Title

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Journal

Journal of the American College of Cardiology, 79(6)

ISSN

1558-3597

Authors

Vuong, Jacqueline T
Stein-Merlob, Ashley F
Nayeri, Arash
et al.

Publication Date

2022-02-15

Data Availability

The data associated with this publication are within the manuscript.

Peer reviewed

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 79, NO. 6, 2022

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Immune Checkpoint Therapies and Atherosclerosis: Mechanisms and Clinical Implications

JACC State-of-the-Art Review

Jacqueline T. Vuong, MD,[a] Ashley F. Stein-Merlob, MD,[b] Arash Nayeri, MD,[b] Tamer Sallam, MD, PHD,[b] Tomas G. Neilan, MD, MPH,[c] Eric H. Yang, MD[b,d]

ABSTRACT

Immune checkpoint inhibitor therapy has revolutionized the treatment of advanced malignancies in recent years. Numerous reports have detailed the myriad of possible adverse inflammatory effects of immune checkpoint therapies, including within the cardiovascular system. However, these reports have been largely limited to myocarditis. The critical role of inflammation and adaptive immunity in atherosclerosis has been well characterized in preclinical studies, and several emerging clinical studies indicate a potential role of immune checkpoint targeting therapies in the development and exacerbation of atherosclerosis. In this review, we provide an overview of the role of T-cell immunity in atherogenesis and describe the molecular effects and clinical associations of both approved and investigational immune checkpoint therapy on atherosclerosis. We also highlight the role of cholesterol metabolism in oncogenesis and discuss the implications of these associations on future treatment and monitoring of atherosclerotic cardiovascular disease in the oncologic population receiving immune checkpoint therapy. (J Am Coll Cardiol 2022;79:577-593) © 2022 by the American College of Cardiology Foundation.

EMERGENCE OF IMMUNE CHECKPOINT INHIBITORS

Modern-day immunotherapy originates from the cancer immunosurveillance hypothesis, which states that immune cells are responsible for the surveillance and elimination of nascent transformed cells in host tissues.[1] Enhanced appreciation for the ability for tumor cells to evade immune surveillance[2] galvanized efforts to develop therapies restoring the host immune system's antineoplastic defenses. The culmination of these efforts led to the development of immune checkpoint inhibitors (ICIs) that restore the host T-cell immune response against cancer cells. The development of ICIs in the last decade has rapidly revolutionized cancer therapy, with applications of ICIs targeting CTLA-4 and PD-1/PDL-1 pathways in cancers including melanoma, non-small-cell lung cancers (NSCLCs), and urothelial carcinomas.[3-5]

When ICIs were being approved, it was anticipated that diffuse leveraging of the immune system would lead to off-tumor adverse events, which occur in up to 70% of patients and may affect any organ system, but are typically easily managed. Initial reports

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From the [a]Department of Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, California, USA; [b]Division of Cardiology, Department of Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, California, USA; [c]Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA; and the [d]UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California at Los Angeles, Los Angeles, California, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 12, 2021; revised manuscript received September 27, 2021, accepted November 8, 2021.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2021.11.048

ABBREVIATIONS AND ACRONYMS

ACAT1 = Acetyl-coenzyme A acetyltransferase

APC = antigen-presenting cell

ASCVD = atherosclerotic cardiovascular disease

CAD = coronary artery disease

CTLA-4 = cytotoxic T-lymphocyte associated protein 4

FDG = fluorodeoxyglucose

GITR = glucocorticoid-induced TNF receptor-related protein

ICI = immune checkpoint inhibitor

ICOS = inducible costimulator

IFN = interferon

IG = immunoglobulin

IL = interleukin

LAG-3 = lymphocyte-activation gene 3

LDL = low-density lipoprotein

MHC = major histocompatibility complex

NSCLC = non-small-cell lung cancer

oxLDL = oxidized low-density lipoprotein

PCSK9 = proprotein convertase substilisin/kexin type 9

PD-1 = programmed cell death protein 1

PD-L = programmed cell death ligand

TCR = T-cell receptor

TGF = transforming growth factor

TNF = tumor necrosis factor

VSMC = vascular smooth muscle cell

detailing the potential cardiovascular effects of ICIs focused principally on the uncommon, but highly morbid, occurrence of myocarditis, mediated by direct T-cell infiltration of the myocardium expressing programmed cell death ligand (PD-L) 1.[6] More recently, the potential for ICIs to affect the cardiovascular system beyond myocarditis has been reported. Specifically, preclinical evidence supports that treatment with ICIs can theoretically promote the development and acceleration of atherosclerosis, and recent emerging clinical evidence suggests an increase in atherosclerotic-related cardiovascular events in patients receiving ICI therapy and a possible connection between ICIs and increased atherosclerotic cardiovascular disease (ASCVD) risk.[7]

