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Review

Drug delivery in aortic valve tissue engineering

Soumen Jana [a], Robert D. Simari [b], Daniel B. Spoon [a], Amir Lerman [a,*]

[a] Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
[b] University of Kansas School of Medicine, 3901 Rainbow Blvd, Kansas City, KS 66160, USA

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ABSTRACT

Over the last 50 years medicine and technology have progressed to the point where it has become commonplace to safely replace damaged or diseased heart valves with mechanical and biological prostheses. Despite the advancements in technology current valve substitutes continue to have significant limitations with regards to thrombogenicity, durability, and inability to grow or remodel. In an attempt to overcome the limitations of currently available valve prosthesis, heart valve tissue engineering has emerged as a promising technique to produce biological valve substitutes. Currently, the field of tissue engineering is focused on delivering complex matrices which include scaffolds and cells separately or together to the damaged site. Additional functional enhancement of the matrices by exposing encoded biological signals to their residing cells in a controlled manner has the potential to augment the tissue engineering approach. This review provides an overview of the delivery of biological reagents to guide and regulate heart valve tissue engineering.

Contents

Abbreviations: α-SMA, α-smooth muscle actin; AVHD, aortic valvular heart disease; bFGF, basic fibroblast growth factor; BMP, bone morphogenetic protein; CS, chondroitin sulfate; EC, endothelial cell; ECGF, endothelial cell growth factor; ECM, extracellular matrix; EMT, transformation of epithelial cells to mesenchymal cells; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; FGF, fibroblast growth factors; GA, glutaraldehyde; GAG, glycosaminoglycan; HA, hydroxyapatite; hDMC, human dermal mesenchymal cell; HGF, hepatocyte growth factor; hMSC, human mesenchymal cell; HSP47, heat shock protein 47; IGF, insulin-like growth factor; MSC, mesenchymal stem cell; NO, nitric oxide; NRG-I, neuregulin-I; PAA, poly(amido amine); PCL, polycaprolactone; PEG, polyethylene glycol; PEGDA, poly(ethylene glycol) diacrylate; PEI-CD-DNA, poly-ethyleneimine-plasmid DNA; PGA, polyglycolic acid; PGS, poly(glycerol sebacate); PHA, polyhydroxyalkanoate; PHB, polyhydroxybutyrate; PHBV, poly(hydroxybutyrate-co-valerate); PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); PVA, polyvinyl acetate; REDV, Arg-Glu-Asp-Val; RGD, Arg-Gly-Asp; RGDS, Arg-Gly-Asp-Ser; SDS, sodium dodecyl sulfate; SMC, smooth muscle cell; Tβ4, thymosin β4; TGF-β, transforming growth factor-beta; TNC, tenascin-C; VEGF, vascular endothelial growth factor; VIC, valvular interstitial cell.

* Corresponding author at: Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55905, USA. Tel.: +1 507 255 2398.
E-mail address: Lerman.Amir@mayo.edu (A. Lerman).

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1. Introduction

A large number of people suffer from aortic valvular heart disease (AVHD) worldwide leading to cardiovascular morbidity and mortality [1,2]. In the United States alone, approximately 5 million people are affected by AVHD every year [3]. Although, number of deaths from AHVD is relatively small (~15000) 30% of people (age >65) suffer from valvular sclerosis and 10% of them face stenosis with degenerative pathology being the predominant cause. [4]. The incidence of AVHD is much higher in developing countries secondary to the persistent burden of rheumatic fever where more than 15 million people worldwide are estimated to be have rheumatic valve disease [5,6].

Due to the hemodynamic consequences of valvular heart disease, systemic blood flow can become compromised leading to morbidity and mortality [7]. Valvular tissue has limited regenerative capacity, and in case of damage or loss, scar tissue forms and calcification occurs leading to valvular impairment [8]. At present, the only effective therapy for severe valvular stenosis is the replacement of the affected valve with mechanical or biological prostheses [7]. In the next thirty years, the number of aortic valve surgeries will be tripled due to increase in population and improved access to healthcare [9]. However, both biologic and mechanical prosthetic valves have significant limitations and degree of survival and clinical improvement after surgery depends on the type of aortic valve substitute used [10]. Mechanical valve prosthesis requires life-long anticoagulation therapy (currently with Vitamin K antagonists) to decrease the risk of blood clotting on the valve surface which can result in valve dysfunction and thromboembolism [11].

