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Atherosclerosis and multi-organ associated pathologies

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Abstract

Atherosclerosis is a chronic inflammatory disease of the vascular system that is characterized by the deposition of modified lipoproteins, accumulation of immune cells and formation of fibrous tissue within the vessel wall. The disease occurs in vessels throughout the body and affects the functions of almost all organs including the lymphoid system, bone marrow, heart, brain, pancreas, adipose tissue, liver, kidneys, and gastrointestinal tract. Atherosclerosis and associated factors influence these tissues via the modulation of local vascular functions, induction of cholesterol–associated pathologies, and regulation of local immune responses. In this review we discuss how atherosclerosis interferers with functions of different organs via several common pathways and how the disturbance of immunity in atherosclerosis can result in disease-provoking dysfunctions in multiple tissues. Our growing appreciation of the implication of atherosclerosis and associated microenviromental conditions in the multi-organ pathology promises to influence our understanding of CVD-associated disease pathologies and to provide new therapeutic opportunities.

Keywords

atherosclerosis; immune cells; inflammation; multiple organs

Introduction

Atherosclerosis remains the underlying cause of cardiovascular disease (CVD) and ultimately the etiological culprit behind myocardial infarction and stroke, which together represent the leading causes of mortality in western nations [1–3]. Research efforts have focused on understanding the complex intricacies of atherosclerotic plaque biology with the goal of obtaining new approaches to allow for plaque prevention, regression, and stabilization. Because of its role in these conditions, investigation of atherosclerosis often focuses on the contribution of outside diseases, comorbidities, biomarkers, lifestyle factors, and how these factors contribute to atherogenesis from an “outside-in” perspective. However, the vascular system is a critical component of all organ systems, whereby atherosclerotic plaques are present within the arteries of major organs, and not just limited

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Disclosure of Interest

Nothing to declare

to the typical anatomical sites of study (coronary artery, aortic valve, or thoracic aorta). These peripheral sites of atherosclerosis and associated atherosclerotic conditions such as dyslipidemia, a dominant Th1/Th17 cell response, dysregulated myelopoiesis, and activated innate responses affect the homeostatic function of multiple organs, thus opening the opportunity for an “inside out” thought paradigm when studying the systemic effects of atherosclerosis. Therefore, the goal of this review is to provide an updated conceptualization of how atherosclerosis, in particular its immunological component in orchestration with other factors, contributes to pathologies of a few selected major organ systems.

Immune implication in atherosclerosis

Atherosclerosis is characterized by vascular dysfunction, formation of calcified necrotic plaques, and a unique pro-atherogenic immune response [1–3]. To date, numerous evidences indicate the implication of the adaptive and innate immune responses in atherogenesis. The innate arm of the immune response represents several subsets of monocytes and dendritic cells (DCs) as well as populations of neutrophils (NΦs), natural killer (NK), and mast cells, all of which are found in the atherosclerotic vessels at different stages of the disease progression [2, 3]. NΦs, NKT, mast cells, and subsets of pro-inflammatory monocytes and DCs play a proatherogenic role. NΦs participate in atherogenesis and destabilization of plaques via production of reactive oxygen species (ROS), myeloperoxidase (MPO), granzymes, pro-inflammatory cytokines and neutrophil extracellular traps (NETs) that activate aortic macrophages (MΦs) [4]. NKT cells that recognize endogenous self-lipid antigens and exogenous lipid antigens support atherogenesis via production of cytokines at earlier stages of plaque formation [5]. While the number of lesional mast cells is relatively modest, the impact of mast cells on plaque stability via the mast cell specific proteases tryptase and chymase has been reported [6]. The recruitment of $Ly6C^{high}$ monocytes is one of the important milestones for atherogenesis that results in generation of pro-inflammatory MΦs secreting IL-1β, IL-6, TNFα, CCL2, and metalloproteases [7]. While it was assumed that uptake of modified low-density lipoproteins (mLDL) leads to an inflammatory MΦ status, recent data challenged this concept demonstrating that non-foamy intima-residing MΦs express a highly pro-inflammatory set of genes [8]. Another interesting subset of monocytes that are involved in atheroma formation are $Ly6C^{low}$ monocytes. These cells patrol the lumen of blood vessels and support endothelium health [3]. Western diet (WD) feeding increases the number of patrolling monocytes, highlighting a sensitivity of monocytes to triggers of CVD [9]. Investigation of Nur77-deficient mice that lack $LyC6^{low}$ patrolling monocytes provided some controversial results [3]. Thus, the role of $Ly6C^{low}$ monocytes in atherosclerosis is still unclear. Overall, this is an interesting example how atherosclerosis-associated conditions shape the function of cell types within tissues. This cell plasticity is also seen in other tissues that are adapting to a highly atherogenic environment. Surprisingly, several studies reported that DCs regulate levels of LDL in circulation and are likely important contributors to cholesterol metabolism. DCs play a dual role in regulation of T cell fate [3]. Interactions of DCs with T cells result in the proatherogenic Th1 cell differentiation. Flt3-dependent $CD103^{+}CD11c^{+}MHCII^{+}$ classical DCs support T regulatory cell (Treg) responses, whereas $CCL17^{+}CD11b^{+}CD11c^{+}MHCII^{+}$ DCs restrict Tregs. Evidence suggests that atherosclerotic changes activate DCs in the

periphery, connecting atherogenesis with skin-associated pathologies [10, 11]. The role of T and B cells in atherosclerosis is subset specific [3, 12]. Th1 cells play a dominant proatherogenic role, whereas Tregs suppress chronic inflammation [1–3]. The implication of Th17 and Th2 cells is a topic of a debate but likely due to differences in experimental design and microbiota repertoires in animal facilities. So far, the major function of B cells in atherosclerosis is the production of antibodies (Abs) [12]. While B1 cells and marginal zone B cells are considered to protect against atherosclerosis, follicular B cells and innate response activator B cells have been shown to promote atherosclerosis [12]. It remains to be determined how other B cell functions such as cytokine production and antigen presentation affect atherogenesis. Overall, the immune system is strongly involved in atherogenesis and generates a unique complex immune response. In this review, we will discuss how some of atherosclerosis–induced changes in the immune landscape accelerate atherosclerosis–associated pathologies within multiple organs.

