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FAPI-PET Opens a New Window for Understanding of Immune-Mediated Inflammatory Diseases

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Running title: FAPI-PET in Fibrosis

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Abstract

In vivo visualization of inflammatory lesions in the body has been revolutionized by positron emission tomography (PET) with F-18-deoxyglucose (FDG) as a tracer and by magnetic resonance imaging (MRI) with gadolinium-labelled contrast media. Apart from other indications, FDG-PET and MRI have substantially improved the diagnosis and monitoring of immune-mediated inflammatory diseases such as arthritis and connective tissue diseases. While the visualization of active inflammation is well established, the detection of tissue response and tissue remodelling processes, which accompany immune-mediated inflammatory diseases (IMIDs) and lead to organ damage, is not well established. Tissue remodelling processes during inflammation are based on mesenchymal stroma cell activation and expansion in parenchymatous organs or the synovial membrane of inflamed joints. These cells express specific markers, such as fibroblast activation protein (FAP), that can be visualized by radiolabelled compounds (e.g. FAP inhibitors; FAPI) using PET. First evidence shows that focal accumulation of FAPI tracer, indicating active tissue remodelling, is observed in patients with IMIDs that are characterized by a combination of chronic inflammation and tissue responses, such as systemic sclerosis, IgG4 syndrome, or spondyloarthritis. Such FAPI-positive remodelling lesions are not always FDG-positive indicating that inflammation and tissue responses can be disentangled by such methods. These data suggest that tracers such as FAPI allow to visualize the dynamics of tissue responses in immune-mediated inflammatory diseases in vivo. This development opens new options for early recognition of tissue remodelling in the context of chronic inflammation.

Activated fibroblasts express fibroblast activation protein (FAP), a type II transmembrane protease with dipeptidyl peptidase and endopeptidase activity. Resting fibroblasts and most other cell types have only minor or no FAP expression. Recently, radiolabelled quinoline-based tracers suitable for positron emission tomography (PET) that act as FAP inhibitors (FAPI) have been developed (1). The initial goal of this development was to image stromal reactions in tumors and metastases (2). Considerable evidence is emerging on the clinical utility of FAPI-PET in oncology (for reviews, see (3) and (4)).

Tissue remodelling is also a consequence of chronic inflammation. Activation of fibroblasts is therefore not only confined to tumours, but also occurs in immune-mediated inflammatory diseases such as systemic sclerosis and IgG4-related disease (IgG4-RD) and inflammatory arthritis. In these diseases, fibroblast activation may eventually lead to severe organ dysfunction causing disability or – when parenchymatous organs are involved – even death. Tissue remodelling is the critical step for eliciting damage in immune-mediated inflammatory diseases (5). To date, imaging methods used in immune-mediated inflammatory diseases are mostly confined to detection of inflammation. PET with F-18-deoxyglucose (FDG) or magnetic resonance imaging (MRI) with gadolinium-labelled contrast media have been used to detect and quantify inflammation. However, these methods do not visualize the process of mesenchymal stromal activation and, therefore, do not allow to detect the process of tissue destruction. Furthermore, techniques such as computed tomography allow the quantification of accumulated damage rather than measuring the dynamic process of tissue changes.

Application of FAPI-PET in immune-mediated inflammatory diseases has revealed localized tracer accumulation reflecting mesenchymal tissue responses in various diseases such as fibrotic lung and liver diseases as well as arthritis and colitis (for a review, see (4)). A striking example of how mesenchymal stroma activation affects organ function is pulmonary fibrosis (PF). PF can arise as idiopathic disorder or in the context of autoimmune diseases such as systemic sclerosis. PF is often a very severe and progressive condition leading to respiratory failure. Diagnosis is established using clinical criteria and high-resolution computed tomography. Two recent publications have shown that FAPIs accumulate in PF: Röhrich et al. reported elevated FAPI

uptake in fifteen patients with different subtypes of fibrotic interstitial lung disease without further specification of their subtypes (6). There was a significant, but moderate correlation between computed tomography indices of fibrosis and FAPI uptake measured in the fibrotic areas. The authors hypothesized that Ga-68-FAPI-PET/CT might have a role in evaluating the course of PF and, in particular, in monitoring the effect of treatment. Bergmann et al. studied a group of 21 patients with systemic sclerosis-associated PF using Ga-68-FAPI-04-PET/CT (7). Systemic sclerosis patients also showed an increased FAPI accumulation in the fibrotic areas of the lungs. FAPI uptake was related to parameters of more active disease as measured by higher clinical activity scores. Furthermore, Bergmann et al. could demonstrate that the magnitude of FAPI uptake correlated with progression of disease independently of the extent of involvement on computed tomography scan and lung function at baseline. In five patients treated with the tyrosine kinase inhibitor and anti-fibrotic agent nintedanib, changes in FAPI uptake paralleled the response to treatment as determined by changes in lung function. These latter findings are in contrast to those published for FDG-PET/CT which were not predictive for treatment response in an article published by Bondue et al. (8) indicating that FAPI-PET based detection of fibrotic tissue responses is more closely related to the pathological process of systemic sclerosis than the detection of an inflammatory FDG signal by PET. In any case, larger studies are required to clarify and establish a role of FAPI-PET in monitoring the treatment response of interstitial lung disease.

