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Perspective

Self-Assembling Peptide Hydrogels as Injectable Scaffolds for Enhanced Cardiac Regeneration Post-Myocardial Infarction

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DESCRIPTION

Myocardial Infarction (MI) leads to irreversible cardiomyocyte loss and subsequent cardiac remodeling, often progressing to heart failure despite current interventions. Cell-based therapies have shown limited success, primarily due to poor retention and survival of transplanted cells in the hostile post-infarct environment. We have developed a novel self-assembling peptide hydrogel that forms a nanofibrous scaffold capable of both improving transplanted cell survival and directly modulating the inflammatory microenvironment to promote endogenous repair mechanisms. The core peptide sequence incorporates alternating hydrophobic and hydrophilic amino acids that undergo spontaneous assembly into nanofibers (10 nm-15 nm diameter) upon exposure to physiological conditions, forming a hydrogel with viscoelastic properties closely matching native myocardium.

Rheological characterization demonstrated shear-thinning behavior ideal for catheter-based delivery, with rapid recovery of mechanical properties (>80% within 60 seconds) following injection. The hydrogel's storage modulus of approximately 20 kPa closely approximates healthy myocardial tissue, providing mechanical support to the infarcted region while maintaining sufficient porosity (pores approximately 50 nm-200 nm) for cellular migration and nutrient diffusion. Additionally, the peptide sequence was engineered to include Matrix Metalloproteinase (MMP)-sensitive degradation sites, ensuring gradual scaffold resorption synchronized with native tissue regeneration. *In vitro* degradation studies demonstrated approximately 50% mass loss by day 21 when exposed to pathologically relevant MMP concentrations, while maintaining structural integrity under physiological conditions.

Cell compatibility studies using Induced Pluripotent Stem Cell-derived Cardiomyocytes (iPSC-CMs) demonstrated excellent viability (>90%) and functional integration within the hydrogel construct. Calcium imaging and contractility assessments revealed synchronized beating behavior within 72 hours of encapsulation, with electrophysiological coupling between adjacent cellular clusters. Transcriptomic analysis of encapsulated iPSC-CMs revealed upregulation of genes associated with maturation and metabolic adaptation compared to standard 2D culture conditions. Furthermore, co-culture experiments incorporating cardiac fibroblasts and iPSC-CMs within the hydrogel resulted in formation of organized micro-tissues with enhanced expression of connexin-43 at intercellular junctions, suggesting improved electrical connectivity.

In a rat model of myocardial infarction, ultrasound-guided intramyocardial injection of the hydrogel containing iPSC-CMs was performed 7 days post-MI. Bioluminescence imaging demonstrated approximately 4-fold improvement in cell retention at 28 days compared to direct cell injection. Echocardiographic assessment revealed significant improvements in ejection fraction (52% *vs.* 37% in control groups) and prevention of adverse ventricular remodeling, as evidenced by reduced end-systolic volumes. Pressure-volume loop analysis at 12 weeks post-treatment demonstrated preserved contractile function and improved diastolic properties compared to cell-only or saline-treated controls. Histological analysis revealed extensive vascular network formation within the hydrogel region, with evidence of functional integration between host and transplanted cells as confirmed by electrophysiological mapping studies.

Immunohistochemical characterization at various time points demonstrated a marked shift in macrophage polarization from pro-inflammatory M1 to reparative M2 phenotypes within the infarct region following hydrogel treatment. This immuno-modulatory effect was associated with significant reduction in pro-inflammatory cytokines and increased expression of regenerative growth factors, including Vascular Endothelial Growth Factor (VEGF) and Insulin-like Growth Factor 1 (IGF-1). Terminal studies revealed substantial preservation of myocardial wall thickness and reduced fibrosis compared to controls, with evidence of newly formed cardiomyocytes expressing both host and donor cell markers, suggesting potential paracrine-mediated endogenous regeneration in addition to direct replacement by transplanted cells. This injectable peptide hydrogel platform represents a promising approach for cardiac regeneration,

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combining favorable mechanical properties with biologically active components to create an optimal microenvironment for both transplanted and endogenous repair mechanisms following myocardial infarction.