Bioinspired collagen-targeting adhesive hydrogel for scarless skin regeneration

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Statement of Purpose: Skin scarring after most deep dermal injuries is a major clinical challenge with high psychological and aesthetic concerns. Unfortunately, current options remain clinically unsatisfactory most likely due to poor understanding of complex mechanisms underlying scarring. Deeper comprehension of structural and composition alterations in extracellular matrix leading to scarring can allow us to find a potential therapeutic target for scarless wound healing. Particularly, the alteration in collagen organization during tissue remodeling is critically related to pathological scarring, affecting cellular activities, structural integrity, and tissue-specific functions by modifying cell-matrix interactions.

Methods: Here, by inspiration of fundamental roles of decorin (a collagen-targeting proteoglycan) in collagen organization, we constructed three recombinant types of fusion mussel adhesive proteins (MAPs) containing different collagen-binding peptides and selected the most functional fusion MAP based on *in vitro* collagen-binding ability and fibrillogenesis tests. Then, to emulate the biochemical cues of decorin, dermatan sulfate (DS) was simply incorporated in the functional MAP-based system by electrostatic interaction. Next, the collagen-targeting adhesive hydrogel containing a collagen-binding MAP and the specific glycosaminoglycan was used to demonstrate its efficacy in promoting wound healing and preventing scar formation via in *vivo* rat skin excisional model.

Results: We found that the fusion MAP-mCPR protein functioned to specifically bind to collagen and effectively delay or inhibit fibrillogenesis *in vitro*, similarly to decorin. In an *in vivo* rat skin excisional model, the treatment of collagen-targeting MAP hydrogel glue clearly acted to encourage initial wound healing by stimulating reepithelialization, neovascularization and rapid collagen synthesis during the early stage and to prevent pathological scar formation by regulating collagen fibril growth, tissue-specific reassembly and the expression of fibrogenic factors during remodeling phase.

Conclusions: Taken together, our bioinspired MAP-based collagen-targeting system successfully demonstrated effective wound regeneration and significantly enhanced collagen architecture with fibril diameter and distribution similar to those of normal skin. Therefore, our novel biomimetic engineering approach can offer a promising therapeutic option aiming at improvement of healing rate with quality and effective inhibition of scarring for treatment of deep dermal injuries, which can also serve as reliable guidance for other clinical problems with heavy scarring such as spinal cord rupture, myocardial infarction or corneal scarring through further detailed investigations.

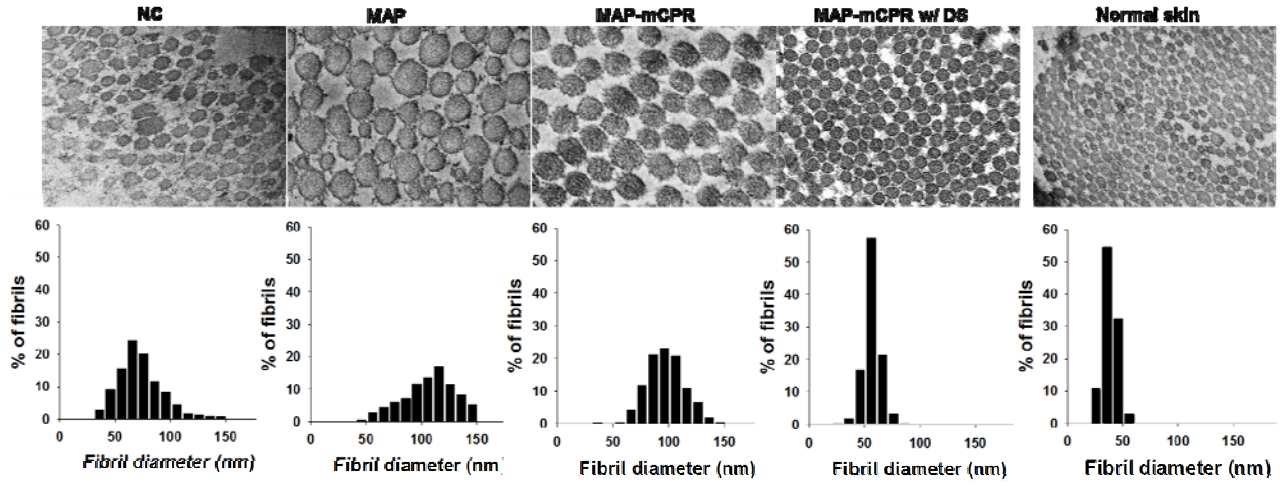

Figure. Representative TEM images of cross-sectioned collagen fibrils and histograms of total range of fibril diameters from excisional wounds treated by none, MAP, MAP-mCPR, MAP- mCPR w/ DS, and normal skin at 21 days post-wounding ($n \geq 1000$).