[O22] MICRORNA 210 ROLE FOR WOUND HEALING IN DIABETES

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Aim: The specific therapeutically options for diabetes foot ulcers are limited because the pathogenic mechanisms for delayed wound healing in diabetes are still unraveled. Even though prolonged exposure of the tissues to hyperglycaemia is the primary causative factor for chronic complications of diabetes it has recently become increasingly evident that hypoxia plays an important role. Tissues' response to hypoxia is mediated by transcription factors called Hypoxia Inducible Factors (HIFs), which regulates various genes that adapt the cells to low oxygen concentration. In diabetes, however, the cellular response to hypoxia is impaired as a consequence of the repression of HIF-1. Reactivating the HIF signaling in diabetes is followed by improved wound healing rate despite chronic hyperglycemia. MicroRNA 210 (miR210) is a robust target gene of HIF and mediates an important part of the hypoxic response by modulating cell cycle, mitochondria metabolism with direct effects on angiogenesis and cell survival. In this study, we aim to investigate the contribution of miR 210 for the HIF signature during wound healing aiming for a potential narrower specific therapeutic target.

Method: The effect of diabetes on mir210 expression in skin and wounds was studied in two diabetic mouse models characterized by delayed wound healing: – db/db mice and streptozotocin induced diabetic mice. The wound model consists of full-thickness wounds made on the dorsum of the animals. The wound area was determined every second day using a digital camera. The modulation of miR210 by glucose and oxygen was investigated in human dermal fibroblasts (HDF) cultured in normal (5mM) and high (30mM) glucose concentrations exposed to normoxia (21% O_2) or hypoxia (1% O_2) for 24 hours. The expression of mir210 was evaluated both *in vitro* and *in vivo* by qPCR. The direct influence of mir210 for wound healing in diabetes was studied in mir210 knockout mice where diabetes was induced by streptozocin (50mg/kg i.p for 5 days). The wound model consists of full-thickness wounds made on the dorsum of the animals. The wound area was determined every second day using a digital camera.

Results/Discussion: In concordance with the HIF repression in diabetes the expression of miR210 in the skin of db/db mice was significantly reduced compared with the skin from the control mice ($p<0.01$, t-test; n=10). Moreover miR 210 was induced by 1.7 folds in wounds compared with uninjured skin ($p<0.01$, t-test; n=10) but markedly reduced in the wounds of diabetic animals ($p<0.05$, n=10). The expression of miR 210 *in vitro* followed the HIF signaling regulation being increased (8 folds) in HDF cultured in hypoxia and normoglycemia ($p<0.01$, t-test; n=5) but repressed in the cells cultured in high glucose and hypoxia ($p<0.05$, n=5). *In vivo* the wound healing rate was delayed by diabetes and further modulated by the lack of mir210 KO.

Conclusion: miR 210 is part of the HIF signature for wound healing both in diabetic and non diabetic conditions.