

CD8⁺ T cells in atherosclerosis and coronary artery disease

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Abstract

Cardiovascular diseases remain a global health challenge, with >600 million cases reported annually. Atherosclerosis is a common pathology that underlies various cardiovascular diseases, such as myocardial infarction and stroke. Both the innate and adaptive immune systems have crucial roles in the progression of atherosclerosis. CD8⁺ T cells are the most clonally expanded adaptive immune cells in human atherosclerotic plaques, but whether these cells are pro-atherogenic or atheroprotective during the different stages of atherosclerosis development and progression is unclear. In this Review, we summarize the latest knowledge on the role of CD8⁺ T cells in atherosclerosis. We discuss the phenotypic, functional and transcriptional features of CD8⁺ T cells in atherosclerosis and shed light on their involvement in comorbidities to understand the landscape of CD8⁺ T cells during the progression of atherosclerosis. We also highlight key research gaps and questions that need to be addressed to improve our understanding of the functions of CD8⁺ T cells in atherosclerosis. Targeting CD8⁺ T cells could provide potential therapeutic avenues to prevent and mitigate adverse cardiovascular events in patients with atherosclerosis and coronary heart disease.

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Key points

- CD8⁺ T cells infiltrate early atherosclerotic lesions and clonally expand, leading to higher numbers of these cells in fibroatheroma than in early lesions, localized especially within artery tertiary lymphoid organs.
- CD8⁺ T cell migration is guided by CC-chemokine receptor 5 (CCR5)–CC-motif chemokine 3 (CCL3)/CCL4/CCL5 and C-chemokine receptor type 4 (CXCR4)–CXCL12 signalling, and CD69, CD103 and HOBIT define tissue-resident subsets and increase local retention.
- Antigen stimulation and clonal expansion in atherosclerotic plaques and artery tertiary lymphoid organs promote the generation of effector-like CD8⁺ T cells, and CD8⁺ T cells specific to *Chlamydia pneumoniae*, Epstein–Barr virus, influenza virus and cytomegalovirus increase atherosclerotic plaque vulnerability.
- CD8⁺ T cells that express CD25, CD103 and/or CBL-B, as well as Qa-1-restricted CD8⁺ T cells, confer protection against atherosclerosis, in part by limiting the activation, proliferation and pro-inflammatory function of CD4⁺ T cells and macrophages.
- CD8⁺ T cells promote monocyte recruitment and vascular smooth muscle cell transdifferentiation, and secrete cytotoxic molecules and inflammatory cytokines to drive atherosclerotic lesion instability and inflammatory progression.
- Lessons from autoimmunity and cardiovascular comorbidities (rheumatoid arthritis, cancer and diabetes mellitus) might provide insights into the mechanisms involved in the regulation of CD8⁺ T cells in atherosclerosis and guide the development of targeted therapies for atherosclerotic cardiovascular disease.

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally, accounting for >20 million deaths annually¹. In the USA alone, CVDs cause one in every five deaths and impose an annual financial burden of nearly US\$250 billion². Atherosclerosis, characterized by the formation of a plaque rich in lipids and immune cells in the arterial wall, is the primary underlying cause of approximately 80% of CVD-related deaths³. Current treatments for atherosclerotic CVD primarily focus on the management of hypercholesterolaemia or on interventional revascularization⁴. Although studies such as the CAN-TOS and COLCOT trials demonstrated positive outcomes with the use of immunosuppressive therapies in patients with atherosclerotic CVD, systemic immunosuppression led to increased rates of infections and other adverse events^{5,6}. Therefore, there is an impetus to develop new, more targeted therapeutic approaches to manage atherosclerosis, which requires a deeper understanding of the underlying cellular and molecular mechanisms that regulate its initiation and progression.

Given that atherosclerosis has an autoimmune component, a greater understanding of the role of adaptive immune cells, particularly T cells, in atherosclerosis can aid the development of novel diagnostic and therapeutic approaches. Advanced techniques such as RNA sequencing (RNA-seq), in vivo imaging, cell-lineage tracing and knockout studies in mice have provided insights into the specific roles

of T cells in atherosclerosis⁷. Accumulating evidence indicates that the activation and dysfunction of CD8⁺ T cells, which are cytotoxic lymphocytes essential for immune surveillance (Box 1), drive vascular inflammation and atherosclerotic plaque instability. However, whereas the role of CD4⁺ T cells in atherosclerosis has been extensively studied and well characterized, the role of CD8⁺ T cells in this setting remains under debate. The inconsistent findings in the literature could be attributed to several factors, including the experimental settings (for example, investigation of early versus late atherosclerosis timepoints) or the use of a wide range of genetically modified mouse models to assess immune function, such as *Gzmb*^{-/-}, *Prf1*^{-/-}, *CD8*^{-/-}, *B2m*^{-/-}, *Tap-1*^{-/-} or *Cblb*^{-/-} mice or atherosclerotic models including *ApoE*^{-/-} or *Ldlr*^{-/-} mice^{8–14}.

In this Review, we discuss the diverse phenotypes of CD8⁺ T cells in atherosclerosis, the mechanisms and drivers of infiltration and homing of CD8⁺ T cells into atherosclerotic plaques, and the role of CD8⁺ T cells in the different stages of atherosclerosis. We also appraise the functions of CD8⁺ T cells in the setting of comorbidities of atherosclerotic CVD as well as in other diseases similar to atherosclerosis, given that this knowledge might aid in our understanding of the role of CD8⁺ T cells in atherosclerosis. Finally, we discuss the potential therapeutic strategies targeting CD8⁺ T cells and highlight outstanding questions that might shape future research.

CD8⁺ T cell phenotypes and localization in atherosclerosis

The presence of CD8⁺ T cells in human carotid artery plaques was first demonstrated by immunohistochemistry in 1986¹⁵. Later studies using more advanced approaches, including single-cell RNA-seq and cytometry by time-of-flight (CyTOF), revealed the heterogeneity of CD8⁺ T cell subsets by identifying a wide spectrum of phenotypes and functions within atherosclerotic plaques^{16,17}. Although the phenotypes of CD8⁺ T cells in atherosclerosis have been defined, the causative role of these cells in the development of atherosclerosis requires further investigation.

Patients with coronary artery disease (CAD) have higher numbers of cytotoxic CD8⁺ T cells in the blood than healthy individuals¹⁸. CD8⁺ T cells are also abundant in atherosclerotic plaques from both humans and mice^{13,16,19–24}. Single-cell RNA-seq and CyTOF studies report that CD8⁺ T cells account for 31–41% of all T cells in the plaques of mouse models of atherosclerosis, and 50% of T cells in human plaques¹⁶. Of note, in humans, femoral artery atherosclerotic plaques seem to have lower CD8⁺ T cell numbers than carotid artery atherosclerotic plaques²⁴. These findings warrant further research into how plaque location in the body can influence CD8⁺ T cell localization and phenotype (Fig. 1).

During atherogenesis, CD8⁺ T cells infiltrate early intimal lesions and become enriched in the intima and adventitia, with fewer numbers in the media^{25,26}. An analysis of plaque CD8⁺ T cell numbers at various stages of atherosclerosis found that CD8⁺ T cells accounted for 29% of all plaque CD45⁺ leukocytes in early-stage lesions, to 37% in atheroma lesions, and to 50% in fibroatheroma and complicated lesions²⁷. This finding suggests that the percentage of CD8⁺ T cells increases with atherosclerotic plaque progression²⁷. In advanced atherosclerotic lesions, CD8⁺ T cells outnumber CD4⁺ T cells, and are mainly located in fibrous cap area¹⁸, the plaque shoulder and around the necrotic core¹⁸. CD8⁺ T cells are also found in artery tertiary lymphoid organs (ATLOs)^{26,28}.

CD8⁺ T cell subsets

A study using CyTOF comprehensively described the heterogeneity of CD8⁺ T cells in human carotid artery atherosclerotic plaques, including

Box 1 | CD8⁺ T cells

The immune system is classified into two subsystems: innate and adaptive immunity. Adaptive immunity is a highly specific, antigen-based immune response mediated by T cells and B cells. T cells are further divided into CD4⁺ T helper cells, CD8⁺ cytotoxic T cells, $\gamma\delta$ T cells and natural killer T cells. T cells originate in the thymus, where bone marrow progenitors differentiate into CD4⁺CD8⁻ T cells and then into either $\alpha\beta$ ⁺ or $\gamma\delta$ ⁺ T cells. $\alpha\beta$ T cells develop into CD4⁺CD8⁻ T cells and further mature into either CD4⁺ T helper cells or CD8⁺ cytotoxic T cells. During thymic development, T cells undergo positive and negative selection to ensure tolerance against self-antigens and the ability to recognize foreign and pathogenic antigens presented by major histocompatibility complex (MHC) class I molecules on cells²³⁴.

After maturation, naive CD8⁺ T cells circulate through secondary lymphoid organs, such as lymph nodes and the spleen, where they reside until they encounter their specific antigen. Antigen recognition occurs when CD8⁺ T cells interact with antigen-presenting cells that display peptide–MHC class I complexes. This interaction is stabilized by the CD8 co-receptor, which enhances T cell receptor (TCR) signalling^{235,236}. After antigen recognition, CD8⁺ T cells become activated, proliferate and differentiate into different subsets^{218,237,238}.

CD8⁺ T cell subsets

Naive T (T_N) cells. characterized by CD45RA⁺ and CCR7⁺ expression; antigen-inexperienced cells that circulate through lymphoid organs and serve as the foundational cell population for adaptive immune responses^{218,237–239}.

Central memory T (T_{CM}) cells. defined by CD45RO⁺, CCR7⁺ and CD62L⁺ markers, and have strong proliferative potential and lymph node homing ability, forming a key reservoir for durable immunity^{218,237–239}.

Effector memory T (T_{EM}) cells. distinguished by a CD45RO⁺CCR7⁻CD62L⁻ phenotype; rapidly exert cytotoxic functions and migrate to peripheral tissues during infection^{218,237–239}.

Stem cell memory T (T_{SCM}) cells. express CD45RA, CCR7, CD95 (also known as FAS) and CD122 (also known as IL-2R β), are long-lived, have self-renewal capacity and can differentiate into T_{CM} and T_{EM} cells^{218,237–239}.

Terminally differentiated effector memory T (T_{EMRA}) cells. re-express CD45RA and downregulate CCR7, CD27 and CD28, and represent terminally differentiated CD8⁺ T cells with potent cytotoxicity but limited proliferative capacity^{218,237–239}.

Tissue-resident memory T (T_{RM}) cells. often marked by CD69⁺ and CD103⁺ expression; remain permanently in non-lymphoid tissues to provide localized protection against reinfection^{218,237–239}.

Effector T (T_{EFF}) cells. include KLRG1⁺CD127⁻ short-lived effector cells; arise during acute infections and execute immediate cytotoxic functions by releasing perforin and granzymes to compromise the integrity of the target cell membrane by forming membrane pores and inducing apoptosis. CD8⁺ T_{EFF} cells also produce cytokines to mobilize immune cells. Following antigen clearance, most CD8⁺ T_{EFF} cells undergo apoptosis, which is crucial for maintaining immune homeostasis. However, a subset of cells differentiates into long-lived memory T cells (T_{CM} and T_{SCM}), which provide rapid and robust responses upon re-exposure to the same antigen. These memory T cells can reside in peripheral tissues or circulate in the bloodstream, ensuring long-term immunity^{218,237,238}.

Exhausted CD8⁺ T cells. arise during chronic infections or cancer, and, compared with functional CD8⁺ T cells, show sustained expression of inhibitory receptors (such as programmed cell death protein 1 (PD1) and metalloproteinase inhibitor 3), reduced cytokine production and impaired cytotoxicity, representing a distinct differentiation state that impairs the control of the immune response^{218,237,238}.

CD8⁺ regulatory T (T_{reg}) cells. such as the CD122^{high}LY49⁺ subset; suppress immune responses via perforin-dependent and FAS ligand (FASL)-dependent mechanisms, help to maintain immune tolerance and are crucial for controlling germinal centre reactions and autoimmunity, even though they do not express FOXP3, like CD4⁺ T_{reg} cells^{240,241}.

CD8⁺ T cell tolerance

The breakdown of central and peripheral tolerance contributes to atherosclerosis²³⁴. Central and peripheral tolerance is a complex regulatory state that prevents autoimmunity but also limits antitumour immunity. Self-reactive CD8⁺ T cells that escape thymic deletion diverge early from effector cell differentiation, acquiring unique transcriptional and epigenetic profiles characterized by impaired TCR signalling, defective protein translation and reduced proliferative capacity^{231,242,243}. Studies in transgenic mice reveal that repeated antigen exposure — whether from self or foreign peptides — induces a tolerant state marked by suboptimal calcium mobilization, diminished CD25 upregulation and increased sensitivity to cell death^{244,245}. This state is further enforced by checkpoint receptors such as PD1, which curb full effector differentiation to prevent tissue damage, as seen in skin models, where PD1 maintains local tolerance despite the presence of antigen-specific CD8⁺ T cells. Conversely, strong inflammatory cues combined with robust TCR engagement can break tolerance by boosting MYC proto-oncogene protein expression and restoring effective protein synthesis, thereby reactivating antitumour responses^{242,243}. This intricate balance underscores the challenges and opportunities in modulating peripheral tolerance for improved immunotherapeutic strategies.

naive T (T_N) cells, terminally differentiated effector memory T (T_{EMRA}) cells and effector memory T (T_{EM}) cells, which were the main CD8⁺ T cell subset¹⁹ (Box 1). Several studies have also assessed CD8⁺ T cell subsets in peripheral blood in patients with atherosclerotic CVD. Patients with

acute coronary syndrome have decreased numbers of CD8⁺ T_N cells and expanded T_{EM} subsets in peripheral blood compared with patients with stable CAD^{29,30}. CD8⁺ T_N counts inversely correlate with Gensini scores (an angiography-based scoring system that assesses the severity

