Inflammation Imaging

Subjects: Others

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Inflammation Imaging means using imaging to provide insights into individual and temporospatial biology and grade of inflammation which can be of diagnostic, therapeutic, and prognostic value.

molecular imaging inflammation

1. Introduction

Inflammation is a fundamental and well-balanced physiological process necessary for wound healing, protection against pathogens, and tissue homeostasis. Restrained or excessive inflammation, however, can have detrimental effects leading to pathological alterations that can worsen the outcome of patients or even form the basis of the disease itself. Consequently, the immune system and its response to pathological changes play a major role in virtually all diseases ranging from bacterial or viral infectious diseases, neurological disorders, cancer, autoimmune diseases, and cardiovascular diseases.

The adaptability of the human immune system is one of the reasons why it can react effectively and rapidly against pathogens; at the same time, it may render many novel therapies targeting inflammation or involving the immune system effective in some patients whereas other patients with the same condition do not respond at all. Accordingly, the immune response is being understood as a very individual process that demands customized therapies. Because inflammation is a very dynamic process that involves many immune cell subtypes, it can be challenging to identify the appropriate molecular target and timing for optimal intervention. In this context, molecular imaging has emerged as a helpful research tool to non-invasively visualize and study inflammation in vivo in a variety of diseases especially in a preclinical setting. However, molecular imaging may also provide insight into the individual biology of inflammation which can have diagnostic, therapeutic, and prognostic value for patients.

In recent years, many novel radiotracers and newly developed protocols for inflammation imaging have been particularly applied in the field of nuclear cardiology. Special emphasis is put on tracers that have already been successfully applied in the clinics (Table 1).

Table 1. Overview of radiotracers and their molecular targets for PET inflammation imaging.

Target	PET Radiotracer	Cell Types Targeted by the Radiotracer	Evaluated Diseases	Advantages	Limitations	Approved for Use in Humans?
Glucose metabolism (predominantly glucose transporter 1 and 3 (GLUT1-3))	^{18}F-FDG	High-glucose-using cells such as immune cells, cancer cells, cardiomyocytes, neurons, brown adipocytes, kidney cells	Myocardial infarction [1], cancer [2], atherosclerosis [3], sarcoidosis [4], endocarditis [5], IgG4-rel. diseases [6], arthritis [7], infection and others [8]	High sensitivity, fast technique completed in one session, broad availability [8]	High background signal, often need for non-physiological suppression techniques, not inflammation-specific, limited use in some clinical settings	Yes
Mannose receptor	^{18}F-FDM, ^{68}Ga-NOTA-MSA, ^{68}Ga-NOTA-anti-CD206 nanobody	Mainly expressed by macrophages (M2 > M1), immature dendritic cells, and liver sinusoidal endothelial cells	Mainly atherosclerosis [9][10][11] and cancer [12]	Higher cell specificity than ^{18}F-FDG (M2 > M1 macrophages)	Correlation of mannose-directed PET signals with histology of leukocytes and distinction from ^{18}F-FDG signal remains to be determined	No
Somatostatin receptors (SSTR)	^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC	Overexpressed mainly on pro-inflammatory M1 macrophages	Atherosclerosis [13][14], sarcoidosis [15][16][17], other sources of myocardial inflammation (i.e., pericarditis, myocarditis, MI) [18], and others [19] (i.e., idiopathic pulmonary fibrosis, histiocytosis, tuberculosis, cardiac allograft rejection, and small vessel vasculitis)	higher cell specificity and improved signal-to-background-ratio of DOTA-peptides compared to ^{18}F-FDG imaging (in particular advantageous for cardiac inflammation imaging)	Often labelled with gallium-68 (need for on-site generator)	Yes

Target	PET Radiotracer	Cell Types Targeted by the Radiotracer	Evaluated Diseases	Advantages	Limitations	Approved for Use in Humans?
C-X-C motif chemokine receptor 4 (CXCR4)	^{68}Ga-pentixafor, ^{64}Cu-DOTA-FC131	Expressed on several pro-inflammatory immune cells, particularly overexpressed on macrophages and T cells	Cancer [20], atherosclerosis [21][22][23][24][25], myocardial infarction [26][27][28][29][30][31], osteomyelitis [32], urinary tract infections [33] and others	Potential theranostic target in atherosclerosis and MI; superiority over ^{18}F-FDG in atherosclerosis; superior in chronic bone infections over granulocyte-directed ^{99m}Tc-besilesomab and ^{99m}Tc-labelled leukocytes	Not yet clinically approved, larger clinical trials needed to determine prognostic and diagnostic value in different inflammatory conditions; unspecific cellular source as various inflammatory cells express CXCR4	No; several early phase I clinical trials for cancer imaging ongoing (i.e., NCT04504526)
C-C motif chemokine receptor 2 (CCR2)	^{68}Ga/^{64}Cu-DOTA-ECL1i	Mainly expressed on pro-inflammatory monocytes, natural killer cells and T cells	Lung inflammation [34], cardiac injury [35], abdominal aortic aneurysm [36], pulmonary fibrosis [37]	Promising results regarding prognostic and therapy-monitoring abilities	unspecific cellular source as various inflammatory cells express CCR2; toxicity and biodistribution still need to be examined for a safe translation into the clinics	No; several phase I clinical trials ongoing, i.e., for imaging atherosclerosis (NCT04537403) and lung inflammation (NCT03492762)
Mitochondrial translocator protein (TSPO)	^{11}C-PK11195 and 2nd and 3rd generation TSPO tracers, such as ^{18}F-flutriciclamide (^{18}F-GE180) or ^{18}F-DPA-714	Protein located in the outer mitochondrial membrane; upregulated in activated macrophages, particularly in microglia	Myocardial infarction [38], atherosclerosis [39], vascular inflammation [40][41], rheumatoid arthritis [42][43][44]	ability to visualize peripheral and central inflammatory networks; superiority over MRI regarding detection of subclinical synovitis	Limited use in detection of peripheral inflammation; multicellular receptor expression profile; presence of radiolabelled metabolites; variability between individuals regarding tracer binding	No; several clinical trials are ongoing especially in the field of neuroinflammation (NCT03457493, NCT04412187, NCT03662750 and others)

