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Review

Positron Emission Tomography Imaging of the Adaptive Immune System in Cardiovascular Diseases

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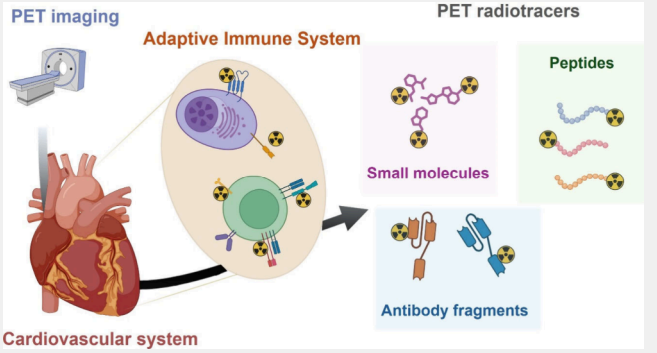
ABSTRACT: Cardiovascular diseases are the leading cause of death around the globe. In recent years, a crucial role of the immune system has been acknowledged in cardiac disease progression, opening the door for immunomodulatory therapies. To this ongoing change of paradigm, positron emission tomography (PET) imaging of the immune system has become a remarkable tool to reveal immune cell trafficking and monitor disease progression and treatment response. Currently, PET imaging of the immune system in cardiovascular disease mainly focuses on the innate immune system such as macrophages, while the immune cells of the adaptive immune system including B and T cells are less studied. This can be ascribed to the lack of radiotracers specifically binding to B and T cell biomarkers compatible with PET imaging within the cardiovascular system. In this review, we summarize current knowledge about the role of the adaptive immune system (e.g., B and T cells) in major cardiovascular diseases and introduce key biomarkers for specific targeting of these immune cells and their subpopulations. Finally, we present available radiotracers for these biomarkers and propose a pathway for developing probes or optimizing those already used in other fields (e.g., oncology) to make them compatible with the cardiovascular system.



KEYWORDS: *PET, imaging, cardiovascular disease, B cells, T cells, adaptive immune system, cardioimmunology, radiotracers*

1. INTRODUCTION

Cardiovascular diseases are the leading cause of death worldwide, with millions of lives lost each year. Over the past few decades, a growing body of evidence has identified inflammation as a critical determinant of cardiac outcomes in various conditions, ranging from atherosclerosis to chronic heart failure.[1] For example, the understanding of atherosclerosis has evolved from a simple fat accumulation in the blood vessels to a well-coordinated immunological response to this lipid deposition.[2] This shift highlights the immune system's crucial role in the disease's progression and has sparked significant interest in the emerging field of cardioimmunology.[1]

Recently, therapeutic strategies targeting the immune system have been proposed to improve the outcome of cardiovascular disease,[3,4] highlighting the immune cells' important role in the cardiovascular system. Yet, due to the nature of the cardiovascular system, identifying novel molecular biomarkers can be challenging.[5,6] Tissue analysis offers a very comprehensive picture of the cellular landscape. However, human tissues are difficult to acquire and are often from specimens with advanced or final stages of the disease. This leaves a big gap in information about the early stages and development. In animal studies, tissues are easily available but at the expense of the subject, which limits longitudinal studies, and individual trends cannot be observed. Moreover, histological tissue analysis accounts for only small portions of the affected area, and single-cell analysis allows for the analysis of larger tissue volumes but with limited spatial resolution.

In contrast, noninvasive imaging allows for visualizing the subjects at different stages of the disease, obtaining a more comprehensive picture of the immune system landscape and gaining mechanistic insights of disease development. This feature has been exploited, especially in oncology, but is still in an early stage in cardiology.[7] Among different techniques, positron emission tomography (PET) has emerged as a particularly advantageous approach relative to other imaging modalities by providing high sensitivity to detect low abundance biomarkers and subtle biological changes at the molecular levels. It allows visualizing and quantifying immune

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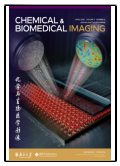

cell activity in almost real-time, offering insights into understanding systemic and localized inflammation mechanisms. Moreover, PET can be coupled with other modalities that provide anatomical information, such as computed tomography (CT) or magnetic resonance imaging (MRI), to combine molecular and morphological information, thus enhancing diagnostic accuracy. In addition, due to the typically low concentrations used in PET imaging, i.e., subpharmacological concentrations, it offers a straightforward pathway for clinical translation that other imaging modalities lack of.[8] In this context, PET-based molecular imaging appears as an appealing tool to study the immune landscape.[9,10]

Based on the molecular weights and physicochemical properties, PET radiotracers can be divided into multiple categories. However, a key feature when designing a radiotracer is that the biological lifetime of the tracer matches the decay half-life of the radioisotopes. Therefore, different classes of tracers must be radiolabeled with corresponding radionuclides and, thus, follow different radiochemical procedures. Next are described the canonical classes of radiotracers and the radiolabeling strategies for each case.

Small Molecule-Based Radiotracers

Small molecule-based radiotracers offer several advantages due to their small sizes, typically of a few hundred Dalton (Da). First, they display fast pharmacokinetics mainly through the renal system, with low retention in blood. Second, their small sizes enable tissue penetration and crossing of some biological barriers, such as the blood-brain barrier, without specific transport mechanisms. Moreover, small molecules can be easily modified to enhance specificity, as well as other physicochemical properties that might improve imaging capacities. Additionally, the synthesis of small molecules can be scaled up to lower the cost facilitating the clinical translation.[11,12]

When designing a small molecule-based radiotracer, the half-life of the radioisotope must match the *in vivo* biological half-life of the small molecules. Since the last is typically short, radioisotopes with relatively fast decay are used. Generally, fluorine-18 (^{18}F) is preferred due to its straightforward radiochemistry, high positron emission (97% β^+ decay), and favorable half-life ($t_{1/2}$ = 109.8 min).[13] Carbon-11 (^{11}C) is also very common due to established radiolabeling strategies and desirable nuclear properties ($t_{1/2}$ = 20.3 min and 99.8% β^+ decay).[14] These radioisotopes can be added to the chemical structure of small molecules without significantly altering their physicochemical properties and binding affinities for *in vivo* targeted imaging.

Peptide-Based Radiotracers

Peptide-based radiotracers are especially attractive for targeting specific cell-surface receptor and are gaining a lot of attention due to their advantageous characteristics in cardiovascular research.[15] Peptides are relatively small, i.e., from a few hundred to a few thousands Da. Due to their small size, they show features similar to other small molecules, such as fast pharmacokinetics and straightforward production.[16] Additionally, their sequences can be optimized for high binding specificity toward certain biomarkers. Moreover, screening of de nuovo peptides has been significantly improved thanks to biotechnological tools such as phage display screening.[17,18]

Radiolabeling of peptide-based radiotracers is generally achieved by using radioactive metal cations. Typically, the peptide is conjugated to a multifunctional chelator, where the radioactive cation can be complexed, through amides, thioesters or thiourea bonds.[16] This allows for fast, straightforward, and efficient radiolabeling procedures. A common radioisotope for cardiovascular PET imaging is gallium-68 (^{68}Ga) due to the short half-life ($t_{1/2}$ = 68 min), high positron emission (88.9% β^+ decay), and available production via ^{68}Ge/^{68}Ga generator.[19,20] In addition, copper-64 (^{64}Cu) has been largely utilized despite its relatively long half-time ($t_{1/2}$ = 12.7 h), which allows for shipping to a second site for radiolabeling and PET imaging to expand its accessibility compared to other short-lived radioisotopes. Although ^{64}Cu has lower positron emission yield (19% β^+ decay) than other PET radioisotopes, the smaller energy of the emitted positrons (E_{max} = 657 keV) increases the imaging resolution, which can be crucial when studying the vessels of small animals.[21] Moreover, the versatile chelator chemistry also enables the ^{18}F radiolabeling of peptide via Al^{18}F approach to expand its imaging applications.[22]

