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Novel Adaptive and Innate Immunity Targets in Hypertension

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Abstract

Hypertension is a worldwide epidemic and global health concern as it is a major risk factor for the development of cardiovascular diseases. A relationship between the immune system and its contributing role to the pathogenesis of hypertension has been long established, but substantial advancements within the last few years have dissected specific causal molecular mechanisms. This review will briefly examine these recent studies exploring the involvement of either innate or adaptive immunity pathways. Such pathways to be discussed include innate immunity factors such as antigen presenting cells and pattern recognition receptors, adaptive immune elements including T and B lymphocytes, and more specifically, the emerging role of T regulatory cells, as well as the potential of cytokines and chemokines to serve as signaling messengers connecting innate and adaptive immunity. Together, we summarize these studies to provide new perspective for what will hopefully lead to more targeted approaches to manipulate the immune system as hypertensive therapy.

Keywords

adaptive immunity; innate immunity; lymphocytes; antigen presenting cells; hypertension

Over 50 years of evidence has established a prominent role for adaptive and innate immune mechanisms in the development of hypertension (HTN), vascular disease and renal disease^{1–6}. Our lab's interest in immune mechanisms in HTN arose from studies in which we observed that inflammation amplifies salt-sensitive hypertension (SSHTN) and end-organ damage in Dahl SS rats⁴. In Dahl SS rats, as in the clinical condition, HTN is greatly accelerated by a high salt diet⁴. Moreover, inflammation is a common feature of experimental and clinical HTN, with lymphocytes and macrophages localizing to regions of injury^{4,7–9}. The amplifying effect of immune mechanisms on HTN are illustrated in Figure 1, in which we demonstrate the change in mean arterial blood pressure in Dahl SS rats and Dahl SS deficient in T and B lymphocytes (SS-Rag1^{−/−})¹⁰. The difference in the degree of salt-sensitive hypertension between the groups illustrates the role of immune mechanisms to amplify the HTN disease phenotype. As summarized below, a number of studies have

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illustrated the importance of adaptive and innate immune mechanisms in HTN; these mechanisms are the focus of this brief review.

Targets of Adaptive Immunity

T and B Lymphocytes

The hallmark cell types of the adaptive immune system are T and B lymphocytes. T cells are activated after interaction with an antigen presenting cell (APC), then proliferate and differentiate into one of three effector subtypes: cytotoxic, helper, or regulatory T cells. Recent work shows an evolving role of the T cell in the development of HTN and chronic kidney disease. Studies utilizing genetic knockout of the recombination activating gene 1 (RAG1) gene, which is essential for T and B cell maturation, in the mouse¹¹ and later the rat¹⁰ have shown a clear attenuation in the development of angiotensin II (AngII)-induced and SSHTN (Figure 1). Genetic knockout of the CD247 gene, essential in T cell survival and receptor function, led to a severe depletion of T cells but left B cells intact. Compared to wild type rats, Dahl SS with CD247 knockout demonstrated an attenuation of SSHTN and end-organ damage¹². Rodriguez-Iturbe et al also showed that systemic administration of the immunosuppressive agent mycophenolate mofetil led to a decrease in infiltrating immune cells in the kidney and a reduction in blood pressure in spontaneously hypertensive rats (SHRs)¹³. Clearly, affecting lymphocyte populations on a global scale has been shown to have dramatic effects in hypertensive animal models.

More recently, scientists have focused upon mechanisms of T cell survival and activation in HTN. One gene product required for T cell survival is the receptor tyrosine kinase TAM family member Axl. Korshunov et al first demonstrated attenuation of DOCA/salt-induced HTN in an Axl^{-/-} mouse strain and also observed improved endothelium-dependent vasorelaxation compared to Axl^{+/+}¹⁴. It was later discovered that Axl^{-/-} mice exhibited severe depletion of peripheral blood T and B lymphocytes¹⁵, and adoptive transfer of Axl^{-/-}Rag^{+/+} T cells into Axl^{+/+}Rag^{-/-} mice had significantly slower CD4⁺ repopulation than transfer of Axl^{+/+}Rag^{+/+} T cells, underscoring the importance of Axl in T cell expansion.