The role of inflammation in atherosclerosis has been well established, with the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study), LoDoCo (Low-Dose Colchicine), and COLCOT (Colchicine Cardiovascular Outcomes Trial) trials demonstrating that targeting immune responses can improve clinical cardiovascular outcomes.[8-10] These studies showed that targeting innate immunity, such as inhibition of interleukin (IL)-1β via canakinumab and neutrophil function via colchicine, may mitigate the progression of ASCVD. Because adaptive immunity via T-cell activation has also been shown to play a crucial role in the development and progression of atherosclerosis, ICIs may have important implications on atherosclerotic disease.[11] This review aims to describe the role of T-cell-mediated immunity in atherogenesis, the molecular implications of various pathways of immune checkpoint alteration in atherosclerosis, the current clinical associations between treatment with ICIs and atherosclerosis, and the potential treatment avenues.

HIGHLIGHTS

- Immune checkpoint therapy may increase ASCVD.
- Cholesterol metabolism modulates the response to immune checkpoint therapies and may be a common target for treatment of both cancer and atherosclerosis.
- Further research should define cardiovascular endpoints for patients receiving immune checkpoint therapies and standardize treatment and surveillance strategies.

OVERVIEW OF T-CELL–MEDIATED IMMUNITY AND KEY IMMUNE CHECKPOINT PATHWAYS

OVERVIEW OF T-CELL–MEDIATED IMMUNITY. Tumor-associated antigens are recognized and phagocytosed by antigen-presenting cells (APCs) such as dendritic cells and macrophages. These antigens are presented via major histocompatibility complex (MHC) molecules on the surface of APCs, which interact with T-cell receptors (TCRs) and serve as the primary stimulatory signal leading to the intracellular cascade that activates naïve CD4+ and CD8+ T cells. However, full T-cell activation is dependent on the presence of costimulatory signals involving the binding of CD28 on T-cell surfaces to B7-1 (CD80) or B7-2 (CD86) on APCs (Figure 1A).

Subsequently, the cytokine composition of the surrounding environment determines the fate of T-cell differentiation into various subclasses, including CD8+ cells into cytotoxic T cells, and CD4+ T cells into helper T cells (T_h1, T_h2, and T_h17) and regulatory T cells (T_{reg}) (Figure 1A). Cytotoxic T cells secrete cytotoxins and promote apoptosis of its target cells. Of the CD4+ T-cell derivatives, T_h1 promotes cell-based immunity by activating macrophages and cytotoxic T cells, whereas T_h2 cells promote antibody-mediated immunity and the recruitment of eosinophils. T_h17 cells assist with extracellular pathogen clearance at mucosal surfaces and promote antibody production.[12] T_{reg} cells promote peripheral tolerance by secreting inhibitory cytokines, promoting cytolysis, and suppressing the activation, proliferation, and cytokine production of CD4+ and CD8+ T cells.[13]

T-CELL ANERGY AND COINHIBITORY SIGNALING. Several mechanisms exist to prevent immune overactivation and promote self-tolerance. Activation of T cells requires binding of a second costimulatory signal with stimulatory checkpoint molecules, such as CD28 to B7-1/B7-2, without which T cells would remain anergic. Another class of immune checkpoint molecules induce coinhibitory signals, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death protein-1 (PD-1) receptor.

