Understanding and not only observing: The key to success in tissue engineering?

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See related article on pages 2227-33.

The article by Stacy and colleagues¹ in this issue of the *Journal of Thoracic and Cardiovascular Surgery* evaluates the role of a noninvasive single-photon emission tomography/x-ray computed tomography (SPECT/CT) imaging method to quantify the matrix metalloproteinase (MMP) activity in tissue-engineered vascular grafts remodeling after implantation in a growing animal model. Stacy and colleagues¹ clearly demonstrate the feasibility of this innovative imaging method to assess MMP activity and conclude that such activity remains elevated in tissue-engineered grafts 6 months after implantation, which may indicate remodeling.

Many articles have demonstrated promising results of the application of the concept of tissue-engineering to the surgery of congenital cardiac defects, as such tissue-engineered devices (patches, grafts, valves, or valved tubes) undergo a biologic remodeling and display a growth potential, which is essential to this specific population. Nevertheless, little is still known about the exact mechanisms of this complex in vivo remodeling and the factors that could influence the quality of the biologic steps allowing a beneficial and sustainable transition of a cell-seeded (or not) polymeric (or biologic) scaffold to an autologous, living, and growing new anatomic structure (such as a vessel or a valve). This justifies and emphasizes the need for studies such as this article, which comes from the group of Breuer and Shinoka that has been now working successfully on that exciting topic for many years.

On the basis of voluminous evidence that MMPs (especially MMP-2 and MMP-9) may play a role in the remodeling of tissue-engineered vascular grafts, Stacy and colleagues¹ demonstrates the utility of a noninvasive method of imaging (SPECT/CT) in assessing a biologic activity that seems to be related to the remodeling occurring in these vascular devices. Imaging revealed higher MMP activity in grafts than in native tissue and in unseeded than in seeded grafts. These results are definitely interesting and pave the

way for the use of a new tool to understand the underlying remodeling process in a noninvasive way. Indeed, this type of molecular imaging (or any other type, actually) may assist the surgical and scientific community in making progress in the clinical application of tissue engineering by allowing a serial assessment of remodeling in tissue-engineered devices (even beyond the field of pediatric cardiac surgery).

This study has some limitations, including the small number of animal implantations and the absence of a precise biologic explanation of why unseeded scaffolds have a higher MMP activity. Indeed, the marker that was used in this study identifies a large group of MMPs that are different from each other in biologic roles, explaining why Stacy and colleagues¹ cannot determine the role of those MMPs specifically involved in the vascular remodeling. Moreover, this SPECT/CT imaging reflects the MMP activity without reflecting the activity of MMP inhibitors; such an incomplete picture is of limited interest because it is the coupling of MMP and inhibitor (and not MMP alone) that determines the biologic effects in terms of extracellular matrix deposition and remodeling. Finally, Stacy and colleagues¹ do not demonstrate in this article a direct correlation between MMP activity observed with SPECT/CT imaging on the one hand and immunohistochemical evidence of vascular remodeling on the other hand. This study thus is unable to validate fully this noninvasive molecular imaging method as a true marker of biologic remodeling. Future studies (which will need a larger number of animal implantations to meet a better statistical power) should definitely focus on the demonstration of such a direct correlation between molecular imaging and histopathology.

Despite these limitations, the article of Stacy and colleagues¹ is definitely of major interest, especially for the new generation of cardiothoracic surgeons who will probably have the routine opportunity to implant tissue-engineered devices in patients.

To conclude, I believe that the main merit of this article is to emphasize the need for new tools (especially noninvasive tools because of their clinical application) to provide a better understanding of the biologic in vivo remodeling of tissue-engineered devices after implantation, which is an indispensable step in the promotion of regenerative therapy.

Reference

1. Stacy M, Naito Y, Maxfield MW, Kurobe H, Tara S, Chan C, et al. Targeted imaging of matrix metalloproteinase activity in the evaluation of remodeling tissue-engineered vascular grafts implanted in a growing lamb model. *J Thorac Cardiovasc Surg*. 2014;148:2227-33.

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