Though adaptive immunity is important in the development of hypertension, the mechanisms activating these immune mechanisms are largely unknown. Seminal work published by the Harrison group revealed that the activation of T cells in AngII-induced HTN was dependent upon the production of highly reactive isoketals by dendritic cells¹⁶; moreover, the administration of various isoketal scavenging agents demonstrated a blunted hypertensive response. In addition, the isoketal scavenger 2-HOBA reduced AngII-induced renal fibrosis, renal T cell infiltration, IL-6 and IL-1 β cytokine production, and T cell survival and proliferation. In an additional study, treatment with 2-HOBA or the antioxidant Tempol led to a decrease in production of IL-17A and IFN γ by T cells in tgsm/p22phox mice. Though it is well-established that reactive oxygen species (ROS) are linked to vascular damage in HTN¹⁷, these studies provide a link to adaptive immunity.

Similarly, work by Rodriguez-Iturbe and colleagues indicated that heat shock proteins (HSP), may also serve as an antigen triggering adaptive immunity in HTN^{18,19}. Their work

indicated that HSP70 could serve as an antigen mediating cellular immunity in experimental and human HTN. Studies by Macconi and colleagues demonstrated that proteolytic cleavage of albumin in proximal tubule cells could generate antigenic peptides²⁰. The isoketal protein adducts, heat shock proteins, albumin cleavage products, or other molecules may serve as antigens which trigger the adaptive immune responses which amplify HTN and end organ damage.

Though the complete depletion of the T cell population has generated many interesting insights, the role of specific T cell subtypes has not been as deeply interrogated. In a study investigating the role of AngII on human T cells in a humanized mouse model, AngII treatment was found to increase total CD3+ and CD4+ T helper cells as well as CD45RO+ T memory cells in the kidney, which was abolished by the prevention of HTN through coadministration of hydrochlorthiazide (HZT) and hydralazine²¹. By controlling blood pressure, these experiments demonstrated that AngII did not directly affect the activation state of T cells. Trott et al also investigated the role of specific T cell subtypes in AngII as well as DOCA/salt-induced HTN and observed a blunted response in CD8^{-/-} mice but not in MHCII^{-/-} or CD4^{-/-} mice²². In adoptive T cell transfer experiments into Rag1^{-/-} mice, transfer of CD8+ cytotoxic T cells significantly increased blood pressure, whereas transfer of CD4+/CD25- T cells did not. Although these results implicate a more direct effect of CD8+ cytotoxic T cells on the hypertensive phenotype, the role of CD4+ helper T cells needs to be explored more thoroughly.

Compared to T cells, the contribution of B cells to hypertensive pathology is being investigated at a much slower pace despite clear evidence that antibodies are elevated in patients with essential HTN²³. Chan et al explicitly investigated the role of B cells in AngII-induced HTN, and found AngII increased B cell activation, the number of plasmablasts and plasma cells, and serum IgG²⁴. B cell activating factor receptor deficient (BAFF-R^{-/-}) mice that lack B cells did not exhibit the same increase in blood pressure observed in WT mice in response to AngII, but importantly, adoptive transfer of B cells into BAFF-R^{-/-} mice restored AngII-induced HTN. In apparent contradiction to the study by Trott et al, who found an increase in CD4+ and CD8+ T cells in the kidney, analysis of T cell subsets revealed no change in CD8+ cells and an increase in CD4+ cells in the aorta upon AngII administration. The integral role of B cells in adaptive immunity as well as understanding its crosstalk with T cells will be important in the holistic investigation of HTN pathogenesis.

T regulatory cells

T regulatory cells (Tregs) are a specialized subset of T cells that are responsible for the maintenance of immune homeostasis and self-tolerance²⁵. In humans, Tregs comprise about 5–10% of peripheral CD4+ T cells, and they express CD4+, CD25+ and forkhead/winged helix transcription factor P3 (FoxP3)²⁶. FoxP3 is a major regulatory gene required for the development and regulatory function of Tregs²⁷. Tregs are reported to play a pivotal role of suppression of both the innate and the adaptive immune system. Through multiple mechanisms, Tregs turn off immune responses of T cells and dendritic cells by suppression of T cell proliferation and cytokine production as well as the release of immunosuppressive cytokines such as IL-10 and TGF- β ²⁸. While Tregs have been identified as protectors against

autoimmune and inflammatory diseases²⁹, the role of Tregs in the progression of cardiovascular diseases, including HTN, is not sufficiently understood.

