Obstacles To Therapy for Dystrophic Epidermolysis Bullosa

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Structure of Type VII Collagen and Anchoring Fibril Assembly

1. \( \alpha(\text{VII}) \)
2. \([\alpha(\text{VII})]_3\)
3. 
4. 

\( \alpha(\text{VII}) \)
PROTEIN THERAPY

Intradermal Injection of Recombinant Type VII Collagen Restores Type VII Collagen Expression and Function in Dystrophic Epidermolysis Bullosa In Vivo

Nature Medicine, 10:693, 2004
Type VII Collagen Purification from Gene-corrected RDEB Fibroblasts

Nature Medicine, 2004
Prepare 1.5 cm X 1.5 cm de-epidermalized acellular dermis

Seed with RDEB keratinocytes

Mature and develop *in vitro* for 2 weeks

Inject type VII collagen intradermally

Transplant skin equivalents onto nu/nu mice and heal for 4-6 weeks

Obtain skin biopsies at various time points and analyze by

DIF  H & E  IEM
Intradermally Injected Human Type VII Collagen Incorporates into the BMZ of RDEB Skin Tissue *In Vivo*
Restoration of Anchoring Fibrils in Regenerated RDEB Skin \textit{In Vivo}
Conclusions

- Recombinant type VII collagen IL injection produces sustained BMZ deposition of the human protein and reverses the RDEB features.
- Same thing happens with: A) IL injection of gene-corrected RDEB fibroblasts, B) normal dermal fibroblasts, or C) lentiviral vectors expressing type VII collagen which incorporate into resident cells in the skin.
Implication

• Dermatologists have great skill in injecting type I collagen into the high dermis of patient’s skin for the improvement of wrinkles and photoaging.

• Why not inject type VII collagen into the skin of RDEB patients? Collagen is a device, not a drug.
Preclinical Animal Model for DEB

Prior to using any of these approaches in DEB patients, we need studies in a preclinical animal model to determine the safety, efficacy, and potential immune responses with these approaches. A mouse model has been developed for DEB by targeted inactivation of the $COL7A1$ gene and these DEB mice recapitulate many of the clinical and ultrastructural features of severe RDEB patients.
Clinical, Histological and Immunological Presentation of DEB Mice
Restoration of Dermal-Epidermal Separation and C7 Expression in DEB Mice by Protein Therapy

Day 1

before injection

Day 3

2 inject (10-15µg/ per inject) in back
Conclusion

• Intradermal injection of type VII collagen or lentiviral vectors restores correctly localized type VII collagen expression at the DEB mouse’s BMZ.
• Type VII collagen is detected at the injection sites, but also in the sites far away from injection sites.
• Restoration of type VII collagen expression reverses dermal-epidermal separation, reduces new blister formation and increases survival.
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