WOUND HEALING

TRAF4 PROMOTES PROLIFERATION OF KELOID BY INHIBITING P53 PATHWAY VIA INTERACTING WITH USP10

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Introduction: Keloids represent one extreme of aberrant dermal wound healing. One of the important characteristics of keloids is uncontrolled fibroblasts proliferation. However, the mechanism of excessive proliferation of fibroblasts in keloids remains elusive.

Objective: In this study, we aim to identify new factors involved in keloid proliferation and develop relevant blocking strategies for keloid therapy.

Materials and Methods: Fibroblasts were cultured from keloid tissues and healthy skin tissues. The expression of TRAF4 in tissues was detected by immunohistochemistry. The protein levels of TRAF4 in fibroblasts were detected by Western blot. The proliferation of fibroblasts was detected by cell counting, CCK8 and EdU assays. The interaction between TRAF4 and USP10 was detected by immunoprecipitation.

Results: Expression of TRAF4 was markedly higher in keloid than in normal skin. Knock-down of TRAF4 inhibited keloid fibroblasts proliferation, whereas overexpression of TRAF4 promoted proliferation of fibroblasts from normal skin. We next dissected the underlying molecular mechanism and showed that TRAF4 down-regulated p53 pathway in keloid. Importantly, knock-down of p53 in TRAF4 knock-down keloid fibroblasts rescued its proliferation, suggesting that the regulation of proliferation by TRAF4 in keloid relied on p53. To determine the mechanism in depth, we found that TRAF4 bound to the p53 deubiquitinase USP10 and blocked the access of p53 to USP10, resulting in the loss of p53 deubiquitination and its stabilization. Knock-down of USP10 in TRAF4 knock-down keloid fibroblasts inhibited p53 expression and enhanced cell proliferation. Consistent with these findings, we found TRAF4 expression correlated with p53 inhibition in clinical samples.

Conclusions: Our study suggests that TRAF4 promotes cell proliferation by inhibiting p53 pathway in keloid. In mechanism, TRAF4 inhibits p53 pathway by interacting with USP10 and competes with p53 for USP10 binding. These findings will provide valuable insight towards understanding keloid development and discovering novel targets for keloid

treatment.