Tregs have been reported to be protective against increases in blood pressure in various animal models of HTN, such as the Dahl SS rat. Using zinc-finger nuclease-mediated genetic mutation, a 6 base pair deletion in the highly conserved region of the SH2B3 gene resulted in an attenuation of HTN in response to the high salt diet relative to Dahl SS rats. Dahl SS rats with a mutation in the SH2B3 gene had an increased percentage of Tregs in both the spleen and circulation compared to Dahl SS rats³⁰. Additionally, Viel et al demonstrated that the presence of the Brown Norway rat chromosome 2 on the Dahl SS background in the consomic rat (SSBN2) resulted in an upregulation of Treg markers and activity as well as other anti-inflammatory markers, IL-10 and TGF- β ³¹. These results suggest that the increased number of Tregs provided protection from deleterious high salt-induced effects normally seen in Dahl SS rats.

Mian et al took a mechanistic approach to demonstrate the protective nature of Tregs and their interplay within the immune and cardiovascular systems during HTN. They examined the protective role of Tregs in an AngII-induced model of HTN. In Rag1^{-/-} mice infused with AngII and coinjected with Tregs, blood pressure was comparable to vehicle-treated controls. Furthermore, adoptive transfer of T cells from Scurfy mice, which are deficient in Tregs due to a missense mutation in the FoxP3 gene, into Rag1^{-/-} mice also resulted in the onset of AngII induced HTN³². Yet, coinjection of Tregs into these Rag1^{-/-} mice adoptively transferred with T cells from Scurfy mice only delayed the onset of AngII induced HTN, suggesting that Tregs alone might not be sufficient to prevent HTN in this model. When endothelial function was examined in secondary mesenteric vessels of these animals, the mice that received T cells from Scurfy mice exhibited AngII-induced endothelial dysfunction compared to WT mice. Furthermore, when animals were coinjected with Tregs, endothelial dysfunction was reduced but not normalized to control mice³². The cotransfer of Tregs blunted the levels of proinflammatory cytokines and infiltration of immune cells within the mesenteric vessels and the cortical regions of the kidney; however, it did not prohibit the development of HTN and endothelial dysfunction.

A therapeutic role for Tregs has also been demonstrated in the treatment of preeclampsia, a pregnancy specific form of HTN. The immune system is implicated in the pathology of preeclampsia with an imbalance of Tregs in favor of proinflammatory CD4⁺ T cells, leading to proinflammatory cytokine production and chronic inflammation³³. In the reduced uterine perfusion pressure (RUPP) rat model of preeclampsia, circulating CD4⁺ T cells are elevated in rats at day 19 of gestation compared to normal pregnant animals while there was a significant decrease in circulating Tregs in the RUPP rats³⁴. Further studies demonstrated that supplementation of Tregs from normal pregnant rats into RUPP rats normalized levels of circulating Tregs and attenuated HTN³⁵. While Treg supplementation did not affect IL-10 levels, TGF β levels were increased in RUPP supplemented rats to levels comparable with normal pregnant rats. Adoptive transfer of normal pregnant Tregs also blunted the inflammatory response by decreasing circulating levels of IL-17 and TNF α in RUPP rats³⁵. These studies together establish that Tregs offer varying degrees of protection against the

development of HTN in a number of animal models, and further experiments are required to determine the mechanism by which Tregs are a promising therapeutic target for HTN.

Cytokines and chemokines

In order for the adaptive immune system to be effective, signals are conveyed through cytokines and chemokines; this section will discuss some of the major players being investigated. T-bet^{-/-} mice, characterized by impaired production of TNF α and IFN γ and the inability to elicit a Th1 response, retained the same hypertensive response to AngII as WT mice but lacked the associated renal damage assessed by nephrin excretion³⁶. Delineating the effects of these two cytokines, TNF α ^{-/-} mice displayed attenuated AngII-induced increases in blood pressure, albuminuria, nephrinuria, and renal histological damage while IFN γ ^{-/-} mice were phenotypically similar to WT mice³⁶, designating TNF α as a major cytokine contributing to AngII-induced HTN and renal end-organ damage. Renal transplantation experiments attributed these protective effects in TNF α ^{-/-} mice to increased renal eNOS expression and NO bioavailability.

