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Engineered systems for therapeutic angiogenesis

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Ischemic disease caused by insufficient blood supply leads to a lack of oxygen and nutrients and a build-up of waste products in the affected tissue. Therapeutic angiogenesis, as a means to enhance perfusion of tissues with an inadequate blood supply, holds great promise for the treatment of ischemic disease. A wide range of factors that play a key role in physiological angiogenesis have been identified and trialed as pro-angiogenic agents. However, as yet pro-angiogenic treatments have failed to be translated clinically, owing to both lack of efficacy and safety concerns regarding the use of doses considerably larger than is typical present under physiological conditions. Thus, there is a clear need for the design and development of systems to overcome these hurdles and allow for the translation of safe and efficacious treatments to induce angiogenesis. In this regard, much progress has been made in the development of biomaterials as delivery systems for angiogenic factors to control the delivery and release of angiogenic therapies to induce vascularization. Thus, we review progress towards the development of translatable biomaterial-based systems to deliver angiogenic therapies, and point towards burgeoning advances in the field.

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Introduction

Tissue ischemia and insufficient vascular supply as a result of cardiovascular disease leads to a lack of oxygenation and nutrients, along with a build-up of waste products of metabolism. This results in organ and tissue failure, which can lead to limb amputation or death in the longer-term. In fact, cardiovascular disease is listed as the cause of death in approximately one in three deaths in the United States of America [1]. With cardiovascular disease, including peripheral arterial disease, such a prevalent cause of mortality there is a clear demand and need for clinical therapies to revascularize ischemic tissue. In particular, treatments that can vascularize ischemic tissue and promote the regeneration of damaged tissue are urgently needed.

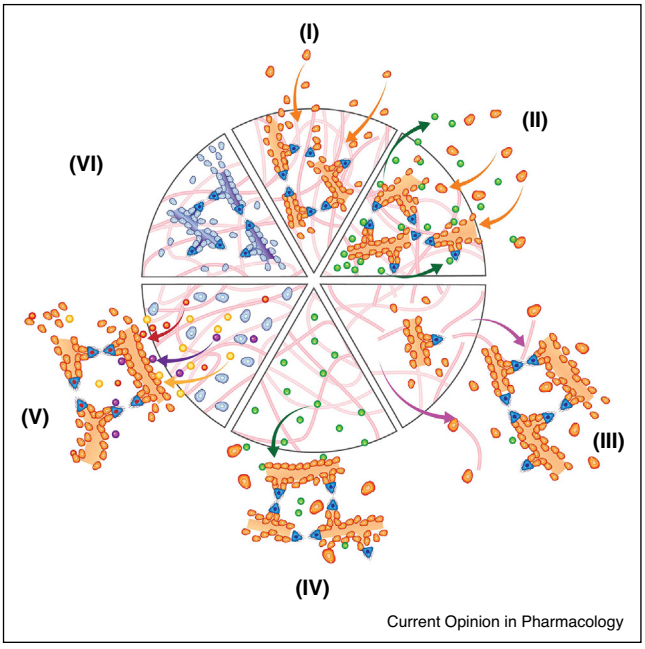
An understanding of the molecular mechanism of angiogenesis has allowed for the identification of key pathways, growth factors and cells that can promote the formation of vasculature. Typically, tissue hypoxia triggers the upregulation of a range of pro-angiogenic growth factors and the creation of gradients of factors [2]. This leads to enhanced endothelial cell migration and proliferation, resulting in the formation of new blood vessels. However, the endogenous capacity for revascularization is not always sufficient to compensate for blockage of major arteries supplying the extremities of the body. Thus, the delivery of exogenous factors, possibly including cells, is required to promote angiogenesis and revascularization [3,4].

Basic and translational research has helped to identify multiple factors capable of stimulating angiogenesis [5,6]. Furthermore, many cell types have been tested as a cell therapy to induce vascular network formation, either directly or through paracrine support [7–9]. Regardless of the therapeutic or its mode of action, delivery and retention near the ischemic site is crucial. In this context, biomaterials are ideally suited as they can be used for local delivery and retention of the therapeutic near the application site, as well as the delivery of multiple factors [10].

