5-19-2022

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COLLAGEN-MIMETIC PEPTIDES FOR DELIVERY OF THERAPEUTICS IN CHRONIC WOUNDS HEALING APPLICATION

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Key Words: Collagen mimetic peptides, Gene/Drug delivery, Growth factor, Wound infection, Chronic wounds

The enormous economic and societal burdens associated with chronic wounds suggest a critical need for new approaches to manipulate the wound microenvironment to support improved repair and prevent secondary complications**.** The main factors that lead to chronic wounds are the lack of growth factors to stimulate cellular healing responses, as well as the concomitant occurrence of wound infections that cause prolonged inflammation. Current treatments include wound dressings, topical application of growth factors or antibiotics, and various combination therapies that increase the accessibility of growth factors while eradicating microorganisms in the wound bed. However, the harsh wound environment often clears topically administered therapeutics from the wound, which reduces the local concentration of therapeutics and thus their effectiveness. The overall objective of our work is to improve the efficacy of topically administered therapeutics using peptide-mediated interactions between nanocarriers and matrices. We specifically utilize collagen mimetic peptides (CMP) to tether nanostructure carriers onto collagen-containing matrices through the strand invasion of CMPs into native collagen, resulting in control over the delivery of the cargo in response to cell-mediated collagen degradation.

Our studies have revealed that in general, nanocarriers modified with CMPs enable extended control of cargo release. Nanoparticles comprising EMP-CMP (Elastin-Mimetic Peptide and Collagen-Mimetic Peptide) conjugates facilitated the controlled, zero-order release of the antibiotic vancomycin, compared to the first-order release of vancomycin by a commonly used, liposomal drug nanocarrier. Furthermore, nanocarriers with CMP modification could be sequestered in collagen containing matrices to a greater extent than nanocarriers without CMP modification. As a result, the CMP-modified nanocarriers showed sustained release profiles. Also, CMP modification of polyethyleneimine (PEI)/DNA nanocomplexes, when sequestered within collagen-containing matrices, enhanced overall gene expression for at least 7 days.

Additionally, our studies have demonstrated that the controlled delivery of therapeutics driven by CMP modification can also control their spatiotemporal action *in vitro*. The delivery of vascular endothelial growth factor (VEGF)-A via the use of CMP-modified PEI/DNA in collagen-containing matrices enhanced cellular signaling; murine fibroblasts differentiated to pro-healing myofibroblasts for at least 7 days and murine endothelial cells formed complete tubular networks with significantly greater volume and larger diameter than matrices lacking the CMP modification. Moreover, the delivery of vancomycin using EMP-CMP-nanoparticles tethered in collagen-containing matrices improved the half-life of vancomycin activity, resulting in the prevention of growth of methicillin-resistant *Staphylococcus aureus* (MRSA). Therefore, CMP modification of nanocarriers enables not only the controlled release of therapeutics from collagen-containing matrices through CMP retention within collagen, but also modulation of the bioactivities of therapeutics *in vitro*. Future work will include *in vivo* excisional wound studies to evaluate the efficacy of therapeutics, delivered by CMP-tethered nanocarriers, on wound healing, and evaluation of the platform for tissue regeneration applications.

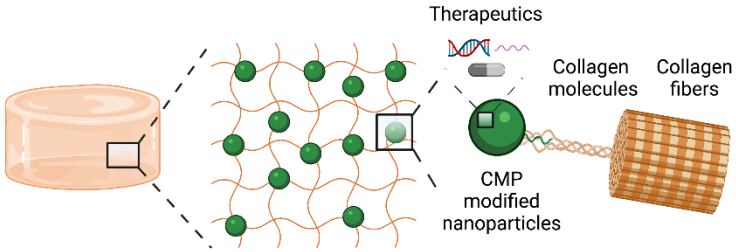

Figure - Schematic representation of collagen-mimetic peptide (CMP)-modified nanocarriers tethered to collagen-based matrices (Created with Biorender.com).