CTLA-4 is an analog similar to CD28 that is constitutively expressed on T_{reg} cell surfaces and upregulated on other T-cell classes after initial

activation. It exerts inhibitory effects in the early phases of T-cell activation within lymphoid tissues by directly competing with CD28 to bind to B7-1 and B7-2 ligands on APCs with higher affinity. Its binding launches a signaling cascade preventing TCR signal transduction.[14] Later studies showed a signaling-independent mechanism of inhibition via activation of transendocytosis that removes B7 ligands from the surfaces of APCs.[15] CTLA-4 expression has been demonstrated in T cells of atherosclerotic plaque,[16] and CTLA-4 inhibition has been linked to multi-organ lymphocyte infiltration, including the heart, leading to ICI fulminant myocarditis.[17]

The PD-1 receptor is present on activated T cells and exerts an inhibitory effect via binding its 2 ligands PD-L1 (CD274) and PD-L2 (CD273) in peripheral tissues. Although PD-L2 is present mostly on macrophages and dendritic cells, PD-L1 is expressed in hematopoietic cells and tissue cells in various organs, including in cardiomyocytes, vascular endothelial cells, and leukocytes within atherosclerotic plaque.[18-20] The binding of PD-1 to PD-L1 or PD-L2 leads activation of the Akt pathway that decreases the production of inflammatory cytokines and cell survival proteins.[21] Disruption in the PD-1/PD-L1 pathway in PD-1 knockout mice led to rapid-onset autoimmune-mediated dilated cardiomyopathy with diffuse immunoglobulin G (IgG) deposition, and is a potential mechanism of cardiotoxicity in ICI-induced myocarditis.[19]

IMMUNE CHECKPOINT ALTERATIONS IN CANCER AND THE ADVENT OF ICIs. In the tumor microenvironment, tumor cells promote recruitment and production of CTLA-4-expressing T_{reg} cells via transforming growth factor (TGF)-β secretion.[22] In addition, prolonged activation of T cells in the cancer immune response leads to exhaustion, where T cells up-regulate inhibitory molecules, including PD-1 and CTLA-4, to limit their own proliferative potential (**Figure 1B**).[23] The surrounding tissue hypoxia promotes an increase in PD-L1 expression in various tumors.[18]

