Tailoring *in situ* crosslinked oxidized hyaluronic acid based hydrogels for soft tissue engineering

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Mechanical cues at the cellular scale play a pivotal role in guiding the development, function, and behavior of individual neural cells [1]. Understanding how these microscale forces interact with the local microenvironment is essential for uncovering mechanisms of injury and disease progression, particularly in neural tissues [2]. In this context, biomaterials that closely mimic the extracellular matrix (ECM) and provide tunable mechanical properties are key to advancing neural tissue engineering. Hyaluronic acid (HA), due to its natural presence in the brain and favorable biological properties, is a particularly promising candidate for such applications [3].

We developed ECM-mimicking hydrogels based on oxidized hyaluronic acid (OHA) with tunable mechanical characteristics tailored for soft tissue applications. HA was oxidized using sodium periodate ($NaIO_4$), enabling Schiff base formation with gelatin (GEL). The hydrogel network was further stabilized through enzymatic crosslinking with microbial transglutaminase (mTG), resulting in dual-crosslinked hydrogels. Physicochemical characterization revealed that increasing the GEL content significantly enhanced mechanical stiffness, whereas higher OHA content only slightly improved mechanical properties and primarily affected swelling behavior. The amount of mTG was found to influence stiffness and play a crucial role in the longevity of the hydrogels. OHA-based hydrogels with lower mechanical properties supported the 3D culture of various cell types, including primary neurons, indicating a cell-friendly and ECM-like environment. These findings highlight the potential of OHA–GEL hydrogels for mimicking neural tissue mechanics in soft tissue engineering applications.

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