Interleukins also play a major role in cytokine signaling and their expression varies by cell type. Chatterjee et al investigated whether treatment with anti-inflammatory cytokines IL-4 and IL-10, both secreted by Th2 cells, could prevent HTN in pregnant mice³⁷. Treatment with IL-4, IL-10, or IL-4/IL-10 in combination reduced Poly I:C-induced preeclampsia, restored aortic acetylcholine-mediated relaxation, and returned expression of pro-inflammatory cytokines IL-6, IFN γ , TNF α , and TGF β back to control levels. However, only the combination treatment of IL-4/IL-10 prevented proteinuria, the increased incidence of fetal demise, and the increase in T cells and dendritic cells observed during preeclampsia. This evidence shows the anti-inflammatory effects of IL-4 and combination IL-4/IL-10 treatment in a model of preeclampsia. Other interleukins known to be secreted by both adaptive and innate immune cells, like IL-6 and IL-1 β , will be discussed in more detail in the following section.

As discussed, Tregs contribute to immune response modulation by suppression of proliferation and signaling; however, T-helper 17 (Th17) cells act in opposition, upregulating pro-inflammatory mechanisms. Upon stimulation, primarily through IL-23R and IL-1R, Th17 cells are activated to produce IL-17 along with IL-21 and IL-22. Studies by Wu et al³⁸ have demonstrated that in IL-23R^{-/-} cells, downstream serum glucocorticoid kinase-1 (SGK1) is critical for Th17 function. IL-23R signaling through SGK1 also appears to contribute to the increase of Th17 cells in response to a high salt diet, which is consistent with SGK1 being involved in NaCl transport³⁹. Kleinewietfeld et al have similarly shown that stimulated Th17 cells demonstrate increased IL-17 production and *in vitro* pathogenicity in response to increased salt concentration. *In vivo*, high salt diet also increased IL-17a production and the clinical score of experimental autoimmune encephalomyelitis⁴⁰. Madhur et al worked to translate the role of IL-17 in an AngII-induced model of HTN⁴¹. AngII treatment increased T cell production of IL-17 and the percentage of circulating IL-17-producing CD4⁺ cells. IL-17^{-/-} mice had an attenuation in AngII-induced HTN and superoxide production. In addition, IL-17^{-/-} mice had phenylephrine-induced vascular contraction comparable to untreated mice and preserved endothelium-dependent

vasodilation. These KO mice also had a complete attenuation of aortic infiltration of CD45+ and CD3+ T cells. In addition, their group found dramatic increases in serum IL-17 in human hypertensives compared to normotensives, validating this paradigm in human HTN.

In SHRs, AngII treatment of vascular smooth muscle cells suppressed expression of the anti-inflammatory cytokine IL-10. Administration of the chemokine CCL5, or RANTES, resulted in upregulation of IL-10, and attenuation of AngII-induced vascular dysfunction and systolic blood pressure, suggesting a protective, antihypertensive role for CCL5⁴². However, a more recent contradicting study demonstrated protection from AngII-induced endothelial dysfunction and reduced vascular and perivascular adipose tissue T cell infiltration in RANTES^{-/-} mice⁴³. AngII-infused RANTES^{-/-} mice have decreased infiltrating IFN γ -producing CD8+ T cells as well as CD3+CD4-CD8- T cells that have an impaired ability to produce IFN γ compared to WT mice. Although the specific role of such signaling messengers remains to be clearly identified, cytokines and chemokines provide more finely tuned immune-based therapeutic targets than systemic downregulation, mitigating some, but not all, of the risks associated with immunosuppressive treatments.

Targets of Innate Immunity

Antigen Presenting Cells

While many studies have documented the contribution of the adaptive immune response in HTN, it is classically understood that activation of innate immunity through APCs is a required and initiating step. This was substantiated by experiments performed by Vinh et al, which demonstrated that T cell activation and the development of DOCA/salt HTN was dependent upon T cell coreceptor CD28 costimulation by APC B7 ligands⁴⁴. Furthermore, depletion of APCs such as macrophages and neutrophils, or inhibition of their accumulation has been shown to impair disease progression in multiple models of experimental HTN, including the RUPP, DOCA/salt, and AngII-induced models of HTN⁴⁵⁻⁴⁷. As previously mentioned, work by Harrison's group suggests the production of highly reactive isoketals by dendritic cells during HTN are the mechanistic link to T cell stimulation¹⁶. High salt has been shown to directly activate macrophages, which may be helpful for antimicrobial functions during infection⁴⁸, but pathogenic salt stimulation may cause an overall imbalance in immune homeostasis by detrimentally promoting T cell activation characteristically observed during salt-sensitive HTN^{49,50}. Additionally, salt has recently been demonstrated to promote proinflammatory Th17 cells and suppress anti-inflammatory Tregs⁵¹. The established regulation of T cell activation by these various APCs makes these early innate immunity components attractive targets for hypertensive therapeutic interventions.