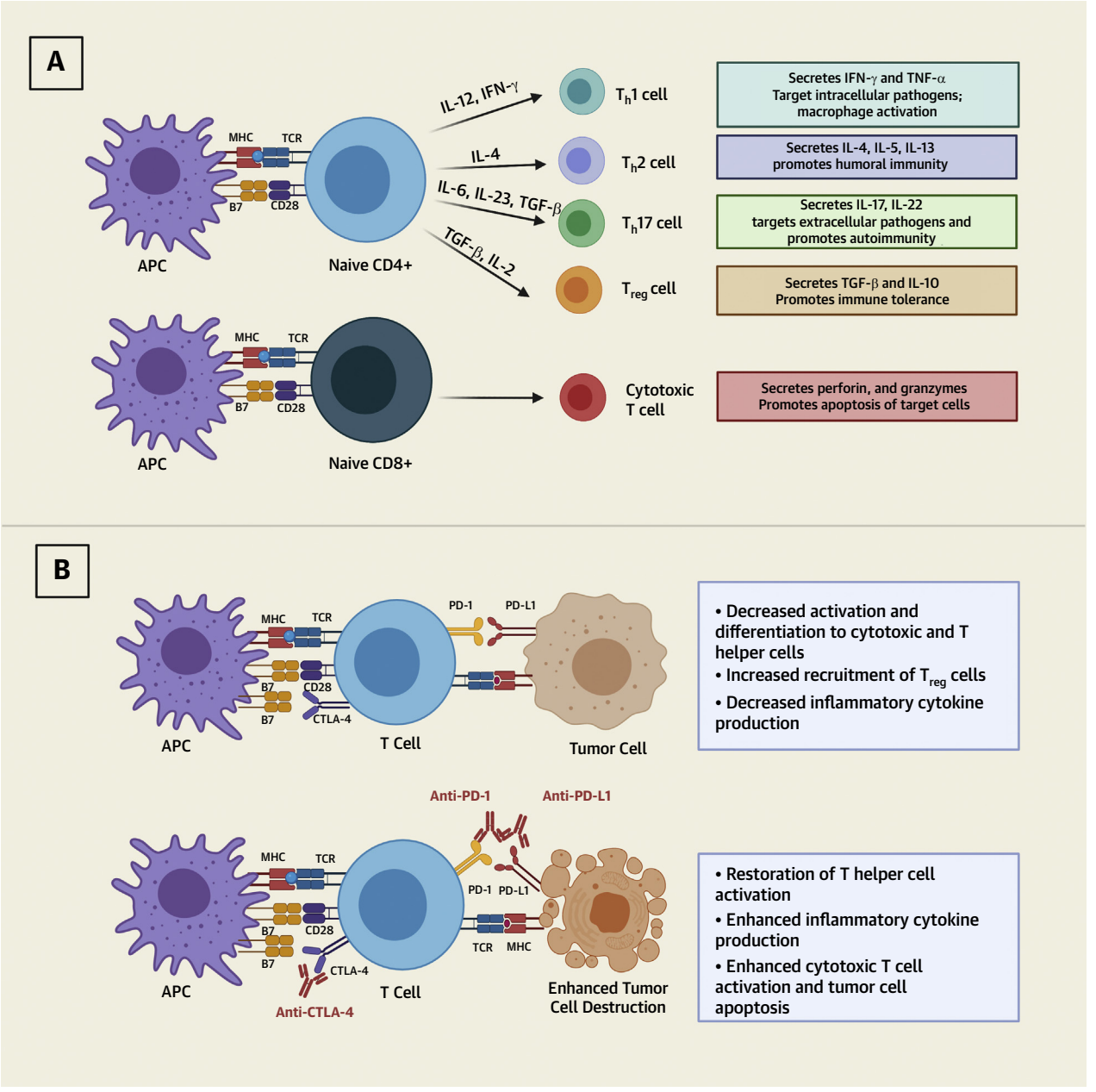
Targeted ICIs use the altered oncologic expression of immune checkpoints to augment the host immune response, beginning with the approval of the CTLA-4 checkpoint inhibitor ipilimumab (Yervoy) for use in metastatic melanoma in 2011.[4] Shortly after came approval for PD-1 inhibitors pembrolizumab (Keytruda) and nivolumab (Opdivo) (**Figure 1B**).[3,5] Since their initial U.S. Food and Drug Administration approval, the indications for ICIs have expanded rapidly to include NSCLCs, non-Hodgkin's lymphoma, urothelial carcinoma, colorectal cancers, and more. Several investigational therapies targeting other immune checkpoints are in various stages of development.[24] The pathways used in anti-CTLA-4 and PD-1/PD-L1 inhibitor therapies as well as those of investigational immune checkpoint agents have been implicated in atherogenesis (**Central Illustration, Table 1**).

ROLE OF IMMUNE CELLS IN ATHEROSCLEROSIS AND EFFECTS OF CURRENT IMMUNE CHECKPOINT INHIBITORS

OVERVIEW OF ATHEROGENESIS. The pathophysiology of atherosclerosis begins with damaged endothelial cell expression of cellular adhesion molecules that attract monocytes to enter the subendothelium, where they transform into macrophages that are polarized into subtypes depending on their microenvironment. The classically activated proinflammatory phenotype is promoted by exposure to free fatty acids, oxidized lipids, and factors such as interferon (IFN)-γ whereas the alternatively activated anti-inflammatory phenotype is promoted by factors such as IL-4, IL-13, and IL-10. Proinflammatory macrophages predominate in early atherosclerotic plaque and are responsible for the accumulation of intracellular lipids, formation of foam cells, and secretion of proinflammatory cytokines such as IL-1β and IL-6[25] (**Figure 2**). Anti-inflammatory macrophages promote collagen formation and effective lipid clearance, and are associated with atherosclerosis regression.[26] Necrotic core formation is the hallmark of chronic inflammation in atherosclerosis, and is rich in lipids and cellular debris as a result of foam cell and vascular smooth muscle cell (VSMC) apoptosis and necrosis.[27]

