**Stiff matrix instigates type I collagen biogenesis by mammalian cleavage factor I complex- mediated alternative polyadenylation**

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**Presenter：**Yun-Chen Huang                   **Date/Time：**2020/0319, 17:10 -18:00

**Commentator：**Pro.Wen-Tai Chiu         **Location：**Room 601, Med College Building

**Background：**Excessive synthesis of the extracellular matrix (ECM) to make matrix stiffening in the lung has been identified as a critical factor that amplifies pulmonary fibrosis. Alternative polyadenylation (APA) is a widespread mechanism that involves in cleavage and addition of a poly(A) tail at the 3’end of pre-mRNAs. It is an essential step for RNA processing. The choice of different polyadenylation signal (PAS) causes different length of 3’UTR and leads to regulation of mRNA localization, degradation or stability. Previous study has shown that overexpression of cleavage factor Im 25 (CFIm25) inhibits expression levels of pro-fibrotic key factors in fibroblasts isolated from human idiopathic pulmonary fibrosis (IPF). However, the roles of other essential components of the CFIm complex in lung fibrogenesis remain to be determined.

**Objective/Hypothesis：**To investigate whether mechanical stimuli derived from the stiffened matrix substrates simulating fibrotic lungs regulate expression levels of CFIm complexes in human lung fibroblasts.

**Results：**Primary human lung fibroblasts were cultured on soft or stiff matrix generated from varies concentrations of polyacrylamide hydrogels mimicking the stiffness grades of normal and fibrotic lungs. Surprisingly, they found that expression levels of the CFIm complexes were decreased while expression levels of ECM proteins such as type I collagen (COL1A1) and fibronectin (FN1) were increased when lung fibroblasts were cultured on stiff matrix. Further investigation revealed that increase of ECM protein expression was mediated through CFIm-mediated APA. Stiff matrix condition promoted the proximal poly (A) site usage in the transcripts of ECM and resulted in overexpression of ECM proteins. Furthermore, losses of CFIm subunits were also observed *in vivo* by using bleomycin-induced lung fibrosis in the mouse model.

**Conclusion：**Taken together, this article has identified a potential mechanism for regulation of the CFIm complex expression by matrix stiffness during lung fibrosis and it might be a potential cause of excessive synthesis extracellular matrix.

**References：**J Clin Invest. 2019 May 1; 129(5): 1984–1999. doi: 10.1172/JCI122106. Cleavage factor 25 deregulation contributes to pulmonary fibrosis through alternative polyadenylation.