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Activated Notch1 signaling has repressive effects on wound healing in diabetes

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Background: Diabetic wounds are characterized by impaired coordination of several cellular processes such as angiogenesis and cell differentiation. Notch signaling is a major player in cell differentiation and angiogenesis being a cell-cell system activated upon the interaction between the membrane-bound Notch receptors (Notch1-4) and their ligands (Jagged 1-2, delta 1, 3, 4). Binding of the ligands is followed by proteolytic cleavage of the receptor by γ-secretase complex which results in activation of the signaling with specific outcome depending on the members of the Notch system involved.**Methods:** The modulation of Notch system by hyperglycemia was studied *in vitro* in human dermal fibroblasts (HDF), human endothelial cells and *in vivo* in several animal models (db/db mice and Goto-Kakizaki (**GK**) **rat**) using the corresponding technique (western blot, transitory transfections with reporter gene assay or evaluation of target genes by quantitative RT-PCR). 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 nonspecific by γ-secretase inhibitors (DAPT, L-685,458) 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 is activated in the skin of several animal models of diabetes. Hyperglycemia activates Notch pathway at multiple levels and has repressive effect on fibroblasts migration and angiogenesis. Blocking Notch signaling with γ-secretase inhibitors improves wound healing rate just in diabetic (db/db mice) but not in control non-diabetic animals. Using loss-of-function genetic approaches we demonstrate both at the cellular level (fibroblasts, endothelial cells) as well as in an animal model that the Notch1 activation is the key player of the repressive effects of Notch on wound healing in diabetes, which is confirmed in the biopsies from patients with diabetic foot ulcers. **Conclusions:** We propose specific targeting of Notch1 signaling as potential therapy for diabetic wounds.