Overall, peptide-based radiotracers are in a sweet spot where fast blood clearance and high specificity enable optimal conditions for PET imaging of the cardiovascular system. However, their *in vivo* stabilities need to be thoroughly validated since several peptidases are present in the bloodstream and in the liver that can hydrolyze the peptide chain and compromise the binding and targeting efficiency. Several strategies are used to increase the stability of the peptides, from introducing unnatural amino acids that are less reactive to peptidases to favoring tertiary structures by cyclizing the peptide chain. In general, these strategies prevent undesired degradation, yet they can affect to the binding affinity.[23,24]

Protein/Antibody-Based Radiotracers

Antibodies have outstanding specificity toward their targeted antigens/receptors. However, due to their large molecular weight (~150 kDa) and size, rapid renal clearance is hampered, leading to long blood retention times (~110 h).[25,26] Thus, antibody/protein-based radiotracers present certain limitations for PET imaging of the cardiovascular system.[5] An attractive approach is to use antibody fragments such as nanobodies, which contain the specific binding domain to the target and are small enough to allow rapid renal and blood clearance for cardiovascular imaging.[27]

Relatively long living radioisotopes such as zirconium-89 (^{89}Zr, $t_{1/2}$ = 78.4 h) or ^{64}Cu are typically used for antibodies radiolabeling,[28,29] whereas for nanobodies ^{68}Ga can be used as well.[30] Like peptide radiotracers, metal chelators are often conjugated to the residues of cysteines or lysins of antibodies.[31] However, antibodies and nanobodies are prone to aggregation, which constrains reaction and storage conditions.

Nanoparticle-Based Radiotracers

Nanoparticles have also been proposed for imaging cardiovascular diseases.[32] They can be functionalized with different ligands (e.g., small molecules, peptides or antibodies) as targeting moieties to achieve high specificity and improved target-to-background ratios.[33] In addition, they can be used in multimodal imaging, since fluorescent or MRI reporters can be included in the nanoparticle design.[34,35] Moreover, the blood retention time can be fine-tuned to enable relatively fast renal clearance for small nanoparticles.[36] Due to the different features of nanoparticles, several labeling strategies can be used, ranging from chelator-based radiolabeling to direct ^{18}F labeling,[37] or intrinsic radiolabeling such as ^{64}Cu/CuO.[38−40] So far, radiolabeled NPs have been used for imaging of activated macrophages[41] and activated immune cells.[42−46]

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However, NPs often require complex synthetic procedures that limit their large-scale production, batch-to-batch reproducibility, and ultimately, their clinical translation and integration into clinical routine.

Status of PET Imaging of the Immune System in the Cardiovascular Context

Nowadays, PET imaging is routinely used in various cardiovascular diseases, such as ^{18}F-FDG which images glucose metabolism and can therefore detect abnormal metabolic activity during inflammation.[47] However, the high glucose metabolism and, therefore, high ^{18}F-FDG uptake of the cardiomyocyte can mask inflammatory cells near or within the heart. In addition, different factors affect myocardium uptake such as fasting state, insulin blood levels and cardiac energy requirements, challenging precise and accurate imaging-based diagnosis.[48] In the past decade, with the increasing interest in cardioimmunology and acknowledging some of the limitations of ^{18}F-FDG, imaging the immune system has emerged as a key tool for diagnostic purposes and understanding the mechanism behind cardiovascular diseases.[9]

Imaging the immune system in a cardiovascular context entails some challenges. First, the radiotracers must have a high binding affinity and specify the targeted biomarker. Second, radiotracers need to have rapid pharmacokinetics so they can be quickly washed out from the bloodstream to generate high target-to-background contrast. In contrast to the macromolecules such as labeled antibodies or nanoparticles showing high binding affinities and extensive blood retention,[25] small molecule-based radiotracers are more appealing due to their fast pharmacokinetics and high targeting efficiencies.

Despite the large portfolio of possible radiotracers, when it comes to the immune system in the cardiovascular context, most of the focus has been on the innate immune system. Particularly, many small molecule- and peptide-based radiotracers have been developed targeting characteristic biomarkers expressed in macrophages and/or monocytes.[6,12,42,49−52] Currently, translational PET imaging studies on cardioimmunology using radiotracers targeting these cells (e.g., ^{64}Cu/^{68}Ga-DOTA-ECL1i and ^{68}Ga-DOTA-TATE) are showing more accurate detection of inflammation and disease status (Figure 1a,b). This has remarkably sharpened our comprehension of immune cell trafficking in chronic and acute cardiovascular disease and opened opportunities for more accurate diagnostic and new theragnostic approaches.

In contrast, much less attention has been directed to the adaptive immune system (e.g., B cells and T cells).[52] Thus, half of the immune landscape is being overlooked. In this review, we will summarize the current understanding of the role of the adaptive immune system in major cardiovascular pathologies and introduce radiotracers and biomarkers of interest for imaging of the B and T cells in these diseases.

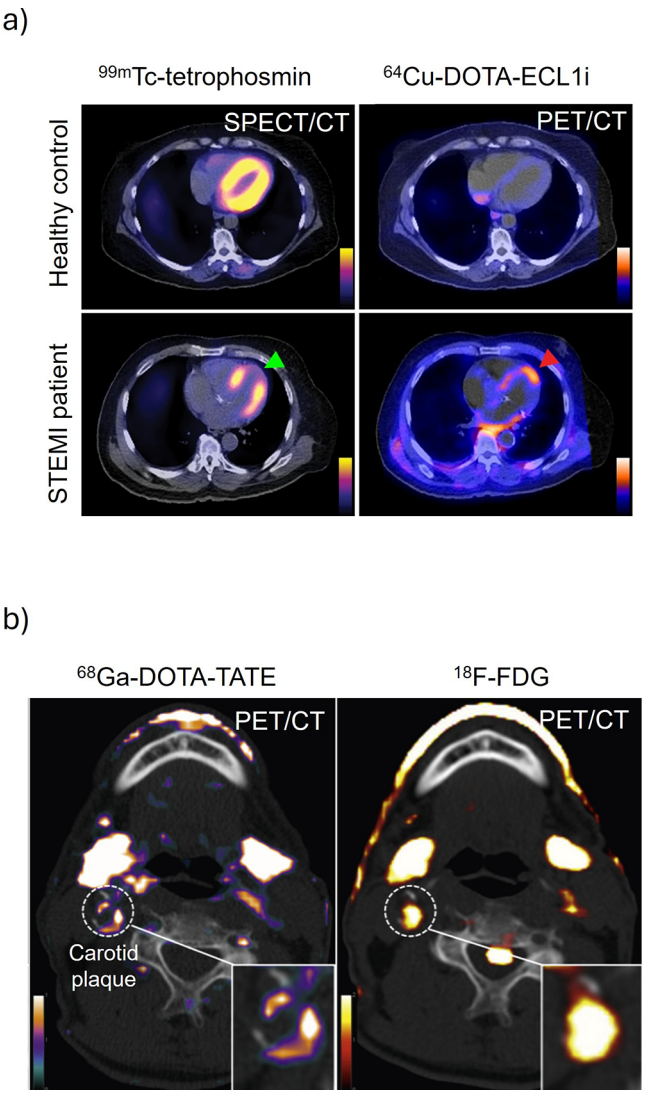

Figure 1. a) ^{64}Cu-DOTA-ECL1i PET visualizes CCR2+ immune cells, allowing for accurate imaging and diagnosis of inflammatory cardiovascular disease such ST-segment elevation MI (STEMI). Reproduced with permission from ref 49. Copyright 2023 Springer Nature. Healthy patient is characterized by homogeneous and high ^{99m}Tc-tetrofosmin uptake in the myocardium and low ^{64}Cu-DOTA-ECL1i. In a patient STEMI, low ^{99m}Tc-tetrofosmin uptake is colocalized with the high ^{64}Cu-DOTA-ECL1i indicating the mobilization of CCR2+ cells in the ischemic region. Adapted with permission from ref 49. Copyright 2023 Springer Nature. b) ^{68}Ga-DOTA-TATE shows improved detection of somatostatin receptor positive macrophages in the atherosclerotic plaques in contrast to ^{18}F-FDG. Adapted with permission from ref 50. Copyright 2017 Elsevier.