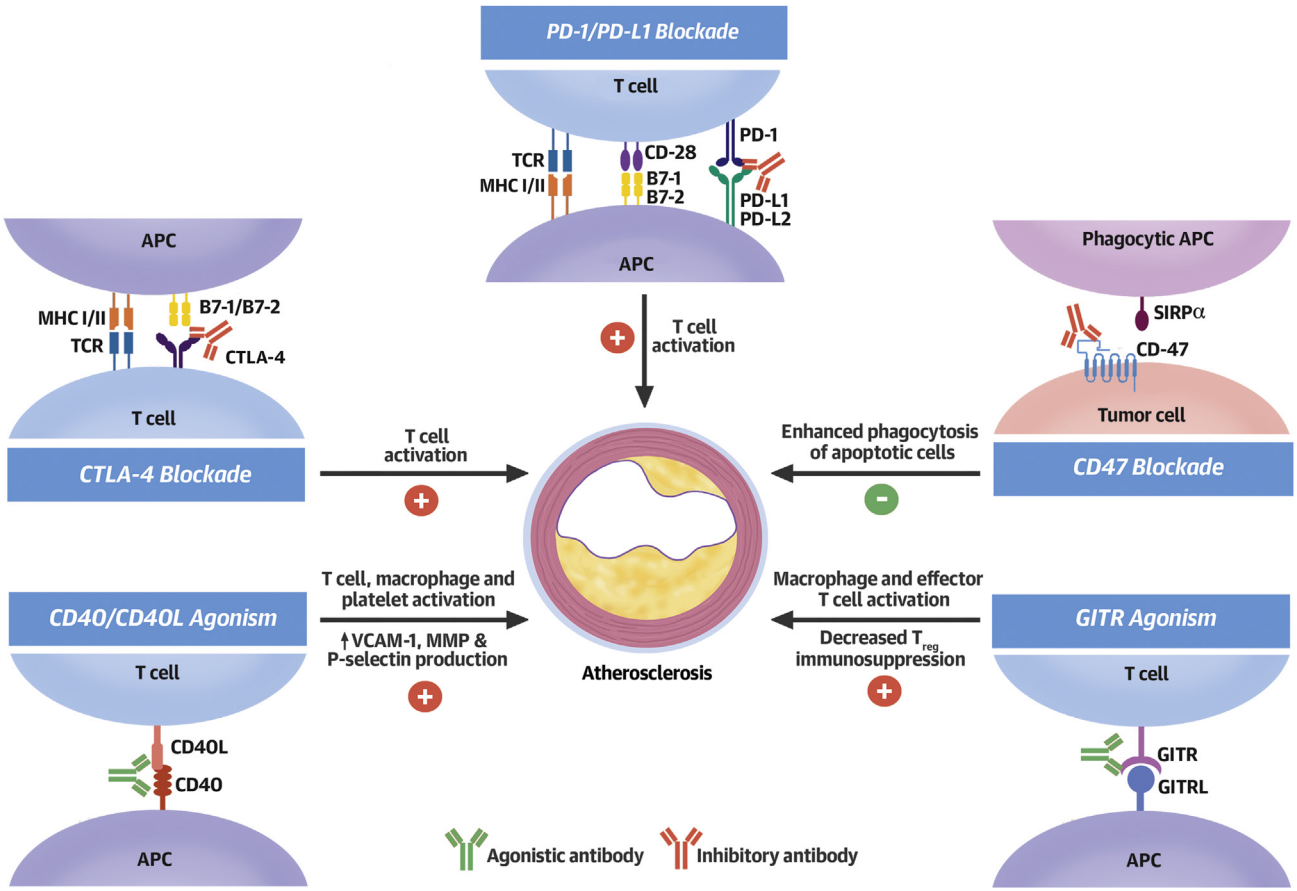
T-cell activation is also integral to atherogenesis. During early atherosclerosis, APCs present atheroma-related antigens to naïve T cells in lymphoid tissues, leading to T-cell migration toward the plaque.[28] The initial recruitment of T cells is nonspecific, and they undergo further selective activation and clonal expansion into atherogenic T-cell subtypes.[28,29] Atheroma-related T-cell antigens have been difficult to identify, but include oxidized low-density lipoprotein (oxLDL) particles, heat shock proteins, and Apolipoprotein B.[30] OxLDLs are abundant in atheromatous plaque, and serve as an antigen triggering T-cell autoimmune response that leads to inflammation and macrophage activation via IFN-γ secretion.[31] CD8+ cytotoxic T cells, T_h1 cells, T_h2 cells, T_h17 cells, and T_{reg} cells have all been identified in atherosclerotic plaques.[30]

