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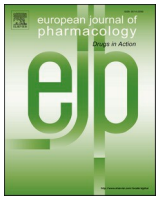

Recent advancements in targeting the immune system to treat hypertension

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ABSTRACT

Hypertension is the key leading risk factor for death globally, affecting ~1.3 billion adults, particularly in low- and middle-income countries. Most people living with hypertension have uncontrolled high blood pressure, increasing their likelihood of cardiovascular events. Significant issues preventing blood pressure control include lack of diagnosis, treatment, and response to existing therapy. For example, monotherapy and combination therapy are often unable to lower blood pressure to target levels. New therapies are urgently required to tackle this issue, particularly those that target the mechanisms behind hypertension instead of treating its symptoms. Acting via an increase in systemic and tissue-specific inflammation, the immune system is a critical contributor to blood pressure regulation and is considered an early mechanism leading to hypertension development. Here, we review the immune system's role in hypertension, evaluate clinical trials that target inflammation, and discuss knowledge gaps in pre-clinical and clinical data. We examine the effects of anti-inflammatory drugs colchicine and methotrexate on hypertension and evaluate the blockade of pro-inflammatory cytokines IL-1β and TNF-α on blood pressure in clinical trials. Lastly, we highlight how we can move forward to target specific components of the immune system to lower blood pressure. This includes targeting isolevuglandins, which accumulate in dendritic cells to promote T cell activation and cytokine production in salt-induced hypertension. We discuss the potential of the dietary fibre-derived metabolites short-chain fatty acids, which have anti-inflammatory and blood pressure-lowering effects via the gut microbiome. This would limit adverse events, leading to improved medication adherence and better blood pressure control.

1. Introduction

Hypertension is a leading risk factor for death globally, as it leads to cardiovascular diseases such as heart failure and stroke (Arima et al., 2006; McManus and Liebeskind, 2016; Oparil et al., 2018). Globally, 30% of adults are classified as hypertensive, making hypertension the most prevalent non-communicable disease (Poulter et al., 2022). This represented 1.3 billion people in 2019 (Risk Factor Collaboration, 2021). Within this staggeringly high number of people living with hypertension, only half are treated, with two-thirds of hypertensive patients having uncontrolled high blood pressure (BP) (Poulter et al., 2022). Common treatments for hypertension include β-blockers, ACE inhibitors, calcium channel blockers, and diuretics, delivered usually as a combination, ideally in a single pill combination (Unger et al., 2020). However, many patients are unable to control BP through medications. Reasons include lack of diagnosis and appropriate BP measurement, limited access to medications, adverse effects that lead to non-adherence, and resistance against currently available medications (Thomopoulos et al., 2016; Van Wijk et al., 2005). With such a high proportion of the world's population having hypertension, there is an unmet clinical need to develop new drugs that can lower the incidence of hypertension. Most of these medications treat symptoms (i.e., increased plasma volume) rather than treating mechanisms that increase BP in the first place. This is an issue as new drugs for hypertension have not been developed for decades, and drugs that have a precise mechanism based on genetic studies are 2.6 times more likely to be tested and approved for clinical use (Minikel et al., 2024).

Hypertension is a multi-factorial disease (Oparil et al., 2018). A growing body of evidence, particularly in the past 2 decades, has shown the causative roles of the immune system in the development and maintenance of hypertension (Guzik et al., 2024; Nguyen et al., 2024). Therefore, targeting the immune system may be the next frontier for drug development in hypertension. In this review, we discuss the recent advancements in targeting the immune system as a treatment for

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hypertension and highlight new and future opportunities in this area.

2. Evidence of immune system activation in hypertension

Immune system activation has long been recognised as a feature of hypertension (Fig. 1), reviewed in detail here (Guzik et al., 2024; Nguyen et al., 2024). Here we discuss evidence of the immune system in hypertensive patients, and how this is reflected by the causative data implicating the immune system in experimental rodent models of hypertension.

2.1. Immune system activation in hypertension: evidence from hypertensive patients

A potential causal relationship was identified between elevated white blood cell count and elevated BP (Siedlinski et al., 2020; Xu et al., 2023). Many immune cells, such as neutrophils, monocytes and γδ T cells are increased during hypertension (Caillon et al., 2017; Delaney et al., 2021; Tatsukawa et al., 2008). A higher neutrophil-to-lymphocyte ratio has also been described (Jhuang et al., 2019; Liu et al., 2015). While B cells are not elevated in hypertension, elevated serum antibodies, particularly IgG, are a consistent feature of hypertension, implicating a role for B cells in the pathogenesis of hypertension or its complications (Hilme et al., 1989; Suryaprabha et al., 1984).

Circulating CD4 and CD8 T cells have the capability to produce inflammatory cytokines, such as interferon-γ (IFNγ). These are higher in hypertension (Itani et al., 2016; Ji et al., 2017; Youn et al., 2013). In contrast, whether a higher number of T_H17 cells are present in hypertension remains controversial (Delaney et al., 2021; Ji et al., 2017; Youn et al., 2013). This inconsistency may be explained by night-time dipping, where non-dippers (with reduced BP less than 10% at night-time) had higher circulating T_H17 cells, compared to dippers, who have a reduction of BP greater than 10% at night-time (Ji et al., 2017). This highlights the need to measure BP accurately with ambulatory BP monitoring, which measures night-time dipping, compared to office BP measurement, which does not. Together, these illustrate an association of circulating immune cells, particularly T lymphocytes, with hypertension.

Other immune cells, such as T regulatory cells (Tregs), which have an immunoprotective role, are lower in hypertension (Alexander et al., 2023). Lower levels of Tregs, particularly those with enhanced immunosuppressive functions expressing the chemokine receptor CCR10, were reported in hypertensive people, together with lower numbers of memory T cells exhibiting an exhausted phenotype (Alexander et al., 2023). This highlights that the inflammation and immune responses observed during hypertension are not likely to be the result of only one immune cell type, but a result of an unbalance of the network of immune cells.

Accumulating evidence suggests that circulating immune cells may infiltrate peripheral tissue to mediate hypertension-mediated organ damage. Elevated T_H17 cells and reduced Tregs were associated with microvascular remodelling in hypertensive patients (De Ciuceis et al., 2017). Hypertensive participants with nephrosclerosis had renal infiltration of CD8 and CD4 T cells, as well as elevated T cell chemokines, such as CXCR3 (Youn et al., 2013). Additionally, increased circulating CD4 T cells and CD8 effector/memory T cells correlated with left ventricular hypertrophy in adolescent hypertensives (Gackowska et al., 2018).

Resistant hypertension also has immune features, with a higher circulating neutrophil-to-lymphocyte ratio (Belen et al., 2015). Patients with resistant hypertension also have higher circulating CD4 T and T_H17 cells, but not Tregs, compared to normotensive controls (Imiela et al., 2022).