Atherosclerosis-associated changes in the bone marrow

The bone marrow is the primary site for the production of immune cells from hematopoietic stem and progenitor cells (HSPCs). A balance between lymphopoiesis and myelopoiesis is important for maintaining healthy physiology. However, atherosclerosis affects heath of HSPCs via the reduction of their regenerative capacities and a shift of HSPCs towards myeloid cell differentiation [13] (Figure 1). In line with these data, the transcriptome analysis of HSPC populations revealed enrichment of NΦ- and monocyte-related pathways in patients with severe CVD [14]. Notably, cholesterol metabolism is involved in proliferation of HSPCs via LXRs, ABCA1, ABCG1-dependent mechanisms and HDL exerts an anti-atherogenic effect by suppressing proliferation of HSPCs [15, 16]. With atherosclerosis, this protective response is significantly impaired due to insufficient cholesterol efflux. HSPCs with defective cholesterol efflux display increased plasma membrane cholesterol, elevated expression of the common β-subunit receptor of the IL-3, IL-5 and GM-CSF and increased proliferation [15, 16]. TLR ligands generated in atherosclerosis also regulate HSPC functions leading to increased myelopoiesis [17]. Infection-induced activation of myeloid cells leads to the development of the trained immunity characterized by long-lasting adaptations based on transcriptional and epigenetic modifications. Recently, it has been also reported that HSPCs undergo transcriptomic and epigenomic reprograming in the bone marrow upon hyperlipidemia, leading to increased proliferation and enhanced innate immunity [18]. This discovery echoes with a demonstration of transcriptionally activated hyper-responsive monocytes in patients with dyslipidemia despite statin treatment, suggesting a persistence of trained immunity in cholesterol–reducing conditions [19].

Another feature of bone marrow biology in atherosclerosis is a high rate of clonal hematopoiesis of indeterminate potential (CHIP) that is characterized by the presence of an expanded somatic blood-cell clone without progressing to cancerogenic status. There is an important connection between the rate of CHIP and atherosclerosis as mutations in DNMT3A, TET2, ASXL1 and JAK2 strongly correlate with the incident of CVD [20, 21]. Additionally, mutations in JAK2 and TET2 disturb normal homeostasis and accelerate atherogenesis via an increased inflammasome activation [21, 22]. Finally, using

a mathematical modeling and animal models of atherosclerosis, Heyde and colleagues demonstrate that increased HSCs proliferation expedites expansion of clones with driver mutations and this process accelerates atherogenesis via at least partially the TET2-dependent mechanisms [23]. While the system-wide impact of atherosclerosis-associated effects in bone marrow still needs to be elucidated, it is conceivable that they would influence pathologies associated with atherogenesis in different tissues and promote the manifold inflammatory immune responses. Excessive myelopoiesis observed in chronic hyperlipidemic conditions would result in elevated numbers of peripheral blood pro-inflammatory monocytes and NΦs that will migrate to various tissues and promote an unsolicited local immune response, which can be seen in metabolically disturbed tissues such as pancreas, adipose tissues, or gut.

One example of atherosclerosis-derived organ pathology is its impact on various conditions of bone health and function (Figure 1). Bone is a richly vascularized connective tissue and the networks of arteries and arterioles within the bone structures provide the blood supply. Thus, bones are clearly dependent on the heath of blood vessels. It is not a surprise that there is a strong correlation between CVD, aortic plaque calcification and bone-associated pathologies [24]. Coronary microvascular endothelial dysfunction is an independent predictor of osteoporosis in women over 50 years [25]. Gene expression of bone remodeling proteins correlated positively in bone and aorta, independently of age and sex of donors suggesting a close relationship between bones and vessels in the context of atherosclerosis and osteoporosis [26]. Studies in *Apoe*$^{-/-}$ mice suggest pathways that might be implicated in pathophysiology of CVD-related osteoporosis. Hyperlipidemia decreases bone mass by induction of anti-osteoblastogenic cytokines including IL-1, IL-6, and TNFα, shifts the balance towards monocytes, and decreases expression of pro-osteoblastogenic WNT ligands in the bone marrow [27]. Thus, increasing data highlights a strong bone–vessel connection and further studies are needed to investigate this association in men and in women with various co-morbidities.

