The Editor's Choice

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Bone morphogenetic protein-7 inhibits endothelial-to-mesenchymal transition in primary human umbilical vein endothelial cells and mouse model of systemic sclerosis via Akt/mTOR/p70S6K pathway

Systemic sclerosis (SSc) is an autoimmune inflammatory and vascular disorder that causes tissue fibrosis of the skin and internal organs. Endothelial-to-mesenchymal transition (EndoMT) has been considered an important mechanism in the pathogenesis of vascular remodeling in SSc. Recent studies suggested that bone morphogenic protein 7 (BMP-7) has anti-fibrotic effects in several fibrotic diseases. Shen C et al investigated the mechanism of BMP-7 in inhibiting TGF-beta-induced EndoMT in systemic sclerosis (SSc). The expression of BMP-7 was decreased in the basal layer of epidermis and dermis of SSc patients. EndoMT in TGF-β-treated HUVECs and skins of SSc mouse model were markedly attenuated after treatment with rh-BMP-7. Moreover, Akt/mTOR/p70S6K phosphorylation was involved in EndoMT and BMP-7 suppressed TGF-β- or bleomycin-induced theses phosphorylation in HUVECs or SSc mouse model. BMP-7 reduced the production of TGF-β-induced EndoMT in HUVECs and SSc mouse model through Akt/mTOR/p70S6K signaling pathway. These findings suggested that BMP-7 can be employed as a promising antifibrotic therapy for SSc.

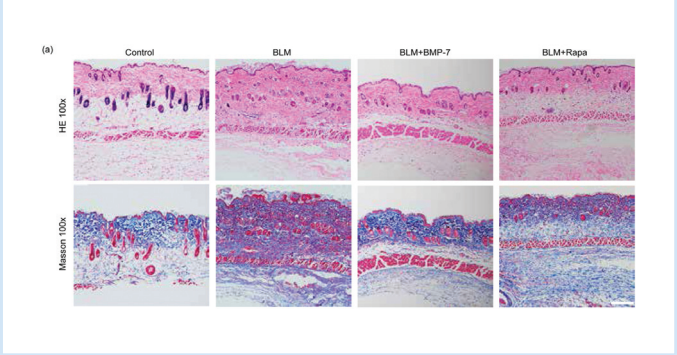

Fig. 4. BMP-7 ameliorated dermal fibrosis in a BLM-induced mouse model. (a) and (b): Representative images of HE and Masson's trichrome staining results. Thicknesses of dermis and subcutaneous fat were calculated at 100×microscopic magnification by HE staining, while the numbers of capillaries were calculated at 200× . Scale bar, 100 μm.

H3K27Ac modification and gene expression in psoriasis

Numerous alterations in gene expression have been described in psoriatic lesions compared to uninvolved or healthy skin. However, the mechanisms which induce this altered expression remain unclear. Epigenetic modifications play a key role in regulating genes' expression. Only three studies compared the whole-genome DNA methylation of psoriasis versus healthy skin. Moamen M et al explored the pattern of H3K27Ac modifications in psoriatic lesions compared to uninvolved psoriatic and healthy skin, in order to identify new genes involved in the pathogenesis of psoriasis. The authors found a differential H3K27Ac pattern between psoriatic compared to uninvolved or healthy skins. The authors found that many of the overexpressed and H3K27Ac enriched genes in psoriasis, harbor a putative GRHL transcription factor-binding site. In the most overexpressed genes in psoriasis, there is an enrichment of H3K27Ac. However, the loss of H3K27 modification does not correlate with decreased gene expression. GRHL appears to play an important role in the pathogenesis of psoriasis and therefore might be a new target for psoriasis therapeutics.

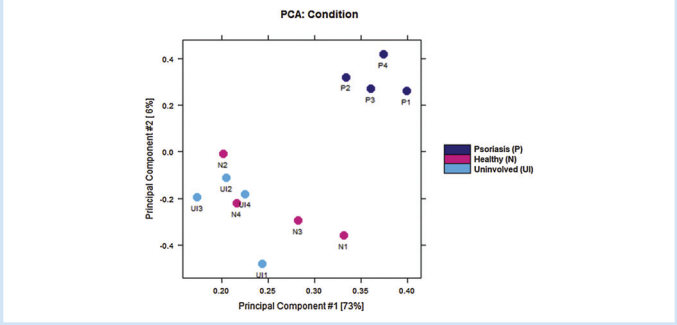

Fig.1. H3K27Ac differential enrichment. PCA plot of H3K27Ac enrichment in P vs. N vs. UI samples. The match number in samples P and UI indicates that they were taken from the same patient.

Serum lactate dehydrogenase level as a possible predictor of treatment preference in psoriasis

The efficacy of small molecule inhibitors for intracellular signal mediators varies among the individuals, and their mechanism of action is broad. A phosphodiesterase 4 inhibitor apremilast shows a dramatic effect on a certain proportion of psoriatic patients by modulating the cellular metabolism and regulating the production of pro-inflammatory molecules. Koguchi-Yoshioka H et al identified the indices which predict the efficacy of apremilast in psoriasis, and to investigate the impact of metabolic activity in immune cells on the psoriatic pathogenesis. There was a correlation between clinical improvement and the serum LDH level in the patients treated with apremilast but not in those with biologics. Serum LDH level did not correlate with the cutaneous disease severity but correlated with the oxygen consumption rate of blood T cells. Psoriatic patients with high serum LDH level can be benefitted by apremilast. The serum LDH level reflects the augmented respiratory activity of T cells in psoriasis. These results would highlight the importance of regarding metabolic skew in immune cells as a treatment target in psoriasis.

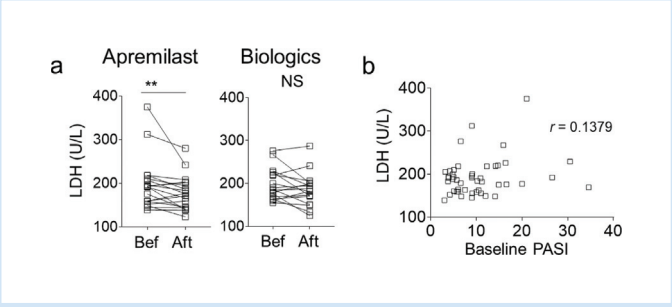

Fig. 2. The serum LDH level decreases after apremilast treatment and does not necessarily reflect the severity of skin inflammation. a) The alteration in the serum LDH level before and 4 weeks after the treatment with apremilast (left, n = 19) and biologics (right, n = 17). ** $p < 0.01$, NS: not significant. b) Correlation of the baseline PASI score and the serum LDH level in the psoriatic patients (n = 47).