2. THE ADAPTIVE IMMUNE SYSTEM

The adaptive immune system, together with the innate immune system, is a defense mechanism that provides long-term and highly specific protection in front of pathogens. Unlike the innate immune system which provides a nonspecific and preprogrammed response to general pathogens, the adaptive immune system can target specific antigens. In addition, the adaptive immune system builds immunological memory to the exposed antigens, ensuring a faster and more robust response in front of antigen re-exposure. The cells composing the adaptive immune system are lymphocytes, which are divided into two major classes, B-lymphocytes and T-lymphocytes, or B cells and T cells (Scheme 1). Each class can be further divided into subtypes depending on their specific function and cell receptors of the lymphocyte.[53]

B Cells

B-lymphocytes, or B cells, are a class of immune cells dedicated to recognizing and targeting pathological and exogenous agents. In mammals, they originate in the bone marrow and undergo subsequent maturation, first in the same bone marrow and later in the spleen. B cells express surface receptors known as membrane-bound antibodies, which consist of a constant

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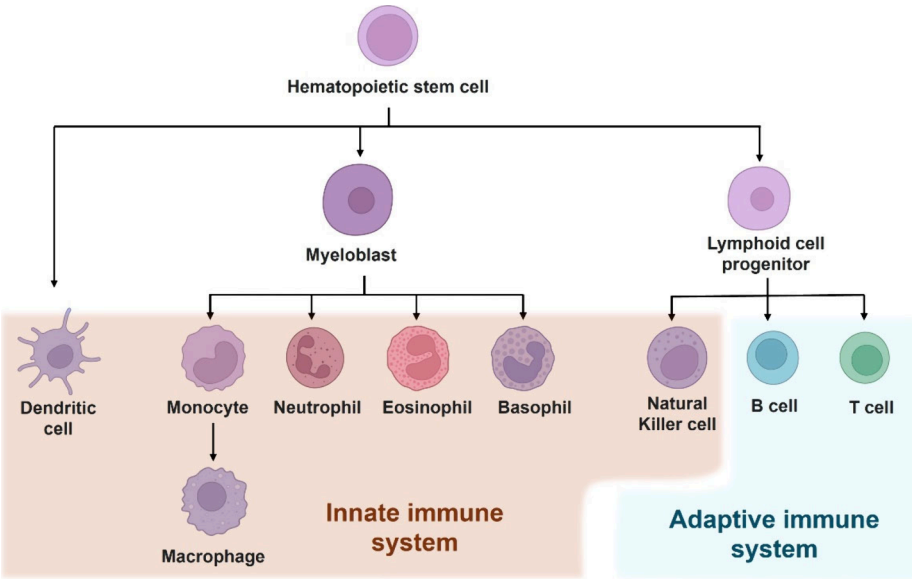
Scheme 1. Simplified Lineage of the Immune Cells Comprising the Innate Immune System and the Adaptive Immune System



region shared by all B cells and a unique variable region for each B cell. With several millions of distinct variable regions, B cells can recognize a vast array of potential antigens.[54−57]

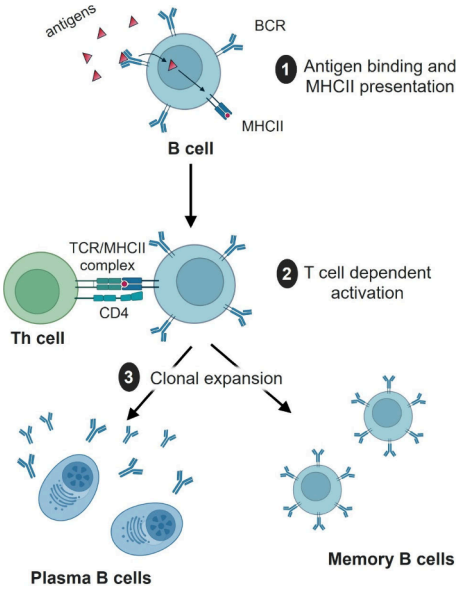
During B cell maturation, those expressing surface antibodies binding to self-antigens are eliminated to prevent autoimmune reactions. Thus, allowing the adaptive immune system to theoretically respond to any non-self-antigen. The surface antibodies together with the cluster of differentiation 19 (CD19) surface protein and others, compose the B cell receptor (BCR), which plays a central role in antigen recognition and antigen internalization.[58] Typically, B cell recognized antigens are internalized and digested by the immunoproteasomes, and the resulting antigenic peptides are then expressed onto MHC molecules (Scheme 2).[59] Then it can be recognized by specific T cells triggering B cell activation by means of another protein CD20 colocalized with the MHCII.[60,61] Then, B cells start proliferating in a process known as clonal expansion and differentiate into (i) memory B cells, which present the same BCR and provide long-term immunity, and (ii) plasma cells, which start massively producing free antibodies against the antigens. These antibodies target the antigens for the rest of immune cells facilitating the elimination and reducing the pathologic effect by a process known as opsonization.[57,62]

Finally, B cells can modulate their immune activity by means of proteins such as CD22, thus preventing excessive inflammation.[63] This surface biomarker, together with CD19 and CD20 proteins are well recognized biomarkers for B cells, making them emerging targets for diagnosis and therapy in cardiovascular diseases.[64,65]

T Cells

T-lymphocytes or T cells are the other main class of lymphocytes in the adaptive system. In mammals, T cells originate also in the bone marrow and then migrate to the thymus for further maturation. Mature T cells express the T cell receptor (TCR) that allows T cells to recognize antigens that other cells present through the major histocompatibility complex.[66] Since different cell populations present specific antigens via MHC, T cells can discriminate between healthy cells and those that are foreign or unhealthy such as infected or

Scheme 2. Simplified Activation of B Cells through Th Cell Mediation[a]



[a]Upon antigen binding on the B cell receptor (BCR), the B cell internalizes and processes it, finally expressing the antigen epitope in the MHCII. When CD4+ T helper (Th) cells recognize the antigen via the T cell receptor (TCR)/MHCII complex, it triggers the B cell activation and posterior clonal expansion and differentiation.

cancerous cells. When the TCR recognizes one of these antigens, it triggers the activation of the T cells to proliferate and differentiate into different subtypes (Scheme 3). Moreover, activated T cells display certain surface receptors that modulate the T cell response. Each T cell subtype has distinct responses and mechanisms of action upon activation.[67,68] There are several subtypes of T cells with distinct roles in the immune response including cytotoxic T cells (Tc), helper T cells (Th), and regulatory T cells (Treg).[69] Tc cells display a CD8 protein that allows the TCR to bind to the MHC I receptor present in other cells. After activation, CD8+ cytotoxic T cells secrete cytotoxic molecules such as granzyme

