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Contribution of Th17 cells to tissue injury in hypertension

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Abstract

Purpose of the review: Hypertension has been demonstrated to be a chief contributor to morbidity and mortality throughout the world. Though the etiology of hypertension is multifactorial, emerging evidence, obtained in experimental studies, as well as observational studies in humans, points to the role of inflammation and immunity. Many aspects of immune function have now been implicated in hypertension and end-organ injury; this review will focus upon the recently-described role of Th17 cells in this pathophysiological response.

Recent findings: Studies in animal models and human genetic studies point to a role in the adaptive immune system as playing a contributory role in hypertension and renal tissue damage. Th17 cells, which produce the cytokine IL17, are strongly pro-inflammatory cells which may contribute to tissue damage if expressed in chronic disease conditions. The activity of these cells may be enhanced by physiological factors associated with hypertension such as dietary salt or Ang II. This activity may culminate in the increased sodium retaining activity and exacerbation of inflammation and renal fibrosis via multiple cellular mechanisms.

Summary: Th17 cells are a distinct component of the adaptive immune system that may strongly enhance pathways leading to increased sodium reabsorption, elevated vascular tone and end-organ damage. Moreover, this pathway may lend itself toward specific targeting for treatment of kidney disease and hypertension.

Keywords

Angiotensin II; dietary salt; lymphocytes; fibrosis

Introduction

Many different lines of evidence point to a role of inflammation and immunity in human hypertension and renal end-organ damage. Lymphocytes (1), other mononuclear cells (2), and the deposition of immunoglobulins and complement proteins (3) have been demonstrated in the renal interstitium adjacent to damaged renal tubules and glomeruli in

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hypertensive humans. More recently it was shown that hypertensive individuals exhibit glomerulosclerosis and renal fibrosis which accompanies infiltration of macrophages and T-lymphocytes in the renal interstitium (4). These correlative observations are supported by functional evidence demonstrating that immunotherapeutic modulation alters blood pressure in patients with HIV (5), psoriasis (6) or rheumatoid arthritis (6). In addition, genetic markers in the regions of several genes important in immune signalling have been linked with hypertension or kidney disease in GWAS and other genetic association studies (7, 8, 9, 10, 11). These observations demonstrate the impact of inflammation and immunity in human hypertension. Mechanistically-based experimental studies, largely performed in rodents (12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24), have illustrated the importance of immune mechanisms in hypertension and renal disease (14, 20, 25, 26, 27, 28*).

T Cells in Hypertension and End-Organ Damage

Though multiple immune mechanisms have been elucidated in experimental models of hypertension (12, 13, 14, 15, 26, 27, 28*, 29*, 30, 31), several studies point specifically to the importance of adaptive immune mechanisms in the development of experimental hypertension in mice (20, 21, 22, 23, 24). Of particular note were landmark studies performed by Harrison's group in which they observed that the degree of hypertension developed during chronic infusion of Angiotensin II was blunted in mice lacking both T- and B-lymphocytes (Rag $1^{-/-}$) (22). Following the adoptive transfer of T cells, but not B cells, hypertension caused by angiotensin II was restored in the Rag $1^{-/-}$ mice (22). These studies were recently confirmed in the Dahl salt-sensitive rat, an experimental model of salt-sensitive hypertension and renal end-organ damage. Dahl SS rats deficient in T cells ($SS^{CD247-/-}$) were shown to have no difference in arterial pressure or renal damage when fed low salt, but the high salt-induced hypertension and renal damage was attenuated in the $SS^{CD247-/-}$ which lack T cells following high-salt feeding (32). The subsequent replacement of T cells (via splenocyte transfer) in the $SS^{CD247-/-}$ rats lacking endogenous T cells led to a restoration of the salt-sensitive disease phenotype as both hypertension and renal damage returned to levels observed in the wild type Dahl SS rats (33**).

