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Wound healing rate is impaired by a glucose-induced overactive Delta 4-Notch 1 loop

Sergiu-Bogdan Catrina[1],Vivekananda Gupta Sunkari[1], Ileana Ruxandra Botusan[1,,2]Jacob Grünler[1,] Anca Irinel Catrina[3,]Freddy Radtke[4], Xiaowei Zheng, Kerstin Brismar[1] [1]Dept. of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden[2] Dept. of Endocrinology, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania [3] Dept.of Rheumatology, Karolinska Institutet, Karolinska University Hospital, Solna, Sweden [4]Ecole Polytechnique Fédérale de Lausanne, Swiss Institute for Experimental Cancer Research, Switzerland

Background: Notch signaling is central for cell differentiation and angiogenesis. It is a cell-cell system composed by several Notch receptors (Notch1-4) and their ligands (Jagged 1-2, delta 1, 3, 4). The signaling is activated after binding of the ligands to the receptor which is followed by proteolytic cleavage of the receptor by γ-secretase complex with specific outcome depending on the members of the Notch system involved. Diabetic wounds are characterized by impaired coordination of several cellular processes such as angiogenesis and cell differentiation. We have studied the potential role of Notch signaling in diabetic wound healing. **Materials and Methods:** Human dermal fibroblasts (HDF), human endothelial cells where used for in vitro studies and several animal models of diabetes (db/db mice and streptozotocin-induced diabetic mice) were used for in vivo studies. The functional consequence of the notch system modulation was studied *in vitro* by assessment of the migration of HDF and by angiogenesis assay. Notch pathway inhibition was induced either by γ-secretase inhibitors or by specific siRNA silencing of the Notch receptors (1-4). Using cre-lox system we have generated mice that lack Notch 1 in the skin. Wound healing rate was evaluated both in db/db mice and in skin specific Notch1 knock-out mice in which diabetes was induced by streptozocin (STZ). **Results:** Notch signaling was activated in the skin of several animal models of diabetes and biopsies from patients with diabetic wounds. Hyperglycemia activated Notch pathway and had repressive effect on fibroblasts migration and angiogenesis. Mechanistically, we found that hyperglycemia enhances delta 4 expression in a Notch-1-dependent manner and this positive delta 4-Notch 1 feedback loop contributed to the impaired wound healing in diabetes. This was confirmed in vivo where Notch signaling with γ-secretase inhibitors improved wound healing rate just in diabetic (db/db mice) but not in control non-diabetic animals. Using loss-of-function genetic approaches we demonstrated both at the cellular level (fibroblasts, endothelial cells) as well as in an animal model that the Notch 1 activation was the key player of the repressive effects of Notch on wound healing in diabetes, which was confirmed in the biopsies from patients with diabetic foot ulcers. **Conclusions**: Glucose activates a positive feedback loop (delta4-Notch1) that contributes to deleterious wound healing in diabetes.