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EDITORIAL COMMENT

Eosinophils Confer Protection Following Myocardial Infarction*

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Innate and adaptive immune responses are increasingly recognized as important contributors to left ventricular (LV) remodeling, myocardial tissue repair, and heart failure progression. Components of the innate immune system, including neutrophils, monocytes, and macrophages, have garnered substantial attention and are the subject of extensive investigation by laboratories worldwide. A key message that has emerged from these studies is that incredible diversity exists among myeloid cell populations. For example, macrophages can be divided into distinct cell types with divergent functions, developmental origins, and repopulation dynamics (1). Even rare populations impart substantial impact on functional outcomes.

These findings have raised the possibility that less abundant immune cell populations may similarly influence LV remodeling and tissue repair. Mast cells, innate lymphoid cells, and eosinophils reside within the mouse and human heart and accumulate in the context of myocardial infarction or pressure overload. The role of mast cells and innate lymphoid cells has recently been explored. Masts cells release potent cytokines (tumor necrosis factor), peptides (renin), and enzymes (chymase, tryptase) that promote myocardial fibrosis, reduce cardiomyocyte contractility, and contribute to heart failure remodeling (2). The exact role of cardiac innate lymphoid cells, including NK cells and ILC2 cells, remains to be fully elucidated (3).

Eosinophils have been long appreciated to inhabit the human heart and to accumulate following myocardial injury. The presence of eosinophils in endomyocardial biopsies obtained from patients who underwent transplantation represents a classic hallmark of rejection. Eosinophilic myocarditis is a well-described clinical entity characterized by endocardial eosinophil accumulation, fibrosis, and thrombus formation. Little is understood regarding the role of eosinophils following myocardial infarction (MI) or in the context of chronic ischemic and nonischemic cardiomyopathies. Similar to mast cells, eosinophils release a broad array of mediators ranging from growth factors and cytokines to potent enzymes present within pre-formed granules. Thus, eosinophils cells have remarkable potential to affect myocardial remodeling and/or tissue repair through a variety of different mechanisms.

In this issue of *JACC: Basic to Translational Science*, Toor et al. (4) examined the role of eosinophils following acute MI. Previous observational studies reported conflicting associations between eosinophil abundance and clinical outcomes. Using a cohort of 732 patients, the investigators showed that blood eosinophil counts dropped following acute MI and further demonstrated that eosinophils accumulated within the infarct in autopsy specimens. The investigators similarly observed accumulation of eosinophils within the infarct of mice that underwent left coronary artery ligation. They noted that

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eosinophils were often located within epicardial regions and in adjacent pericardial adipose tissue. Based on a recent study that suggested that pericardial cavity macrophages might directly invade the myocardium following MI (5), the investigators suggested that pericardial adipose tissue could represent a potential source of these cells. Although this represents one possibility, future work will be required to delineate whether eosinophils originate from the bone marrow, spleen, and/or adjacent structures (e.g., pericardial adipose tissue).

Using complementary models of eosinophil deficiency and reconstitution, the investigators provided convincing evidence that eosinophils are protective and reduce LV remodeling following experimental MI. Genetic absence of eosinophils (δdblGATA4 mice) and acute pharmacological depletion of eosinophils (Siglec F antibody) resulted in larger infarct sizes, LV dilation, and reduced LV systolic function. Careful examination of collagen gene expression and collagen crosslinking indicated a role for eosinophils in collagen maturation. Loss of eosinophils did not affect initial infarct area or coronary angiogenesis. These findings were highly significant because of robust effect sizes, appropriate sample sizes, and use of 2 independent eosinophil depletion strategies in distinct genetic backgrounds with differing immune properties.

Eosinophils are known to elicit type 2 immune responses characterized by the production of cytokines (interleukin [IL]-4, IL-5, IL-10, IL-13) that support tissue repair and regeneration (6). Consistent with this concept, reduced expression of each of these cytokines was found in eosinophil deficient mice with contaminant increases in pro-inflammatory mediators (IL-18, CCL5, CXCL1, CXCL2). Consequently, eosinophil deficient mice displayed increased neutrophil and macrophage abundance within the infarct. Reconstitution of eosinophils via adoptive transfer was sufficient to correct cytokine levels.