Though these and other studies illustrate the important role of T lymphocytes in the development of hypertension and end-organ damage (12, 13, 14, 15, 26, 27, 28*, 29*, 30, 31), there is not complete agreement in regard to these observations. Recent studies have been unable to demonstrate an attenuation of angiotension II-induced hypertension in mice lacking T and B cells (34**), while other studies point to an important role for B-cells, since activation of B cells and increased IgG production accompany an increased in angiotension II, and B cell deficiency blunted the hypertensive response to angiotension II in mice (35). In addition, multiple other immune cell types have been demonstrated to influence hypertensive disease phenotypes (12, 13, 14, 15, 26, 27, 28*, 29*, 30, 31).

Despite these observations, the preponderance of evidence points to an important role for T cells as a causative factor in hypertension and subsequent renal damage (12, 13, 14, 15, 26, 27, 28*, 29*, 30, 31). The activation of the T-cell response is initiated by engagement of antigen presenting cells with the T-cell receptor (TCR) and involvement of co-stimulatory factors such as CD80/86 or B7-CD28. Underlying injury in the kidney may serve as an

initial trigger for the expression of neo-antigens and the activation of T cells in the setting of renal injury or hypertension. This point was recently illustrated in a study that aimed to distinguish effects of perfusion pressure from other circulating factors on renal inflammation in the setting of Ang II induced hypertension. In response to Ang II infusion, the resulting elevation in renal perfusion pressure was associated with peritubular capillary damage and an increase leukocyte infiltration, including T- and B-lymphocytes. Interestingly, the application of a servo-control system to maintain renal perfusion pressure to the contralateral kidney at control (pre-infusion) levels substantially reduced infiltration of lymphocytes vs the kidney exposed to elevated pressure (36**). Similar observations were previously made in the Dahl SS rat (37). These observations are consistent with the hypothesis that pressure-induced damage may initiate renal lymphocyte activation in the kidney in the setting of hypertension. However, there remains debate about the identity of specific antigens which contribute to activation of adaptive immune responses. For example, HSP70 has been identified as a common antigen in salt-sensitive hypertension, however, other potential neo-antigens (e.g, ketal adducts) have been described in models of Ang II or DOCA-salt induced hypertension (29*, 38, 39, 40)(41**) Once activated, T-cells can produce cytokines, free radicals, and other factors capable of influencing the development of hypertension and related end-organ damage (12, 13, 14, 15, 26, 27, 28*, 29*, 30, 31). Among the factors produced by different T cell subtypes are IL-17 and related cytokines which are produced by Th17 cells.

T-helper 17 cells (Th17 cells)

Overview of differentiation and function.

An important component of the adaptive immune system is the differentiation of naïve T cells into various effector T-helper cells (reviewed in (42*)). The original paradigm outlined the differentiation of naïve CD4+ T-cell cells (i.e., Th0 cells) into either T-helper 1 (Th1) or T-helper 2 (Th2) cells, classified based on the profile of cytokines each type secreted to help fulfill their function in immunity (43). Th1 cells differentiate under the control of STAT1 and T-bet. These cells secrete IFNγ, IL2, IL12 and TNFα and function primarily to promote macrophage responses in fighting intracellular pathogens such as virus or bacteria (44*). Th2 cells differentiate under the control of STAT6 and GATA3 and secrete IL4, IL10, IL13 as well as other cytokines. Th2 cells role function classically to promote host-defense against invading parasites (44*, 45).

Th17 cells are characterized by the signature cytokine IL17A, as well as IL17F, IL22, IL23 and TNFα (46, 47, 48). Similar to Th1 or Th2 cells, Th17 cell cells are thought to derive from a naïve Th0 phenotype. The factors that lead to Th17 activation have been extensively reviewed (49, 50) . Importantly, RORγt (RAR related orphan receptor gamma T) is considered the key lineage specific transcription factor regulating Th17 cell differentiation and the expression of Th17 specific cytokines such as IL17A. The process is dependent on the activity of the pro-inflammatory cytokine IL-6 and the activation of STAT3 (46, 47, 48).

