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INSIGHTS

Macrophage-adipocyte communication and cardiac remodeling

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In obesity complicated by hypertension, multicellular processes integrate to orchestrate cardiac fibrosis; the underlying mechanisms, however, remain elusive. In this issue of *JEM*, Cheng et al. (2021. *J. Exp. Med.* https://doi.org/10.1084/jem.20210252) describe adipocyte–macrophage collaboration to foster cardiac fibrosis through the actions of angiotensin II in obesity.

Obesity and hypertension, major risk factors for cardiovascular disease, play key roles in the pathogenesis of heart failure (Virani et al., 2021). Both obesity and hypertension promote left ventricular (LV) pressure and volume overload and exacerbate inflammation and fibrosis and lead to heart failure (Anthony et al., 2019; Oparil et al., 2018; Mouton et al., 2020; Lumeng et al., 2007; Gyöngyösi et al., 2017). Studies point to overlapping and potentially synergistic mechanisms by which obesity and hypertension promote inflammation and cardiac fibrosis. In obesity, adipose tissue expansion is accompanied by an increase in infiltrating immune cells and a shift in macrophage polarization toward a pro-inflammatory activation state. Further, adipose tissue–derived adipokines promote the development and progression of fibrosis and cardiac hypertrophy (Anthony et al., 2019; Oparil et al., 2018; Mouton et al., 2020; Lumeng et al., 2007; Gyöngyösi et al., 2017). In addition, cardiac fibrosis, caused by activation of fibroblasts, fosters excessive extracellular matrix (ECM) deposition, thereby contributing to LV stiffening and diastolic dysfunction (Anthony et al., 2019; Oparil et al., 2018; Mouton et al., 2020; Lumeng et al., 2007; Gyöngyösi et al., 2017). Together, hypertension and obesity amplify pro-fibrosis mechanisms in the heart consequent to stress-induced signaling pathways in cardiac fibroblasts and macrophage-induced inflammation (Travers et al., 2016; Cavalera et al., 2014; Suetomi et al., 2018). Activation of fibroblasts by macrophage secreted TGF-β1, IL-10, and ECM proteins have been linked to cardiac fibrosis. However, comprehensive and integrated mechanisms driving cardiac fibrosis/cardiac hypertrophy in obese-hypertensive hearts remain to be understood. In this context, the study by Cheng et al. provides evidence for adipocyte–macrophage axis in promoting cardiac fibrosis in angiotensin II (AngII)–treated obese mice (Cheng et al., 2021).

Cheng et al. (2021) showed that expression of full-length platelet-derived growth factor-D (PDGF-D) was increased in all adipose depots and secreted into the circulation in high-fat diet (HFD)–fed mice. PDGF-D is secreted primarily in an inactive full-length form and would require urokinase plasminogen activator (uPA) or matriptase to be activated. These authors showed that adipocyte-specific PDGF-D KO mice, on HFD, were protected against pathological cardiac remodeling after AngII infusion. In addition, adipocyte-specific PDGF-D transgenic mice (PA-Tg) showed exacerbation of cardiac remodeling after AngII infusion without HFD treatment. Macrophage depletion studies demonstrated that CSF-1R antibodies could block the effect of PA-Tg–accelerated cardiac remodeling in hypertension. Importantly, Cheng et al. showed that macrophage recruitment to the heart was higher in AngII-treated HFD mice and that these activated macrophages produce uPA that spliced full-length PDGF-D into an active form. Bone marrow–specific uPA knockdown reduced the generation of the active form of PDGF-D and, thereby, improved cardiac remodeling in HFD hypertensive mice. Furthermore, transcriptomic and signaling studies revealed that active PDGF-D promoted fibrosis by activating PI3K-Akt signaling cardiac fibroblasts. Taken together, these findings indicate that the direct interaction between

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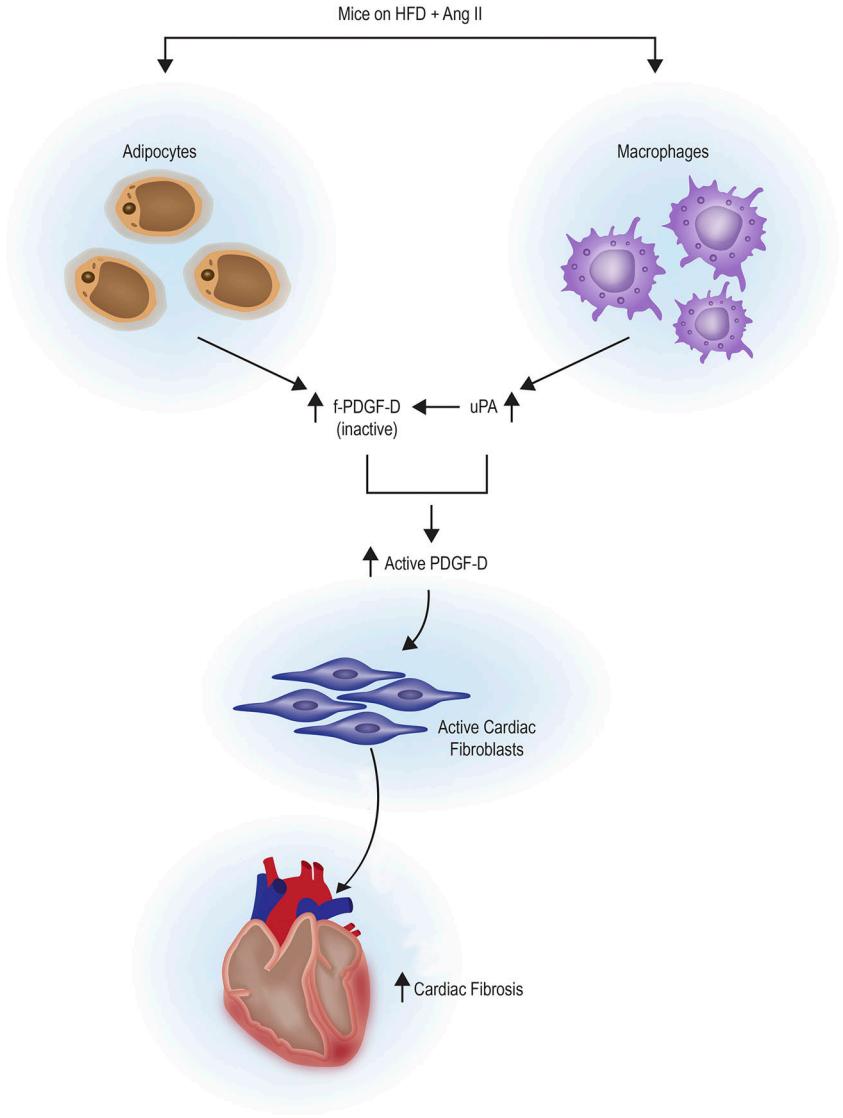

