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Virus-derived immune modulating proteins significantly improve wound healing

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Nonhealing dermal wounds represent major medical and financial burdens. Numerous treatments have been developed to promote wound healing in severe non healing skin wounds. Hemorrhage, clotting and associated inflammation regulate early wound healing. Viruses have developed highly potent immune modulating proteins over millions of years of evolution. We have examined two of these immune modulators in wound healing models demonstrating accelerated healing; 1) A SERine Protease INhibitor (SERPIN), Serp-1, that inhibits thrombolytic proteases and inflammation in two mouse excisional wound models and M-T7 a chemokine modulating protein, M-T7. Saline, recombinant Serp-1 or M-T7 were applied directly to wounds as single doses of 1µg or 2µg or as two 1µg boluses. A chitosan-collagen hydrogel was also tested for Serp-1 delivery in excisional wounds and a silk fibroin suture was also tested in incisional wounds. Wound size was measured daily for 15 days and scarring assessed by Masson's trichrome, Herovici's staining and immune cell dynamics and angiogenesis by immunohistochemistry.

Serp-1 treatment significantly accelerated wound healing but was blocked by uPAR antibody. A single application of Serp-1-loaded chitosan-collagen hydrogel or in silk fibroin overlay was effective. Serp-1 treatment of wounds increased arginase-1-expressing M2-polarized macrophage counts and peri-wound angiogenesis in the wound bed. Serp-1 improves collagen maturation and organization at the wound site. Topical treatment with recombinant chemokine modulating protein M-T7 also accelerated wound healing and with greater efficacy than Serp-1, when compared to saline treatment alone.

Healed wounds exhibited improved remodeling and collagen maturation with accelerated peri-wound angiogenesis and increased levels of TNF, VEGF and CD31. M-T7 treatment was associated with retained CCL2 levels and increased arginase-1-expressing M2 macrophages and CD4 T cells. Thus, topical treatment with Serp-1 or recombinant M-T7 promotes a pro-resolution environment in healing wounds with potential as novel treatments to improve cutaneous tissue repair.

Recent publications

1. Lucas A, Yaron JR, Zhang L, Ambadapadi S. Overview of Serpins and Their Roles in Biological Systems. Methods Mol Biol. 2018;1826:1-7. doi: 10.1007/978-1-4939-8645-3_1. PMID: 30194590.

2. Alexandra R Lucas, Brian P Mahon, Sriram Ambadapadi, et al. Crystal Structure of Cleaved Serp-1, a Myxomavirus-Derived Immune Modulating Serpin: Structural Design of Serpin Reactive Center Loop Peptides with Improved Therapeutic Function. Biochemistry 2018, 57, 7, 1096–1107.

3. Lucas A, Chen H, Ambadapadi S, Wakefield D, et al. Selective Deletion of Heparan Sulfotransferase Enzyme, Ndst1, in Donor Endothelial and Myeloid Precursor Cells Significantly Decreases Acute Allograft Rejection. Sci Rep. 2018 Sep 7;8(1):13433

Speaker Biography

Alexandra Lucas is a physician scientist at the Biodesign Institute at Arizona State University. Dr Lucas has been developing a new class of immune modulating therapeutics over the past 25 years as a professor, practicing clinician and scientist in Canada and the US. She has over 150 publications and has been funded by grants in the US and Canada as well as serving as an editorial board member and reviewer for peer reviewed journals.

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