Th17 cells are strongly pro-inflammatory and prominently induce the infiltration of neutrophils for defense against pathogens such as extracellular bacteria, which are not typically targeted by Th1 or Th2 cells (44*, 48*). Mouse models of IL17 deficiency show

increased susceptibility to infections from a large range of different bacterial and fungal pathogens, including in the setting of urinary tract infection (51, 52). In humans, impaired Th17 differentiation has been identified in patients with primary immunodeficiencies (PID) due to mutations of IL17A or IL17F (53).

Despite the important role of Th17 cells in mediating adaptive immune responses, dysregulated activation of Th17 cells can promote tissue damage in auto-immune disorders due to their strong pro-inflammatory activity. Hyperactivation of Th17 cells may mediate inflammation in conditions such as psoriasis, inflammatory bowel disease, rheumatoid arthritis and autoimmune encephalitis (54). Th17 cells have been described as a potential contributor to inflammatory kidney diseases such as glomerular nephritis (reviewed in (55)). Systemic lupus erythematosus (SLE), is an autoimmune disorder based on the production of auto-antibodies which can deposit in the kidney and can lead to hypertension and kidney damage (56). SLE patients are reported to manifest an increase in circulating conventional Th17 cells (CD4+/IL17+) (57) and studies from animal models of SLE such as the MRL/lpr mouse, the Roquinsan/san model or pristine administration suggest that inhibition of IL17 or mutation of the *IL17* gene attenuates the severity of inflammation and injury (58, 59**, 60**).

Modulation of Th17 activity

As described above, Th17 differentiation is driven primarily by the RORγT transcription factor under influence of TGFβ and IL6 and the activation of STAT3. The differentiation pathway may be dependent on the activity of the store operated calcium channel, Orai1, which was previously shown to promote nuclear accumulation of NFAT-5 and RORγT (61). Recent studies from our lab demonstrated that Orai-1 is essential for expression of IL17A in CD4+ cells, since IL17A was detected only in CD4+ cells which expressed the channel and inhibition of this channel attenuated induction of Th17 cells following renal ischemia/reperfusion injury (62**).

Th17 activity appears to be strongly modulated by dietary sodium. Following kidney ischemia reperfusion injury, subsequent exposure of rats to elevated dietary sodium (from 0.4% to 4%) results in hypertension, progression of chronic kidney disease and is associated with a dramatic expansion of Th17 cells. However, the effect of dietary salt on Th17 activity is not limited to models of kidney injury, but rather has been observed in other models of inflammation including psoriasis or autoimmune encephalomyelitis (63, 64, 65, 66). Elegant studies by Klitterfeld et al., demonstrated that elevation of extracellular sodium (to 170 mM) hastened the differentiation of Th0 to Th17 cells in vitro (67) and this response appears to be dependent on signaling through SGK1 (67, 68**). Elevated extracellular sodium, in combination with Ang II, increased IL17 production of lymphocytes isolated from post-ischemic rat kidneys or PBMCs of patients diagnosed with acute kidney injury (62**, 69). The response appeared to be specific for sodium since equimolar amounts of mannitol or choline chloride did not induce a response (62**).

Whether the biological effect of extracellular sodium on IL17 activity in vitro is directly related to the stimulatory effect of dietary sodium on Th17 activation is not clear. In recent years, it has been shown that the skin can sequester large amounts of sodium in response to

high sodium intake, being complexed to extracellular glycosaminoglycans. The local extracellular sodium concentration may be higher than the extracellular fluid, and it has been suggested that leukocytes (i.e., lymphocytes or macrophages) perfusing through these areas may be exposed to higher local sodium concentrations vs extracellular fluid (70, 71). Interestingly, it was recently reported that patients with salt-losing tubulopathies have lower skin sodium content relative to non-salt losing control patients. These patients manifest reduced levels of Th17 cells and are more susceptible to a variety of infections relative to controls (72**).

