



Research Article

An injectable anti-vascularization functionalized hydrogel for degenerative nucleus pulposus repair



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ABSTRACT

Neovascularization and inflammatory cell invasion within the nucleus pulposus (NP) constitute pivotal pathological changes during the acceleration stage of intervertebral disc degeneration (IDD). Mesenchymal stem cells (MSCs), renowned for their remarkable capacity in intervertebral disc (IVD) regeneration, also exhibit the capability to secrete pro-angiogenic factors, expediting IDD progression under hypoxic conditions. Consequently, we developed a hydrogel comprised of methacrylated hyaluronic acid (HAMA), rat tail collagen I (COL), and MSCs, incorporating the vascular endothelial growth factor receptor (VEGFR) inhibitor cabozantinib (Cabo@HAMA-COL/MSCs hydrogel). This innovative construct aimed to facilitate NP regeneration while mitigating vascularization and inflammation. Our findings revealed that the hydrogel aptly mimicked the mechanical characteristics of NP tissue, exhibiting injectability, low cytotoxicity, and the preservation of the cellular phenotype of NP cells. Co-culturing of MSCs and human umbilical vein endothelial cells (HUVECs) promoted migration, tube formation, and sprouting of HUVECs, which will be inhibited by cabozantinib. In vivo experiments demonstrated that Cabo@HAMA-COL/MSCs hydrogel maintained disc height, protected NP, and alleviated vascularization and inflammation in a puncture-induced rat caudal IDD model. Consequently, our results substantiate that Cabo@HAMA-COL/MSCs hydrogel can prevent IDD degeneration by ameliorating the vascularization-inflammation pathological microenvironment, offering a promising therapeutic strategy for IDD.

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1. Introduction

Low back pain (LBP), experienced by 60 %–80 % of individuals at some point in their lives [1], represents the most prevalent consequence of lumbar intervertebral disc degeneration (IDD). The intervertebral disc (IVD) comprises the central nucleus pulposus (NP), the peripheral annulus fibrosus (AF), and cartilaginous endplates (EP) [2]. The NP, a highly hydrated gel-like tissue containing collagen II and aggrecan, affords motion flexibility and serves as a stress cushion for the spine. The AF, primarily composed of collagen I, is a dense fibrous tissue that confines the NP and provides stability for the IVD. One research indicated that the vascularization of NP tissue constitutes the most crucial pathological change during the acceleration stage of IDD [3]. As vessels invade, oxy-

gen and inflammatory cells permeate, disrupting the previously hypoxic, avascular, and immune-cell-free microenvironment, thereby significantly hastening IDD progression. Additionally, inflammatory monocyte/macrophage infiltration not only accelerates the degradation of the extracellular matrix (ECM) but also secretes pro-vascular factors such as vascular endothelial growth factor (VEGF) [4], further intensifying vascularization and perpetuating a pathological cycle of “vascularization-inflammation”.

As of now, no medication or treatment capable of retarding or reversing IDD in clinics. While spinal fusion stands as the conventional surgical treatment, it restricts spinal mobility and might induce degeneration in adjacent segments. With advancements in biomaterials and regenerative medicine, the focal point of current research lies *in-situ* injectable NP tissue engineering materials for IVD repair [5]. Clinical practice has witnessed artificial NP transplantation, such as *in situ* hydrating synthetic polymers (PDNTM) and *in situ* forming synthetic polymers (NuCoreTM and BioDiscTM) [6]. Nonetheless, their disparity in mechanical properties and low cell affinity could predispose implant failures,

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