**The Impact of Diabetes on Myofibroblasts and its Potential Therapeutic Treatment and Its Non-Invasive Diabetic Wound Healing**

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### INTRODUCTION

- According to the International Diabetes Federation, ~463 million adults (age 20-79 years) were living with diabetes in 2019, which is projected to rise to 760 million by 2045.
- Those with diabetes are 10-20% more likely to undergo an amputation due to chronic ulcers.
- In normal wound healing there is a predictable progression of inflammation, proliferation, tissue remodeling. Chronic hyperglycemia can alter this normal remodeling process and myofibroblast activity which leads to a lack of cellular proliferation and an increase in proteolytic activity that prevents sufficient deposition of the ECM.

### SIGNALING PATHWAYS THAT AFFECT MYOFIBROBLASTS IN DIABETES

**TGF-β/Smad Signaling Pathway**

- TGF-β promotes myofibroblast formation directly through the canonical pathway.
- The interplay between TGF-β isoforms and specific transcription factors, including Smad proteins, leads to transcription and differentiation of α-SMA, a marker for myofibroblast differentiation.

**HIF-1 Signaling Pathway**

- HIF-1 is a transcription factor that is primarily found in the epithelium at the later stages of granulation that is responsible for the migration action of myofibroblast proliferation and fibroblast differentiation.
- It also plays a key role in ECG collagen synthesis and stimulation of fibroblasts and keratinocytes.

**FGF Signaling Pathway**

- Fibroblasts were found to be resistant to growth factors such as EGF after injury, creating a hyperglycemic environment as fibroblast culture.
- An absence of GGF-1 protein was noted at the edge of the diabetic foot wounds in humans, which led to a decrease in myofibroblasts and overall wound healing and repair.

**HIF-1α Signaling Pathway**

- HIF-1α triggers fibroblast differentiation into myofibroblasts by increasing tissue acid and decreasing extracellular pH.
- Silencing, inhibition of HIF-1α expression inactivates TGF-β1-induced myofibroblast differentiation.
- Tissues from a diabetic ulcer biopsy displayed reduced HIF-1α expression compared to non-diabetic controls.
- Hypoxic inhibitory HIF-1α mRNA expression directly by lowering the HRE promoter transcription which is thought to decrease amount of myofibroblasts.
- Hypoxia–glycolysis–mitochondria axis regulated by HIF-1α by improving its protective activity against degradation.
- HIF-1α deletion in pre-clinical models showed a failure of VEGF and SDP-1 formation response in hypoxic environments and led to impaired myofibroblast function and chronic tissue hypoxia in wounds.

**Notch-1 Signaling Pathway**

- The Notch1 signaling pathway was recently identified as a key regulator of the plasticity and function of fibroblasts in wound healing and angiogenesis.
- An experimental study found that the Notch1 signaling pathway was only activated in the diabetic mouse but not in normal skin or non-diabetic wounds.

### IMPACT OF MYOFIBROBLASTS ON ECM IN DIABETIC WOUNDS

**MMPs and TIMPs**

- Myofibroblasts produce MMPs and TIMPs during the remodeling and maturation phase of wound healing to balance the build up and degradation of the ECM to ensure complete remodeling.
- Hyperglycemic conditions found in diabetes are reported to induce higher levels of MMPs and reduced TIMPs resulting in abnormal ECM modification and chronic wound healing.

- A study on murine scars found TIMP-1 significantly reduced levels of α-SMA, TGF-β1 and subsequently induced transformation of fibroblasts to myofibroblasts.

- Research on diabetic mice has shown severe impairment in VEGF production in combination with the proaggregative activity of diabetes due to the increased amount of MMP-9.

**Outlook of ECM**

- By using 3D biomechanical in vitro models of diabetic foot ulcers, the analyzed fibroblastic cell strains responded abnormally to TGF-β1 and produced significantly thinner ECM, which was covered in fibronectin for an increased duration of time.

- Isolated primary fibroblasts in diabetic foot ulcers were also found to have impaired angiogenesis, enhanced proliferation of keratinocytes, and diminished re-epithelialization of the ECM.

- In type 1 diabetic humans, subjects were found to have impaired hypoxia-activating, a major form of protein in collagen produced by myofibroblasts, which resulted in improper tissue stabilized and ECM.

### CONCLUSION

- Myofibroblasts play an essential role in all phases of wound healing.
- Hyperglycemic conditions in diabetes can alter to myofibroblast differentiation and function.
- This interference of myofibroblast activity leads to inappropriate ECM modulation and wound contraction, which is necessary for wound regeneration.
- Understanding the role of myofibroblasts in diabetic wound healing can further benefit management for non-healing diabetic wounds.

### REFERENCES

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