IgE and TGF-β Signaling: From Immune to Cardiac Remodeling

Abstract: Cardiac remodeling is accompanied by cardiac hypertrophy, fibrosis, and dysfunction, eventually leading to heart failure (HF). However, the molecular mechanisms involved in cardiac remodeling are complicated, especially the association with immune. Immunoglobulin E (IgE) is a class of immunoglobulins involved in immune response to specific allergens. Recently, Zhao et al characterized a novel specific role of IgE and its high affinity receptor (FcεR1) in directly promoting pathological myocardial remodeling and cardiac dysfunction. Additionally, upon blocking IgE-FcεR1 signaling using FcεR1 genetic depletion or by administering the anti-IgE monoclonal antibody omalizumab (Oma) in mice, they observed that cardiac hypertrophy and cardiac interstitial fibrosis induced by angiotensin II (Ang II) or transverse aortic constriction (TAC) were significantly suppressed. In contrast, IgE administration alone can aggravate pathological cardiac remodeling and dysfunction. RNA-seq and downstream analysis indicated that TGF-β was the common pathway and the most pivotal mediator in IgE-FcεR1-induced cardiac remodeling and dysfunction. Furthermore, the administration of a TGF-β inhibitor could ameliorate cardiac remodeling and improve cardiac function. Therefore, these findings suggest that IgE-FcεR1 maybe promising therapeutic targets for cardiac remodeling and provide an experimental basis for the use of omalizumab for HF patients combined with high serum IgE levels or allergic diseases.

Keywords: cardiac remodeling, IgE-FcεR1, immunoglobulins, TGF-β

Pathological cardiac remodeling is an adaptive response to cardiac stress, accompanied by myocardial hypertrophy, interstitial fibrosis, cell death, cardiac dysfunction, and eventually leading to heart failure (HF). Immunoglobulins, as major host proteins in plasma, function as anti-bacterial and anti-viral agents by strengthening cell phagocytosis. Immunoglobulin E (IgE) is a class of immunoglobulins involved in immune response to specific allergens. They play a central role in the development and manifestation of allergic reactions. Functionally, allergen-induced crosslinking of FcεR1-bound IgE activates basophils and mast cells, followed by degranulation. The degranulation of basophils and mast cells results in the liberation of proinflammatory and vasoactive mediators, inducing classical symptoms of an allergic reaction. Allergic diseases, including immediate hypersensitivity reactions, anaphylaxis, allergic asthma, atopic dermatitis, chronic spontaneous urticaria (CSU), etc. are primarily mediated by the IgE-FcεR1 signaling pathway. A previous study indicated that total serum IgE levels before anti-IgE antibodies intervention correlate negatively with the time-to-relapse in patients with CSU, which is consistent with the pathological molecular mechanism of the IgE-FcεR1 signaling path.
pathway. However, IgE-FcεR1 also critically contributes to host defense against parasites and venoms.\textsuperscript{7}

Although much focus regarding the biological properties of IgE is centered around immune response to specific allergens, increasing evidence has uncovered unexpected pathological roles of IgE in the cardiovascular system. A population-based cohort study suggested that the elevation of serum IgE levels may be a risk factor for increased cardiovascular mortality.\textsuperscript{8} Existing literature also revealed that IgE and the FcεR1α were present in human atherosclerotic lesions, which are localized particularly in macrophage-rich areas. IgE deficiency in ApoE\textsuperscript{−/−} mice reduced atherosclerosis by decreasing the lesion macrophage content and inflammation.\textsuperscript{9} In addition, blocking the IgE-FcεR1 axis reduced inflammation and apoptosis both in atherosclerotic plaques and abdominal aortic aneurysms (AAAs).\textsuperscript{9,10} However, whether IgE-FcεR1 signaling is involved in cardiac remodeling remains elusive.

A recent study in Circulation by Zhao et al identifies IgE as a novel promoter of cardiac remodeling in mice and humans, which functions in an IgE-FcεR1-dependent manner.\textsuperscript{11} Statistical analysis of 4671 participants from the National Health and Nutrition Examination Survey (NHANES) showed a strong positive relationship between serum IgE and NT-pro BNP in HF patients. In concordance with the HF patients, high serum IgE levels and cardiac FcεR1 expression were observed in mice subjected to transverse aortic constriction (TAC) or angiotensin II (Ang II). In addition, upon blocking IgE-FcεR1 signaling using FcεR1 genetic depletion or administrating the anti-IgE monoclonal antibody omalizumab (Oma) in mice, cardiac hypertrophy and cardiac interstitial fibrosis induced by Ang II or TAC were significantly suppressed. In contrast, IgE administration alone can aggravate pathological cardiac remodeling and dysfunction. Moreover, chimeric mice generated by bone marrow transplantation (BMT) demonstrated that the effect of IgE on Ang II-induced cardiac remodeling was not mediated by bone marrow-derived cells. To further determine whether IgE can directly function in cardiomyocytes (CMs) and cardiac fibroblasts (CFs), they first verified that FcεR1 was expressed in CMs and CFs. In addition, IgE-induced hypertrophy, CFs activation and matrix protein production were remarkably alleviated by FcεR1 knockdown. All above suggested that IgE directly promoted cardiac remodeling in an FcεR1-dependent manner in CMs and CFs.

