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Seminars in
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PET/CT in Inflammatory and Auto-immune Disorders: Focus on Several Key Molecular Concepts, FDG, and Radiolabeled Probe Perspectives

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Chronic immune diseases mainly include autoimmune and inflammatory diseases. Managing chronic inflammatory and autoimmune diseases has become a significant public health concern, and therapeutic advancements over the past 50 years have been substantial. As therapeutic tools continue to multiply, the challenge now lies in providing each patient with personalized care tailored to the specifics of their condition, ushering in the era of personalized medicine. Precise and holistic imaging is essential in this context to comprehensively map the inflammatory processes in each patient, identify prognostic factors, and monitor treatment responses and complications. Imaging of patients with inflammatory and autoimmune diseases must provide a comprehensive view of the body, enabling the whole-body mapping of systemic involvement. It should identify key cellular players in the pathology, involving both innate immunity (dendritic cells, macrophages), adaptive immunity (lymphocytes), and microenvironmental cells (stromal cells, tissue cells). As a highly sensitive imaging tool with vectorized molecular probe capabilities, PET/CT can be of high relevance

Abbreviations: B-cells, B Lymphocytes; bDMARDs, biological disease-modifying antirheumatic drugs; CAD, Coronary artery; CMS, Cardiometabolic syndrome; CRP, C-reactive protein; CVD, Cardiovascular disease; CT, Computed tomography; CTLA-4, Cytotoxic T lymphocyte-associated protein 4the programmed cell death protein 1 (PD1) and; DMARDs, disease-modifying antirheumatic drugs; EORA, Elderly Onset Rheumatoid Arthritis; ESR, Erythrocyte sedimentation rate; EULAR, European league against rheumatism; ESSDAI, EULAR Sjögren's syndrome disease activity index; FAPI, Inhibitor of fibroblast activation protein; FDG, Fluorodeoxyglucose; FUO, fever of unknown origin; GCA, Giant cell arteritis; IgG4-RD, IgG4-related disease; IL-6, Interleukin-6; irAEs, Immune-related adverse events; LAFOV, Large-Axial-Field-of-View; LoSpA, Late Onset Spondylarthropathy; LVV, Large vessel vasculitis; M1, Pro-inflammatory macrophages; M2, Anti-inflammatory macrophages; MALT, Mucosa associated lymphoma; MCP-1, Monocyte chemotactic protein-1; MRI, Magnetic resonance imaging; PAD, Peripheral arterial disease; PD1, Programmed cell death protein 1; PDL1, Programmed cell death protein ligand 1; PET, Positron emission tomography; PMR, Polymyalgia rheumatica; pSS, Primary Sjogren's syndrome; RA, Rheumatoid arthritis; RNS, Nitrogen species; ROS, Reactive oxygen; SS, Sjogren's syndrome; SSTR, Somatostatin receptor; SUV, Standardized uptake value; TAK, Takayasu; TBR, Target-to-background ratio; T-cells, T Lymphocytes; TLG, Total lesion glycolysis; TLS, Tertiary lymphoid structures; TNF-α, Tumor necrosis factor-alpha; TSPO, Translocator protein; VAT, Visceral adipose tissue; WBC, White Blood Cell

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No funding was available for this review.

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https://doi.org/10.1053/j.semnuclmed.2023.10.005

in the management of numerous inflammatory and autoimmune diseases. Relying on key molecular concepts of immunity, the clinical usefulness of FDG-PET/CT in several relevant inflammatory and immune-inflammatory conditions, validated or emerging, will be discussed in this review, together with radiolabeled probe perspectives.
Semin Nucl Med 54:379-393

Introduction: Concept of Inflammation and Immunity

Chronic immune diseases mainly including autoimmune and inflammatory diseases, can affect more than 10% of the general population. Recent evidence suggests that their incidence is on the rise.[1] The classification of autoimmune diseases distinguishes between systemic autoimmune diseases, such as lupus, Sjögren's syndrome, and scleroderma, and organ-specific autoimmune diseases, including autoimmune thyroiditis and type 1 diabetes. Besides, chronic inflammatory disorders may include giant cell arteritis, IgG4-related diseases, or autoinflammatory disorders.[2] Recently also, the use of novel immunotherapies in cancer aimed at targeting the host' immune system has raised the problem of immune-related adverse effects (irAEs) of these therapies, presenting as systemic organ-specific autoimmune diseases.[3] Managing chronic inflammatory and autoimmune diseases has become a significant public health concern, and therapeutic advancements over the past 50 years have been substantial. In 1950, the discovery of cortisol by Kendall, Tadeusz Reichstein, and Hench earned them the Nobel Prize in Medicine, marking the first therapeutic application of corticosteroids in rheumatoid arthritis.[4] The 1980s witnessed the development of disease-modifying antirheumatic drugs (DMARDs), and in the 2000s targeted biological DMARDs (bDMARDs) emerged, focusing on specific cellular and molecular players in these pathologies. Apart from specific organ damages due to each disease's manifestations, chronic inflammatory and autoimmune diseases share common complications due to inflammation *per se* such as atherosclerosis of neurocognitive disorders that deserve monitoring. As therapeutic tools continue to multiply, the challenge now lies in providing each patient with personalized care tailored to the specifics of their condition, ushering in the era of personalized medicine. Precise and holistic imaging is essential in this context to comprehensively map the inflammatory processes in each patient, identify prognostic factors, and monitor treatment responses and complications.

The question, therefore, is how PET/CT imaging can be valuable in the management of patients with inflammatory and autoimmune diseases. To answer this, the major pathophysiological mechanisms involved in these conditions have to be considered. While there is no consensus formal definition of autoimmune diseases, their identification relies on a few key elements: tissue infiltration by immune cells, the presence of autoantibodies in autoimmune diseases, and the effects of immunosuppressants. Also, one hallmark of chronic inflammatory disorders is the existence of elevated biomarkers of inflammation produced by immune cells such as monocytes and macrophages. The immune system is a sophisticated machine composed of a first-line defense called "innate" immunity and an adaptable immunity capable of rapid responses to assailants, known as "adaptive" immunity. Innate immunity involves cells such as monocytes and macrophages, dendritic cells, neutrophils, and mast cells, which can phagocytose and produce mediators of the acute inflammatory phase and chemotactic factors that facilitate the influx of immune cells, notably adaptive immune actors like lymphocytes.[5] Lymphocytes, characterized by their antigen specificity and memory, are central in autoimmune diseases where self-tolerance is disrupted, leading to an excessive inflammatory response against host tissue cells expressing misrecognized autoantigens, gradually resulting in permanent tissue damage.[6] Both innate and adaptive immunity are involved in autoimmune and inflammatory diseases, activated by diverse sources of antigens with varying degrees of involvement by specific actors depending on the pathology. Multiple factors influence the outcome of the aberrant inflammatory process, including the affected tissue or organ, the extent of tissue injury, the types of activated cells, the quantities of locally and systemically secreted protein and lipid mediators, and the activation of immune regulatory checkpoints. Collectively, these factors constitute the microenvironment. The microenvironment of inflamed tissues comprises various cell types that secrete an array of mediators, including cytokines, chemokines, growth factors, lipid mediators, reactive oxygen and nitrogen species (ROS and RNS), remodeling enzymes, and neuropeptides. These mediators originate from both tissue and stromal cells and orchestrate the recruitment of new cells to the inflammatory site, their interactions, and their functions. This microenvironment plays a central role in perpetuating the inflammatory process in autoimmune diseases.[7] Therefore, capturing it during imaging in patients is essential. In summary, imaging of patients with inflammatory and autoimmune diseases must provide a comprehensive view of the body, enabling the mapping of systemic involvement. It should identify key cellular players in the pathology, involving both innate immunity (dendritic cells, macrophages), adaptive immunity (lymphocytes), and microenvironmental cells (stromal cells, tissue cells). PET/CT can address these challenges effectively.