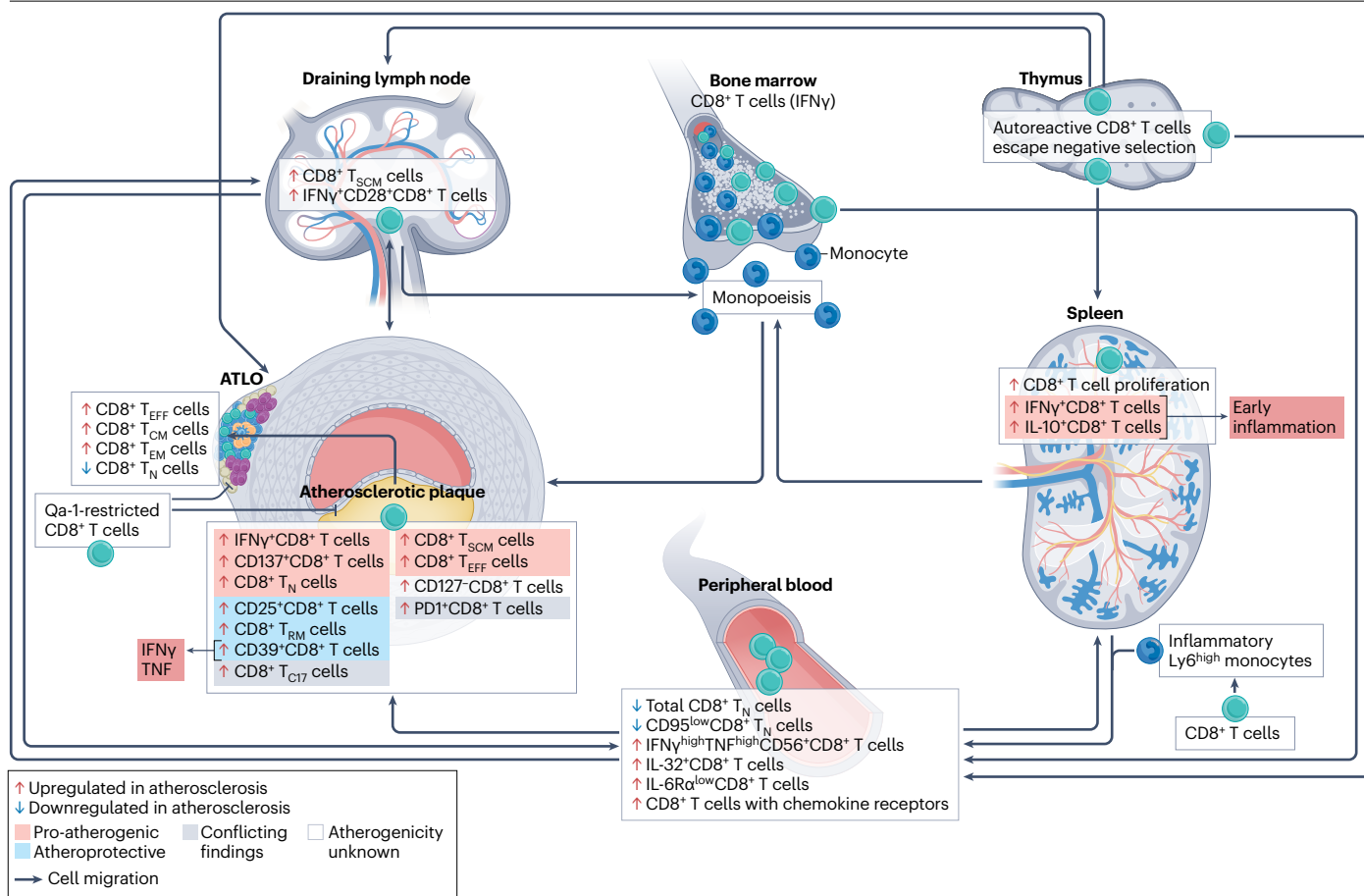


Fig. 1 | CD8⁺ T cell subsets and their migration, enrichment and role in atherosclerosis. The changes in and functions of CD8⁺ T cell subsets in atherosclerosis. CD8⁺ T cells migrate systemically⁹⁸. Autoreactive CD8⁺ T cells might escape negative selection in thymus and enter the peripheral blood circulation^{231–233}. In blood, the number of naive CD8⁺ T cells decreases whereas the number of CD8⁺ T cells expressing activation markers, chemokine receptors and inflammatory cytokines increases. In the spleen, proliferation of CD8⁺ T cells expressing interferon- γ (IFN γ) and IL-10 occurs, causing early systemic inflammation^{78,116}. CD8⁺ T cells can also promote monopoiesis in the bone marrow, leading to an increase in monocyte recruitment to atherosclerotic plaques^{8,96}. In the atherosclerotic plaque, there is an enrichment of CD8⁺ stem cell memory T (T_{SCM}) cells, resident memory T (T_{RM}) cells, effector T (T_{EFF}) cells,

naive T (T_N) cells and T_{CR17} cells, along with CD8⁺ T cells expressing IFN γ , CD137, CD25, programmed cell death protein 1 (PD1) and/or CD39, compared with steady-state conditions. CD8⁺ T cells expressing CD28 and/or CD25 are atheroprotective^{57,109}, whereas CD8⁺ T cells expressing IFN γ and/or CD137, as well as T_N cells, are atherogenic. In draining lymph nodes, CD8⁺ T cells expressing CD28 and IFN γ are enriched in atherosclerosis compared with healthy conditions¹¹⁶. In advanced atherosclerosis, artery tertiary lymphoid organs (ATLOs) form and exhibit increased numbers of CD8⁺ central memory T (T_{CM}), effector memory T (T_{EM}) and T_{EFF} cells, and reduced numbers of CD8⁺ T_N cells compared with early-stage lesions lacking ATLOs. Qa-1 restricted CD8⁺ T cells in ATLOs protect against atherosclerosis¹¹⁰. TNF, tumour necrosis factor; IFN γ , Interferon- γ ; IL-10, interleukin-10.

of CAD), suggesting increased CD8⁺ T cell differentiation or migration to lymphoid or lesion sites with increased disease severity^{31–33}. Individuals with a high risk of CAD (Gensini >30) had elevated numbers of CD8⁺ stem cell memory T (T_{SCM}) cells (CD95⁺CD45RA⁺CCR7⁺) in blood due to the loss of CD8⁺ T_N cells (CD95^{low}CD45RA⁺CCR7⁺) from the blood compartment³³. The elevated levels of T_{SCM} cells correlated positively with the risk of CVD in these individuals, and these cells were pro-atherogenic and an indicator of advanced atherosclerosis in mouse models³³. The proportion of CD8⁺ T_{SCM} cells was sevenfold higher in blood and twofold higher in draining lymph nodes in *Apoe*^{-/-} mice than in wild-type mice, and 1.7-fold higher in aortas from *Apoe*^{-/-} mice fed a Western diet than in aortas from *Apoe*^{-/-} mice fed a normal diet³³. Of note, adoptive transfer of CD8⁺ T_{SCM} cells into T cell-deficient *Apoe*^{-/-} mice

aggravated atherosclerosis³³. T_{EM} and T_{EMRA} cell subsets were also found to be enriched among circulating CD8⁺ T cells in patients with more severe CAD compared with patients with less severe CAD²⁹.

In humans, the proportion of CD8⁺ T cells with a memory or activated phenotype is larger in atherosclerotic plaques than in the blood³⁴. A single-cell RNA-seq analysis of human atherosclerotic plaques found three distinct CD8⁺ T cell clusters: T_{EM} and T_{EMRA} subsets and a quiescent, central memory T (T_{CM}) subset³⁵. Another study also reported the presence of CD69⁺CD8⁺ T cells and CD45RO⁺CD27⁺CD8⁺ T_{EM} cells in human atherosclerotic plaques³⁶. Most CD8⁺ T cells in human atherosclerotic plaques express the CD45RO isoform of CD45 (which is an activation marker) and α 1 β 1 integrin (also known as VLA-1)³⁷. CD45RO is classically associated with memory T cells, whereas α 1 β 1 integrin is often

upregulated on activated T cells undergoing tissue infiltration³⁷. Genes such as *CD8A*, *CD8B*, *NKG7* and *GZMK* are differentially expressed in CD8⁺ T cells¹⁶. Furthermore, the costimulatory molecule CD137 (also known as 4-1BB ligand receptor) was found to be expressed by activated T cells in human atherosclerotic plaques in a T cell receptor (TCR)-independent manner, suggesting a role for chronic inflammation in the activation of T cells in this setting^{38,39}. Another study in patients with atherosclerosis found more CD25⁺CD8⁺ T cells and HLA-DR⁺CD8⁺ T cells in plaques compared with blood³⁴.

In *Apoe*^{-/-} mice and aged wild-type control mice, CD8⁺ T cells were associated with increased expression of programmed cell death protein 1 (PD1; also known as CD279, and encoded by *PDCDI*), CD69 and CXCR3, and decreased expression of CD103 (also known as α_E integrin, and encoded by *ITGAE*) compared with wild-type young mice²¹. In mice, a higher percentage of CD8⁺ T_{EM} and effector T (T_{EFF}) cells is found in atherosclerotic plaques and ATLOs compared with secondary lymphoid organs and the spleen^{40–42}. Several studies have reported the presence of classic CD8⁺ tissue-resident memory T (T_{RM}) cells in atherosclerotic plaques, characterized by the expression of CD69, CD103, HOBIT (also known as ZNF683), α_1 integrin (also known as CD49a), granzyme K (GZMK) and protein NKG7 (refs. 19,22,43) (Table 1).

Single-cell RNA-seq of peripheral blood mononuclear cells (PBMCs) from female patients with human immunodeficiency virus (HIV) infection with or without carotid artery atherosclerotic lesions showed that RUNX transcription factor expression in PBMCs was lower in the patients with atherosclerotic lesions⁴⁴. Of note, among patients with atherosclerosis, RUNX expression was higher among those receiving cholesterol-lowering agents⁴⁴. RUNX transcription factor expression is known to suppress CD4 expression in CD8⁺ T cells and is required for lineage determination in T cells⁴⁵. A meta-analysis of single-cell RNA-seq and CyTOF data from mouse aortas revealed the presence of CD4⁺CD8⁺ T cells expressing *Sox4* in healthy and atherosclerotic aortas, which probably represent immature T cells⁴⁶. Furthermore, another study found that patients with HIV infection and subclinical atherosclerosis had a higher number of CD4⁺CD8⁺ double-positive T cells in blood than patients with HIV infection without atherosclerosis⁴⁷. Double-positive CD4⁺CD8⁺ $\alpha\beta$ ⁺ T cells have also been reported in the thymus, mediastinal adipose tissue and aortic adventitia of healthy and atherosclerotic mice⁴⁸. Peripheral CD4⁺CD8⁺ T cells have long been reported in humans in several autoimmune diseases such as rheumatoid arthritis as well as in viral infections and cancer^{49–51}. Single-cell RNA-seq of CD8⁺ T cells from PBMCs from patients with CAD revealed the presence of mucosal-associated invariant T (MAIT)-like cells in addition to T_{NV}, T_{EM} and T_{EMRA} clusters²⁹. Interestingly, MAIT cells are atheroprotective through their capacity to clear VLDLs⁵². The role of other non-conventional CD8⁺ T cells in atherosclerosis, such as MAIT, CD8⁺ $\gamma\delta$ T cells and CD8⁺ invariant natural killer (NK) T cells, has been discussed previously^{53–55}. Overall, both human and mouse studies show that aged or advanced atherosclerotic plaques contain CD8⁺ T cells with high exhaustion, cytotoxicity and senescence characteristics (Fig. 1).

Exhausted CD8⁺ T cells. CD8⁺ T cells are abundant in atherosclerotic plaques, where TCR engagement and clonal expansion suggest that a subset of these cells acquires an exhaustion phenotype. The inhibitory receptors PD1 and T cell immunoglobulin mucin receptor 3 (TIM3; also known as HAVCR2), which are key regulators of CD8⁺ T cell activation, are expressed in blood-derived CD8⁺ T cells from patients

with atherosclerosis, and these cells also show reduced production of effector cytokines (interferon- γ (IFN γ) and tumour necrosis factor (TNF)), indicating functional exhaustion⁵⁶. Similar T cell exhaustion features were present in plaque cells from patients with symptomatic atherosclerotic CVD, suggesting that CD8⁺ T cells gradually transition to an exhausted state under chronic inflammation¹⁹.

In *Apoe*^{-/-} mice, plaque-resident CD8⁺ T cells produce less IFN γ and TNF compared with spleen CD8⁺ T cells⁵⁷. However, this phenotype of plaque CD8⁺ T cells was associated with elevated CD39 expression rather than with expression of classical markers of exhaustion, such as PD1, TIM3 and lymphocyte activation gene 3 protein (LAG3)⁵⁷. CD39 is an immunosuppressive ectonucleotidase linked to cell exhaustion, and is highly upregulated in CD8⁺ T cells from human plaques versus CD8⁺ T cells from matched blood, driven by sustained TCR signalling⁵⁸. Even CD8⁺ T_N cells from patients with acute coronary syndrome have reduced IL-2 and increased PD1 expression compared those from patients with stable CAD, probably due to exposure to oxidized LDL³⁰.

CD8⁺ T cell migration in atherosclerosis

In an in vitro assay using human artery tissue, CD8⁺ T cells activated with TNF, IFN γ and phytohaemagglutinin infiltrated healthy or mildly atherosclerotic intima tissue samples, whereas control CD8⁺ T cells only infiltrated advanced lesion samples²⁷. However, the chemokines involved in this process were not explored. In addition, activated CD8⁺ T cells migrated more efficiently into the adventitia compared with control CD8⁺ T cells²⁷. Another study in humans found that CD69, CX3CR1, CC-chemokine receptor type 5 (CCR5) and CCR7 were differentially expressed in a CD45RO⁺ subset of CD8⁺ T cells in blood versus CD45RO⁺CD8⁺ T cells in plaques³⁶. Consequently, the infiltration of CD8⁺ T cells into human atherosclerotic plaques was found to be primarily supported by the CCR5–CC-motif chemokine 3 (CCL3) and CX3CR1–CX3CL1 (also known as fractalkine) axes³⁶. Among the CCR5 ligands, CCL4 and CCL5 were found in atherosclerotic plaques and thus might also support T cell migration in the plaque along with CCL3³⁶. Interestingly, a study using a combined protein and transcript single-cell RNA-seq approach found that among patients with HIV infection and CVD, those who were taking cholesterol-lowering medications had reduced numbers of CXCR3⁺CD8⁺ T cells in PBMCs compared with those who were not⁴⁴.