To explore the potential mechanisms of the IgE-FcεR1 axis, RNA-seq was performed on both CMs and CFs treated with or without IgE. The transcriptomes profiling showed reduced expression of TGF-β and its downstream signaling molecules, including PI3K, AKT, pSmad1/5/9, and pSmad2/3, in the hearts of FcεR1-KO mice compared to WT mice after Ang II infusion. Similar effects were demonstrated in omalizumab-treated mice. However, TGF-β inhibitor SB431542 significantly alleviated CM hypertrophy and CF activation induced by IgE treatment. In summary, TGF-β is likely to be the most pivotal mediator in IgE-FcεR1-induced cardiac remodeling and dysfunction (Figure 1).

As it often happens, this study opens a range of interesting questions. First, existing literature suggested that rituximab (RTX), an antibody against CD20, can reverse cardiac remodeling and improve cardiac function through inhibiting Th2 cytokine-mediated IgG production from B cells.\textsuperscript{12} A marked increase in B cell accumulation in vasculature was observed in Zhao’s work, which may account for the elevation of serum IgE. As we known, IgE is the prototypical antibody class produced during type 2 immune responses, which are induced during tissue remodeling.\textsuperscript{13–15} Although the role of IgE in promoting cardiac remodeling has been just reported, whether there is an increased level of IgG with the accumulation of B cells and how it functions during this process remains to be clarified. Second, can...
elevated IgE, locally and in circulation, influence the cardiac microenvironment or activate other cardiac resident cells, such as endothelial cells and macrophages? What’s the contributions during the development of cardiac remodeling? Finally, regarding the specific mechanisms underlying cardiac cells hypertrophy and cardiac fibroblast activation, Zhao et al have demonstrated the crucial role of TGF-β signaling in this process. However, bioinformatic analyses show that other pathways, such as the β-AR signaling pathway, chemokine-related pathway, and cytokine-mediated inflammation, are also significantly changed in this process. According to the reports describing cross-talk and mutual regulation between β-AR and TGF-β signaling, we wonder that whether β-AR contributes to TGF-β activation and regulates cardiac hypertrophy via activation of the cAMP-PKA pathway in cardiomyocytes? Additionally, previous studies have suggested that FcεR2, the low affinity IgE receptor, may contribute to the production of chemokines, that have also been shown to function directly in cardiac remodeling. Therefore, we speculate that elevated IgE induces the expression of FcεR2 in cardiomyocytes and then activates the chemokine-related pathway. The expression of FcεR2 in cardiomyocytes and its contact with chemokine-related pathway are worth being discussing. Nevertheless, further study should be conducted to address the issues mentioned above and identify more effective therapeutic targets for HF.

In summary, Zhao et al demonstrate the potential implication of high serum IgE to pathological cardiac remodeling. Targeting the IgE-FcεR1 axis via the activation of TGF-β signaling in the heart, which highlights how immunoglobulins affect cardiac functions other than inflammation and immunity. In addition, the application of omalizumab, a clinical IgE antagonist, provides important preclinical evidence for the treatment of HF patients combined with allergic reactions. A recent study by their team has verified that elevated serum IgE promotes pathological cardiac fibrosis by modulating miR-486a-5p and downstream factor Smad1. These findings have broadened our horizons for the upstream regulators of the IgE-FcεR1 signaling pathway. Although the specific mechanisms were not completely elucidated, the work of Zhao et al has further clarified the linkages between immunity and cardiac remodeling. To the best of our knowledge, this is the first study to elucidate the association between serum IgE levels and cardiac remodeling. Overall, IgE-FcεR1 may be promising novel therapeutic targets for the treatment of cardiac remodeling, with high translational potential, especially for patients with HF combined with high serum IgE levels or allergic diseases.

Funding
This work was supported by the National Natural Science Foundation of China (81900678) and the Natural Science Foundation of Hunan Province (2019JJS0555), the Open Project Program of Guangxi Key Laboratory of Centre of Diabetic Systems Medicine, Guilin Medical University (GKLCDSM-20200101-03), the Hunan Province Technology Innovation Guidance Program-Clinical Medical Technology Innovation Guidance Project (2018SK51603), and the Science Foundation of The Health and Family Planning Commission in Hunan Province of China (B2019122, No. 20201920).