In this review, the clinical usefulness of FDG-PET/CT in several relevant inflammatory and immune-inflammatory conditions, validated or emerging, will be discussed, together with radiolabeled probe perspectives, relying on key molecular concepts of immunity.

1) FDG PET/CT for the management of FUO

One of the early applications after the introduction of FDG-PET/CT was fever of unknown origin (FUO), since the non-specific uptake of FDG, normally considered a limitation, is actually a strength in this indication. After all, FUO can be the result of a variety of diseases, including autoimmune diseases, but also infections, inflammatory diseases, and malignancy. In all these cases, increased FDG uptake can help in identifying and localize the cause of FUO. Early and accurate identification and localization of the cause of FUO is essential to start appropriate treatment as soon as possible or to guide biopsy or surgery plans. Laboratory parameters such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and leukocyte counts, should be performed but have limited added value for determining the cause of FUO.[8] CRP, however, can be useful for the decision-making on whether FDG-PET/CT should be performed or not. When CRP levels are normal, FDG-PET/CT is usually not indicated.[9,10] There is no consensus on if and which diagnostic procedures should be performed prior to FDG-PET/CT imaging. First-line imaging usually consists of easy and cheap imaging procedures, such as chest X-ray and in specific cases abdominal ultrasound. More advanced imaging modalities such as CT or magnetic resonance imaging (MRI) may be performed based on the preference of the referring clinician, however, it should be stated that FDG PET/CT is superior to CT of chest-abdomen-pelvis in reaching a final diagnosis in FUO with a diagnostic yield beyond CT estimated at around 30%.[11] FDG-PET/CT has several advantages in comparison to the imaging techniques mentioned before. It has the possibility to perform a whole-body examination in a single imaging technique with good resolution and high sensitivity and is able to detect early-stage inflammation with relatively low radiation exposure. Regarding other nuclear medicine imaging techniques, it has become obvious the last years that FDG PET/CT has replaced scintigraphy with radiolabeled white blood cells (WBC) or Ga-citrate, and that in case of FUO FDG-PET/CT should be used if available.[12]

Diagnostic Yield in Adults

The existing literature on FDG-PET/CT in FUO is heterogenous regarding included populations, the exact timeline in the diagnostic work-up of FDG PET/CT, in population size, in the used definition of FUO, in used scan parameters, used camera systems, and in defining whether FDG-PET/CT was useful or not. Comparison of all those studies, therefore, is difficult. In our regards, not only true positive scans leading to a biopsy location or leading to a diagnosis, are helpful, but also true negative findings should be regarded as helpful, since those patients often show a spontaneous clinical regression or remission.[13,14] Several meta-analyses showed the added value of FDG-PET/CT in establishing a final diagnosis of FUO with a diagnostic yield between 56%-60% (at least 30% higher than conventional CT).[15] A recent systematic review of 63 articles evaluating 5094 patients provided a good diagnostic accuracy of FDG PET/CT with a weighted mean sensitivity of 84.4%.[16] Overall, all literature studies mention a clear contribution of FDG PET/CT in patients with FUO, by (1) identifying the potential cause, (2) localizing sites for further evaluation, and (3) guiding further management.

Diagnostic Yield in Children and Intensive Care Patients

In addition to the general adult population, FDG-PET/CT has also been evaluated in subpopulations: children and intensive care patients. In all these specific subpopulations, the diagnostic yield of FDG-PET/CT was comparable to the above-mentioned results in adults. In children, the largest study in 110 children with FUO, FDG PET/CT identified the cause of fever in almost half (48%) of the children, and in 53% treatment modifications were done bases on the scan results.[9] A prospective study of 35 patients admitted to the intensive care, reported 32 of 35 scans being helpful (21 true positive, 11 true negative) leading to an overall accuracy of 91%.[17] Another retrospective study in 30 intensive care patients with a bloodstream infection led to detection of an infection focus in 21 patients, and to changes in clinical management in 14 patients.[18]

Positioning of FDG-PET/CT in the Diagnostic Work-up of FUO

In the past, FDG PET/CT was regarded as a last attempt in the diagnostic flowchart of patients with FUO and only performed when other (conventional) imaging modalities failed to detect the cause of the fever. However, this opinion has shifted, based on the above-mentioned evidence, towards early application of FDG-PET/CT in the diagnostic process. FDG-PET/CT has become the imaging modality of choice in the work-up of patients with FUO, and should be performed directly after the basic investigations (laboratory parameters (CRP, ESR, and WBC count) and a chest X-ray) (Fig. 1).

Role of LAFOV System

The recent development of Large-Axial-Field-of-View (LAFOV) PET/CT camera systems may even further enhance the use of FDG-PET/CT in patients with FUO. These LAFOV systems enable fast whole-body scanning within 2-3 minutes, which is particularly beneficial for children (no need for sedation), intensive care patients, and patients suffering from pain and discomfort. Furthermore, the increased sensitivity may enable us also to detect low metabolically active inflammatory processes such as biofilms on prosthetic materials, and inflammation of the small cranial vessels. Maybe differentiation between the different causes of FUO may come into our hands, without the need for biopsy, by using the dynamic possibilities of this LAFOV system with all the major organs in the same field of view. This dynamic imaging may help in showing differences in glucose metabolisms kinetics between the different causes of fever.[19]

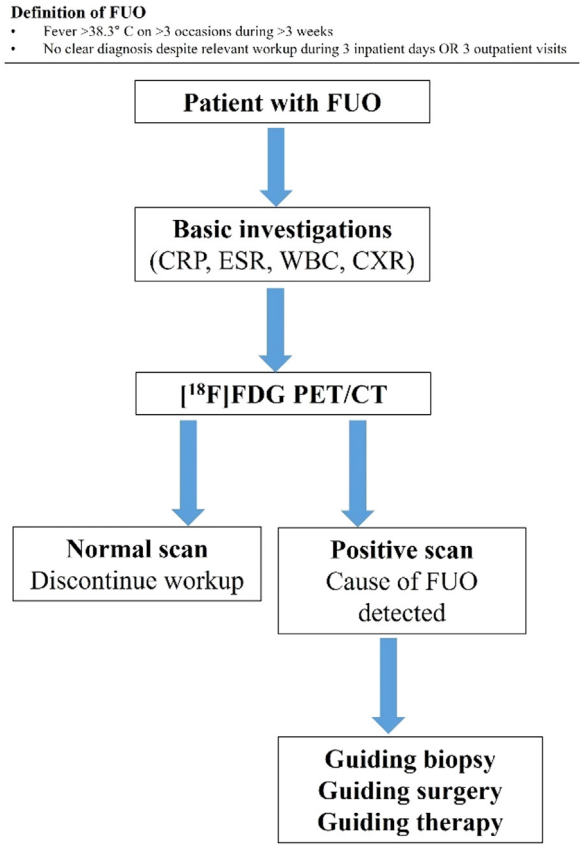

Figure 1 Diagnostic work-up for FUO including FDG-PET.

