

Hypersensitive or hypertensive? IgE–FcεR1 signalling in mast cells adds a new piece to the immunity and hypertension puzzle

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The joy from eating does not come from the exclusivity of the food but instead from the sensitivity that we eat it with (Nino Gruettke). Just like allergic reactions, blood pressure can increase or decrease depending on what we eat, and this can vary from individual to individual. For example, excess dietary salt increases blood pressure, leading to increased cardiovascular risk, and salt-sensitive people are particularly vulnerable. Hypertension remains the leading cause of cardiovascular morbidity and mortality despite aggressive and widespread use of blood pressure-lowering medications.¹ One of the biggest challenges is the residual cardiovascular risk in patients treated with antihypertensive medications.² Moreover, up to 15% of patients with hypertension are treatment-resistant³ and cannot reach adequate blood pressure control with the available treatment options, representing a major unmet need to better understand and treat hypertension.

Research in the last decade has demonstrated that inflammation is a key player in the development of hypertension, and both innate and adaptive immunity have been implicated. Ample evidence has shown that T cells infiltrate the perivascular space and the kidney, leading to cytokine release and subsequent endothelial and renal injuries that mediate end-organ damage in hypertension.⁴ Immune cells that have been implicated in the genesis of hypertension include dendritic cells, macrophages, other myeloid cells, and B and T lymphocytes.^{5–7} However, much remains to be learned on the precise roles of each component of the immune system within close liaison between inflammation and hypertension. Emerging evidence suggests a role of allergic immune signalling in hypertension. We recently discovered the role of eosinophils and eosinophil marker interleukin-5 in hypertension.⁸ People with allergic conditions, such as asthma and allergic rhinitis, have higher blood pressure and prevalence of hypertension.⁹ However, the precise mechanisms contributing to hypertension in allergy are not fully understood.

In this issue of *Cardiovascular Research*, Wang et al. discovered an important role of mast cells and immunoglobulin E (IgE), the major mediators of allergic reactions, in the genesis of hypertension.¹⁰ In rigorously designed mechanistic studies, the authors investigated whether the interaction of IgE with its high-affinity receptor, Fcε receptors 1 (FcεR1), can modulate blood pressure responses to hypertensive stimuli such as angiotensin II, DOCA, and high salt. They identified a new pathway in which IgE-induced FcεR1 signalling activates mast cells and up-regulates interleukin 6 (IL-6) production, resulting in high blood pressure through endothelial dysfunction.

First, Wang et al. found a significant correlation between serum IgE levels and hypertension in 553 people with hypertension that are not under treatment, when compared to 320 controls. Similarly, angiotensin II infusion induced accumulation of IgE and increased binding of IgE to FcεR1 in aortic adventitia of mice. Treatment with anti-IgE monoclonal antibody or IgE antagonist omalizumab attenuated the angiotensin II-induced elevation in blood pressure compared to littermates treated with IgG1 as a control. IgE blockage also prevented the angiotensin II-induced increase in arterial media thickness and collagen deposition in the aortic adventitia. Second, using global and conditional cell-specific FcεR1 deletion in mast cells, endothelial cells, and vascular smooth muscle cells, the authors demonstrated that IgE-mediated hypertension was mainly driven by FcεR1 action in mast cells. While the baseline blood pressures of wild and global FcεR1 knockout mice were similar, global FcεR1 knockout mice were protected from angiotensin II and DOCA/salt-induced hypertension and arterial remodelling. The same phenomenon was observed in mast cell-specific but not smooth muscle- or endothelial-specific FcεR1-depleted mice. Interestingly, FcεR1 action in mast cells was found to regulate endothelium-dependent vascular relaxation, as these mice were protected from angiotensin II-induced impairment in acetylcholine-mediated vasodilatation.

The study also demonstrated a crucial role of IL-6 expression in IgE-mediated hypertension (Figure 1). In transcriptome analysis, a marked increase in IL-6 expression was noted in IgE-treated mouse primary bone marrow mast cells *ex vivo*. This observation was confirmed *in vivo*, indicating increased serum IL-6 levels in hypertensive

