In situ heart valve tissue engineering: Using the innate immune response to do the hard work

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Induced regenerative response: inflammatory, proliferative, and remodeling phases.¹

Central Message

In situ heart valve tissue engineering, which uses an induced regenerative process to recapitulate native tissue, appears to be a potential alternative approach for heart valve replacement.

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In this issue of the *Journal*, Bennink and colleagues² present an investigation comparing the use of a synthetic bio-absorbable, polymer-based, pulmonary-valved conduit (Xeltis BV, Eindhoven, The Netherlands) with the use of a Hancock aortic-valved Dacron polyester fabric conduit (Medtronic Inc, Minneapolis, Minn) for pulmonary valve replacement in sheep. Their study demonstrated functional and morphologic changes in the polymer-based valves at 2, 6, and 12 months. Although this is a limited preliminary study and presents some concerning findings at 12 months, there are several positive take-home points. There was “acceptable” valve function, neointima formation (non-thrombogenic), degradation of polymers (which may represent remodeling), deposition of native matrix, and lack of calcification out to 12 months. This study promotes a tissue-engineering approach toward the use of scaffolds (biologic or nonbiologic), allowing the native cells to populate the scaffold and lay down their own extracellular matrix along with resorption of the exogenous scaffold. This approach of in situ tissue engineering relies on the host response to the exogenous scaffold and the interplay between the immune and progenitor cells in the microenvironment provided by the scaffold, with additional influence from the hemodynamic environment.¹ Although it is logistically (in terms cost and availability) superior to the traditional tissue-engineering approaches (cell based), in situ tissue engineering is still in its infancy and is fraught with occasional unexpected failures.

Bennink and colleagues² showed tears and fragmentation of valve leaflets at 12 months, coinciding with shrinkage of the leaflet, rolling of the free edge, and associated progressive increase in regurgitation. The hemodynamic performance in these sheep appeared worse in all categories than with the Hancock conduit (limited to 24 weeks), with the Xeltis conduit having greater than mild insufficiency after 40 weeks. They demonstrated neointimal

hyperplasia and thickening of the conduit wall and leaflet in some cases.² These problems have also been noted in other studies examining in situ tissue engineering of heart valves³⁻⁵ and are commonly attributed to 3 broad factors: (1) scaffold design (porosity, rate of degradation, etc), (2) hemodynamic environment (low vs high pressure, flow, shear stress, etc), and (3) cellular response (proinflammatory vs proregenerative, cell adhesion molecules, cell polarization and chemoattractive cytokines, etc). The process is not a static tissue formation but rather a functional tissue regeneration in continuously changing biomechanical microenvironments, ranging from initial acellular scaffold to degrading scaffold with variable matrix and cell infiltration. It is therefore extremely important to understand the fundamental reasons for failure in these devices and make adaptations to continue to make progress in this promising approach. Bennink and colleagues² used a novel polycaprolactone- and polycarbonate-based supramolecular, ureido-pyrimidinone polymer. Ureido-pyrimidinone polymer is a unique polymer with high dimerization constant and hydrogen-binding motifs, resulting in tunable morphologies.⁶ Similar design changes, such as reducing fiber diameters to minimize blood activation, increasing pore size to promote cell infiltration, and modulating degradation rates to be compatible with extracellular matrix resorption, have been proposed by others.¹ Changing fiber

arrangements in the arterial versus the ventricular side to account for flow and shear stress differences, supplementing scaffolds with vascular endothelial growth factor (promoting angiogenesis) and interleukin 10 (promoting macrophage polarization to M2) are some other considerations being investigated.

We are far from a robust clinically applicable device that we can claim will remodel into native tissue. In situ tissue engineering of heart valves appears promising and appealing because it is based on creating the environment in which nature can do the hard work of valve creation.

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