2) FDG PET and cardiometabolic disorders: chronic inflammation

Cardiovascular disease (CVD) remains the primary cause of morbidity and mortality on a global scale (Tsao 2023). The chief underlying pathology is atherosclerosis, which silently progresses over numerous years and often reaches an advanced stage by the time clinical symptoms manifest. Late-stage manifestations commonly encompass coronary artery disease (CAD), peripheral arterial disease (PAD), and cerebrovascular disease. Addressing atherosclerosis in its early stages is crucial to mitigate potential declines in quality of life; patients typically remain asymptomatic until advanced disease stages, posing challenges for timely detection. Consequently, there has been a concerted effort to identify markers indicating preclinical disease, when preventive interventions yield maximal efficacy. Cardiometabolic syndrome (CMS) denotes a cluster of metabolic dysfunctions typified by insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension, and central adiposity. This syndrome significantly contributes to avoidable conditions like heart attacks, strokes, diabetes, and nonalcoholic fatty liver disease. There is a global upsurge in the prevalence of these conditions throughout individuals' lifetimes. Notably, smoking, sedentary habits, excessive alcohol consumption, and an unhealthy diet have emerged as the primary drivers behind this escalating trend. Numerous pathophysiological factors related to cardiometabolic health have been linked to the risk of atherosclerosis-related cardio-metabolic disorders.[20] Inflammation stands out as a hallmark of atherosclerosis, culminating in arterial rigidity and the development of cardiovascular diseases.[21] While these processes are intricately interconnected, scant clinical data exist regarding their longitudinal association. PET facilitates detailed molecular imaging of active atherosclerotic processes,[22] offering insights into visceral abdominal fat tissue as an indicator of adipose tissue inflammation, as observed in prior studies.[23,24] The most commonly used PET tracer to date, FDG, predominantly reflects the metabolic activity of macrophages. FDG's uptake, primarily by macrophages, correlates with metabolic processes pivotal to atherogenesis, furnishing data for disease quantification and risk stratification (Fig. 2). PET can identify atherosclerosis in earlier stages, surpassing the capabilities of anatomical modalities,[25] enabling early intervention and heightened prospects of disease reversal. Serial imaging also facilitates the tracking of disease progression and the evaluation of therapeutic interventions.

Clinical Significance of FDG-PET in Atherosclerosis

Figueroa et al.[26] assessed the incremental predictive value of vascular PET imaging beyond the Framingham risk score in a study encompassing 514 participants who met specific inclusion criteria. Over a median follow-up period of 4.2 years, 44 individuals experienced cardiovascular events.

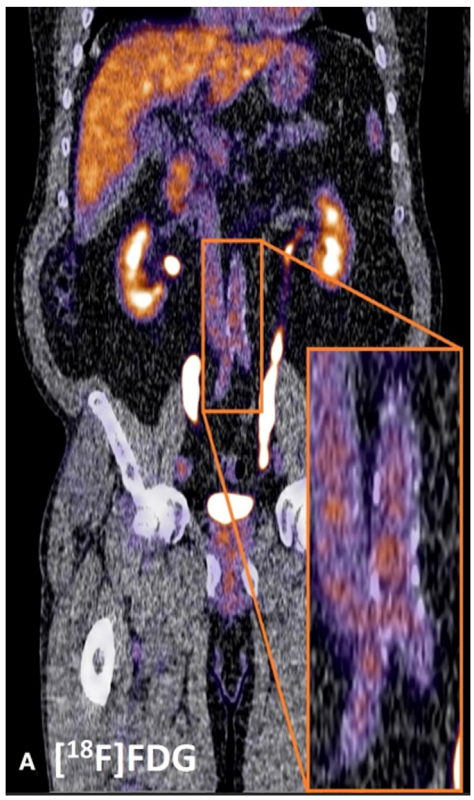

Figure 2 Metabolic active cells are visualized by FDG uptake can be found in the liver, heart, and more focal in arterial tissue (pop-up). Adapted from.[164]

The intensity of FDG uptake, quantified using target to background ratio (TBR) in the ascending aorta, not only independently predicted cardiovascular events but also improved risk assessment beyond traditional factors in this population.[26] Marnane et al.[27] conducted a prospective study involving 60 patients with recent stroke, transient ischemic attack, or retinal embolism, coupled with ipsilateral carotid stenosis (≥50%) who underwent FDG PET imaging. Patients exhibiting the highest FDG uptake in ipsilateral carotid plaques faced the greatest risk of early recurrent stroke during follow-up. Among this small cohort, high FDG uptake in carotid plaques emerged as the sole independent predictor of stroke recurrence, according to a Cox regression model.[27]

Abdominal Fat

Accumulating evidence underscores the pivotal role of dysfunctional visceral adipose tissue (VAT) in underpinning CAD risk by fomenting chronic inflammation in atherosclerotic arterial lesions.[28] Visceral obesity, especially, is known to transform healthy VAT into a dysfunctional and inflamed state.[29,30] As an activated endocrine organ, dysfunctional VAT generates pro-inflammatory cytokines—such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemotactic protein-1 (MCP-1)—accelerating the infiltration of inflammatory cells, predominantly classically activated (M1) macrophages, into VAT. This cascade exacerbates VAT inflammation.[31] Research demonstrates that VAT glucose uptake, assessed via FDG-PET/CT, increases proportionally with the number of metabolic syndrome components.[31] VAT evaluation through FDG-PET/CT correlates with CAD severity and is synchronized with carotid artery inflammation in CAD participants.[32] In a ^{18}F-FDG-PET study by Reijrink et al.,[33] it was found that CT-assessed VAT volume in the abdomen was associated with FDG-PET-assessed arterial inflammation as marker of premature atherosclerosis in early diabetes type 2.

Quantifying FDG Uptake in Atherosclerotic Plaques

Accurately quantifying ^{18}F-FDG activity in arterial walls or plaques on PET images can be challenging. The standardized uptake value (SUV) stands as the most frequently utilized parameter for lesion activity measurement on PET/CT. When quantifying FDG uptake in atherosclerotic plaques, employing the TBR is recommended over standardized uptake value (SUV). This ratio approach minimizes the impact of errors in patient weight, radiotracer dose, and imaging timing on signal quantification.[22] Assessing the most diseased segment offers a pertinent approach when gauging inflammation levels in individual atherosclerotic plaques within a patient.[22]

Improvements

Consider acquiring PET images 2 hours postinjection for dependable quantification of FDG uptake in arterial vessel walls and/or plaques. This imaging delay strikes a balance between minimal background signal in blood and a reasonable duration for the PET study.[22] Precise and swift quantification of vascular and fat FDG activity will contribute to future clinical acceptance. Further evaluation of the added value of dynamic LAFOV PET/CT is warranted, given its potential for higher resolution, superior TBR, and kinetic modeling.[34]

3) Usefulness of FDG-PET/CT in several key auto-immune disorders

In 2013 the first guidelines endorsed by EANM and SNMMI for the use of FDG PET in inflammation and infection were published.[35] During the last twelve years, PET has become a widely available tool in standard practice in high-income countries, reaching industrial maturity that favors its use for various diseases. In this context, several auto-immune disorders have progressively benefited from this powerful imaging modality, whose whole-body capabilities provide holistic insight into the metabolic involvement of the diseases. In this section several auto-immune disorders of interest will be discussed for which the clinical use of FDG-PET has been recently endorsed by international expert communities, or is currently emerging: giant cell arteritis, chronic immune-mediated rheumatologic disorders, IgG4-related disease, and Sjögren's syndrome.

