secretion profiles. In hypertensive disorders, it is proposed that IL-6 blocks the TGF-β-mediated generation of T_{regs} in favor of enhanced Th17 responses.

In addition to these intriguing findings, several recent studies point toward an imbalance of Th17 and T_{reg} responses as a major disease contributor that is common to all three hypertensive conditions. This imbalance is centered on the role of transforming growth factor-β (TGF-β) in driving the differentiation of both T_{regs} and Th17 cells from naïve $CD4^+$ T cells. In the presence of IL-6, the differentiation of immunosuppressive, IL-10 producing T_{regs} by TGF-β is blocked, in favor of Th17 cells, which perpetuate inflammatory responses through the production of IL-17, IL-21, and IL-22 (171) (Fig. 2). This imbalance contributes to the development of hypertension in the DOCA-salt rat model, which is marked by increased Th17 activation and a reduction in T_{regs}, positive for the transcription factor FoxP3 (3), as well as in the angiotensin II mouse model, which exhibits increased activation of Th17 cells and manifests with decreased severity in IL-$17^{-/-}$ mice (87). Importantly, exposure of naïve T cells to high salt concentrations alone is sufficient to polarize these cells toward a Th17 phenotype (68), highlighting a potential trigger of excessive inflammatory activation in disease.

In preeclampsia, IL-17 infusion or the adoptive transfer of Th17 cells from the RUPP model are both sufficient to induce hypertension in pregnant rats (23, 35). The contribution of Th17 responses, which are also elevated in patients (31), to the pathogenesis of preeclampsia appears to occur via AT1 receptor activation, as blocking AT1 receptors with losartan was found to inhibit IL-17-induced hypertension and diminish placental oxidative stress (35). PAH patients also exhibit increased IL-17 production by $CD4^+$ T cells in response to activating stimuli (49), accompanied by an overall reduction of T_{regs} in the hypertensive lung (160). Enhanced Th17 activity is also a prominent feature of the chronic hypoxia mouse model of PAH, which is marked by the pulmonary accumulation of Th17 cells and increased expression of the Th17 cytokines IL-17 and IL-21 (48). Interestingly, IL-$21^{-/-}$ mice are protected from pulmonary hypertension in this model, which is also blocked by the IL-6 receptor antibody MR16–1, highlighting the importance of the IL-6/Th17/IL-21 axis in disease.

IL-6 is produced by a variety of cell types, including macrophages, T cells, and vascular smooth muscle cells. Studies targeting IL-6 further support an important role for this cytokine as a driver of inflammatory disease mechanisms in animal models of hypertension, preeclampsia, and PAH. IL-$6^{-/-}$ mice are protected from both angiotensin II-induced hypertension (11) and hypoxia-induced pulmonary hypertension (132). Moreover, mice overexpressing IL-6 have been shown to spontaneously develop pulmonary hypertension and manifest more severe disease in response to chronic hypoxia (145). The infusion of recombinant IL-6 is also sufficient to induce hypertension in rat models of pregnancy (41). In addition to the impact of this cytokine on $CD4^+$ T cell differentiation, IL-6 can also drive hypertension through direct actions on vascular smooth muscle cells (86), as well as through the stimulation of antibody production from B cells (36, 69, 146).

In contrast to the proinflammatory contribution of IL-6 and Th17 responses to disease, several studies have demonstrated the capacity of T_{regs} and their primary cytokine product IL-10 to prevent hypertension in both the pulmonary and systemic circulation. The adoptive transfer of T_{regs} into pregnant rats reverses hypertension and placental oxidative stress in the RUPP model (22), indicating that impairment of these cells is an important contributor to the development of disease. Similar findings have been reported in rat models of PAH, where the adoptive transfer of $CD4^+CD25^+$ T_{regs} into athymic rats treated with Sugen reduces the severity of PAH to levels observed in immunocompetent rats (151). The role of T_{regs} in PAH and preeclampsia is further supported by studies examining the therapeutic delivery of exogenous IL-10 in animal models of both conditions. Administration of IL-10 prevents the development of pulmonary hypertension in IL-$10^{-/-}$ mice exposed to hypoxia (76) and has been shown to block the elevation of systemic blood pressure in the RUPP rat model of preeclampsia (47). Preadministration of an IL-10-expressing vector also prevents the elevation of pulmonary arterial pressure and pulmonary vascular remodelling in the monocrotaline rat model of PAH (64).

