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Protein Replacement Therapies for Recessive Dystrophic Epidermolysis Bullosa (RDEB)

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Abstract

Recessive dystrophic epidermolysis bullosa (RDEB) is a debilitating genetic disorder caused by mutations in the COL7A1 gene encoding type VII collagen (C7), an essential component of the dermal-epidermal junction (DEJ). This deficiency results in extreme skin fragility, blistering, and chronic wounds, significantly impairing patients' quality of life and increasing the risk of skin cancer (1, 2).

Recent advancements in protein replacement therapy have shown promise in addressing the underlying cause of RDEB by restoring C7 function. Studies in murine models lacking C7 have demonstrated that intravenous and topical administration of recombinant human C7 (rhC7) can effectively incorporate into the DEJ, leading to the reformation of anchoring fibrils and improved skin integrity (3). This approach reduces skin fragility and blistering, ultimately extending the survival of affected animals. The potential of rhC7 to serve as a therapeutic agent for RDEB is further bolstered by its ability to evade significant immune responses, particularly when mechanisms like the CD40-CD40L pathway are inhibited to prevent antibody generation (2, 4).

The half-life of C7 in the DEJ is approximately 30 days, necessitating considerations for dosage and frequency to maintain therapeutic levels in human applications (5). Innovations in recombinant technologies have facilitated the production of stable, disulfide-bonded C7 trimers that form effective dermal-epidermal anchors, even in pathogenic mutations (6). Such mutations, while posing challenges due to the potential for protein misfolding or increased proteolytic sensitivity, underscore the importance of tailoring protein therapy to individual genetic profiles (6).

Furthermore, topical applications of recombinant C7 in mouse models have demonstrated efficacy in promoting wound closure and minimizing scar formation by modulating transforming growth factors, suggesting additional therapeutic pathways for chronic wound management beyond genetic correction (7). This indicates a dual potential for C7 therapies to restore structural integrity and enhance

regenerative healing processes, emphasizing the need for comprehensive approaches that integrate gene, protein, and immune modulation strategies in treating RDEB (8, 9).

Complementing direct protein therapies, biomaterial advancements such as RHC-conjugated chitosan hydrogels offer innovative solutions for wound management. These hydrogels, incorporating recombinant human collagen-peptide (RHC), support enhanced mechanical properties and bioactivity, addressing the typical limitations of traditional chitosan hydrogels (10). The thermosensitive properties of such hydrogels enable better handling and application flexibility, which is critical for treating complex wounds like burns.

In vitro and in vivo studies reveal that RHC-chitosan hydrogels significantly promote cell viability, infiltration, and vascularization, which are crucial for tissue regeneration and repair (10). The hydrogel matrix provides a supportive environment that facilitates cell migration and integration, which, paired with increased mechanical stiffness and optimized water vapor transmission, accelerates the healing process and improves clinical outcomes (10).

This dual focus on structural and therapeutic attributes highlights the promising future of combined cell-based, protein, and biomaterial therapies for RDEB and other conditions characterized by structural protein defects. Continued research and clinical evaluation will be vital to refine these techniques and verify efficacy and safety in human populations, potentially transforming treatment paradigms for genetic skin disorders (1, 10).

In summary, the convergence of protein replacement therapies and advanced biomaterials like RHC-conjugated hydrogels represents a significant leap forward in treating severe dermatological conditions. These emerging strategies provide a foundation for innovative, personalized therapeutic interventions that may soon extend beyond the scope of RDEB to tackle a range of complex wound healing challenges (2, 9, 11).

Keywords: Recessive Dystrophic Epidermolysis Bullosa (RDEB)**,** Protein Replacement Therapy**,** Recombinant Biomaterials**,** Chitosan Hydrogels

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