Dual siRNAs Nanoplex Targeting IL-4RA and SPARC Enhance Collagen Reduction in IL-4 Activated Skin Fibroblasts

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BACKGROUND:

Currently, there is a need for more effective preventive methods or treatment for hypertrophic scars or keloids. To target important proteins involved in the T helper 2 inflammatory microenvironment and ECM production during scar formation, we designed dual siRNAs targeting interleukin−4 Receptor α (IL−4Rα) and secreted protein acidic and cysteine rich (SPARC) as a novel preventive solution and treatment to reduce pathological scars. In this study, the effect of dual siRNAs (siIL−4Rα and siSPARC) nanoplex in reducing collagen expression for interleukin−4 stimulated human dermal fibroblasts (HDFs) was investigated.

METHODS:

As unmodified siRNA is easily degraded by endogenous enzymes, we encapsulated the siRNAs using positively charged gelatin−tyramine (Gtn−Tyr) to form a nanoplex to achieve protection and targeted delivery to dermal fibroblast, studied gene knockdown, decrease in collagen production, and compared internalization of the siRNA−nanoplex by dermal fibroblasts with keratinocytes. Simultaneously, we tested the effect of siRNA nanoplex on cell cytotoxicity and proliferation.

Separately, three individuals with hypertrophic scars and keloid volunteered to test the dual siRNA−nanoplex delivered via microneedles for treatment and their scars were assessed at different timepoints.

RESULTS:

The results demonstrated that siRNA−nanoplex preferentially enhances fibroblast uptake in comparison to naked siRNA, and when compared with keratinocytes. Majority of the siRNA−nanoplex is also not present within lysosomal associated membrane protein−1

(LAMP −1) −positive late endosomes for degradation even after 24h of treatment. Simultaneously, the dual siRNAs nanoplex of siIL −4Rα and siSPARC could inhibit collagen production of HDFs in the presence of IL −4, and dual siRNAs nanoplex treatment does not cause any cytotoxic effect on cells or inhibit cell proliferation.

Volunteers that tested the microneedle delivered dual siRNA−nanoplex had reduction of scar volume together with reduction of pain or itch, with no adverse effects reported.

CONCLUSION:

Overall, targeting both IL−4Rα and SPARC using the siRNA nanoplex demonstrates a promising solution for preventing and treating hypertrophic scars or keloids.

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