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Radiotheranostics of the tumor microenvironment: The magic bullet?

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Different to specific molecular tumor targets such as the somatostatin receptor of neuroendocrine tumors and the prostate specific membrane antigen of prostate cancer more recently the tumor microenvironment has been identified as a suitable target for cancer diagnosis and therapy. Malignant tumors do not only consist of cancerous cells but also a vast majority of endogenous host stromal cells (e.g., fibroblasts, vascular and immune cells) and extracellular matrix (ECM) components, collectively known as tumor microenvironment (TME). Among all cells within the TME matrix, fibroblasts are dominant cells that have a strong association of their biological functions to all stages of cancer progression and metastasis. Cancer-associated fibroblasts (CAFs) have been implicated to have a strong tumor-modulating effect and are commonly found in most solid tumors. Generally, CAFs account for up to 80% of all fibroblasts in the TME. FAP contains two types of enzymatic activity: dipeptidyl peptidase and endopeptidase. FAP appears to be a promising target in oncology due to its non-expression in normal fibroblasts and the stroma of benign epithelial tumors compared to its significantly high accumulation mainly on the stromal compartments of a variety of malignant tumors. The challenge to radiopharmaceutical chemistry is to develop molecular targeting vectors of high affinity to FAP und high selectivity to related proteases. Recently, molecular antibodies, small peptides and inhibitors have been turned into molecular imaging probes, with inhibitors utilizing the (4-quinolinoyl)glycyl-cyanopyrrolidine scaffold representing the most exciting class (nanomolar affinity to FAP compared to micromolar affinity to PREP such as the difluoro-version UAMC1110).

Radiopharmaceutical chemists from the German Cancer Research Centre Heidelberg, Germany, pioneered in translating this FAP inhibitor into potent diagnostic radiopharmaceuticals by coupling chelators to the amine of the quinoline-part of the inhibitor introducing a number of linker and spacer motifs. The University of Mainz, Germany, utilized a squaric acid (SA)-based linker bridging between several bifunctional chelators (DATA, DOTA, and DOTAGA) to the inhibitor. Currently, 68Ga labelled derivatives such as DOTA-FAPi-04, DOTA-FAPi-46 etc. and DATA5m.SA.FAPi or DOTA.SA.FAPi etc. are showing promising value in diagnosing many different kinds of tumors yielding new information even when compared to the 18F-FDG glycolysis tracer or PET tracers specific to neuroendocrine tumors or prostate cancer.

However, those FAPi-based derivatives show a relatively short retention times in the tumor lesions and seem to be unable to deliver a sufficient radiation dose profile. Recent work demonstrated that the tumor retention could be increased by going from a FAPi monomer to a FAPI dimer. The use of the DOTA-derivatives as chelator radiolabeled with attached to the first-in-human FAPi dimer [177Lu]Lu-DOTAGA.(SA.FAPi)2 resulted in an agent that was well tolerated in patients up to 4 cycles and demonstrated promising tumor doses and doses to healthy organs.
This lecture summarizes the design of the theranostics compounds, the radiochemical and in vitro evaluations, and reports on the clinical application of the theranostic pair [68Ga]Ga-DOTA.SA.FAPi monomer vs. [177Lu]Lu-DOTAGA(SA.FAPi)2 dimer.

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