The chemokine CCL18 has also been found in human atherosclerotic plaques⁵⁹. In *Apoe*^{-/-} mice and mice overexpressing a PCSK9 (both models fed a high-fat diet), administration of CCL18 increased plaque burden accompanied by greater fibrosis, reduced macrophage content, increased T cell infiltration, and higher numbers of activated T cells in a CCR6-dependent manner⁵⁹. However, the CCL18-dependent increase in CD8⁺ T cell recruitment was shown in a model of ear inflammation with intradermal CCL18 injections rather than in atherosclerotic plaques. Nevertheless, the CCL18–CCR6 axis could have a role in CD8⁺ T cell recruitment to plaques⁵⁹, given that CCR6 is expressed on CD8⁺ T cells, especially in T_{EM} subsets, and often co-expressed with CCR5⁶⁰. Indeed, upregulation of CCR5, CXCR6 and CXCR3 in CD8⁺ T cells has been observed in ageing and in atherosclerosis in humans, and in aged mice was shown to favour an increase in the infiltration of CD8⁺ memory T cells, especially CD8⁺ T_{EM} cells, into the plaque²¹. CD8⁺ T cells in human carotid artery plaques were also found to express CCL5, suggesting that CD8⁺ T cells in plaques contribute to further recruitment of other immune cells, including other T cell subtypes²². Furthermore, plaque CD8⁺ T cells from patients with symptomatic atherosclerotic CVD expressed higher levels of CCL5, whereas plaque CD8⁺ T cells from

Table 1 | CD8⁺ T cell subsets and clusters present in human atherosclerotic plaques

CD8 ⁺ T cell subset	Gene and protein markers	Relevance in atherosclerosis	Species; model	Technique	Refs.
Naive T (T _N) cells	CCR7 ⁺ , CD45RA ⁺	Found in atherosclerotic plaques and blood; decreased numbers in blood negatively correlate with Gensini score	PBMCs from patients with coronary artery disease	scRNA-seq, CyTOF, flow cytometry	19,29,32,33
	CD95 ^{low}	Numbers in blood decrease in atherosclerosis; levels in blood inversely correlate with risk of CVD	PBMCs	CytoF	33
Central memory T (T _{CM}) cells	<i>LEF1</i> , <i>SELL</i> (which encodes CD62L), <i>IL7R</i> (which encodes CD127), <i>LTB</i>	NI	Human carotid artery plaques	scRNA-seq	35
Effector T (T _{EFF}) cells	HLA-DR ^{low}	NI	PBMCs from control individuals and patients with coronary artery atherosclerosis	CytoF	31
Effector memory T (T _{EM}) cells	CD69 ⁺ , CCR5 ⁺ , PD1 ^{int} , CD127 ⁻ , HLA-DR ⁺ , CD38 ⁺ , CD26 ⁻ , CD27 ⁻ , CCR7 ⁻	Clonal expansion in atherosclerotic plaques	PBMCs and atherosclerotic plaques	scRNA-seq, CyTOF	19
	<i>GZMK</i> , <i>GZMA</i> , <i>CD69</i>	Recent TCR stimulation	Carotid artery plaques	scRNA-seq	35
	CD45RO ⁺ , CD27 ⁻	Enriched in plaques compared with blood	Blood and atherosclerotic plaques	Flow cytometry	36
	HLA-DR and PD1 decreased compared with control individuals	NI	PBMCs from control individuals and patients with coronary artery atherosclerosis	CytoF	31
	<i>LMNA</i> , <i>MCL1</i> , <i>CXCR3</i> , activation-related genes (<i>CD44</i> , <i>FOS</i> and <i>KLF6</i>)	T cells that cause chronic inflammation in plaques	Carotid artery plaques and blood from patients with cancer	scRNA-seq	154
Terminally differentiated effector memory T (T _{EMRA}) cells	<i>GZMB</i> , <i>TBX21</i> (which encodes T-bet), <i>NKG7</i> , <i>GNLY</i> , <i>ZNF683</i> (which encodes Zinc finger protein 683; also known as HOBIT), <i>CX3CR1</i> ; lack <i>CD69</i> expression	NI	Carotid artery plaques	scRNA-seq	35
Resident memory T (T _{RM}) cells	CD69 ⁺	Recent TCR stimulation	Blood and atherosclerotic plaques	Flow cytometry	36
	<i>ZNF683</i> , <i>RUNX3</i>	NI	Carotid artery plaques and blood from patients with cancer	scRNA-seq	154
	CD103 ⁺ , HOBIT ⁺ , CD103 ⁺ GZMK ⁺ , NKG7 ⁺	NI	Carotid artery plaques	scRNA-seq and CITE-seq	22
	CD69 ⁺ and/or CD103 ⁺	Enriched in plaques compared with blood	Atherosclerotic plaques	CytoF	19
	<i>GZMK</i> , <i>ZNF683</i> , <i>CD69</i> , <i>ITGA1</i> (which encodes α1 integrin; also known as CD49a), <i>ITGAE</i> (which encodes CD103)	Decreased intralésional macrophage numbers and increased collagen content in the plaque	Carotid artery plaques	scRNA-seq	43
Stem cell memory T (T _{SCM}) cells	CD95 ⁺ , CCR7 ⁺ , CD45RA ⁺	Increased numbers in blood in atherosclerosis; positively correlate with risk of CVD	PBMCs	CytoF	33
Exhausted T cells	PD1 ⁺ , TIM3 ⁺	Reduced IFN γ and TNF production and increased IL-10 production compared with T cell subsets	Arterial blood mononuclear cells and PBMCs from healthy individuals and patients with atherosclerosis	Flow cytometry	56
Other subsets	CD28 ⁻	Increased in PBMCs from patients with atherosclerosis compared with individuals without atherosclerosis; independent risk factor for the development of atherosclerosis in patients with HIV infection	PBMCs from patients with HIV infection	Flow cytometry	47
	<i>JUNB</i> , <i>LCK</i> , <i>IL32</i>	Increased numbers in blood in atherosclerosis and reduced numbers after cholesterol-lowering treatment	PBMCs from female patients with HIV infection with or without carotid artery atherosclerotic lesions	Combined protein and transcript-based scRNA-seq	44

Table 1 (continued) | CD8⁺ T cell subsets and clusters present in human atherosclerotic plaques

CD8 ⁺ T cell subset	Gene and protein markers	Relevance in atherosclerosis	Species; model	Technique	Refs.
Other subsets (continued)	Genes encoding pro-inflammatory cytokines (<i>TNF</i> and <i>IFNG</i>) or involved in T cell activation (<i>CD69</i> , <i>JUN</i> , <i>FOS</i>), or mitochondria-related metabolic programming (<i>MT-ND2</i> , <i>MT-CO1</i> , <i>MT-ND6</i>)	Pro-inflammatory phenotype in atherosclerotic plaques	Carotid artery plaques and blood from patients with cancer	scRNA-seq	154
	PD1 ⁺ ; increased CD28 and ICOS; activation molecules HLA-DR, CD27 and CD38	PD1 ⁺ cells in plaque do not resemble exhausted CD8 ⁺ T cells in cancer	Carotid artery plaques and blood from patients with cancer	scRNA-seq, CyTOF	154
	CD39 ⁺	Reduced cytokine production (IFN γ and TNF) in plaques compared with CD39 ⁺ T cell subset	Carotid artery plaques and blood	Flow cytometry	57

CCR, CC-chemokine receptor; CITE-seq, cellular indexing of transcriptomes and epitopes sequencing; CVD, cardiovascular disease; CyTOF, cytometry by time-of-flight; GZMK, granzyme K; HIV, human immunodeficiency virus; ICOS, inducible T cell costimulatory; IFN γ , interferon- γ ; NI: not investigated; PBMC, peripheral blood mononuclear cell; PD1, programmed cell death protein 1; scRNA-seq, single-cell RNA sequencing; TCR, T cell receptor; TIM3, T cell immunoglobulin mucin receptor 3 (also known as HAVCR2); TNF, tumour necrosis factor.

patients with asymptomatic atherosclerotic CVD expressed higher levels of CCL3 and CCL4²².

In a study of human carotid atherosclerotic plaques, CD8⁺ T cells infiltrating the plaque were enriched near intraplaque neovessels, mediated by the activation of CXCR4 signalling in CD8⁺ T cells by CXCL12 derived from neovessels that had expression of atypical chemokine receptor 1 (ACKR1)⁶¹. In mice, endothelial cell-derived CXCL12 is known to drive atherosclerosis via CXCR4 interaction⁶², and another CXCL12 receptor on vascular endothelial cells, ACKR3, has also been shown to potentiate atherosclerosis via increased immune cell recruitment and inflammatory signalling⁶³. Interestingly, ACKR3 was found to be expressed in a small percentage of blood CD8⁺ T cells from healthy donors, its expression was higher in naive T cells than in memory CD8⁺ T subsets, and was shown to aid T cell migration through CXCL12 signalling⁶⁴. However, the role of ACKR3 in atherosclerosis-related lymphocyte migration is yet to be explored.

CD69 is a marker of CD8⁺ T_{RM} cells in atherosclerotic plaques and supports T cell retention within tissues. CD69 facilitates the internalization and degradation of sphingosine-1-phosphate receptor 1 (S1PR1), leading to the loss of the T cell's ability to sense the S1P gradient and egress the tissue^{36,65}. A single-cell RNA-seq and single-cell TCR-seq study in an *Apoe*^{-/-} mouse model of advanced atherosclerosis and ageing found that expanded T_{EFF} and memory T cell subsets from aorta-draining renal lymph nodes and ATLOs exhibited reduced egress-related gene expression (*Ccr7*, *Sell* (which encodes L-selectin; also known as CD62L) and *S1pr1*) compared with non-expanded T_{EFF} and memory T cell subsets in the renal lymph nodes of wild-type mice⁴¹. In addition, plaque-resident CD8⁺ T_{EFF} and memory T cell subsets, regardless of expansion status, show pronounced decreases in the expression of egress-related genes and increases in the expression of genes related to activation and migration (*Gzmk*, *Nkg7*, *Ccl5*, *S100a4*, *S100a6* and *Ctsu*)⁴¹. This expression pattern was also observed in human plaque CD8⁺ T_{EFF} and memory T cells⁴¹.

Antigen-specificity versus bystander effect

The data described in the previous sections, along with the CD8⁺ T cell subset data summarized in Table 1, support the hypothesis that CD8⁺ T cells undergo antigen stimulation and clonal expansion in atherosclerotic plaques and ATLOs, leading to enrichment of activated CD8⁺ T cells with an T_{EFF} and T_{EM} phenotype in the plaque. However, the atherosclerosis-relevant major histocompatibility complex (MHC)

class I (MHC-I)-restricted epitopes that activate the CD8⁺ T cells remain unknown.

Antigens associated with atherosclerosis

Apolipoprotein B (APOB) is the backbone protein component in all atherogenic lipoproteins and exists in two main forms: APOB-48 and APOB-100 (ref. 66). In patients with established CAD, elevated levels of IgG autoantibodies against native APOB-100 peptides have been associated with slower progression of CAD and a lower risk of myocardial infarction, suggesting a protective role for these antibodies against CVD⁶⁷. The APOB-100 peptide fragments p45 and p210 have been linked to atherosclerosis in mice⁶⁸. In vitro stimulation of PBMCs from patients with acute coronary syndrome with the APOB-100-p210 peptide led to an increase in CD8⁺ T_{EFF} and T_{EM} phenotypes, suggesting the presence of antigen-experienced CD8⁺ T cells in the blood of these patients with atherosclerosis⁶⁹.

Other self-antigens involved in atherosclerosis include heat shock protein 27 (HSP27), HSP60, β 2-glycoprotein 1, cardiolipin and APOA1 (refs. 70–72). In addition, the endoplasmic reticulum chaperone BIP (also known as GRP78, a marker of endoplasmic reticulum stress) and mitochondrial δ 1-pyrroline-5-carboxylate dehydrogenase have also been identified as autoantigens in atherosclerosis in both humans and mice^{67,73}. The discovery of these peptides opens new avenues for the detection and assessment of antigen-specific T cells in atherosclerosis, as well as for the development of peptide immunization approaches.

Mouse models of atherosclerosis. *Apoe*^{-/-} mice expressing the bacterial transgene β -galactosidase in vascular smooth muscle cells (VSMCs) developed robust CD8⁺ T cell responses after immunization with dendritic cells presenting a β -galactosidase-derived immunogenic peptide, resulting in larger atherosclerotic lesions compared with *Apoe*^{-/-} control mice⁷⁴. Certain circulating CD8⁺ T cells might also be specific to HSP60 and produce IFN γ ^{75–77}. The APOB-100-p210 peptide has been shown to bind to the chimeric MHC-I allele HLA-A*02:01/Kb in *Apoe*^{-/-} mice⁶⁹. MHC-I pentamer staining showed that the number of p210-reactive CD8⁺ T cells increased after 6 weeks of high-fat diet and then plateaued⁶⁹. These cells positively correlated with an increase in aortic plaque size and were detectable in the mouse aortas⁶⁹. Consistent with in vivo data⁶⁹, in vitro stimulation of CD8⁺ T cells from mouse spleens with APOB-100-p210 led to an increase in the proportion of T_{EM} cells and a decrease in T_{CM} cells⁷⁸, in addition to an increase in

IFN γ ⁺CD8⁺ and IL-10⁺CD8⁺ T cells⁷⁸. Furthermore, in male *ApoE*^{-/-} mice, immunization with APOB-100-p210 reduced atherosclerosis by approximately 50%, along with reductions in the number of dendritic cells, macrophages and CD8⁺ T cells in aortic sinus plaques⁶⁹. One week after the primary immunization, the proportion of CD62L⁺CD8⁺ T cells and CD25⁺IL-10⁺CD8⁺ T cells in the spleen was increased compared with the control groups⁶⁹. However, these changes were not apparent in mice after booster doses and the initiation of high-fat diet⁶⁹. In addition, in an in vitro assay of T cell proliferation after stimulation with APOB-100-p210, CD8⁺ T cells isolated from wild-type mice immunized with APOB-100-p210 showed higher proliferation rates than CD8⁺ T cells from wild-type controls⁷⁹. CD25⁺CD8⁺ T cells from mice immunized with APOB-100-p210 had increased lytic activity against dendritic cells from syngeneic *ApoE*^{-/-} mice, and this lytic activity was antigen specific⁷⁹. Further studies showed that in *ApoE*^{-/-} mice with angiotensin II stimulation, APOB-100-p210 immunization increased the lytic activity of CD8⁺ T cells against macrophages^{80,81}. These data indicate that epitope-specific vaccination can reprogramme CD8⁺ T cells to adopt both regulatory and cytotoxic roles, disrupting antigen presentation and effector cell recruitment to the vessel wall, thereby substantially limiting atherosclerotic lesion development.

A study using paired single-cell RNA-seq and TCR profiling in *ApoE*^{-/-} mice showed that memory CD8⁺ T cells were enriched in atherosclerotic plaques and ATLOs compared with in secondary lymphoid organs⁴¹. Analysis of tissue-specific TCR $\alpha\beta$ maps revealed that the percentage of clonally expanded CD8⁺ T cells was 2.7% in aorta-draining renal lymph nodes from wild-type mice, whereas in *ApoE*^{-/-} mice, the percentage of clonally expanded CD8⁺ T cells was 7.8% in renal lymph nodes, 14.7% in ATLOs and 36.0% in atherosclerotic plaques⁴¹. In addition, in the plaques of *ApoE*^{-/-} mice, approximately 61.1% of TCR α and 52.9% of TCR β in clonally expanded CD8⁺ T cells had identical amino acid sequences in the TCR complementarity-determining region 3 (CDR3) to those observed in clonally expanded CD8⁺ T cells in ATLOs and renal lymph nodes⁴¹. This finding suggests a shared clonal origin or antigen specificity among these T cells in different tissues⁴¹.

