BIOACTIVE HYDROGELS FOR CARDIOVASCULAR TISSUE ENGINEERING

Deon Bezuidenhout

Cardiovascular Research Unit, Chris Barnard Building, Faculty of Health Sciences, Anzio Road, Observatory 7925 SA
Deon.Bezuidenhout@uct.ac.za

ABSTRACT

Apart from its well-known antithrombotic properties, heparin has been shown to moderate smooth muscle cell proliferation, reduce inflammatory response, and facilitate angiogenesis by the stabilization and potentiation of growth factors (GF)[1]. These properties are potentially useful in tissue engineering applications, especially when delivered as hydrogels in a localized fashion by deposition or injection, as they may facilitate the formation or regeneration of tissues without adverse systemic effects.

To test this hypothesis, heparin was modified so that it would (i) allow covalent incorporation into polyethylene glycol (PEG) gels formed by spontaneous nucleophilic addition, (ii) result in controlled hydrolytic release of the heparin from the gels in its original, unmodified state, with or without concomitant degradation of the PEG gels, (iii) retain its antithrombotic potential and (iv) facilitate the incorporation and controlled release of growth factors.

Heparin was acrylated and copolymerized with multiarm PEG prepolymers using either 4-arm PEG thiols or cysteine-flanked oligopeptide sequences cleavable by matrixmetaloproteases (MMP) to form persistent, hydrolytically unstable[2] or enzymatically degradable[3] gels. Modification, gelation kinetics, elastic moduli, crosslink density, heparin elution, heparin activity, as well as growth factor incorporation and release were studied in vitro. Subcutaneous implants of porous polyurethane scaffolds containing gels were performed in a rat model (28d) to determine the effect of the controlled release of heparin and GF on healing and angiogenesis, while enzymatically-degradable gels were investigated for the treatment for myocardial infarction (MI), including its use as a vehicle for delivery of stem cells to the infarcted area.

Gels, formed within minutes of admixture, had equilibrium storage moduli ranging from 1-8kPa. Incubation in PBS resulted in equilibrium swelling followed by either (i) steady decrease in crosslink density until disintegration over 3 weeks (hydrolytically degradable gels) or (ii) constant swelling ratios over extended time (persistent and enzymatically degradable gels). Controlled zero and first order release of heparin was achieved with hydrolytically and persistent gels respectively. Heparin was active in its ability to delay the clotting of whole blood, either in the original form, after modification, or after the incorporation and release. The gels showed controlled GF delivery in vitro, and resulted in increased vascularization of porous scaffolds in vivo. Enzymatically degradable gels had a positive effect on wall thickness, heart function[4], and the survival of stem cells in the MI model.

These gels are useful for cardiovascular and other tissue engineering and regeneration applications such as vascular grafts and the treatment of myocardial infarction, as they are antithrombotic, able to facilitate angiogenesis and improve cell retention.

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References

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