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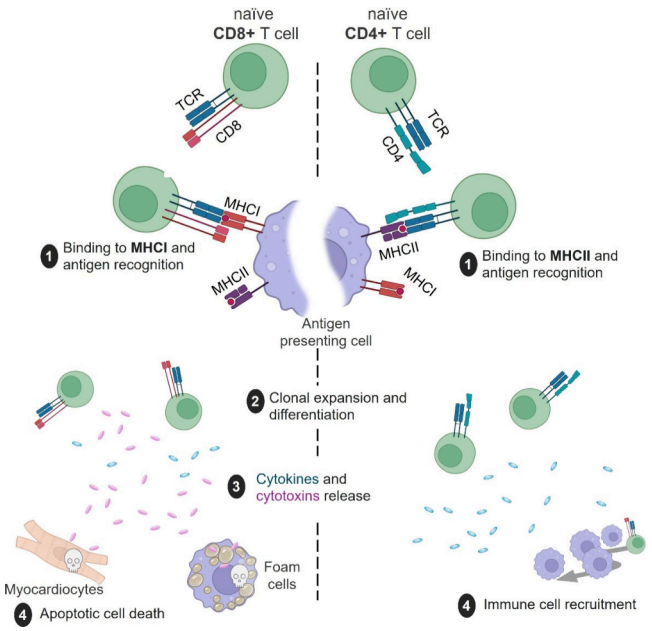
Scheme 3. Simplified CD4+ and CD8+ T Cell Activation[a]



[a]Naïve T cells recognize the antigens present in either MHCI (for CD8+ T cells) or MHCII (for CD4+ T cells) of antigen presenting cells. In a second step, they start proliferating and differentiating in different T cell subtypes. This process is driven by an increased cytokine and cytotoxic production that can further increase immune response and damage the affected tissues.

B and perforins, causing apoptotic death in targeted cells. On the other hand, Th cells present CD4 glycoprotein allowing them to recognize MHC II receptors expressed in professional antigen-presenting cells including macrophages and B cells.[70] Upon activation, Th secrete pro-inflammatory cytokines to further promote the immune response and cell recruitment, as well as activating B cells.[71]

Tregs, a less understood CD4+ subtype, play an anti-inflammatory response by controlling the immune response and preventing autoimmunity.[72] Tregs secrete anti-inflammatory cytokines such as interleukin-10 and interleukin-35 and can induce apoptotic death of effector T cells and antigen-presenting cells.[73−75] In addition to Tregs, T cells display other mechanisms to control the autoimmunity and prevent excessive inflammation. The main known routes are the expression of immune checkpoint proteins such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Upon binding to the corresponding ligands, PD-1 and CTLA-4 deactivate the immune activity of T cells to prevent excessive tissue damage.[76]

3. ADAPTIVE IMMUNE SYSTEM IN CARDIOVASCULAR DISEASES AND IMAGING TARGETS

Role of the Adaptive Immune System in the Cardiovascular System

As mentioned above, inflammation is a key player in cardiac outcomes, particularly in the context of cardiovascular diseases. Adaptive immune cells, such as T and B cells, actively participate in the inflammatory process through several mechanisms. These cells can directly promote inflammation by releasing pro-inflammatory cytokines. They can also recruit additional immune cells, including those from the innate immune system, such as macrophages, to the site of tissue damage. Macrophages, in turn, contribute to the inflammatory environment by engulfing dead cells and releasing further inflammatory mediators.[1,52,77]

However, this inflammatory response is not always beneficial. In the context of chronic cardiovascular stress such as high blood pressure or myocardial infarction (MI), prolonged immune activation can lead to pathological cardiac remodeling.[78] T cells, for instance, can contribute to fibrosis by activating fibroblasts, which deposit excessive amounts of collagen in the heart tissue.[79] This results in stiffening of the heart, impairing its ability to contract and relax properly. Additionally, the constant recruitment of immune cells can exacerbate tissue damage, leading to thinning or thickening of heart walls and alterations in the overall structure of the heart. These maladaptive changes, driven by both immune and nonimmune cells, ultimately compromise heart function and can lead to heart failure if left unchecked.[1]

MI Remodeling

Myocardial infarction is caused by a decreased or complete cessation of blood flow to a region of the myocardium. It may be presented without evident effects and undetectable, or it could be a catastrophic event, leading to sudden death. Generally, MI is due to the underlying coronary artery disease. After coronary artery partial or total occlusion, the myocardium region receives insufficient oxygen leading to myocardial cell death and necrosis.[80] After this dramatic event, in the case of survival, the infarcted myocardium begins a healing and remodeling process.[81] Triggered by the death of millions of myocytes, immune cells infiltrate the region. In the early inflammatory phase, granulocytes, especially neutrophils, infiltrate and phagocyte necrotic cardiomyocytes and cellular debris and secrete inflammatory cytokines that promote monocyte/macrophage recruitment. Similarly, recruited monocytes polarize into inflammatory macrophages that also participate in phagocytosis of dead tissue and secrete more pro-inflammatory cytokines. Then, T cells are recruited and activated via antigen presentation and further contribute to the inflammatory response by the secretion of cytokines and cytotoxins. At the same time activated B cells secrete antibodies against specific antigens exposed by necrotic cardiomyocytes.[80] In a later inflammatory stage, macrophages and T cells secrete anti-inflammatory cytokines promoting angiogenesis, matrix remodeling, and scar formation.[80] The inflammatory response may persist for a variable period, and when resolved, fibrotic scar will replace the infarcted area, while the noninfarcted cardiomyocytes may undergo hypertrophy to compensate for the loss of contractile tissue to finally restore the cardiac function. However, very often, this process reshapes the cardiac architecture and geometry, increasing the likelihood of heart failure and mortality. Therefore, it is crucial to monitor and control the inflammation to ensure a correct healing process.[78,82]

In normal conditions, the T cell population is relatively low in the heart but can drastically increase after MI.[83] First, Th and Tregs infiltrate in the infarcted area and subsequently, T cells start to infiltrate.[84,85] Each T cell type plays a different role although these roles are not completely understood yet, it has been shown that depletion of CD4+ T cells prevents adverse cardiac remodeling.[85] On the other hand, CD8+ T

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cells have a complex role, they contribute to cardiomyocyte death by secreting cytotoxic molecules, i.e., granzyme B and perforin, and promote macrophage infiltration, further enhancing the inflammatory response but facilitating scar formation which prevents fatal cardiac rupture.[86] Recently, a granzyme B tracer (^{68}Ga-grazytracer) has been utilized to monitor the cytotoxic activity of T cells after MI and during cardiac remodeling in a mice model[87] (Figure 2a,b).