Giant Cell Arteritis: A Success Story for PET Imaging in Nononcological Disorders

Giant cell arteritis (GCA) can be considered the best success story in this field. This inflammatory dysimmune disorder of undetermined etiology, relatively common in people over 50 years of age in western countries, is characterized by pathological infiltration of the arterial wall of large and medium-sized arteries by activated CD4+ lymphocytes. This infiltration promotes local inflammation, destruction, and remodeling of the vascular wall, ultimately leading to vessel wall hyperplasia. These multilayer parietal damages (adventitia/media/intima = panarteritis), typically segmental and focal, concern the aorta and/or its main branches (intra or extra-cranial), and are responsible for regional vascular and systemic unspecific clinical symptoms. High-dose corticosteroids – followed by gradual reduction over 12-24 months – remain the treatment of reference, and the rate of long-term recurrence is estimated between 20% and 50% of cases. Historically, the diagnosis was based on empirical clinical and biological criteria,[36] including a positive temporal artery biopsy, which was frequently false negative, particularly in the extra-cranial forms). The use of FDG PET emerged in GCA, following the pioneering work of Blockmans et al.,[37] who had firstly reported vascular FDG uptake related to GCA in patients with polymyalgia rheumatica, and described the currently well-known FDG PET findings in GCA, namely linear and segmental smooth hypermetabolism of the vascular wall. By using computer-driven methods and multimodal

imaging data across 4 independent cohorts (1068 patients), Gribbons et al.[38] recently validated the whole-body patterns of vascular wall involvement in both GCA (n = 382) and Takayasu (TAK, n = 685), another form of immune-mediated large vessel vasculitis, rarer and mainly observed among young women in the Mediterranean area, the Middle East and Southeast Asia: GCA is more likely to be diffuse (thoracic and abdominal aorta, carotids) or involved the bilateral axillary/subclavian arteries, while TAK is more frequently observed in the left carotid or subclavian arteries, abdominal aorta, mesenteric and renal arteries. Few meta-analyses confirmed the good sensitivities and specificities of FDG PET to diagnose large vessel vasculitis (LVV, GCA and TAK).[39-41] Based on the cumulated literature in this field over the past 20 years, FDG-PET has entered in 2018 the evidence-based recommendations endorsed by European League Against Rheumatism (EULAR) for the use of imaging modalities in primary LVV, and since this date, has been considered as a first-line diagnostic imaging procedure for the diagnostic of extracranial GCA.[42] In particular, a positive FDG PET - defined as a visually smooth and linear FDG uptake of the vessel walls superior to the liver - together with high clinical suspicion is now sufficient to make the diagnosis of GCA (or relapse), without the need of biopsy (Fig. 3). A very recent EULAR update this year extended the use of FDG PET to cranial GCA, and also specified the optimal delay time between the infusion of FDG and image acquisition (initially recommended at 60 minutes, now suggested at 90-120 minutes).[43] Under treatment, and despite the pooled evidence of decrease in FDG uptake during clinical remission,[44] residual vascular uptake may persist in the long term of LVV patients,[45,46] and its physiopathological significance remains unknown (quiescent disease? inflammatory vascular remodeling?). In the same way, PET criteria seem discordant in predicting relapses.[47,48] For these reasons, FDG-PET is still not recommended to monitor the response to treatment in LVV. PET metrics, in particular those combining the grade of uptake together with the number of vascular territories at the whole-body level,[49] are under investigation to clarify the relevance of FDG-PET for disease monitoring or relapse.

Chronic Auto-Immune Rheumatologic Disorders: An Emerging Entity for PET Imaging

Partially linked to GCA, Polymyalgia rheumatica (PMR) is an emerging application for FDG PET. PMR is the second most common chronic inflammatory rheumatism of the elderly,[50] and is associated with GCA in up to 29% of the cases.[51] Although it is currently not recommended for the diagnosis nor the assessment of treatment response of isolated PMR patients, FDG PET has progressively emerged in the diagnostic work-up of PMR patients with suspected GCA, and more broadly in patient with atypical PMR-like symptoms, including auto-immune rheumatologic disorders of the elderly, such as elderly onset rheumatoid arthritis (EORA) or late onset spondylarthropathies (LoSpA). In typical RA, which affects middle-aged people, the well-known key features are arthritis/erosion of peripheric anatomical sites (like hands, feet, and knees), and serological tests including anticitrullinated protein antibody and rheumatoid factor. However, EORA is more characterized by larger proximal joints involvement (such as the knees or shoulders), lower rheumatoid factor positivity, and higher systemic inflammation, and may mimic PMR.[52-54] SpA is a group of heterogeneous auto-immune disorders sharing similar genetic predisposition, axial and peripheric enthesitis and tenosynovitis, and may be erosive or nonerosive. Compared to standard SpA, LoSpA are characterized by more peripheric arthritis, more general symptoms, and less extra-rheumatologic manifestations, which may also mimic PMR.[55-57] Despite different physiopathological foundations, all these entities may involve the same anatomical unit termed the synovio-entheseal complex, characterized by close spatial and functional relationships between the bursa, the synovium, and the enthesis at multiple sites in the body, in the vicinity of insertions and also within the joints capsule.[58] As a consequence, overlaps of bursitis, synovitis, or enthesitis have been reported in several FDG-PET studies applied to PMR, RA, and SpA.[59-61] In their study comparing 16 seronegative PMR, 16 RA, and 21 SpA patients, Yamashita et al.[59] found higher FDG uptake in

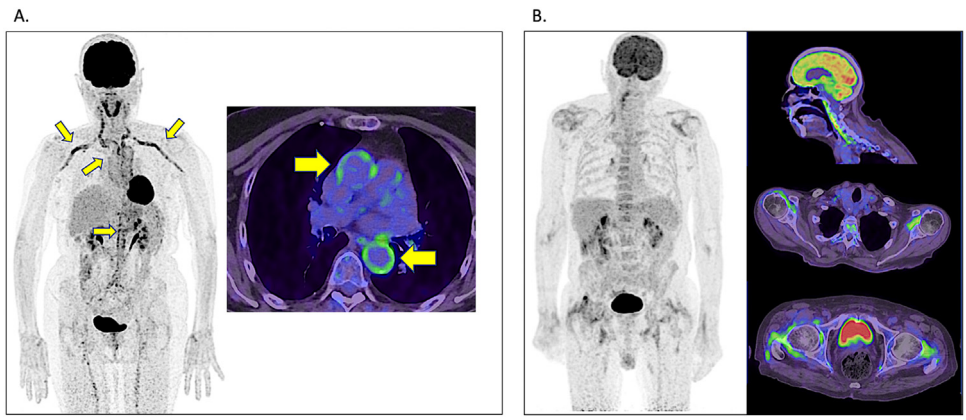

Figure 3 FDG-PET for the diagnosis of GCA, validated by EULAR. (A) In the case of typical clinical symptoms, primary diagnosis may be now confirmed by FDG-PET/CT, avoiding invasive biopsy. (B) In the case of atypical PMR presentations, FDG-PET is of relevance to rule-out GCA.