Human atherosclerotic plaques. Whether antigen presentation to T cells within or outside the plaque occurs remains an open question. A study published in 2023 that involved single-cell RNA-seq and TCR-seq of paired samples of human atherosclerotic plaques and PBMCs found clonal expansion of plaque CD8⁺ T cells⁸². However, where this expansion occurred is unknown. The study also identified CD8⁺ T cell clusters in the plaque that expressed genes related to cytotoxic and TCR activation, including *CD69*, *FOS* and *FOSB*, suggesting recent TCR engagement⁸². The atherosclerotic plaques also harboured a notable subset of CD127⁺CD8⁺ T cells, and these cells strongly expressed numerous markers of T cell activation and differentiation (HLA-DR^{high}, CD38^{high}, CD26^{low}, CD27^{low} and CCR7^{low})⁸². The proportion of these cells also positively correlated with TCR clonality, indicating clonal expansion⁸². Moreover, a separate study reported that although most of the CD127⁺CD8⁺ T cells are proliferative (Ki67⁺), a minor fraction had senescence-like features (CD57^{high}Ki67^{low})¹⁹, implying effects from chronic antigen stimulation. Of note, the 2023 study mentioned above found that CD8⁺ T cell clonal expansion was not restricted to plaques and was also observed in PBMCs⁸². This finding was corroborated by a single-cell RNA-seq study showing that CD8⁺ T cells from PBMCs from patients with severe CAD had increased expression of genes related to TCR signalling (*CD3E*, *ITGB2*, *JUNB* and *ZAP70*) and enrichment of cytotoxic and exhaustion pathways compared with

CD8⁺ T cells from patients with low CAD severity, further confirming the exposure of CD8⁺ T cells to antigens in patients with high CAD severity²⁹.

CD8⁺ T cell clonal expansion seems to vary depending on plaque stage. In a study of human atherosclerotic plaques, clonality was low in fatty streaks and in fibrocalcific plaques and increased in fibroatheroma and complex lesions⁸³. One CD8⁺ T cell cluster enriched in cytolytic and pro-inflammatory markers increased twofold during atherosclerosis progression from fatty streak lesions until the complex-lesion stage and then dwindled after plaque rupture⁸³. These findings raise several questions about the fate of clonally expanded CD8⁺ T cells after their function in fibroatheroma and complicated lesion stages.

In addition, studies assessing CD8⁺ T cells in humans and in mouse models show oligoclonal expansion of CD8⁺ T cells in atherosclerotic plaques^{83,84}, suggesting the presence of both self and foreign (viral) antigens in the plaque. Unstable atherosclerotic plaques in patients with carotid artery disease have been associated with CD8⁺ T cells specific for *Chlamydia pneumoniae*⁸⁵. Spatial transcriptomics analysis showed that the T cell gene signature was enriched at the most stenotic and proximal regions of the plaque, where plaque rupture occurs⁸⁶. Studies of human atherosclerotic plaques found that plaque CD8⁺ T cells were specific for Epstein–Barr virus, influenza, cytomegalovirus (CMV) and coronaviruses, with the highest clonotype prevalence in fibroatheroma^{82,83}. Moreover, these studies found a positive correlation between viral infections and atherosclerosis-related major adverse cardiovascular events^{82,83}. Virus-associated CD8⁺ T cells were more abundant, clonally expanded and tissue-enriched in atherosclerotic lesions compared with blood⁴³. Despite their activated phenotype, and similarly to other lesion-resident CD8⁺ T cells, these virus-associated CD8⁺ T cells probably do not undergo antigen-specific activation in the atherosclerotic lesion, in light of findings from human endarterectomy samples showing an absence of virus-derived peptides on HLA class I (HLA-I) complexes in the lesions⁴³.

These data suggest that the presence of virus-specific CD8⁺ T cells in the plaque might promote plaque instability via mechanisms such as molecular mimicry and bystander activation of other plaque T cells by the virus-specific CD8⁺ T cells. For example, the viral epitopes identified by Chowdhary and colleagues shared sequences found in genes expressed by VSMCs, vascular endothelial cells and cardiomyocytes⁸³. Given that CMV-specific CD8⁺ T cells are found in atherosclerotic plaques and that CMV infection is closely associated with atherosclerosis and major adverse cardiovascular events⁸⁷, a deeper dive into the mechanisms linking viral infections and immune regulation in atherosclerosis is needed. At present, the exact mechanism of antigen presentation to CD8⁺ T cells, the cellular specificity of both self and foreign antigens, and the CD8⁺ T cell response to the antigen presentation remain largely unknown in the context of atherosclerosis.

Antigen-independent mechanisms

In addition to antigen recognition, CD8⁺ T cells can also be activated in an antigen-independent (bystander) manner, mainly driven by pro-inflammatory cytokines including type I IFN, IL-12 and IL-18 (refs. 43,88). These activated CD8⁺ T cells can exert cytotoxic effects through NKG2D type II integral membrane protein (also known as CD314) and granzymes. The mechanisms regulating bystander activation have been reviewed previously^{88,89}.

Several virus-associated diseases that involve CD8⁺ T cell-mediated mechanisms but lack local viral antigen presentation, such as virus-induced neuropathology, rheumatoid arthritis and type 1

diabetes mellitus (T1DM), have been shown to involve bystander activation of CD8⁺ T cells^{88–90}. In a mouse model of virus-associated neuropathology induced by Zika virus infection, the severity of neurological disease correlated with the infiltration of bystander-activated NKG2D⁺CD8⁺ T cells into the brain but not with viral load in the brain, highlighting the potential role of these CD8⁺ T cells in disease progression⁹⁰. NKG2D-dependent mechanisms have been shown to be pro-atherogenic⁹¹ and associated with cerebral stroke⁹² and other inflammatory and autoimmune disorders⁹³. However, the NKG2D⁺CD8⁺ T cell subset or the role of bystander activation of CD8⁺ T cells in atherosclerotic plaques have yet to be explored. An analysis of human carotid artery atherosclerotic plaques identified two clusters of CD8⁺ T cells: CD3⁺ cells (characterized by expression of GZMK, NKG7, CD5, NKG2D and PD1) and CD8α⁺ cells (characterized by expression of HOBIT, CD103, NKG2D and β7 integrin)²², with CD8α⁺ cells suggesting the presence of a T_{RM} subset with bystander activation. Similarly, a single-cell RNA-seq study found upregulation of genes encoding cytotoxic proteins (*KLRC4*, *KLRK1* (which encodes NKG2D), *CTSW*, *GZMK*, *PRF1* (which encodes perforin 1) and *GZMB*) in CD8⁺ T cells from PBMCs from patients with high CAD severity compared with cells from patients with low CAD severity, suggesting that NKG2D-expressing cells, or potentially bystander CD8⁺ T cells, might have a role in CAD progression²⁹. In addition, among patients with HIV infection and CVD, those who were receiving cholesterol-lowering treatment had reduced expression levels of *KLRC4* and *KLRK1* (NKG2D) in circulating CD8⁺ T cells compared with those not receiving cholesterol-lowering treatment⁴⁴. This finding raises the question of whether NKG2D⁺CD8⁺ T cells are already within the atherosclerotic plaque and are activated by the pro-inflammatory conditions of the plaque, or whether these cells are recruited to the plaque in response to the inflammatory conditions of the plaque, or a combination of both scenarios.

Autoimmunity, immune checkpoints and CD8⁺ T cells atherosclerosis

CD8 T cells are increasingly recognized as key drivers of pathology across broad range of autoimmune diseases⁹⁴. Similarly, CD8 T cells could play a role in the autoimmune component atherosclerosis⁹⁵. Indeed, a single-cell TCR-seq study comparing carotid artery plaques and PBMCs from patients with atherosclerosis with synovial fluid and PBMCs from patients with psoriatic arthritis found overlapping CD8⁺ T cell populations between atherosclerosis samples (both carotid artery plaque tissue and PBMCs) and psoriatic arthritis synovial fluid⁷². The shared clonally expanded clusters expressed both effector-related genes (*CCLS*, *GZMH*, *GZMA*, *GZMK* and *NKG7*) and TCR activation markers (*FOS* and *JUN*). *GZMH* and *FOSB* were upregulated in CD8⁺ T cell subsets from plaques, whereas *ZNF683* (HOBIT) expression was elevated in CD8⁺ T cells in both plaque and synovial fluid⁸².

The checkpoint inhibitor-related proteins programmed cell death 1 ligand 1 (PDL1; encoded by *Cd274*) and galectin 3 (encoded by *Lgals3*) regulate T cell functions by interacting with PD1 and LAG3 on T cells. In *Apoe*^{-/-} mice, renal lymph nodes, ATLOs and plaques show tissue-specific and cell-subset-specific dysregulation of these genes in myeloid cells⁴¹. The most pronounced disruption occurred in plaques, suggesting compromised regulation of CD8⁺ T cell immunity, which can drive inflammation and the loss of immune tolerance in advanced atherosclerosis. In addition, in wild-type mice, plaque-resident CD8⁺ T_{EM} cells show increased interactions between PD1 and its ligands (including programmed cell death 1 ligand 2 (PDL2; also known as CD273 and encoded by *PDCD1LG2*), protein FAM3C and PDL1) compared with

CD8⁺ T_{EM} cells from renal lymph nodes⁴¹. The increased interaction between PD1 and its ligand raises the possibility that at least some plaque CD8⁺ T_{EM} cells are exhausted, further underlining the immune dysregulation and impaired functionality of CD8⁺ T cells in advanced atherosclerotic plaques⁴¹.

CD8⁺ T cell functions in atherosclerosis

Although the presence of CD8⁺ T cells positively correlates with atherosclerosis progression, the exact role of these cells in the initiation and progression of atherosclerosis is not fully understood. In addition, several studies provide contrasting evidence pertaining to the atheroprotective versus pro-atherogenic role of CD8⁺ T in a stage-dependent manner^{18,53,96–99} (Fig. 2). Furthermore, the pro-atherogenic versus an atheroprotective role of CD8⁺ T cells can also depend on their phenotype or subset. For example, in a mouse model of advanced atherosclerosis, CD8⁺ T_{C17} cells (which are characterized by the production of IL-17A) accumulate in atherosclerotic lesions but do not exacerbate disease¹⁰⁰. By contrast, undifferentiated T_N cells have been shown to promote lesion growth in mouse models of atherosclerosis, probably through differentiation to T-bet⁺IFNγ⁺ T_{C1} cells (CD8⁺ effector cells with a T helper 1-like cytokine profile and cytotoxic capacity)^{100,101} (Fig. 1). The Malmö Diet and Cancer study has linked elevated CD8⁺ T cell fractions in blood to reduced cytokine output from activated blood leukocytes and increased rates of coronary events and insulin resistance¹⁰². However, IFNγ⁺CD8⁺ T cells promote pro-inflammatory cytokine secretion from activated blood leukocytes, but the number of these cells in blood inversely correlated with the degree of carotid stenosis and glycated haemoglobin (HbA1c) levels, indicating functional heterogeneity among CD8⁺ T cell subsets in CVD¹⁰².

Atheroprotective functions

To investigate the role of CD8⁺ T cells in atherosclerosis, several studies used various in vivo models, including a humanized mouse model (HLA-A2 transgenic *H-2Db*^{-/-}*B2m*^{-/-}*Ldlr*^{-/-} mice) immunized with APOB-100 (ref. 14) or female *Apoe*^{-/-}*Cd8*^{-/-} mice fed a high-fat diet for 18 weeks and 1 year⁹. In these studies, no notable differences in atherosclerotic lesion size were observed between immunized and non-immunized mice in the humanized APOB-100 model, nor between *Apoe*^{-/-}*Cd8*^{-/-} mice and *Apoe*^{-/-} mice fed a high-fat diet, indicating that either induction or genetic deletion of CD8⁺ T cells did not substantially alter plaque development. However, in other studies whereby atherosclerotic *Apoe*^{-/-} or *Ldlr*^{-/-} mice were fed a high-fat diet for 6–8 weeks, depletion of CD8⁺ T cell with the use of monoclonal antibodies reduced atherosclerotic lesion size, plaque lipid content and macrophage accumulation in the plaques^{8,13}. To further define the role of effector cytokines and cytotoxic molecules secreted by CD8⁺ T cells, the investigators performed separate adoptive transfer experiments of wild-type, *TNF*^{-/-}, *Ifng*^{-/-}, *Prf1*^{-/-} or *Gzmb*^{-/-} CD8⁺ T cells in lymphocyte-deficient *Apoe*^{-/-} mice¹³. Only *Prf1*^{-/-} CD8⁺ T cells and *Gzmb*^{-/-} CD8⁺ T cells failed to induce cell death in atherosclerotic lesions compared with wild-type CD8⁺ T cells¹³. These data suggest that CD8⁺ T cells promote early atherosclerotic disease through the perforin 1–granzyme B axis. Indeed, *Gzmb*^{-/-}*Apoe*^{-/-} and *Prf1*^{-/-}*Apoe*^{-/-} mice showed reduced atherosclerotic plaque areas compared with their wild-type counterparts¹¹.

Another study used MHC-I-deficient mice (*B2m*^{-/-} mice on a C57BL/6 background), which lack CD8⁺ T cells, and reported increases in atherosclerotic lesion area compared with wild-type C57BL/6 mice¹⁰. By contrast, *Tap1* deletion in *Apoe*^{-/-} mice (which leads to severely reduced surface levels of MHC class I molecules and a marked

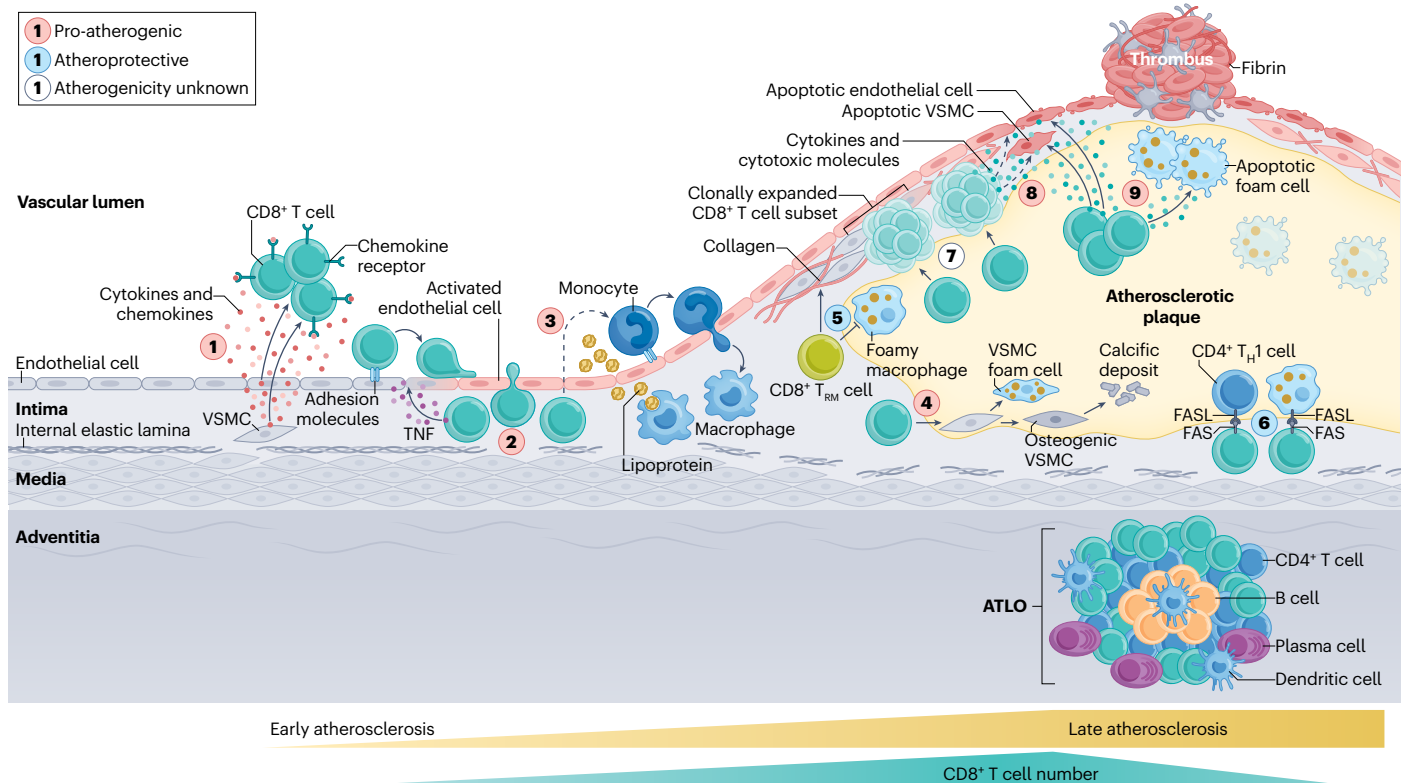


Fig. 2 | Role of CD8⁺ T cells in the different stages of atherosclerosis.