$CD8^+$ T cells. Beyond the actions of $CD4^+$ T cells, recent studies have also demonstrated an important role for $CD8^+$ T cells in disease, particularly in systemic hypertension. $CD8^{-/-}$, but not $CD4^{-/-}$ or MHC-$II^{-/-}$, mice are protected from hypertension, as well as sodium and water retention in response to angiotensin infusion, which is associated with the renal infiltration of oligoclonal $CD8^+$ T cells in immunocompetent mice (158). Moreover, the adoptive transfer of $CD8^+$ T cells, but not $CD4^+$ T cells, into $RAG1^{-/-}$ mice is sufficient to restore the hypertensive response to angiotensin II in these animals (158). More recently, $CD8^+$ T cells infiltrating the kidney were shown to increase sodium ion retention and drive salt-sensitive hypertension by upregulating the sodium-chloride transporter in distal convoluted tubules, providing greater insight on how these cells might contribute directly to disease progression (84). A similar role for $CD8^+$ T cells has yet to be identified in preeclampsia and PAH, which have been associated with decreased $CD8^+$ T cell levels in the placenta and the circulation, respectively (104, 160).

B cells. Increased autoantibodies have been reported in patients with essential hypertension, preeclampsia, and PAH (72, 122, 169). These findings have been expanded by work in animal models demonstrating a direct contribution of these autoantibodies, as well as overall B cell activation, to the pathogenesis of hypertensive diseases. The angiotensin II mouse model of hypertension is marked by an increase in activated splenic B cells, increased circulating IgG, and IgG accumulation in the aorta (17). These changes are not found in $BAFFR^{-/-}$ mice, which lack mature B cells and exhibit an attenuated hypertensive response to angiotensin II infusion. Angiotensin II-induced hypertension is also diminished by the depletion of B cells with an anti-CD20 antibody, further supporting a role for these cells in hypertension (17).

In PAH and preeclampsia, transfer of immunoglobulins alone is sufficient to induce disease (21, 183). Autoantibodies from rats with monocrotaline-induced pulmonary hypertension have been shown to cause vascular remodelling through the promotion of a proinflammatory phenotype in pulmonary adventitial fibroblasts and can induce PAH when administered to naïve rats (21). In a unique model of PAH, mice developed disease in response to the combined administration of ovalbumin and urban ambient particulate matter (110). Although knockout mice lacking B cells did not develop pulmonary hypertension in response to this challenge, disease was restored in these knockout animals following the injection of antigen-specific IgG.

IgG autoantibodies specific for the AT1 receptor are a key feature of preeclampsia. These autoantibodies are produced by $CD19^+CD5^+$ B cells, which are increased in preeclamptic mothers (65), and have been shown to activate the AT1 receptor in place of angiotensin II, causing excessive vasoconstriction and exacerbating ROS production (34, 172). Injection of patient-derived AT1 receptor-specific autoantibodies is sufficient to induce disease in pregnant rats (183). It is noteworthy that an increased prevalence of AT1 autoantibodies has also been reported in patients with essential hypertension (82), suggesting the possibility of a common disease mechanism with preeclampsia. While the importance of B cell activation to preeclampsia is further supported by work in the RUPP model demonstrating the attenuation of disease in response to B cell depletion with the anti-CD20 antibody rituximab (78), additional work in rodent models of preeclampsia and systemic hypertension place the contribution of B cells downstream of the T cell-mediated mechanisms detailed in the previous section. B cell reconstitution alone is insufficient to restore the hypertensive response in $RAG1^{-/-}$ mice infused with angio-

tensin II (44). Furthermore, elevated AT1 autoantibody production is observed in pregnant mice that develop hypertension in response to IL-17 infusion (35). These findings suggest that B cell activation in hypertensive diseases occurs downstream of Th17 responses, a model that is supported by the established role for IL-6 and IL-21 in promoting B cell activation and antibody production (36, 39, 69, 146).