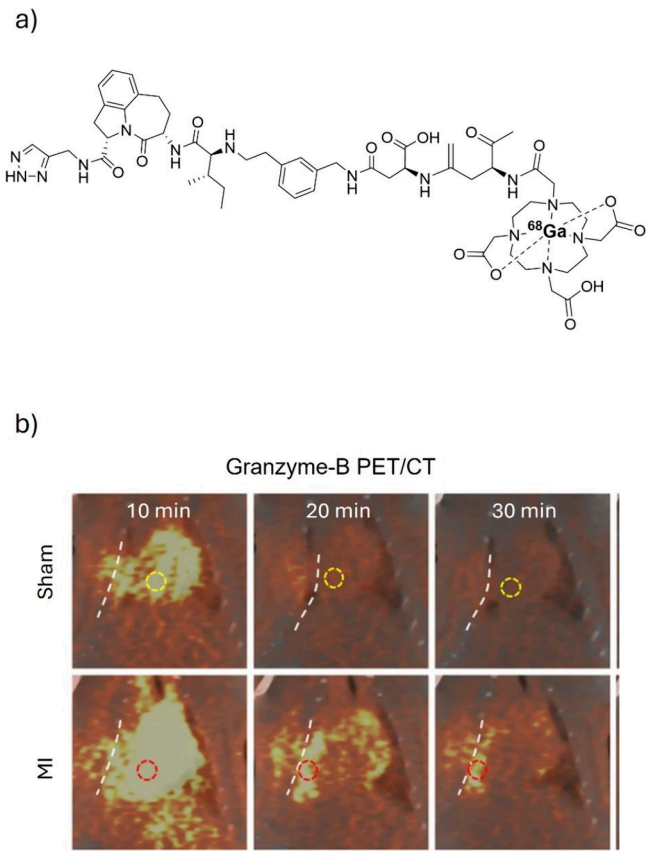

Figure 2. ^{68}Ga-Grazytracer can image granzyme B-related T cell activity following MI and provide an image-guided immunomodulatory theragnostic strategy in a rat model. a) Chemical structure of ^{68}Ga-Grazytracer. b) PET/CT images 10−30 min after injection of ^{68}Ga-Gracytracer in the sham and MI rats. White dashed lines separate the uptake in the myocardium from that in surgical wounds. Higher tracer uptake is observed in MI mice, suggesting higher Tc cell activity.

Interestingly, a peak in ^{68}Ga-grazytracer uptake was observed on days 1 and 3 after MI in the ischemic zone, suggesting a high CD8+ T cell migration and activity, continued by a progressive decrease to baseline levels at day 28. In addition, ^{68}Ga-grazytracer uptake in the early stage post-MI was correlated with infarct size and worse cardiac function. Moreover, granzyme B blockade improved long-term function. Thus, granzyme B imaging can provide early predictive for cardiac function after MI and offers an image-guided immunomodulatory theragnostic target to improve cardiac outcome.[87] This is the very first and preliminary example of how imaging the activity of the adaptive immune system is key to developing new therapeutic strategies and paves the way for studying granzyme B in other cardiovascular diseases.

B cells also infiltrate the heart tissue after MI. Activated and mature CD19+ B cells contribute to inflammation by recruiting pro-inflammatory monocytes and secreting cytokines that promote collagen production in the myocardium and, subsequently, fibrosis.[88] However, certain populations of B regs cells prevent adverse cardiac remodeling by secreting anti-inflammatory cytokines that mitigate monocyte and macrophage recruitment.[89−91]

Myocarditis

Inflammation of the myocardium, known as myocarditis, can be triggered by multiple causes, from viral and bacteriological infections to autoinflammatory diseases. Regardless of the original cause, it generally results in a cardiac malfunction, abnormal cardiac remodeling, or cardiac failure.[92]

Analogously to MI, T cell infiltration, especially CD4+ T cells, occurs in myocarditis.[93] They recruit monocytes and macrophages that further promote pathological inflammation.[78] Similarly, overexpression of activated B cells in the myocardium has been found in preclinical and clinical studies of myocarditis, suggesting a certain role of these lymphocytes. However, very little is known about their mechanisms of action and future studies will be needed to elucidate their participation in myocarditis.[65,94] Currently, no study has performed PET imaging of the adaptive immune system in myocarditis. However, an immune therapy blocking the CD3 receptor of T cells has been revealed to be effective against pediatric acute myocarditis in some patients.[95] This protein complex is associated with TCR and is a fingerprint for T cells. Therefore, PET imaging of CD3 could be exploited as a theranostic tool to assess whether a patient would respond to this immunotherapy therapy. An ^{89}Zr-labeled CD3 antibody has been used to image T cell infiltration in tumors during immunotherapy.[96] However, as mentioned before, antibodies present a prolonged blood retention time, limiting their use in cardiovascular systems. Therefore, an optimized probe should be designed to assess CD3+ cell PET imaging in the cardiovascular system. Recently, a CD3-binding nanobody has been reported (17 kDa).[97] However, to the best of our knowledge, it has not been developed as an imaging agent yet. Future evaluation of this nanobody or others could pave the way for CD3 PET imaging in the cardiovascular system.

CD20+ B cells are also known to contribute to myocardium inflammation. Recently, an immunotherapy targeting this receptor has been proposed to alleviate inflammation and promote cardiac improvement and a first observational study in patients is in progress.[98] This may highlight the potential of CD20 as an important target for theragnostic applications. Currently, similar approaches are being utilized in other inflammatory diseases such as rheumatoid arthritis, where PET imaging with ^{89}Zr-rituximab (a human anti-CD20) can predict treatment response.[99] However, rituximab presents large blood circulation times, limiting its application in imaging the cardiovascular system. In this direction, a new probe targeting CD20 has been developed using a monobody based in the 10th type III domain of human fibronectin (FN3) displaying high affinity to CD20 protein.[100] The new probe (FN3-CD20) has a smaller size (10 kDa) compared with rituximab (∼145 kDa) and provides much faster blood clearance and better signal-to-background ratios. However, FN3-CD20 still requires a few hours after injection to obtain an optimal imaging contrast. This might hamper the implementation of this probe in a cardiovascular context, requiring further structural optimization to achieve the desired pharmacokinetics.

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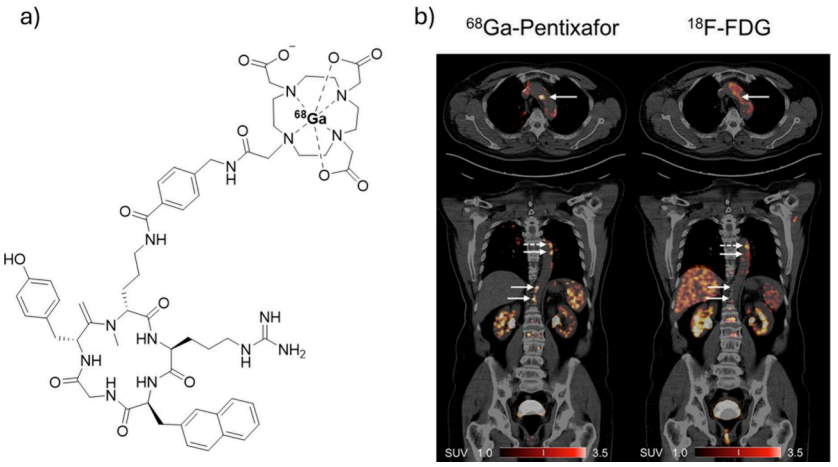

Figure 3. a) Chemical structure of ^{68}Ga-Pentixafor. b) PET/CT images of the same patient were imaged with ^{68}Ga-Pentixafor and ^{18}F-FDG. ^{68}Ga-Pentixafor detects more atherosclerotic lesions (white arrows) compared to those of ^{18}F-FDG within the thoracic aorta. Reproduced with permission from ref 120. Copyright 2020 Society of Nuclear Medicine and Molecular Imaging.