(1) Vascular endothelial cells and vascular smooth muscle cells (VSMCs) secrete IL-15, and vascular endothelial cells secrete chemokines and express integrins to promote binding and infiltration of CD8⁺ T cells^{120–122}. (2) CD8⁺ T cells secrete tumour necrosis factor (TNF) to activate endothelial cells and promote further infiltration of immune cells and lipids¹²⁰. (3) CD8⁺ T cells can indirectly increase monocyte production in bone marrow and aid in their recruitment to the atherosclerotic plaque^{8,96}. (4) CD8⁺ T cells potentiate the differentiation of VSMCs into foam cell-like cells and to an osteogenic phenotype, leading to plaque instability¹³². (5) Tissue-resident CD8⁺ resident memory T (T_{RM}) cells promote collagen deposition and restrict macrophage activation, thereby stabilizing the

plaque⁴³. (6) CD8⁺ T cells eliminate CD4⁺ T helper 1 (T_H1) cells and macrophages via FAS–FAS ligand (FASL) interaction, thereby promoting plaque stability¹¹⁵. (7) Oligoclonal expansion of CD8⁺ T cells into viral-specific and other expanded cell clones⁸³. (8) Some CD8⁺ T cell clones express cytotoxic molecules and inflammatory cytokines and have cross-reactivity against VSMCs and vascular endothelial cells^{82,83}. (9) Activated CD8⁺ T cells secrete interferon- γ (IFN γ), TNF, perforins and granzymes, leading to the elimination of VSMCs, endothelial cells and macrophages, thereby increasing plaque instability¹³. The number colours indicate whether the function of the CD8⁺ T cells is pro-atherogenic (red), atheroprotective (blue) or the atherogenicity is unknown (white). The dashed lines indicate proposed mechanisms. ATLO, artery tertiary lymphoid organ.

reduction in the pool of peripheral CD8⁺ T cells) did not alter atherosclerotic plaque formation¹². Both approaches disrupt the MHC-I antigen presentation pathway but lead to distinct outcomes. This discrepancy probably arises because *B2m*^{-/-} mice lack both classical and non-classical MHC-I molecules, whereas *Tap1*^{-/-} mice maintain non-classical MHC-I molecules, such as Qa-1 (refs. 103,104), but lack classical MHC-I molecules¹⁰⁵. Another research group assessed mice with knockout of *Cblb* (encoding E3 ubiquitin-protein ligase CBL-B), which have CD8⁺ T cells with increased IL-2 production and cytotoxicity (granzyme B production). This cytotoxicity leads to increased macrophage killing, thereby driving inflammation and atherosclerosis¹⁰⁶. These findings suggest that CD8⁺ T cells expressing CBL-B might not undergo excessive activation during atherogenesis, leading to reduced plaque inflammation¹⁰⁶. This notion confirms other study findings mentioned above demonstrating that adoptive transfer of CD8⁺ T cells from *Gzmb*^{-/-} mice did not induce cell death in atherosclerotic lesions compared with transfer of CD8⁺ T cells from wild-type mice¹³. Of note, however, the seemingly atheroprotective phenotype of CD8⁺ T cells in the

above-mentioned models could be a reflection of other confounding factors, such as compensatory mechanism(s) for the absence of one cell type, including effects on other immune cells such as CD4⁺ T cells¹⁰⁷.

The atheroprotective function of CD8⁺ T cells in advanced but asymptomatic plaques also could be attributed to CD8⁺ regulatory T (T_{reg}) cells⁹⁶. CD8⁺ suppressor subsets are characterized by the expression of cytotoxic T lymphocyte protein 4 (CTLA4), IL-10, IL-16, CD11c, transforming growth factor- β (TGF β), CD103, IL-2 receptor subunit- β (IL-2R β ; also known as CD122) and PD1 (ref. 96). CD8⁺ T_{reg} cells suppress T_{EFF} cells by capturing IL-2 via increased expression of IL-2R. In particular, IL-2R α (also known as CD25) has been linked to suppressor functions in both mice and humans, whereas CD122 expression is a marker of CD8⁺ T_{reg} cells in mice (and corresponds to the CXCR3⁺ CD8⁺ T cell subset in humans)¹⁰⁸. Of note, CD122⁺ CD8⁺ T cells have been shown to suppress colitis in mice¹⁰⁸. CD25⁺ CD8⁺ T_{reg} cells have also been shown to have reduced cytotoxic activity, and adoptive transfer of these cells blunted the development of atherosclerosis in *Apoe*^{-/-} mice, partly by suppressing CD4⁺ T cell proliferation in the spleen¹⁰⁹.

Furthermore, Qa-1-restricted CD8⁺ T_{reg} cells regulate CD4⁺ T follicular helper cells and thereby germinal centre B cell activation and function, leading to potential downregulation of pro-atherogenic IgGs¹¹⁰ (Fig. 1).

CD8⁺ T_{reg} cells expressing killer cell immunoglobulin-like receptors (KIRs) have been found in inflamed tissues in autoimmune diseases, COVID-19 and vasculitis¹¹¹. KIR⁺CD8⁺ T_{reg} cells from patients with coeliac disease were shown to kill gliadin-specific autoreactive CD4⁺ T cells in vitro¹¹¹. In patients with highly severe CAD, two CD8⁺ T cell clusters in blood showed elevated expression of KIRs compared with cells from patients with less severe CAD¹¹², although the role of these cells in atherosclerosis remains unexplored. In patients with acute coronary syndrome, CD28⁻CD4⁺ T cells have been shown to express KIRs¹¹². Moreover, carotid artery plaques from patients with symptomatic atherosclerotic disease showed upregulated KIR–HLA-A, HLA-C and β2-microglobulin interactions across CD8⁺ T cell–CD8⁺ T cell and CD8⁺ T cell–CD4⁺ T cell pairs compared with plaques from patients with asymptomatic atherosclerotic disease¹⁹.

CD8⁺ T_{RM} cells from patients with atherosclerosis express CD103, CD69 and HOBIT. In patients with colorectal cancer, CD8⁺ T_{RM} cells limit tumour cell invasion and metastasis through FAS (also known as CD95)–FAS ligand (FASL) signalling and CXCL13 secretion, promoting the formation of tertiary lymphoid structures¹¹³. NOTCH and TGFβ signalling regulate the differentiation of CD8⁺ T_{RM} cells¹¹³. CD103⁺CD8⁺ T cells also show protective roles in oral mucosa. In a mouse model of atherosclerosis, transplantation of bone marrow with severely reduced T_{RM} cell numbers (from *Znf683*^{KO/CRE}*Prdm1*^{fllox/fllox} mice, in which *Znf683* (HOBIT) is knocked out and *Prdm1* is conditionally disrupted in cells with an active *Znf683* promoter) reduced plaque stability and increased plaque macrophage content compared with transplantation of bone marrow from wild-type mice, suggesting that T_{RM} cells promote collagen deposition and limit macrophage-driven inflammation¹¹⁴ (Fig. 2). Similarly, CD8⁺ T cells have been shown to preserve lesion integrity by reducing the proportion of macrophages and CD4⁺ T helper 1 cells via FAS–FASL signalling¹¹⁵ (Fig. 2).

Pro-atherogenic functions

Atherogenesis and early atherosclerosis. Preclinical studies have demonstrated pro-atherogenic effects of CD8⁺ T cells at the early stages of atherosclerosis. In hyperlipidaemic female mice (AAV8-D377Y-PCSK9 or *Ldlr*^{-/-}), CD8⁺ T cell depletion via the anti-CD8α antibody reduced atherosclerosis in aged but not young mice²¹. Transferring splenic CD8⁺ T cells from aged, but not young, mice also worsened disease in CD8-deficient recipients, underscoring the pro-atherogenic role of CD8⁺ T cells²¹. In *ApoE*^{-/-} mice fed a high-fat diet, CD8⁺ T cells amplified early inflammation, as evidenced by increased numbers of IFNγ-producing CD28⁺CD8⁺ T cells in mediastinal lymph nodes and in the spleen, along with heightened IFNγ and IL-10 expression and polyclonal proliferation in the spleen, compared with *ApoE*^{-/-} mice on a chow diet¹¹⁶. However, the mechanisms underlying these changes remain unclear.

Ly6C^{high} monocytes, which often are spleen derived, differentiate into pro-inflammatory macrophages^{117,118}. In *Ldlr*^{-/-} mice fed a high-fat diet, anti-CD8α treatment decreased circulating and tissue Ly6C^{high} monocyte numbers, implicating CD8⁺ T cells in monopoiesis via IFNγ^{8,96}, a process also seen during viral infections¹¹⁹. IFNγ from CD8⁺ T cells indirectly stimulates haematopoietic progenitors to differentiate towards the myeloid lineage via cytokine release from bone marrow stromal cells, triggering emergency myelopoiesis¹¹⁹.

In a non-human primate model of HIV-associated atherosclerosis, endothelial CX3CL1 and IL-15 was shown to recruit activated

CX3CR1⁺CD8⁺ memory T cells, enhancing TNF-mediated endothelial activation¹²⁰. IL-15-driven CD8⁺ T cell recruitment could be antigen independent, pointing to bystander mechanisms^{121,122}. IFNγ induces the expression of IL-15 and IL-15 receptor-α in endothelial cells and, following complement activation, IL-15–IL-15 receptor-α complex translocate to the cell surface and present IL-15 to CD8⁺ T_{EM} cells, promoting artery graft rejection in SCID–beige mice¹²³. Inflammatory signalling via the NLRP3 inflammasome and IL-1β in vascular cells amplifies this process, increasing vascular inflammation, which promotes CD8⁺ T cell activation and further contributes to artery graft rejection¹²⁴. IL-15 also promotes CD8⁺ T cell adhesion to endothelial cells as well as endothelial cell activation, angiogenesis and cytokine release^{122,125}. In *Ldlr*^{-/-} mice, vaccination with IL-15 induced the generation of IL-15-specific CD69⁺CD8⁺ T cells^{126,127}, hinting at potential cytotoxicity against IL-15-expressing plaque cells. CD69 expression – which is triggered without TCR engagement via IL-15, intercellular adhesion molecule 1 and vascular cell adhesion protein 1 – primes CD8⁺ T cells for tissue residency. CD69⁺CD8⁺ T cells show increased expression of α1 integrin, CD103, CXCR6, PD1 and CD57, and reduced expression of CD62L and S1PR1 (ref. 128), similar to phenotypes seen in anti-neutrophil cytoplasmic antibody vasculitis, whereby the expression of angiogenic CD28⁻CD8⁺ T cells (Box 2) worsen endothelial dysfunction¹²⁹. However, CD8⁺ T cell crosstalk with vascular endothelial cells in atherosclerosis needs to be further elucidated in a stage-dependent manner.

Mice expressing β-galactosidase in cardiomyocytes and arterial smooth muscle (SM-LacZ) developed myocarditis and arteritis after immunization with dendritic cells presenting an immunogenic β-galactosidase peptide⁷⁴. SM-LacZ-*ApoE*^{-/-} mice showed increased vascular inflammation, higher infiltration of CD8⁺ T cells into atherosclerotic lesions and bigger lesion size compared with non-immunized *ApoE*^{-/-} mice⁷⁴. This finding suggests that higher background inflammation can exacerbate atherosclerosis partially through antigen-specific CD8⁺ T cells.

Mid-to-late asymptomatic atherosclerosis. CD8⁺ T cells have been shown to be involved in mid-to-late asymptomatic stages of atherosclerosis, phases that are characterized by plaque progression without overt clinical symptoms but with substantial immune activation and plaque vulnerability. CD8⁺ T cells have been shown to exacerbate atherosclerosis in *ApoE*^{-/-} mice fed a high-fat diet by inducing apoptosis in macrophages, VSMCs and endothelial cells through perforin, granzyme B and TNF, thus contributing to plaque vulnerability¹³ (Fig. 2). These findings further support the role of CD8⁺ T cells in vascular inflammation and cell death.

VSMCs have been shown to promote plaque calcification¹³⁰ and thereby plaque destabilization¹³¹, but the role of CD8⁺ T cells in this process is just emerging. Depleting CD8⁺ T cells in *Ldlr*^{-/-} mice increased VSMC content in atherosclerotic plaques¹³². In addition, single-cell RNA-seq revealed CD8⁺ T cell-driven reprogramming of VSMCs into osteoblastic and macrophage-like cells via IFNγ-induced *Runx1* expression¹³² (Fig. 2). CD8⁺ T cell-derived IFNγ can also repress osteoclasts, further enhancing calcification¹³³. CD8⁺ T cells in plaques from patients with asymptomatic atherosclerotic CVD expressed genes related to cell activation (*IFNG* and *TNF*), type I IFN and IL-6 signalling pathways, and activator protein 1-regulated stress and chemokine genes¹⁹. In addition, the high expression of *CXCR4*, *GZMB* and *CCL4L2* in these CD8⁺ T cells in plaques suggests targeted cytotoxicity, and IL-1 signalling might maintain effector function in these cells¹⁹.

Box 2 | Abiotic stress in atherosclerotic plaques

Abiotic stress refers to environmental or physiological factors, such as reactive oxygen species (ROS), hypoxia and nutrient deprivation, that disrupt cellular homeostasis and trigger adaptive or pathological responses in immune and metabolic systems.

