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Key Words: cardiovascular magnetic resonance imaging, drug delivery system, growth factor, myocardial repair, tissue engineering

EDITORIAL COMMENTARY

The clinical application potential of extracellular matrix in cardiac tissue engineering

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An extracellular matrix (ECM) scaffold derived from porcine small intestinal submucosa (SIS) is currently used clinically for various disorders and constitutes one of the most extensively characterized decellularized ECM materials. A SIS-ECM scaffold can provide an ideal extracellular environment for cells and serve as a possible substitute for damaged tissue because of its high content of natural ECM components, such as collagens, fibronectin, elastin, glycosaminoglycans, and various growth factors.¹ In cardiovascular tissue engineering, the SIS-ECM patch has been investigated experimentally and clinically as an on-lay patch or an interposition graft to promote tissue reconstruction.²⁻⁶ Polytetrafluoroethylene and polyester (Dacron) grafts conventionally have been used successfully for vascular and intraventricular repair (eg, surgical ventricular restoration). However, major concerns related to these synthetic grafts include reactive inflammation, calcification, infections, adhesions, and local stiffness over a long period. An ECM-based scaffold could carry a lower risk of these complications because of its nontoxic, nonimmunogenic, biodegradable, and contractile properties. Furthermore, SIS-ECM has a predominant potential for cellular repopulation and ingrowth of the host cells, neovascularization, and ultimately, restoration of regional tissue functionality.

The potential of SIS-ECM scaffolds for cardiac regeneration.

Central Message

A SIS-ECM patch with sustained release of FGF-2 has potential as a plausible approach to regenerate damaged myocardium.

See Article page 1280.

See Editorial page 1035.

The research reported in this issue of the *Journal* by Tanaka and colleagues⁷ shows that a SIS-ECM patch with sustained release of basic fibroblast growth factor-2 (FGF-2) improved regional contractility and tissue perfusion in a porcine right ventriculotomy model compared with groups treated with a SIS-ECM patch alone or a Dacron patch. The authors assessed regional functionality using cardiovascular magnetic resonance and electrophysiologic-anatomic mapping. These techniques could provide comprehensive assessment of in situ myocardial reconstruction, such as electrical conductivity. Ramos and colleagues³ and Yanagawa and colleagues⁴ have demonstrated the effects of a SIS-ECM patch for porcine left ventricular and human intraventricular repair, although

a long-term investigation is still required. SIS-ECM coated with a gelatin hydrogel incorporating FGF-2, which was constructed by the same procedure as Tanaka and colleagues, also has been investigated in an abdominal wall defect rat model.⁸ In this setting, a SIS-ECM patch incorporating FGF-2 showed better reconstruction of the abdominal wall compared with SIS-ECM alone. Taken together with this article by Tanaka and colleagues, a SIS-ECM patch incorporating FGF-2 could be an approach to myocardial regeneration because the prosthetic ECM materials and sustained protein therapy promote endogenous myocardial remodeling.

Okada and colleagues⁹ reported the different effects between 2 forms of injectable SIS-ECM gels, SIS-B and SIS-C, in a murine myocardial infarction model. In their study, SIS-B showed better functional efficacy after transplantation compared with SIS-C, and the 2 forms of SIS-ECM had different FGF-2 content, suggesting that the FGF-2 content might influence the therapeutic effects of myocardial remodeling. A wide range of doses from 1 ng to 200 μ g have been tested in previous studies; however, optimal doses and delivery kinetics/dynamics of FGF-2 to maximally exploit its therapeutic effect have not been established for clinical application because of its rapid diffusion and short half-life. In this regard, Unger and colleagues¹⁰ reported that a high dose of FGF-2 induced adverse effects in humans, such as bradycardia and thrombocytopenia. As in the study by Tanaka and colleagues, controlled, local FGF-2 exposure might avoid the toxic side effects usually associated with systemic administration, keeping the therapeutic and localized dose in the defect's site. Boni and colleagues⁵ examined histopathologic changes at 1, 3, and 6 months after SIS transplantation in a lamb surgical model and confirmed that remodeling and growth potential in the explanted patches are time-dependent. In either case, further investigations on different doses of FGF-2 and long-term observation are needed for the clinical setting. SIS-ECM materials also have been used with stem cells for treating damaged and infarcted myocardium. Toeg and colleagues¹¹ reported that injectable SIS-ECM with circulating angiogenic cells improves cardiac function and promotes cellular restoration of myocardial infarction in mice. The combination strategy of ECM with growth factors or stem cells thus holds promise as an effective modality in cardiac regeneration.

Application of xenogenic grafts in humans should meet various required properties. As previously noted, the majority of researchers confirm that SIS-ECM is likely nonimmunogenic, because a noncellular material does not have immunologic information. However, Zheng and

colleagues¹² have identified a pig gene on the SIS-transplanted membrane in rats even after decellularization and sterilization, which may explain the presence of a local inflammatory response. It was also reported that the porcine ECM matrix formed undesirable tissue types, such as cartilage, in the myocardium after transplantation,⁶ which suggests that the ECM-based matrix may not provide cardiac-specific cues to cells in the cardiac environment.

Further studies are required to evaluate the clinical safety, stability, and efficacy of SIS-ECM implantable materials, with the aim of finally achieving a positive clinical impact. It is interesting to note that after 15 years of intense cell therapy research, at least part of the research on myocardial regeneration is back to decellularized materials and (now sustained) protein therapy. In this context, the article by Tanaka and colleagues reveals potential clinical advantages for using the SIS-ECM patch as an interposition graft or an on-lay patch to deliver protein in a sustained fashion and promote endogenous myocardial remodeling.

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