Can Statins Modify the Wound Healing Process After Myocardial Infarction?

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Hear failure (HF) is the major complication in patients who survive an acute myocardial infarction (MI).¹⁾ After MI, the dilatation combined with interstitial fibrosis of the left ventricle (LV) causes HF with poor clinical outcomes. Therefore, it is important to develop a novel drug therapy to prevent LV remodeling. It has been reported that monocytes/macrophages that infiltrate into injured myocardium are major factors in the pathophysiology of tissue repair after MI. Recent studies have suggested that there is a close relationship between the progression of LV remodeling and the wound healing process of infarcted heart tissue in a mice MI model.²⁾

There is strong evidence that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, so called “statins”, which are the most widely used agents for the treatment of dyslipidemia, reduce cardiovascular events such as MI. In addition to their LDL cholesterol-lowering effect, statins have various pleiotropic effects such as anti-inflammation, anti-oxidation, and angiogenesis.³⁾ Many animal studies have demonstrated that statins have the ability to inhibit the progression of HF by inhibiting the progression of cardiac hypertrophy and fibrosis.^{4,5)} Pitavastatin, which is a domestically produced lipophilic statin, has high bioavailability.⁶⁾ The Pitavastatin Heart Failure (PEARL) study, which was designed to evaluate the beneficial effects of pitavastatin in Japanese HF patients, revealed that pitavastatin did not reduce cardiac death and hospitalization for worsening HF overall, but did significantly reduce those events in the subgroup of patients with LVEF $\geq$ 30%.⁷⁾ These effects of pitavastatin suggest its potential to be a promising treatment for CHF in the future. Since statins have a small but real risk of predominantly musculoskeletal side effects such as creatine kinase elevation, myalgia, and rhabdomyolysis, it is difficult to use high doses of statins in patients. To overcome these problems, it is useful to deliver statins directly to target organs or cells by *in vivo* drug-delivery systems.

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In this article, Mao, *et al* demonstrated that Pitavastatin-incorporating nanoparticle (Pitavastatin-NPs) delivery to monocytes/macrophages can be a novel therapeutic strategy to protect the heart from post-infarct LV remodeling through the inhibition of monocyte mobilization from mainly the bone

marrow.⁸⁾ Bioabsorbable poly (lactic-acid/glycolic acid) (PLGA) nanoparticles (NPs) are the most interesting polymeric drug carrier in many clinical applications, because they are commercially available, easily degraded in physiological conditions, and have sustained drug release properties.⁹⁾ In addition, PLGA-NPs are reported to have a very low probability of causing major adverse reactions such as inflammatory responses. The authors already had an abundance of data about the efficient and effective delivery of Pitavastatin-NPs to inflammatory monocytes/macrophages after intravenous administration and had confirmed their therapeutic availability using various cardiovascular disease animal models.^{10,11)} In this issue, Mao, *et al* used a permanent coronary artery ligation mouse MI model and obtained detailed observations of the heart by echocardiography and histopathological analysis.⁸⁾ Flow cytometric and fluorescence microscopic analyses after the injection of FITC-NPs revealed that PLGA-NPs were delivered to CD11⁺Lin⁻ monocytes/macrophages in the peripheral blood, spleen, and heart, but not to cardiomyocytes. Treatment with Pitavastatin-NPs for 3 consecutive days after MI attenuated post-infarct LV remodeling with reduction of monocytes/macrophages in the heart, whereas the treatment with pitavastatin solution did not. Pitavastatin-NPs inhibited the mobilization of monocytes from the spleen after MI. Interestingly, Pitavastatin-NPs still decreased the number of monocytes/macrophages in the infarcted heart and inhibited post-infarct LV remodeling in splenectomized mice. In vitro migration assays also showed that angiotensin II-induced migration of a human monocyte cell line was inhibited by Pitavastatin-NPs as compared with the control group. Finally, they evaluated the number of monocytes/macrophages in bone marrow at several time points after MI because bone marrow-derived monocytes that arise from hematopoietic stem cells become a major source of circulating monocytes just after the establishment of MI. On the first day after MI, there were no significant differences in the number of CD11b⁺Lineage⁻ cells in bone marrow between the 3 groups. On day 3, the number of CD11b⁺Lineage⁻ cells in the bone marrow decreased in mice treated with vehicle, but not in mice treated with Pitavastatin-NPs, suggesting that MI caused a reduction of CD11b⁺Lineage⁻ cells in the bone marrow by promoting monocyte mobilization to the peripheral blood and Pitavastatin-NPs suppressed this process. Interestingly, this effect was also observed in splenectomized mice. They conclud-

