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Using comparative transcriptomic profiling *ex vivo* to identify novel, potential targets for acute and chronic wound healing

Ilaria Piccini¹, Markus Fehrholz¹, Ralf Ludwig^{1, 2}, John Zibert³, Jan Alenfal^{3, 4}, Anna Hultgårdh Nilsson⁵, Jan Nilsson⁴, Ralf Paus⁶, Marta Bertolini^{*1}

¹Monasterium Laboratory Skin and Hair Research Solutions GmbH, a QIMA Life Sciences Company, Münster, Germany, ²Lübeck Institute of Experimental Dermatology, Department of Dermatology, Lübeck, Germany, ³Coegin Pharma AB, Lund, Sweden, ⁴Department of Clinical Sciences Malmö, Lund University, Sweden, ⁵Department of Experimental Medical Science, Lund University, Sweden, ⁶Dr Phillip Frost Department of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine, FL, United States

Introduction & Objectives:

Chronic, non-healing wounds represent a major economic burden to the healthcare system and significantly reduce the quality of life of those affected. However, the development of effective treatment strategies requires a better understanding of the underlying molecular mechanisms of chronic or pathological wound healing (WH).

Materials & Methods:

To gain new insights, we used healthy full-thickness human skin punches and created central, partial wounds (punch-in-punch model). The wounded skin punches were then cultured under physiological or pathological (hyperglycaemic, oxidative and hypoxic) conditions to mimic acute and chronic wounds, respectively. Afterwards, an unbiased, long-term comparative transcriptome profiling was performed by bulk RNAseq analysis. RNA was isolated at day 0 and after 1, 3 or 5 days of culture.

Results:

Several known wound repair associated genes (e.g. *KRT6A-C*, *PTX3*, *KRT1*, *KRT10*, *COL1A1*) and pathways, including Wnt signaling and actin cytoskeleton organization, were differentially regulated between acute and chronic wounds, reflecting an impaired wound healing process. In addition, the comparison between chronic and acute wounds showed that overall gene expression was downregulated in chronic wounds. This suggests that genes required for proper wound healing may not be transcribed in experimentally induced pathological conditions, potentially resulting in less protein transcription and impaired wound closure. While a significant downregulation of *FGF7* was detected in chronic wounds at day 5, *MMP10* was significantly increased in chronic wounds on all analyzed days. As a proof-of-principle and to validate our model system, we counteracted their dysregulation by applying recombinant FGF7 protein and a MMP10 neutralizing antibody (α -MMP10) to acute and chronic wounds *ex vivo*. Topical administration of α -MMP10 significantly increased the wound tongue length in acute wounds *ex vivo* while application of recombinant FGF7 did not have any effect. Yet, their combined application significantly promoted re-epithelization in both acute and chronic wounds. Our transcriptomic analysis also revealed osteopontin (*SPP1*) as one of the gene significantly upregulated on day 3 and 5 in acute compared to chronic wounds. Thus, to stimulate the osteopontin pathway, we administered the osteopontin-derived peptide, FOL005, which contains a similar active site (RGD-domain), to experimentally induced wounds *ex vivo*. Treatment with FOL005 significantly increased skin re-epithelization under both, physiological and pathological culture conditions.

Conclusion:

Thus, our transcriptomic database serves as an excellent tool to identify novel therapeutic targets and to support drug development for the treatment of chronic wounds. In this context, we also highlight the therapeutic potential of FOL005 for acute and chronic wound management.

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