Many of these immune cells produce cytokines, which are commonly elevated during hypertension. Cytokines that drive inflammation, such as IL-6 and TNF-α, together with C-reactive protein (CRP), are consistently elevated as hypertension develops (Bautista et al., 2005; Sesso et al., 2015; Wang et al., 2011). Other cytokines, including IL-17 and IL-22 are reportedly increased in the circulation once hypertension has been established (Madhur et al., 2010; Ye et al., 2017). Plasma TNF-α

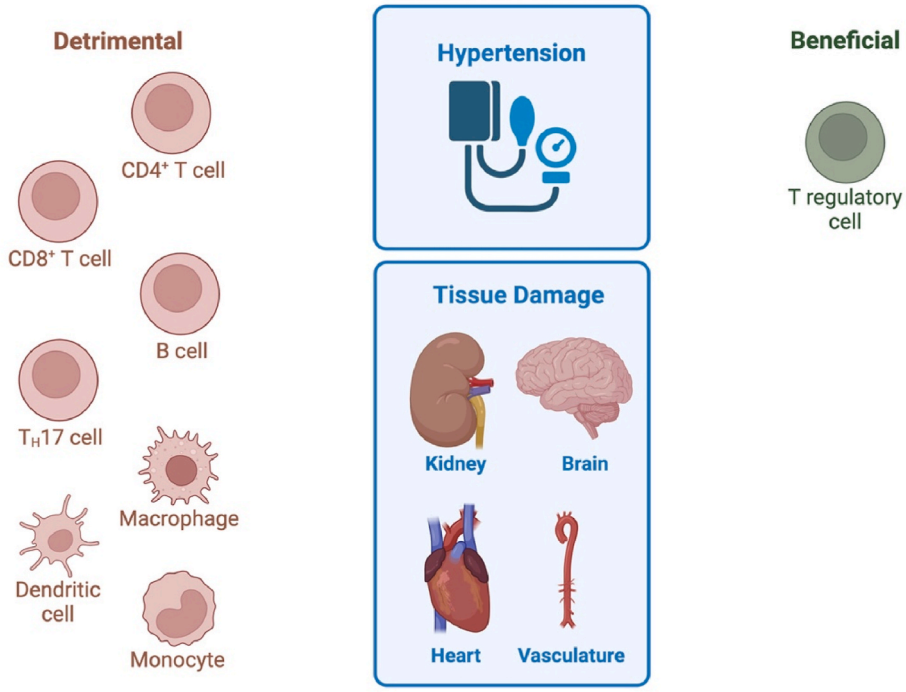

Fig. 1. Immune cells involved in hypertension. Illustrated are some of the immune cells that promote hypertension and the associated tissue damage, including B cells, $CD4^+$ T cells, $CD8^+$ T cells, T_H17 cells, monocytes, macrophages and dendritic cells. T regulatory cells (Tregs) have protective effects against hypertension. Created with BioRender.com.

and CRP have also been associated with BP variability in healthy participants (Abramson et al., 2006; Chae et al., 2001) suggesting a mechanistic role for TNF-α in BP regulation.

IL-1β is an inflammatory cytokine that is mediated by the inflammasome, and acts upstream of other pro-inflammatory cytokines, such as IL-6 and TNF-α. IL-1β and IL-18, both inflammasome-mediated cytokines, are elevated in established hypertension (Dalekos et al., 1997; Hung et al., 2005, 2008; Vilarrasa et al., 2006), but have not been consistently associated with prehypertension or elevated hypertension risk (Mauno et al., 2008; Wang et al., 2011). A meta-analysis of all available cohort studies (a total of 21) investigating the association between inflammation and hypertension incidence found that circulating CRP and IL-6, but not IL-1β, were associated with an increased risk of developing hypertension (Jayedi et al., 2019). Together, these findings highlight that while IL-6 may be used as a predictor of hypertension, IL-6, IL-1β and IL-18 may be more ideal as therapeutic targets for established hypertension.

2.2. The causative role of the immune system in hypertension: evidence from rodent models

Many observations have been made regarding the role of inflammation in experimental hypertension. This includes the observation that normotensive male spontaneously hypertensive rats (SHRs) have increased renal inflammation consisting of T cell and macrophage infiltration, with elevated NF-κB activation as early as 3 weeks of age compared to Wistar-Kyoto (WKY) controls, which is prior to changes in BP (Biswas and de Faria, 2007; Rodriguez-Iturbe et al., 2004).

Current research in experimental models linking the immune system and hypertension could broadly be categorised into i) specific immune cell types or mediators, such as cytokines or chemokines, or ii) target organ of immune activation, such as immune-driven fibrosis in the kidneys, iii) stimulus activating the immune system such as lipopolysaccharide (LPS), or iv) neoantigens such as isolevuglandins, and v) mechanisms downregulating inflammation, such as the dietary fibre-derived metabolites short-chain fatty acids.

The causative role of the immune system in models of experimental hypertension was first established in RAG1 knockout mice, lacking both B and T lymphocytes, which were protected from both angiotensin II (Ang II) and deoxycorticosterone acetate (DOCA)-induced hypertension usually combined with 1% sodium in uninephrectomised mice, called the DOCA-salt model (Guzik et al., 2007). The adoptive transfer of T cells from wild-type C57BL/6 mice into RAG1 knockout male mice, that lack both B and T cells, revealed that T cells played a key role in the development of hypertension (Guzik et al., 2007). A body of work has since implicated important roles for other immune cells in the onset and development of hypertension or hypertension-driven tissue damage, including both innate and adaptive immune cells such as monocytes, B cells, T_H17 cells, γδ T cells, $CD4^+$ T cells and $CD8^+$ T cells (Fig. 1) (Caillon et al., 2017; Chan et al., 2015; Crowley et al., 2010; Madhur et al., 2010; Wenzel et al., 2011). Intriguingly, targeting just one of these cell types in experimental hypertension resulted in complete or partial protection from hypertension, highlighting the interplay between different immune system components. These cells usually act via pro-inflammatory mechanisms, further discussed below. Other immune cells, such as Tregs, have an anti-inflammatory role and are protective against hypertension in rodents (Barhoumi et al., 2011).

This data discussed above is largely obtained from male rodents models, as premenopausal female rodents are protected from hypertension (Sandberg and Ji, 2012). Factors leading to this premenopausal protection from hypertension include differences in the renin-angiotensin system, sympathetic tone oxidative stress, nitric oxide and the immune system, some of which may be hormone-mediated (Elmarakby and Sullivan, 2021). As mentioned, the adoptive transfer of T cells into RAG1 knockout male mice renders RAG1 knockout male mice susceptible to hypertension (Guzik et al., 2007). This effect was found to be consistent in postmenopausal, but not premenopausal female mice in Ang II-induced hypertension (Pollow et al., 2014, 2019). Interestingly, the depletion of Tregs in premenopausal mice led to elevated BP in Ang II-induced hypertension (Pollow et al., 2019). These findings suggest a hormonal effect on the immune cells of female mice, which impacts BP regulation. Indeed, hormonally-regulated molecular pathways have been identified in $CD4^+$ T cells and Tregs, which may impact hypertension in postmenopausal mice (Uhlorn et al., 2021).

