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Sonic hedgehog intradermal gene therapy using a biodegradable poly (β-amino esters) nanoparticle to enhance wound healing

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ABSTRACT

Biodegradable cationic poly(β-amino esters) (PBAE) nanoparticles are promising tools for delivering genes into various types of cells and tissues. Specific end-modification of the PBAE terminal parts significantly improves the efficiency of gene delivery *in vitro* and *in vivo*, and reduces cytotoxicity. Here, we demonstrated that amine end-modified PBAE nanoparticles can be used for intradermal delivery of therapeutic genes for wound healing in an animal skin wound model. Sonic hedgehog (SHH), a prototypical morphogen with angiogenic potential, was applied as a therapeutic gene to regenerate skin tissue. Amine end-modified PBAEs showed higher gene transfection efficiency *in vitro* than the commercial reagent, Lipofectamine 2000. Intradermal delivery of the SHH gene using amine end-modified PBAEs was tested in a readout mouse model of SHH signaling. We evaluated its therapeutic efficacy in mice with full-thickness skin wounds. SHH gene therapy significantly increased the expression of the angiogenic growth factor, vascular endothelial growth factor, and the stromal cell-derived factor-1α chemokine within the wounded regions early after injection. Ultimately, wound closure was accelerated in mice receiving the PBAE/SHH gene therapy compared to mice receiving intradermal delivery of a control gene (β-galactosidase plasmid) by PBAE nanoparticles. Quantitative real-time polymerase chain reaction and histological analysis revealed that there were significant improvements in epidermis regeneration and blood vessel formation in the mice treated with PBAE/SHH nanoparticles. In conclusion, SHH intradermal gene therapy using biodegradable PBAE nanoparticles is a potential treatment to promote wound healing.

1. Introduction

Gene delivery to the skin has shown potential for healing skin wounds and diabetic ulcers. Intradermal gene delivery methods previously applied include direct injection, gene gun, electroporation, and microneedle [1–3]. These approaches enhanced the wound healing process in diabetic animals and in animals with skin wounds. However, more efficient delivery techniques are needed to improve intracellular gene transfer to skin cells [3]. Many researchers focus on the use of delivery vectors to facilitate intracellular gene transfer, most often viral vectors due to their capacity to efficiently infect cells and induce long-term gene expression [4–6]. Intradermal or intraulcer administration of growth factor genes using adenoviral vectors led to improvements in wound and ulcer healing in animals and humans, likely due to enhanced epithelialization and/or angiogenesis [4–6]. Unfortunately, the use of viral vectors is limited due to serious safety concerns about insertional mutations that result in tumors and immunogenicity. Viral vectors are also challenging to produce and manufacture and have limitations to their capacity to carry nucleic acid cargo [7].

For these reasons, nonviral vectors such as cationic polymers and lipids are gaining attention as safe agents to deliver therapeutic nucleic acids into the skin [8,9]. Nonviral vectors possess advantages over viral vectors, some of which are low tumorigenic potential, low immunogenicity, production/manufacturing reproducibility, and genetic material size flexibility [10–13]. Cationic nonviral vectors efficiently condense nucleic acids with negative

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