Acta Biomaterialia 48 (2017) 2–19

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Review article

Biodegradable and biomimetic elastomeric scaffolds for tissue-engineered heart valves

Yingfei Xue [a], Vinayak Sant [a], Julie Phillippi [b,c,d,e], Shilpa Sant [a,b,d,*]

[a] Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261, USA
[b] Department of Bioengineering, Swanson School of Engineering, University of Pittsburgh, Pittsburgh, PA 15219, USA
[c] Department of Cardiothoracic Surgery, University of Pittsburgh, Pittsburgh, PA 15213, USA
[d] McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA 15219, USA
[e] Center for Vascular Remodeling and Regeneration, University of Pittsburgh, Pittsburgh, PA 15219, USA

A R T I C L E I N F O

Article history:
Received 24 May 2016
Received in revised form 13 October 2016
Accepted 22 October 2016
Available online 22 October 2016

Keywords:
Biodegradable elastomers
Heart valve tissue engineering
Anisotropy
Microarchitecture
Biomaterial property
Biocompatibility
Synthetic elastomers

A B S T R A C T

Valvular heart diseases are the third leading cause of cardiovascular disease, resulting in more than 25,000 deaths annually in the United States. Heart valve tissue engineering (HVTE) has emerged as a putative treatment strategy such that the designed construct would ideally withstand native dynamic mechanical environment, guide regeneration of the diseased tissue and more importantly, have the ability to grow with the patient. These desired functions could be achieved by biomimetic design of tissue-engineered constructs that recapitulate *in vivo* heart valve microenvironment with biomimetic architecture, optimal mechanical properties and possess suitable biodegradability and biocompatibility. Synthetic biodegradable elastomers have gained interest in HVTE due to their excellent mechanical compliance, controllable chemical structure and tunable degradability. This review focuses on the state-of-art strategies to engineer biomimetic elastomeric scaffolds for HVTE. We first discuss the various types of biodegradable synthetic elastomers and their key properties. We then highlight tissue engineering approaches to recreate some of the features in the heart valve microenvironment such as anisotropic and hierarchical tri-layered architecture, mechanical anisotropy and biocompatibility.

Statement of Significance

Heart valve tissue engineering (HVTE) is of special significance to overcome the drawbacks of current valve replacements. Although biodegradable synthetic elastomers have emerged as promising materials for HVTE, a mature HVTE construct made from synthetic elastomers for clinical use remains to be developed. Hence, this review summarized various types of biodegradable synthetic elastomers and their key properties. The major focus that distinguishes this review from the current literature is the thorough discussion on the key features of native valve microenvironments and various up-and-coming approaches to engineer synthetic elastomers to recreate these features such as anisotropic tri-layered architecture, mechanical anisotropy, biodegradability and biocompatibility. This review is envisioned to inspire and instruct the design of functional HVTE constructs and facilitate their clinical translation.

Contents

* Corresponding author at: 808A Salk Hall, 3501 Terrace Street, Pittsburgh, PA 15261, USA.
E-mail address: shs149@pitt.edu (S. Sant).

http://dx.doi.org/10.1016/j.actbio.2016.10.032
1742-7061/

1. Introduction

Valvular heart diseases represent a major public health issue affecting more than 5 million adults in the US alone [1]. Valvular heart disease remains a serious concern and economic burden, particularly in pediatric patients with the incidence of 1–2 cardiac valve defects in 1000 births in US, and 8 in 1000 births globally [2,3]. Each year, more than 25,000 deaths in the US and 3% of sudden deaths in the European Union are caused by cardiac valve defects [4]. In addition, recent epidemiology forecast a dramatic increase in the prevalence of valvular heart disease in the next 50 years due to the increasing aging population [5]. In spite of the tremendous interdisciplinary efforts in understanding heart valve pathology, drug/therapy development and clinical healthcare over the past few decades, a substantial unmet clinical need in treating valvular heart diseases remains. Currently available heart valve replacements including mechanical valves and bioprosthesis suffer from thromboembolic complications and low durability, respectively [6–8]. More importantly, both valve replacements are not viable and cannot grow with patients [9]. In addition, mechanical valves require lifelong administration of anticoagulants and bioprosthetic valves likely need re-operation, often multiple re-operations, especially for pediatric patients [10].

To overcome the drawbacks of current therapies, heart valve tissue engineering (HVTE) has been proposed as a promising strategy for regenerating and/or repairing diseased valve tissue [11–14]. Tissue engineering can enhance the limited self-healing capacity of damaged, malformed, or diseased tissue by guided reconstruction of native extracellular matrix (ECM)-mimetic microenvironment with adequate biomechanical integrity and by providing the necessary biomimetic physical and biological cues [15]. HVTE is of special significance and potential because valvular heart diseases often result in substantial loss of healthy cells as well as disruption of normal tissue microenvironment that are beyond the repair capacity of native valves [16]. Therefore, biomimetic tissue-engineered heart valve constructs that can deliver cells, provide mechanical support and biological cues to promote valve regeneration are in critical need [17,18]. Among different strategies of HVTE, constructs prepared from synthetic materials have been well established and recognized as one of the promising tools to engineer microenvironments mimicking native heart valve ECM [19]; however, they are yet to be tested in a clinical setting [4]. Ideally, HVTE scaffolds should mimic the complex hierarchical and anisotropic structure of valve leaflet ECM and withstand the dynamic mechanical environment *in vivo*. In HVTE, biodegradable synthetic elastomer-based constructs offer a wealth of benefits including: 1) more controllable material composition and structure than natural materials, thus minimizing the variance between batches (although the use of recombinant proteins can also circumvent this problem) [20]; 2) high mechanical compliance and elastic behavior, which enables them to endure the high demand of cyclic stretch and relaxation processes experienced by native valve tissue *in vivo* [21]; 3) low immunogenicity and toxicity because the degradation products are mostly endogenous metabolic molecules [22]; 4) tunable degradation rates that will balance evolving mechanical properties due to gradually degrading matrix and new ECM secretion by the regenerating tissue [23,24]; and 5) ease of processability by common material fabrication methods such as molding, spraying, spinning and stereolithography [20]. Therefore, synthetic biodegradable elastomers are especially suitable material candidates for HVTE scaffolds [20,21,25–28].

In spite of the exponential growth in HVTE research, a mature tissue-engineered heart valve construct made from synthetic biodegradable elastomers has yet to be developed for clinical use [4]. Such slow progress towards clinical translation can be attributed to several challenges in the field. One important feature responsible for valve function is the complex multiscale hierarchical architecture and tri-layer structure of native valve leaflets. This consists of anisotropic fibrous layers of ventricularis and fibrosa which are instrumental for closing and opening of the leaflets. In addition, middle proteoglycan-rich spongiosa provides shock-absorbing properties (discussed in section 3). Recapitulation of such intricate structure in synthetic elastomers is still challenging although this may aid in the design of functional valve. Many researchers in the materials science as well as tissue engineering field are working towards developing functional heart valves, yet lack of materials with tunable degradation rates and processability to capture fibrous structure with mechanical compliance along