Atherosclerosis-associated conditions and the blood-lymphoid tissues axis

Many events in bone marrow occur during atherogenesis in response to increasing levels of cytokines and misbalanced cholesterol metabolism. As a mirror of these changes, the composition of peripheral blood cells reflects changes occurred in the bone marrow. Quantity and phenotype of circulating immune cells are strongly associated with CVD and accompanied pathologies and peripheral blood is characterized by neutrophilia and monocytosis with a dominant increase in pro-inflammatory Ly6C^{hi} monocytes [28–30]. Importantly, the expansion of human circulating monocytes and NΦs positively correlates with hyperlipidemia and CVD risk and circulating human NΦ counts accurately predict future adverse cardiovascular events [31, 32]. Not only the numbers but also the quality of circulating myeloid cells is changed in atherosclerosis. Monocytes from patients with CVD are characterized by an increased cytokine production and higher glycolytic metabolism [33, 34]. The circulating number of Ly6C^{hi} monocytes and NΦs also correlates with lesion burden in mice [28–30, 35]. Emerging evidence suggests that hyperlipidemia induces sustained epigenetic reprogramming that result in the development of a trained innate immunity in monocytes and NΦs [36]. Activated NΦs release pro-inflammatory granules

and NETs, adhere to endothelial layers, and support recruitment of LyC6^{hi} monocytes and T cells, lesional MΦ accumulation, coagulation, and production of type I interferon from plasmacytoid DCs. All of these events result in EC damage and the promotion of chronic inflammation. These features of activated NΦs and MΦs in hyperlipidemic conditions would support atherosclerosis-associated pathologies such as T2D, rheumatoid arthritis, psoriasis, and cystic fibrosis, in development of which hyperactivated myeloid cells are also involved (Figure 1).

In addition to myeloid populations, an increased proportion of effector memory T cells (CD3+CD4+CD45RA−CD45RO+CCR7−) is detected in the peripheral blood of CVD patients and correlates with the extent of plaque formation [37]. In line with this evidence, several other studies reported the strongest association of effector memory T cells with atherosclerosis in various vascular beds at different stages of disease [38]. Interestingly, while elevated levels of Th1 and Th17 cells are found within atherosclerotic vessels and the blood, there is only a strong correlation between levels of Th1/Th17 cells in symptomatic coronary artery disease but to a lesser degree in CVD. While numerous studies in mice clearly show a protective role of Tregs, studies in humans have not reached completely conclusive results as the circulating levels of peripheral blood Tregs in CVD patients show little correlation with carotid and coronary atherosclerosis [39]. Although there is a wealth of evidence that altered Ab production is associated with CVD, little is known about the composition of circulating B cell populations in mouse models of atherosclerosis or subjects with CVD.

The lymphatic system is a network of lymphatic vessels, lymph nodes and lymphoid organs. By transporting interstitial fluid, antigens and antigen-presenting cells as well as inflammatory cytokines, the lymphatic system maintains tissue homeostasis and supports the immune response [40]. Lymphatics also play a key role in providing a route for clearance of lipoproteins and other macromolecules. In the aorta, lymphatic vessels occupy the adventitial layer, clearing and metabolizing lipoproteins [41]. This clearance is mitigated through cholesterol efflux from MΦs via the MΦ reverse cholesterol transport system (RCT) [42]. After phagocytosis, cholesterol exits the cell through plasma membrane transporters, ATP binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1), to be further processed by extracellular high-density lipoprotein (HDL). The interstitial fluid that leaves the arterial wall through the lymphatic system is then composed of these HDL particles.

The lymphatic network has gained attention for its possible role in the pathogenesis of atherosclerosis [41]. Typically, lymphangiogenesis occurs during pathological conditions due to a need for removal of tissue fluid, immune cells, and cytokines. Indeed, both *Ldlr*$^{-/-}$ and *Apoe*$^{-/-}$ mice develop adventitial lymphangiogenesis and reduction of cholesterol in *Apoe*$^{-/-}$ mice mitigates the lymphatic expansion [40]. When lymphatic drainage is impaired, plaque burden is aggravated and RCT is severely impaired. This suggests a protective role of peri-adventitial lymphatics in preventing lipid accumulation and plaque burden. It would be further important to test how lymphatic structures might be implicated in atherosclerosis regression and identify molecular targets that may support proper growth and functions of lymphatics during atherosclerosis.

As lymphatic vessels are involved in draining of various tissues in the body, it is anticipated that lymphangiogenesis might be affected by atherosclerosis not only in the aorta. Indeed, the network of lymphatics is increased in ischemic and inflamed hearts and heart valves [43], in the adventitia of large arteries [44], and in advanced aortic stenosis [45]. Based on an important role of lymphatics in skin [42] and a strong association of atherosclerosis and psoriasis [46], we can speculate that atherosclerosis also affects remodeling of lymphatic vessels in psoriasis. The importance of this remodeling is unclear and further studies would be necessary in this area.

Hypertension is a complex pathology with various genetic and environmental factors contributing to the progression of this disease. One of the major contributing factors in hypertension is a defective regulation of sodium and water in tissues. Studies now show that the reduction in skin-associated lymphatic structures induces salt-sensitive hypertension [47, 48]. Similarly, a key role of lymphangiogenesis has been also reported for the kidneys as the induction of kidney-specific overexpression of VEGF-D diminished renal leukocyte accumulation and hypertension [49]. As atherosclerosis is strongly associated with hypertension, one of the possible mechanisms for this connection could be the impairment of lymphatic functions in both pathologies. Another question that arises in relation to the cross-talk between atherosclerosis and the lymphatics is whether impaired lymphatic function leads to pathological conditions, including inherited and acquired forms of lymphedema, autoimmune disorders, and immune deficiency [40].