Macrophages and dendritic cells. Macrophages and DCs sit at the vanguard of the immune response. Cytokines and chemokines produced by these cells in response to vascular injury, excessive vasoconstriction, or ROS production, shape the maturation and activation status of innate and adaptive lymphocytes, such as T, B, and natural killer (NK) cells. Macrophages and DCs can also influence T cell-mediated adaptive immune responses through their role as antigen presenting cells. In addition to driving lymphocyte-mediated immune responses, these cells can also respond to $CD4^+$ T cell-derived factors, such as TNF-α and IL-21, by producing inflammatory factors like IL-6 (145) and leukotriene B4 (155), which can directly promote endothelial injury and excessive vascular smooth muscle cell proliferation (155).

As detailed above, changes in the M1/M2 balance of macrophages in the decidua during pregnancy speak to the ability of these cells to govern the inflammatory or immunosuppressive responses that influence reproductive success (12). Dendritic cells derived from preeclampsia patients also exhibit changes that can promote inflammatory responses in disease, including a higher expression of costimulatory molecules for T cell activation, the increased production of inflammatory cytokines like IL-23, a higher expression of toll-like receptors, and a greater ability to differentiate T cells into the Th1 and Th17 subsets than cells from normal pregnant females (109, 170).

Macrophage infiltration into vascular walls in the lung and kidney is also major a feature of both animal models and clinical cases of essential hypertension and PAH, respectively (20, 128, 131). The importance of this infiltration to the pathogenesis of these two conditions is exemplified by the limitation of disease progression in rodent models lacking these populations. In both the angiotensin II and DOCA-salt mouse models, hypertension was prevented in mice lacking monocytes or macrophages (33, 173). Prevention of macrophage infiltration into the kidney through the inhibition of MCP-1 signaling also prevents systemic hypertension in the angiotensin II mouse model (63). Similar results have been observed in the chronic hypoxia model of PAH, in which monocyte depletion using clodronate liposomes was found to prevent disease onset (40).

Innate lymphocytes. In addition to adaptive lymphocytes, like T and B cells, innate lymphocyte populations, such as NK cells, have also been shown to influence the progression of hypertensive diseases. NK cells are traditionally viewed as the cytotoxic effector cells of innate immunity charged with the identification and lysis of stressed, cancerous or virally infected cells. In addition to this basic functionality, work examining the role of uNKs in pregnancy has highlighted a role for these cells in the regulation of uterine vascular remodelling (9, 46, 140, 162). This capacity is linked to the production of angiogenic and inflammatory cytokines, including VEGF, PlGF, IFNγ, and the angiopoietins (4, 46, 81) by uNKs, as well as matrix degrading enzymes, such as matrix metalloproteinase (MMP)-9 (99). Mice lacking NK cells or NK cell-derived IFNγ exhibit impaired uterine vascular remodeling, marked by the reduced diameter and persistent muscularization of the arteries in the decidua (4, 10). Although this impaired vascular remodeling is a critical first step in the development of hypertension in pregnant humans (Fig. 1), mice are particularly refractory to preeclampsia. Instead, diminished placental perfusion in NK-deficient models results in reduced pup weight (10).

While this angiogenic activity of NK cells was thought to be an exclusive feature of the specialized NK cells of the uterus, recent reports have suggested that uNKs are not a developmentally distinct NK cell subset, but may instead originate as peripheral NK cells that acquire a specialized phenotype in pregnancy through exposure to decidual factors (16, 67). This model is supported by recent studies demonstrating a vascular activity of NK cells outside the uterus as part of the angiogenic response to peripheral ischemia (162) and the vascularization of solid tumors (13). In PAH, NK cells from both patients and animal models of disease are reduced in number and exhibit signs of this angiogenic dysfunction, including impaired cytolytic activity, increased TGF-β signaling, and elevated production of MMP9 (105). Additional work has linked deficiencies in NK cells and $CD8^+$ killer T cells to an increased risk of death in the PAH patient population (38), further supporting a role for NK cell impairment in disease.