Choice of biomaterials

Angiogenesis is a multi-stage process involving multiple regulators that play a key role at different stages [11,12]. Increased matrix metalloproteinase (MMP) activity leads to degradation of the vascular basement membrane and the loosening of endothelial cells of the local vasculature [12–14]. Temporal expression of growth factors and the creation of gradients of both soluble and immobilized factors stimulate endothelial cell proliferation and migration through the extracellular matrix (ECM), interacting with adhesion ligands present on collagen, fibronectin and elastin [15]. Furthermore, biomaterials may induce angiogenesis through a wide range of mechanisms, as shown in Figure 1, including through the temporal release of factors and the creation of gradients of factors. However, there exists a wide variety of biomaterial systems that exhibit significant variations in terms of capacity to bind and release factors, as well as intrinsic biological activity and the ability to stimulate angiogenesis. In terms of the choice of material, synthetic polymers, natural

Figure 1



Mechanisms mediated through biomaterials to induce angiogenesis. (I) Providing a scaffold for cell infiltration and vessel formation. (II) Allowing for the formation of gradients of factors promoting cell infiltration and vessel formation. (III) Components and degradation products of the scaffold promote angiogenesis in the surrounding tissue microenvironment. (IV) The release of factors to promote angiogenesis in the surrounding tissue microenvironment. (V) The encapsulation of implanted cells that release paracrine factors to promote angiogenesis in the local microenvironment. (VI) Encapsulated cells may themselves align into vascular networks and form blood vessels.

ECM-based materials and hybrid materials may be used. Synthetic materials are typically simpler to process and manipulate than ECM-based materials, and have less batch-to-batch variation. However, synthetic materials lack bioactivity, cell adhesion domains and are not capable of MMP-mediated degradation, unless these properties are specifically engineered into the material. Furthermore, synthetic materials and their degradation products can potentially be toxic to cells and tissues, limiting the number of suitable materials available. In contrast, ECM-based materials are intrinsically bioactive, support cell adhesion and can be remodeled by cell-secreted enzymes and MMPs. Furthermore, many natural biopolymers, including collagen and fibrin [16], themselves stimulate angiogenesis without the need for the incorporation of angiogenic stimulants. The inherent angiogenic properties of ECM-biomaterials and their degradation products highlight them as suitable for the promotion of angiogenesis. ECM-based biomaterials can act as templates for the formation of vasculature due to the angiogenic signals present in the ECM [17,18•]. A number of wound healing products such as Dermagraft® and Apligraf® take advantage of this process to encourage vascularization and wound healing of diabetic foot ulcers without the complexity that addition of a therapeutic angiogenic factor would bring. Hybrid materials are engineered to combine the optimal properties of synthetic and ECM-based materials, which allow increased control over mechanical properties without compromising bioactivity and biodegradation.

As well as the choice of material and therapeutic, the form it takes is also a key consideration in designing angiogenic systems (Figure 2). For example, angiogenic promoting cells or factors may be delivered in materials taking the form of particles, solid scaffolds or injectable hydrogels. Each form has distinct advantages and properties that make them attractive for particular applications. For example, particle-based systems and *in situ* forming hydrogels can typically be injected into tissue, allowing for minimally invasive delivery. In contrast, solid scaffolds require surgical implantation that can itself be a cause of trauma. However, solid scaffolds have an increased structural integrity compared to hydrogels or particle systems. Thus, solid scaffolds are more appropriate for load-bearing applications such as bone. Hence, the choice of material and the form it takes must be considered carefully with regards to the application.

Delivery of growth factors

Growth factors play a key role in physiological angiogenesis, and many have been identified for their potential as angiogenic therapeutics. However, promising pre-clinical data has failed to translate to the clinic due to disappointing results in clinical trials. The failure of growth factor therapies has been explained by their short half-life *in vivo*, poor retention kinetics and the use of either insufficient or excessive doses. Material-based delivery strategies do exist, such as their conjugation to poly (ethylene glycol) (PEG), known as PEGylation. In a first-in-man study, it was shown that PEGylation of insulin-like growth factor (IGF-1) enhanced its half-life in circulation following subcutaneous injection or intravenous administration [19]. Regranex®, which is composed of recombinant human PDGF in a hydrogel delivery system, has also been approved for the treatment of diabetic ulcers of the lower extremities. Thus, modes of delivery and retention within the tissue of interest are key to the development of such therapeutics. Biomaterial systems, engineered to ensure delivery to the appropriate tissue as well as the correct retention kinetics are key to the realization of growth factor-based therapies.

The primary aim of delivery systems is to protect their cargo and deliver it to the local tissue in a temporal manner. In this respect, many combinations of growth factors and biomaterials have been trialed (Table 1). Having been identified as a key player in physiological angiogenesis, vascular endothelial growth factor (VEGF)