Atherosclerosis and Secondary lymphoid tissues

Lymph nodes (LNs) are present along every major lymphatic route from tissues to bloodstream, providing sites for antigen-presentation and differentiation of specific Th phenotypes. Recognition of oxLDL, and specifically peptides from Apolipoprotein B by CD4+ Th cells is a key process in the induction of a strong Th1 response in atherosclerosis [3]. Not only Th1 but also CD4+IL-17+ cells are detected in LNs, spleen, and the aorta. Studies have demonstrated that Tregs may adapt to environmental cues to undergo plasticity, generate Teffector/Treg hybrid cells, and control inflammation [3]. We and others demonstrated that numbers and functions of Tregs are compromised as atherosclerosis promotes Treg plasticity to form a dysfunctional subset of IFNγ+Th1/Tregs or Th17/Treg, or Tfh/Treg populations, which fail to adequately suppress atherogenesis [3]. Thus, atherosclerosis-associated conditions promote the differentiation of specific Th cell subsets that have a powerful meaning to induce inflammatory responses in various tissues (Figure 1). Indeed, atherosclerosis is strongly connected and shares common pathways with multiple autoimmune diseases. Attenuated Treg functions and the increase in Th1 and Th17 cell subsets have been implicated as culprits in a plethora of autoimmune and other inflammatory diseases in mice and humans [50]. Psoriasis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), as well as T2D are strongly associated with the signatures of the T cell response in atherosclerosis. Additionally, a chronic low grade inflammation in atherosclerosis provides high levels of inflammatory mediators such as TNFα, IL-6, and IL-1β that are known to support development of autoimmune pathologies including psoriasis, RA, and SLE. These diseases are particularly worrisome when paired with atherosclerosis, as cardiovascular death is the most common cause of mortality in patients

suffering from SLE and the risk of myocardial infarction is doubled compared to the normal population [51]. These elevated risks might be attributed to the increased frequency of vasculitis, which may result from elevated levels of antibody/antigen complexes, as well as increased circulating levels of IL-6 and IL-17 [52]. Additionally, atherosclerosis-associated risk factors such as age, high blood pressure, and hyperlipidemia, in orchestrations with a unique atherogenic immune response support development of autoimmune diseases with a high rate of atherosclerosis.

In atherosclerosis, the spleen acts as a reservoir for $Ly6C^{hi}$ monocytes [53] that infiltrate the plaque and contribute to atheroma remodeling and instability by expression of pro-inflammatory interleukins, ROS, and metalloproteinases. Dysregulated cholesterol efflux pathways observed in atherosclerosis also contribute to production of splenic monocytes and NΦs through expansion or differentiation of HSPCs by GM-CSF and IL-3 expression [53]. Atherosclerosis-induced elevated myelopoiesis in the spleen not only supports further plaque burden but also influences pathophysiology of other organs such as MI-damaged heart. It would be important to investigate other atherosclerosis-associated diseases for which myeloid cells play an essential role and identify to which extent splenic myelopoiesis contribute to these pathologies.

Additional key features of the spleen and LNs upon atherogenesis is a formation of germinal centers (GC) and generation of high affinity IgG, IgE, and IgM Abs [3, 12]. Both natural and antigen-specific IgM Abs play an atheroprotective role via blockade of oxLDL uptake by MΦs. These anti-IgM Abs are produced by B1a and B1b cells and recognize oxidation-specific epitopes such as oxLDL. There is a strong correlation between the levels of IgE and CVD events likely via IgE deposition in the atherosclerotic plaques and a subsequent activation of mast cells. The role of IgG is generally thought to exacerbate atherosclerosis by activating MΦs and vascular smooth muscle cells (VSMCs), but recent studies suggest a role for antigen specificity and Ab isotypes [12]. OxLDL-specific IgG Abs are detected in atherosclerotic plaques and plasma of CVD patients, but their role in atherogenesis is not well understood [12]. In late-stage atherosclerosis, development of arterial tertiary lymphoid organs (ATLO) occurs in the adventitia surrounding plaque formation and is likely a result of the chronic inflammatory environment. Hu and colleagues showed that ATLO is protective against atherogenesis and ATLO disruption promotes lesion formation [54]. In contrast, another study found that the Tfh-GC B cell axis present in ATLOs promote lesion formation and exacerbates atherogenesis [55]. Thus, the role of ATLO remains elusive and further studies should be focused on the questions of relative importance of ATLO in the production of specific immunoglobulins, formation of Th responses, and support of Treg functions. In the light of the impact of atherosclerosis on pathology of multiple tissues, it might be worth to investigate whether TLO are formed and have a functional activity in other non-lymphoid chronic inflammatory tissues that are associated with atherosclerosis.

Atherosclerosis–associated pathologies of the heart and brain

Perhaps the most well-known and well-characterized resulting pathology of atherosclerosis is coronary artery disease. Atherosclerosis plays a critical role in the propagation of myocardial infarction (MI) and the healing of the tissue that follows thereafter (Figure