Oxidative stress

Oxidative stress, primarily driven by increased reactive oxygen species (ROS), modulates CD8⁺ T cell activation and metabolism via mitochondrial reprogramming²⁶⁰. Elevated ROS levels impair CD8⁺ effector functions²⁶¹, with effector T (T_{EFF}) subsets being particularly vulnerable to ROS-induced cell death²⁶². In atherosclerosis, ROS contributes to endothelial dysfunction, chronic inflammation and lipid dysregulation^{263,264}. Although a direct role of ROS in CD8⁺ T cell activity in the atherosclerotic plaque remains unexplored, parallels from other diseases suggest its involvement. In vitiligo, ROS-induced endoplasmic reticulum stress triggers CXC-motif chemokine 16 expression in keratinocytes, promoting CXCR6⁺CD8⁺ T cell infiltration and melanocyte loss²⁶⁵, a migratory pathway potentially relevant to vascular lesions. In addition, CD3 and CD28 stimulation promotes T_{CI} differentiation in CD8⁺ T cells, alongside increased ROS and CD39 expression, both suppressed by inhibiting NADPH oxidases such as GP91Phox²⁶⁶. Human CD39⁺CD8⁺ T cells suppress interferon- γ (IFN γ) production from CD39⁺CD8⁺ T cells, via adenosine-mediated paracrine signalling, a phenotype seen in Crohn disease and also detected in atherosclerotic aortas, where low IFN γ and tumour necrosis factor (TNF) levels suggest the presence of a potentially immunoregulatory CD8⁺ T cell population⁵⁷.

Amino acid stress

Amino acid stress, particularly the restricted availability of cysteine, tryptophan and glutamine, disrupts CD8⁺ T cell survival, cytokine

secretion and metabolic fitness in tumour environments^{267–270}. Similar dysregulation related to tryptophan is reported in atherosclerosis²⁷¹. However, targeted studies remain scarce.

Hypoxia

Hypoxia shapes CD8⁺ T cell functionality. In ischaemic tissue, CD8⁺ T cells promote collateral vessel development via IL-16 secretion, which recruits monocytes and CD4⁺ T cells to the perivascular niche²⁷². In a mouse model of femoral artery ligation, CD8^{-/-} mice had poor blood flow recovery and increased fibrosis after ischaemia, whereas CD8⁺ T cell reconstitution in these mice restored IL-16 levels and tissue integrity²⁷². In mice with oxygen-induced retinopathy, CD8⁺ T cells mediate neovascularization through TNF, IFN γ , perforin and granzymes, and blockade of CXC-chemokine receptor type 3 reduces their retinal infiltration and disease severity²⁷³. Conversely, in mice with tumours or lung ischaemia, CD8⁺ T cell-derived IFN γ suppresses endothelial cell proliferation and promotes apoptosis, thereby inhibiting angiogenesis^{274–276}. Hypoxic conditions also skew CD8⁺ T cells towards PD1⁺TIM3⁺CXCR5⁺ exhausted subsets, and in this setting, vascular endothelial growth factor A (VEGFA) enhances their proangiogenic transcriptional profile despite stable TNF and IFN γ expression²⁷⁷. LDL downregulates TNF receptor 1, disrupting the activation of hypoxia-inducible factor driven by TNF–nuclear factor- κ B and limiting VEGF-mediated angiogenesis²⁷⁸—a regulatory axis that is relevant to plaque neovascularization²⁷⁹. Anti-angiogenic therapies targeting VEGF pathways reduce atherosclerotic progression in animal models, although these strategies have been associated with cardiovascular risks in clinical trials²⁷⁸. Notably, exhausted PD1⁺TIM3⁺CD8⁺ T cells with low cytokine output are enriched in atherosclerosis⁵⁷.

The levels of the costimulatory molecule CD137 correlate with CD8⁺ T cell activation and plaque instability in humans^{38,96,134}. IL-6R α ⁺CD57⁺CD8⁺ T cells, which are linked to cytotoxicity and senescence, are enriched in the peripheral blood of patients with CAD compared with healthy controls, driven by increased IL-6 and IL-15 signalling¹³⁵. These cells proliferate independently of TCR signalling and exhibit heightened inflammatory potential¹³⁵.

In *ApoE*^{-/-} mice, PDL1 blockade increases CD8⁺ T cell infiltration, boosting cytokine secretion (TNF, IFN γ , perforin 1, granzysin, granzyme B and lymphotxin- α), and worsening endothelial dysfunction and tissue injury¹³⁶. In vitro, the blockade of PDL1 in endothelial cells amplified IFN γ ⁺CD8⁺ T cell responses, reinforcing their pro-inflammatory function¹³⁶.

Plaque erosion and rupture. Acute ischaemic events occurring in the heart and brain often stem from atherosclerotic plaque instability, either rupture or erosion. Plaque rupture involves the macrophage-driven breakdown of the fibrous cap, whereas erosion is driven by neutrophils and strips endothelial layers, exposing VSMCs and proteoglycans to the lumen without disturbing the fibrous cap^{137–139}. The OPTICO-ACS trial¹⁴⁰ found elevated peripheral blood CD4⁺ and CD8⁺ T cell numbers and granzyme A and perforin 1 levels in patients with ruptured plaques versus those with intact fibrous caps,

suggesting that CD8⁺ T cells might contribute to endothelial injury and erosion. Plaque rupture typically occurs proximal to the site of stenosis, where T cell density is higher and VSMC content lower than in distal regions⁸⁶. However, RNA-seq analyses using the GEO database showed that human unstable plaques contain more M0, M1 and M2 macrophages, but fewer CD8⁺ T cells and NK cells than stable plaques¹⁴¹. CD8⁺ T cells in carotid artery plaques from patients with symptomatic atherosclerotic CVD displayed increased TCR, IFN and non-canonical WNT signalling and cytokine pathway activation, alongside greater exhaustion and senescence features compared with plaque cells from patients with asymptomatic disease¹⁹.

In fibroatheromas, loss of VSMC and degradation of collagen (Box 3) gradually thin the fibrous cap, increasing the risk of rupture¹⁴². CD8⁺ T cells interact with VSMCs and macrophages in the fibrous cap via ligands such as amphiregulin, with pro-fibrotic properties⁸³. Spatial transcriptomics and Gene Set Enrichment analysis revealed upregulated antigen presentation, pro-inflammatory cytokine levels and innate immune activation, along with intense lymphoid–non-lymphoid cell interactions in human unstable plaques versus stable plaques⁸⁶. These findings implicate CD8⁺ T cells in plaque destabilization by inducing osteogenic VSMC differentiation and calcification, triggering cytolytic activity against VSMCs and endothelial cells, and enhancing inflammatory signalling to recruit macrophages.

Clonal expansion alters the functionality of the CD8⁺ T_{EM} cells in plaques, ATLOs and regional lymph nodes. Single-cell RNA-seq and TCR-seq showed that non-expanded T_{EFF} or memory T cell subsets in renal lymph nodes from wild-type mice expressed genes associated with activation (*Slamf7*, *Gzmk* and *Prfl1*) and dysregulation of exhaustion (*Pdcd1*, *Tigit* and *Lag3*)⁴¹. In *Apoe*^{-/-} mice, expanded T_{EFF} or memory T cell subsets showed increased expression of exhaustion-related markers (*Pdcd1*, *Ctla4* and *Tox*) compared with their non-expanded counterparts. In *Apoe*^{-/-} mice, CD8⁺ T cell dysfunction was most profound in plaques, followed by ATLOs and renal lymph nodes. Notably, specific genes associated with activation, tolerance checkpoints and metabolism (such as *Cxcr6*, *Cd81*, *S100a6*, *Lgals1* and *H2-D1*) were uniquely upregulated in plaques, whereas mitochondrially encoded genes (*Mt-Atp8*, *Mt-Co3* and *Mt-Co*) were downregulated in plaques⁴¹.

Overall, the role of CD8⁺ T cells is highly dependent on their phenotype or subtype (Fig. 1), the stage of disease (Fig. 2) and the antigen specificity. As was also proposed by Schafer and colleagues⁹⁶, CD8⁺ T cells can migrate into the intima or resident CD8⁺ T cells can mobilize in the intima via antigen-independent mechanisms to promote

pro-inflammatory and pro-atherogenic mechanisms in early disease stages. As atherosclerosis progresses, certain CD8⁺ subsets, such as CD8⁺ T_{reg} cells, display atheroprotective characteristics. However, given the plaque microenvironment, antigen-specific clonally expanded CD8⁺ T cells become activated and exhibit increased cytotoxic and pro-inflammatory functions, ultimately leading to plaque instability and CD8⁺ T cell exhaustion.

Ageing and comorbidities

A greater understanding of the role of CD8⁺ T cells in ageing and in CVD comorbidities, as well as in autoimmune diseases, including rheumatoid arthritis and diabetes, can provide insights into how CD8⁺ T cells drive atherosclerotic disease progression. The overlap in underlying mechanisms reveals shared immune pathways that mediate chronic inflammation and tissue damage. Events such as calcification, fibrosis, extracellular matrix remodelling and hypoxia-induced angiogenesis also occur in other pathologies, including chronic viral infections, fibrotic diseases, cancer and autoimmune diseases, in which CD8⁺ T cells have a pivotal role. Insights from these parallels (Boxes 2 and 3) can clarify the contributions of CD8⁺ T cells in atherosclerosis.

Box 3 | CD8⁺ T cells in fibrosis and extracellular matrix remodelling

Vascular fibrosis involves proliferation of vascular smooth muscle cells, extracellular matrix accumulation, particularly collagen and fibronectin, and impaired matrix degradation, all of which lead to structural remodelling and arterial stiffening. Cardiovascular risk factors, such as hypertension, hyperglycaemia and dyslipidaemia, drive the progression of vascular fibrosis, and are influenced by renin–angiotensin signalling, oxidative stress, inflammation, growth factors and endothelial dysfunction^{246–248}. This process contributes to atherosclerosis and is driven by intercellular interactions among vascular smooth muscle cells, macrophages, T lymphocytes and endothelial cells²⁴⁸. Fibrosis is often characterized by the formation of myofibroblasts, leading to the deposition of excessive collagen.

Kidney fibrosis is observed in advanced chronic kidney disease, and atherosclerosis is often a comorbidity of chronic kidney disease²⁴⁹. In kidney fibrosis, CD8⁺ T cells infiltrate the kidney early in the disease process and might have a protective role^{250,251}. Conversely, CD8⁺ T cell-related fibrosis processes in atherosclerosis have not been studied in as much depth as those in kidney disease. In obstructed kidneys, CD11c⁺CD8⁺ T cells might trigger fibroblast apoptosis²⁵². Of note, interferon- γ -producing CD8⁺ T cells have been shown to protect against renal fibrosis by limiting CD4⁺ T helper 2 differentiation, which dampens inflammation and fibrosis²⁵¹. CD4⁺ T cell–CD8⁺ T cell crosstalk is implicated in several other pathologies but has not been explored in atherosclerosis. In addition, vaccination with apolipoprotein B-100-p210 led to a CD8⁺ T cell-mediated amelioration of angiotensin II-induced hypertension and renal fibrosis in mice²⁵³. This finding further suggests the importance of assessing CD8⁺ T cell-mediated mechanisms through the body to gain insights into CD8⁺ T cell functions in the setting of atherosclerosis and its comorbidities.

CD69⁺CD103⁺ CD8⁺ tissue-resident memory T cells (which are also found in atherosclerosis), promote liver fibrosis, are abundant in fibrotic areas and recruit hepatic stellate cells in a

CC-chemokine receptor type 5-dependent manner to induce FAS–FAS ligand-mediated apoptosis²⁵⁴. CD8⁺ T cells induce endothelial cell hyperplasia and fibrosis in the thyroid in a tumour necrosis factor-dependent manner, exacerbate fibrosis in the lungs, and induce pro-fibrotic mechanisms in several other tissues, including skin and muscle²⁵⁵.

In the setting of hypertension, cardiac fibrosis is driven by crosstalk between CD8⁺ memory T cells and stressed cardiomyocytes, as shown in a mouse model of hypertension²⁵⁶. In this model, CD8⁺ T cell depletion reduced cardiac fibrosis and cardiac apoptosis and improved cardiac relaxation. This interaction relies on CD8⁺ T cells expressing NKG2D type II integral membrane protein and cardiomyocytes displaying its ligand, retinoic acid early-inducible protein 1, leading to perforin-mediated apoptosis, macrophage-driven transforming growth factor- β 1 production and fibrosis²⁵⁶.

The interplay between atrial fibrosis, inflammation and hypercoagulability–thrombogenicity promotes atrial cardiomyopathy and atrial fibrillation, and involves endothelial activation, inflammation, oxidative stress, fibrosis and blood flow changes caused by hypercontractility (echoing the mechanisms underlying atherosclerosis)^{257,258}. Patients with a first diagnosis of atrial fibrillation have increased activation of CD8⁺ T cells, which correlates with cardiac fibrosis and atrial dysfunction²⁵⁹. CD8⁺ T cell effector function in atrial fibrillation is driven by activation of proteinase-activated receptor 1, with high levels of thrombin-activated PAR1⁺CD8⁺ T cells in blood linked to worse outcomes²⁵⁹. Proteinase-activated receptor-targeting therapies (factor IIa and factor Xa inhibitors) modulate CD8⁺ effector T cell activity, with broad effects. Interestingly, factor IIa and FXa inhibitors attenuate atherosclerosis^{258,259}. However, any mechanism of action of these inhibitors involving CD8⁺ T cells in atherosclerosis remains unexplored.

Ageing

Ageing is a key risk factor for atherosclerosis²¹, and peripheral CD8⁺ T cells show similar phenotypes in aged and atherosclerotic mice. In aged mouse models of atherosclerosis, CD8⁺ T cell depletion reduced both plaque size and CD8⁺ T cell density within plaques, effects not seen in young mice²¹. Young *Ldlr*^{-/-} mice had similar proportions of circulating naive CD8⁺ T cells to those in wild-type controls but had elevated circulating numbers of CD8⁺ central memory T cells²¹. These findings indicate that the CD8⁺ T cell phenotype in atherosclerotic mice shares features with that in both young and aged wild-type mice. Notably, transfer of CD8⁺ T cells from aged mice into young mice lacking CD8⁺ T cells before induction of atherosclerosis aggravated the atherosclerotic burden²¹.

Obesity and type 2 diabetes mellitus

Obesity-driven chronic inflammation promotes insulin resistance and type 2 diabetes, a key comorbidity of CVD, and alters CD8⁺ T_{reg} cells (towards CD25⁺⁺ and CD127^{-/low} expression¹⁴³). In visceral adipose tissue in individuals with obesity, CD8⁺ T_{reg} cells with high CCR5 expression polarize towards T_{Cl}-like (CCR5⁺CCR6⁺) and T_{Cl}-T_{Cl7} subsets, often expressing PD1, reflecting strong immunosuppressive potential¹⁴³. Individuals with pre-diabetes had reduced numbers of TIM3⁺CD8⁺ T_{reg} cells in PBMCs and PD1⁺CD8⁺ T_{reg} cells in adipose tissue compared with age-matched and sex-matched healthy volunteers¹⁴³. Given the importance of the balance between CD4⁺ T_{reg} cells and CD4⁺ T helper 17 cells in atherosclerosis^{81,144}, the regulatory roles of PD1 and TIM3 pathways in CD8⁺ T cell function⁵⁶, and the effect of hyperglycaemia, dyslipidaemia and other metabolic alterations on the CD8⁺ T cell phenotype¹⁴⁵⁻¹⁴⁷, investigating the role of CD8⁺ T_{reg} cells in atherosclerotic plaques is warranted.

