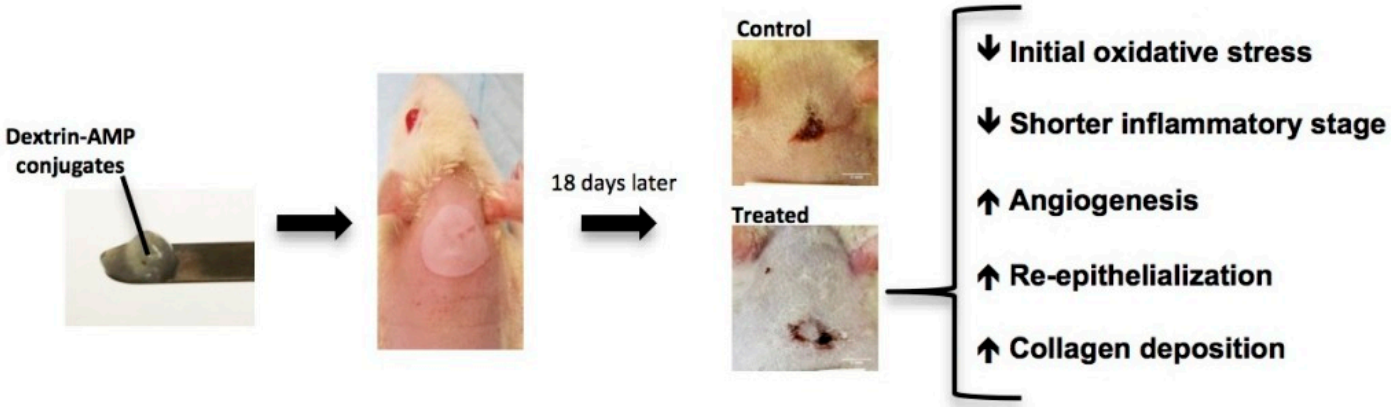
Topical administration of an antimicrobial peptide as a new strategy for improved burn wound healing

Burn wounds represent a major global concern, as more than 100 million people worldwide are estimated to experience burn injuries every year. These may be caused upon exposure to heat, radiation, chemicals or electric shocks, often resulting in reduced quality of life and increased morbidity. They often result in long hospital stays and take up significant health resources in developed countries.

Current therapies, involving the use of silver sulfadiazine, iodine, medical grade honey or other therapeutic agents (e.g. growth factors and hormones) are usually toxic, expensive or fail to achieve complete healing.

In this context, Antimicrobial Peptides (AMPs) arise as promising candidates for wound treatment. AMPs are usually small (20-60 amino acids), positively charged (cationic) and amphipathic peptides belonging to the innate immune system of many living organisms. Their activity is not limited to the antimicrobial action, as some of these peptides have also been reported to play key roles in processes like leukocytes chemotaxis, angiogenesis and wound healing. Nevertheless, their clinical use has been hindered due to limited stability and solubility in the organism, as well as to some toxicity issues that may occur. All these can be overcome by using a suitable administration method. Moreover, analogues of AMPs have been engineered to enhance their antimicrobial properties and decrease cytotoxicity. This is the case with LLKKK18, a chemically synthesized analogue of the human AMP LL37. The higher cationicity and hydrophobicity of the former results in higher antimicrobial and chemoattractant activity.



In a collaboration between the University of Minho (Braga, Portugal) and UC Riverside (CA, USA) we developed a new approach to improve wound healing, namely burns, by conjugating LLKKK18 with dextrin and further incorporating the conjugates in Carbopol®. Dextrin is an FDA-approved, biocompatible polysaccharide that stabilizes the peptide and protects it from being degraded by proteases. Degradation of dextrin occurs upon contact with amylases present within the wound

site, thus sustainedly releasing the peptide over time. Carbopol® is a commercially available hydrogel, whose good biocompatibility, viscosity, thermal stability and bioadhesive properties make it ideal as a vehicle for topical administration. Of note, the hydrogel provides the adequate moist environment within the wound site, absorbs wound exudates, reduces pain and healing time and is painless on application and removal.

We observed that the release of LLKKK18 significantly improved the healing process in rat burns, by accelerating wound closure and enhancing the quality of the regenerated tissue, when compared with controls treated with the hydrogel alone. This was achieved by reducing the initial oxidative stress and inflammation levels characteristic of burn wounds. Noteworthy, the inflammatory stage that follows the initial response to injury was shorter, enabling the earlier formation of new tissue. Also, the peptide stimulated the formation of new blood vessels (important for a more effective transport of nutrients and signaling molecules to the wound area). The quality of the healed tissue was also improved after LLKKK18 administration, as it promoted the proper deposition of collagen, one of the main constituents of skin tissue.

In conclusion, we developed an effective, safe and non-expensive formulation, based on the release of LLKKK18, which holds a great potential for burn wound treatment. Moreover, this formulation: 1) is able to maintain a suitable moist environment within the wound; 2) can be easily applied and removed; and 3) has the potential to maintain the wound area free from infections due to the presence of the AMP. As such, said formulation may highly impact society, by promoting faster patient recovery and improving their quality of life.

Publication

Improved burn wound healing by the antimicrobial peptide LLKKK18 released from conjugates with dextrin embedded in a carbopol gel.
Silva JP, Dhall S, Garcia M, Chan A, Costa C, Gama M, Martins-Green M
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