

FIBROBLAST ACTIVATION PROTEIN ALPHA EXPRESSION IN TUMOR STROMA AND ITS ASSOCIATION WITH IMMUNO-REGULATORY CIRCUITS ACROSS EPITHELIAL TUMORS

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Background Carcinoma associated fibroblasts (CAFs) play important roles in modulating tumor development and prognosis through biochemical and biomechanical signals, but also through their immuno-modulatory characteristics. Fibroblast activation protein alpha (FAP), a serine protease with selectively high expression on CAFs, may be an ideal target for therapeutic intervention, including cancer immunotherapy. Therefore, a thorough understanding of FAP expression, but also immune cell composition and especially their interaction is key to optimally inform drug development and patient enrichment strategies.

Methods Formalin-fixed paraffin embedded tissue specimens comprising 253 primary tumors and 277 metastatic lesions were included in this study. Tumor sections were analyzed by digital immunohistochemistry (IHC) to assess tumor-stroma composition, FAP content and immune cell infiltration, complemented by transcriptomic analyses.

Results Across different types of epithelial tumors, FAP was detected by digital IHC in the tumor-associated stroma at a low to moderate proportion and with heterogeneous distribution patterns. Primary tumors in breast and lung cancer demonstrated a higher median FAP content (6.5% and 6.6% area coverage, respectively) compared to renal cell carcinoma (0.2% area coverage), which was confirmed on mRNA expression level. Median FAP levels were similar between primary and metastatic lesions in most tumor types except for renal cancer, for which FAP levels were significantly increased in metastasis lesions (3.3% area coverage). FAP content positively correlated with the density of FoxP3 positive regulatory T cells, but indication and tissue type specific differences were observed. Transcriptomic analysis revealed that both stroma-richness as well as higher FAP content were positively correlated with macrophage and dendritic cell gene signatures. However, while a higher stromal content was associated with signatures related to endothelial cells and preadipocytes, higher FAP content showed a stronger correlation with regulatory T cells. These findings are suggestive of a distinct biological role of FAP positive stroma in human tumors.

Conclusions FAP-targeted therapy is a promising strategy to optimize accumulation and action of anti-cancer drugs in the tumor microenvironment, potentially leading to more specific and effective therapies. Our study further elucidates the role of FAP by providing a comprehensive and granular landscape of FAP content in primary and metastatic tumor lesions derived from the same patient population and its association with immune cell composition. Future studies aim to elucidate the complex and dynamic interplay between malignant, stromal and immune cell populations in both temporal and spatial contexts and how that contributes to outcome in cancer immunotherapy.

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