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Hydrogels for therapeutic cardiovascular angiogenesis☆

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ABSTRACT

Acute myocardial infarction (MI) caused by ischemia is the most common cause of cardiac dysfunction. While growth factor or cell therapy is promising, the retention of bioactive agents in the highly vascularized myocardium is limited and prevents sustained activation needed for adequate cellular responses. Various types of biomaterials with different physical and chemical properties have been developed to improve the localized delivery of growth factor and/or cells for therapeutic angiogenesis in ischemic tissues. Hydrogels are particularly advantageous as carrier systems because they are structurally similar to the tissue extracellular matrix (ECM), they can be processed under relatively mild conditions and can be delivered in a minimally invasive manner. Moreover, hydrogels can be designed to degrade in a timely fashion that coincides with the angiogenic process. For these reasons, hydrogels have shown great potential as pro-angiogenic matrices. This paper reviews a few of the hydrogel systems currently being applied together with growth factor delivery and/or cell therapy to promote therapeutic angiogenesis in ischemic tissues, with emphasis on myocardial applications.

Contents

1. Introduction

Vascular disease has become one of the leading causes of death in the Western world and increasingly in the developing world. The primary cause of this disease is atherosclerosis, the narrowing of the arteries and small blood vessels by plaque deposition. It commonly attacks the blood vessels of the brain, heart and lower limbs — which then results in vessel occlusion and blockage of blood flow. The subsequent ischemia leads to tissue damage and dysfunction. Currently, there are several treatment options for blocked blood vessels such as angioplasty, stenting, thrombolysis and surgical bypass. While these treatments are well established, they have their inherent limitations and complications and also typically do not regenerate the damaged organs. Therefore, there is a need to develop new strategies for regenerating tissue following ischemia. These strategies aim to augment tissue repair by improving the natural mechanism by which new blood vessel growth is induced. This process is known as therapeutic angiogenesis and it is one of the most active areas of research in tissue engineering.

There are two main processes that are responsible in the formation of blood vessels. They are vasculogenesis and angiogenesis. Vasculogenesis tends to occur in embryos where new vessels are formed de novo via the assembly of mesoderm-derived endothelial precursors known as angioblasts, creating primitive vessel networks [1]. While it was often associated with embryonic development, it has also been reported to

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take place in postnatal development [2]. The endothelial progenitor cells (EPCs) associated with vasculogenesis are generally identified as CD34, Flk-1, or CD133 antigen-positive cells and can be derived from bone marrow or peripheral blood. They are capable of differentiating in situ into mature endothelial cells (ECs) for blood vessel formation.

Angiogenesis involves outgrowth of new blood vessels from pre-existing ones [3–5]. The angiogenic process is more complex as compared to vasculogenesis and, consists of 4 chronological steps. First is the stimulation of ECs by angiogenic factors such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Next is the degradation of the surrounding capillary basal lamina by activated ECs via extracellular proteinases such as matrix metalloproteinases (MMPs). This is followed by capillary sprout formation and migration of ECs mediated by their integrins. Lastly, vessel maturation occurs through the actions of growth factors such as angiopoietin-1 (Ang-1) or platelet derived growth factor (PDGF). Two important players in vessel maturation include differentiated pericytes and smooth muscle cells that are known to suppress EC growth [6].

Although growth factors such as PDGF and VEGF are potent regulators of the cellular events leading to formation of new and stable blood vessels, ample evidence also points to an equally important role of the extracellular matrix (ECM) in this process. ECM components bind cells directly through specific interactions with adhesion molecules present on the cell surface [7]. In addition, the ECM sequesters the growth factors that interact either directly or indirectly with cell surface receptors to stimulate morphogenesis and tissue repair. Understanding the duality of the ECM's role in binding cells and liberating sequestered growth factors is crucial for designing instructive bioactive materials that effectively guide tissue morphogenesis [8]. In angiogenesis, there are several ECM components – both soluble and insoluble – that are capable of binding angiogenic growth factors such as VEGF and liberating them in response to cell-mediated enzymatic degradation of the ECM [9]. The exact role of growth factor binding motifs and the liberation of growth factors in this process is highly complex and variable, involving the formation of gradients in vivo that can guide directional sprouting of new vessels [10]. Heparin sulfates, for example, which are sulfated proteoglycans of the ECM, are capable of binding various isoforms of VEGF with selectivity in order to produce such gradients [11].

