Interleukin-10 stiffens the heart

Cardiac-resident macrophages are a diverse population of cells that have a critical role in the pathogenesis of heart failure. A new understanding of communication between macrophages and cardiac fibroblasts could lead to novel therapeutic strategies for heart failure with preserved ejection function.

Insight from Daniela Cihakova

In this issue of JEM, Hulsmans et al. demonstrate that cardiac-resident MHC II^{high} macrophages have a pathogenic role in heart failure with preserved ejection fraction (HFpEF) through their IL-10 production. The profibrotic effect of IL-10 autocrine loop promotes macrophages to secret osteopontin (OPN) and TGFβ. These mediators activate cardiac fibroblasts to produce collagen that results in cardiac fibrosis and increased cardiac stiffness.

An estimated 8.5 million Americans will have heart failure (HF) by 2030, and nearly half of them will have HFpEF (Borlaug, 2014). The impaired cardiac performance in HFpEF is a consequence of an increased left ventricular filling pressure caused by diastolic dysfunction. HFpEF is a life-threatening clinical problem with a paucity of therapies. General inflammatory markers are increased in HFpEF, indicating the presence of systemic inflammation. It has been shown before that the number of cardiac macrophages increases after a cardiac injury, such as myocardial infarction or myocarditis. In addition, myeloid cells play a pathogenic role in cardiac remodeling and heart failure (Baldeviano et al., 2010; Heidt et al., 2014). Hulsmans et al. (2018) is the first study to examine how cardiac macrophages contribute to the pathogenesis of HFpEF.

Hulsmans et al. (2018) examined two murine models of HFpEF, as well as people with the disease. The first model induces hypertension by combining salty drinking water, unilateral nephrectomy, and chronic exposure to aldosterone (SAUNA). The majority of patients with HFpEF have hypertension (Valero-Muñoz et al., 2016). The second model utilizes physiologically aged mice with impaired diastolic function. A majority of people with HFpEF are more than 60 yr old, and the pathology of HFpEF resembles changes that appear during normal cardiac aging (Borlaug, 2014). Hulsmans et al. (2018) found that the number of macrophages in the heart increased in both models and in hearts of people with HFpEF. This increase in the number of cardiac macrophages was accompanied by an increase in myelopoiesis and in the number of blood monocytes migrating through CCR2 to the heart with HFpEF. The authors observed that cardiac macrophages are predominantly MHCII^{high} and have increased IL-10 production compared with macrophages in a healthy heart. IL-10 is a cytokine produced by many leukocytes and stroma cells. It is important because of its antiinflammatory activity but also has profibrotic potential. Specific deletion of IL-10 from macrophages and monocytes using CX3CR1 Cre crossed to IL-10 floxed mice resulted in improvement of diastolic function with reduced left ventricular end-diastolic pressure and improved diastolic relaxation. IL-10 was deleted from all monocytes/macrophages because there is no specific cardiac macrophage marker that could be used for a targeted deletion. An interesting twist is that IL-10 does not directly act on cardiac fibroblasts, which lack the needed receptors, but has an autocrine effect on cardiac macrophages and induced their profibrotic phenotype. The IL-10–induced profibrotic macrophages activate the proliferation of myofibroblasts and production of collagen, which then leads to fibrosis-mediated cardiac stiffness. One of the mediators in this interaction between macrophages and fibroblasts was identified as OPN. The production of OPN was induced by IL-10 in macrophages by an autocrine manner (see figure, part A). The IL-10 induction of OPN as paracrine activator of cardiac fibroblasts was confirmed by in vitro co-culture of fibroblasts and macrophages. Similarly, macrophage-derived TGFβ can also activate cardiac fibroblast. IL-10–deficient SAUNA mice had an increased proportion of MHCII^{low} macrophages in their hearts. MHCII^{low} macrophages had higher protease and metalloproteinase (MMP) activity, as well as decreased expression of OPN and TGFβ (see figure, part B). The IL-10 pathogenic effect in HFpEF is especially interesting in light of a report of IL-10 antiinflammatory action on macrophages in various organs such as intestines (Ip et al., 2017).

