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Commentary

Cancer Associated Fibroblasts in Esophageal Squamous Cell Carcinoma

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DESCRIPTION

Abnormal metabolism is recognized as an oncogenic hallmark that is correlated with tumor progression and therapeutic resistance. Here, we used multi-omics, including phosphoproteomics, untargeted metabolomics and lipidomics to demonstrate that the Cancer-Associated Fibroblasts (CAFs)-derived AKT2/choline-phosphate Cytidylytransferase α (CCTα)/Phosphatidylcholines (PCs) axis mediated the resistance of Focal Adhesion Kinase (FAK) inhibitor-defactinib in Esophageal Squamous Cell Carcinoma (ESCC) treatment. We first identified extremely low levels of FAK Tyr397 expression in CAFs, which might possibly provide no available target for defactinib exerting its anti-growth effect in CAFs. Consequently, defactinib upregulated the intracellular concentration of Ca^{2+} in CAFs, and facilitated the formation of AKT2/CCTα protein complex to phosphorylate CCTα Ser315/319/323 sites, and finally enhanced the production of stromal PCs, which activated intratumoral Janus Kinase 2 (JAK2)/Signal Transducer and Activator of Transcription 3 (STAT3) pathway to induce resistance of FAK inhibition. Pseuo-targeted lipidomics and further validation cohort quantitatively demonstrated that plasma PCs allow to distinguish the malignant extent of ESCC patients. Overall, inhibition of stroma-derived PCs and related pathway might be used as potential therapeutic strategies for tumor treatment.

The prognosis for patients with Esophageal Squamous Cell Carcinoma (ESCC) is dismal, with the 5-year survival rate less than 15%. This poor survival rate is driven by the lack of therapeutic efficacy from cytotoxic, targeted and immune-based therapeutics. The critical mechanism of therapeutic resistances is the ESCC cells surrounding Tumor Microenvironment (TME), especially its major component Cancer-Associated Fibroblasts (CAFs). The crosstalk between ESCC and their surrounding CAFs has important effect on the biological behavior of tumor cells. CAFs tightly interact with tumor cells *via* cell-cell contact, cytokine release and exosomal transmission.

Focal Adhesion Kinase (FAK) is a cytoplasmic non-receptor protein tyrosine kinase and is ubiquitously expressed. Many reports indicate that FAK overexpression in several types of solid tumors is associated with tumor malignancy and functions as the nexus to transit the TME-derived signaling into tumor cells. These findings have encouraged the development of FAK inhibitors for tumor treatment. However, even though some FAK inhibitors have obtained excellent antitumor effect in preclinical studies only using tumor cell lines, the clinical effect of FAK inhibitors is still controversial.

While several studies have investigated cytokines or chemokines secreted by tumor cells or CAFs mediate the crosstalk between these two types of cells. A thorough understanding of TME-derived metabolites regulating tumor and CAFs communications in therapeutic resistance of tumor cells is still underexplored. In the present study, we aim to investigate whether CAFs-derived metabolites can be used as biomarkers to determine tumor malignancy and how these metabolites lead to alter the antitumor effect of FAK inhibitor through regulating the intercellular signaling crosstalk between tumor cell and CAFs.

However, CAFs-derived metabolites, the important signaling mediators, have ramifications for the function of tumor cells. To manage the metabolic challenges imposed by the TME, tumor cells and CAFs cooperatively interact to support tumor malignancy. It is not clear what are the metabolic profiles of CAFs and how CAFs-derived metabolites act on tumor malignancy and the response of tumor cells toward therapeutic agents.

We hypothesize that this discrepancy is at least in part induced by CAFs, which secrete some substances to facilitate the dysregulation of intratumoral signaling pathways, and resultantly impair the antitumor efficacy of chemotherapies.

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