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Review

Scaffolds for tissue engineering of cardiac valves

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ABSTRACT

Tissue engineered heart valves offer a promising alternative for the replacement of diseased heart valves avoiding the limitations faced with currently available bioprosthetic and mechanical heart valves. In the paradigm of tissue engineering, a three-dimensional platform – the so-called scaffold – is essential for cell proliferation, growth and differentiation, as well as the ultimate generation of a functional tissue. A foundation for success in heart valve tissue engineering is a recapitulation of the complex design and diverse mechanical properties of a native valve. This article reviews technological details of the scaffolds that have been applied to date in heart valve tissue engineering research.

1. Introduction

Valvular heart disease (VHD) is a major health problem that results in substantial morbidity and death worldwide [1]. In the western world, 2.5% of the population have a dysfunctional or diseased valve [2,3]. Secondary to the aging of the population, it is predicted that there will continue to be an increase in VHD in industrial nations, owing primarily to an increase in degenerative pathology [2]. In the UK alone, more than 4 million people from 75 to 84 years of age could develop VHD by 2018, and this figure could double by 2028 [4]. In developing countries, VHD is primarily caused by the persistent burden of rheumatic fever rather than degenerative pathology, and tends to affect younger individuals [5,6].

The pathophysiology of valvular heart disease is broad and the specific etiology varies by the particular valve affected. The semilunar valves, consisting of the aortic and pulmonic valves, are commonly affected and have distinct primary pathologic mechanisms of failure. Pulmonic valve disease is most commonly related to congenital abnormalities and tends to present early in life. Aortic valve disease most commonly presents as calcific aortic valve stenosis secondary to calcific degeneration [7,8], while the presence of a congenitally bicuspid aortic valve predisposes to subsequent valvular stenosis and regurgitation usually at the earlier age [9].

Calcific aortic valve stenosis is the most common valvular pathology requiring valve replacement and is present to some degree in 2.8% of adults over the age of 75 years, with a far larger population showing some evidence of aortic valve thickening, known as valvular sclerosis [10,11]. Despite the frequency of calcific aortic valve stenosis, our understanding of its pathogenesis remains incomplete. While there are similarities between the risk factors and mediators between calcific aortic valve disease and atherosclerosis, as many as 50% of patients with calcific aortic valve disease do not show any evidence of significant atherosclerosis [12,13]. Recent data demonstrate that valvular calcification is not a passive process, as originally thought, but rather an active process that relies on the activation of pro-osteogenic signaling cascades, such as bone morphogenetic protein and Wnt/β-catenin, for the induction and progression of disease [14,15]. Additionally, our understanding of the cellular mediators of valvular calcification continues to expand. Conventionally, the differentiation of valvular interstitial cells into an osteoblast-like phenotype with the capacity to produce calcification has been thought to be the primary cellular driver of valvular calcification [16]. Recently, valvular endothelial cells have been implicated through a process of endothelial–mesenchymal transformation, as have circulating progenitor cells through differentiation or paracrine signaling [17–20]. The calcification process results in the mechanical disruption of valve function, which can lead to stenosis or regurgitation, or a combination of the two.

Unfortunately, the treatment of dysfunctional heart valves requires surgical or interventional repair or replacement. Replacement options currently include mechanical or bioprosthetic valves. Mechanical valves have excellent durability; however, the risk of thromboembolism necessitates the use of anticoagulation therapy and its attendant morbidity. Bioprosthetic valves are less thrombogenic; however, they are less durable and more prone to degeneration, particularly when implanted in younger individuals

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[21]. Bioprosthetic valves are generally treated with glutaraldehyde (GA) to stabilize the tissue by preventing rejection of the xenogenic scaffold. However, such treatments stiffen the fiber network and diminish the cushioning function of the spongiosa layer [22]. In addition, GA is toxic and inhibits the repopulation of cells after implantation [23]. Both mechanical and bioprosthetic valves share another disadvantage: they cannot grow and remodel, which may necessitate sequential surgeries in pediatric patients [24].

Nevertheless, the current generation of bioprosthetic pericardial valves are adequate substitutes for the majority of elderly patients as they typically do not require anticoagulation and their durability is usually sufficient for the lifespan of this population. In the pediatric and young adult populations requiring aortic valve replacement, the Ross procedure has been used, and has been shown to have low perioperative mortality and rates of reoperation [25,26]. In this procedure, a patient's diseased aortic valve is replaced with his/her own modified pulmonic valve (autograft) and then a cadaveric pulmonic valve allograft is used to replace the pulmonic valve. This procedure has several advantages, including minimal thromboembolism, favorable hemodynamics and the potential for valve growth. A disadvantage of the procedure is the harvesting of the healthy pulmonic valve, which can lead to the development of pulmonary valve disease in addition to aortic valve disease. As an alternative, tissue engineering is a promising approach for the treatment of defective or diseased heart valves [27]. In this method, living cells are grown (in vitro or in vivo) onto a supporting three-dimensional (3-D) biocompatible structure to proliferate, differentiate and ultimately grow into a functional tissue construct (Fig. 1) [28–30]. Importantly, a tissue engineered valve may be capable of growth and remodeling, and may mitigate the need for anticoagulation.