Bioactive material systems that are specifically designed to promote angiogenesis should mimic – to some extent – the complexity in which natural ECM presents growth factors to resident cells in vivo. Hydrogels are by far the most prevalent type of biomaterial that has been engineered to sequester growth factors and liberate them with spatial and temporal coordination. There are a number of different types of hydrogels that can be used as the basic building elements of the pro-angiogenic material system, including those derived from natural building block such as hyaluronic acid or fibrin, or those that are synthesized from polymeric precursor molecules such as polyethylene glycol (PEG). Irrespective of how they are derived, hydrogels must be further modified, or engineered, in order to properly display growth factors and/or cell binding motifs in such a way as to effectively interact with vascular cells and to promote functional angiogenesis.

In this review, we focus on the recent developments in the field of hydrogels as biomaterial scaffolds for angiogenesis in cardiovascular diseased models such as myocardial infarction (MI) and hind limb ischemia (HLI). Tables 1 and 2 provide a summary of various hydrogel-based approaches used for MI and HLI. We underscore the importance of applying the substantial knowledge available from basic vascular biology research into biomaterial-based therapeutic approaches – such as hydrogel design and development – in order to realize the true clinical potential in this field.

2. Hydrogels in therapeutic angiogenesis

Various types of biomaterials with different physical and chemical properties have been developed to improve the localized delivery of growth factors for therapeutic angiogenesis in ischemic tissues (Fig. 1). Hydrogels are attractive scaffold biomaterials because they are structurally similar to the tissue extracellular matrix (ECM); they can be processed under relatively mild conditions and can be delivered in a minimally invasive manner. Moreover, hydrogels can be designed to degrade in a timely fashion that coincides with the angiogenic process. For these reasons, hydrogels have shown great potential as pro-angiogenic matrices.

Several natural and synthetic hydrogel matrices have been used as agents to deliver angiogenic factors. Natural molecules that have been used in hydrogel design include proteins such as collagen, gelatin and

Table 1
Summary of biomaterials used to deliver growth factors in diseased animal models.

Biomaterial	Growth factors used	Diseased animal model	Results	Reference
Alginate	VEGF	Mouse hindlimb ischemia	Superior degree of vascularization observed	L.Y. Kee et al. (2000)
Heparinized alginate	bFGF	Chronic porcine myocardial ischemia	Significant angiogenesis, no acute hemodynamic effects, no significant toxicity, smaller infarct size	K. Harada et al. (1994)
Heparinized alginate	bFGF	Chronic porcine myocardial ischemia	Significant angiogenesis, no acute hemodynamic effects, no significant toxicity, smaller infarct size	J.J. Lopez et al. (1997)
Alginate-sulfate	HGF	Rabbit ischemic hindlimb	Improved tissue perfusion and mature blood vessel formation	E. Ruvinov et al. (2010)
Alginate	VEGF and PDGF-BB	Rodent myocardial infarction	More mature vessels with improved cardiac function	X. Hao et al. (2007)
Chitosan	FGF-2	Chronic rabbit myocardial infarction	Improvement in systolic pressure at the left ventricle, larger amount of viable myocardium and blood vessels	M. Fujita et al. (2005) [28]
Fibrin	NIL	Rabbit hindlimb ischemia	Augmentation of collateral vessel development and improved limb perfusion	C.L. Fan et al. (2006) [33]
Fibrin	NIL	Rabbit hindlimb ischemia	Augmentation of collateral vessel development and improved limb perfusion	V.S. Chekanov et al. [34]
Heparin-conjugated fibrin	bFGF	Murine hindlimb ischemia	Enhanced neovascularization and significant reduction in muscle fibrosis and inflammation	H.S. Yang et al. (2010) [44]
Fibrin	Engineered variant of $VEGF_{164}$; α_2-PI_{1-8}-VEGF-A_{164}	Rodent hindlimb ischemia and wound healing	Stable and functional angiogenesis with improved perfusion	V. Sacchi et al. (2014) [45]
PEG-fibrinogen hydrogel	VEGF	Rodent myocardial infarction	Enhanced vascularization in the ischemic myocardium and improved cardiac function observed	A.J. Rufaihah et al. (2013) [47]
PLG	VEGF	Murine hindlimb ischemia	Improved lower extremity perfusion, greater degree of mature vasculature	Q. Sun et al. (2005) [54]
PLGA polymer scaffold	VEGF and PDGF	Mouse hindlimb ischemia	High proportions of mature blood vessels and increased number of collaterals	T.P. Richardson et al. (2001) [55]