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Editorial

A New Era of Targeting Pathogenic Immune Mechanisms in Cardiovascular Disease

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▸ See the article "Treatment with 3-Bromo-4,5-Dihydroxybenzaldehyde Improves Cardiac Function by Inhibiting Macrophage Infiltration in Mice" in volume 48 on page 933.

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The 3-bromo-4, 5-dihydroxybenzaldehyde (BDB) is a natural compound from red algae, which has anti-inflammatory effect. BDB is reported to inhibit the production of interleukin (IL)-6 secreted from murine macrophages and to show the anti-inflammatory potency reducing infiltration of inflammatory cells.[1] In this issue of the *Korean Circulation Journal*, Ji et al.[2] investigated the potential role of BDB on cardiac function recovery after myocardial infarction (MI) in mice. More specifically, the present study aimed to investigate the effect of BDB on macrophage infiltration and related cytokines production in a mouse model of acute MI. MI leads to intense and complex inflammatory responses, and the inflammatory cascade causes post-infarction ventricular remodeling. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), IL-1β, IL-6 are overexpressed after MI and play a key role in activating inflammatory reaction. In particular, IL-6 activates the janus tyrosine kinase/signal transducer and activator of transcription (JAK/STAT) cascade to modulate the inflammatory and reparative response of myocardium, and have been a potential therapeutic target for patients with MI.[3] In this study, BDB administration improved cardiac function recovery, and decreased mortality and infarcted size after MI. The anti-inflammatory effect of BDB reduced macrophage recruitment and inhibits the production of pro-inflammatory cytokines such as IL-6 as well as TNF-α, IL-1β, and monocyte chemoattractant protein (MCP)-1. Furthermore, BDB inhibited phosphorylation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a protein that plays an important role in the production of IL-6 and TNF-α, suggesting a clue to explain the pharmacological mechanism of BDB.

Various anti-inflammatory agents have been tried for MI treatment. The attempt to use glucocorticoids for MI was predominant in 1990s. Because the glucocorticoid receptor is present in most cells, glucocorticoids work on a variety of cells, and the anti-inflammatory effect also varies with the type of glucocorticoid. The results of clinical trials using glucocorticoids in MI were conflicting. Although some studies have shown cardiac protective effects of glucocorticoid, most studies have not shown positive changes in outcomes. In addition, some studies have raised safety concerns such as cardiac rupture or arrhythmia.[4]

As the molecular cascade of the inflammatory reaction after MI was revealed, targeted treatment was started. Animal experimental evidence suggested that targeting specific inflammatory signals, such as the complement cascade, chemokines, cytokines, proteases,

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selectins and leukocyte integrins, may hold promise. However, clinical translation has proved challenging. Rovelizumab, anti-CD11/18, was not effective for reducing infarct size in randomized clinical trial (RCT) of 420 ST-elevation myocardial infarction (STEMI) patients who underwent primary angioplasty (HALT-MI study). Anakinra, IL-1 receptor antagonist, reduced inflammatory markers, but increase major adverse cardiac events at 1 year in RCT of 182 non-ST-elevation myocardial infarction (NSTEMI) patients, who received standardized treatment (MRC-ILA-Heart study). Canakinumab, anti-IL-1β, significantly reduced recurrent cardiovascular events, but the incidence of fatal infection and sepsis is increased in RCT of 10,061 previous MI patients (CANTOS study). Pexelizumab, anti-C5, was not effective on mortality, cardiogenic shock and heart failure in RCT of 5,745 patients who underwent primary angioplasty (APEX-AMI study). Matrix metalloproteinases (MMP) inhibitor could not reduce ventricular remodeling or cardiovascular adverse outcome in RCT of 253 STEMI patients (PREMIER study).[5]

Although immune cells are known to be involved in the pathogenesis of post-MI remodeling, it is unclear which subpopulation of immune cells contribute to the pathologic left ventricle (LV) remodeling. Potential pathogenic mechanism of immune system in various cardiovascular diseases can be found in immunosenescence.[6] Age-related changes in the immune system, commonly termed 'immunosenescence,' is characterized by restricted diversity, hypo-responsiveness to antigens, and paradoxically, enhanced pro-inflammatory responses. Immunosenescence affects both the innate and adaptive immune systems; however, the most notable changes are in T cell immunity, including thymic involution, the collapse of T cell receptor (TCR) diversity, the imbalance in T cell populations, and the clonal expansion of senescent T cells. Senescent T cells can produce large quantities of pro-inflammatory cytokines and cytotoxic mediators; thus, they have been implicated in the pathogenesis of many chronic inflammatory diseases. A growing body of evidence has suggested that, senescent immune cells are involved in the pathogenesis of various cardiovascular diseases, including MI, hypertension and heart failure.[7-10] A detailed characterization of pathogenic immune mechanisms, especially in terms of immunosenescence and their potential therapeutic intervention with natural compound such as BDB might offer new opportunities for the prevention and treatment of cardiovascular diseases.

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