Molecular Therapy
Nucleic Acids
Letter to the Editor

Increasing angiogenesis factors in hypoxic diabetic wounds using siRNA nanotherapeutics

Dear Editor,

I read with interest the article by Shaabani et al. on small interfering RNA (siRNA)-mediated prolyl hydroxylase domain protein 2 (PHD2) silencing to promote angiogenesis in diabetic wounds.[1] The authors demonstrate a layered gold nanoparticle delivery system for enhanced cytosolic release of PHD2 siRNA. Co-treatment with the endosomolytic agent desloratadine led to amplified gene knockdown *in vitro*. This is a significant advance given inefficient intracellular delivery remains a fundamental limitation of siRNA therapeutics.

Compared to previous works on pro-angiogenic siRNA therapies for diabetic wounds, this study demonstrates several strengths.

(1) Selection of the PHD-2 target: many other studies have similarly focused on PHD-2 silencing to stabilize HIF-1α and induce VEGF/FGF expression.[2] However, Shaabani et al. provide a more extensive mechanistic rationale for why PHD-2 inhibition can enhance angiogenesis in the ischemic and inflammatory context of diabetic wounds.
(2) Tunable LbL nanocarrier design: the assembly of siRNA polyplexes with gold nanoparticles and subsequent outer layer coating provides fine control over surface charge, stability, and endosomal escape properties. This represents an advance over simpler nanoparticle formulations used previously.
(3) Combination with desloratadine: co-administration with an endosomolytic agent like desloratadine to amplify siRNA delivery is a novel approach not explored in other wound angiogenesis studies. This demonstrates the synergistic effects possible by integrating drug and gene delivery.
(4) By first optimizing silencing in NIH3T3 cells, Shaabani et al. provide better insights into the intracellular trafficking and gene knockdown efficiencies of their nanosystem.

However, some critical knowledge gaps remain. Firstly, it is unclear whether PHD2 silencing can induce sustained pro-angiogenic effects specifically in the chronically inflamed wound microenvironment or whether compensatory negative feedback mechanisms may limit efficacy over time. Dynamic tracking of VEGF/FGF expression in cytokine-stimulated fibroblasts could provide insight.

Secondly, the specificity of the gene knockdown approach could be improved. Silencing individual anti-angiogenic microRNAs like miR-26a or miR-29a allows for finer tuning of the neovascularization response compared to broad PHD2 inhibition.[3,4] However, delivery of miRNA mimics or inhibitors poses additional pharmaceutical challenges. Direct comparative assessment between miRNA- and siRNA-based pro-angiogenic strategies is limited.

Furthermore, the study lacked comparisons to other leading siRNA nanocarriers. Lipid-, polymer-, and peptide-based systems have shown promise for wound applications yet were not benchmarked.[5] The additive effects of desloratadine-mediated endosomal escape were also rather modest. Testing in other cell types would better elucidate on-target effects and advantages over existing delivery platforms.

Finally, combination delivery with chemical enhancers like desloratadine requires an in-depth investigation of off-target toxicities and wound-healing outcomes. Desloratadine may influence histamine receptor signaling on resident immune cells, possibly exacerbating inflammation. And while *in vitro* assays offer preliminary screening, ultimately prolonged *in vivo* biocompatibility studies in diabetic wound models are essential to validate clinical utility.

In summary, Shaabani et al. have developed an interesting PHD2 siRNA gold nanosystem as a pro-angiogenic therapeutic. Evaluation of sustained activity in inflammatory conditions, comparisons to miRNA-based approaches, benchmarking to other nanocarriers, and in-depth *in vivo* biocompatibility studies would strengthen conclusions regarding real-world efficacy and safety. I look forward to seeing this work address these gaps while evolving into a combination treatment approach optimized for the complex diabetic wound microenvironment.

Sincerely,

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the author used Claude.ai in order to improve the readability of the text. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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