Despite these findings in pregnancy and PAH, work in the angiotensin II-infused mouse suggests that NK cells act to perpetuate hypertension in this model. Knockout mice lacking either IFNγ or T-box expressed in T cells (T-bet), a transcription factor that governs IFNγ production and NK cell maturation (157), exhibit protection from angiotensin II-induced hypertension (70). This protection has been linked to the recruitment of NK cells to the vascular wall and the localized production of IFNγ. Beyond innate lymphocytes like NK cells, a recent report has also implicated γδT cells, which sit on the boundary of innate and adaptive immunity, in the pathogenesis of angiotensin II-induced hypertension (15). The contribution of γδT cells to preeclampsia and PAH has yet to be addressed. However, IL-17 producing γδT cells have been reported at the maternal fetal interface in normal pregnancy (113).

Mediators of immune activation in hypertensive disease. While the studies detailed above provide extensive data to support a critical role for specific immune processes in perpetuating and amplifying hypertensive disease, these works do not address how early disease processes can initiate immune cell activation or why chronic inflammation fails to resolve in hypertension the way it does in cases acute injury or infection.

The process of immune activation has been examined most thoroughly in systemic hypertension, where several studies have identified activation of the sympathetic nervous system, and the resultant actions of norepinephrine, as potential initiators of inflammatory disease processes. Although norepinephrine has been shown to induce an immunosuppressive effect on T lymphocytes (95), it can also enhance inflammation through direct actions on DCs (177). In vivo, the localized blockade of sympathetic activation through renal denervation has been shown to prevent kidney inflammation and fibrosis in a manner that is independent of blood pressure (177). This effect is dependent on the activation of DCs by norepinephrine, as transfer of splenic DCs from angiotensin II-treated mice to naïve recipients was sufficient to prime T cell activation and

hypertension. These actions appear to be downstream of the central nervous system, as lesioning of the anteroventral third cerebral ventricle region of the brain eliminated T cell activation and hypertension in response to angiotensin II but not norepinephrine (92). Although the impact of the sympathetic nervous system on immune activation has not been studied as extensively in preeclampsia and PAH, sympathetic activation is a well defined feature of both conditions (133, 163), offering a potential common trigger for immune mechanisms in all three conditions.

Sex hormones have also been identified as potential mediators of immune activation in hypertensive disease. Essential hypertension occurs at earlier ages in men, who exhibit higher blood pressure than age-matched women before menopause (88). A similar sex bias is observed in rodents, where male rats develop higher blood pressure in the SHR model (121) and male mice exhibit more severe hypertension in response to angiotensin II infusion (179). Interestingly, this sex bias is lost in RAG1$^{-/-}$ mice infused with angiotensin II (66, 114). Reconstitution of male RAG1$^{-/-}$ mice with T cells from males, but not females, is sufficient to restore hypertensive disease in these animals (66). This sex bias also appears to be somewhat host specific, as male RAG1$^{-/-}$ mice, but not females, exhibit more severe angiotensin II-induced hypertension following adoptive transfer of T cells from male animals (114). While a similar comparison between male and female subjects is not possible in preeclampsia, studies into the impact of sex on disease progression in PAH highlight potential similarities with systemic hypertension. Although PAH is more common in women than in men (83), men with PAH develop more severe disease and exhibit higher mortality than female patients (59). This enhanced severity of PAH in males is recapitulated in the hypoxia and monocrotaline rat models of disease (118) and has been linked to the protective actions of estradiol (75, 161, 178). Despite these similarities, the contribution of T lymphocytes to this sex-specific bias in PAH has yet to be examined.

