

COMMENTARY



The impact of FAP imaging in lung cancer and beyond: a new chapter

Emil Novruzov^{1*}, Yuriko Mori², Abbas Alavi² and Frederik L. Giesel¹

Despite the widespread screening measures and imaging methods with their steadily increasing diagnostic accuracy, lung cancer remains one of the most lethal malignancies worldwide. Given the limitations of conventional structural imaging modalities, the introduction of FDG-PET/CT made a great leap forward due to enhanced glycolytic activity of cancer cells known as the Warburg effect [1]. Combined FDG-PET/CT has enhanced the role of imaging in staging and re-staging lung cancer, guiding the type of therapy and therapy response monitoring [1, 2]. However, FDG-PET imaging is suboptimal due to its low specificity in making a distinction between inflammatory and malignant disorders, and requires hours of fasting. Furthermore, diabetes and other chronic diseases and disorders lead to substantially reduced accuracy due to reduced glucose uptake at the disease sites [1, 2]. In view of such limitations of FDG imaging, attempts have been made to introduce novel radiotracers based on fibroblast activation protein inhibitors (FAPi), which appear to be highly promising and effective in assessing cancer as well as inflammatory-fibrosing processes. This concept relies on the distinctive role of the tumor stroma in the cancer cell growth and progress by intense interaction between

tumor cells and various elements of extracellular matrix (ECM), particularly fibroblasts [2, 3].

Although the exact mechanism is not yet fully understood, certain conditions such as acute and chronic inflammation and fibrosis are known to trigger fibroblast activation [3–5]. The activated fibroblasts are termed as cancer-associated fibroblasts (CAF) and arise from healthy resident tissue fibroblasts, bone marrow, and mesenchymal, epithelial, and endothelial cells. These are the main pro-tumorigenic factor in tumor stroma of epithelial malignancies, which modulate the tumor growth as well as inflammatory-fibrosing processes by expressing several surface biomarkers like TGF- β or FAP- α , among which fibroblast activation protein (FAP) being the most relevant target for diagnostic and theranostic purposes. Besides, this close similarity of fibroblast activity in tumorous and inflammatory processes explains the background for referring to malignancy as a “not-healing wound” [5, 6].

FAP, a type II transmembrane glycoprotein on CAFs, significantly influences ECM through enzymatic functions. Overexpressed in more than 90% of epithelial cancers and inflammatory-fibrosing processes, FAP is upregulated in lung cancer as well, varying by subtype. While NSCLC shows FAP expression levels of up to 100%, small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNC) are known to express FAP biomarker in up to 67% [7]. Aggressive tumors correlate with increased FAP expression, indicating poor outcomes. FAP's absence in normal tissues underscores its value for theranostic and diagnostic purposes [2, 6]. Novel FAP ligands act via inhibiting the enzymatic activity of FAP (endopeptidase activity), leading to ⁶⁸Ga- and ¹⁸F-labeled FAPi radiotracers for PET imaging. FAPi PET/CT, requiring no special preparation, offers a

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