As FDG-PET detects inflammatory processes, it may be asked if FAPI radioligands provide additional insights into chronic inflammation process beyond that given by FDG. In this context, interesting data have been published for IgG4 -related disease (IgG4-RD), a rare prototypical disorder that combines autoimmune inflammation with tumefactive tissue fibrosis affecting the pancreas and biliary tree, the salivary glands, the kidneys, the aorta and other organs. Immune-targeted therapies effectively inhibit inflammation but may not be suited to tackle fibrotic tissue changes, requiring to detect whether IgG4-RD is primarily based on inflammatory or fibrotic lesion in an individual patient. Evidence from histopathology indicates that IgG4-RD can progress from an inflammatory-proliferative to a fibrotic phase, each of which requiring different therapeutic approaches. The majority of IgG4-RD patients shows FDG-positive inflammatory lesions, however also FAPI-positive lesions have been described (9). Schmidkonz et al. studied a group of 27 IgG4-

RD patients using both FDG- and FAPI- PET (10). They demonstrated that FDG-positive lesions showed dense lymphoplasmacytic infiltrations of IgG4-positive plasma cells in histology, whereas FAPI-positive lesions harboured abundant activated fibroblasts. Moreover, they could also show that FAPI uptake was not correlated with that of FDG suggesting that both tracers visualize two different aspects of IgG4-RD. In their patient cohort, the responsiveness of fibrotic lesions to immunotherapy treatment was far less pronounced than that of inflammatory ones. This suggests that FAPI-PET might find a role in guiding more specific therapy in this disorder.

In summary, the above-discussed paradigmatic evidence is just the start for a wider use of FAPI-PET imaging in IMID. Other potential indications for FAPI-PET are spondyloarthritis, in which tissue responses lead to ankylosis (see Figure 1), rheumatoid arthritis, which is associated with resident tissue responses that manifest in “synovial hyperplasia”, and colitis, in which tissue responses trigger strictures in the gut. These examples may further extend the clinical role of FAPI-PET as it offers a completely new view on tissue remodelling, fibrosis and damage in chronic inflammatory diseases. These findings also offer new possibilities for early recognition of tissue remodelling process, prediction of damage and response to anti-fibrotic therapies. Hence, nuclear medicine of the future will likely step out of what has been called “hegemony of ^{18}F-FDG” (11) also in rheumatology.

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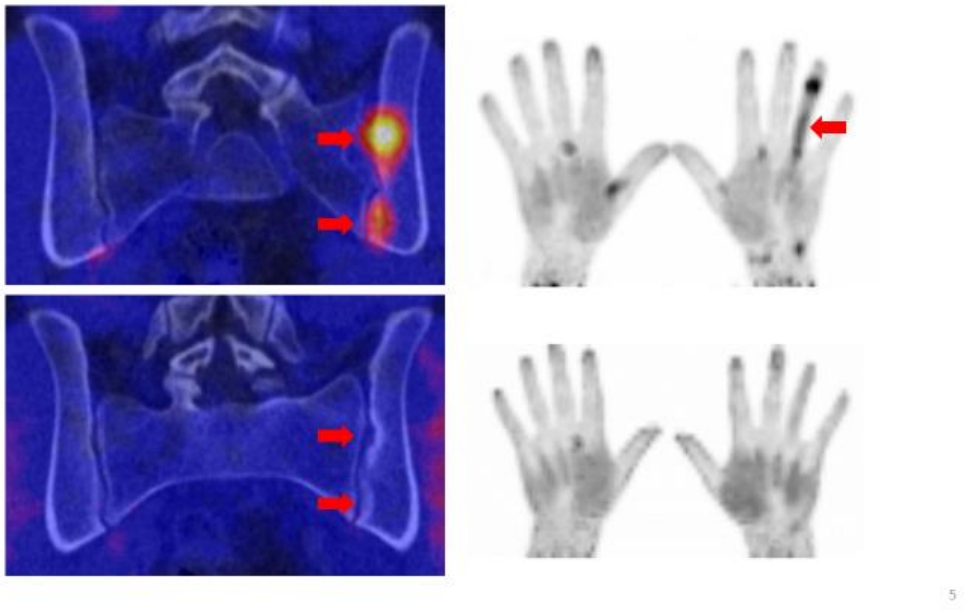

Figure 1: Ga-68-FAPI-PET images before (upper row) and after treatment (lower row) in a patient with spondyloarthritis manifesting with sacroiliiitis (left panel) and dactylitis of the fourth finger. Red arrows indicate tracer accumulation.