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Editorial: Inflammation in hypertensive disorders

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Editorial on the Research Topic
Inflammation in hypertensive disorders

Introduction

Hypertension is a leading cause of global mortality and is the primary modifiable risk factor for renal, cardiovascular, and cerebrovascular disease (Kearney et al., 2005). Nonetheless, the factors regulating the pathogenesis and progression of hypertension remain incompletely elucidated. In recent years the pivotal role of the immune system in the development of hypertensive disorders has been increasingly recognized (Harrison et al., 2011; Mattson, 2014; Madhur et al., 2021; Ertuglu and Kirabo, 2022). Renal immune cells are a common feature of both experimental and clinical hypertension (Hughson et al., 2008; Crowley et al., 2010; De Miguel et al., 2011; Xiao et al., 2015; Evans et al., 2017; Banek et al., 2019; Maaliki et al., 2022). Lymphocytes and macrophages migrate to regions of injury in the kidney, and immunosuppression, whether pharmacologically or genetically induced, reduces blood pressure in preclinical models (Guzik et al., 2007; Boesen et al., 2010; Crowley et al., 2010; Madhur et al., 2010; Mattson et al., 2013; Moes et al., 2018). The articles by Itani et al. and Chaundhari et al. in this Research Topic focus on the involvement of the immune system in the development of hypertension.

While the factors driving hypertension are varied and complex, what is clear is that the prevalence of the condition is increasing. This increase is most notable in low and middle-income countries. It is hypothesized to be the result of a dietary shift from a Mediterranean-style diet to a western-style diet, high in sodium and fructose (Schutte et al., 2021). The role that diet plays in the development and prevalence of hypertension is the focus of the review by Labban et al.

Memory T cells in hypertension

Memory T cells are a hallmark of the adaptive immune system. They mount a rapid immune response to recurrent antigen exposure. The migration of T cells from lymphoid organs to the circulation depends on the interaction between the chemoattractant sphingosine-1-phosphate (S1P) and sphingosine-1-phosphate receptors one and 2 (S1PR1+2). FTY720 is a functional agonist of S1PR1 that prevents the egression of lymphocytes from secondary lymphoid organs to the circulation (Matloubian et al., 2004; Garris et al., 2014; Itani et al., 2022).

The report by Itani et al. uses FTY720 to examine the role of effector memory T cells in the hypertensive response to repeated high-salt challenges. Mice were treated with L-NAME to inhibit nitric oxide synthase and then exposed to two high-salt (HS) challenges, separated by a wash-out period (L-NAME-HS1-HS2 protocol). Pretreatment with L-NAME induced salt-sensitive hypertension in naïve mice. Blood pressure increased during the HS challenges and returned to baseline in the intermittent washout period. Administration of FTY720 during the second HS challenge blunted the second hypertensive response. The group theorized that this protection from hypertension was due to decreased T cell migration to the kidneys. They demonstrated that following FTY720 treatment, CD8⁺ effector memory T cells accumulated in the bone marrow, supporting the concept that the drug blocks their egression to the periphery. Finally, the group used elegant T cell adoptive transfer studies to examine whether memory T cells could program salt-sensitive hypertension. Naïve mice, which received memory T cells from mice exposed to the L-NAME-HS1-HS2 protocol, developed hypertension when fed a HS diet. In contrast, the transfer of effector memory T cells from mice treated with FTY720 during the second HS challenge did not result in salt-sensitive hypertension. This suggests that memory T cells can induce salt sensitivity following exposure to hypertension (Itani et al., 2016a; Itani et al., 2016b). These data add to a growing body of research that highlights the importance of chemokine signaling in hypertension (Liao et al., 2008; Mikolajczyk et al., 2016; Rudemiller and Crowley, 2017) and suggests that blocking memory T cell egression may be a therapeutic approach to protect the kidney from hypertensive injury.

Targeting renal inflammation for the treatment of hypertension

The review by Chaudhari et al. provides a comprehensive overview of how targeting renal inflammation may have therapeutic potential for the treatment of hypertension. The authors begin by highlighting the anti-inflammatory

properties of many first-line treatments for hypertension. They propose that reducing renal inflammation may be responsible for some of these medications' antihypertensive effects. The review focuses next on the vast experimental evidence supporting the idea that kidney inflammation contributes to the development and maintenance of hypertension. Finally, the article discusses how a renal involvement in autoimmune conditions often leads to hypertension. Systemic lupus erythematosus (SLE) is an autoimmune condition affecting the kidneys (Lupus nephritis) in up to 50% of cases. When this occurs, it is frequently associated with the development of hypertension (Singh and Saxena, 2009; Cojocaru et al., 2011). Therefore, SLE is a model to study the link between renal inflammation and hypertension. Indeed, studies using female NZBWF1 mice, a murine model of SLE, have demonstrated the critical role of the immune system in hypertension associated with autoimmunity (Mathis et al., 2014; Mathis et al., 2017; Taylor and Ryan, 2017; Taylor et al., 2019).

The effect of dietary shifts on hypertension and cardiovascular disease

The review by Labban et al. explores the roles that high sodium and fructose diets play in the development of hypertension and cardiovascular disease. They focus on Lebanon, where there has been a three-fold increase in the incidence of hypertension in the past decade. The authors draw a connection between this increase and the increased consumption of processed foods high in sodium and fructose. Next, the article summarizes the complex mechanisms underlying sodium- and fructose-induced hypertension. Both high-sodium and high-fructose intake affect the immune system, and renal inflammation is a characteristic of experimental hypertension induced by high-sodium and high-fructose diets.

Interestingly, innate immune cells scan the gut epithelia for antigens and are abundant in the intestinal mucosa (Pott and Hornef, 2012). Recent studies found that consuming a high-salt diet reduced the abundance of *Lactobacillus* in the gut microbiome. In humans, this was associated with increased blood pressure and increased circulating T_H17 cells (Wilck et al., 2017). Therefore, the interindividual heterogeneity in blood pressure responses to salt may be influenced by changes in the microbiome. The review by Labban et al. concludes by discussing strategies to reduce sodium and fructose consumption in Lebanon. The authors address challenges, including the lack of both existing initiatives and national targets for consumption levels. They advocate for a multifaceted approach targeting the food industry, increasing consumer awareness, and improving food labels. It is anticipated that reducing dietary fructose and

sodium will lessen the burden of hypertension and cardiovascular disease.

Conclusion

The articles in the Research Topic contribute to a growing body of evidence implicating the immune system in the development of hypertensive disorders. What is apparent from the articles is the complex nature of hypertension, which is driven by a range of factors, including, in some incidences, inflammation. Therefore, identifying biomarkers that enable the stratification of patients into subpopulations: those in which blood pressure is reduced by anti-inflammatory therapies *versus* those in which it is not, is a valuable area of future research.

Author contributions

HAI edited the manuscript, LCE drafted and edited the manuscript.

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