FIGURE 1 T-Cell Activation and Effect of Immune Checkpoints



(A) T-cell activation. Antigen-presenting cells (APCs) present antigens via major histocompatibility complex (MHC) molecules that bind to T-cell receptors (TCRs) on naïve CD4+ and CD8+ T cells. T-cell activation requires the binding of costimulatory molecules B7.1(CD80) or B7.2(CD86) on APCs to CD28. Naive CD8+ T cells are activated into cytotoxic T cells that secrete perforins and granzymes, leading to apoptotic cascades in target cells. The presence of particular cytokines and growth factors in the microenvironment determine naïve CD4+ T-cell differentiation. **(B)** Immune alterations in cancer and effect of immune checkpoint inhibitors. Prolonged inflammation in cancer leads to T-cell exhaustion that promotes recruitment of T_{reg} cells and increased expression of cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 receptor (PD-1) on T cells. Programmed cell death protein 1 receptor ligand (PD-L1) on tumor cells binds to PD-1 to decrease the production of inflammatory cytokines. Immune checkpoint inhibitors enhance tumor cell killing by targeting PD-1, PD-L1, and CTLA-4 to restore T-cell activation and inflammatory cytokine production. Created with BioRender.

CENTRAL ILLUSTRATION **Summary of Immune Checkpoint Alterations and Their Effects on Atherogenesis**



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CTLA-4 and PD-1/PDL-1 blockade are well-studied examples of coinhibitory molecule blockade that worsen atherosclerosis. CD40/CD40L agonism and GITR agonism are examples of costimulatory molecule agonism that worsens atherosclerosis. CD-47 blockade restores efferocytosis and may be atheroprotective. APC = antigen presenting cell; CD = cluster of differentiation; CTLA4 = cytotoxic T-lymphocyte-associated protein 4; GITR = glucocorticoid-induced tumor necrosis factor family-related protein; GITRL = glucocorticoid-induced tumor necrosis factor family-related protein ligand; MHC = major histocompatibility complex; MMP = matrix metalloproteinase; PD-1 = programmed cell death protein 1 receptor; PD-L1 = programmed cell death protein 1 receptor ligand; SIRP-α = signal-regulatory protein alpha; TCR = T-cell receptor; T_{reg} = regulatory T cell; VCAM = vascular cell adhesion molecule.

ROLE OF DIFFERENTIATED T CELLS IN ATHEROGENESIS. T_h1 cells are the predominant CD4+ T cell present in plaques[32] and are the most directly associated with atherogenesis due to their production of inflammatory cytokines, including IFN-γ and tumor necrosis factor (TNF)-α.[33,34] (**Figure 2**). The production of IFN-γ enhances recruitment of macrophages and T cells and promotes macrophage polarization, cytokine secretion, and foam cell formation.[35] IFN-γ is also thought to inhibit VSMC proliferation, thereby contributing to decreased plaque stability.[36] The atherogenic role of IFN-γ is most clearly demonstrated in a study where mice with dysfunctional IFN-γ receptors developed smaller and more phenotypically stable atheromas compared with controls.[37] TNF-α promotes atherosclerosis through leukocyte recruitment, inflammatory cytokine production, and promotion of endothelial cell damage and oxidative stress.[38] TNF-α-deficient mice have been shown to exhibit smaller plaque lesions,[33] and the presence of TNF-α is associated with increased lesion necrosis and more advanced plaque progression in mice.[39] The inhibition of T_h1 differentiation in mice is also atheroprotective and reduces the amount of IFN-γ detected in plaques.[40]

