Department of Materials Science and Engineering,

MS Defense

Date & Time: 10:00am May 20th, 2021
Where: https://drexel.zoom.us/j/89118055032

Title: Extracellular Matrix Engineering of Porcine Bioprosthetic Heart Valves

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Abstract

Valvular heart disease affects about 2.5% of the United States population and its incidence is projected to increase as a result of the increasing global prevalence of cardiometabolic disease. Once valve disease is severe enough and valve replacement surgery is indicated, patients and their medical teams can choose between mechanical and bioprosthetic heart valves (BHVs). BHVs are derived from animal tissue which results in more favorable hemodynamic properties and obviates the need for concomitant anticoagulation. However, the utility of BHVs is limited to certain patient populations because of their poor durability compared to mechanical valves. Histological analysis of failed BHVs, such as those derived from porcine aortic valves, suggests that deterioration of the tissue extracellular matrix (ECM), and loss of proteoglycans (PGs) and glycosaminoglycans (GAGs) specifically, leads to diminished mechanical performance, enables nucleation and propagation of tears, and ultimately results in failure of the prosthetic. Several strategies have been proposed to address this deterioration, including novel chemical fixatives to

stabilize more of the ECM and incorporation of small molecule inhibitors of catabolic enzymes implicated in the deterioration of the BHV ECM.

Biomimetic proteoglycans (BPGs) developed at Drexel University were recently demonstrated to engineer the mechanical properties of cartilage in animal models of osteoarthritis of the knee and temporomandibular joint and of stress urinary incontinence. Here, it was demonstrated that BPGs can be easily introduced into porcine aortic valves and the molecules distribute throughout the valve leaflets. Incorporation of BPGs into the heart valve leaflet restored the GAG content of the spongiosa, the middle region of the leaflet whose mechanics are most compromised by the aforementioned loss of PGs and GAGs. The presence of BPGs also significantly increased the indentation modulus of the spongiosa without compromising the chemical fixation process used to sterilize and strengthen tissue before it is made into a BHV. BPGs may restore hydrostatic pressure within the tissue by increasing negative fixed charged density and also may facilitate intermolecular interactions between existing ECM components observed in fresh tissue. These findings suggest that a targeted molecular engineering approach of the valve leaflet ECM may be a viable way to improve the durability of BHVs.