

017

HIF-1alpha is repressed in diabetes and it is an important pathogenic mechanism for diabetic ulcers

Sergiu-Bogdan Catrina, Ileana Ruxandra Botusan*, Vivekananda Gupta Sunkari*

Octavian Savu, Kerstin Brismar Dept. of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden * These authors have equally contributed to this work

Relative hypoxia is essential in wound healing since it plays a pivotal role in regulation of all the critical processes involved in tissue repair, i.e. cell motility, recruitment of endothelial precursors cells (EPC), and angiogenesis. Hypoxia inducible factor alpha (HIF-1alpha) is the critical transcription factor that regulates the adaptive responses to hypoxia. HIF-1alpha stability and function is regulated by oxygen-dependent soluble hydroxylase enzymes targeting critical proline and asparaginyl residues. We and others showed that hyperglycemia complexly affects both HIF-1alpha stability and activation.

Here we show both *in vitro* and *in vivo* (db/db mice) the detailed mechanisms that lie behind the repressive effect of hyperglycemia on HIF-1 alpha. Furthermore we show that by blocking HIF-1alpha hydroxylation through chemical inhibition it is possible to reverse the negative regulatory effect of hyperglycemia and to improve the wound healing process in diabetic animals. Local HIF-1 alpha induction was able to improve several processes essential for wound healing i.e. granulation, vascularisation, epidermal regeneration, and recruitment of EPC. Local adenovirus-mediated transfer of two stable HIF constructs demonstrated that stabilisation of HIF-1alpha is necessary and sufficient for promoting wound healing in a diabetic environment and point out on the necessity to develop specific hydroxylase inhibitors as therapeutic agents for chronic diabetes wounds.