1). As atherosclerosis progresses, vulnerable plaques destabilize and result in occlusions in the coronary arteries that result in MIs that even when not deadly, result in long-term, irreversible damage to the organ [56]. Multiple factors and cell types contribute to plaque rupture, including formation of necrotic cores due to impaired efferocytosis, production of ROS that trigger angiogenesis, and release of extracellular proteases that break down the fibrous cap [1, 2, 56]. Atherosclerosis continues to affect the heart after MI. Post-MI, elevated number of monocytes and NΦs in the blood plays a role in the progression to heart failure [56, 57]. Cardiac fibroblasts in the infarcted myocardium produce increased levels of GM-CSF, which stimulates the production of chemokines, including CXCL2, which attracts NΦs, and CCL2, CCL3, CCL5, and CCL7, which all attract monocytes [56]. Attracted NΦs and $Ly6C^{hi}$ monocytes phagocytose dead tissue, but also produce inflammatory mediators [56, 57]. Impediment of this two-phase system, as through the alteration of immune cell populations in atherosclerosis, results in impaired tissue repair of the infarcted area [57]. $Ly6C^{hi}$ monocytes lingered in the infarct, contributing to a pro-inflammatory environment that also resulted in accelerated ventricular dilation and lower ejection fraction [56, 57]. Not only does atherogenesis support MI, but also post-MI events such as MI-triggered monocytosis, which increase the number of emigrated monocytes to the atherosclerotic aorta [58]. While the impact of innate immune cells is becoming apparent, there are still limited opportunities to precisely control the supply of myeloid cells into the infarcted heart. Further studies are also needed to evaluate how the atherogenic adaptive response characterized by a “specific signature” of Th1/Th17 cells and attenuated Treg pool influences MI and post-MI recovery.

Stroke, a cerebrovascular accident, is a significant cause of morbidity and mortality [59, 60]. Atherosclerosis can lead to ischemic stroke, characterized by the dysfunction and blockade within the blood vessel in the brain, leading to hypoxia-induced neuronal damage [60, 61]. Rupture of atherosclerotic plaques in the intracranial arteries can lead to occlusion of small vessels in the brain. Importantly, intracranial atherosclerosis is one of the most common causes of stroke and likely a driver for stroke recurrence. As stroke often induces cognitive impairment, data suggest that progression and calcification of plaques in the carotid arteries accelerates cognitive dysfunction, positively correlating with post-stroke cognitive impairment in patients [62]. It is also noteworthy that stroke and atherosclerosis are associated with common risk factors such as hypertension, T2D, and metabolic syndrome, thus highlighting a close relationship between these two pathologies [59]. Likewise, biomarkers for atherosclerosis act as predictors of mortality in stroke patients [60]. C-reactive protein, which is expressed in VSMCs and functions in plaque destabilization, has been found to independently predict mortality in stroke patients as well as recurrent stroke [60, 63].

Atherosclerosis plays a role in cognitive impairment outside of stroke as well. Alzheimer’s disease (AD) is a neurodegenerative disease characterized by progressive cognitive decline linked to the aggregation of Amyloid β (Aβ) in the brain. Recent data has tied cardiovascular risk factors to increased risk for AD (Figure 1). Intracranial atherosclerosis is associated with increased odds ratio for dementia [64]. Circle of Willis atherosclerosis is positively associated with plaque density and cerebral amyloid angiopathy severity, but not with APOE4 genotype, despite its known link to AD [65]. Higher carotid intimal

medial thickness also correlates with faster cognitive decline in AD patients [66]. Advanced atherosclerosis can also lead to hypoxia in the brain, which cleaves APP into Aβ via upregulation of the β– and γ–secretase pathways [67]. Vascular dysfunction caused by atherosclerosis might also result in dysfunctional small vessels, a breakdown of the blood brain barrier, inflammation, and ultimately neurovascular dysfunctions. Recent studies demonstrated that hyperlipidemia and associated inflammation reduce lymphatic vessel functions. The discovery of meningeal lymphatic vessels [68] opens a new question on an impact of atherosclerosis on lymphatic biology in the brain. There is increasing evidence that neuroinflammation and atherosclerosis-associated immune response have a role in the pathogenesis of AD. AD is characterized by a significant efflux of myeloid cells to the brain and are found in areas with Aβ deposits [69]. As atherosclerosis primes monocytosis and neutrophilia, and a profound activation of myeloid cells, we speculate that this is an additional pathway how atherogenesis might accelerate brain-associated pathologies.

A cross-talk between adipose tissue and atherosclerosis

The various adipose tissue depots throughout the body are critical sites of inflammation under conditions of CVD and several of its comorbidities including obesity and T2D [70]. Obesity is an established cardiovascular risk factor, which supports development of metabolic syndrome and CVD [70]. Recent data clearly demonstrate that Perivascular Adipose Tissue (PVAT) is directly involved in vascular endothelial function under both homeostatic and pathological conditions, including CVD [71]. The proximity of PVAT to vascular endothelial cells and VSMC allows for direct communication via the release of proinflammatory adipocyte-derived cytokines. Induction of atherosclerotic lesion via early endothelial cell injury leads to the migration of myeloid cells and T cells into the perivascular adventitia and adipose tissue [71]. At later stages of atherogenesis, proliferation of MΦs and B cell recruitment further enhance the inflammatory status of PVAT. Inflammatory processes in the aorta also affect the health of PVAT mainly via release of pro-inflammatory mediators from the vascular wall and altered adipocyte differentiation and intracellular lipid formation. From the immune point of view, recent clinical findings have revealed that the densities of CD68+ MΦs and CD20+ B cells in PVAT positively correlate with percentage of arterial obstruction [72]. Thoracic PVAT samples revealed elevated expression levels of *IL1β, CCL2,* and *IL-6* that correlated to CVD burden [73], suggesting a close relationship between the vessel wall and PVAT. Interestingly, Srikakulapu et al. have shown that the large majority of B cells within PVAT of *Apoe*$^{-/-}$ mice are atheroprotective IgM-producing B1 cells [74]. Pro-inflammatory Th1 and Th17 cells are also found within the metabolically dysregulated adipose tissues in atherosclerotic mice and the phenotype of these cells mirror their functional activities within the aorta as they regulate MΦ phenotype and MΦ infiltration to the PVAT [71]. Treg cells are found in the lean mice, but their numbers decline in adipose tissues of obese mice [71]. It remains to be determined whether a phenomenon of Treg plasticity demonstrated in atherosclerosis also unarms Treg functions in PVAT. Aberrant activation of NΦs in atherosclerosis results in elevated ROS, cytokine productions, and NETosis, factors which are known to be detrimental for proper functions of adipose tissues [75]. NΦs are important players in the induction of insulin resistance in adipose tissues and evidence suggests that activated NΦs

are one of the important drivers of atherosclerosis-associated metabolic dysfunctions [75]. The aforementioned studies highlight the complex interactions of infiltrating immune cells within PVAT, and the opposite directional impact that PVAT can have on atherosclerosis.

