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EDITORIAL COMMENT

Resolution of Heart Failure Inflammation*

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An appropriate immune response is crucial for protecting us against harmful stimuli, whereas a maladaptive immune response ultimately causes harm. The dysregulated chronic inflammation behind atherosclerosis and its cardiovascular consequences is largely caused by a failure in the resolution of inflammation. This leads to a persistent recruitment and activation of leukocyte subtypes, which fail to skew the immune response to adequate healing of the inflammatory site and for the re-establishment of cardiovascular homeostasis. The acute cardiovascular inflammation can also be maladaptive, as illustrated by immune activation in response to acute myocardial infarction and in myocarditis.

Specialized proresolving mediators (SPMs) transduce an active coordination toward the resolution of inflammation through ligation with G protein-coupled receptors (GPRs).[1] The ALX/FPR2 receptor is activated by the SPM lipoxin A_4 (LXA_4) derived from the omega-6 arachidonic acid and by resolvin D1 (RvD1) from the omega-3 docosahexaenoic acid.[1] Importantly, ALX/FPR2 transduces both proinflammatory responses when activated by, for example, formyl peptides and serum amyloid A in contrast to the proresolving responses transduced through ALX/FPR2 by LXA_4, RvD1, and annexin A1.[1] In addition to several ligands for the SPM GPRs, the SPMs are agonists at multiple GPRs. In the absence of ALX/FPR2, RvD1 transduces atheroprotection through GPR32,[2] reflecting the receptor-transduced resolution of atherosclerosis inflammation. This underlines that the SPM ligand biosynthesis and SPM receptor expression are crucial for the tip of the immune balance toward either inflammation or its resolution and illustrates the complexity of these pathways.

In this issue of *JACC: Basic to Translational Science*, Val-Blasco et al[3] show that the ALX/FPR2 receptor agonist BML-111 reduced cardiac immune cell infiltration in a murine autoimmune myocarditis model. This is in line with previous work showing that ALX/FPR2 is up-regulated during acute myocardial ischemia and limits myocardial necrosis and neutrophil granulocyte infiltration after experimental coronary obstruction.[1] By showing that ALX/FPR2 stimulation prevented myocarditis-induced left ventricular dysfunction, the observations in this issue introduce the notion of stimulating a resolution of inflammation by SPMs to improve cardiac function.[3]

Cardiomyocytes isolated from mice subjected to autoimmune myocarditis exhibited mishandling of intracellular Ca^{2+}, which was prevented by in vivo stimulation of ALX/FPR2 through treatment with BML-111. These observations may reflect the systemic response, characterized by a limitation of the myocardial immune cell infiltration and inhibition of oxidative stress. Importantly, 15-epi-LXA_4, which is a stable SPM ligand for ALX/FPR2, directly counteracted mishandling of intracellular Ca^{2+} in isolated cardiomyocytes by stopping a down-regulation of the Ca^{2+} channel SERCA2a through activation of NRF2.[3]

Val-Blasco et al[3] also present the translational implications by transcriptomic exploration of human cardiac samples. These results show the cardiac presence of the SPM biosynthesis enzymes and point to the ligand being crucial because the ALX/FPR2 receptor was not altered between healthy myocardium and cardiac tissue from individuals with myocarditis.

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In their study,[3] stimulating the resolution of inflammation through SPM signaling emerges as a therapeutic tool to prevent cardiac dysfunction and deleterious cardiac damage associated with myocarditis. COVID-19 as a trigger of myocarditis is an important issue at present. It, however, remains to be established how the results from a murine model of autoimmune myocarditis can be extrapolated to infectious agents. Myocardial injury frequently occurs in infection with, for example, SARS-CoV-2 and influenza virus (47.8% and 65.5%, respectively),[4] illustrating the failure of a resolution of myocardial inflammation. The higher mortality and long-term cardiac consequences of SARS-CoV-2[4] also implicate differential cardiac responses to myocarditis-triggering stimuli.

Another key question that sprouts from this study[3] is whether SPM signaling through ALX/FPR2 also can be used as a therapeutic tool to resolve heart failure. The Ca^{2+} transport by SERCA2a during the cardiac cycle is a fundament for cardiac function, and its dysregulation is a hallmark of heart failure. Because the study by Val-Blasco et al[3] indicates that the resolution of inflammation can directly improve Ca^{2+} handling in cardiomyocytes through ALX/FPR2, the notion of extrapolating the results to a resolution pharmacology to improve systolic function, regardless of the underlying pathogenesis, may open up novel therapeutic avenues for heart failure.

The importance of the lymphocyte response in myocarditis has been reinforced by murine studies identifying microRNA from $CD4^+$ and T helper type (Th) 17 cells, for which the human homologue distinguished patients with myocarditis from those with myocardial infarction.[5] D-resolvin signaling through GPR32 regulates adaptive immune circuits by preventing T-cell differentiation toward Th1 and Th17, as well as promoting the generation of regulatory T cells,[1] which warrant further exploration of how to optimize SPM responses in myocarditis for a beneficial immunomodulation.

In summary, SPM signaling through ALX/FPR2 emerges as a therapeutic target to improve cardiac function in myocarditis through a resolution of myocardial inflammation and direct improvement of cardiomyocyte function. The novel findings in this issue of *JACC: Basic to Translational Science* have important implications for COVID-19 and extend to a possible general applicability for a resolution of cardiac inflammation to open a resolution pharmacology avenue for the management of heart failure.

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