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Opinion Article

Incorporation of Extracellular Matrix-Binding Peptides into Hydrogel Network: A Strategy to Mimic the Stem Cells Microenvironment in 3D Conditions

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Abstract

The advancement of science and medicine in recent decades has improved human health care resulting in increased quality and length of life. The progress of regenerative medicine has opened new venues for therapeutic techniques to treat cancer and traumatic injuries. The development of three-dimensional materials that can closely mimic the conditions cells are presented with in vivo is a great challenge in biomaterials development for regenerative medicine applications. Synthesised scaffolds should be tuneable in terms of their mechanical properties to be suited for regenerative applications. In addition, these materials should provide cells with a platform such that they can survive, differentiate, and proliferate. The incorporation of ECM proteins binding peptides into the polymeric network can be an effective strategy to provide cell-supporting biomaterials with the additional benefit of supporting cells to generate their in vivo-like microenvironment within hydrogels.

Keywords: Hydrogels; Peptides, ECM proteins, Regenerative medicine.

Introduction

Extracellular matrix (ECM) molecules are known to play a crucial role in determining stem cell behaviours, such as adhesion, migration, proliferation, and differentiation. The ECM is a highly dynamic system that is both produced and remodelled by the cells. Variations in the ECM give rise to the different structures that contribute to the characteristics of different tissues and organs. ECM molecules could interact specifically with each other to form three-dimensional networks that create supportive microenvironments for cells that are dynamically modulated (degraded and

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rebuilt) by the same cells [1]. The ECM consists of a multitude of different molecules, including proteins, glycoproteins, proteoglycans, and glycosaminoglycans (GAG). Providing a scalable, degradable synthetic hydrogel platform that enables cells to remodel their microenvironment (as they would in vivo), and, that allows for the recruitment or templating of cell-secreted ECM proteins, would represent a significant step forward in the field of tissue engineering [2]. Many of the current synthetic hydrogel systems are unable to recapitulate such remodelling characteristics of the cell secretome, excepting their ability to degrade protein/polymer chains throughout such hydrogels. Therefore, a need to develop biomaterial systems capable of capturing ECM proteins that are secreted from cells can enhance the effectiveness of these polymeric systems for regeneration medicine applications.

ECM proteins contain domains that bind other ECM proteins; these can be identified and reproduced as peptides to bind specific ECM molecules without the need to replicate the entire protein sequence [3]. For instance, through binding to the secreted fibronectin, fibronectin-binding peptides can allow the creation of a platform for the retention of other proteins. It helps maintain the fibrillar organization of collagen I by cross-linking to the α1(I) region of collagen. It also possesses binding sites to collagen VII which is a component of the basement membrane in cells. Since Collagen I and VII, bind to fibronectin, incorporating a fibronectin-binding peptide within the biomaterial network can improve the retention of fibronectin and other ECM proteins secreted by cells that bind to fibronectin. Therefore, this strategy can be beneficial in cases where there are not enough peptide binding sites in the backbone polymeric network. Collagen I, which is the most abundant protein structure in the ECM proteins, can be a great candidate to derive ECM-mimicking peptides. Type I collagen also provides the major framework needed for mesenchymal tissues to function [4]. Laminin-binding peptides can also be incorporated into biomaterials. Laminin interacts with other ECM proteins such as collagen IV, nidogen heparin sulphate proteoglycan [5] and heparin through multiple specific binding sites.

When designing biomaterials capable of incorporating protein bind peptides, the number of available binding sites for the peptides is important. Functionalised star polymers can be a good candidate as they can provide several binding sites for binding a different peptide as well as cross-linking. In addition, they provide the luxury of tuning the peptides ratios that can potentially enable researchers to push the differentiation of stem cells into the desired lineage via remodelling of the cells' microenvironment. Polyethylene glycol (PEG)-base hydrogels are a suitable biomaterial due to their bioinert and non-fouling properties, as well as ease of end-group functionalisation. These hydrogels have also been functionalised to mimic the properties of ECM [6]. It is shown that using PEG, it is possible to make hydrogels with a wide range of mechanical properties [3]. One way to synthesise and conjugate PEG-based hydrogels is using click chemistry. Click chemistry is referred to reactions that are fast, simple to use, easy to purify, and with high reaction yields. This technique is of interest

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due to the high yields that are achievable under mild physiological conditions. This technique enables researchers to generate substances quickly by joining small units together.

Another important factor in designing such protein-binding-peptide-based biomaterials is the final 3D conformation of peptides presented within the biomaterials network. The presentation of the peptide can make a difference in the effectiveness of these peptides. When presented in a 2D surface network, the availability of peptides to bind specific proteins is significantly higher than when presented in the 3D conformation. Noting that in many cases, there might be a need to add specific amino acid to one terminus of the peptide to bind the peptide to the specific group in the network. There might also be a need to add spacer peptides to increase the availability of peptides for binding to the specific protein. Great care must be taken to these additional amino acids to ensure the binding affinity of the peptides is not compromised. Peptide length is another factor that affects the conformation of presented peptides in 3D and therefore their binding affinity. Furthermore, the synthesized peptides should be biocompatible. The cytotoxicity of these peptides should be factored in when adding to the network. Attention to the purity of peptides that is synthesis and removal of all toxic by-products of peptide synthesis is paramount.

Although the development of biomaterials (hydrogels) based on the ECM-protein binding peptides has gained researchers' attention in recent years, there is a lack of information in animal studies. Researchers have successfully shown that these peptides can recruit the ECM protein secreted from the cell in ex vivo [2], however, these hydrogels should be applied in animal studies to better understand their effectiveness under in vivo conditions.

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