ischial tuberosity, great trochanter, and spinous processes of PMR patients compared to RA patients, while no difference were observed between PMR and SpA patients at these sites. Conversely, sacroiliac joint abnormalities were highly discriminant for SpA, and were consistent with MRI findings in 57 % of the SpA cases. Wakura et al.[60] compared FDG-PET uptake in 15 PMR and 7 EORA. Interestingly, FDG uptake at enthesis and bursa territories were mainly observed in PMR patients, while articular/periarticular joints FDG PET abnormalities (scapulohumeral, sternoclavicular, hip) were observed in the two entities. In a collaborative study comparing 35 PMR and 27 atypical and heterogeneous SpA cases, Pean-de-Ponfilly Sotier et al.[61] observed high overlap in the ischial tuberosities, shoulders, and interspinous FDG uptakes. As observed previously, the FDG uptake of sacroiliac joints was highly specific to SpA, but concerned only 15% of the SpA cases. From these emerging studies, and despite overlap in FDG PET abnormalities, one can retain the more "articular" FDG PET foreground pattern in RA patients compared to the two other entities, while SpA and PMR exhibit more similar bursitis/enthesitis foreground FDG PET features, making the diagnostic potentially more challenging between these two entities in the case of atypical symptoms mimicking PMR. In this context, the relevance of several FDG PET composite scores targeting predefined articular/periarticular / enthesis/bursae territories is currently investigated in PMR patients.[62-65] The emergence of LAFOV systems in practice will probably be of relevance in this field of applications.[66]

IgG4-Related Disease: Mapping the Whole-Body Multisystem Inflammatory Load

Another promising indication for FDG PET in this field is IgG4-related disease (IgG4-RD), an emerging physiopathological concept recognized as a clinical entity since 2003.[67] This auto-immune-mediated multisystem disorder is characterized by IgG4-positive plasma cell infiltration of organs, resulting in fibrosis with typical storiform pattern.[68] Historically reported under some entities such as auto-immune pancreatitis,[69,70] salivary/lacrimal glands infiltration (Mikulicz disease or chronic sclerosing sialadenitis-Küttner tumor),[71,72] any organ may be in fact involved (Fig. 4). Based on the 2019 EULAR classification for IgG4-RD, the most frequently reported sites are lacrimal and salivary glands, chest (parenchyma, pleura, and mediastinum), pancreas and biliary tree, kidney, and retroperitoneum.[73] To note, two-thirds of reported cases of idiopathic retroperitoneal fibrosis may be in fact IgG4-RD.[74] Pituitary gland and pachymeningitis, orbits, thyroid gland, breast, liver, cardiovascular, genitourinary, lymph nodes, and skin involvements have also been reported in FDG-PET studies.[75] Clinical symptoms remain nonspecific and may partially mimic lymphoproliferative disorders or malignancies. 2020 revised comprehensive diagnostic criteria for IgG4-RD include (1) clinical and radiological features (mono/multiorgan swelling), (2) high serum level of IgG4 (> 135 mg/dL) and (3) key histological

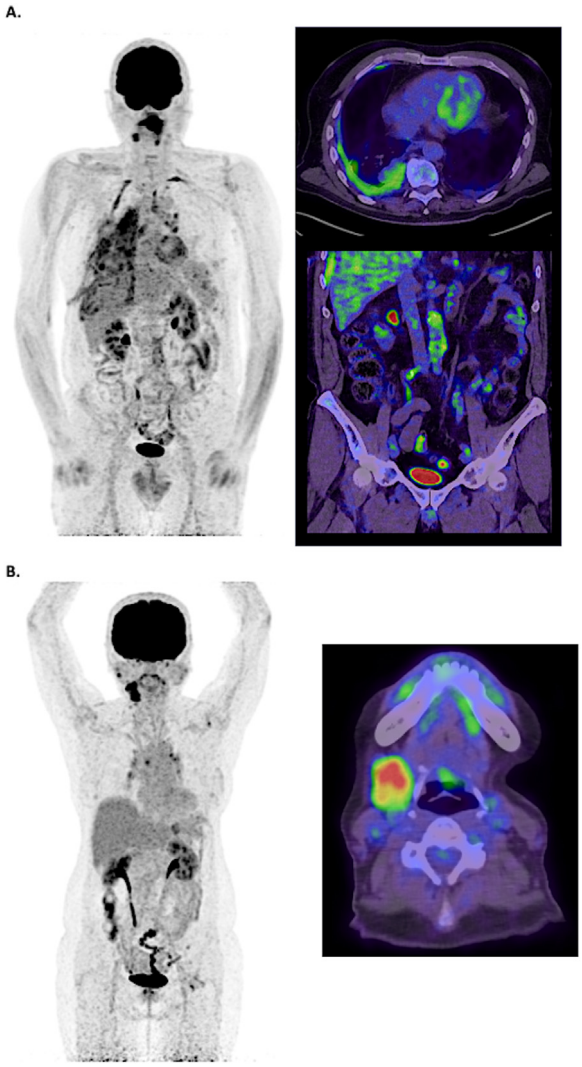

Figure 4 IgG4-RD: a wide variety of patterns on FDG PET. The most frequently reported sites are lacrimal and salivary glands, chest (parenchyma, pleura and mediastinum), pancreas and biliary tree, kidney, and retroperitoneum. (A) Pleural effusion and retroperitoneal fibrosis; (B) Right submandibular gland involvement.

