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Estrogen receptor-β modulates wound healing in diabetes

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Aims: Impaired wound healing in diabetes is a major medical and economical problem. It is therefore a need to find new therapeutical approaches. The effects of estrogen on cutaneous wound healing are well established and it might explain the defective wound healing in elderly. Estrogen receptors beta (ERβ) have been linked to venous ulcers. However, the effect on diabetic wounds is still unexplored. The present study analyzed the contribution of the Estrogen receptors (ERα and ERβ) to wound healing in diabetic mice.
Methods: We studied the effect of streptozotocin induced diabetes on wound healing rate in estrogen receptor knock out (ERα–ERKO & ERβ–BERKO) and in wild type mice (C57BL/6). The wound model consists of full-thickness wounds made on the dorsum of the animals. The wound area were determined every second day using a digital camera. Wound granulation, dermal and epidermal regeneration were evaluated by hematoxylin and eosin staining and angiogenesis by GS-1 isolectin staining. Markers for inflammation, endothelial precursor´s cell recruitment and cell migration were analyzed by qRT-PCR. Invitro cell migration assay was carried out in Human dermal fibroblasts (HDFs) in order to determine rate of migration in presence of agonists for estrogen receptors alpha and beta Results:
Diabetic BERKO mice but not diabetic ERKO mice have a faster wound healing rate compared to diabetic wild type mice (50% wound closure at 3.4 +/- 0.3 days ($p<0.05$), 4.5 +/- 0.5 days respectively 4.7 +/- 0.5 days). HDFs treated with either specific alpha or beta estrogen receptor agonists showed a significant increase in migration rate. Conclusions:
After induction of diabetes β-receptor knock-out (BERKO) mice display an accelerated wound healing rate when compared to α-receptor knock-out (ERKO) or wild type mice (C57BL/6). These data suggest the use of specific ER agonists for therapeutic trials. The different effect of the ERs on wound healing rate is not due to a specific effect on fibroblast migration rate.