Inhibition of microRNA-34a signaling impairs hypoxia responses in diabetic wounds through metabolic reprogramming and macrophage polarization

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Diabetes foot ulceration (DFU) is a devastating chronic diabetes complication with large impact on morbidity and mortality. The therapeutic possibilities are limited due to incomplete understanding of the underlying mechanisms. Impaired adaptive responses to hypoxia have been recently suggested as an important mechanism.

In this study, we found that the hypoxia-induced expression of miR-34a was inhibited by hyperglycemia in macrophages. The regulation of miR-34a by hypoxia and hyperglycemia was found to be exerted on the transcriptional level, mediated by upstream regulator p53. Both p53 and miR-34a expression were inhibited in hypoxic wounds from patients with diabetic foot ulcer and from mouse model of diabetes compared to wounds from normoglycemic controls. Local administration of miR-34a improved wound healing in mouse model of diabetes. RNA-sequencing data suggested that miR-34a treatment affects the oxidative metabolism and inflammatory response in the hypoxic wounds.

Mechanistically, miR-34a reconstitution in diabetic conditions increased mitochondrial oxygen consumption rate and intracellular ATP whilst decreasing extracellular lactate production in macrophages, resulting in pro- to anti- inflammatory polarization changes. Fluorescent immunohistochemistry confirmed an increase in prevalence of anti-inflammatory macrophages in miR-34a-treated wounds.

In conclusion, our results suggest that the inhibition of p53 and microRNA-34a signaling contributes to the impaired hypoxia responses in diabetic wounds through metabolic reprogramming and macrophage polarization. miR-34a reconstitution can be a novel potential therapeutic strategy to promote wound healing in diabetes.