CONNECTIVE TISSUE DISEASES

Is epigenetic modification the future of antifibrotic therapy?

A study by Hossein Hemmatazad and colleagues from Zurich, Switzerland suggests that silencing of histone deacetylase 7 (HDAC7), a class II HDAC, using small interfering RNA could be a specific and effective target in the treatment of systemic sclerosis (SSc).

SSc is characterized by increased fibroblast activity, resulting in abnormal growth of connective tissue, vascular damage and fibrosis. Hemmatazad *et al.* have previously shown that treatment with the HDAC inhibitor trichostatin A (TSA) reduces total collagen production and prevents the dermal accumulation of extracellular matrix proteins *in vivo* in a bleomycin-induced mouse model of fibrosis. “Based on that project”, says Hemmatazad, the current study’s lead investigator, “we decided to carry out further research to analyze the

molecular mechanisms by which TSA exerts its antifibrotic effects in the dermal fibroblasts of patients with SSc.”

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Before and after treatment with TSA, the investigators used polymerase chain reaction to measure messenger RNA expression of all known HDAC genes. They found almost complete downregulation of HDAC7 in TSA-treated fibroblasts. Furthermore, silencing of HDAC7 using small interfering RNA reduced the cytokine-induced and constitutive expression of collagen types I and III, as well as the production of total soluble collagen. Fascinatingly, however,

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the profibrotic molecules connective tissue growth factor and intracellular adhesion molecule 1 were upregulated following TSA treatment but not after HDAC7 silencing. “This led us to conclude that knockdown of HDAC7 in SSc fibroblasts has less undesirable effects than treatment with TSA,” says Hemmatazad, “and that HDAC7 could be a more-specific target for the antifibrotic treatment of SSc.”

These findings highlight exciting avenues for potential future research. “Besides antifibrotic effects on dermal fibroblasts, silencing of HDAC7 has profound effects on other cells,” explains Hemmatazad. “In our future work, we aim to analyze how silencing of HDAC7 affects endothelial cells, as well as its role in angiogenesis in the skin of patients with SSc.”

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