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An efficacious opportunity for diagnosis and treatment of cancers: Radiolabeled fibroblast activation protein (FAP) inhibitors

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Abstract

Despite the revolutionized diagnostic effect of fluorine-18 -fludeoxyglucose ([^{18}F]-FDG) as a positron emission tomography (PET) radiotracer in oncological divisions, lack of specificity and sensitivity in discovery of some tumor subtypes was inevitable. Fibroblast activation protein (FAP) is overexpressed in a vast majority of neoplasms, particularly in more than 90% of epithelial tumors which could be an appropriate target for evaluation of tumor's molecular and metabolic functions by FAP inhibitor (FAPI) ligands. Considerably extensive radiolabeled FAPIs have been investigated during clinical trials for diagnostic as well as theranostic applications with encouraging outcomes. In the same cancers, PET/CT imaging by FAPIs are demonstrating to be valuable alternative to [^{18}F]-FDG in assessment of cancers in which [^{18}F]-FDG PET performance is suboptimal due to [^{18}F]-FDG high background uptake or relatively low avidity. Furthermore, the propensity to specifically target FAP expression through FAP-targeted medications or radiotracer therapy creates prospects for image-guided treatment in both cancer and non-cancer indications. FAPI PET will remain a fascinating field of study in the future years.

Keywords: Cancer, Diagnosis, Imaging, Treatment, FAPI, Theranostic, PET/CT/MRI

Fibroblast activation protein (FAP), a 760 amino acid type II transmembrane glycoprotein belongs to serine protease series, significantly associated with tumor invasion and metastases.[1] It is demonstrated that FAP is expressed in wide ranges of stromal fibroblasts in more than 90% of epithelial tumor cells in various cancers.[2,3] Overexpression of FAP and increasing of tumor invasion, lower survival, and poor prognosis are correlated.[4] This noteworthy characteristic of FAP makes it as an applicable target in order to identifying and diagnosis as well as treatment of various sorts of malignancies including cancers.[5] Since the first FAPI radiopharmaceutical was introduced in 2018 varieties of clinical trials have been accomplished which approved the high potential with more accuracy of radiolabeled FAPIs in comparison to fluorine-18 (^{18}F)-fludeoxyglucose (FDG) for diagnostic purposes.[6,7] It turned out of the all mentioned radiolabeled FAPI derivatives, FAPI-02 and FAPI-04 represented the most promising characterizations for clinical indications including fast accumulation at FAP-positive tumors and rapid clearance from the body, resulting in very fast internalization into tumor sites and comparable tumor-to-organ ratios.[8] All in all it is concluded that clinical utilities of FAPI-04 particularly as theranostics is so much better than its precursor (FAPI-02), since FAPI-04 has higher effective tumor uptake compared to the latter.[9] The next considerable point can be mentioned about FAPIs' capability to make radiolabeled compounds with variety of radionuclides. Different derivatives of FAPIs can be coupled through 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), N,N′-bis-[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N′-diacetic acid (HBED-CC), 1,4,7-Triazacyclononane-1,4,7-triacetic acid (NOTA), hydrazinonicotinic acid (HYNIC) to make radiolabeled compounds with different species of radionuclides including ^{18}F, Technetium-99m (^{99m}Tc), Gallium-68 (^{68}Ga), yttrium-90 (^{90}Y), Lutetium-177 (^{177}Lu), actinium-225 (^{225}Ac), indium-111 (^{111}In).[10]

FAP-targeting platforms possess a remarkable potential for achieving broad acceptance in the field of medicine.[11-13] The latest advancements in FAPI positron emission tomography/computed tomography (PET/CT) indicate a wide array of potential uses in both cancer and non-oncological indications. Although investigations

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into various non-oncological applications are still in their early stages, accumulating evidence highlighting the FAPI PET outperforms [^{18}F]-FDG PET in several cancer types, particularly in tumors where [^{18}F]-FDG PET has shown to be either insensitive or nonspecific. This includes cancers of the liver, stomach, pancreas, lungs, colon, breast, and ovaries, where the increased sensitivity of FAPI compared to [^{18}F]-FDG PET is clear. Despite FAPI PET consistently showing greater sensitivity than FDG in numerous cancers, it is important to note that FAPI has its limitations due to its accumulation in cases of benign fibrosis and inflammation. Now, there are some gaps in understanding the performance of PET scan by FAPI. One such gap involves how effectively the radiotracer can distinguish between benign and cancerous lesions, given its affinity for both. Distinguishing inflammatory lesions from tumor remains a significant challenge that requires more investigation. There is some optimism in the finding that different time-point scans conducted over several hours can reveal a clearance of activity in inflammation, while activity increases or plateaus in cancer; however, some degree of overlap between the two conditions is unavoidable. Furthermore, it is necessary to consider the correlation between histopathological and clinical findings to avoid misdiagnosis.[13] Comprehensive immunological assessments of FAP overexpression in various infectious or inflammatory diseases may provide clarity on this matter. It is now evident that FAPI uptake may differ among distinct histological subtypes, especially in conditions with low FDG avidity. Various studies indicated that tumors with recognized low FDG avidity, like signet-ring gastric carcinoma or lung adenocarcinoma, gain the most advantages from employing FAPI PET.[14] More extensive clinical investigations categorized by FDG uptake and histologic subtype are necessary to accurately define the role of FAPI PET.[15,16]

A remaining knowledge gap is how much FAPI-PET uptake indicates prognostic evidence and if it can serve as a substitute for disease consequences. Numerous studies explored the prognostic significance of FAPI PET, revealing that the intensity of the FAP signal is related to disease extent clinical and severity, which in certain instances can predict disease outcomes; nonetheless, further research is necessary. The outlook for FAPI PET is very encouraging. Nonetheless, we must also take into account alternative radionuclidic types of FAPI imaging such as SPECT imaging by ^{99m}Tc-labeled FAPI, which, despite having lower resolution, will be more adaptable and economical, and potentially more advantageous in settings with limited PET scanner availability.[17] On the opposite end of the cost spectrum, FAPI PET/magnetic resonance imaging (MRI) could also enhance flexibility in clinical decisions, since MRI is considered the standard imaging technique for various cancers such as soft tissue sarcomas, breast, brain or liver cancer.[18]

Study Highlights

- Fibroblast activation protein (FAP) has attracted attention as a promising tumor biomarker for Theranostic applications.
- FAP-based radiopharmaceuticals have demonstrated superior diagnostic imaging capabilities of cancers.

In conclusion, properly executed clinical trials involving adequately large patient cohorts to permit reliable subgroup analysis, thorough examination of histological subtypes, and the relationship with long-term clinical outcomes will be crucial in shaping the future of FAPI PET. Recent advancements in ultra-sensitive PET imaging technology will undoubtedly enhance the effectiveness of FAPI imaging. Eventually, the ability to focus on FAP expression through either FAP-targeted platforms or radiotracer treatment creates extra possibilities for image-guided therapy in the future years. FAPI-derived radiopharmaceuticals will significantly contribute to improving human health care worldwide. FAPI's trajectory suggests a paradigm shift in precision oncology, but larger trials and innovative imaging protocols are needed to realize its potential fully.

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