Atherosclerosis

Atherosclerosis is the main underlying cause of heart attack and stroke and is termed plaque formation in the intima of large arteries. It is initiated with lipid deposition and accumulation within the aortic arteries, which triggers the recruitment of monocytes and macrophages to engulf the deposited lipid, forming the foam cells. Also, smooth muscle cells can differentiate into foam cells triggered by fat deposition. Then, macrophages and other professional antigen-presenting cells activate T cells, which further promote inflammation by secreting pro-inflammatory cytokines and enhancing monocytes and macrophage recruitment in a positive-loop manner. At the same time, Th cells activate B cells causing their clonal expansion and production of antibodies that increase the engulfing activity of macrophages and foam cells.[101] In the late state of atherosclerotic plaques, their stability is compromised due to the large presence of lipidic zones and lack of structural cells, increasing the risk of rupture and subsequent heart attack and stroke.[2,102]

The presence of T cells in the atherosclerotic regions has been observed in tissue samples. Particularly, CD4+ T cells are commonly found within the plaque.[103] Among them, Th cells have a pro-atherogenic role by promoting immune cell infiltration, while Tregs have an antiatherogenic role by down-regulating immune response. However, studies suggested that some subsets of Tregs can evolve into pro-atherogenic actors under certain conditions.[104] Finally, the role of CD8+ T cells remains unclear while they contribute to plaque instability by promoting apoptosis of foam cells, certain protective effects have also been reported.[105] Overall, T cells in atherosclerotic seem to have a dual role, opening the door to therapeutic opportunities; however, a better understanding of the mechanisms and dynamics is required.[106] In this context, it would be highly informative to image T cell subpopulation during disease progression. However, no study to date has tackled this issue in atherosclerosis development. Yet, there are some radiotracers targeting CD8 and CD4 surface proteins. But once again, they are mainly based on antibodies, with slow blood clearance and are commonly used in cancer research or other inflammatory diseases.[107,108] Recently, nanobodies and minibodies with high binding affinities and rapid pharmacokinetics have been developed for imaging these receptors.[109−112] Despite faster pharmacokinetics, the background intensity of the circulating probe can compromise the accuracy of quantification within the cardiovascular system. Therefore, optimization of the nanobodies or developing new peptide-based or small molecule-based radiotracers targeting CD8 and CD4 proteins should be pursued.

The presence of B cells in atherosclerosis plaque has been widely confirmed in both animals and humans. In addition, an increased presence of immunoglobulins secreted by B cells has also been found in atherosclerotic lesions. These lymphocytes generate antibodies against oxidized low-density lipoproteins (oxLDL). Among them, IgM antibodies increase oxLDL clearance to reduce immune response.[113] On the other hand, IgG antibodies also create complexes that enhance oxLDL clearance via phagocytosis but may further promote macrophage activation and foam cell formation. The overall role of B cells in plaque progression is ambiguous, studies in mice suggest a protective effect of B cell infiltration,[114] and recent clinical studies correlate higher concentrations of IgM and IgG with lesser coronary diseases.[115] However, other findings showed that different B cell subpopulations play proatherogenic and antiatherogenic roles.[101] Recently, chimeric antigen receptors (CARs) T cell therapy targeting CD19+ B cells in B-cell lymphoma has shown a significant decrease in atherosclerotic burden, suggesting a benefit in depleting CD19+ B cells.[64] Once more, PET imaging studies of B cells in atherosclerosis are missing. Considering the clinical benefits of CAR T cell therapy against B cells, it is reasonable that PET imaging targeting the CD19 surface protein would provide valuable theragnostic information regarding the efficiency of the therapy and the expected outcome. Actually, CD19 PET imaging has already been assessed using ^{64}Cu-antihuman-CD19 antibody in B-cell lymphoma patients.[116] Due to the prolonged blood circulation of this antibody, it is suboptimal for imaging the CD19+ B cells in the atherosclerotic plaques. However, the role of B cells in plaques indicates the need to develop molecular probes (i.e., mini- or nanobodies or peptides) with optimized pharmacokinetics for B cell imaging in atherosclerosis.

Additionally, despite not being exclusively expressed in a certain specific immune cell population, C-X-C chemokine receptor type 4 (CXCR4) is highly expressed in T and B cells and contributes to immune cell trafficking (monocytes/

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macrophages recruitment), inflammation and tissue repair.[117] Moreover, it is also expressed in endothelial cells and vascular smooth muscle cells.[118] Therefore, it is an inflammation biomarker intimately related to the adaptive immune system and can be utilized to assess inflammation in atherosclerotic lesions among others.[119−121] Interestingly, different peptide-based radiotracers binding to CXCR4 are available.[120,121] Among them, ^{68}Ga-Pentixafor is the most popular and has fast blood clearance allowing for its use within the cardiovascular system (Figure 3a). Actually, ^{68}Ga-Pentixafor imaging has revealed efficiency for PET imaging of atherosclerotic lesions in patients (Figure 3b), identifying more lesions than when using ^{18}F-FDG and with higher uptake and better signal-to-noise ratio.[120] This highlights the relevance of CXCR4 PET imaging for assessing atherosclerosis imaging. However, due to its expression across different immune cells, it might be challenging for direct imaging of specific immune cell populations. Nevertheless, it holds a lot of potential for inflammation monitoring and assessment of the aforementioned immune-modulation therapies at the preclinical and clinical levels.

Abdominal Aortic Aneurysm

An abdominal aortic aneurysm (AAA) is a swelling of the aorta that occurs due to weakening of the aortic wall. Around 65−85% of patients who suffer from aneurysm rupture die suddenly.[122] There is no clear cause for AAA development, but the main risk factors include smoking, aging, and male gender. Additionally, atherosclerotic lesions in the infrarenal portion of the abdominal aorta can evolve in AAA. Current knowledge accepts that AAA is a multifactorial process consisting of inflammatory responses, oxidative stress and matrix metalloproteinase activation that causes smooth muscle apoptosis and extracellular matrix degeneration, which weaken the vessel wall and lead to the ultimate rupture of AAA.[123]

Again, the inflammatory response is characterized by several immune cells, including macrophages and neutrophils from the innate immune system and B and T cells from the adaptive system. Among them, T cells are the most predominant infiltrated inflammatory cells in AAA lesions.[124] Particularly Th CD4+ T cells, play a critical role in disease progression by secreting cytokines that promote macrophage activation and induce vascular smooth muscle cells apoptosis, which are the main cellular constituent of the aortic wall.[125] On the other hand, Treg can suppress the inflammation by regulating other T cell subsets. However, their presence is low in AAA lesions.[126,127] Cytotoxic CD8 T cells are also found in the AAA walls, although their role is not fully understood. On the one hand, it is suggested that they promote apoptosis of inflammatory cells. On the other hand, they also produce inflammatory cytokines with similar effects as Th cells. Future studies will be required to understand the pro-inflammatory and protective role of CD8+ T cells.[123] To this date, all the PET imaging studies on AAA are focused on macrophages and not on T cells.[128] In this particular disease, imaging CD4+ and CD8+ populations could elucidate the role of T cells and help us understand the Th dynamics that promote inflammation. As mentioned, there is a lack of radiotracers with desirable imaging characteristics to target CD8+ and CD4+ cells within the cardiovascular system. Yet, in AAA, due to the protective role of T regs, a radiotracer targeting this specific cell population would be of high interest in mechanistic and theragnostic approaches. Tregs highly express CD25, making this cell receptor a promising target for Tregs imaging. Antibodies targeting CD25 proteins can be labeled with ^{89}Zr (^{89}Zr-anti-CD25) and have been used for imaging T cell lymphomas.[129] However, before they are used for Treg imaging in the AAA, their blood retention must be optimized. In addition, despite being highly expressed in Treg, CD25 is not exclusive to these cells. Moreover, the low abundance of this subset of T cells also proposes a challenge for their accurate detection within AAA. Actually, current strategies for nuclear imaging of Treg rely on transplants of engineered Treg capable of reacting with a radio-labeled administered molecule.[130,131]

