Cardiac fibrosis, which occurs mainly because of increased collagen formation by activated cardiac fibroblasts (myofibroblasts), impairs cardiac function, metabolism, and electric coupling of myocardium, resulting in various cardiac diseases, such as heart failure, arrhythmias, and sudden cardiac death. Therefore, prevention of excessive cardiac fibrosis is important for the treatment of these cardiac diseases.

After myocardial infarction (MI), cardiomyocyte death immediately ensues, followed by the infiltration of a variety of inflammatory and immune cells. Cardiac fibroblasts are activated to proliferate and secrete extracellular matrix proteins to form a fibrotic scar with significant tensile strength that replaces regions of cardiomyocyte dropout (ie, replacement fibrosis).

This fibrotic process is thought to be essential for prevention from the cardiac rupture after MI, whereas continuous and excessive cardiac remodeling, such as cardiomyocyte hypertrophy in the infarct border zone, wall thinning, and chamber dilation, has deleterious effects on the cardiac structure and function. In the remote regions of the infarcted heart, reactive interstitial fibrosis also occurs subsequently.

Periostin, a secreted and soluble extracellular matrix protein with 4 repetitive fasciclin domains, interacts with other extracellular matrix proteins and shows various functions. Periostin is expressed in the developing endocardial cushions and re-expressed in adult hearts in response to pathological stresses, such as angiotensin II, as well as mechanical stretch through upregulation of transforming growth factor-β and platelet-derived growth factor-BB. There are 4 isoforms of periostin, Pn-1 to Pn-4, caused by alternative splicing at exon 17 or exon 21. Pn-1 is a full-length form, Pn-2 lacks exon 17, Pn-3 lacks exon 21, and Pn-4 lacks exons 17 and 21. The periostin gene was reported to be highly expressed in a rat heart after MI. Also in a study by Taniyama et al, gene expression levels of all 4 isoforms of periostin reached a peak at 5 to 7 days after MI. In situ hybridization showed that periostin was strongly induced in the border zone of MI on day 5 and thereby gradually propagated into an ischemic-free wall.

Overexpression of the full-length periostin Pn-1 using an HVJ (Hemagglutinating Virus of Japan) liposome method in rat hearts was shown to induce left ventricular remodeling with the accelerated accumulation of interstitial collagen and left ventricular dysfunction, which was the first report showing the contribution of periostin to cardiac remodeling. Consistently, mice lacking the periostin gene were more prone to ventricular rupture in the 10 days after MI, but surviving mice showed less fibrosis and better cardiac performance. After these reports, however, the inconsistent results described below were reported, thereby leading to the dispute on the role of periostin in cardiac remodeling. Administration of Pn-2, which lacks exon 17, to infarcted rat hearts using epicardial Gelfoam patches induced cardiomyocyte cell cycle reentry and mitosis, as well as angiogenesis, resulting in reduced fibrosis and remodeling, and improved cardiac function. However, these findings were not replicated in an experiment using mice lacking the periostin gene and inducible overexpression of full-length Pn-1. In addition, the overexpression of Pn-4, which lacks exons 17 and 21, prevented cardiac rupture after MI in mice lacking the periostin gene. Amid such a controversial situation, a detailed study using selective blockade of periostin isoform was needed to bring this dispute to an end.

Taniyama et al selectively inhibited Pn-1 in a rat MI model using neutralizing antibody against periostin exon17, which inhibits Pn-1 but not Pn-2/4. When compared with the control IgG group, the group treated with neutralizing antibody showed less fibrosis and remodeling, as well as better cardiac performance. No cardiac rupture after MI was observed in this antibody-treated group, which was in contrast to the findings in mice lacking the periostin gene. Although this antibody treatment restored the MI-induced decrease in diameter of cardiomyocytes, neither cardiomyocyte proliferation nor angiogenesis was altered. In cultured cardiac fibroblasts, the administration of this antibody inhibited transforming growth factor-β1–induced gene expression of α-smooth muscle actin, collagen I, and collagen III and decreased the viability of myofibroblasts. Finally, Pn-1 was shown to inhibit adhesion of cultured cardiac fibroblasts, as well as myocytes, but Pn-2 had an opposite effect. Using a Matrigel tube formation assay, Pn-2 significantly increased tube formation, whereas Pn-1 did not.

In this study, by selective blockade of Pn-1, differences in the properties of Pn-1 and Pn-2/4 were clearly demonstrated, bringing us a settlement of the dispute on the role of periostin in cardiac remodeling after MI (Figure). Pn-1 promotes
cardiac fibrosis and remodeling after MI, whereas Pn-2/4 prevents cardiac rupture of the infarcted area. It would be interesting to compare a group treated with the neutralizing antibody against all isoforms of periostin with a group treated with the selectively neutralizing antibody against Pn-1. If the neutralizing antibody could block the function of all isoforms of periostin completely, this fully blocked group rat may potentially be prone to cardiac rupture after MI like periostin knockout mice. Such a direct comparison of responses to MI between the present selective blockade and the full blockade would prove the advantage of selective blockade of Pn-1. MI between the present selective blockade and the full blockade would prove the advantage of selective blockade of Pn-1. Judging from in vitro experiments, Pn-1 and Pn-2 have mutually opposite effects on cell adhesion and angiogenesis, which can account for their opposite effects on cardiac remodeling. Simply stated, Pn-2 is beneficial, whereas Pn-1 is deleterious. Although it is uncertain to which extent endogenous Pn-2 promotes cell adhesion and angiogenesis in infarcted myocardium under selective blockade of Pn-1, the present selective blockade of Pn-1 could be favorable also from that viewpoint.

There remain some issues to be addressed before clinical application of this selective blockade. First, the distribution of expression levels of Pn-1 and Pn-2/4 could vary according to the type and strength of pathological stresses. Also, it remains unknown how the expression of Pn-2/4 is regulated when Pn-1 is selectively blocked. These issues influencing the therapeutic effects of selective blockade should be explored. Secondly, it would be interesting to determine the therapeutic effects on reactive fibrosis. In contrast with scar formation (ie, replacement fibrosis), interstitial fibrosis in the remote regions of the infarcted heart is reactive. Actually, a molecular imaging study using an MI mouse model revealed that there are clear differences in the timing of the collagen syntheses and the distribution of newly formed thin collagen fibers between the infarcted area (ie, replacement fibrosis) and the remote regions (ie, reactive fibrosis). Reactive fibrosis in the remote regions and replacement fibrosis in the infarcted area might be regulated in a distinct manner. Reactive fibrosis influences profoundly the long-term prognosis in patients having pressure overload and MI. Therefore, it would be interesting to clarify the role of periostin in the reactive fibrosis of these diseases using neutralizing antibody. Considering the previous result in periostin knockout mice, the selective blockade of Pn-1 would be also effective for the suppression of interstitial reactive fibrosis induced by pressure overload. These studies would provide us with a rationale for extensive clinical use in patients with nonischemic heart failure and cardiac remodeling because of pressure overload.

Disclosures

None.

References

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