In mice with type 2 diabetes, CD8⁺ T cells shift from angiogenic T_{RM} to T_{EFF} or T_{EM} phenotypes¹⁴⁸. Their interaction with endothelial cells via granzyme A–proteinase-activated receptor 1 (also known as F2R) impairs endothelial regeneration¹⁴⁸. This interaction is also enriched in atherosclerotic plaques, implicating CD8⁺ T cells in endothelial layer disruption¹⁴⁹. Given that endothelial impairment accelerates lipid and immune cell infiltration to the arterial wall, CD8⁺ T cells could actively contribute to atherosclerotic disease initiation and progression.

Cancer

A meta-analysis of 46 studies revealed that cancer accelerates atherosclerosis progression, impairs vascular structure and function, and increases cardiovascular risk¹⁵⁰. VSMC populations in both mouse and human atherosclerotic lesions exhibit tumour-like phenotypes¹⁵¹. In mouse models, the anticancer drug niraparib (which targets DNA damage repair mechanisms) reduced atherosclerotic lesion size and disease progression¹⁵². These parallels highlight the potential of using cancer research findings to help elucidate CD8⁺ T cell-related mechanisms in atherosclerosis. Immune checkpoint inhibitor therapy, which is used in cancer, suppresses T cell activation via PD1–PDL1/PDL2 interactions. PD1⁺CD8⁺ T cells are present in atherosclerotic plaques but differ phenotypically from exhausted T cells found in tumours; notably, plaque-specific PD1⁺CD8⁺ T cells are pro-inflammatory¹⁵³. A retrospective study of a cohort of patients with cancer found that treatment with anti-PD1 monoclonal antibodies significantly reduced atherosclerotic plaque burden compared with the burden before therapy initiation¹⁵⁴. Mechanistically, IgG Fc receptor (FcγR)-binding anti-PD1 antibodies engage FcγRs on myeloid cells, functioning as proxy PD1 ligands to suppress T cell activation. A prospective study

confirmed that only FcγR-binding variants effectively reduced atherosclerotic plaque size¹⁵⁴. In addition, a hub-gene analysis of atherosclerotic plaques from patients with CAD and patients with different cancer types identified three ubiquitination-related genes (*FBXO7*, *RAD23A* and *MKRNI*), the expressions of which positively correlated with the degree of CD8⁺ T cell infiltration into atherosclerotic plaques as well as with CAD progression¹⁵⁵. This finding suggests that CD8⁺ T cell activity in atherosclerosis might potentiate proteotoxic and inflammatory stress programmes and that ubiquitination pathways might be potential markers or modulators of immune-driven vascular injury.

Autoimmune disorders

Type 1 diabetes mellitus. T1DM is driven by CD8⁺ T cell-mediated destruction of pancreatic β cells. A rare population of stem-like β-cell-specific CD8⁺ T cells can independently induce T1DM^{156,157}. T1DM-induced hyperglycaemia increases the risk of atherosclerosis and plaque rupture^{158,159}. CD69⁺CD103⁺CD8⁺ T_{RM} cells are involved in the pathogenesis of T1DM¹⁶⁰. FABP4 increases the survival of these T_{RM} cells and the CXCL10-mediated recruitment of CD8⁺ T cells to the pancreas¹⁶⁰. In non-obese diabetic (NOD) mice, which spontaneously develop T1DM, *Fabp4* deletion or depletion of T_{RM} cells reduced the expression of TNF, CCL2, granzyme A, granzyme C, CCR2, IFNγ and CXCL10 in the pancreas and delayed the onset of T1DM¹⁶⁰. Further, pharmacological inhibition of FABP4 reduce atherosclerosis and diabetes mouse models¹⁶¹. However, the role of FABP4 in modulating CD8⁺ T cells in this context has not been characterized.

Insulin-specific CD8⁺ T cells destroy pancreatic β cells and endothelial cells in T1DM. Pancreatic endothelial cells can cross-present antigens generated by other cells¹⁶², a phenomenon also seen in other pathologies such as multiple sclerosis¹⁶³, which leads to CD8⁺ T cell activation, adhesion to endothelial cells and homing into the tissue. This process provides a rationale to explore antigen-specific interactions between CD8⁺ T_{EFF} and T_{EM} populations and vascular endothelial cells to better understand the adhesion, migration, and diapedesis of CD8⁺ T_{EFF} and T_{EM} cells into the plaques.

CD8⁺ T cells specific to native or citrullinated forms of GRP78 are associated with T1DM^{164,165}. GRP78-reactive CD8⁺ T can also have cross-reactivity against gut bacteria¹⁶⁵. GRP78 was found to be highly expressed in inflammatory cells and endothelial cells in human atherosclerotic plaques, and the expression levels were higher in vulnerable plaques than in stable plaques¹⁶⁶. GRP78 is also a known biomarker for metabolic syndrome¹⁶⁷, a major comorbidity of atherosclerosis. Atherogenic shear stress induces endothelial cell GRP78 expression and transiently reduces endoplasmic reticulum stress¹⁶⁸. *ApoE*^{-/-} mice develop anti-GRP78 autoantibodies that bind to endothelial cell surface GRP78, activate nuclear factor-κB to upregulate the expression of intercellular adhesion molecule 1 and vascular cell adhesion protein 1, and accelerate lesion growth¹⁶⁹. Peptidyl arginine deiminase (PAD)-mediated citrullination (arginine to citrulline) regulates immunity in rheumatoid arthritis, T1DM, multiple sclerosis, sepsis and cancer^{170,171}. PAD inhibition was shown to reduce vascular damage in *ApoE*^{-/-} mouse models of atherosclerosis¹⁷². However, whether GRP78 in plaque endothelial cells engages CD8⁺ T cells remain to be determined.

Rheumatoid arthritis. Rheumatoid arthritis is associated with increased risk and propensity of atherosclerosis and CVD-associated mortality¹⁷³. Patients with rheumatoid arthritis and coronary artery calcification exhibited increased CD8⁺ T cell activation (HLA-DR⁺), differentiation into CD28⁻ T_{EM} cells and acquisition of NK receptors

(CD56⁺ and/or CD57⁺) compared with patients with rheumatoid arthritis without calcification¹⁷⁴. CD28⁺ CD8⁺ T cells were also found to be enriched in the blood from patients with CMV-positive rheumatoid arthritis compared with patients with CMV-negative rheumatoid arthritis, and the percentage of CD28⁺ CD8⁺ T cells was positively associated with subclinical atherosclerosis, as measured by intima-media thickness¹⁷⁵. This finding was corroborated by a study reporting enrichment of CD56⁺ CD28^{low} CD8⁺ T cells in PBMCs from patients with CAD compared with controls; these cells produced high levels of IFN γ and TNF and showed features of immuno-ageing¹⁷⁶, and might therefore be potentially pro-atherogenic.

The pathogenesis of rheumatoid arthritis is closely linked to the presence of anti-citrullinated protein antibodies (ACPA), which are found in most patients. In ACPA⁺ rheumatoid arthritis, expanded clonal populations of GZMB⁺ and GZMK⁺ CD8⁺ T cells display cytotoxic, inflammatory and tissue-homing properties¹⁷⁷. When exposed to citrullinated antigens via HLA-I, these cells proliferate, secrete cytotoxic mediators and attack target cells, potentially driving synovitis and joint damage. Elevated levels of citrullinated proteins, including citrullinated fibrinogen and vimentin, have been detected in human atherosclerotic plaques¹⁷⁸. In addition, in patients with rheumatoid arthritis, the plasma levels of antibodies targeting citrullinated antigens were positively correlated with increased plaque burden¹⁷⁸. Although citrullination seems to bridge autoimmunity and cardiovascular pathology, the role of CD8⁺ T cell specificity for citrullinated epitopes and the effect of PAD inhibition on CD8⁺ T cells in atherosclerosis remain underexplored.

Clinical relevance

CD8⁺ T cells have emerged as a compelling target in atherosclerosis therapy because of their dual role in promoting inflammation and mediating immune regulation. Restoring the balance between these pro-inflammatory and regulatory subsets can potentially stabilize vulnerable plaques and reduce cardiovascular events. Innovative immunotherapies, such as adoptive T cell transfer and checkpoint blockade, that have already been explored in other inflammatory conditions could be repurposed to fine-tune these responses in atherosclerosis. Moreover, advances in spatial transcriptomics and in vivo imaging are enhancing our understanding of CD8⁺ T cell localization and interaction within plaques⁸⁶, paving the way for the discovery of novel biomarkers and personalized therapeutic strategies.

A clinical study in patients with peripheral artery disease highlighted how a minimally invasive angioplasty procedure that induced vascular injury triggered a rapid immune response, involving particularly effector CD8⁺ T cells¹⁷⁹. Analyses of peripheral blood conducted immediately before and after the angioplasty procedure revealed a marked decline in immunosenescent and activated effector CD8⁺ T cells. This reduction probably reflects the swift adhesion and recruitment of these T cell subsets to the injured vessel wall, a phenomenon supported by emerging insights suggesting that injury-induced signals drive CD8⁺ T cells into the vascular tissue, where they could modulate subsequent repair and remodelling processes¹⁷⁹.

Inflammatory signalling and CD8⁺ regulatory T cells

A study assessing the genetic basis of shared immune regulation in cancer and CAD revealed a key role of CD8⁺ T cells¹⁵⁵, and might inspire future therapeutic strategies that could be applied to treat atherosclerosis. For example, the IL-6–JAK–STAT3 pathway, which is crucial in tumour growth and immune checkpoint modulation, could be targeted to reduce inflammation and improve CD8⁺ T cell-mediated responses in

atherosclerosis^{155,180}. Similarly, pathways such as TNF–nuclear factor- κ B and PI3K–AKT–mTOR, known for their roles in cancer progression and endothelial damage, could be inhibited to mitigate immune-driven mechanisms in CVD¹⁵⁵. A study using an IL-15 vaccination strategy in *Ldlr*^{-/-} mice fed a Western diet found reduced lesion size but no change in lesion stability, and a reduced ratio of CD4⁺ T cells to CD8⁺ T cells¹²⁶, which is indicative of reduced inflammation. This finding suggests that the response could have been partly mediated by changes in CD8⁺ T cells¹²⁶.

Multiple anti-inflammatory strategies have shown promise for the treatment of atherosclerosis, with growing evidence of CD8⁺ T cell involvement. Inhibition of dipeptidyl peptidase 4 (DPP4; also known as CD26) improves plaque stability and reduces diabetes-related inflammation in mice^{181,182}. Inhibition of DPP4 increased CD8⁺ T_{EM} cell activity in T1DM models and suppressed antigen-stimulated proliferation of mouse CD8⁺ T cells¹⁸³. Human CD26^{high} CD8⁺ T cells, which are part of the early T_{EM} subset, exhibit enhanced cytotoxicity via granzyme B, TNF, IFN γ and FASL¹⁸⁴. The distinct phenotypes, migration capacity and polyfunctionality of CD26^{high} CD8⁺ T cells suggest their utility in adoptive or chimeric antigen receptor T cell therapies^{185–188}.

Invariant NK T cells have been shown to be pro-atherogenic¹⁸⁹. A CD1d-dependent lipid antagonist of invariant NK T cells was shown to ameliorate atherosclerosis in *ApoE*^{-/-} mice, associated with reduced CD8⁺ T cell numbers in atherosclerotic plaques¹⁹⁰. Another potential approach is low-dose IL-2 therapy, which suppresses inflammation by boosting CD4⁺ T_{reg} cell regulation of autoreactive CD8⁺ T cells¹⁹¹. IL-2 also promotes the expansion of CD25⁺ FOXP3⁺ CD8⁺ T cell subsets, which are linked to atheroprotection^{109,191}. Together, these findings highlight how immune modulation, especially of CD8⁺ subsets, can represent novel therapeutic approaches for atherosclerosis.

Antibody and vaccination strategies

Lipid-based or related self-antigens. Atherosclerotic plaques contain diverse antigens, including oxidation-specific epitopes, such as ASA6, oxidized phospholipids and malondialdehyde from oxidized LDL^{192,193}. Patients with atherosclerosis often have IgM and IgG antibodies against these epitopes, and the levels of IgMs specific to oxidation-specific epitopes inversely correlated with CAD incidence¹⁹⁴. These epitopes can be targeted for diagnosis and plaque monitoring via imaging techniques such as near-infrared imaging, MRI and positron emission tomography–MRI^{192,195}.

Vaccination against lipid-based antigens (such as APOB-100, cholesteryl ester transfer protein and PCSK9) and non-lipid antigens (such as HSP60 and HSP65) has shown efficacy in reducing atherosclerosis in mouse models^{195–197}. Several of these strategies modulate CD8⁺ T cell phenotype and function^{197–200}. Vaccination of *ApoE*^{-/-} mice with APOB-100-p210 nanoparticles reduced plaque burden and increased CTLA4⁺ CD8⁺ T cell numbers, promoting immune tolerance⁶⁹. Previous studies confirm the CD8⁺ T cell-mediated protection, and a similar vaccination approach in a humanized mouse model also prevented atherosclerotic disease and induced CD8⁺ T cell recall responses⁶⁹. PCSK9 vaccination in mice also leads to plaque reduction^{201,202}. In mouse models of cancer, administration of PCSK9 impaired CD8⁺ T cell function by blocking the recycling of the LDL receptor and TCR, leading to cell exhaustion²⁰³. Combined PCSK9 and PD1 inhibition boosted CD8⁺ tumour infiltration and activity^{203–205}. Given that lipid dysregulation alters CD8⁺ T cell function in tumours¹⁴⁶ and is a hallmark of atherosclerosis, these mechanisms are likely to affect CD8⁺ T cell responses in atherosclerotic plaques, offering potential for targeted therapies.

