Histone-targeted nucleic acid delivery for tissue regenerative applications

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Abstract:

Nucleic acid delivery has garnered significant attention as an innovative therapeutic approach for treating a wide variety of diseases. However, the design of non-viral delivery systems that negotiate efficient intracellular trafficking and nuclear entry represents a significant challenge. Overcoming these hurdles requires a combination of well-controlled materials approaches with techniques to understand and direct cellular delivery. Recent investigations have highlighted the roles histone tail sequences play in directing nuclear delivery and retention, as well as activating DNA transcription. We established the ability to recapitulate these natural histone tail activities within non-viral gene nanocarriers, driving gene transfer/expression by enabling effective navigation to the nucleus via retrograde vesicular trafficking.

The work described in this dissertation builds off of these fundamental insights to facilitate the translation of this histone-targeted delivery approach toward regenerative medicine applications. During native tissue repair, actively proliferating mesenchymal stem cells (MSCs) respond to a complex series of growth factor signals that direct their differentiation. Accordingly, the investigations in this work focused on utilizing histone-targeted nanocarriers to enhance osteogenic growth factor gene transfer in dividing MSCs leading to augmented MSC chondrogenic differentiation, an essential first step in skeletal tissue repair. Concurrently, additional studies focused on optimizing the histone-targeted nanocarrier design strategy to enable improved plasmid DNA (pDNA) binding stability and controlled harnessing of native cellular processing pathways for enhanced gene transfer.

Overall, the work presented herein demonstrated substantial increases in growth factor expression following histone-targeted gene transfer. This enhanced expression enabled more robust levels of chondrogenesis in MSCs than treatments with equivalent amounts of recombinant growth factor protein. Additionally, nanocarrier design optimization provided effective pDNA condensation and controllable interactions with native histone effectors. Importantly, these optimized nanocarriers conferred stable nanoplex formation and maintained transfection efficiency under physiologically relevant conditions. Taken together, these advances may help drive the clinical translation of histone-targeted nucleic acid delivery strategies for the regeneration of damaged tissue following traumatic injury.