Although less known, B cells also have an important role in AAA. Several studies support the accumulation of immunoglobulins in the AAA area including autoantigens.[132−134] In addition, B cells produce cytokines that (i) activate macrophages and other innate system cells that contribute to oxidative stress, (ii) lead to vascular smooth cells apoptosis, and (iii) activate CD4+ Th cells.[135] Moreover, the depletion of B cells has been shown to significantly decrease AAA growth in animal models.[136] Overall, the pathogenic effect of B cells in AAA suggests their prognostic potential for AAA.[137]

Takayasu's Arteritis

Takayasu's arteritis (TA), also known as pulseless disease, is a rare inflammatory chronic disease affecting large arteries such as aorta and its major bifurcations that causes a thickening of the intima and a subsequent narrowing of the lumen. Severe and advanced stages can lead to aneurysm formation, with an increased risk of rupture. Despite being a rare disease, it has a relatively high incidence in certain Asian populations, especially affecting young women.[138,139]

Currently, the causes and mechanisms behind TA development are largely unknown. However, it is acknowledged that a central role of the immune system drives chronic inflammation and vascular damage. TA lesions originate in the vasa vasorum of large arteries, where immature dendritic cells become activated and instigate monocytes and macrophage recruitment. This immune activity causes T cell activation, causing CD4+ Th recruitment that releases INF-γ and further promotes inflammation.[140] In addition, CD8+ Tc can promote endothelial and smooth muscle cell apoptosis by releasing perforin and granzyme B, contributing to fibrosis and stenosis of the vascular wall. This CD8+ Tc activity against vascular cells is driven by antiendothelial antibodies that are commonly found in TA lesions and are produced by infiltrated B cells.[138] Thus, increasing attention has been directed toward the pathogenic role of B cells in orchestrating the inflammatory response, and the importance of B cell disturbance.[141] Interestingly, B cell depletion therapy, using rituximab (anti-CD20 antibody), has shown effectiveness in clinical remission in certain patients.[142] This highlights the role of the adaptive immune system and how immune therapies can improve the outcome of vascular diseases. Yet, the processes behind TA are not fully understood, and current experience suggests complex cross-talk between different immune cells. And, even though B cells are a promising therapeutic target, new mechanistic insights might reveal novel therapeutic targets. Thus, PET imaging in preclinical models could help to identify the main processes that promote disease progress, which could then be translated into therapeutic or theragnostic strategies. In this context, PET imaging of CD20+ B cells using the new probe FN3-CD20 or optimized versions in combination with other

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radiotracers to monitor CD8+ Tc activity such as 68Ga-Grazitracer is a promising strategy to monitor cross-talk between these two cells populations.

Immune Checkpoint Inhibition-Caused Cardiotoxicity

Immune checkpoint inhibition (ICI) has emerged as a therapy with huge potential and clinical success to treat cancer, especially metastatic melanoma, and non-small-cell lung cancer.[143] As mentioned, T cells have surface receptors that help to regulate the immune response to avoid excessive or prolonged inflammatory responses, such as those of PD1 and CTLA-4. By blocking this regulating mechanism, ICI boosts T cells aiming for a more aggressive immune response against tumor cells.[144] However, this overresponsive immune response can trigger immune-related adverse events (irAEs), including those affecting the cardiovascular system as what is reported for conventional chemotherapeutic drugs.[145] Several meta-analyses showed a relevant incidence (8.32%) of cardiovascular events in patients receiving ICI, with symptoms ranging from mild arrhythmia to fatal myocarditis. A combination of ICIs has shown a higher frequency of myocarditis (1.22%), about double that when ICIs are given alone (0.54%).[146,147] Moreover, animal studies and clinical studies suggested that ICI treatment provokes accelerated atherosclerosis and progression toward pathological phenotypes.[148,149]

Despite the clinical relevance of cardiac irAEs induced by ICI, this is a relatively new field, and the mechanism behind cardiotoxicity and the role of the adaptive immune system are largely unknown. Recent studies are focused on understanding cardiovascular inflammatory aggravation in mice undergoing anti-PD1 treatment.[148,150] In these studies, PET imaging of the ICI-induced inflammation was achieved using a radiotracer (^{64}Cu-DOTA-ECL1i) targeting CCR2 that is highly expressed in immune cells, particularly on macrophages and monocytes. Interestingly, higher tracer uptake was observed in the groups treated with ICI compared to baseline and control groups, which was associated with a worsened cardiovascular inflammatory disease, i.e., myocarditis or atherosclerosis (Figure 4a–c). However, tissue analysis suggests that, in ICIs-induced irAEs, macrophages are activated through CD8+ T cells and mediated via an interferon-gamma (INF-γ) signaling pathway that promotes an inflammatory response. In addition, anti-CD8 or anti-INF-γ treatment significantly decreased ICIs-induced vessel inflammation, indicating the potential of the strategic immunomodulation of the adaptive immune system to improve cardiac outcomes. Yet, silencing certain receptors and signaling pathways could conflict with antitumor response. Therefore, the spatiotemporal resolution of CD8+ T cell trafficking needs to be addressed to define the appropriate timing for optimal therapeutic effect. Thus, PET imaging of activated T cells would contribute to further understanding the mechanism, monitoring patients' outcomes, and designing optimal therapeutic strategies.

Apart from probes for CD8 and CD4 proteins, performing PET-imaging of those receptors that are exclusively displayed on activated T cells could enrich the understanding of the different irAEs induced by ICI therapy. Certain antibody- or nanobody-based PET radiotracers have been developed to target PD-1 and CTLA-4 to predict and monitor tumor response during ICIs therapy. Similarly, imaging PD-1 and CTLA-4 in a cardiovascular context may help to assess the status and risk of irAEs. However, current available probes must be optimized and tailored for a cardiovascular context.

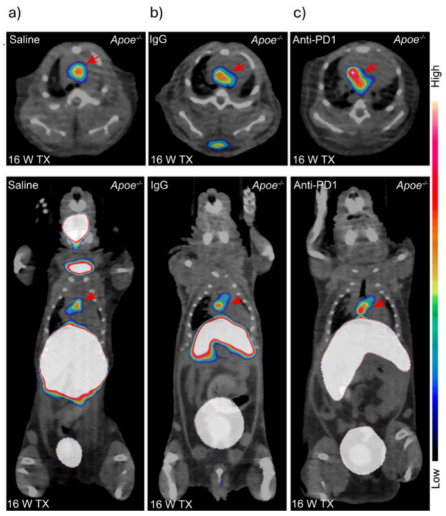

Figure 4. CCR2 PET/CT after injection of ^{64}Cu-DOTA-ECL1i in an atherosclerotic mouse model after 16 weeks of saline (a), IgG (b), or anti-PD1 antibody treatment (c). The arrow denotes robust tracer accumulation in the aortic arch of mice in all groups. Higher uptake is observed in the mice undergoing anti-PD1 treatment, suggesting an enhanced inflammatory response within the aortic arch. Reproduced with permission from ref 148. Copyright 2024 Wolters Kluwer Health, Inc.