features, of whom 2 must be present (dense lymphocyte and plasma cell infiltration with fibrosis; ratio of IgG4-positive plasma cells/IgG-positive cells > 40% and the number of IgG4- positive plasma cells > 10 per high powered field; storiform fibrosis).[76] Based on these criteria, patients are classified as definite (1, 2 & 3 are present), probable (1 & 3) or possible (1&2) IgG4-RD. Because high serum level of IgG4 is neither sensitive nor specific,[77-79] histological proof remains strongly recommended. In this context, the inherent capability of FDG PET to map the extent of inflammatory load at the whole-body level or guide biopsy has been demonstrated in numerous IgG4-RD studies.[80-89] However, the interlinks between FDG uptake and disease activity look consistent at baseline. Mitamura and coworkers reported good correlation between FDG PET overall inflammatory load and serum inflammatory biomarkers at baseline.[90] In another study by Berti et al.,[91] the metabolic activity of IgG4-RD assessed by FDG PET at baseline was correlated with the level of

circulating plasmablasts, a relevant biomarker of disease activity in IgG4-RD.[92] To note, the authors observed no correlation between FDG-PET and standard biomarkers of disease activity (clinical activity, serum level of IgG4 or ESR/CRP). Under treatment, while a significant decrease in FDG uptake in involved sites has been massively reported,[81,82,90,91,93,94] the correlation between FDG-PET changes and standard serum inflammatory biomarkers appeared controversial. Around 50% of the available studies reported good correlation between FDG-PET and serological biomarkers,[81,91,93] while 50% reported no correlation.[82,90,94] In their recent prospective study, Cheng et al.[95] assessed the prognostic value of baseline FDG PET in 48 patients with IgG4-RD who subsequently received standard induction steroid therapy as the first-line treatment. Relapse occurred in 81.3% of patients (median time of relapse: 7 months) and, among the clinical, serological (serum level of IgG4) and FDG PET parameters assessed, FDG PET whole-body inflammatory load (total lesion glycolysis, TLG) was the only one significant prognostic factor of relapse-free survival. Based on these data, powerful mapping of the IgG4-RD inflammatory load by FDG PET appears demonstrated, but further works will be necessary to potentially establish a relevance of FDG-PET compared to clinical and serological assessment for treatment monitoring.

Sjogren's Syndrome: Potential for Guiding Biopsy and Identify Lymphoma Transformation

Sjogren's syndrome (SS) is a rare auto-immune disorder of middle-aged women mainly, characterized by immune-mediated lymphocytic infiltrate of the salivary and lacrimal glands.[96] Hyperactivation of B-lymphocytes, Ro/SSA, La/SSB autoantibodies and rheumatoid factor are key components of SS. Clinical symptoms are nonspecific, including dryness (eyes and mouth), salivary gland swelling, fatigue and joint pain. In the presence of eyes or mouth dryness, the diagnosis of SS is based on the 2016 American College of Rheumatology/EULAR classification criteria.[97] These criteria are mainly driven by immunological features (Ro/SSA autoantibodies) and biopsy of oral saliva accessory glands showing lymphocytic infiltrate (focus score – defined by the number of mononuclear cell infiltrates containing at least 50 inflammatory cells in a 4 mm^2 glandular section). Systemic involvement may be observed in up to 40% of the patients, including the airways / lungs (interstitial disease, cysts), kidneys, central nervous system, skin or muscles.[96] Furthermore, SS may be isolated, (primary Sjögren's syndrome - pSS) or associated with other auto-immune disorders (RA, systemic lupus erythematosus, systemic sclerosis). The assessment of disease activity is currently based on the EULAR Sjögren's syndrome disease activity index (ESSDAI).[98,99] Because historically, standardized therapeutic framework was lacking, a recent task force from EULAR recently developed evidence and consensus-based recommendations for the management of patients with SS.[100] In 5%-10% of the cases, non-Hodgkin lymphoma may occur (mainly mucosa associated lymphoma, MALT), and represents the most serious complication, up to 10 time more frequent than in the general population.[101] In the presence of risk factors (clinical impairment - fatigue, recurrent swelling of parotid glands; or biological - monoclonal immunoglobulin and rheumatoid factor), targeted biopsy is therefore mandatory to search for malignant transformation. FDG-PET is currently not recommended in the standard work-up of pSS, but the use of PET imaging has progressively emerged in practice, thanks again to its whole-body inflammatory load mapping capabilities. In 2013, Cohen et al.[102] retrospectively describe FDG-PET findings in a large controlled population of 32 SS (27 pSS, 5 SS associated with other auto-immune disorders – 2 systemic sclerosis, 1 antisynthetase syndrome, 1 RA, 1 systemic lupus erythematosus). FDG uptake was reported in 75% of patients, and concerned lymph nodes (60%), bilateral salivary glands (53%), lungs (interstitial lung disease, 28%), and thyroid (5%). To note, lung parenchymal consolidations were related to MALT lymphoma. While the patients with lymphoma exhibited higher FDG uptake, the intensity of uptake in involved sites did not correlate with ESSDAI score at the whole population level. More recently, Keraen et al.[103] specifically addressed the usefulness of FDG-PET to identify lymphoma patients among pSS populations. The authors showed, in a retrospective bicentric study comparing 15 pSS with lymphoma and 30 pSS without lymphoma, no between-group difference in terms of lymph node extent, pattern, or FDG uptake, which concerned 85% of the study population. However, lymphoma patients exhibited higher uptake in parotid glands and parenchymal lung nodular or focal consolidations were specific to lymphoma. Importantly, biopsies guided by the highest sites of uptakes led to the diagnosis of lymphoma in more than one-third of the patients who benefited from a PET-guided biopsy. The higher FDG uptake in parotid and submandibular glands in lymphoma patients was recently confirmed by another study including 70 patients with pSS, of whom 26 had lymphoma.[104] Also, nodular lung consolidations were highly specific to lymphoma (93%). Combining FDG uptake in parotid and submandibular glands together with lung nodules provided negative predictive value of 87% (2/3 present) and 94% (1/3 present) for lymphoma in pSS. From these studies one may consider FDG-PET a useful tool in the case of suggestive symptoms, to rule out lymphoma and avoid invasive procedure in the case of negative PET results, or to guide biopsy for optimized diagnostic work-up in the case of positive findings (Fig. 5).

4) PET/CT and auto-immunity in the era of immunotherapies: beyond tumor metabolic load

Thanks to its very high sensitivity and inherent non-specificity, FDG-based PET molecular imaging has unparallel capabilities to map the carbohydrate metabolism of a wide variety of human cells at the whole-body level. In the 1990s, PET studies have highlighted the role of inflammatory immune cells – notably fibroblasts and macrophages - in the

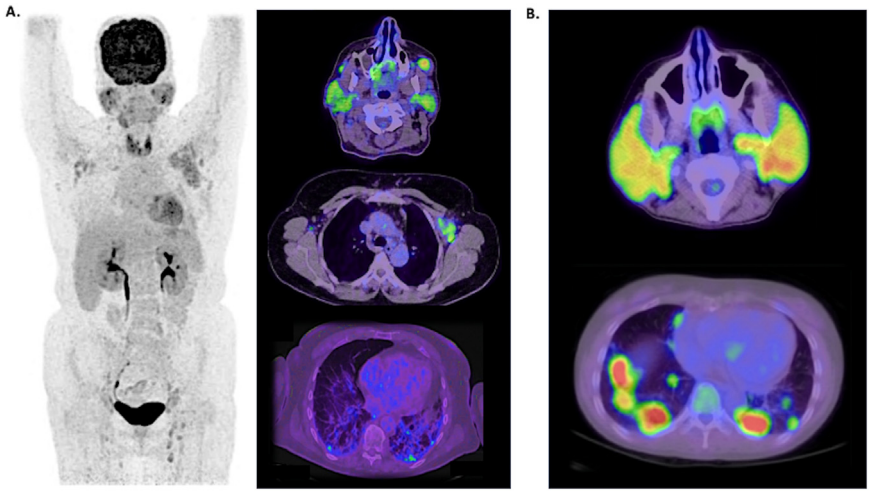

Figure 5 Sjögren syndrome. (A) Typical FDG-PET/CT pattern of pSS: involvement of parotid/lacrimal glands, lymph nodes at sus and sub-diaphragmatic levels, and interstitial lung disease. (B) Red flags highly suggestive of lymphoma transformation: increased size of parotid glands with high FDG uptake; hypermetabolic nodular opacities in the lungs.

