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Cancer cells from large cell carcinoma of the lung induce pro-tumorigenic senescence in fibroblasts through aberrant MMP1 secretion

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Large cell carcinoma (LCC) is among the most aggressive histologic subtypes of non-small cell lung cancer, but the mechanisms underlying such aggressive nature remain unknown. We recently showed that fibroblasts from LCC patients exhibit premature senescence *in vitro*, and that co-culturing LCC cells (but not cancer cells from other lung cancer subtypes) with normal fibroblasts in transwells is sufficient to induce senescence in the latter in an oxidative stress-dependent manner, supporting that fibroblast senescence is induced by a secreted factor(s) from LCC cells. Remarkably, we also found that senescent fibroblasts secrete factors that stimulate the growth and invasion of LCC cells beyond the stimulation elicited by non-senescent fibroblasts, revealing that fibroblast senescence may contribute to the aggressive nature of LCC. Whole-genome transcriptional profiling of a panel of lung cancer cell lines identified MMP1 among the genes with larger expression in LCC compared to other subtypes. Since MMPs can induce oxidative stress, we examined whether MMP1 secreted by LCC cells was involved in the induction of fibroblast senescence in co-cultures. Knocking-down MMP1 in LCC cells was sufficient to abrogate fibroblast senescence in co-cultures as well as the growth and invasion enhancement elicited by the conditioned medium of fibroblasts in LCC cells. In contrast autophagy, which has been associated with senescence, was not upregulated in fibroblasts upon co-culture with LCC cells. These results support that the selective aberrant expression of MMP1 in LCC cells plays a major role in their ability to induce a pro-tumorigenic senescent phenotype in adjacent fibroblasts through a mechanism that is independent of autophagy. Moreover our observations identify MMP1 as a potential therapeutic target against the aberrant cancer cell-fibroblast crosstalk in LCC.

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