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Metabolic and Epigenetic Regulation of SMAD7 by Stanniocalcin-1 (STC1) Ameliorates Lung Fibrosis

Shinya Ohkouchi ; **Masahiko Kanehira** ; **Daisuke Saigusa** , **Manabu Ono** , **Ryushi Tazawa** ; **Hideya Terunuma** , **Taizou Hirano** , **Tadahisa Numakura** , **Hirotsugu Notsuda** , **Chihiro Inoue** , **Ryoko Saito-Koyama** ,

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Abstract

As shown in our previous studies, the intratracheal-administration of 0stanniocalcin-1 (STC1) ameliorates pulmonary fibrosis by reducing oxidative and endoplasmic reticulum stress through the uncoupling of respiration in a bleomycin (BLM)-treated mouse model. However, the overall effect of STC1 on metabolism was not examined. Therefore, we first conducted a comprehensive metabolomics analysis to screen the overall metabolic changes induced by STC1 in an alveolar epithelial cell line using capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS). The results were subsequently validated in multiple alveolar epithelial and fibroblast cell lines by performing precise analyses of each substance. STC1 stimulated glycolysis, acetyl-CoA synthesis, and the methionine and cysteine-glutathione pathways, which are closely related to the uncoupling of respiration, modulation of epigenetics and reduction in oxidative stress. These results are consistent with our previous study. Subsequently, we focused on the inhibitory factor SMAD7, which exerts an antifibrotic effect and is susceptible to epigenetic regulation. STC1 upregulates SMAD7 in an uncoupling protein 2-dependent manner, induces demethylation of the SMAD7 promoter region and acetylation of the SMAD7 protein in human alveolar epithelial and fibroblast cell lines and a BLM-treated mouse model, and subsequently attenuates fibrosis. The antifibrotic effects of STC1 may partially depend on the regulation of SMAD7. In the evaluation using lung tissue from idiopathic pulmonary fibrosis patients, SMAD7 expression and acetylation were high in the alveolar structure-preserving region and low in the fibrotic region. The intratracheal-administration of STC1 may prevent the development of pulmonary fibrosis by regulating the metabolism-mediated epigenetic modification of SMAD7 in patients.