FDG avidity of tumor structures.[105,106] In parallel, the last 15 years have been marked by major advances in understanding and characterizing the immune microenvironment of tumor cells,[107] providing the foundation for immune-mediated therapy strategies in Oncology.[108] By restoring the immunes T-cells own response capabilities, cytotoxic T lymphocyte-associated protein 4 (CTLA-4), the programmed cell death protein 1 (PD1) and the programmed cell death protein 1 (PD1)/ programmed cell death protein ligand 1 (PD-L1) constitute a paradigm shift in treatment strategy of numerous cancers, and represent today the corner stones of these new therapeutic strategies, with success in a fraction of patients. By restoring the immune system, these therapies produce numerous systemic immune-related adverse events (irAEs), which vary depending on the cancer and the immune-mediated drug.[109-111] Any organ may be involved,[112,113] up to 76% of the patients may be concerned,[110] and the main range of onset concerns the first 16 weeks.[114] Among irAEs, colitis, hypophysitis rash and pruritus have been observed preferentially with CTLA-4 drugs, whereas pneumonitis, myalgia, hypothyroidism, arthralgia, and vitiligo have been more reported with PD1 drugs.[111] Are also reported cumulated evidence of PMR-like syndromes under immune-mediated drugs,[115] potentially characterized by higher prevalence of peripheric arthritis compared to classical PMR.[116]

Issues related to these complex biological response behaviors observed in FDG-PET studies have motivated in 2018 the writing of dedicated recommendations on the use of FDG-PET for assessment of immunotherapy and reporting irAEs.[117] In this context, several interesting irAEs PET results deserve to be highlighted. In 2019, Lang et al.[118] observed auto-immune colitis - characterized by diffuse increased FDG uptake in the colon — in 49% of the 100 stage IV melanoma patients under immunotherapy they prospectively assessed with PET. To note, 57% of them had no clinical symptoms. Furthermore, the authors compared their results with those reported by Bronstein and coworkers in a previous CT-based large retrospective study of 119 stage IV melanoma patients, where evidence of CT-based colitis — diffuse colonic wall thickening — was observed in only 5% of the cases, of whom 43% had clinical evidence of enterocolitis.[119] These results emphasize the unparallel sensitivity of PET to detect homeostasis abnormalities, far before morphological consequences. Although PET-colitis did not correlate with tumor response or survival, other irAEs assessed by FDG PET may be of prognostic significance. Indeed, the same authors observed better prognosis (disease control, progression-free, and overall survival) in patients with FDG PET evidence of hypophysitis and hepatitis, but not colitis.[118] Previously, Sachpekidis et al.[120] found colitis and arthritis to be prognosis factors in metastatic melanoma patients. Beyond PET studies, the prognostic significance of iRAEs has been demonstrated in a recent systematic review and meta-analysis by Hussaini and coworkers.[121] Based on pooled clinical data from 51 studies (mainly focusing on melanoma and non-small cell lung cancer patients, median number of patients per study = 105), the authors found a positive association between irAEs and survival metrics in all the studies except one, whatever the disease type, immune-mediated drug or irAEs. As discussed by the authors, a relevant potential key explanation for such interlinks is the tissue cross-reactivity, defined by the common overall response behavior shared by healthy and pathological tissue structures, leading to global systemic T-cell-mediated response. In other words, and from a PET perspective, the overall metabolic load of immune reactivity assessed by FDG-PET at the body level may be a holistic biomarker of personalized autoimmune response potential (Fig. 6). To note, high bone marrow uptake and enlargement with diffuse uptake of the spleen - characterized by an inversion of the metabolic liver-to-spleen uptake ratio - which are also considered surrogates of immune activation, appear associated with poorer prognosis in human.[122-125] Relevant PET-based stratification of patients' immune systemic response potential

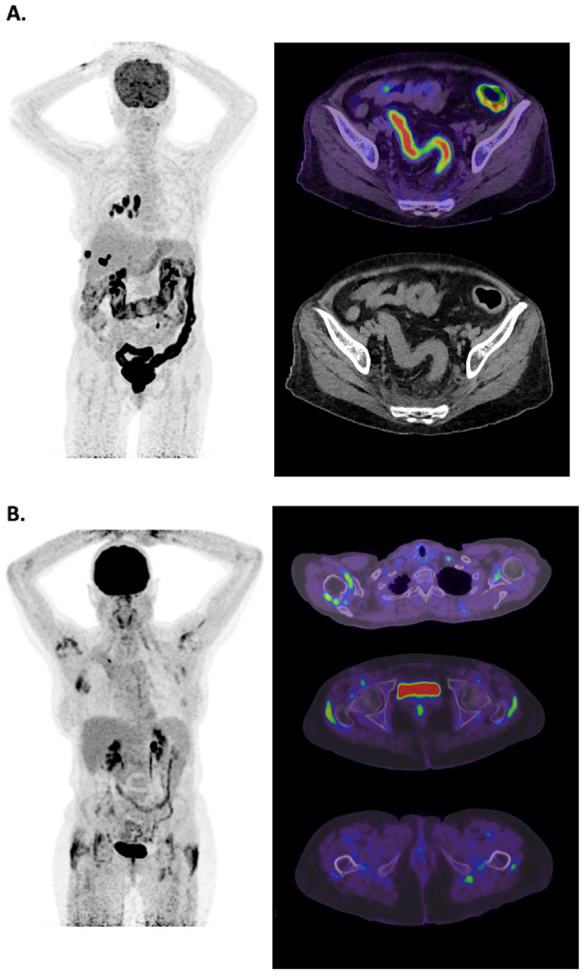

Figure 6 irAEs as potential surrogate of immunity response capabilities. The overall metabolic load of immune reactivity assessed by FDG-PET at the body level may be a holistic biomarker of personalized autoimmune response potential. (A) colitis in a patient with lung cancer stage IV under immune checkpoint inhibitor therapy (anti-PD-L1, Durvalumab). (B) PMR-like syndrome in a patient with lung cancer stage IIIB under immune checkpoint inhibitor therapy (anti-PD-L1, Durvalumab).

is currently a research topic of interest.[126] The recent availability of PET systems with extended field of view will probably enhance our capability to capture at exactly the same time the biological cross talk between key immunes organs at the total body level.[127]

5) Beyond FDG: to go further insight phenotype of immune-inflammatory conditions

As previously mentioned, the microenvironment of any immune-mediated process involves numerous cell subtypes, whose local dynamic and adaptive interactions promote or modulate inflammation and its consequences, namely tissue destruction and remodeling. Accumulating evidence of the clinical relevance of FDG-PET is observed in a broad spectrum of immune-inflammatory conditions, including those mentioned above. While FDG may be considered a general surrogate of carbohydrate upregulation of any activated immune cells, targeting more specific features is an active field of research in PET imaging, boosted by improved molecular knowledges of both oncological and non-oncological immune pathways. In this highly stimulating and evolving context, and for the sake of simplicity, PET probes may be categorized into 4 superclasses: macrophages, lymphocytes, fibroblasts and chemokines. Describing all these vectorized PET probes is out of the scope of this review. To illustrate the high phenotyping capabilities of PET molecular imaging in immune-inflammatory conditions, in this section several emerging PET radiotracers beyond FDG, not yet validated but applied to patients, which have been reported with success in a wide variety of immune-inflammatory conditions, will be described.