Conclusions: Immunomodulatory Therapies For Treatment of Hypertensive Diseases

The last decade has seen a remarkable expansion in our understanding of the contribution of inflammation and immunity to hypertensive diseases of the pulmonary and systemic circulation. Although this research has proceeded largely in isolation, with laboratories studying a particular condition using disease-specific animal models, the findings arising from these studies, when examined together, point toward common mechanisms by which cells of the innate and adaptive immune system contribute to systemic hypertension, preeclampsia and PAH. Moving forward, the recognition of these shared mechanisms raises the possibility of common treatment approaches that target the immune component of hypertension across multiple disorders.

It is noteworthy that a number of interventional approaches targeting immune-mediated contributions to systemic and pulmonary hypertensive disease have already been validated in preclinical studies using small animal models (Table 1), with some strategies also showing some degree of efficacy in clinical use. One of the earliest examples of an immune-targeted therapy for hypertension involves the use of the T and B cell-targeting immunosuppressant mycophenolate mofetil, which prevented salt-sensitive hypertension in angiotensin II-treated rats (123) and reduced blood pressure in hypertensive patients receiving this compound for the treatment of psoriasis or rheumatoid arthiritis (52). Despite this success, the abundance of safe and effective treatments for essential hypertension has largely precluded the development of immune-targeted therapies for this patient group. In contrast, the absence of effective therapies for PAH has resulted in a more aggressive investigation of immune-targeted therapies, both in animal models and early clinical trials. In addition to these strategies that directly target immune dysfunction, additional experimental treatments that have been investigated in PAH for their actions in vascular cells, including tacrolimus (143), rapamycin (56, 137), hydroxychloroquine (85), and imatinib mesylate (42,

Table 1. *Therapeutic strategies targeting immune dysfunction in systemic and pulmonary hypertension*

			Disease Model			
Cellular Target	Molecular Target	Therapeutic	Systemic Hypertension	Preeclampsia	PAH	References
T and B cells	Inosine monophosphate dehydrogenase	Mycophenolate mofetil	Angiotensin II rats, hypertensive patients with psoriasis, rheumatoid arthiritis			122, 52
Th1 responses	TNF-α	Etanercept (TNF-α ligand trap)	Angiotensin II mice	RUPP model	Monocrotaline rats, Sugen-hypoxia rats	44, 61, 76, 146
Th17 responses	IL-17	αIL-17 MAb	DOCA-salt rats		Ineffective in the chronic hypoxia mouse	3, 48
	IL-6	αIL-6R MAb			Chronic hypoxia mouse	48
		Tociluzumab (αIL-6Ra MAb)			TRANSFORM-UK clinical trial	
B cells	CD20	Rituximab (αCD20 MAb)		RUPP model	Clinical Case: PAH with SLE	77, 51
		aCD-20 MAb	Angiotensin II mice			17
Macrophages	Leukotriene B4	Bestatin			Sugen-treated athymic rats	154
		CP-105,696	SHR			90

PAH, pulmonary arterial hypertension; RUUP, reduced uterine perfusion pressure; TNF-α, tumor necrosis factor-α; IL, interleukin; DOCA, deoxycorticosterone acetate; MAb, monoclonal antibody; SLE, systemic lupus erythematosus; SHR, spontaneously hypertensive rats.

106), also possess immunomodulatory effects that could account for their activity in disease models.

Perspectives and Significance

When considering that a small but increasing number of individuals with systemic hypertension exhibit disease that is refractory to treatment with four or more antihypertensive drugs (19), a demonstration of efficacy for immune-targeted treatments in the PAH population could help to expedite the translation of these new immune-targeting therapies into hypertensive diseases of the systemic circulation. A similar logic applies to preeclampsia, where many treatments for systemic hypertension cannot be used safely in pregnancy. As immune-targeted approaches are translated from the laboratory to the clinic, an appreciation of the common mechanisms underlying these diseases can help to expedite the application of these new therapies across a range of conditions.

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AUTHOR CONTRIBUTIONS

S.J. and M.L.O. drafted manuscript; M.L.O. prepared figures; M.L.O. edited and revised manuscript; M.L.O. approved final version of manuscript.

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