Myocardial Metabolism Under Control of a Cytokine Receptor

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In recent years, the heart has been rediscovered under the lenses of immunology. Immune cells and immune mediators have been widely reported to influence the heart under a wide range of physiological and pathological conditions, such as healing after myocardial infarction, pressure-overload-induced cardiac remodeling, heart failure, and myocardial aging. Now, in the current issue of JAMA, Amit et al bring the emerging field of immunocardiology a step forward by showing that interleukin (IL)-13 receptor chain alpha 1 (IL-13Rα1), a component of a common receptor to IL-4 and IL-13, can modulate baseline myocardial metabolism and contractile function.

From the immunological perspective, IL-4 and IL-13 are related cytokines with considerable (though not complete) functional overlap. These cytokines are the major drivers of the so-called type II immune responses, characterized by the involvement of type 2 helper cells, alternative macrophages (M2), eosinophils, basophils, mast cells, type 2 innate lymphoid cells, and immunoglobulin E. These cytokines are mainly recognized for their capacity to suppress some inflammatory responses and also for their role in allergies. However, beyond taking part in classical immune reactions, IL-4 and IL-13 can also modulate other physiological processes, such as tissue repair, extracellular matrix remodeling, and metabolism homeostasis. This has led some groups to hypothesize that IL-4 and IL-13 could influence myocardial infarction and heart failure. Nevertheless, the potential roles of these cytokines in cardiac diseases has remained controversial so far. For instance, it has been reported that IL-13-deficient animals exhibit a worsened outcome in experimental models of myocardial infarction and myocarditis, whereas the opposite was found true for the IL-4-deficient animals. These seemingly contradictory findings can be attributed, at least in part, by the complex way that these cytokines signal to their receptors (Figure). Both IL-4 and IL-13 can signal through a common type II receptor, which is a heterodimer composed by an IL-13 receptor chain α1 (IL-R13α1) and an IL-4 receptor α chain (IL-4 receptor α). These type II receptors are expressed on immune cells, but also in nonlymphoid tissues, such as the myocardium. However, IL-4, but not IL-13, can also interact with type I receptors, which are mainly expressed on immune cells. The type I IL-4 receptors are heterodimers comprising an IL-4Rα chain and a common gamma chain (γC), which is also shared by the cytokines, IL-2, -4, -7, -9, -15, and -21. Both IL-4 and IL-13 receptors transduce signal through the Janus kinase/signal transducer and activator of transcription pathways and ultimately modulate the transcription of responder genes.

Considering that both IL-4 and IL-13 would signal in the myocardium through a common type II receptor (IL-13Rα1/IL-4 receptor α), Amit et al decided to focus on the role of these receptors, rather than on the cytokines, as it has been done in previous studies. The main advantage of this approach, the authors argue, is that IL-13-deficiency can be compensated by IL-4 upregulation, and vice versa, potentially leading to confounding results. Accordingly, Amit et al report that the murine and human myocardium express the IL-13Rα1 and the IL-4 receptor α chains under physiological conditions. Furthermore, the authors found the expression of these cytokine receptors to be downregulated in myocardial samples obtained from end-stage heart failure patients. Next, in order to uncover the biological significance of their signaling in the myocardial tissue, the authors sought to perform a comprehensive cardiac phenotyping of mice deficient for IL-13Rα1. Male, but not female, knockout mice exhibited significant contractile impairment and dysynchrony under baseline conditions, as compared with wild types. A transcriptome analysis on myocardial samples revealed that 549 genes were differentially expressed in hearts of naïve IL-13Rα1 knockout animals, as compared with wild type controls. This can be regarded as a significant impact in cardiac function, especially if it is considered that healthy animals present no patent ongoing type II immune responses. Furthermore,
bioinformatics analyses indicated that IL-4/IL-13 signaling might regulate several aspects of myocardial homeostasis, including also nonimmune functions. Accordingly, gene-related extracellular matrix biology, apoptosis, cell cycle, and, most notably, glucose metabolism were found to be differently expressed in hearts of IL-13Rα1-deficient animals, as compared with wild type controls. Using a genome-scale metabolic modeling, the authors further observed that IL-13Rα1 deficiency was related to a downregulation of genes associated to the glycolytic pathway and to the tricarboxylic acid cycle in the myocardium, and to an upregulation of genes associated with pyruvate metabolism.9 Although unexpected, these results are in line with previous observations by Stanya et al,16 who observed that IL-13 signaling modulates hepatic glucose metabolism.

Despite the advances brought by the study of Amit et al,9 important questions also remain unsolved. The cellular distribution of these cytokine receptors in the myocardium remains elusive. Future studies will eventually dissect whether IL-13Rα1 is primarily expressed on cardiomyocytes, endothelial cells, cardiac fibroblasts, or on resident leukocytes. The cellular source of myocardial IL-4/IL-13 also remains to be established. Does low-level IL-4/IL-13 production take place in the healthy myocardium, where they modulate local metabolism in an autocrine/paracrine fashion, or do they act systemically as blood-borne factors? Furthermore, considering that the same cytokine receptors may also regulate glucose metabolism in the liver, glycemia, and influence the inflammatory basal tone, further systemic integrative analyses will be necessary to resolve the current contradictions in the field. In addition, the sex-specific alterations observed in this and in other studies focusing on IL-13 signaling in the heart might also be an issue to be further elucidated in future studies.9,11

Last, but not least, the demonstration by Amit et al9 that baseline myocardial glucose metabolism—such a central aspect in cardiac physiology—could be under the control of a cytokine receptor may have far-reaching implications. The
immune system does not only regulate “inflammatory reactions in the injured myocardium,” but is also important for tissue homeostasis under baseline and in stressed conditions.

Disclosures
None.

References

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