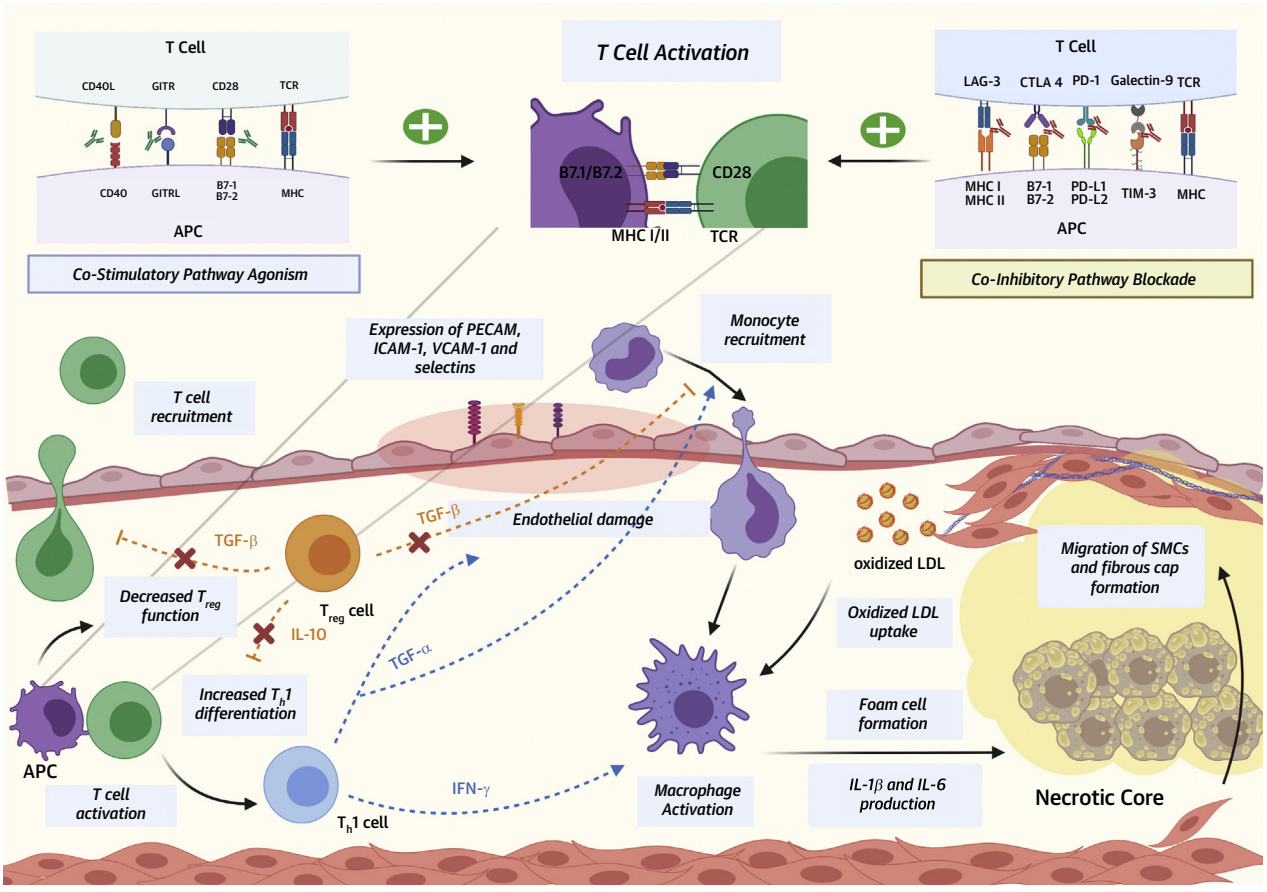
TABLE 1 Summary of Immune Checkpoint Pathway Alterations and Effects on Cancer Therapy and ASCVD