Sex-dependent immune responses during hypertension have also been observed in SHR rats. While no differences in inflammation were observed between normotensive male and female SHRs at 5 weeks of age (Sullivan and Gillis, 2017), female SHRs had more renal Tregs and greater levels of the anti-inflammatory cytokines IL-10 compared to males, which had more renal T_H17 cells and IL-6 expressing cells once hypertension developed (Tipton et al., 2012, 2014). Interestingly, the immunosuppressive drug mycophenolate mofetil was able to normalise BP in both male (Rodriguez-Iturbe et al., 2002) and female SHRs (Tipton et al., 2012). However, the depletion of Tregs led to lower BP in female, but not male SHRs (Belanger et al., 2020), highlighting that Tregs may be the key player in the immune-regulated differences in SHRs.

Sex hormones were implicated in these sex differences, as sex hormones can influence the immune system. For example, estrogen enhances Treg expansion (Tai et al., 2008), while progesterone has modulatory effects on Th2 cytokines (Piccinni et al., 1995). Testosterone reportedly also has anti-inflammatory effects (Fijak et al., 2011; Page et al., 2006). Gonadectomy was used to study the role of sex hormones in SHRs. Gonadectomy attenuated BP increases in male, but not female SHRs (Chen and Meng, 1991), implicating sex hormones in hypertension regulation. However, gonadectomy resulted in decreased renal T cells in both male and female SHRs, suggesting the effects of hormones on BP are independent of inflammation (Tipton et al., 2014).

These data highlight the importance of immune cells in rodent models, but suggest caution when interpreting data from different sexes. These findings also illustrate the need to ensure clinical trials include male and female participants so that sex differences can be thoroughly examined.

2.3. Blocking cytokines to prevent or treat hypertension in rodent models

One way to target the effects of immune cells is by inhibiting the cytokines or chemokines that are elevated during hypertension. Consistent with data in hypertensive patients, circulating TNF-α, IFNγ, IL-17, IL-1β and IL-22 are elevated in hypertensive Ang II-treated mice (Guzik et al., 2007; Madhur et al., 2010; Ye et al., 2017). Additionally, hypertensive SHRs also have elevated serum IL-1β and IL-6 (Sanz-Rosa et al., 2005). The key cytokines mechanistically evaluated in mice include IFNγ, IL-17, IL-22, TNF-α, IL-1β and IL-18, which are produced by immune and non-immune cells. The use of knockout mice lacking chemokines and cytokines or their receptors, as well as pharmacological inhibitors, have facilitated the study of the effects of these cytokines on BP regulation during hypertension.

TNF-α knockout mice were protected from Ang-II-induced hypertension and cardiac hypertrophy (Sriramula et al., 2008). Furthermore, the intraperitoneal administration of the TNF antagonist Etanercept prevented the development of Ang II-induced hypertension (Guzik et al., 2007). Renal infusion of Etanercept attenuated the development of hypertension in uninephrectomized Dahl salt-sensitive rats (Huang et al., 2016), highlighting the importance of renal TNF-α in hypertension.

IL-17 knockout mice had attenuated BP elevation during Ang II-induced hypertension, with reduced renal and vascular dysfunction (Madhur et al., 2010). Importantly, neutralizing antibodies to the IL-17 subunit IL-17A lowered established Ang II-induced hypertension (Saleh et al., 2016), highlighting the therapeutic potential of targeting IL-17. Neither IFNγ receptor knockout or IFNγ knockout mice were protected from BP changes during Ang II-induced hypertension (Kossmann et al., 2013; Markó et al., 2012). However, IFNγ receptor knockout mice had

reduced cardiac and renal inflammation and cardiac hyperterophy (Markó et al., 2012), while IFNγ knockout mice had improved vascular function compared to controls (Kossmann et al., 2013). Targeting IL-22, an inflammatory cytokine produced by Th22 cells, through the use of a neutralizing antibody also partially blocked BP elevation in Ang II-treated mice (Ye et al., 2017).

Ang II-treated uninephrectomized IL-1 receptor knockout mice, which lack both IL-1β and IL-1α signaling, were partially protected from BP increases and renal inflammation (Zhang et al., 2016). Importantly, this was phenocopied through pharmacological inhibition (Zhang et al., 2016). IL-18 knockout mice exhibited reduced BP elevation in response to DOCA/Salt, with reduced renal injury and inflammation (Thomas et al., 2021). The NLRP3 inflammasome plays a crucial role in the maturation of cytokines IL-1β and IL-18. NLRP3-knockout mice, which lack cannonical NLRP3-dependent IL-1 and IL-18 production, had reduced BP and endothelial dysfunction following Ang-II infusion (Li et al., 2022).

While these provide a proof-of-concept of the role of cytokines in hypertension development, it does not evaluate the impacts of dampening cytokine signaling in established hypertension. Pharmacological cytokine and chemokine inhibitors in established hypertension highlight the potential clinical relevance of targeting cytokines or chemokines during hypertension. There are several examples where pharmacological inhibition of cytokines lower BP in established hypertension – this is more relevant to human treatment. Intervention with the IL-1 receptor antagonist anakinra reduced systolic BP in 1 Kidney (1K)/DOCA/salt-treated male mice with established hypertension by ~20 mmHg (Fig. 1) (Ling et al., 2017). Anakinra treatment reduced renal fibrosis but had no impact on renal immune cell infiltration (Ling et al., 2017), suggesting that the functional capacity of immune cells induces tissue damage, and not merely their presence. The NLRP3 inflammasome inhibitor MCC950 lowered BP, renal inflammation, and fibrosis in 1K/DOCA/salt-treated male mice with established hypertension (Krishnan et al., 2016, 2019). Blocking the chemokine receptor CCR2 with a CCR2 antagonist reduced BP and led to a fewer macrophages infiltrating the aortas of DOCA-salt hypertensive mice (Chan et al., 2012). Blocking IL-17 with an antibody against IL-17A and its receptor IL-17RA lowered established high BP in Ang II-treated mice (Saleh et al., 2016). Together, these data indicate that targeting inflammatory signaling and immune cell trafficking may be a potential therapeutic option during hypertension.

3. Clinical trials targeting the immune system in hypertension

The evidence that immune cells play a causative role in experimental hypertension led to the speculation that reducing inflammation may lower BP in hypertensive patients. Below, we evaluated clinical trials that have evaluated targeting inflammation in hypertension or cardiovascular disease, as well as trials targeting inflammation in inflammatory diseases with BP as a secondary outcome (Table 1).