We propose that other factors may potentially contribute to Th17 activation in response to high-salt intake. For example, chronic salt loading has been shown to increase renal adenosine levels, a response that was proposed to promote adaptive natriuresis (73). Adenosine, which can also be liberated from injured cells, affects lymphocytes either directly or secondarily via the activity of dendritic cells, an effect that is likely mediated by the A2A receptor subtype (74, 75). Adenosine has been suggested to increase the prevalence of Th17 cells in autoimmune disease models (74, 75, 76**). In addition, endothelin A expression is enhanced in kidney under high salt diet conditions (77, 78) and may modulate the activity of a variety of inflammatory cells including lymphocytes. Endothelin antagonists have been shown to block the induction of Th17 cells in psoriasis (41**), while they were also shown to abrogate the expression of IL17 in CD4 cells isolated from lymph nodes of mice with multiple sclerosis (79). However few studies have directly addressed the effects of endothelin A antagonists on lymphocyte activity in the kidney. In one study, Boesen et al., demonstrated that the ET-A antagonist ABT-627 significantly reduced the infiltration of lymphocytes into injured kidney and showed a strong trend at reducing CD4+/RorγT+ Th17 cells (80).

Angiotensin II may also participate in the modulation of Th17 activity. Several studies have shown that Ang II infusion can increase the expression of circulating Th17 cells and decrease T-regulatory cells and that this response is mediated in part by SGK-1 (81). Ang II synergistically increased the IL17 response to elevated sodium in isolated lymphocytes from post-ischemic rat kidneys, and the number of Th17 cells in post ischemic rats treated with high salt diet was abrogated by treatment with the AT1 receptor antagonist, losartan.

Mice overexpressing TGFβ display enhanced Th17 activation in a model of auto-immune encephalopathy (50). A recent study indicated that high glucose induced activation of latent TGFβ in T cells from mice with autoimmune disease, resulting in an increase in the expression of IL17A (82**). Finally, vitamin D status may also influence Th17 responses. Th17 cells are exacerbated in states of vitamin D deficiency, and this effect may be due to direct inhibitory effect of 1,25 hydroxy-vitamin D3 on CD4 cells (83**, 84).

Role in hypertension and tissue injury

Whether Th17 cells play a role in human hypertension remains unclear. With notable exceptions, there is a relative dearth of clinical studies highlighting Th17 cells or IL17 activity in the setting of hypertension. However, some recent studies have reported elevated levels of circulating IL17 in patients with pre-hypertension (85) or in diabetic patients with hypertension vs non-hypertensive diabetic patients (86). Ji et al., evaluated T-helper cells in

hypertensive vs non-hypertensive patients and demonstrated elevated percentage of circulating Th17 cells and IL-17 and also reported that IL17 independently associated with the presence of non-dipper hypertension (87). Finally, increased circulating levels of IL17 have been demonstrated in patients with pre-eclampsia (88).

More direct support of Th17 cells in the development of hypertension derive from studies in animal models. Most notably, studies have demonstrated that Ang II infusion in mice results in an increase Th17 cells. In response to chronic infusion on Ang II, *IL17−/−* mice showed a reduced level of blood pressure vs. wild type control mice (86). In Dahl S rats infused with Ang II, inhibition of IL17 with a decoy IL17 receptor attenuated the development of hypertension (89). In addition to Ang II dependent models, elevated Th17 cells (and/or reduced T-regulatory cells) have been demonstrated in mineralocorticoid dependent hypertension, hypertension in response to cyclosporine A, or in a model of pre-eclampsia. In each of these examples, the importance IL17 in the hypertension and renal injury response was suggested by an attenuation in the response by using *IL17−/−* mice or by inhibition with IL17 receptor blockade (90, 91, 92).

