Biomimetic fibril-like injectable hydrogels for wound management

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Soft tissue repair and regeneration present a significant clinical challenge. Soft hydrogels have emerged as a promising solution for promoting stem cell differentiation and facilitating soft tissue formation [1]. Various materials, including synthetic polymers like polydimethyl siloxane and natural polymers like proteins, have been used as hydrogel matrix for hydrogel preparation [2, 3]. However, the limited biodegradability, inhomogeneous network structure, and inadequate mechanical properties of these hydrogels hinder their long-term application in complex environments in vivo. Inspired by the nanostructure of collagen fibrils, Li et al. developed a strategy for creating injectable nanofibrillar hydrogels by combining self-assembly and chemical crosslinking of nanoparticles [4]. Moreover, injectable hydrogels offer advantages as implantable materials, including better defect filling and reduced risk of infection compared to prefabricated hydrogels [5].

The extracellular matrix of most soft tissues primarily consists of water-insoluble fibrous proteins such as collagen. The assembly of collagen molecules into collagen protofibrils imparts low solubility and exceptional mechanical strength to the extracellular matrix [6]. The presence of hydrophobic groups in collagen molecules contributes to the reduction of water binding to the fiber network. Additionally, the layered filamentous structure of collagen aids in efficient energy dissipation [7]. As a result, biomimetic nanofiber hydrogels have garnered significant interest in the scientific community [7]. Hydroxypropyl chitosan, which is a chitosan derivative, utilizes hydrophobic interactions and intermolecular hydrogen bonding to self-assemble in aqueous solutions and form aggregates [8]. By mimicking the nanostructure and amphiphilic nature of collagen fibers, Li and his colleagues proposed a strategy or creating biomimetic fibril-like hydrogels. This approach involves the combination of self-assembly and chemical cross-linking. Firstly, they formed self-assembled nanoparticles by combining methacryllyl hydroxypropyl chitosan with Laponite (Lap), a 2D nanosized silicate disc with a negatively charged surface and positively charged rim. The electrostatic binding between Lap and positively charged hydroxypropyl chitosan plays a crucial role in the preparation of methacryllyl hydroxypropyl chitosan/Lap (HML) nanocomposite. Then HML nanoparticles were cross-linked using photo-crosslinking to form collagen fibril-like nanostructured hydrogels (Figure 1) [4]. This research by Li et al. presents a promising strategy for the development of biomimetic fibril-like hydrogels, which hold significant potential for long-term biomedical research and applications.

Li and his colleagues successfully synthesized a range of HML hydrogel with varying proportions. They classified these nanocomposites as HMLx, where “x” denotes the hydroxypropyl substitution degrees (DS, 1: 53%, 2: 67%, 3: 75%, 4: 82%) of methacryllyl hydroxypropyl chitosan, and “x” represents the concentrations (mg/mL) of Lap. To evaluate the efficacy of HML nanocomposite in promoting wound healing, the researchers selected HM(Lap) hydrogel as a representative and investigated its impact on cell migration during skin wound healing as cell migration plays a crucial role in wound contraction and late-stage healing [4]. In vitro scratch assays revealed that 1.929 dermal fibroblasts in the HM(Lap) hydrogel group exhibited faster migration compared to the control group (untreated Lap). Additionally, after 4 h, the HM(Lap) hydrogel group showed a significant increase in capillary formation in human umbilical vein endothelial cells.

In comparison to existing wound dressings, the HML hydrogel exhibits remarkable application potential. Its ability to fill irregular wound shapes with diverse pore structures is a notable advantage. Moreover, a growing body of experimental studies has demonstrated the outstanding wound healing properties of HCS or Lap, either alone
or in combination with other factors [9]. Li et al., through wound healing experiment, provided evidence that HMβ4 hydrogel treatment significantly enhanced wound healing by day 3, surpassing the control group [10]. This improvement was sustained in the subsequent days, with an increased presence of new granulation tissue observed by day 7. H&E staining on day 11 revealed complete healing of wounds in the HMβ4 hydrogel group, characterized by a robust connection between the epidermis and dermis. In contrast, the control group still exhibited granulation tissue infiltrated with inflammatory cells. Collectively, these findings support the notion that bionanofiber hydrogels can promote wound healing by facilitating fibroblast migration and revascularization.

These findings have significant implications for future advancements in wound treatments. The self-assembled HML nanocomposites, which form a collagen fibril-like Injectable hydrogel through cross-linking, demonstrate remarkable biocompatibility and the ability to boost wound closure. Compared to other wound dressings, this hydrogel exhibits superior adaptability to the intricate environment within the human body. However, for further clinical applications of HML wound dressings, some issues such as biodegradability and immune response must be carefully considered. Furthermore, the nanocomposite hydrogels can be transformed into 3D printable microgels with exceptional shape fidelity, enabling their use as bioinks for complex structures and larger sizes. This holds immense potential for personalized tissue engineering applications [4].

Moving forward, the advancement and examination of biomimetic nanofiber hydrogels remain a serious challenge. While certain biomimetic nanofiber hydrogels possess fibrous structures and customizable stiffness, many still exhibit limitations in terms of energy dissipation mechanisms and injectivity due to unregulated self-assembly and cross-linking. Consequently, their application in complex environments is restricted. Nonetheless, the approach of utilizing self-assembly and cross-linking to fabricate nanomaterial-based hydrogels presents a promising and versatile strategy for the development of biomimetic hydrogels dressings.

To conclude, the research conducted by Li et al. has significantly enhanced our knowledge of soft hydrogels in wound treatment. Their study sheds light on the intricate process of developing hydrogels through self-assembly and chemical cross-linking strategy. We are eagerly anticipating further advancements in the initiation of clinical trials. The potential impact of this hydrogel on clinical treatments is immense, as they have the capacity to revolutionize the way we approach and treat wounds using hydrogels.

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Competing interests
The authors declare no conflicts of interest.

Abbreviations
Lap, Laponite; HML, hydroxypyrol chitosan/Lap.

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