3.1. TNF-α

TNF-α is an important immune modulator that plays a vital role in hypertension as well as in other immune disorders, such as rheumatoid arthritis (Farrugia and Baron, 2016; Mehaffey and Majid, 2017). Many commercially available inhibitors specifically target TNF-α. Importantly, these inhibitors target TNF-α directly, thereby inhibiting both TNF receptor I and II signaling pathways. TNF-antagonism has been well-studied as a treatment for rheumatoid arthritis. BP was a secondary outcome in some of these studies, providing insights into the benefits of TNF inhibition on hypertension. One study revealed no significant change in BP in Australian rheumatoid arthritis patients after receiving 6-weeks of treatment with a TNF-α inhibitor, with the TNF-α inhibitors etanercept, adalimumab or infliximab all included in the study (n = 14 participants) (Van Doornum et al., 2005).

The BeSt study evaluated the effects of 4 treatment strategies on BP in 508 Dutch rheumatoid arthritis participants (Klarenbeek et al., 2010). One group were treated with the TNF-α inhibitor infliximab, every 8 weeks for 12 months (N = 128). A Posthoc analysis of the BeST study revealed infliximab resulted in a larger decrease in office systolic (4.7 mmHg) and diastolic (3.9 mmHg) BP after 12 months of treatment (Klarenbeek et al., 2010). Interestingly, in this study, the discontinuation of infliximab also increased office BP to pre-treatment levels (Klarenbeek et al., 2010).

Another study in Japanese patients with rheumatoid arthritis revealed decreased systolic BP after infliximab treatment, from 127.4 ± 1.8 mmHg to 120.1 ± 3.4 mmHg two weeks after infliximab treatment (n = 16) (Yoshida et al., 2014). This change, measured by ABPM, is a significant drop in BP for such a short time. However, only 7 (44%) of the participants were hypertensive, and a separate analysis based on hypertension status was not performed (Yoshida et al., 2014). This suggests that either the reported effect was greater in hypertensive participants or that TNF inhibition also reduced BP in normotensive participants.

A retrospective cohort study investigating the association of hypertension with TNF-α inhibitor treatment in rheumatoid arthritis patients found that the use of TNF-α inhibitors was not associated with lower hypertension risk in American participants (4822 TNF-α inhibitor users vs 2400 controls) (Desai et al., 2016b). It is important to note that some of these participants were also taking methotrexate. Furthermore, as

Table 1
Completed trials investigating inflammation in hypertension.
RA, rheumatoid arthritis.

Study	Drug regime	Participants	Endpoint	Effect on BP	Reference
TNF-inhibition	Etanercept, adalimumab or infliximab	14 Australian RA patients	6 weeks	No change in office BP	Van Doornum et al. (2005)
TNF-inhibition	Infliximab, every 8 weeks	508 Dutch RA patients	12 months	Decreased office systolic (4.7 mmHg) and diastolic (3.9 mmHg) BP. Discontinuation increased BP to pre-trial levels.	Klarenbeek et al. (2010)
TNF-inhibition	3 mg/kg infliximab	16 Japanese RA patients	2 weeks	Decreased ambulatory systolic BP (7.3 mmHg)	Yoshida et al. (2014)
TNF-inhibition	TNF-inhibitors with methotrexate	7222 American RA patients	Retrospective study	No association	Desai et al. (2016b)
Cardiovascular risk factors	TNF-inhibitors	169 American RA patients (35 TNF-inhibitor vs 134 controls).	Cross-sectional study	No association	Rho et al. (2009)
Cardiovascular risk factors	Methotrexate	169 American RA patients (120 methotrexate vs 49 controls).	Cross-sectional study	No association	Rho et al. (2009)
CANTOS	50, 150 or 300 mg anti-IL-1β antibody Canakinumab or placebo every 3 months	10,061 patients from 39 countries with previous myocardial infarction, >2 mg/L hs-CRP (BP evaluated in N = 9549)	Myocardial infarction, stroke or cardiovascular death	No change in BP. No change in HTN onset in normotensives.	Rothman et al. (2020)

mentioned above, a study examining the effects of various medications on cardiovascular risk in American rheumatoid arthritis patients revealed no change in office BP in the 35 patients using TNF-α inhibitors, compared to 134 controls (Rho et al., 2009). Given the discrepancy in these findings, long-term studies are necessary to confirm these findings using valid tools and outcomes. TNF-α inhibitors may reduce BP in specific subsets of patients, such as those with inflammatory diseases like rheumatoid arthritis. Additionally, in the reported studies, many participants remained on concomitant medications, such as methotrexate, which may create a synergistic effect that needs further delineation to truly assess the potential benefits of TNF-α inhibition on hypertension. Future studies could leverage large datasets of available medical records or databases such as the UK BioBank that would allow statistical power for endophenotype analysis.

3.2. IL-1β

One of the attempts to decipher the immune system's role in hypertension has focused on the relationship between various cytokines, particularly IL-1β, and high BP. IL-1β is considered a master regulator of the immune system with many downstream effectors and thus considered a potent therapeutic target. In an early study, plasma IL-1β was found to be significantly higher in hypertensive participants (n = 28) who were either treatment naïve or after discontinuation of antihypertensive drugs for at least a month, compared to healthy age and sex-matched controls (n = 35) (Dalekos et al., 1997). The authors also found that among the hypertensive participants, IL-1β levels correlated with mean plasma triglyceride levels, suggesting that IL-1β may also be linked to atherosclerosis (Dalekos et al., 1997). In contrast, another study showed that while no difference in plasma IL-1β was observed in hypertensive participants (n = 21 hypertensive participants; n = 42 healthy controls), blood cells from hypertensive participants had a greater capacity to produce IL-1β following LPS stimulation *ex vivo* (Peeters et al., 2001). This, together with other studies, warranted the evaluation of IL-1β as associated, and possibly promoting, high BP in people (Dörffel et al., 1999; Li et al., 2005).

IL-1β has not been evaluated as a primary outcome in a clinical trial in hypertension. The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS; NCT01327846) trial investigated the role of inhibiting inflammation in the context of cardiovascular disease through the use of Canakinumab, a monoclonal antibody targeting IL-1β (Ridker et al., 2017). The basis for the study was that thrombosis is strongly linked with inflammatory markers such as hs-CRP and IL-6, which are associated with an increased cardiovascular risk independent of cholesterol levels (Ridker et al., 1997, 2000). In the double-blinded placebo-controlled CANTOS trial, subcutaneous Canakinumab (50 mg, 150 mg or 300 mg) or placebo was administered every 2 weeks for the first 2 doses, then every 3 months. 10,061 participants (25.7% women) with previous myocardial infarction were enrolled from 39 countries. An additional criterion was hs-CRP levels higher than 2 mg/L, which indicates persistent elevated inflammatory biomarkers despite standard care. This provided the rationale for lowering inflammation in this sub-group of patients. The primary endpoint was myocardial infarction, stroke or cardiovascular death. It is important to note that 80% of participants were hypertensive at the commencement of the trial, as determined by office BP measurement.

