Hypoxia triggers dermal fibrogenesis by activating intracellular and extracellular collagen maturation processes

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Following skin injury, the disruption of the vascular network and the increased metabolic demands required for repair create a local hypoxic microenvironment. The subsequent activation of hypoxia-inducible factor (HIF) is pivotal for effective wound healing, yet its dysregulation can contribute to pathological conditions such as chronic wounds or excessive fibrosis. To elucidate how hypoxia influences the balance between normal fibrogenesis and pathological fibrosis, we explored the involvement of HIF in collagen biosynthesis and maturation in primary dermal fibroblasts.

Our findings show that hypoxic conditions (1% O_2) prompt fibroblast differentiation into myofibroblasts and enhance collagen I secretion into the extracellular medium. We further delved into the molecular mechanisms underlying this fibrogenesis, and we observed that while hypoxia did not significantly elevate collagen I expression, it markedly influenced several steps of collagen maturation. Specifically, HIF upregulated the expression of several intra- and extracellular enzymes responsible for collagen hydroxylation and reticulation, such as collagen prolyl hydroxylase 1 (CP4H1) and PLOD2. Conversely, transcriptional levels of Bone Morphogenetic Protein 1 (BMP-1), the principal protease responsible for the cleavage of the fibrillar collagen C-propeptide—a crucial step for integrating collagen triple helices into the extracellular matrix—remained unchanged under hypoxic conditions. However, inhibiting BMP-1 activity entirely abolished the effects of hypoxia on collagen deposition, suggesting a role of hypoxia on BMP-1 activity rather than transcription.

These findings suggest that hypoxia promotes collagen maturation both intracellularly and extracellularly. Our ongoing investigations aim to elucidate the interplay between HIF and BMP1 activity, thereby further depicting the role of hypoxia in normal and pathological wound healing processes.