Pancreas and atherosclerosis

The risk of CVD disease stemming from conditions involving pancreatic dysfunction such as T1D and T2D has been extensively studied. Most of the body of knowledge focuses on how various metabolic deficiencies, namely insulin resistance and obesity, play a contributory role in the progression of atherosclerosis [76]. Under the steady state, pancreatic islets are home to a small population of resident MΦs that are involved in homeostatic maintenance, yet these cells proliferate and contribute to the demise of insulin producing β cells during obesity [77]. This phenomenon is also due in part to the effects of obesity related dyslipidemia, whereby cholesterol accumulation in islets can lead to β cell dysfunction [78]. Despite the known connections of CVD and T2D, there is a lack of research pertaining to pancreatic inflammation under conditions of atherosclerosis. We can speculate that clusters of factors in the innate immunity (such as monocytosis with a dominant Ly6C^{hi} production, differentiation to pro-inflammatory MΦs) and hyperlipidemia-induced metabolic dysfunctions likely play a detrimental role in physiology of the pancreas (Figure 1). Indeed, Lohmann et al. showed that CD68+ MΦs dominate the inflammation of islets in atherosclerotic *Apoe*$^{-/-}$ mice [79]. Another commonly shared proinflammatory pathway that promotes both atherosclerotic plaque progression and islet dysfunction is the 12/15-lipoxygenase pathway [80]. Further studies that can elucidate the shared mechanisms of MΦ accumulation/activation could pave the way for novel therapeutics to ameliorate MΦ inflammation in both CVD and diabetes. Despite the fact that the pancreas contains several major blood vessels, little is known about atherosclerotic plaque development in these tissues. Therefore, it is likely that atherogenesis has a significant impact on the functions of the pancreas via a decrease of the blood flux and hypoxia in the pancreatic islets with a consecutive functional decline of β-cells. Thus, further studies in this important area of research should shed light on the close relationship between atherosclerosis and pancreas dysfunctions.

Effects of atherosclerosis on biology of Vascular Smooth Muscle

The arterial media is primarily composed of VSMCs with the main functions of providing vessel contractility and extracellular matrix synthesis [81]. VSMCs are a critical component of nearly every stage of atherosclerosis development [1]. Our classical understanding of VSMCs in atherosclerosis mainly encompasses their role in extracellular matrix production as a protective mechanism to stabilize plaques via fibrous cap maintenance and ultimately protection from plaque rupture [82]. VSMCs have also been viewed as victims of plaque inflammation and hyperlipidemic conditions. Unique VSMC plasticity in atherosclerosis has become increasingly evident, whereby these cells can adopt phenotypic changes that result in expression of markers typically associated with MΦs, foam cells, and osteochondrogenic cells [81]. This important shift in our understanding of VSMC plasticity has benefited from advances in genetically engineered murine models, namely those employed in fate mapping studies. Shankman and colleagues revealed that ~80% of SMC-derived cells within plaques

of high-fat diet fed *Apoe*$^{-/-}$ mice adopt new phenotypic identities akin to mesenchymal stem cells (SCA1+), MΦs (LGALS3+), and foam cells (ACTA2+PDGFβR+) as determined by co-staining of VSMC-derived YFP expression within plaques [83].

VSMCs have dynamic interactions with nearly every immune cell type during all stages of atherosclerosis [84]. ICAM-1 and VCAM-1-expressing VSMCs support the retention of MΦs within the plaque where MΦs modulate the microenvironment of surrounding tissue. Butoi et al. have shown that the co-culture of VSCMs and MΦs reduces ECM synthesis in VSMCs and increases expression of matrix metalloproteinase 2, 9, which could lead to decreased plaque stability [85]. However, a more recent study by Gomez et al. has shown that blockade of IL-1β, presumably secreted by MΦs, during late stage plaque development in *Apoe*$^{-/-}$ mice reduced VSMC collagen production and increased MΦ numbers within the fibrous cap, resulting in increased susceptibility to rupture [86]. Another key immune cell that influences VSMC behavior are NΦs. NΦs activate VSMCs via ROS and cytotoxic granule release, and production of NETs promotes VSMC apoptosis and ultimately plaque destabilization via NET-derived histone H4 [4]. These mentioned studies and others, which have been discussed in detail by Ramel et al. [84] demonstrate that there are both positive and negative consequences between the cross-talk of various immune cells and VSMCs during atherogenesis.