Canakinumab treatment significantly reduced CRP levels at all doses compared to placebo (Ridker et al., 2017). High dose (150 mg) Canakinumab also resulted in a lower recurrent rate of cardiovascular events (Ridker et al., 2017). However, Canakinumab treatment did not affect all-cause mortality and was associated with a statistically significant risk of fatal infections (0.31 vs 0.18 events per 100 person-years) (Ridker et al., 2017). In a secondary analysis of the CANTOS trial, the onset of hypertension was investigated in the 9549 participants who had baseline office BP measured (Rothman et al., 2020). IL-1β blockade did not affect the BP of the hypertensives at any evaluated timepoint up to 1 year at any dose, compared to placebo (Rothman et al., 2020). Furthermore, Canakinumab treatment did not affect hypertension onset in non-hypertensive participants (Rothman et al., 2020). As office BP was measured, the effect of the treatment on BP may be underestimated.

Together, these data suggest that targeting IL-1β may not benefit hypertensive patients with high inflammation. While the participants in the CANTOS trial had residual inflammatory risk determined by high CRP levels, plasma IL-1β was not measured. This information may have facilitated a further stratification to identify patients that may benefit from this treatment. Whether patients with lower inflammatory risk would benefit from IL-1β blockade is unknown. It is also possible that IL-1β needs to be targeted during the early stages of hypertension for a benefit to be seen. Future studies investigating the role of IL-1β may still be warranted in other well-defined patient subsets. In addition, increasing our understanding of the mechanisms promoting an increase in IL-1β production during hypertension will allow us to directly target these instead of IL-1β, which may yield better responses. Unfortunately, while inflammasome inhibitors are reportedly well tolerated (Hissaria et al., 2024; Kluck et al., 2020; Wohlford et al., 2020), no clinical trials assessing the inflammasome during hypertension have been performed to date.

3.3. Colchicine

Colchicine is an anti-inflammatory drug with broad effects including modulating neutrophil and dendritic cell function, as well as the inflammasome and downstream IL-1β processing (Cronstein et al., 1995; Martinon et al., 2006; Mizumoto et al., 2005). Historically, colchicine has been used to treat inflammatory diseases, and more recently, its effects on cardiovascular disease have been investigated. Mechanistic pre-clinical studies demonstrate that colchicine is linked to neutrophil recruitment and activation, both linked to atherosclerosis and unstable plaques (Meyer-Lindemann et al., 2022; Roubille et al., 2021; Schwarz et al., 2023). One of the earliest clinical trials to modulate the immune system in cardiovascular disease used low-dose colchicine (LoDoCo; ACTRN 12610000293066), administered at 0.5 mg/day in patients with clinically stable coronary disease (Nidorf et al., 2013). The LoDoCo trial (n = 532) had a median follow-up of 3 years with a primary endpoint of recurrent atherothrombotic event or out-of-hospital cardiac arrest (Nidorf et al., 2013). This occurred in 5.3% of patients receiving colchicine, which was significantly lower than 16% of patients in the control arm (Nidorf et al., 2013). While the findings of this study demonstrated the possibility of modulating the immune system in cardiovascular diseases, BP data was not available from this cohort.

While the LoDoCo trial investigated the role of colchicine in stable coronary artery disease, the Colchicine Cardiovascular Outcomes Trial (COLCOT; NCT02551094) aimed to determine whether low-dose colchicine (0.5 mg daily) would prevent the recurrence of an atherothrombotic event or death as the primary endpoint (Tardif et al., 2019). A total of 4745 participants were enrolled and followed up for almost 2 years. The primary endpoint was significantly lower in the colchicine group (5.5% of patients) compared to the placebo group (7.1%) (Tardif et al., 2019).

Many studies have investigated the role of colchicine in cardiovascular diseases, summarised here (Zhang et al., 2022). Colchicine is currently on trial for peripheral artery disease (NCT04774159) and heart failure with preserved left ventricular ejection fraction (NCT05637398). There are also studies currently investigating the role of colchicine in hypertension (1 completed and the other recruiting when this review was written).

Repurposing Colchicine to Improve Vascular Function in Hypertension (RECTIFHY; NCT04303689) is a single-blind placebo controlled-intervention study that recruited 31 participants to investigate the effect of low-dose colchicine compared to placebo for 3 weeks. Vascular function using Doppler flow changes as the primary outcome, with secondary outcomes including BP measurement by home BP monitoring

and vascular compliance. Despite the small sample size and recruitment of only males, this is one of the first studies to exclude chronic co-morbidities, making the effects on hypertension more transparent.

An interesting trial currently underway is the Colchicine Hypertension Trial (COHERENT, NCT04916522; trial still enrolling participants when this review was written). This Danish trial aims to enrol 150 participants with hypertension on at least 1 anti-hypertensive drug to receive either LoDoCo daily or placebo. The broad inclusion criteria of at least one anti-hypertensive drug in addition to either diagnosed with type 2 diabetes or on lipid-lowering medication may make the impacts of colchicine on hypertension challenging to unravel if it affects a small sub-group of patients.

3.4. Methotrexate

Methotrexate has anti-inflammatory and immune-modulatory effects, and is commonly used to treat inflammatory diseases such as rheumatoid arthritis (Bedoui et al., 2019). To assess the effects of suppressing inflammation on cardiovascular disease, the Cardiovascular Inflammation Reduction Trial (CIRT; NCT01594333) assessed the secondary prevention of atherothrombosis in high-risk patients, including patients with a previous history of myocardial infarction or multivessel coronary artery disease in addition to metabolic syndrome including type 2 diabetes (Ridker et al., 2019). In the double-blinded placebo--controlled CIRT trial, low-dose methotrexate (15–20 mg) was administered weekly, and all participants received daily folate supplementation until the primary endpoint of a major cardiovascular adverse event (Ridker et al., 2019). A total of 4786 eligible participants were randomised to receive methotrexate (n = 2391) or placebo (n = 2395) (Ridker et al., 2019). The cohort was older (median age 66 years old), mostly men (81%) and white (78%). Following a median follow-up of 2.3 years, the trial was stopped. Methotrexate did not lower any inflammatory markers including IL-1β, IL-6, or CRP, compared to placebo (Ridker et al., 2019). The groups also had no statistical difference between the number of primary endpoints (atherothrombotic event or death). In addition, methotrexate was associated with elevated liver enzymes, lower leukocyte counts and haematocrit levels, and a higher incidence of non-basal-cell skin cancers, compared to placebo. Unfortunately, BP was not measured in this trial.

One study examined cardiovascular risk factors in 169 American rheumatoid arthritis patients receiving different medications, including methotrexate and TNF-inhibitors amongst others (30.8% males). Methotrexate (N = 120 vs 49 controls) or TNF-inhibitors (N = 35 vs 134 controls) did not alter office BP in these patients (Rho et al., 2009). Together, this indicates that methotrexate may not have lowering BP effects.

