Acta Biomaterialia xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Acta Biomaterialia

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

Review article

Integrated approaches to spatiotemporally directing angiogenesis in host and engineered tissues

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ARTICLE INFO

Article history:
Received 26 September 2017
Received in revised form 15 December 2017
Accepted 15 January 2018
Available online xxxx

Keywords:
Angiogenesis
Biomaterials
Vascularization
Growth factors
Cardiac tissue
Tissue engineering

ABSTRACT

The field of tissue engineering has turned towards biomimicry to solve the problem of tissue oxygenation and nutrient/waste exchange through the development of vasculature. Induction of angiogenesis and subsequent development of a vascular bed in engineered tissues is actively being pursued through combinations of physical and chemical cues, notably through the presentation of topographies and growth factors. Presenting angiogenic signals in a spatiotemporal fashion is beginning to generate improved vascular networks, which will allow for the creation of large and dense engineered tissues. This review provides a brief background on the cells, mechanisms, and molecules driving vascular development (including angiogenesis), followed by how biomaterials and growth factors can be used to direct vessel formation and maturation. Techniques to accomplish spatiotemporal control of vascularization include incorporation or encapsulation of growth factors, topographical engineering, and 3D bioprinting. The vascularization of engineered tissues and their application in angiogenic therapy *in vivo* is reviewed herein with an emphasis on the most densely vascularized tissue of the human body – the heart.

Statement of Significance

Vascularization is vital to wound healing and tissue regeneration, and development of hierarchical networks enables efficient nutrient transfer. In tissue engineering, vascularization is necessary to support physiologically dense engineered tissues, and thus the field seeks to induce vascular formation using biomaterials and chemical signals to provide appropriate, pro-angiogenic signals for cells. This review critically examines the materials and techniques used to generate scaffolds with spatiotemporal cues to direct vascularization in engineered and host tissues *in vitro* and *in vivo*. Assessment of the field's progress is intended to inspire vascular applications across all forms of tissue engineering with a specific focus on highlighting the nuances of cardiac tissue engineering for the greater regenerative medicine community.

Contents

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https://doi.org/10.1016/j.actbio.2018.01.017
1742-7061/

1. Introduction

The regenerative potential of the human body after injury or disease is variable across different organs and tissues. In any healing scenario, there is a need for local microvasculature so that cells and proteins can be transported to the site of the injury to initiate and support the wound-healing response [1]. Furthermore, a hierarchical vascular bed is necessary to efficiently deliver blood to tissues, which necessitates a balance of capillaries and larger arteriolar vessels. The wound healing process is particularly paramount in organs like the brain and heart that have little regenerative potential, but where functional recapitulation of the damaged tissue is necessary for the continued health of the host. However, even with therapeutic intervention it is not yet possible to achieve this. For example, the high metabolic demand of cardiac tissue necessitates a high density, perfusable vascular network for sufficient nutrient and oxygen flux throughout the tissue. Consequently, the human heart has a dense vessel network of 2000–3000 capillaries/mm^2 and ~108 arterioles/mm^2, which supports the terminally differentiated, non-proliferative cardiomyocytes that endow contractile function [2–5]. Major coronary events such as a myocardial infarction (MI) can cause localized cell death if the tissue is not quickly supplied with adequate oxygen and nutrients, followed by fibrous scar tissue formation over the infarct area [6]. Post-MI complications such as reduced ejection fraction, ventricular hypertrophy, and arrhythmias can arise and lead to progressive heart failure wherein the heart is unable to pump enough blood to the rest of the body [7]. Cardiac tissue engineering seeks to regenerate the contractility of the heart that is lost following MI, but efforts up to this point have been unable to achieve full functional restoration, which may be partially attributed to the fact that currently implantable engineered constructs evaluated *in vivo* develop microvascular densities ~7-fold lower than that of the native heart [8]. The only suitable therapy for end-stage heart failure patients is a heart transplant, but a lack of available donors and potential surgical complications make this a limited option for clinicians and patients [3]. Indeed, the shortage of donor organs is a ubiquitous issue across many conditions, and tissue engineering solutions hold promise to alleviate this problem through the development of therapies to restore tissue function.

In tissue engineering, scaffolds made of degradable biomaterials are commonly used to facilitate the creation, growth, implantation, and integration of cells with the host [7,9]. However, there are a significant number of considerations involved in creating these tissues. One such challenge is the generation of thick, complex engineered tissues with sufficient microvasculature to support oxygen and nutrient transport between cells. The diffusional limit of oxygen restricts cells to being in close proximity to a capillary in order to acquire an adequate flux of oxygen, and the highly metabolic cardiomyocytes of the heart must be within 100–200 μm of a capillary for this reason [10–12]. The presence of a developed vascular network would have significant downstream effects on the success of the whole engineered tissue, namely enabling the development of more dense construct that better approximates the native tissue, allowing for superior inosculation with host vasculature upon implantation, and even having implications in remodeling and maturation, such as electrical syncytium formation in cardiac tissue [9,10]. Thus, one of the major current goals of tissue engineering and regenerative medicine is the vascularization of 3D tissue constructs to mimic the networks of host tissue.

Complex physical and chemical mechanisms act on endothelial cells (ECs) to initiate angiogenesis followed by further processes to remodel and mature vasculature, which tissue engineers seek to emulate *in vitro* and *in vivo* through several methods [13]. Of interest in this review are techniques involving the manipulation of biomaterials to act as topographical signals to direct angiogenesis, and exposure to select growth factors (GFs) to similarly influence network formation [3,10,14]. Excellent reviews on biomaterial formulation and production for tissue engineering are found elsewhere [3,9,15–17]. However, a major obstacle and yet unmet need in the field is developing angiogenic systems of sufficient complexity such that dense and perfused microvascular networks form. Recent studies have attempted to introduce more sophisticated uses of physical and chemical cues to selectively induce angiogenesis in engineered tissues, including *in vitro* prevascularization and encouraging penetration of host vasculature into implants via *in situ* tissue engineering methods. This review summarizes recent methods of spatiotemporally controlling angiogenesis in engineered tissues using biomaterials and combinatorial biological cues, including growth factors. Techniques are drawn from all forms of vascular tissue engineering with the purpose of understanding, inspiring, and applying design considerations for spatiotemporal control across all of tissue engineering and within the subfield of cardiac tissue engineering.

2. Vessel development and physiology

The formation of vascular networks in the body begins early in embryonic development, and dynamic changes to the network occur throughout life in response to both stimulatory and inhibitory signals. Neovascularization arises through both vasculogenesis and angiogenesis, in which EC precursors differentiate into arterial, venous, or lymphatic endothelium. While angiogenesis is more commonly utilized in tissue engineering applications, it is

Please cite this article in press as: R.J. Kant, K.L.K. Coulombe, Integrated approaches to spatiotemporally directing angiogenesis in host and engineered tissues, Acta Biomater. (2018), https://doi.org/10.1016/j.actbio.2018.01.017