Pattern Recognition Receptors: TLRs

Innate immune cells utilize pattern recognition receptors (PRRs) to recognize pathogens and threats to the host, and thus activation of PRRs is an early occurring step. Toll-like receptors (TLRs) are a well-characterized family of membrane-bound PRRs found either on the surface or in the lumen of intracellular vesicles of macrophages, dendritic cells, and mast cells⁵². Recent studies have focused on specific members of the TLR family, including TLR4, TLR9, and TLR2. TLR4 expression is upregulated in experimental models of AngII

and L-NAME-induced HTN^{53–54}; importantly, TLR4 mRNA upregulation also occurs in peripheral monocytes of human hypertensive patients compared to normotensives⁵⁵. This upregulation is functionally important, since TLR4 inhibition by anti-TLR4 antibody has been shown by multiple laboratories to augment vascular contractility, vascular inflammation, and oxidative stress in SHR, ultimately preventing experimental HTN^{53,56,57}. TLR9, which recognizes mitochondrial DNA, a product of tissue damage, is also upregulated in the circulation of SHR, and treatment with TLR9 inhibitory oligodinucleotide ODN2088 resulted in a reduction in systolic blood pressure⁵⁸. This follows with the studies performed by Rodrigues et al in TLR9^{–/–} mice, implicating TLR9 in the cardiac autonomic and baroreflex control of arterial blood pressure⁵⁹. A previously undiscovered link between TLR2 and NLRP3 in renal tubular epithelial cells was recently revealed, where TLR2 ligands induced NLRP3 inflammasome-dependent necrosis, demonstrating the crosstalk between TLRs and other PRRs in the kidney⁶⁰. Interestingly, the same aforementioned hypertensive patients with higher levels of TLR4 mRNA in peripheral monocytes experienced a significantly downregulation of both TLR2 and TLR4 mRNA in response to intensive SBP-lowering treatments, perhaps suggesting a forward feeding mechanism between increased pressure and immune system activation⁵⁵. These recent reports clearly demonstrate an integral role for TLRs in controlling the severity of the pathogenic response to hypertensive stimuli and provide a strong rationale for the potential benefit of clinical TLR pharmacologic inhibition.

Pattern Recognition Receptors: NLRs

Intracellular NOD-like receptors (NLRs) are another family of PRRs, with the most characterized NLR being the NLRP3 inflammasome. It has recently gained notoriety for its diverse recognition of exogenous pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs) derived from disease, and consists of the NLRP3 sensory component, the adaptor protein ASC, and the effector protein caspase-1. When stimulated, these intracellular components oligomerize into large complexes and initiate the cascade leading to IL-1 β maturation and eventual activation of adaptive immunity. The presence of a human NLRP3 gene polymorphism that is associated with increased blood pressure suggests the clinical relevance of further exploring the role of this particular PRR in HTN⁶¹. Preclinical studies in preeclampsia demonstrated protection from AngII-induced HTN in NLRP3^{–/–} but not ASC^{–/–} pregnant mice⁶². This follows with clinical data in isolated monocytes from human preeclamptic pregnant women that were stimulated with uric acid which revealed significantly higher gene expression of the NLRP3 inflammasome components when compared to those isolated from normotensive controls⁶³.

A role of the NLRP3 inflammasome has also been shown in aldosterone-induced renal fibrosis and HTN, where *in vivo* aldosterone administration promoted renal fibrosis via inflammasome activation, but bone marrow transplantation of ASC-deficient mice highlighted the contribution of macrophage-derived inflammasomes in mediating this pathology⁶⁴. Furthermore, ASC^{–/–} mice or mice treated with NLRP3 inhibitor MCC950 were protected from 1K/DOCA/salt-induced HTN, inflammation, and fibrosis⁶⁵. NLRP3 inflammasome involvement has also been established in animal models of SSHTN and was first shown by Qi et al where Dahl SS rats fed a high salt diet resulted in elevated NLRP3

and IL-1 β in the hypothalamic paraventricular nucleus (PVN), which was inhibited by NF κ B blockade, indicating the importance of localized PVN NF κ B activation in the sympathoexcitation that leads to HTN in response to high salt⁶⁶. More recently NLRP3 inflammasome upregulation has also been demonstrated in the renal medulla of Dahl SS rats fed high salt and administration of caspase-1 inhibitor Ac-YVAD-cmk prevented SSHTN⁶⁷.