Scheme displaying the role of adipocyte–macrophage axis in promoting cardiac fibrosis in Ang II–treated HFD-fed mice.

macrophages and adipocytes, via fibroblast signaling, accelerates hypertensive cardiac fibrosis/remodeling during obesity.

These discoveries of Cheng et al. provide a compelling rationale for future investigations to address the intricate details on adipocyte–macrophage communication driving cardiac fibrosis and hypertrophy in the obese-hypertensive heart. Several questions to address include: How does adipocyte–macrophage communication influence modulation of (a) adipocyte secretome, (b) macrophage migration from adipose tissue to the heart, and (c) consequent signaling leading to cardiac hypertrophy and fibrosis? From the macrophage standpoint, since studies have implicated the splenic–cardiac axis in AngII signaling and hypertensive cardiac injury (Mouton et al., 2020; Hulsmans et al., 2018), the potential role of splenic macrophages in cardiac remodeling in obese-hypertensive hearts needs to be pursued. Since epigenetic changes that occur in obese-hypertensive mice may influence intercellular communication signaling systems, including the nitric oxide, angiotensin, and endothelin signaling systems, these aspects also require investigation in future studies.

Current literature is rich with data demonstrating that constituent cells in the heart are in constant flux of signaling and metabolism (Skelly et al., 2018; Litviňuková et al., 2020; Cui et al., 2020; Vidal et al., 2019), both within each cell and in interactions between multiple cell types. To decipher the mechanisms underlying these complex interactions at the cellular and molecular level in the obese-hypertensive heart, several distinct techniques may be used in concert. Combining the applications of genomics, transcriptomics, proteomics, and metabolomics, along with integrated bioinformatic analyses, offers the prospect to link the molecular fingerprints that drive cardiac remodeling in the obese-hypertensive heart. Such insights can also be gained through spatial resolution specific analysis of subregions of the heart, down to the level of individual cells. Technologies with single-cell resolution, such as single-cell transcriptomics and cytometry by time of flight, along with spatial transcriptomics, are enabling intercellular signaling to be investigated across all the different cells that compose the heart. Recent single-cell and single-nucleus transcriptomics of studies of human and mice hearts (Skelly et al., 2018; Litviňuková et al., 2020; Cui et al., 2020; Vidal et al., 2019) have revealed a network of intracellular communications among cardiomyocytes, endothelial cells, fibroblasts, and immune cells, and suggested prevalent sexual dimorphism in gene expression in the heart. These studies have identified (a) the cellular heterogeneity of cardiomyocytes, pericytes, and fibroblasts, and revealed distinct atrial and ventricular subsets of cells with diverse developmental origins and specialized properties; (b) cardiac-resident macrophages with inflammatory and protective transcriptional signatures; (c) transcriptional landscape of five distinct cardiomyocyte populations in healthy, injured, and regenerating mouse hearts; and (d) deterioration of paracrine signatures between fibroblasts and endothelial cells in old hearts. Similar studies in obese-hypertensive hearts have great potential to unveil entirely novel mechanisms that forge inter- and intracellular signaling and interorgan communications that mediate cardiac remodeling.

Despite increasing progress in therapeutic applications for cardiovascular disease, most therapeutic interventions are developed to affect only a single cell population, such as cardiomyocytes or cardiac fibroblasts to limit the progression of fibrosis and heart failure. As several recent studies have shown that the interaction of different cardiac cell types as well as inter-organ crosstalk contribute to the pathogenesis of heart

failure, this dynamic interplay also has to be considered in the strategies for development of therapeutic approaches. Understanding multicellular interactions and communications using comprehensive -omics approaches will unravel insights into this complex communication network within the heart and with circulating immune cells. These essential efforts will guide the discovery of the mediating signaling pathways, which are important for the development of novel therapeutic approaches to treat cardiac remodeling in the obese-hypertensive heart.

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