Healthy adult heart contains mostly embryonically derived macrophages and a smaller pool of macrophages replenished from blood monocytes (Epelman et al., 2014). Cardiac-resident macrophages expand by in situ proliferation and by recruitment of blood monocytes in homeostasis; however, after injury, the uptake of monocytes from blood is the main mechanism of increasing the number of macrophages in the heart (Leuschner et al., 2012). Cardiac-resident macrophages are remarkably diverse. They are defined as CD45^{+} cells expressing CD11b and F4/80 and CD64. Epelman et al. (2014) showed that four

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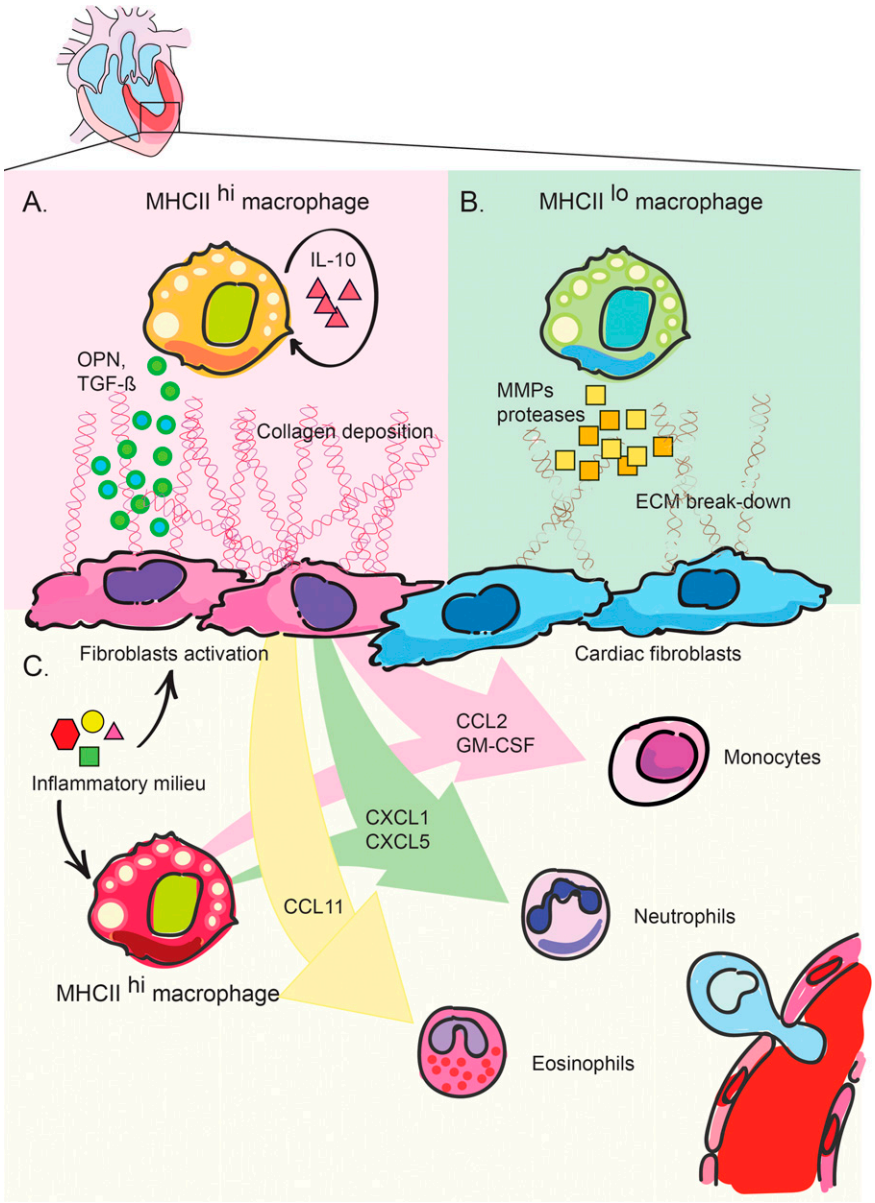
types of macrophages can be found in the healthy heart based on expression of CCR2, MHCII, and Ly6C. These categories replaced previously used M1/M2 phenotypes because cardiac-resident macrophages are exposed to many different stimuli in a complex tissue environment and therefore do not fit well the in vitro defined M1/M2 phenotypes. Hulsmans et al. (2018) identify MHCII^{high} macrophages as the source of IL-10 active in autocrine loop and the main producers of OPN and TGFβ. Their function is mostly profibrotic and possibly proinflammatory. MHCII^{low} might favor matrix breakdown.



(A) MHCII^{high} cardiac-resident macrophage–derived IL-10 induces autocrine macrophage differentiation toward a profibrotic phenotype. Profibrotic macrophages produce OPN. OPN activates cardiac fibroblasts to promote collagen deposition, which results in fibrosis and increased cardiac stiffness. (B) MHCII^{low} macrophages contribute to extracellular matrix breakdown by their MMP production. (C) Cardiac fibroblasts also affect myeloid cells trafficking to the heart by secreting chemokines, cytokines, and growth factors, such as CCL2, GM-CSF, and CCL11 after cardiac injury.