3.5. Lessons from the current clinical data

The focus of immune-based clinical trials in the past has been to reduce the inflammatory effect in patients with higher-than-average risk of cardiovascular events or to assess BP as a secondary outcome in patients with an inflammatory disease. The BP of all hypertensive participants does not benefit from limiting inflammation. A significant challenge made evident by the CANTOS trial are the side effects of immune modulation, such as the increased risk of infections. This may dampen efforts to trial immune-modulating drugs for long-term use. This approach to suppressing inflammation does not target the cause of inflammation itself. Indeed, a recent analysis of drugs approved for clinical use in the last decade showed that those that targeted mechanisms with genetic support were 2.6 times more likely to succeed (Minikel et al., 2024). More work needs to be done to understand how inflammation develops during hypertension and how it affects systems that regulate BP, and thus how to target it effectively.

An approach would be to modulate the immune system indirectly; for example, through changes in diet. Diet is known to have different effects on the immune system. Some specific dietary components that impact the immune system in hypertension include sodium and dietary fibre (Jama et al., 2024, Mattson, 2019). With the gut having one of the most significant numbers of immune cells in the body (Mowat and Agace, 2014) and the microbiota being responsible for priming the immune system (Sanidad and Zeng, 2020), a possibility is that diet regulates inflammatory processes that regulate BP via the gut microbiome, as reviewed in O'Donnell et al. (2023).

4. Targeting the immune system in hypertension through diet and gut microbiome

The gut microbiome (all microbes including bacteria, viruses, fungal, and their genes) (Berg et al., 2020) has emerged as a contributing factor to many health states and diseases (Vos et al., 2022), including hypertension (O'Donnell et al., 2023). The gastrointestinal tract not only harbours the largest collection of microbes compared to other sites in the human body, but also houses the largest compartment of immune cells (Mowat and Agace, 2014). It is, therefore, reasonable that the gut microbiome influences the immune system, and vice-versa (Zheng et al., 2020). These two compartments are separated only by a single layer of cells, primarily epithelial but also Goblet cells and other cell types, which actively produce substances such as mucus to maintain the barrier between the microbes and the host (Snelson et al., 2024). In addition to a physical and chemical barrier, both compartments affect the barrier by affecting tight junctions between the cells (Schreiber et al., 2024). Epithelial cells also express many different receptors to metabolites produced by the gut microbiota, some pro- and others anti-inflammatory (Didriksen et al., 2024; Ghosh et al., 2021; Kim, 2023). These gut microbiota-derived metabolites have been extensively studied in the past decade, but importantly, they influence many facets of physiology, including the immune system (Yang and Cong, 2021; Zheng et al., 2020). The absence of the gut microbiome results in impaired immune function, supporting the fact that the gut microbiome is required for the maturation and maintenance of the immune system (Fiebiger et al., 2016; Round and Mazmanian, 2009).

One of the biggest drivers of the gut microbiome is diet, which has implications for the immune system (Asnicar et al., 2021; Muralitharan et al., 2024). Specifically, diets such as the Mediterranean diet, which are high in fibre and low in meat and processed foods, are cardioprotective and modulate immune function (Sureda et al., 2018). A recent meta-analysis of randomized controlled trials (n = 22) investigated the effects of dietary habits and their relation immune system and found that the Mediterranean diet was associated with significantly lower plasma inflammatory markers such as IL-6 (mean-difference −1.07 pg/ml), IL-1β (mean-difference −0.46 pg/ml) and CRP (mean--difference −1.00 mg/L) compared to control diets (Koelman et al., 2022). In an elegant study conducted by Desai and colleagues, a fibre-free diet was associated with changes in the gut microbiota and with an expansion of mucin-degrading bacteria in mice (Desai et al., 2016a). In addition to changes in the gut microbiota, an upregulation of inflammatory genes was also observed in the epithelial cells of the colon of mice fed a fibre-free diet compared to a fibre-rich diet (Desai et al., 2016a).

4.1. Fibre and short-chain fatty acids

Dietary fibre is any carbohydrate that is not digested or absorbed in the small intestine, with some degree of polymerisation (Jones, 2014). Certain types of fibre are fermented in the colon by the gut microbiota, generating by-products called short-chain fatty acids (SCFAs). Emerging research has demonstrated that SCFAs are critical metabolites in maintaining several aspects of health (Xie et al., 2023). SCFAs play many roles, including effects on the immune system and metabolism (Xie et al., 2023).

SCFAs influence various immune cells through receptor-dependent

and independent mechanisms (Fig. 2), reviewed by Muralitharan and Marques (2021); Tan et al. (2014). Many immune cells, including monocytes, dendritic cells (DCs) and lymphocytes, express SCFA-sensing receptors such as GPR41, GPR43 and GPR109a (Muralitharan and Marques, 2021; Tan et al., 2014). In addition to receptor-mediated effects, SCFAs can also act as histone deacetylase (HDAC) inhibitors (Tan et al., 2023). SCFAs can influence immune cells associated with hypertension, such as Tregs and macrophages (Bartolomaeus et al., 2019; Muralitharan et al., 2020; Yang et al., 2020).

Our group demonstrated that a high-fibre diet or supplementation with acetate, one of the most abundant SCFAs, blunts the development of hypertension and its associated complications in mice (Marques et al., 2017). We and others have utilized GPR41 and GPR43 knockout mice to demonstrate the key role of SCFA-receptor signaling in preventing hypertension (Kaye et al., 2020; Muralitharan et al., 2023; Pluznick et al., 2013). The BP-lowering effects of SCFAs have been recapitulated in people living with hypertension. A phase II randomised placebo-controlled cross-over clinical trial examining the effects of a high-fibre supplement enriched in the SCFAs acetate and butyrate, (acetylated and butyrylated high-amylose maize starch also known as HAMSAB) led to a clinically relevant placebo-controlled reduction in 24-h systolic BP of 6.1 mmHg in 20 untreated hypertensive participants (Jama et al., 2023). While there was no change in plasma cytokine levels (IL-1β, IL-17A, IL-10, TNF-α) (Jama et al., 2023), it is not possible to know if immune cell accumulation and cytokine production within key tissues that regulate BP, such as kidneys, changed. While it remains to be elucidated whether this high SCFA delivery impacts the immune system in humans via similar mechanisms to mice, a dietary intervention study provides some insight into the impacts of high levels of SCFAs on the immune systems of healthy humans (Gill et al., 2022). The randomised crossover dietary intervention study in 22 healthy participants revealed that a diet high in SCFAs led to a reduction in various circulating immune cells including B cells, $CD8^+$ T cells and Th1 cells, when compared to a diet low in SCFAs (Gill et al., 2022). Taken together, this suggests that SCFAs remain a likely avenue to regulate an over-active immune system during hypertension.

Many mechanisms that drive the BP-lowering effects of SCFAs have been proposed, but the specific mechanisms responsible for gut-to-host communication remain unclear. Given the differential effects SCFAs have on various inflammatory pathways in many different cell populations, the immune system is likely a key player. For example, butyrate increases the number of colonic Treg cells via the SCFA receptor GPR109a (Singh et al., 2014). Furthermore, GPR109a signaling is required for T cell differentiation as well as IL-10 and IL-6 production (Singh et al., 2014). Other immune cells such as neutrophils, B cells and others, have also been reported to be influenced by SCFAs (Li et al., 2021).

