The specific receptor targeted by naltrexone to enhance diabetic wound closure is OGFr

October 10 2014

A major complication associated with diabetes is delayed cell replication in epithelium and skin. Researchers at The Pennsylvania State University College of Medicine, Hershey, Pennsylvania have reported the presence and function of the opioid growth factor (OGF) and its nuclear-associated receptor (OGFr) in skin. OGF, an inhibitory growth factor, chemically termed [Met5]-enkephalin, can be upregulated in diabetes leading to depressed cell proliferation. Topical naltrexone, a general opioid antagonist, stimulates cell replication but the specific ligand - opioid receptor pathway was previously unknown. Using rat auricular fibroblasts, and NIH 3T3 fibroblasts, selective antagonists and specific ligands for mu, delta, and kappa opioid receptors were shown to have no acceleratory effect on cell proliferation. Molecular knockdown of receptors using siRNAs demonstrated that only when the OGFr receptor expression was diminished did naltrexone become ineffective. In vivo studies using a diabetic rat model of full thickness cutaneous wounds revealed that topical application of selective antagonists (i.e., nalmefene, naltrindole, CTOP) for classical opioid receptors had no effect on wound closure.

These findings, reported in the October 2014 issue of *Experimental Biology and Medicine*, demonstrate that the specific opioid ligand – receptor pathway mediated by naltrexone in the process of enhanced cell replication is the OGF-OGFr regulatory pathway.

Professor Patricia McLaughlin, senior author of this study, said "These findings show conclusively that the inhibitory factor OGF, and its

receptor OGFr, play an integral role in maintaining the homeostasis of cell replication, and that blockade of their interfacing directly influence diabetic wound healing". Dr. McLaughlin served as the thesis advisor for Jessica Immonen, the first author of the study who is now an Assistant Professor at Rocky Mountain University of Health Professions. Also co-authoring the article is Dr. Ian Zagon, Distinguished Professor of Neural and Behavioral Sciences at the Pennsylvania State University College of Medicine.

This information will support clinical trials on topical naltrexone therapy for complications in wound healing associated with diabetes, and will also encourage the design of more specific OGFr antagonists that can be used clinically to enhance closure of epithelial, surgical, or full-thickness coetaneous wounds in normal or diabetic individuals. Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said "These important studies by Dr. McLaughlin and colleagues suggest that naltrexone will be able to improve skin repair in patients with impaired wound healing capability such as in diabetics."

More information: Selective blockade of the OGF–OGFr pathway by naltrexone accelerates fibroblast proliferation and wound healing, Published online before print July 16, 2014, DOI: 10.1177/1535370214543061

Provided by Society for Experimental Biology and Medicine