This detailed phenotyping of resident macrophages was preceded by several papers showing different roles of Ly6C^{high} and Ly6C^{low} monocyte subtypes in cardiac pathology (Nahrendorf et al., 2007; Panizzi et al., 2010). In mice, Ly6C^{high} CCR2^{hiigh} CX3CR1^{low} inflammatory subset is the main producer of inflammatory cytokines and chemokines, and it is the predominant subset migrating to the heart after an injury, followed by Ly6C^{low} CCR2^{low} CX3CR1^{high} patrolling monocytes. Similar subsets can be found in humans, where CD16^{-} CD14^{+}CCR2^{+} monocytes have characteristics similar to Ly6C^{high} monocytes, and CD16^{+} CD14^{-} is an equivalent to Ly6C^{low} monocytes. After a cardiac injury, inflammatory mediators act on the periphery, and increase monocytopoiesis in the bone marrow and spleen. Hulsmans et al. (2018) have also shown this mechanism in mouse models of HFpEF. Chemokines such as CCL2 are produced locally in the heart, mostly by cardiac fibroblasts after a cardiac injury and attract monocytes to the injured heart (Wu et al., 2014). Ly6C^{high} monocytes differentiate to macrophages in the heart. Together with the resident macrophages, their profile is affected by an interaction with cardiac-resident cells, mainly cardiac fibroblasts. Cardiac fibroblasts can produce large amounts of granulocyte-macrophage colony-stimulating factor (GM-CSF) that determine the severity of cardiac remodeling and fibrosis in models of myocarditis, myocardial infarction, and Kawasaki disease by changing the profile of myeloid cells in the heart (see figure, part C; Wu et al., 2014; Stock et al., 2016; Anzai et al., 2017). Interestingly, cardiac fibroblasts can also produce CCL11 (eotaxin), which attracts eosinophils to the heart in the Th2 type of cardiac pathology in eosinophilic myocarditis (see figure, part C; Diny et al., 2016). Hulsmans et al. (2018) also showed that IL-10 is produced not only by macrophages but also by cardiac fibroblasts, suggesting fibroblast contribution to IL-10 conditioning of macrophages. At the same time, cardiac fibroblasts are a target of myeloid cell–derived inflammatory mediators that

lead to activation of fibroblasts, induce production of collagen, fibrosis, and cardiac remodeling. Hulsmans et al. (2018) identified OPN and TGFβ as the mediators produced by macrophages and promoting collagen expression by cardiac fibroblasts. MHCII^{high} monocytes, which are the main source of OPN and TGFβ, are also a source of many other inflammatory mediators. Further research is needed to define the role of myeloid cells and cardiac fibroblast in heart failure.

There is no effective therapy for HFpEF. It is a clinical issue of high importance, given that the incidence of HFpEF in the United States has grown by ∼10% per decade, as the result of population aging, as well as the increased incidence of the main risk factors for HFpEF, such as hypertension, obesity, and metabolic syndrome (Owan et al., 2006). The pathophysiology of HFpEF used to be exclusively linked with diastolic dysfunction. However, we know now that there are other pathophysiological changes in the heart function, such as systolic impairment and decreased chronotropic reserve. In addition, peripheral abnormalities affecting skeletal muscle, endothelium, and autonomic nervous system are part of HFpEF pathology. Therefore, it is likely that HFpEF has a range of pathways of development, and it will be needed to identify subgroups of patients with HFpEF for targeted therapies. However, it is essential that a large clinical study is done to follow up on this possible new pathogenic mechanism in HFpEF.

Based on earlier findings that HFpEF subjects have more collagen and less MMP activity (Kasner et al., 2011), we can speculate that if IL-10 produced by MHCII^{high} macrophages is shown to be also increased in larger and more diverse populations of HFpEF, then biological therapies that would modify cardiac macrophage phenotype and target mostly the MHCII^{high} subtype might decrease interstitial fibrosis and cardiac stiffness, thereby addressing some symptoms of HFpEF. However, even MHCII^{high} macrophages with their inflammatory and profibrotic phenotype have important functions in the heart, especially in an acute response to injury after myocardial infarction and during myocarditis. Systemic neutralization of IL-10 might be a safer and more realistic biological therapy. It could perhaps be followed by a myeloid-specific targeting of IL-10. Future research should also examine how changes in the profile of cardiac-resident macrophages and cytokine production affect cardiomyocytes because the increased stiffness observed in HFpEF is considered to also be caused by changes in cardiomyocytes.

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