SCFAs can reduce NLRP3 inflammasome activation in astrocytes, as well as in vascular endothelial cells (Gao et al., 2022; Yuan et al., 2018). However, the reverse is true in colonic epithelial cells, where SCFAs induced inflammasome activation via GPR43, contradicting their direct effects on immune cells (Macia et al., 2015). Pathogen recognition receptors, such as toll-like receptor 5 (TLR5), are also influenced by SCFAs. Ex-vivo stimulation of colonic epithelial cells with butyrate and the TLR5 agonist flagellin resulted in increased production of IL-10 and TGF-β, and inhibition of TNF-α, IFN-γ and IL-6 (Ruan et al., 2022).

Other mechanisms by which SCFAs influence the immune system include by regulation of local pH. SCFAs produced in the colon lower the luminal pH (Xie et al., 2022). This can influence the cytokine profiles of immune cells such as macrophages and T cells (Erra Díaz et al., 2018; Xie et al., 2023). Immune cells and epithelial cells that line the colon can detect changes in the pH by pH-sensing receptors such as GPR65 and GPR68, reviewed in detail here (Xie et al., 2023). Our group is actively studying the role of these receptors and their link to hypertension (Xie et al., 2022).

Epithelial cells lining the gastrointestinal tract form the barrier between the host and the lumina content of the gastrointestinal tract, reviewed by Snelson et al. (2024). There is bidirectional communication

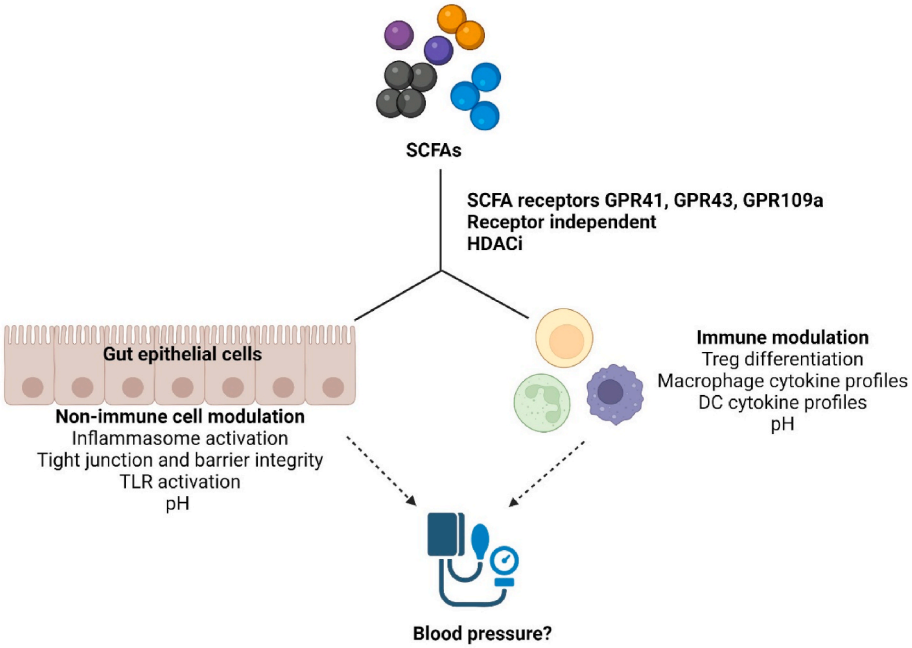

Fig. 2. Targeting short-chain fatty acids (SCFA) and their downstream signaling pathways to reduce blood pressure via immune modulation. SCFAs produced by the gut microbiota can be detected by the host through SCFA receptors G-protein coupled receptor (GPR) 41, GPR43, GPR109a. Alternatively, SCFAs such as butyrate can act as histone deacetylase inhibitors (HDACi). Other receptor independent pathways for SCFAs also exist. How SCFAs can affect blood pressure is unclear but may involve both immune and non-immune cell modulation. In the gut epithelial cells, SCFAs and their signaling can affect inflammasome activation, tight junction and barrier integrity, toll-like receptor (TLR) activation, and tissue pH. In the immune compartment, SCFAs influence immune cell differentiation and cytokine profiles of immune cells including T regulatory cells (Treg) and dendritic cells (DC). Created with BioRender.com.

between the microbiota and its metabolites, and the host, which is mediated by the epithelial cells (Snelson et al., 2024). Goblet cells can produce mucus and other chemicals required to maintain the barrier between the luminal content and the host, and together with epithelial cells, produce cytokines and chemokines necessary for immune activation (Snelson et al., 2024). As previously described in this review, SCFAs can regulate inflammation in non-immune cells, such as inflammasome activation in colonocytes (Macia et al., 2015). SCFAs can also influence tight junction protein expression to enhance gut barrier integrity (Okumura and Takeda, 2017). In experimental hypertension, there is emerging evidence that increased gut barrier permeability may occur in the hypertensive state, while robust human data is still lacking (Snelson et al., 2024).

Mechanistically, how increased gut permeability could affect the immune system to promote hypertension is still being examined. One possibility is the translocation of bacteria or bacterial components, such as LPS through the leaky gut, which triggers TLR4-signaling and inflammation. Indeed, one study showed that GPR41/GPR43 double knockout mice, which have elevated BP in Ang II-induced hypertension compared to controls, also have decreased gut barrier integrity and renal inflammation (Muralitharan et al., 2023). This increased BP and renal inflammation was reduced by blocking LPS-signaling with a TLR4 antagonist, suggesting that the translocation of bacteria or bacterial components across the epithelial barrier promotes renal inflammation and hypertension (Muralitharan et al., 2023). Indeed, TLR4 signaling has long been implicated in a role in hypertension. Blocking TLR4 signaling with an anti-TLR4 antibody lowered BP in SHRs (Bomfim et al., 2012). While TLR4 knockout mice were not protected from Ang II-induced hypertension, they were protected from cardiac hypertrophy (Singh et al., 2019). This highlights the potential for targeting gut barrier integrity to dampen inflammation for the treatment of hypertension and is a possibility that requires further exploration.

4.2. Sodium

A diet high in sodium/salt increases BP (Ha, 2014). While adherence to dietary guidelines or using potassium-enriched salt would improve BP control (Gupta et al., 2023; Stamler et al., 2018), this is complicated by several factors, such as the addition of salt in processed and ready-to-eat food. As such, the mechanisms driving salt-induced hypertension are still relevant as a target to treat hypertension.