Although the precise source of the preceding pro-inflammatory mediators was not evaluated in detail, a compelling hypothesis was that eosinophils communicate with cardiac macrophages or recruited monocytes and macrophages derived from the spleen and bone marrow. Increased production of pro-inflammatory mediators might indicate loss of a key anti-inflammatory signal that controls the behavior or fate of cardiac monocytes and macrophages. Consistent with this possibility, characterization of macrophages within the infarct of eosinophil-deficient mice demonstrated reduced expression of CD206 and Retnla mRNA, which are transcripts associated with reparative macrophage phenotypes.

Among the cytokines produced by eosinophils, IL-4 has a clear and obvious potential to influence macrophage behavior and fate specification. By using a long-acting IL-4 agonist construct that consisted of recombinant IL-4 complexed to an anti-IL4 antibody, the investigators provides evidence that exogenous IL-4 signaling is sufficient to rescue the impact of genetic eosinophil deficiency following MI. Although these data are provocative, they are not conclusive, because the IL-4 agonist complex may signal in aberrant and unexpected ways. Adoptive transfer of IL-4$^{-/-}$ eosinophils would have been a more ideal and rigorous experimental approach. Nonetheless, the findings by Toor et al. (4) suggested that IL-4 signaling might represent the key signal by which eosinophils communicate with resident macrophages and/or infiltrating monocyte-derived macrophages.

In addition to cytokines, eosinophils store and release numerous substances compartmentalized within the cytoplasmic granule. Examples include potent proteases, cationic proteins, hydroxylases, peroxidases, lipid mediators, and vasoactive peptides. Whether release of these substances influences inflammation and LV remodeling following MI is not currently understood. Similarly, it is unclear whether release of these substances is regulated independently of type 2 cytokines. Finally, little is yet known regarding diversity among tissue eosinophils. It is possible that distinct eosinophil subtypes may exist with specialized function analogous to tissue resident and recruited macrophages. This and other related studies will likely provide the necessary motivation to address these important questions.

In conclusion, Toor et al. (4) provided an informative and interesting study that established a protective role for eosinophils in LV remodeling following MI. The investigators defined a potential mechanism of benefit and suggested that modulation of eosinophil cytokine expression favoring IL-4 might be a target for therapeutic intervention. The underlying mechanisms by which eosinophils are activated in this beneficial capacity will undoubtedly be the subject of future investigations.

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REFERENCES

1. Lavine KJ, Pinto AR, Epelman S, et al. The macrophage in cardiac homeostasis and disease: JACC Macrophage in CVD Series (Part 4). J Am Coll Cardiol 2018;72:2213–30.

2. Zhang W, Chancey AL, Tzeng HP, et al. The development of myocardial fibrosis in transgenic mice with targeted overexpression of tumor necrosis factor requires mast cell-fibroblast interactions. Circulation 2011;124:2106–16.

3. Bracamonte-Baran W, Chen G, Hou X, et al. Non-cytotoxic cardiac innate lymphoid cells are a resident and quiescent type 2-commited population. Front Immunol 2019;10:634.

4. Toor IS, Rückerl D, Mair I, et al. Eosinophil deficiency promotes aberrant repair and adverse remodelling following acute myocardial infarction. J Am Coll Cardiol Basic Trans Science 2020;5:665–81.

5. Deniset JF, Belke D, Lee WY, et al. Gata6(+) pericardial cavity macrophages relocate to the injured heart and prevent cardiac fibrosis. Immunity 2019;51:131–40.e5.

6. Xu JY, Xiong YY, Lu XT, Yang YJ. Regulation of type 2 immunity in myocardial infarction. Front Immunol 2019;10:62.

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