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ABSTRACTS

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THE ROLE OF PROTEIN KINASE C (PKC) α AND δ IN INSULIN PHYSIOLOGY DIRECTS THE DEVELOPMENT OF HO/03/03 AS A NOVEL THERAPEUTIC FOR NON HEALING WOUNDS

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Wound healing impairment is one of the hallmarks of diabetes and other pathologies such as obesity. However, molecular skin mechanisms underlying this impairment are poorly understood. We have investigated the role of PKCα and PKCα in the insulin signaling pathway utilizing adenovirus constructs expressing WT and DN forms of PKCα and PKCα as well as in skin of PKCα and PKCα null mice. Our results show that in skin of PKCα null mice, similarly to diabetic skin, levels of IR were increased, Raf-1 expression was reduced and skin exhibited enhanced Erk1/2 expression. In contrast, in PKCα null skin, IR levels were unchanged, Raf-1 was constitutively activated while Akt activation was abrogated. This was associated with changes in skin physiology expressed by altered proliferation, differentiation, migration and regulation of the inflammatory processes in vitro and wound healing in vivo. While PKCα null mice exhibited impaired wound closure, PKCα null mice demonstrated more efficient wound closure and significantly decreased skin inflammation, in comparison to wild type animals.

These findings identified PKCα and PKCα as molecular switches in skin cells and set the basis for the development of a topical drug for wound healing. In preclinical studies, the drug*, consist of a PKCδ activator and a PKCα inhibitor succeeded to synergistically overcome diabetes-associated wound healing impairment to a level similar to healthy controls and was subsequently advcned to human testing. In conclusion, PKCα and PKCα play a role as a divergence point in signaling related to wound healing and skin regeneration.

*HO/03/03

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CELL-BASED THERAPY FOR DIABETIC WOUNDS: FROM THE BENCH TO THE PATIENT

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Aim: The development of effective treatments for diabetic wounds largely depends on understanding the pathogenic mechanisms responsible for healing impairment. The aim of the present work was to obtain biological clues from preclinical tools to be translated to the clinical practice.

Methods: The therapeutic potential of fibrin-based bioengineered dermis containing human fibroblasts was evaluated in a diabetes-induced delayed humanized wound healing model. In addition, two diabetic patients with refractory chronic wounds were treated with the bioengineered dermis under compassionate use. Global gene expression studies were performed in the preclinical animal model.

Results: The treatment with bioengineered dermis improved hard-to-heal wounds in 2 diabetic patients. Analysis of microarray in the preclinical model revealed 49 differentially regulated transcripts ($p < 0.05$) in diabetic wounds and most of the Gene Ontology terms in the functional enrichment analysis were related to extracellular matrix remodelling and collagen deposition. These biological alterations were reverted by using fibroblast-containing fibrin-based dermal scaffolds in the diabetes-induced delayed humanized model.

Conclusions: Biological mechanisms involved in wound healing improvement were unravelled in a preclinical model. These findings could be used for designing new therapeutic approaches with clinical relevance.