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					affinity due to TSPO polymorphisms	
$\alpha_v\beta_3$ integrin receptor	^{18}F-galacto-RGD, ^{68}Ga-PRGD2, ^{18}F-fluciclatide	Mediates cell adhesion; important role in angiogenesis, expressed on a variety of cells such as activated endothelial cells, solid tumor cells, immune cells	Atherosclerosis [45][46], myocardial infarction [47][48][49], rheumatoid arthritis [50]	Superiority over ^{18}F-FDG regarding evaluation of disease severity in rheumatoid arthritis (^{68}Ga-PRGD2)	Not yet clinically approved, larger clinical trials needed to determine prognostic and diagnostic value in different inflammatory conditions; unspecific cellular source as various cell types express integrins	No; clinical trials have been conducted in rheumatoid arthritis (NCT01940926) and MI (NCT01813045)
Folate receptor (FR) (in particular the beta isoform (FR-β))	^{18}F-Fluoro-PEG-folate;^{18}F-AzaFol; ^{68}Ga-Ga-NOTA-folate (^{68}Ga-FOL)	High expression on cancer cells and activated M1-macrophages (and monocytes) with restricted FR expression in normal tissues	Rheumatoid arthritis [51][52][53][54][55], myocarditis [56], atherosclerosis [57], interstitial lung disease [58]	Important transport route for methotrexate making it an interesting target for rheumatoid arthritis; better target-to-background-ratio of ^{18}F-fluoro-PEG-folate as compared to ^{11}C-PK11195; significantly higher plaque-to-healthy vessel wall ratio of ^{68}Ga-FOL as compared to ^{18}F-FDG PET	Not yet clinically approved, larger clinical trials needed to determine prognostic and diagnostic value in different inflammatory conditions;	No; clinical trial for ^{18}F-AzaFol in cancer imaging has been conducted (NCT03242993)
Fibroblast activation	Various, mainly ^{68}Ga-	Fibroblasts and tumor cells	Cancer [59][60], rheumatoid	Excellent contrast due to	Further studies are warranted	No; several clinical trials are ongoing, i.e., for

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protein-α (FAP)	labelled FAP inhibitors such as ^{68}Ga-FAPI-04; labelled antibodies directed to FAP		arthritis [61][62][63], IgG4-related disease [64][65], myocardial infarction [66][67]	due to low FAP expression in physiological tissues; theranostic properties since mainly FAP inhibitors are used; superiority over ^{18}F-FDG in IgG4-rel. disease	to assess the prognostic and theranostic value	rheumatoid arthritis(NCT04514614), IgG4-rel. disease (NCT04125511) and inflammatory bowel disease (NCT04507932)

2. Imaging Inflammation with Positron Emission Tomography

Inflammation plays a fundamental role in many medical conditions, but restrained or excessive inflammation can have detrimental effects that can worsen the outcome of patients. Molecular imaging of inflammation has emerged as a helpful tool to non-invasively visualize and study inflammation in vivo in a variety of diseases; it shows value as a strong clinical and preclinical research application and may provide insight into the individual biology of inflammation which can have diagnostic, therapeutic, and prognostic value. The perfect PET radiotracer for inflammation imaging has an excellent predictive value, is cell-type specific, shows a good target-to-background ratio (diagnostic value), has a value as phenotypic biomarker, responds to anti-inflammatory therapy (therapeutic value), has a good correlation with the functional outcome and/or progression of the disease (prognostic value), and is safe for its translation into patients (translational value; Figure 1). Despite promising preclinical and clinical results, none of the herein discussed radiotracers unites all of these desired characteristics, and several obstacles still need to be overcome to establish inflammation imaging in a routine clinical setting and for validated research. Improvement of PET radiotracers for imaging inflammation, accurate and standardized quantification of radiotracer uptake for interpretation and comparability of the results, comparable and reproducible imaging protocols and guidelines, further improvement of spatial resolution of PET devices (particularly important for inflammation imaging of small structures such as vessels), and a broader access to PET imaging facilities for physicians from different medical fields are just a few of the challenges that the community needs to address in the near future. Nonetheless, PET inflammation imaging may provide insight into the individual biology of inflammation which can be of great diagnostic, therapeutic, and prognostic value for patients.

Figure 1. Characteristics of the ideal PET radiotracer for imaging inflammation. The perfect PET radiotracer for imaging inflammation has an excellent predictive value, is cell-type specific, shows a good target-to-background ratio (diagnostic value), has value as a phenotypic biomarker, responds to anti-inflammatory therapy (therapeutic value), has a good correlation with the functional outcome and/or progression of the disease (prognostic value), and is safe for its translation into patients (translational value).

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