Disclosure
The authors report no conflicts of interest in this work.

References
1. Nakamura M, Sadoshima J. Mechanisms of physiological and pathological cardiac hypertrophy. Nat Rev Cardiol. 2018;15(7):387–407. doi:10.1038/s41569-018-0007-y
2. Maurer M, Altichter S, Schmetzer O, Scheffel J, Church MK, Metz M. Immunoglobulin E-mediated autoimmunity. Front Immunol. 2018;9:689. doi:10.3389/fimmu.2018.00689
3. Tanaka S, Furuata K. Roles of IgE and histamine in mast cell maturation. Cells. 2021;10(8):2170. doi:10.3390/cells10082170
4. Gould HJ, Sutton BJ. IgE in allergy and asthma today. Nat Rev Immunol. 2008;8(3):205–217. doi:10.1038/nri2273
5. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. Nature. 2008;454(7203):445–454. doi:10.1038/nature07204
6. Ertas R, Ozuyurt K, Orzu E, et al. Increased IgE levels are linked to faster relapse in patients with omalizumab-discontinued chronic spontaneous urticaria. J Allergy Clin Immunol. 2017;140(6):1749–1751. doi:10.1016/j.jaci.2017.08.007
7. Balbino B, Conde E, Marichal T, Starkl P, Reber LL. Approaches to target IgE antibodies in allergic diseases. Pharmacol Ther. 2018;191:50–64. doi:10.1016/j.pharmthera.2018.05.015
8. Min KB, Min JY. Risk of cardiovascular mortality in relation to increased total serum IgE levels in older adults: a population-based cohort study. Int J Environ Res Public Health. 2019;16(22):4350. doi:10.3390/ijerph1624350
9. Zhang X, Li J, Luo S, et al. IgE contributes to atherosclerosis and obesity by affecting macrophage polarization, macrophage protein network, and foam cell formation. Arterioscler Thromb Vasc Biol. 2020;40(3):597–610. doi:10.1161/ATVBAHA.119.313744
10. Wang J, Lindholt JS, Sukhova GK, et al. IgE actions on CD4+ T cells, mast cells, and macrophages participate in the pathogenesis of experimental abdominal aortic aneurysms. EMBO Mol Med. 2014;6(7):952–969. doi:10.15252/emmm.201303811
11. Zhao H, Yang H, Geng C, et al. Role of IgE-FcεR1 in patho-
gical cardiac remodeling and dysfunction. Circulation. 2021;143
(10):1014–1030. doi:10.1161/circulationaha.120.047852
12. Ma XL, Lin QY, Wang L, Xie X, Zhang YL, Li HH. Rituximab
prevents and reverses cardiac remodeling by depressing B cell func-
tion in mice. Biomed Pharmacother. 2019;114:108804. doi:10.1016/j.
biopta.2019.108804
13. Starkl P, Watzenboeck ML, Popov LM, et al. IgE effector mechan-
isms, in concert with mast cells, contribute to acquired host defense
against staphylococcus aureus. Immunity. 2020;53(4):793–804.e9.
doi:10.1016/j.immuni.2020.08.002
14. Wei L. Immunological aspect of cardiac remodeling: T lymphocyte
subsets in inflammation-mediated cardiac fibrosis. Exp Mol Pathol.
2011;90(1):74–78. doi:10.1016/j.yexmp.2010.10.004
15. Yu Q, Horak K, Larson DF. Role of T lymphocytes in hypertension-induced
cardiac extracellular matrix remodeling. Hypertension. 2006;48(1):98–104.
doi:10.1161/01.HYP.0000227247.27111.b2
16. Leask A. Potential therapeutic targets for cardiac fibrosis: IGFbeta,
angiotensin, endothelin, CCN2, and PDGF, partners in fibroblast
activation. Circ Res. 2010;106(11):1675–1680. doi:10.1161/CIRCRESAHA.110.217737
17. Ando T, Kitaura J. Tuning IgE: IgE-associating molecules and their
effects on IgE-dependent mast cell reactions. Cells. 2021;10(7):1697.
doi:10.3390/cells10071697
18. Li Y, Zhang D, Kong L, et al. Aldolase promotes the development of
cardiac hypertrophy by targeting AMPK signaling. Exp Cell Res.
2018;370(1):78–86. doi:10.1016/j.yexcr.2018.06.009
19. Zhao H, Yang H, Geng C, et al. Elevated IgE promotes cardiac
fibrosis by suppressing miR-486a-5p. Theranostics. 2021;11
(15):7600–7615. doi:10.7150/thno.47845