CD134 also known as OX40, is another interesting surface biomarker of activated T cells. This surface protein is a tumor necrosis factor (TNF) receptor and is highly expressed in activated T cells. When CD134 binds to its ligand, it enhances T cell expansion and proliferation, making it a promising target to predict tumor progression in animals treated with immunotherapy,[151] as well as an imaging biomarker to complement PD-1 and CTLA-4 targeted therapy to minimize ICIs induced irAEs. Another interesting biomarker for activated T cells is the interleukin-2 receptor (IL-2R), which binds to its natural ligand interleukin-2 (IL-2), a pro-inflammatory cytokine (15 kDa) involved in the stimulation of growth, activation, and differentiation of T cells. Radio-labeling of IL-2R with ^{18}F (^{18}F-FB-IL2) has been utilized to visualize activated T cells in inflammatory diseases and tumor response in melanoma patients undergoing ICI therapy.[152,153] Interestingly, this probe displays a fast blood clearance despite its relatively high molecular weight.[154] This fast pharmacokinetics highlights the potential of this probe for PET imaging of the cardiovascular system.

Alternatively, monitoring of CD8+ Tc activity employing PET imaging of granzyme B using ^{68}Ga-Grazytrazer or others could detect potential irAEs in the cardiovascular system while assessing the efficiency of tumor treatment. Actually, this approach has already been exploited in preclinical models, showing as a valuable tool for *in vivo* visualization of irAEs in different organs such as spleen, colon, and kidneys. Interestingly, mice treated with ICIs displayed higher ^{68}Ga-NOTA-GZP uptake in the main organs compared with control groups. Moreover, when these mice were treated with dexamethasone, an immunosuppressor, tracer uptake was significantly decreased, indicating that this approach can potentially monitor irAEs development and resolution.[155] Future studies focused on irAEs within the cardiovascular system could provide interesting mechanistic insights and

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assess possible treatments to mitigate ICIs-induced cardiotoxicity.

4. OUTLOOK

Evidence around the important role of the adaptive immune system in cardiovascular disease is rapidly expanding, driving an increasing need for PET imaging probes that can target these immune cells. Currently, some therapeutic targets have been identified within the adaptive immune system to improve cardiac outcomes. Many cardiac diseases are caused or worsened by an underlying adverse activation of the adaptive immune system. This two-in-one imaging design could speed diagnoses and reduce PET-imaging sessions in clinics. It also could help to understand and monitor disease cross-talk and cardiovascular adverse events related to other pathologies or treatments. For example, CD8+ T cells are involved in ICI-accelerated cardiovascular diseases due to the overstimulation of these cells under anti-PD-1 or anti-CTLA-4 treatment, which is necessary to control tumor cells and their immunosuppressive tumor microenvironment.[112] Thus, an appropriate CD8+ T cell PET radiotracer with compatible characteristics with both the tumor and cardiovascular system could be of paramount importance to predict tumor response to ICIs therapy and simultaneously detect early stage of irAEs in the cardiovascular system.

Similarly, lymphocyte depletion in lymphoma patients has shown a metabolic decrease in atherosclerosis plaque, suggesting a reduction in inflammation. This lead encourages a deeper characterization of the immune landscape of atherosclerotic lesions to unequivocally identify those targets whose depletion would decrease disease burden. We anticipate a major role of T and B cells in orchestrating and maintaining inflammation, and therefore, certain of the biomarkers mentioned in this review might be used as targets for precision therapies. Among them, biomarkers related to activated T cells might be of particular interest since they could be used to selectively eliminate immune cells contributing to inflammation. Nevertheless, the dynamic and diverse landscape of B and T cells in the cardiovascular system is far from being fully understood. Preclinical studies will certainly get us closer to a full comprehension, yet animal models present certain limitations and are unable to completely capture the immunologic perspective of human cardiovascular diseases. Thus, *in vivo* PET-imaging of B and T cell populations within the heart and vessels will need to be addressed to comprehend the adaptive immune system in human cardiovascular disease.

In this context and mainly driven by the proliferation of cancer-immunotherapies, new tracers and imaging targets for the adaptive immune system are being studied and developed. These tracers focus on activated Tc and are demonstrating to be valuable agents for assessment of cancer ICI therapy using PET imaging.[156] For instance, lymphocyte-activation gen 3 (LAG-3 or CD223) is another inhibitory receptor expressed on activated T and B cells and currently is being investigated as a promising target for tumor prognosis biomarker of immunotherapy. Nevertheless, LAG-3 has been identified as a potential biomarker for coronary artery disease.[157] Thus, this target could be repurposed for imaging of activation of the adaptive immune system in the context of cardiovascular diseases. Moreover, ^{68}Ga-labeled peptides targeting LAG-3 have been recently reported, showing a relatively high specificity and fast blood clearance, thus compatible with imaging vascular diseases.[158] Similarly, CD137 (or 4-1BB) is a surface protein member of the tumor necrosis factor receptor superfamily present in activated T cells that has been associated with signaling in atherosclerosis and myocardial infarction.[159,160] Recently, CD137 PET imaging has been carried out to monitor early tumor responses of immunotherapies using a ^{18}F-radiolabeled bicyclic peptide.[161] The availability of a peptide-based radiotracer for CD137, opens the door to PET-imaging of activated T cells within the cardiovascular context. In addition to these biomarkers, CD103 is a surface biomarker for tissue resident memory T cells, which have been implicated in inflammatory disorders and atherosclerosis.[162] Currently, this biomarker has been also found in tumor infiltrating T cells and, thus, CD103 PET imaging has been explored to assess response to cancer immunotherapies.[163] Yet, only antibodies with prolonged blood circulation are available for PET imaging, which severely limits the use in the cardiovascular system.

Overall, although several radiotracers for imaging T and B cell biomarkers have been developed, they are mainly designed to be used in cancer research and are unsuitable for cardiovascular applications due to prolonged blood retention. Thus, new probes displaying faster pharmacokinetics and high binding affinities must be developed to meet this rising demand. On one hand, antibody- and nanobody-based radiotracers can be further optimized to facilitate the clearance. However, this may be challenging without sacrificing their binding affinities. Fortunately, insights gained from innate immune system imaging in cardiovascular disease suggest that radiolabeled peptides and small molecules are likely strong candidates for new T- and B cell imaging probes. A variety of tools, from *in vitro* techniques like phage display to *in silico* methods such as protein-peptide docking, offer promising pathways to develop these probes.[164] With further refinement and second- and third-generation developments, binding affinity and *in vivo* stability of selected peptides are expected to improve significantly to address this unmet need. Overall, we hope this review provides inspiration and guidance for radiochemists and chemists to address the current challenges in adaptive immune system imaging in cardiovascular disease.

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■ VOCABULARY

PET imaging: Positron emission tomography (PET) imaging refers to the use of positron emissive radioisotopes-labeled compounds for *in vivo* imaging of biomolecules within living organism. Emitted positron annihilates with an electron, emitting two energetic photons (511 keV) in opposite direction which are detected by the gamma cameras of the detector.

Cardioimmunology: Cardioimmunology refers to the study of the role of the immune system in the cardiovascular system under homeostatic and disease conditions.

Immunotherapy: Immunotherapy is a type of treatment that modulates and utilizes the immune system to treat a disease.

Inflammation: Inflammation is the natural response of the immune system to a stimulus, such as pathogens or dead cells. Prolonged inflammation can lead to pathogenic scenarios.

Angiogenesis: Angiogenesis consists of the formation of new capillaries from existing blood vessels and is a crucial process in the healing of wounds and tissue regeneration.

Ischemia: Ischemia is the reduction of the blood flow to an organ or tissue, causing a lack of oxygen and nutrients that can lead to tissue damage and cell death.

Cardiac remodeling: Cardiac remodeling is a change in the heart's shape, size and structure that can severely affect the cardiac function. It is typically caused to cardiac diseases and can lead to heart failure.

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