DNA methylation profiling unveils TGF-β hyperresponse in tumor associated fibroblasts from lung cancer patients

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Abstract

There is growing interest in defining the aberrant molecular differences between normal and tumor-associated fibroblasts (TAFs) that support tumor progression. For this purpose, we recently conducted a genome-wide DNA methylation profiling of TAFs and paired control fibroblasts (CFs) from non-small cell lung cancer (NSCLC) patients, and reported a widespread hypomethylation concomitantly with focal gain of DNA methylation; in addition, we found evidence that a fraction of lung TAFs are fibrocytes in origin. Of note, the aberrant epigenome of lung TAFs had a global impact in gene expression and a selective impact on the TGF-β pathway. To get insights on the functional implications of the latter impact, we analyzed the response of lung TAFs to exogenous TGF-β1 in terms of activation and contractility. We found a larger expression of a panel of activation markers including α-SMA and collagen-I in TAFs compared to control fibroblasts. Likewise, TGF-β1 elicited a larger contractility in TAFs than in CFs as assessed by traction force microscopy. These findings reveal that lung TAFs are hyperresponsive to TGF-β1, which may underlie the expansion and/or maintenance of the tumor-promoting desmoplastic stroma in lung cancer.