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Received for publication June 1, 2017. Revised and accepted June 1, 2017.

Released in advance online on J-STAGE July 14, 2017.

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Figure. Mechanisms proposed by Mao, *et al* in which Pitavastatin-NPs inhibit the mobilization of macrophages to the infarcted heart.⁸⁾

ed that the effects of Pitavastatin-NP on post-MI LV remodeling are at least mediated in part by the inhibition of monocyte/macrophage mobilization from mainly the bone marrow.

However, some issues still remain in this paper. Since either the M1 monocyte/macrophage mobilization phase or the M2 monocyte/macrophage mobilization phase is important for the healing process after acute MI, respectively,¹²⁾ Mao, *et al* did not clarify each role of Pitavastatin-NPs on M1 and M2 monocytes/macrophages in the injured heart.⁸⁾ It was reported that 3 phases of the wound healing process (inflammatory phase, reparative phase, and maturation phase) are critical following MI.¹³⁾ In the inflammatory phase, M1 macrophages clear dead myocyte debris through phagocytosis and proteolysis by secreted proteases (MMPs) and secrete inflammatory cytokines (IL-1 β , IL-6 and TNF- α).^{14,15)} Next, in the reparative phase, M2 macrophages promote angiogenesis and secrete anti-inflammatory cytokines (IL-10 and TGF- β), which in turn recruit and activate reparative myofibroblasts. Myofibroblasts secrete large amounts of extracellular matrix (ECM) in order to replace lost ventricular tissue with a stable scar.^{16,17)} In the last phase, the maturation phase, the scar formation and remodeling are completed by apoptosis of the majority of the inflammatory and reparative cells. Since they stated that coordinated mobilization of monocytes/macrophages to the infarcted myocardium may be necessary to promote the appropriate healing of the infarcted tissues and prevent the progression of LV remodeling, Mao, *et al* did not refer to the source (spleen or bone marrow ?) of the M1 and M2 macrophages at each wound healing phase after MI. Moreover, they did not clarify the mechanisms of Pitavastatin-NPs on MCP1/CCR2 inhibition in this model.⁸⁾ Statins have been reported to inhibit cardiac hypertrophy in several animal models.¹⁸⁾ Statins have also

been found to inhibit the synthesis of isoprenoid intermediates of cholesterol biosynthesis and the subsequent activation of Rho family proteins, which have been reported to play an important role in the development of cardiac hypertrophy.¹⁹⁾ Also, there is considerable evidence especially on the role of CD4(+) T-cells in myocardial injury and healing.²⁰⁾ Pitavastatin was reported to inhibit the Th1 and Th17 responses through the inhibition of protein isoprenylation, and pitavastatin-treated T cells failed to differentiate into Th1 and Th17 cells.²¹⁾ In this article, no data about the direct effects of pitavastatin on cardiomyocytes and T cells were presented. Further studies are required to elucidate the detailed mechanisms of pitavastatin on M1/M2 macrophages, cardiomyocytes, T cells, and the healing process in the post MI heart.

Pitavastatin-NP can be a novel and clinically feasible therapeutic strategy to attenuate post-infarct LV remodeling and heart failure in patients after acute MI. The authors previously reported that Pitavastatin-NP also exerts cardioprotective effects on IR injury without apparent adverse side effects in a preclinical conscious porcine model.²²⁾ This nanotechnology-based targeted therapy can hopefully be developed as a novel therapeutic strategy for the treatment of patients with not only MI, but also other cardiovascular diseases.

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