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EDITORIAL COMMENT

Subject- and Leaflet-Specific Remodeling of Polymeric Heart Valves for In Situ Tissue Engineering

Challenges Towards Clinical Translation*

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Tissue-engineered heart valves (TEHVs) have been proposed as a solution to the clinical need for heart valve substitutes for pediatric patients and for a globally aging population. Different from the clinically available prostheses, living heart valves, made with and by the cells of the patient, are endowed with the capability of growing and remodeling, and therefore, with the potential of lasting for a whole lifetime. This eliminates the need for pharmaceutical therapies normally associated with mechanical heart valves and for multiple interventions due to structural degeneration and calcification, as happens with biological prostheses.

Heart valve tissue engineering started with the classical bioreactor-based approach where autologous cells are seeded onto a polymeric scaffold and are conditioned in vitro in a bioreactor under biochemical and mechanical stimulation to guide the tissue formation. Once adequate mechanical properties are achieved, the construct is implanted. Historically, TEHVs reproduced the native heart valve geometry and were meant for surgical implantation. Single leaflets to be individually sutured orthotopically were also proposed. Different materials and fabrication methods have been proposed to create TEHVs. Natural and synthetic polymers have been processed with a variety of fabrication techniques, including molding, fiber-forming techniques (e.g., electrospinning, jet spinning, melt-electrowriting), salt leaching, and additive manufacture. Following the clinical advancements, TEHVs have been also developed for minimally invasive implantation, and the shape of the constructs has evolved to a tubular geometry, which is easier to produce and more robust.

In the last few years, the field of heart valve tissue engineering has witnessed a significant shift toward in situ tissue engineering. This approach proposes the implantation of cell-free scaffolds that elicit a host reaction, ideally toward an endogenous healing process, ultimately resulting in the formation of autologous tissue that is mechanically and biologically equivalent to the healthy native one. This approach simplifies significantly the fabrication phase, by eliminating the bioreactor conditioning, the logistic, by providing off-the-shelf implants, and the regulatory aspects. However, it poses important issues with respect to the capability of the implant to steer the host reaction away from a chronic inflammation. To this end, the temporal polarization of the macrophages from a pro-inflammatory to an anti-inflammatory phenotype is believed to be of key importance. The microenvironment plays a pivotal role in the immunoresponse to the implant, in a complex interplay of many parameters, including the scaffold's structure (e.g., porosity, fiber diameter), the mechanical properties, the (bio)chemical composition, and the mechanical forces acting on the construct. A strategy to guide the host reaction is by pre-operatively seeding the implant with autologous cells (e.g., bone marrow mononuclear cells

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[BMMNCs]). This has been shown to positively affect the remodeling process of polymeric vascular grafts in a cytokine-mediated process (1).

The paper by Fioretta et al. (2) in this issue of *JACC: Basic to Translational Science* investigated the effect of BMMNC pre-seeding on the performance of heart valves made of a biodegradable polymer and minimally invasively implanted as pulmonary valve substitutes in an adult ovine model. The TEHVs were evaluated at different time points (4 h, 4 weeks, and 24 weeks) and compared with unseeded ones, produced with the same polymer (bis-urea-modified polycarbonate) and fabrication method (electrospinning and hand suturing to the stent). The investigators showed a similar early performance of the 2 valve types up to 4 weeks, after which a progressive deterioration of the functionality of the BMMNC-seeded valves) was observed. Unlike the unseeded controls, the BMMNC TEHVs developed tissue overgrowth with partial fusion of adjacent leaflets at the commissures and macroscopic calcium deposits.

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These unexpected findings led the investigators to conclude that BMMNC seeding of bis-urea-modified polycarbonate-based TEHVs should be avoided. Common undesired effects were observed for both valve groups, such as leaflet encapsulation and shortening, and presence of αSMA-positive cells. The endothelialization was spotty in most of the leaflets, with only few of the unseeded leaflets presenting a complete endothelial layer. Substantial intervalve differences in the remodeling were shown independently of BMMNC pre-seeding, highlighting once more the challenge of controlling a process driven by the host's immunoresponse, and therefore, inherently subject-specific. Here, the balance between extracellular matrix deposition and polymer degradation is crucial for the implant's quality and ultimately for the patient's safety. Importantly, and for the first time in the field, the investigators demonstrated with a thorough analysis of each leaflet of all explanted TEHVs that the extent of tissue formation, cellular colonization, and scaffold degradation was not only valve-specific, but also leaflet-specific (2). This is a key observation that further challenges the potential clinical translation of these valves and calls for a deeper understanding of the biological remodeling process, including the cellular mechanobiological response to the hemodynamic conditions.

Interesting recent studies on the flow dynamics post-transcatheter implantation of commercially available aortic prostheses have shown that sinus washout and shear stress at the leaflets are highly sensitive to patient-specific root geometries (3). Salmonsmith et al. (4) investigated the effect of transcatheter aortic valve misalignment with respect to the native commissures on the in vitro valve functionality in silicone mock aortic roots, including mock native leaflets. Misalignment is inherently possible during transcatheter aortic valve procedures. The authors showed that, although it had a negligible effect on the bioprosthesis' performance in terms of effective orifice area and transvalvular pressure drop, it reduced sinus flow and affected flow patterns in the vicinity of the native commissures (4). It is plausible to assume that irregular root geometries would result in region (sinus) specific flow conditions. Furthermore, the coronary flows, not included in these studies, have been shown to have a significant impact on the vortex formation and on the wall shear stress magnitude and directionality at the 3 leaflets, in a leaflet-dependent way (5). Besides pointing out subject- and leaflet-specific flow conditions, which could contribute to the heterogeneity in the TEHVs' remodeling presented by Fioretta et al. (2) in a mechanobiology-mediated way, these studies also indicate that in vitro and in silico models should include the presence of the native leaflets and the coronary flows to obtain more realistic evaluations.

A limitation of the study by Fioretta et al. (2) is the fact that follow-up time did not extend beyond the complete scaffold degradation to validate the safety of the proposed valves. Best et al. (6) have recently demonstrated the differential outcome of the same acellular vascular graft when implanted in the venous and in the arterial system. Despite initial, comparably positive results, the venous vessel developed successfully upon complete scaffold's degradation, whereas the aortic vessel failed catastrophically due to aneurysmal dilatation and rupture. Interesting, the results could be predicted by a numerical model, indicating the potential of computational modeling-supported scaffold design (6). The relatively small number of animals used in the study is a further limitation, which hampers the possibility to detect significant differences among the groups and to compare the results with previously published studies from the same and other authors. Nevertheless, Fioretta et al. (2) raised an important warning with respect to issues that need to be addressed throughout the whole lifecycle of polymeric TEHVs, from the fabrication and the in vitro characterization, to the implantation, the in vivo monitoring, and the explant's detailed evaluation, in order to be able to safely translate these valves to the clinic. The investigators should be congratulated for

yet another important contribution to the field of heart valve tissue engineering. Their study will undoubtedly stimulate further research to understand the complex mechanisms governing the in situ tissue formation and, in this way, advance the field to exciting developments and clinically relevant progress.

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