Table 2 | Disease models to study CD8⁺ T cells in atherosclerosis

Model	Key features	Disadvantages
In vivo		
<i>Ldlr</i> ^{-/-} mice <i>ApoE</i> ^{-/-} mice	Widely used models of atherosclerosis The <i>Ldlr</i> ^{-/-} mouse model mimics the human hypercholesterolaemia profile	<i>Ldlr</i> -knockout impairs CD8 ⁺ T cell activation ²²¹ <i>ApoE</i> -knockout promotes inflammation ²²⁶ Both models do not completely recapitulate human disease ²²⁷
<i>CD8</i> ^{-/-} mice CD8 ⁺ T cell depletion	Widely used to study the role of CD8 ⁺ T cells Not useful for discerning the role of specific CD8 ⁺ T cell populations and their interactions with other immune cells	Can result in changes in non-CD8 ⁺ T cell immune cell populations, such as dendritic cells All populations of CD8 ⁺ T cells are depleted ^{228,229}
MHC class I-deficient mice <i>Tap1</i> ^{-/-} mice <i>B2m</i> ^{-/-} mice	Used to impair MHC class I-mediated antigen presentation to CD8 ⁺ T cells Not useful for discerning the role of antigen presentation in a stage-dependent manner	<i>Tap1</i> ^{-/-} mice and <i>B2m</i> ^{-/-} mice lack CD8 ⁺ T cells ^{105,230} and MHC class I molecules are not completely abrogated ^{103,104}
Ex vivo		
CD8 ⁺ T cell and vascular cell co-culture	Used to study migration and cytotoxicity of CD8 ⁺ T cells in atherosclerosis Can be used with bioreactor systems for increased viability and shear stress	Long-term viability is a challenge Might not recapitulate systemic and metabolic complexities
In vitro		
2D and 3D co-culture	Simplified system that provides direct insights into the interactions between CD8 ⁺ T cells and other cell types Lacks physiological relevance	Restricted to the use of cell lines or HLA-matched CD8 ⁺ T cells and vascular and immune cells
Organoids and organ-on-chip models	Can mimic lymphoid organs and vascular microtissues Provide balance between physiological relevance and experimental tractability (Box 3) Can be used to develop induced pluripotent stem cell -based syngeneic systems to study CD8 ⁺ T cells in atherosclerosis and contribute to personalized medicine	

HLA, human leukocyte antigen; MHC, major histocompatibility complex.

Foreign antigens. In mice, vaccination against microbial antigens, such as against influenza in humans and pneumococcus, *Porphyromonas gingivalis*, intestinal worms and CMV, has shown atheroprotective effects and to reduce the risk of major adverse cardiovascular events^{197,199}. These effects could stem from induced immune tolerance, potentially modulating bystander CD8⁺ T cell activity and molecular mimicry that contribute to atherosclerotic lesion development, despite the lack of direct viral antigen activation^{43,82,83}.

C. pneumoniae infection correlates with increased CD8⁺ T cell infiltration in carotid atherosclerotic plaques and accelerates lesion formation in hypercholesterolaemic mice, a response that was absent in CD8-deficient mice^{85,206}. This finding highlights a crucial, antigen-independent role of CD8⁺ T cells in atherosclerosis progression and points to vaccination as a strategy to mitigate immune-driven vascular damage.

Nanomedicine and immune tolerance. With advances in nanomedicine, nanoparticle-mediated drug delivery to atherosclerotic plaques and immune cells targeting T cells has also been gaining traction for the treatment of atherosclerosis. However, these approaches have so far mostly focused on CD4⁺ T cells²⁰⁷. Such strategies have already been used in the treatment of other autoimmune disorders by targeting CD4⁺ T_{reg} cells and CD8⁺ T_{reg} cells²⁰⁸. These strategies can also be leveraged for atherosclerosis to elicit phenotype and functional changes in CD8⁺ T cells to mediate atheroprotective responses²⁰⁹. Peptide-MHC nanoparticles containing an autoimmune-relevant peptide can increase the number of T_{reg} cells in autoimmunity and can

serve as a therapeutic strategy for atherosclerosis, given that vaccination against APOB-100-p210 in *ApoE*^{-/-} mice using nanoparticles was shown to be atheroprotective⁶⁹.

Immune checkpoint inhibitor therapy

The use of immune checkpoint inhibitors to treat atherosclerosis has shown mixed effects. An FcγR-binding anti-PD1 monoclonal antibody was shown to reduce plaque size in humans¹⁵⁴, but an analysis of human coronary plaques revealed increased CD8⁺ T cell numbers after immune checkpoint inhibitor therapy²¹⁰. CTLA4 blockade in *Ldlr*^{-/-} mice increased the number of CD8⁺ T_{EFF} cells and worsened plaque burden²¹¹, indicating context-dependent CD8⁺ T cell-driven inflammation. Endothelial PDL1 and PDL2 suppress CD8⁺ T cell activation, especially under IFNγ stimulation, which enhances the protective role of these cells²¹²⁻²¹⁴. In mice, PDL1 expression in myocardial endothelium limits CD8⁺ T cell-mediated injury²¹⁵. However, PDL1 blockade in *ApoE*^{-/-} mice exacerbated atherosclerosis, increasing CD8⁺ T cell infiltration and cytokine release (TNF, IFNγ, perforin, granzyme B, granulysin and lymphotoxin-α)¹³⁶. In in vitro assays, PDL1 blockade in mouse aortic endothelial cells increased the activation and cytokine release in cytolytic CD8⁺IFNγ⁺ T cells and reduced endothelial cell production of soluble PDL1 (ref. 136). In patients with CAD, increased levels of soluble PDL1 in blood were associated with and increased risk of cardiovascular events^{216,217}. These findings suggest that PDL1 pathways modulate CD8⁺ T cell-driven inflammation and thus merit careful consideration for cardiovascular therapeutic strategies.

Research gaps and future perspectives

In this Review, we have provided insights obtained from numerous studies that investigated different phenotypes, transcriptomes and TCRs of CD8⁺ T cells relevant to atherosclerosis and comorbidities. Preclinical studies assessing multiple in vitro, ex vivo and in vivo disease models also identified pro-atherogenic and atheroprotective roles of CD8⁺ T cells in atherosclerosis. However, several outstanding questions remain.

First, where are CD8⁺ T cells located, and what are their functions at different stages of atherosclerosis? Single-cell RNA-seq and CyTOF studies have revealed CD8⁺ T cell abundance in advanced atherosclerotic plaques^{19,35,86}, but their spatiotemporal distribution and interactions with macrophages, VSMCs and vascular endothelial cells remain unclear. Tools such as spatial transcriptomics and in vivo imaging can clarify their roles in efferocytosis, matrix remodelling and necrotic core expansion.

Second, how do the CD8⁺ T cell phenotypes and functions evolve over time? CD8⁺ T cells show diverse states – from cytotoxic to exhausted to regulatory phenotypes – shaped by hypoxia, lipid stress and chronic antigen exposure. Their roles in plaque destabilization^{18,99,102,218} versus stabilization require clarification. Disease-relevant subsets, such as the stem-like CD8⁺ T cells seen in autoimmunity, also warrant investigation.

Moreover, how does metabolic dysfunction affect CD8⁺ T cells in atherosclerotic plaques? The environment of lipid overload in plaques might impair CD8⁺ T cell function²¹⁹, as seen with CD36-mediated oxidized LDL uptake by CD8⁺ T cells in tumours²²⁰. Disruptions in cholesterol metabolism, which are poorly characterized in CD8⁺ T cells, can influence their phenotype and activity in atherosclerosis. In addition, commonly used models, such as *Ldlr*^{-/-} mice, might not fully capture these effects owing to impaired CD8⁺ T cell activation²²¹ (Table 2).

Furthermore, what are the key immune crosstalk mechanisms involving CD8⁺ T cells? CD8⁺ T cell interactions with CD4⁺ T cells, macrophages and dendritic cells are insufficiently understood^{115,222}. The influence of CD8⁺ T cells on macrophage polarization, cytokine signalling and endothelial barrier function warrants deeper investigation using spatial transcriptomics, in vivo imaging, co-culture platforms and organ-on-chip technologies (Table 2 and Box 4).

In addition, how do CD8⁺ T cells enter atherosclerotic plaques, and what drives their antigen specificity? Whether CD8⁺ T cell recruitment is antigen dependent or is driven by bystander mechanisms remains unresolved. Identifying signals that govern their migration and mapping MHC-I-restricted antigen epitopes along with corresponding TCR CDR3 sequences, as has been shown for CD4⁺ T cells^{95,223,224}, could pinpoint their cellular targets and clarify their role in plaque progression.

Box 4 | Models to study CD8⁺ T cells in atherosclerosis

Several in vitro and in vivo models have been utilized to assess the role of CD8⁺ T cells in atherosclerosis, as discussed in the main text and Table 2. However, the role of specific CD8⁺ T cell subsets, their mechanisms of action and their regulation during atherosclerosis remains largely unknown. Nevertheless, these studies signify the importance of disease and study model selection, experimental design and confounding factors in in vivo set ups to accurately assess human disease and related phenomena.

Organoids and organ-on-a-chip models provide innovative platforms to capture the complexities and physiological relevance of in vivo systems while maintaining the experimental tractability and simplicity of in vitro systems. Several vasculature-on-a-chip models exist that can be leveraged to study atherosclerosis^{280,281} and customized to address specific aspects of the disease. For example, we previously used a 3D platform that allowed cyclic strain in combination with endothelial cells and fibroblast co-culture to study the progression of aortic valve stenosis (a process that shares pathophysiological aspects with atherosclerosis) in both healthy and diseased extracellular matrices²⁸². Other groups have used similar 3D co-culture models to study monocyte crosstalk with endothelial cells and vascular smooth muscle cells in atherosclerosis^{281,283}, as well as microfluidic chips to study migration of CD8⁺ T cells across the endothelial cell layers²⁸⁴. Such platforms can be further developed and utilized to study the crosstalk between CD8⁺ T cells and the atherosclerotic lesion microenvironment. Carefully designed 3D organ-on-chip systems enabling incorporation of fluid flow and cyclic strains, cell–cell and cell–matrix interactions, which better recapitulate in vivo complexities²⁸³, are an attractive platform to study CD8⁺ T cell infiltration, homing and functions in atherosclerotic plaques. An atherosclerotic-plaque-on-a-chip can serve as a

relevant model to recapitulate altered extracellular matrix, cellular compositions and spatial organization of vascular and immune cells in the plaque in a stage-dependent manner²⁸¹.

Organoid technology recreates human organ characteristics, supporting tissue regeneration and development, and can also be applied to cardiovascular diseases²⁸⁵. Organoids have gained popularity owing to ease of manufacturing and flexibility of disease modelling²⁸⁵. In addition, immune organoids, derived from lymphoid tissues, offer ex vivo models that overcome animal model limitations. Tonsil organoids replicate germinal centre functions, advancing adaptive immunity research. Emerging trends include generating diverse immune organoids, integrating them with cancer organoids, and using bioengineering to refine physiological relevance^{286,287}. In the context of assessing the role of CD8⁺ T cells in atherosclerosis, T cell-enriched organoids can be co-cultured with vascular endothelial cells, smooth muscle cells and other immune cells relevant to atherosclerosis, such as dendritic cells and macrophages, in controlled in vitro settings to assess context-dependent roles in simplified systems free of confounding factors. Although such systems might not recapitulate the in vivo physiology, they are relevant for uncovering simple biological phenomena.

Combinations of immune and cardiovascular organoids and atherosclerotic-plaque-on-a-chip models can be leveraged along with the use of patient-specific induced pluripotent stem cell-derived cell lines to capture an individual's immune repertoire, genetic predispositions and unique microenvironment resulting from comorbidities. In the future, such platforms can be used for drug testing to assess specific immunization strategies to modulate immune responses in atherosclerosis.

Glossary

Artery tertiary lymphoid organs

(ATLOs). Lymph-node-like immune aggregates that arise in the adventitia during atherosclerosis, structurally and functionally resembling secondary lymphoid organs.

Bystander activation

Antigen-independent stimulation of immune cells, typically by cytokines, that enhances infection control but can also drive autoimmunity.

Clonal expansion

The process by which one lymphocyte recognizes a specific antigen and proliferates into genetically identical effector or memory cells to strengthen the response.

Germinal centre

Specialized microenvironments within lymphoid follicles where B cells proliferate, undergo affinity maturation and differentiate into memory and plasma cells.

Immune checkpoint inhibitor therapy

A therapeutic strategy using antibodies to block inhibitory receptor–ligand

pathways, thereby enhancing T cell-mediated antitumor immunity.

Immune tolerance

The immune system's state of unresponsiveness to self and harmless antigens, maintained by central and peripheral mechanisms to prevent autoimmunity.

Inflammasome

A multiprotein complex that detects cellular stress or infection and activates inflammatory responses via caspase 1.

Monopoiesis

The process by which haematopoietic stem cells in the bone marrow differentiate into monocytes.

Qa-1-restricted

T cell responses that recognize antigens presented specifically by the non-classical Qa-1 MHC class Ib molecule in mouse (and the homologue HLA-E in humans).

Finally, can we safely target CD8⁺ T cells to treat atherosclerosis? Immunotherapies such as immune checkpoint inhibition, adoptive T cell transfer and cytokine modulation hold promise but remain underexplored in atherosclerosis. Preclinical studies must assess their safety, efficacy and potential to modulate CD8⁺ T cell activity without triggering adverse immune effects.

By addressing these knowledge gaps, future studies can refine our understanding of the multifaceted roles of CD8⁺ T cells in atherosclerosis. This knowledge will be crucial for developing targeted therapies that mitigate cardiovascular risk and improve patient outcomes.

Conclusions

Atherosclerosis is a complex, multifaceted disease in which CD8⁺ T cells are believed to have a role in inflammation and autoimmune processes. However, the CD8⁺ T cell repertoire is highly variable in the plaques, lymph nodes and peripheral blood, influenced by the individual's lifestyle, existing comorbidities and stage of disease. CD8⁺ T cells clonally expand within fibroatheroma⁸³. Using spatial transcriptomics, T cell gene signature has been shown to be enriched at most stenotic and proximal regions of the plaque, in which plaque rupture most frequently occurs²²⁵. The recruitment of CD8⁺ T cells is orchestrated via several chemokine signalling axes and retention is mediated by CD69. Antigen stimulation and clonal expansion within plaques and ATLOs

result in CD8⁺ T cell subsets exhibiting effector and effector–memory phenotypes, which might compromise plaque stability. Nonetheless, several CD8⁺ T_{reg} subsets show atheroprotective roles by modulating CD4⁺ T cells and macrophages. By contrast, pro-atherogenic CD8⁺ T cells promote monocyte recruitment, drive VSMCs transition into foam and osteogenic phenotypes, and secrete cytotoxic mediators such as IFN γ , TNF and perforin. Cross-disease insights from autoimmune and chronic inflammatory conditions might inform targeted therapeutic strategies to modulate CD8⁺ T cell behaviour in atherosclerosis. Overall, CD8⁺ T cells can have protective or pro-atherogenic roles depending on their specific signature, the stage of the disease and dependence on antigens. However, APOB and other relevant antigen-specific epitopes for CD8⁺ T cells, antigen-independent or bystander mechanisms, and CD8⁺ T cell interactions with other immune cells to potentiate atherosclerosis remain to be elucidated.

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Author contributions

M.Y. wrote the initial manuscript draft. I.T., K.L. and H.A.A. conceptualized the content of the article. I.T., M.Y. and H.S. wrote the article. I.T., A.M.K., H.A.A. and K.L. reviewed and edited the manuscript before submission. I.T. prepared the tables and contributed to the figures.

Competing interests

The authors declare no competing interests.

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