Cytokines IL-1 β and IL-6

IL-1 β , a product of NLRP3 inflammasome activation, is a potent proinflammatory cytokine linked to a wide number of immunological pathologies and its release is typically associated with cells of the innate immune system. However, it is unclear whether this cytokine is involved in potentiating HTN specifically or is perhaps simply a biomarker of disease progression⁶⁸. Interestingly, multiple groups have demonstrated IL-1 β inhibition or IL-1 receptor blockade to have protective, antihypertensive effects^{69–71}. This is an incredibly exciting avenue of study since there exist IL-1 blockers and receptor antagonists clinically approved for the treatment of rheumatoid arthritis. Another cytokine secreted by cells of both adaptive and innate immunity origin is IL-6. Increased IL-6 has been observed in cardiac tissue of SHR⁵⁴, and AngII has been shown to stimulate macrophage-derived IL-6 which drives intrarenal RAS activity in proximal tubular cells and the eventual progression of HTN and renal injury⁷². Recent studies in our laboratory have focused on the role of the proinflammatory cytokine IL-6 in the development of SSHTN⁷³. Dahl SS rats on a high salt diet and treated with an anti-IL-6 antibody had lower mean arterial pressure, a later onset of HTN, lower albumin excretion rate, less glomerular sclerosis and protein casts, and a decrease in infiltrating leukocytes. These protective effects of IL-6 blockade were coupled with reductions in monocyte/macrophage infiltration but not lymphocyte infiltration, perhaps implicating a targeted effect of IL-6 on these innate immune cells and in the progression of SSHTN and kidney damage.

Implications

Recent reports indicate that only 54% of hypertensive patients in 2009–2012 had their hypertension under control⁷⁴. Outside of dietary and lifestyle changes, pharmacological agents, which primarily treat the symptoms rather than the cause of HTN, have been the first line of therapy, but these approaches are not fully effective⁷⁴. This indicates a clear need to identify new and improved treatment strategies; this review, among others, summarizes the role of the immune system and inflammation in the progression of HTN and end-organ disease. As others have discussed⁷⁵, translating this work to clinical investigation and treatment is difficult, as immunosuppressant agents and cytokine inhibitors that may be used to treat HTN will likely have the same unwanted side-effects that immunosuppressive treatments have in other diseases. It is the goal of this research to identify molecular mechanisms unique to HTN that can be used as targeted therapies.

In brief, the field of immunity in HTN is rapidly progressing and evolving. A summary of this brief review is provided in a graphical abstract (Figure 2) which represents the interplay between immune mechanisms and disease progression in animal models of HTN. The studies summarized in this review demonstrate the continuing pursuit for more specific

molecular targets that can be manipulated to yield the best clinical outcomes. This success will likely be determined by the growing understanding of the mediators, mechanisms, and interactions of both the adaptive and innate arms of the immune system in HTN.

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Figure 1.

Development of salt-sensitive hypertension in Dahl SS rats (SS) and SS rats deficient in T- and B-lymphocytes due to the genetic deletion mutation in *Rag1* (SS-Rag1^{-/-}). * P<0.05 vs final day of low salt in the same group; † P<0.05 vs SS on the same day; n=4-5/group.

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Figure 2.

Innate and adaptive immunity targets discussed in this review.

Abbreviations: *AngII*: Angiotensin II, *CCL5/RANTES*: C-C chemokine ligand 5/Regulated upon Activation, Normal T-cell Expressed, and Secreted, *Dahl SS*: Dahl Salt-Sensitive Rat, *DOCA/salt*: deoxycorticosterone acetate/salt, *IFNγ*: interferon γ , *IL-1β*: interleukin-1 β , *IL-6*: interleukin-6, *NLRs*: NOD-like receptors, *NLRP3*: nucleotide-binding oligomerization domain (Nod)-like receptor containing pyrin domain 3, *PRRs*: pattern recognition receptors, *RUPP*: reduced uterine perfusion pressure, *Th17*: IL-17-producing T cells, *TLRs*: Toll-like receptors, *TNFα*: tumor necrosis factor α , *Tregs*: T regulatory cells