Several potential mechanisms for contributions to IL17 in the setting of renal injury and the development of hypertension have been suggested by data from animal models and in vitro studies. Elegant studies performed in mice in response to Ang II infusion have shown impaired natriuretic response to an acute saline load. This response was associated with an increased expression of tubular sodium transporters NHE3 and NCC. These responses were abrogated in *IL17−/−* mice and were dependent on the activity of SGK1 (93, 94). IL17 has also been shown to have vascular effects favoring constriction. IL17 has been shown to negatively regulate NOS activity and has recently been shown to influence vascular remodeling of small arteries (63, 95). To the best of our knowledge, no studies have sought to evaluate the effects of IL17 on renal vascular reactivity.

In addition to its effects on blood pressure, multiple studies from a variety of renal injury models suggest IL17 contributes to end organ damage and fibrosis (55, 96, 97, 98) (99). The activation of pathways leading to inflammation and fibrosis involve the interaction of multiple cells types in the renal interstitium. IL17 is a well-known chemoattractant for neutrophils and contributes to parenchymal cell damage. IL17 stimulates endothelial cells and tubular epithelial cells into a pro-inflammatory state and promotes the release of additional cytokines (100, 101, 102). In gene array studies of human aortic smooth muscle cells, over 30 genes, including those encoding inflammatory cytokines and chemokines, are stimulated by incubation with IL17 (86) and IL17 has been shown to induce inward remodeling of blood vessels independent of blood pressure control (103).

Finally, IL17 is likely to have significant effects on scar formation via effects on macrophages. IL17 administration increased inflammation, aggravated fibrogenic scar formation and delayed wound healing, an effect that was dependent on part on macrophage activity (104). In models of renal injury by UUO or ischemia reperfusion, IL17 blockade reduces accumulation of macrophages and fibrosis (105). However, no firm consensus has developed to determine how IL17 influences macrophage phenotypes to elicit these effect,

although one study suggests that IL17 mediates effects on macrophages by increasing their responsiveness to OxLDL (106).

Conclusion

Taken together, data suggest an important role for Th17 cells in the generation of hypertension and end-organ damage in the kidney. Building on prior important data on the role of the adaptive immune system in hypertension, and summarized in Figure 1, factors that lead to Th17 cell differentiation, such as Ang II or high salt diet may enhance the presence of this T-helper population. The liberation of its key cytokine IL17 may enhance sodium reabsorption or increased vascular tone and contribute to a positive sodium balance and exacerbation of hypertension. In combination with other inflammatory and interstitial cells, IL17 can also promote the development of fibrosis. Conceivably, the potential ability to target the IL17 pathway has been demonstrated for other indications such as psoriasis (107, 108) and thus this approach may enhance precision of potential treatment for conditions of hypertension or progressive chronic fibrosis.

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Key Points:

- There is increasing evidence from both animal models and human genetic studies indicating an important contributory role of the adaptive immune system in the development of hypertension.
- IL17 producing lymphocytes, referred to as Th17 cells, are expressed in inflammatory conditions and may also be elevated in hypertension under the influence factors such as dietary salt or Angiontensin II.
- The activity of IL17 may influence renal sodium handling and lead to positive sodium balance contributing to hypertension, while also promoting inflammation and fibrosis to promote hypertensive renal damage.

