Bioconjugation methods using click chemistry to enhance wound healing

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Technology description

The wound healing response is limited or impaired in many conditions, such as in diabetic ulcers, burns, chemical exposure injuries, neurotropic keratopathy, and nerve damage. There is, therefore, a need in the art for ways to stimulate a regenerative response in order to foster wound healing and restore anatomy and, in turn, tissue functions such as epithelial barrier effects and neural transmission. Cell based therapies such as stem cell transplantation typically provide only cells without the required matrix upon which to grow, or without the stimulatory factors to which respond to by migration, proliferation, and/or differentiation. Topical approaches to wound healing have been reported, such as topical epidermal growth factor, thymosin beta 4, nerve growth factor, Substance P and Insulin-like Growth Factor, and Fibronectin. However, a clinically proven biopharmacologic therapy has not yet been successfully developed. This invention improves upon prior work on applying topical biomolecules and cells by using bioconjugation methods to anchor them to the surface of the damaged tissue, thus increasing their residence time, bioavailability, and bioactivity. We propose a novel strategy to enhance ocular wound healing by delivering and crosslinking therapeutic factors directly to damaged tissue in three ways: (1) through an injectable, in situ-forming growth-factor-eluting membrane that covers ulcers and stimulates rapid re-epithelialization, (2) by binding growth factors directly to the stromal wound bed, and (3) by crosslinking a carrier matrix for human mesenchymal stem cells (hMSCs) to the ocular surface. These approaches are made possible by strain-promoted azide-alkyne cycloaddition (SPAAC), a form of copper-free click chemistry that we and other investigators have safely used on and around living cells in vitro and in vivo, is extremely rapid yet highly specific, and does not require an external trigger such as UV light or a metal-ion catalyst. This research seeks to use SPAAC to build upon the promising but limited effects of both topically applied growth factors and injected hMSC suspensions on ocular wound healing.
Researchers at Stanford have developed methods using click chemistry to immobilize and concentrate therapeutic factors on a tissue to improve wound healing. Tissue regeneration is a complex process involving the temporal and spatial interplay between cells and their extracellular milieu. Often therapeutic approaches to tissue regeneration do not reconstitute this interaction and thus wound healing is limited or impaired. Previous attempts to improve wound healing by topically applying therapeutic factors and biomolecules are limited as these factors are easily removed or washed away. Thus, there is a need for better methods to stimulate the regenerative process and foster wound

healing. To help meet this need the inventors have developed this method which uses copper-free click chemistry to enable topical agents and biomolecules to be immobilized and concentrated on the surface of the damaged tissue. This increases the residence time of therapeutic factors and enables synergistic combinations of multiple proteins to work together. This method promotes faster, more effective wound healing especially in challenging situations.

Application area

Topical wound healing for:
Injuries to the eye Diabetic ulcers Skin injuries Nerve injury

Advantages

Method provides spatial-temporal control over the regenerative process Increases therapeutic residence time, bioavailability and bioactivity Click chemistry:
Rapid yet highly specific Does not require external trigger such as UV light or metal-ion catalyst
Does not require frequent re-administration of active ingredients Enables synergistic combination of therapeutic agents and biomolecules to work together

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