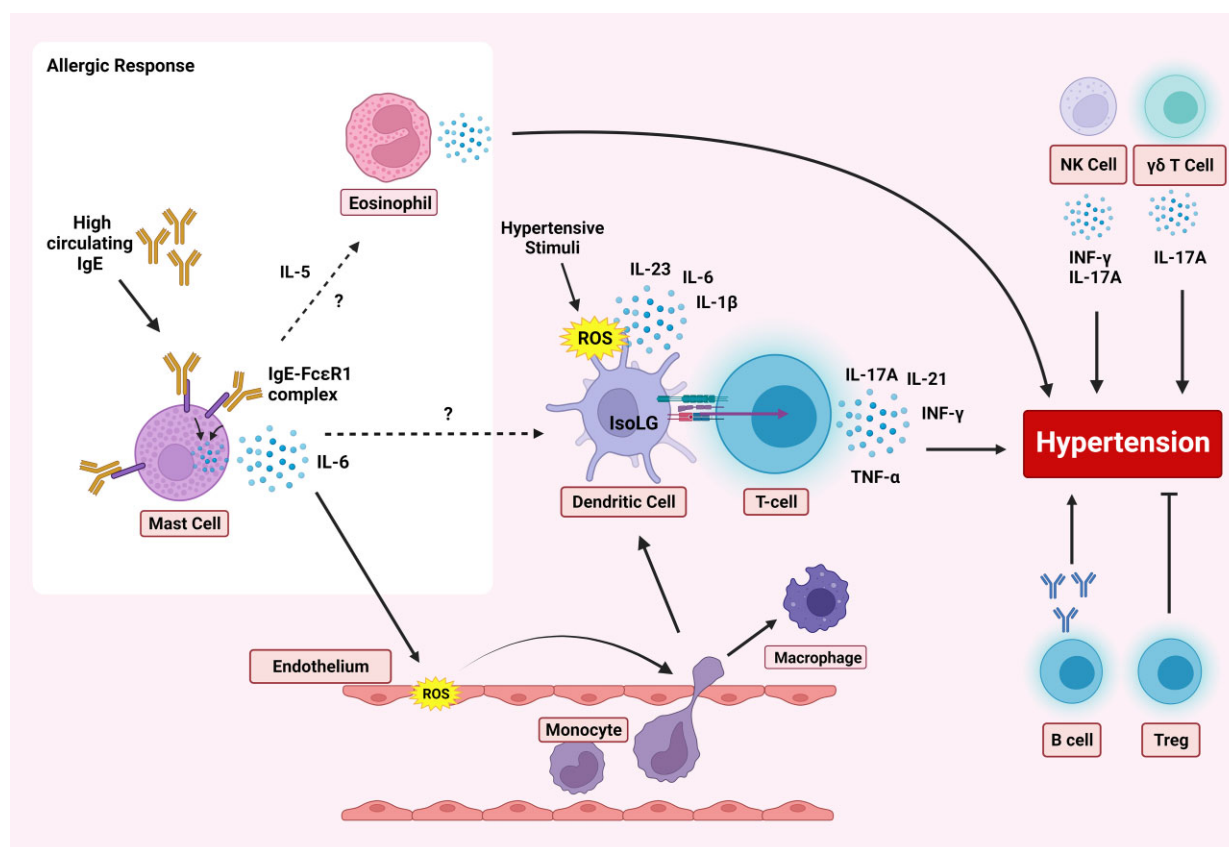


Figure 1 Role of mast cell IgE–FcεR1 signalling in hypertension. Hypertension is associated with high levels of circulating IgE. Binding of IgE to its high-affinity receptor FcεR1 activates mast cells and triggers the production of IL-6. In turn, IL-6 promotes ROS production and decreases p-eNOS in endothelial cells, leading to endothelial dysfunction and vascular remodelling seen in hypertension. Other immune cells activated by various hypertensive stimuli secrete cytokines that induce or inhibit hypertensive response and hypertension-associated end-organ damage.⁷ Oxidative stress in the endothelium has been shown to promote monocyte adhesion and subsequent transmigration. Hypertensive stimuli lead to the production of isolevuglandins in monocyte-derived dendritic cells, which in turn activates T cells and leads to hypertension. Figure created with Biorender.com.

mice. Furthermore, this effect was markedly attenuated in omalizumab-treated and mast cell-specific FcεR1-ablated mice, suggesting that IgE-induced FcεR1 activation was a critical step in IL-6 release. The authors found that IL-6 acts to increase the production of reactive oxygen species (ROS), which in turn promotes endothelial dysfunction in IgE-induced hypertension. In *ex vivo* experiments, they found that ROS production was significantly increased in human aortic endothelial cells when cultured in conditioned medium from human mast cells treated with IgEs. The increase in ROS production and markers of endothelial dysfunction, such as decreased levels of phosphorylated endothelial nitric oxide synthase (p-eNOS), was largely attenuated when the mast cells were treated with anti-IL-6 monoclonal antibodies along with IgEs. Consistent with these *ex vivo* observations, FcεR1 knockout or anti-IgE mAb-treated mice were protected from Ang-II-induced increase in ROS accumulation in the aorta.

These findings open new perspectives for the future of hypertension research and suggest that targeting IgE-mediated pathways in mast cells may help regulate blood pressure and potentially modulate hypertension-associated vascular dysfunction and end-organ damage. However, there are some limitations that need to be put into consideration when interpreting these findings. One concern is that hypertensive patients were enrolled according to the criteria of systolic blood

pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. The new guidelines, according to the American Heart Association and American College of Cardiology, recommend systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg as hypertensive. Another pressing question is that omalizumab is currently being used as a second-line agent for asthma and urticaria, predominantly in the young population, and no study to date has reported any effects on blood pressure. Despite these limitations, Wang's observations, for the first time, introduce omalizumab- and other IgE-targeted therapies currently under investigation, such as ligelizumab, as potential therapeutic options for patients with hypertension. These and other recent findings regarding the role of immunity in blood pressure regulation enlighten the molecular pathogenesis of hypertension that will guide future investigations for new potential therapeutics.

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