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Paradoxical Role of Interleukin-1R2 in Cardiovascular Disorders

LETTER TO THE EDITOR

To the Editor,

I read the article by Chen et al[1] about the role of interleukin (IL)-1R2 in the pathogenesis of coronary artery disease (CAD). Their findings highlight the importance of IL-1R2 in CAD pathogenesis, but no mention is made regarding the underlying molecular mechanisms. As it is known, the biological effects of cytokines are mediated through interactions with receptors which exist in membrane-bound and soluble form.

The existence of cytokine receptors for a cytokine on different cell types, their functional plasticity, and their variable expression leads to complex functional networks. Cellular responsiveness to cytokines can be modified by altering the expression of receptors. Receptor density has an important influence on cellular events, including cell proliferation, apoptosis, and metabolism. Therefore, considerable attention is being devoted to understanding the role of cytokine receptors under normal and pathological conditions.

Interleukin-1R2 is a cytokine receptor that belongs to the IL-1 receptor family. It is recognized as an endogenous inhibitor of IL-1 signaling due to the absence of cytosolic Toll/interleukin-1 receptor domain (which is essential for IL-1R activities). Interleukin-1 signaling may also be inhibited by the soluble type II IL-1 receptor (sIL-1R2), which serves as a competitive inhibitor for IL-1. Experimental researches indicate that variations in the level of IL-1R2 could contribute to the pathogenesis of different diseases, including cardiovascular diseases (CVDs), although the exact mechanism remains unknown.

They may constitute a compensatory response that protects the cardiovascular system from the adverse effects of IL-1 or may play a causal role in disease pathogenesis. The first hypothesis is supported by empirical evidence including the following: (i) benefits of IL-1R2 overexpression on the rat cardiac allograft via reducing the intragraft infiltration of inflammatory cells and inhibition of pro-inflammatory cytokine production; (ii) IL-1R2 upregulation that attenuates cardiomyocyte apoptosis by downregulating the expression of proapototic molecules including Bax[2]; (iii) elevated levels of sIL-1R2 in patients with acute myocardial infarction following interventional therapy[3]; (iv) ameliorative effect of recombinant IL-1RII-Ig on experimental autoimmune myocarditis in rats.[4]

The second hypothesis is based on the functional impact of decreased IL-1R2 production in the pathogenesis of CVD. This concept is supported by empirical evidence including the following: (i) reduced IL-1R2 expression upon stimulation of monocytic cell lines with lipoproteins (a cardiovascular risk factor); (ii) reduced IL-1R2 expression in human atherosclerotic vessels and monocytes/macrophages of hyperlipidemic patients[5]; (iii) association between low circulating levels of sIL-1R2 and worse clinical outcomes in patients with acute myocardial infarction; (iv) increased infarct size and cardiomyocyte apoptosis in IL-1R2-deficient mice; and (v) an enhanced expression of IL-1R2 in PBMCs of patients with severe CAD compared with those with mild-to-moderate CAD and its positive correlation with Ox-LDL.[1] Such alterations may increase the risk of cardiovascular problems via

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several mechanisms, including the development of aberrant inflammatory responses.

Overall, IL-1 plays a critical role in the pathophysiology of heart diseases, and its activities are tightly regulated by IL-1R2. Available data suggest a key role for IL-1R2 variation in the development of different types of heart disease. Therefore, quantification of IL-1R2 has clinical significance, provides insights into pathological processes, and could be useful for diagnosis and treatment.

Editor's Note: Despite our repeated emails, we received no response from the authors.

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