Atherosclerosis and associated liver pathologies

Atherosclerosis and associated metabolic misbalance, chronic inflammation, and ischemia trigger a systemic multi-organ response. The liver is the main metabolic organ of the body. Emerging evidence demonstrates a pathophysiological link between atherosclerosis and systemic liver diseases, particularly, Nonalcoholic Fatty Liver Disease (NAFLD) [87]. The cross talk between NAFLD and CVD is multidimensional and involving various pathways such as endothelial dysfunction, tissue fat accumulation, dyslipidemia, altered glucose metabolism, dysbiosis, and chronic inflammation [88]. Particularly, chronic inflammation develops in NAFLD due to unfavorable changes in the systemic physiology, such as excessive myelopoiesis, high fat diet consumption and lipotoxic fat deposition, as well as sedentary lifestyle, all of which contribute to atherosclerosis and NAFLD (Figure 1). Atherosclerosis and NAFLD are both characterized by the presence of lipid deposition, accumulation of pro-inflammatory MΦs, and dysregulated immune responses [89]. Local MΦs are the predominant mediators of NAFLD and atherosclerosis, and the infiltration of Ly6C^{hi} monocytes is a crucial checkpoint for the progression of both pathologies [89]. The inflammasome activation is critical in hyperlipidemia-mediated reprograming of myeloid cells and is an important factor in the progression of NAFLD and atherosclerosis [87]. As there is currently no approved specific drug treatment for NAFLD, more work is needed for better understanding of NAFLD pathology. Nevertheless, it would be still beneficial to target cardiovascular risk factors, the reduction of which would help to abort many inflammatory pathways leading to NAFLD.

Atherosclerosis and associated skin pathologies

The skin is an important immune organ that protects the body from infection, toxins, and helps prevent autoimmunity. Psoriasis patients have accelerated atherosclerosis, possibly due to poorly controlled tissue inflammation at the skin that leads to systemic inflammation [90]. The chronic inflammatory environment in both atherosclerosis and psoriasis results in many overlapping inflammatory environmental mediators. Possibly, the strongest effects on skin physiology from atherosclerosis would come from the impact of atherogenic Th1/Th17 dominant responses and effects of atherogenesis on lymphatic vessel functions (Figure 1). T cells are prompted to differentiate into Th1 and Th17 cells leading to secretion of TNFα/IFNγ and IL-17A/IL-22, respectively. IL-17A is significantly elevated in psoriasis and atherosclerosis and plays a central role in both pathologies, promoting activation and proliferation of keratinocytes, angiogenesis, and concomitant increase in plaque burden [90, 91]. Treg responses are also shown to play a similar role in mitigating the development of psoriasis and atherosclerosis. Compared to healthy controls, patients with either psoriasis or atherosclerosis have reduced inhibitory Treg functions leading to altered levels of TGFβ further promoting pathogenic Th1 and Th17 cell activation [90]. The chronic inflammatory milieu of atopic dermatitis is hypothesized to be the reason for its coexistence with CVD. However, it is unclear whether the association between atopic dermatitis severity and CVD is a direct correlation or if it is mediated or confounded by other risk factors. The Th2 milieu that is skewed in atopic dermatitis and contributes to its progression [92], has an unclear pathogenetic role in atherosclerosis [3]. Importantly, skin blood flow is significantly diminished upon hyperlipidemia increased systolic blood pressure [93] and recent studies showed that atherosclerosis attenuates lymphatic vessel formation and structures. Further studies are needed to understand what mechanisms contribute to the inflammatory environment in chronic skin diseases in atherosclerosis and to identify the common therapeutic target pathways to lessen concomitant effects of these pathologies on each other.

Atherosclerosis and gut axis

The gut microbiome is an important regulator of whole-body metabolic homeostasis and organ physiology. Increasing evidence highlights a role for the gut microbiome in pathogenesis of atherosclerosis [94]. Alterations in the composition and/or quantity of bacteria in the gut can alter the permeability of the intestinal barrier, resulting in the translocation of bacteria and their byproducts into the circulation. Elevated circulating levels of bacterial biproducts, such as LPS, primes circulating immune cells, especially NΦs, to a heightened inflammatory state [95–97] with a production of NETs along the arterial lumen, which in turn enhances the accumulation of monocytes as well as LPS-primed NΦs in the lesion. Concomitantly, atherosclerosis-associated conditions, such as elevated cholesterol and neutrophilia contribute to the breakdown of the intestinal barrier, resulting in a condition known as metabolic endotoxemia, which further increases the risk of chronic inflammation within the gut [95–98]. While the focus of current research is investigating how the gut microbiome influences atherogenesis, little is known on how atherosclerosis affects gut health and functions. Nevertheless, the progression of several intestinal pathologies are now closely associated with atherosclerosis. Inflammatory bowel disease (IBD) is a chronic

inflammatory disease of the gut caused by the interplay of the host's genetic predisposition and immune responses. IBD causes systemic vascular inflammation and has been recently associated with atherosclerosis [99]. One of the potential mechanisms connecting IBD with atherosclerosis involves elevated levels of circulating IL-6, CRP, and TNFα and thus inflammation in both pathologies; however more studies investigating this link are needed [99]. Small intestinal bacterial overgrowth (SIBO) is a pathological condition where bacteria translocated from the colon to the small intestine changes the quantity and composition of the intestinal microbiome resulting in symptoms such as bloating, abdominal pain, nausea, and fatigue [100]. SIBO has been associated with atherosclerosis and CVD. Unraveling mechanisms by which the gut and inflammatory conditions of atherosclerosis communicate with each other are likely complex and further integral research is needed for identification of new targets and approaches for treatment of both pathologies.

