BMP2-induced Adam12+Fibroblasts Dictate Skin Scarring and Fibrosis

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BACKGROUND

We and others found that Adam12+ fibroblasts were increased and essential for fibrosis in multiple fibrotic diseases. However, the key signaling that regulates the origin of Adam12+ fibroblasts, the cellular progeny of Adam12+ fibroblasts and the mechanism that Adam12+ fibroblasts promote fibrosis in fibrotic diseases remain elusive.

METHODS

We use lineage tracing, cell ablation and conditional knockout technologies to explore these questions in skin wounds.

RESULTS

We found that Adam12+fibroblasts were necessary for skin scarring and fibrosis and they promoted fibrosis by secreting periostin. Lineage tracing and single cell RNAseq results suggested that most of myofibroblasts, the important cells for scarring, were progeny of Adam12 +fibroblasts. We next identified BMP2 as the essential upstream signal for the generation of Adam12+ fibroblasts and showed that Adam12+fibroblasts mainly originated from normal fibroblasts after skin injury. Conditional knockout of the BMP2 receptor in fibroblasts decreased the number of Adam12+fibroblasts, the expression of periostin and the degree of scarring and fibrosis after skin injury. In clinical samples, we found that BMP2, periostin and Adam12+fibroblasts were increased significantly in hypertrophic scar and keloid compared to normal scars, and enhancing BMP2 signaling aggravated skin scarring and fibrosis, implying that abnormally highly expressed BMP2 may lead to skin fibrotic diseases. Treatment of hypertrophic scar mouse model by BMP2 inhibitor decreased the degree of scarring and fibrosis.

CONCLUSION

These findings will help to understand skin abnormal scarring pathogenesis in depth and provide new targets for the therapy of fibrotic diseases.