ImmunoTools *special* Award 2014

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Elucidating tumor-stroma cross-talk in lung cancer

Evidences have shown that initiation and progression of malignant tumors evolve not only from the complex interactions among genetically altered cancer cells, but are also deeply influenced by tumor stroma reactivity and undergo a strict microenvironment control (*1*). It has been demonstrated that a non-permissive stroma can even revert the neoplastic phenotype, while an altered stroma can stimulate abnormal growth from untransformed cells (*2*). Among micro environment cellular components involved in this process a central role is played by stromal fibroblasts (*3*). In particular, cancer-associated fibroblasts (CAFs) contribute to cancer progression by promoting angiogenesis and tumor proliferation through an SDF1/CXCR4 mediated pathway and stimulate the growth of initiated human cancer cells (*4, 5*). Interestingly, CAF appear to be heterogeneous suggesting that distinct subtypes might contribute differently to cancer growth and indicating the need for deeper evaluation of their properties (*6*). In lung cancer, a prognostic value for a gene expression signature derived from CAF has been published, suggesting the potential relevance of identifying determinants of proficient tumor-stroma cross-talk (*7*).

In previous *in vivo* experiments we observed that co-injection of lung cancer cells and human derived lung-fibroblasts resulted in increased tumorigenicity associated with changes in expression of specific genes involved in extracellular matrix (ECM) composition and remodeling. The increased tumorigenic potential elicited by fibroblasts is maintained by co-cultured cancer cells for up to 7 days even after separation. We suppose therefore that fibroblasts induce their pro-tumorigenic effect at least in part by stable priming cancer cells. To clarify the mediators of this interaction, using ImmunoTools ELISA reagents I could evaluate selected cytokines secreted by lung cancer cells co-cultured or not with fibroblasts (human IL-4, human IL-6, human IL-8 and human TNF-alpha). In addition, with *in vitro* experiments, we observed that the expression of ECM related genes is markedly increased in lung cancer cells after co-culture with fibroblasts while only a slight increase is observed when exposed to fibroblasts conditioned medium indicating that tumor stroma cross-talk may

be regulated by direct physical interaction. Since integrins are mandatory in cell adhesion and communication with extracellular matrix and are implicated in the metastatic cascade through the regulation of multiple intracellular signaling pathways, ImmunoTools reagents could provide me with a panel of antibodies (anti-CD18, CD29, CD44, CD47, CD51, CD61) useful to the characterization of the cell surface proteins associated in fibroblast-cancer cells interactions. To evaluate species specific mechanisms the same markers will also be evaluated on murine fibroblasts. Finally with human IL-12 and IL-10 ELISA and antibodies against CD14, CD11b, CD80 and CD86, I could investigate if cancer associated fibroblasts isolated from lung cancers resections are involved in monocytes recruitment and promotion of their polarization towards pro-tumorigenic M2 phenotype ($IL12^{low}$ and $IL10^{high}$)(*8*).

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