Concluding Remarks

It has long been known that atherosclerosis is associated with the development of various multi-organ pathologies characterized by a local chronic inflammation. During the past decade, there have been major advances in our understanding of how hyperlipidemia and the atherosclerosis-tailored adaptive immune response affect bone marrow activity, cell metabolism, lymphatic vessel and vascular cell functions in the different tissues. The discovery of the role of hyperlipidemia in shaping the hematopoietic cell landscape and number and quality of circulating myeloid cells via bone marrow and extramedullary hematopoiesis, and identifying the role of lymphatic vessels in the regulation of RCT open new perspectives on the role of the immune system in atherogenesis. Importantly, these discoveries uncovered additional pathways by which atherosclerosis supports systemic multi-organ responses. It seems that atherosclerosis accompanies the chronic inflammation within several organs via four main ways: a unique adaptive immunity, activated innate immune response, conditions of hyperlipidemia, and finally via affecting blood vessel functions through the plaque formation (Figure 1). In this review, we mainly focused on the known effects of the atherogenic immune response in the support of atherosclerosis-associated pathologies in multiple organs, but certainly a more complex picture would be drawn with the addition of other factors such as atherosclerosis–associated metabolic syndrome, disturbed cholesterol metabolism, and altered biology of vascular cells. While we have discussed the effects of atherosclerosis-associated factors in the induction of chronic inflammation in various tissues, many of those effects are attributed to the manifestation of multi organ damage due to the metabolic syndrome that is strongly connected to the development of atherosclerosis. While it is difficult to some extent to dissect specific pathways affected only by atherogenesis, it is the overall picture that is necessary to be considered for the development of successful therapeutic targets. Further understanding the key role of atherosclerosis-associated inflammation in the activation of vascular beds and the support of leukocyte recruitment into various inflammatory tissues calls for an initiation of studies that take a closer look at mechanisms of leukocyte migration into the target tissues in multiple autoimmune pathologies such as psoriasis, arthritis, IBD, and neuroinflammatory diseases in conditions of atherosclerosis. While much of the interest in lymphatic vessel biology centers on its ability to promote inflammation, modulation

of lymphatic activities may be a promising target to combat atherosclerosis-associated pathologies within skin, lymph nodes, and likely the brain. While atherogenic immunity accelerates chronic inflammatory processes within multiple tissues, the immune response also has mechanisms of protection against uncontrolled inflammation. Is it possible to target these specific pathways via modulation of Treg and B cell subsets while preserving host defense? More studies in this direction would help to generate new therapeutic approaches to reduce the detrimental effects of atherogenesis on other organs. Overall, the diversity of mechanisms by which atherosclerosis induces multiple organ pathologies would require a versatility of approaches for restraining atherosclerosis-associated chronic inflammation in different tissues.

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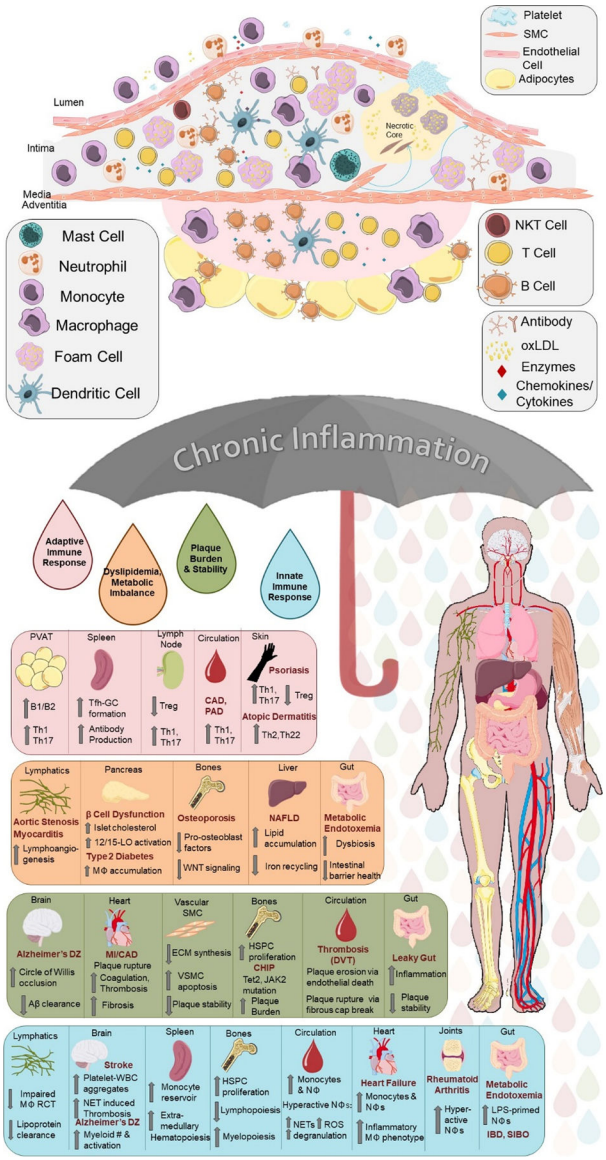

Figure 1. Atherosclerosis directly contributes to multiple organ pathologies through alterations in metabolic balance and ensuing chronic inflammation.

Beyond the acute effects of atherosclerotic plaques to vascular structures, the consequences of atherosclerosis extend elsewhere the vascular wall and directly influence the surrounding tissues and organs. From the molecular to cellular and even anatomic levels, these contributions have been compartmentalized into four main categories: dyslipidemia and metabolic imbalance, innate immune response, adaptive immune response, and plaque burden and stability. Altogether, this figure distills the major molecular and cellular processes that drive the organ-specific comorbidities commonly seen during atherosclerosis.