A high salt diet leads to increased inflammation and pre-disposes cells to a pro-inflammatory state (Jorg et al., 2016; Yi et al., 2015; Zhang et al., 2015). For example, a high salt diet promotes the activation of classical macrophages (Jantsch et al., 2015). Similarly, sodium can suppress the activation of M2 macrophages, which have immunosuppressive and wound-healing functions (Binger et al., 2015). Sodium can also directly impact T cell function independently of antigen presenting cells (Hernandez et al., 2015; Kleinewietfeld et al., 2013; Wu et al., 2013). Specifically, sodium can reduce Treg suppressive function through increased IFNγ production (Hernandez et al., 2015). Sodium also can promote the differentiation and activation of T_H17 cells (Kleinewietfeld et al., 2013; Wu et al., 2013). The impacts of sodium on T_H17 cells via the gut microbiome are discussed below.

During hypertension, DCs are hyper-activated, producing elevated levels of inflammatory cytokines, leading to the subsequent activation of T cells (Fig. 3) (Kirabo et al., 2014). This is enhanced with high sodium intake, which exacerbates the accumulation of isolevuglandin (IsoLGs) in DCs in hypertensive mice (Barbaro et al., 2017; Ferguson et al., 2019). IsoLG accumulation by DCs leads to enhanced activation and increased production of pro-inflammatory cytokines IL-1β and IL-6 (Kirabo et al., 2014), particularly during hypertension (Barbaro et al., 2017). DCs can present IsoLGs as neoantigens to CD4 and CD8 T cells, leading to T cell expansion and increased levels of IFNγ and IL-17A in hypertensive mice (Barbaro et al., 2017; Ferguson et al., 2019). A similar effect was observed in monocytes, which also accumulated IsoLGs, leading to

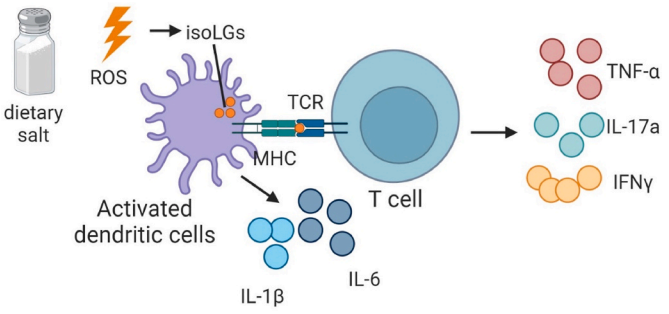

Fig. 3. Dietary salt intake leads to immune cell activation through isoLG formation. An increase in reactive oxygen species (ROS) production due to dietary salt intake results in the production of isoLGs, consequently leading to the production of pro-inflammatory cytokines IL-1β and IL-6 in dendritic cells and other antigen presenting cells. In addition, these activated cells can present isoLG to T-cells, leading to activation, proliferation, and the production of inflammatory cytokines such as TNF-α, IL-17a, and IFNγ. Created with BioRender.com.

increased production of IL-6, TNF-α and IL-1β and subsequent T cell activation (Ruggeri Barbaro et al., 2021).

The causative effects of DCs were highlighted using DC adoptive transfer experiments. Mice treated with a hypertensive stimulus had elevated BP after having received DCs from hypertensive mice, compared to DCs from control mice (Kirabo et al., 2014). Importantly, this effect was blocked by the IsoLG scavenger 2-hydroxybenzylamin (2-HOBA) (Kirabo et al., 2014). Targeting IsoLGs may have the additional benefit of ameliorating cardiac dysfunction (Ngwenyama et al., 2021). While most of the evidence for a role for IsoLGs in hypertension is in mice models, IsoLGs also accumulate in people with a high salt diet, leading higher IsoLGs in the colon (Ferguson et al., 2019).

The primary organ for sodium absorption in the body is the large intestine. As well as driving immune activation, a high salt diet leads to changes to the gut microbiota in both mice and humans (Ferguson et al., 2019; Wilck et al., 2017). Specifically, a high salt diet reduced *Lactobacillus* sp, which can alleviate salt-sensitive hypertension by dampening T_H17 responses (Wilck et al., 2017). Additionally, a fecal transplant from high salt-fed mice into germ-free mice resulted in elevated BP and inflammation after low-dose Ang II treatment, evidenced by elevated serum cytokines (Ferguson et al., 2019). This indicates that the gut microbiota plays a vital role in the inflammation induced by a high salt diet and may, therefore, be an ideal therapeutic intervention to target the immune system in hypertension.

5. Key considerations in developing new immune-modulating treatments

The immune system is a critical component in the development of hypertension. A key approach for the development of new treatments for hypertension is that the underlying causes of immune activation in hypertension should be targeted instead of treating the symptoms. For this to be achieved, we must have a greater understanding of what triggers immune system activation in hypertension. Furthermore, it must be determined whether lowering BP or BP-induced end-organ damage is the primary target. In patients with resistant hypertension or other co-morbidities, perhaps the way forward is focusing on lowering end-organ damage, for example.

A personalised multi-omics approach that encompasses medicine, nutrition, microbiome and other -omics approaches may need to be further developed to better understand how to treat specific subsets of patients. A one-size-fits-all approach will not suffice. Stratifying patients into different sub-groups according to the cause of hypertension or relevant biomarkers will also be key. When specifically targeting the immune system, the patient's sex, inflammation status and other co-

morbidities may be critical in choosing the appropriate medication. One example is the treatment of salt-sensitive hypertension - a group of hypertensive patients that have excessive responses to salt. These patients can be identified (Morimoto et al., 1997) and should be stratified to identify the most appropriate treatments. Another consideration is sex and menopause status. While premenopausal women generally have lower BP than age-matched men, women have more severe hypertension after menopause (Lima et al., 2012). The immune system contributes to this effect, and must be considered.

A consideration for developing new immune-targeting therapeutics for hypertension is that medication would be taken long-term. Suppressing the immune system may result in a decrease in CV events, as shown in the CANTOS trial; however, it could lead to increased rates of infection or other non-communicable diseases where the immune system plays an important role, such as cancer. Therefore, we must ensure specific immune targets that will not drive long-term immunosuppression. A potential treatment option for this salt-sensitive hypertension without inducing immunosuppression is to target isoLGs. A high salt diet leads to the accumulation of isoLGs in salt-sensitive hypertensive patients, which promotes IL-1β production. Therefore, targeting isoLGs may be a specific way to target excessive inflammation and lower IL-1β production without the potential side effects of blocking IL-1β of increased infection events.

Another novel way to target the immune system is through the gut microbiome. For example, it will be important to identify which patients would respond to dietary fibre and SCFAs, and other food-based interventions that lower BP.

6. Conclusion

To effectively lower hypertension rates globally, new treatments are urgently required. Dampening immune system activation and inflammation in targeted patient groups may be an effective way to control BP. A greater understanding of how the immune system is triggered in different patient subgroups is required to facilitate a personalised medicine approach, which may be needed to determine which treatment would likely yield the best results.

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CRediT authorship contribution statement

Rikeish R Muralitharan: Writing – review & editing, Writing – original draft. **Francine Z. Marques:** Writing – review & editing. **Joanne A. O'Donnell:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

None to declare.

Data availability

No data was used for the research described in the article.

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