The scaffold is one of the most important entities to be considered for efficient tissue engineering because its external geometry, surface properties, pore density and size, interface adherence, biocompatibility, degradation and mechanical properties affect not only the generation of the tissue construct in vitro, but also its post-implantation viability and functionality [31,32]. All scaffolds designed for tissue engineering applications must meet basic requirements, such as biocompatibility, sterilizability and mechanical integrity. Scaffolds intended for heart valve tissue engineering face additional distinct challenges due to their direct contact with blood. Specifically, the construct should be resistant to calcification and thrombosis [33]. In addition, the construct must withstand the unique hemodynamic pressures and flows of the cardiac environment from the moment of implantation. These unique challenges underscore the importance of carefully considering the materials and design when fabricating a scaffold for tissue engineered heart valves.

Semilunar valves in human (pulmonic and aortic) consist of three semicircular leaflets (also called cusps) attached to a fibrous annulus called the root [23]. The leaflets are less than 1 mm thick and have a flexible structure consisting of three distinct layers: the fibrosa, spongiosa and ventricularis (Fig. 2). These layers are composed of valvular interstitial cells (VICs) within a matrix of collagen, elastin and glycosaminoglycans (GAGs). Normal leaflets are virtually avascular and obtain nutrients and oxygen from the bloodstream via hydrodynamic convection and diffusion. In contrast, the aortic or pulmonary root is a bulb-shaped fibrous structure, with intimal, medial and adventitial layers. They are primarily populated with endothelial cells in the intima, smooth muscle cells in the media and fibroblasts in the adventitia.

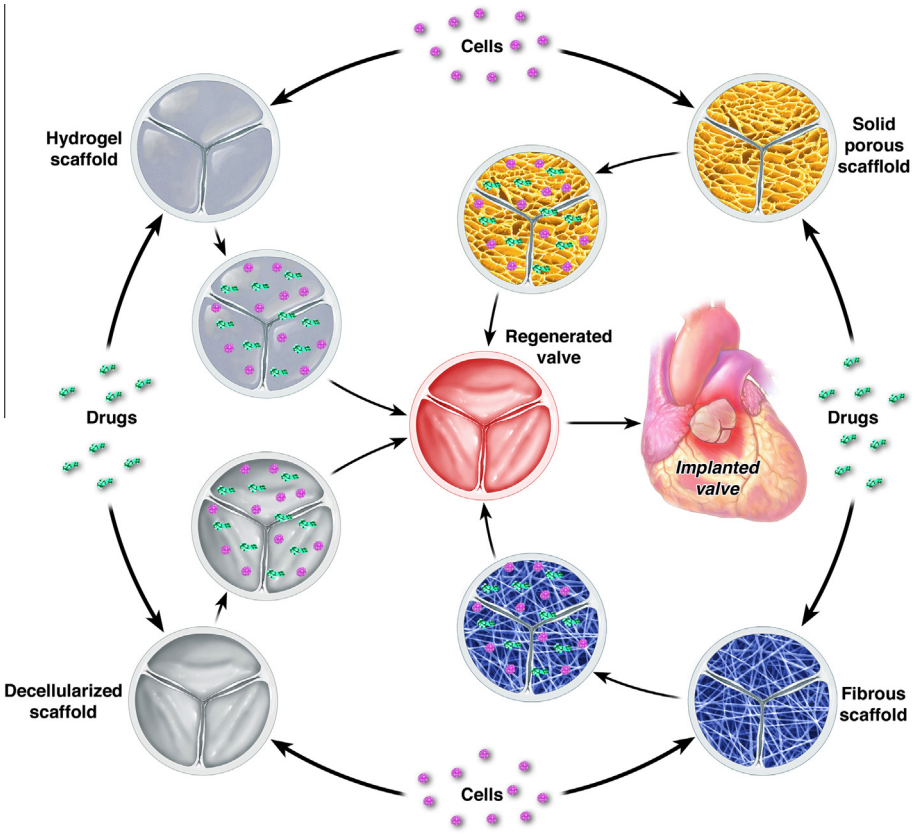

Fig. 1. Schematic diagrams of aortic heart valve tissue engineering. Living cells are grown onto a supporting three-dimensional (3-D) biocompatible structure to proliferate, differentiate and ultimately grow into a functional tissue construct.

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