발표 제목: Specific epigenetic modifications of fibroblasts from human psoriatic skin lesions: New targets for anti-inflammatory therapy?

초록:
Psoriasis is a chronic inflammatory skin disease characterized by hyperproliferation of epidermal keratinocytes, inflammatory cell activation and remodeling of the vasculature. Fibroblasts are the major cellular constituents of the dermis and produce several extracellular matrix (ECM) proteins. In psoriatic skin lesions, fibroblasts are activated and have an altered production of ECM proteins, including the expression of the Extra-Domain A of fibronectin (EDA FN). Importantly, even after successful therapy, skin lesions recur at the same sites as the previously healed lesions, indicating a potential epigenetic memory of skin cells. To investigate potential transcriptional and epigenetic alterations of psoriatic fibroblasts, we isolated dermal fibroblasts from both healthy skin and lesional skin of psoriasis patients. RNA quantification revealed increased expression of several genes including EDA FN and integrin alpha4 in psoriatic fibroblasts even after several passages. We next screened a library of 48 small molecular epigenetic modifiers for their potential to reduce the expression of several target genes including EDA FN. We found that selective CBP/p300 inhibitors consistently reduced the expression levels of the target genes in psoriatic fibroblasts. Next, we investigated the in vivo effects of a specific inhibitor of the histone acetyltransferase of CBP/p300, using the imiquimod-induced mouse psoriasis model. Systemic treatment for 7 days significantly reduced the inflammatory ear swelling, the PASI (Psoriasis Area and Severity Index) score, the weight of the draining lymph nodes and also inflammatory leukocyte recruitment to the inflamed skin. These data indicate that fibroblasts in chronic inflammatory skin lesions undergo epigenetic modifications that impact their transcriptional activities and protein expression, and that epigenetic re-programming might be a promising new approach for the treatment and/or prevention of relapse of chronic inflammatory diseases.

(Short version)
Psoriasis is a chronic inflammatory skin disease that often recurs at the same locations, indicating potential epigenetic changes of lesional skin cells. In this study, we discovered that fibroblasts isolated from psoriatic skin lesions retain an abnormal phenotype even after several passages in culture. Transcriptomic profiling revealed upregulation of several genes, including the EDA splice variant of fibronectin (EDA FN) and integrin alpha 4 (ITGA4) in psoriatic fibroblasts. A phenotypic library screening of small-molecule epigenetic modifier drugs revealed that selective CBP/p300 inhibitors were able to rescue the psoriatic fibroblast phenotype, reducing the expression levels
of EDA FN and ITGA4. In the imiquimod-induced mouse model of psoriasis-like skin inflammation, systemic treatment with A485, a potent CBP/p300 blocker, significantly reduced skin inflammation, immune cell recruitment and inflammatory cytokine production. Our findings indicate that epigenetic re-programming might represent a new approach for the treatment and/or prevention of relapses of psoriasis.

**Research Interests**

• Identification of novel inducers derived from plant extracts in skin lymphatic vessel growth and function (피부 림프관 성장 및 기능을 유도하는 식물 추출물 유래 신규 물질 규명)

• Understanding of transcriptional and epigenetic mechanisms underlying chronic inflammatory diseases (만성 염증 질환에 대하여 유전학적 그리고 후성유전학적 기전 연구 및 새로운 치료법 발굴)