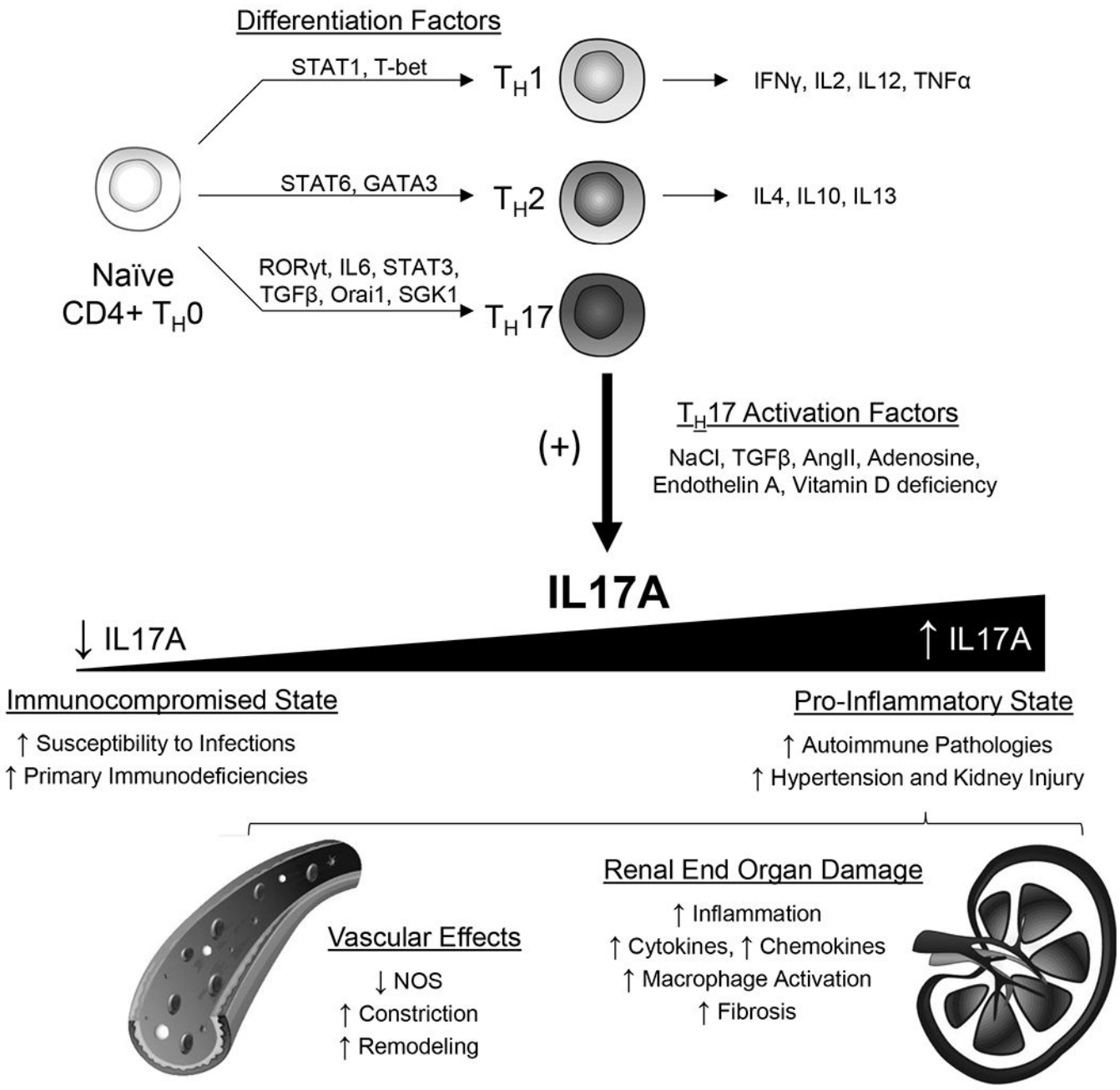

Figure 1. Differentiation and activation factors of TH17 cells, and the effects of differential IL-17A expression.

TH17 cells, under the control of RORγt, IL-6, STAT3, TGFβ, Orai1, and SGK1, are characterized by the production of the signature cytokine IL-17A. An imbalanced level of IL-17A expression dictates an immunocompromised versus pro-inflammatory state. Extensive evidence associates this pro-inflammatory state with a wide range of IL17A-induced effects, including vascular constriction and renal fibrosis, ultimately leading to the progression of hypertension and renal end organ damage.