PET Probes Targeting Macrophages

Macrophages are involved in tissue development, homeostasis, and immunity.[128] Historically classified as organ-specific (Kuppfer cells, Langerhans cells, microglia or osteoclast, respectively in the liver, skin, central nervous system or bone), macrophages are now rather categorized according to their polarization state: pro inflammatory (namely M1) and anti-inflammatory (namely M2) states.[129] While M1 macrophages produce proinflammatory cytokines, and initiate immune responses, M2 macrophages are devoted to anti-inflammatory response and tissue repair. To note, M1/M2 represent the extremes states of a mixed and heterogeneous spectrum of activation, and exhibit their own metabolic pathways - M1 relies on glycolysis and M2 uses oxidative phosphorylation,[130-132] which, however, does not seem to be simply characterizable by FDG-PET.[133-135] As alternative, translocator protein (TSPO) and somatostatin receptor (SSTR) PET probes have gained importance to image numerous immune-inflammatory disorders. TSPO is a transmembrane protein expressed on the outer membrane of mitochondria of M1/M2 macrophages. Different generations of ^{18}F and ^{11}C radiolabeled TSPO PET probes have been clinically tested in immune and inflammatory disorders, in particular in neuro-inflammation, cardiovascular diseases/atherosclerosis and chronic inflammatory rheumatisms (for extensive reviews please refer to.[136-139] SSTR are G-protein coupled receptors expressed by cells of the immune system, including macrophages. SSRT PET probes were mainly tested in atherosclerosis and sarcoidosis.[138,139] In one study, ^{68}Ga-SSR PET showed high affinity for M1 subtype, and overpassed FDG-PET to detect inflammatory plaques in atherosclerosis.[140] Higher performance compared to FDG-PET were also reported in cardiac sarcoidosis.[141] Also, folate-based PET tracers, which targets the β-isoform of the folate receptor in activated macrophage, has been recently assessed in RA patients.[142]

PET Probes Targeting Lymphocytes

T lymphocytes (T-cells) play an important role in the initiation and development of immune-inflammatory processes.[143] In the era of immunotherapies, numerous PET

probes targeting the surface receptors of T-cells have been developed (for extensive review please refer to.[137,144] For example, CD3+, CD4+, CD8+, or CTLA-4 PET probes have been assessed in several preclinical studies. Interestingly, PD-L1 PET probes radiolabeled with ^{89}Zr have been recently assessed in first-in-human studies,[145,146] demonstrating the feasibility of imaging the expression of PD-L1 at the body level in various type of cancer. Although no clinical study has been performed yet in nononcological immune-inflammatory conditions, these targeted probes may be of interest in several auto-immune disorders, in particular in chronic inflammatory rheumatisms. In their excellent review focusing on RA, Van der Krogt et al.[137] highlighted the potential relevance of these probes in RA, both in very early phases of the disease, and in treatment perspective, as CTLA-4 is already used as disease modifying antirheumatic drug. More broadly, because T-cells are involved in early stage of various auto-immune conditions, such as Sjögren's syndrome,[147] T-cells PET probes may open new interesting clinical research opportunities in this field. In a synergistic way, B-cells enhance and perpetuate the immune response by promoting antigen presentation and chemokine release.[148] Very few B-cells PET-probes have been reported,[137,144] and should be mentioned the anti-CD20 probe (Rituximab) radiolabeled with ^{124}I or ^{89}Zr which has been applied to RA.[149,150]

PET Probes Targeting Chemokines

The super family of chemokines play a key role in the regulation of immune-inflammatory conditions, as driving the recruitment and migration of leukocytes. CXCR4, a chemokine receptor belonging to the family of G-protein, has gain interest due to high expression on the surface of numerous immune cells in immune-mediated processes.[151,152] CXCR4 PET probe radiolabeled with ^{68}Ga (^{68}Ga-Pentixafor) has been assessed in several pilot clinical oncological and nononcological studies, and showed promising results in cardiovascular imaging / atherosclerosis (for review please refer to Li 2020). Interestingly, a recent case report in SS showed ^{68}Ga-Pentixafor uptake of the parotids, submandibular salivary glands, multiple lymph nodes, related to benign infiltration of leucocytes, and the spleen, suggesting B-cell stimulation.[153] To note, recent findings suggest the CXCR4 pathway to play a role in IgG4-RD,[154] making this radiotracer conceptually relevant in a wide variety of auto-immune disorders.

PET Probes Targeting Fibroblasts

Fibroblasts are stromal cells involved in extracellular matrix secretion and remodeling, cross talk with surrounding cells, tissue structuration and metabolic regulation.[155] A decade ago, the concept of tertiary lymphoid structures (TLS) — defined as organized clusters of immune and stromal cells at sites of chronic inflammation — observed in cancer, infection and autoimmune diseases, has emerged.[7] Within TLS, resident stromal cells (fibroblast) play a key role by initiating and promoting the inflammatory infiltrate.[156] In cancer, tumor associated fibroblast are involved in tumor progression and drug resistance.[157] This motivated the development of PET probes targeting activated fibroblast (inhibitor of fibroblast activation protein, FAPI) radiolabeled with ^{68}Ga or ^{18}F.[158] Although the majority of current clinical research study concern malignancies, the use of FAPI in nononcological diseases accumulates, mainly represented by cardiovascular, musculoskeletal, hepatobiliary, endocrinology, IgG4-RD or interstitial lung diseases.[159-161] Because fibroblast are relevant targets in RA and Sjögren too,[162,163,156] new FAPI applications could emerge in the future.

Conclusion

PET imaging provides unparallel capabilities to map and quantify inflammatory and immune-mediated conditions at the whole-body level. FDG PET/CT has become the imaging modality of choice in the work-up of patients with FUO, by identifying the potential cause, localizing sites for further evaluation, and guiding further management. In cardiometabolic syndrome, FDG PET facilitates detailed molecular imaging of active atherosclerotic processes, offering insights into visceral abdominal fat tissue as an indicator of adipose tissue inflammation. The growing accessibility to FDG-PET has promoted its use in numerous immune-mediated disorders in standard practice, GCA representing the biggest success story in nononcological conditions. In this momentum, new applications are emerging, such as auto-immune rheumatologic disorders, IgG4-RD, or SS, for which the clinical or prognostic relevance of FDG PET must be confirmed. Beyond imaging the cross-talk of immune reactions at the whole-body level, a better regional characterization of their cellular microenvironment (immune and stromal cells and their mediators) is currently a challenge in precision medicine. The wide variety of radiolabeled probes currently investigated in the field of immune-mediated disorders illustrates the great capacity of PET molecular imaging to adapt to contemporary and emerging medical challenges.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Statement

This review article does not deal with experiments nor with individual patient data and does not require IRB approval.

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