On the other hand, biological prostheses have a low risk of thromboembolism but have limited durability with a significant failure rate at 10 years [12]. Biologic valves are generally treated with glutaraldehyde (GA), sodium dodecyl sulfate (SDS), and other substances to reduce their antigenicity and to prevent calcification. These treatments stiffen the prostheses and disrupt the collagen and glycosaminoglycan (GAG) structure leading to loss of functionality contributing to their decreased durability [13]. Importantly, neither mechanical nor biological prosthesis has the capacity to grow or remodel and thus are even less optimal for pediatric patients [14].

The field of regenerative medicine offers an alternative approach in which living cells, biomaterials, and soluble mediators are employed to create tissue with normal structure and function at the damaged site [15]. In native tissue development, including aortic heart valve generation, multiple growth factors are involved at different stages of growth and maturity [16]. In tissue restoration *in vitro* or *in vivo*, similar kinds of growth factors can be delivered in a controlled manner at the right phases to obtain a functional heart valve construct. Moreover, if the cells at the damaged site are not active or have low concentration, the delivery growth factors as well as specifically transfected cells, a new tissue could potentially be regenerated or damaged tissue could be remodeled [17].

This review summarizes comprehensive information on drug delivery in aortic heart valve tissue engineering. The review first discusses the structure, development, and molecular regulation in the development of aortic valve as well as the disease that cause the damage or impairment of aortic valve function. It then addresses design of drug carriers and materials used to prepare them. Lastly, it describes the delivery of key biomolecules including growth factors, genes and cytokines in heart valve generation through different approaches including substrate-based and cell-based deliveries.

2. Aortic valve

The aortic valve is located central to the pulmonary, mitral, and tricuspid valves and between the left ventricular outflow tract and the ascending aorta [18]. It allows the blood flow from the left ventricle into the aorta during systole and prevents flow in the opposite direction during diastole. The aortic valve is one of the two semilunar heart valves—the other being the pulmonary valve.

2.1. Structure

The aortic valve consists of three cusps: left coronary, right coronary, and non-coronary— named according to their relationship with the coronary arteries (Fig. 1a) [19]. The aortic valve cusps are supported by the aortic valve annulus and commissures. The valve is connected to the heart muscle through an annulus, which is comparable to a tendon that links skeletal muscle and bone. Cusp thickness is generally less than 1 mm, although it varies by region—thicker at the base and tip compared to other areas [20]. Each cusp consists of complex stratified connective tissues forming three layers: fibrosa, spongiosa, and ventricularis (Fig. 1b) [21]. The fibrosa, located nearest the aorta, is composed of circumferentially oriented fibrillar collagens (types I and III), which provide tensile stiffness to the valve [22]. The middle layer (spongiosa) consists of proteoglycans interspersed with collagen fibers. This layer works as a cushioned interface between the two outer layers to provide compressibility and integrity to the valve. The ventricularis, named because of its continuity to the ventricle, is composed of radially oriented filamentous elastic fibers and enables extension and recoiling of the valve under diastole and systole pressures, respectively. The cusps are covered with a layer of endothelial cells (ECs) with fibroblast/myofibroblast like interstitial cells inside [23].

2.2. Development

Embryologically, the heart is the first organ to form and supports continuous growth of the embryo. Initially, the heart is a primitive tube consisting of myocardial cell layer surrounded by endocardial EC layer [21]. At the fourth week of gestation, dextrosuperior and sinistroinferior endocardial cushions and two intercalated endocardial cushions located 90° from the previous ones form in the distal portion of outflow tract [25]. The endocardial cushion formation is characterized by transformation of epithelial cells to mesenchymal cells (EMT) in the presence of signaling factors emanated from myocardium cells [26]. At this stage, mesenchymal cells are highly proliferative and loosely connected in the cardiac gel (ECM), although in remodeling or mature valves, they recycle very little [27]. Mesenchymal cells are responsible for the creation of valvular interstitial cells (VICs). The cardiac gel, which contains proteoglycans, glycosaminoglycans, and other structural proteins, provides the morphology of the endocardial cushions and other parts of the heart [28]. Rhythmic contraction and expansion of extracellular matrix (ECM) gel in the endocardial cushions acts as primitive regulatory controls allowing for unilateral blood flow [29]. In a subsequent stage, the endocardial cushions fuse to form valve primordia, which arise from truncal septum. The valve primordia become thinner and elongate to form valve cusps. At this stage, the ECM goes through major changes in the form of patterning evidenced by gene expression from the surface of the valve. The patterning of the ECM is influenced by direction of blood flow. In the cusps, the ECM remodels into three layers

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