Immune Checkpoint Class	Immune Checkpoint Target	Effect on Cancer Therapy[a]	Effect on ASCVD[a]	Example Therapies
Coinhibitory signal blockade	CTLA-4	Restores T cell activation and enhances cancer cell destruction[3,24]	Increases atherosclerotic lesion size[63-65] Progression to advanced phenotype[65] Decreases collagen content[65]	Ipilimumab[4] Tremelimumab[151,b] Zalifrelimab (AGEN1884)[152,b]
	PD-1 and PD-L1		Increases atherosclerotic lesion size[67-69] Enhances TNF-α secretion[67,68] Enhances lesion helper T-cell, cytotoxic T-cell, and macrophage activation[67-69]	Anti-PD-1: nivolumab,[5] pembrolizumab,[3] cemiplimab,[153] spartalizumab,[154,b] camrelixumab,[154,b] tislelizumab[154,b] Anti- PD-L1: atezolizumab,[155] avelumab,[156] durvalumab,[157] cosebelimab,[154,b] Sugemalimaba,[154] CX-072[154,b]
	TIM-3[b]		Increases atherosclerotic lesion size[105] Increases lesion macrophage content Decreases lesion T_{reg} content Enhances TNF-α and IFN-γ secretion in combination with anti-PD-1 in human cells[106]	Cobolimab,[24,b] BMS-986258,[158,b] MBG453,[158,b] TSR-022,[158,b] Sym023,[158,b] BGB-A425[158,b]
	LAG-3[b]		Effect unknown, a marker positively correlated with ASCVD in a human observational study[109]	Relatlimab,[b] Eftilagimod alpha,[b] Tebotelimab,[b] Favezelimab,[b] LAG525,[b] REGN 3767[159,b]
Costimulatory signal agonism	GITR[b]	Enhances macrophage activity[90] Promotes CD4+ and CD8+ T cell activation[89,90] Decreases immunosuppressive ability of T_{reg}[89]	Promotes macrophage secretion of atherogenic cytokines[94,95] Increases MMP production[95] Enhances plaque leukocyte recruitment via ICAM-1[95] GITR inhibition decreased plaque size and increased plaque stability[94]	AMG228,[b] MEDI-1873,[b] BMS-986156a[160]
	CD40 and CD40L[b]	Enhances antigen presentation by APCs[74] Promotes B-cell proliferation and antibody production[74] Promotes tumor cell apoptosis[75]	Increases secretion of IL-1β, IL-6, TNF-α, IFN-γ[73] Endothelial cell and smooth muscle cell activation in human cells[78] Increases leukocyte recruitment by expression of VCAM-1 and P-selectin[77] Increases MMP production[77] Promotes foam cell production[77] Inhibition of CD40L: Increased plaque stability[82-85] Inconsistently decreased plaque size[82,85] vs no change[83,84] Reduced T_h1 polarization and IFN-γ secretion[87] Reduced atherothrombosis[87]	Selicrelumab,[161,b] dazetuzumab,[162,b] CP-870893,[162,b] JNJ-107,[162,b] APX005M[162,b]
	CD27 and CD70[b]	Enhanced T-cell expansion and survival[96] Enhanced memory T-cell production[96] Polarization toward IFN-γ–producing effector T cells[96]	Decreased lesion size[98,99] Enhanced macrophage efferocytosis[98] Enhanced oxLDL clearing[98] Promotion of T_{reg} survival[98,99]	Anti-CD27: Varlilumab,[b] AMG-172[b] Anti-CD70: Cusatuzumab,[b] BMS-936561[163,b]
	ICOS and ICOSL[b]	Promotion of cytotoxic T cells[100] Enhancing effector T-cell function[100] Promotion of T_{reg} activity[100]	Inhibition of ICOS: Increased atherosclerotic plaque size[101,102] Reduced atherosclerotic T_{reg} population[102] Increased IFN-γ secretion[101] Decreased IL-10 secretion[101]	Anti- ICOS agonists: Feladilimab,[b] vopratelimab[100] Anti- ICOS antagonists: MEDI-570,[b] KY1044[100,b]
"Don't eat me" blockade	CD47[b]	Blockade of interaction with SIRP-α[111] Enhances phagocytosis of apoptotic cells and debris[111] Reduces inflammation[111]	Reduces atherosclerotic lesion size and inflammation[112,113] Decreases macrophage response to IL-1β and IFN-γ[113] Improves clearance of VSMCs[114]	Magrolimab,[115,b] SRF231,[164,b] AO-176,[164,b] CC-90002[164,b]

[a]Findings of preclinical/animal studies unless otherwise specified. [b]Investigational therapies.

AGEN = Agenus; AMG = Amgen; AO = Arch Oncology; APX = Apexigen; APCs = antigen-presenting cells; ASCVD = atherosclerotic cardiovascular disease; BGB-A = BeiGene; BMS = Bristol Myers Squibb; CC = Celgene; CD = cluster of differentiation; CTLA-4 = cytotoxic T-lymphocyte–associated protein; CX = CytomX; GITR = glucocorticoid-induced tumor necrosis factor receptor-related protein; ICAM = intracellular adhesion molecule; IFN = interferon; IL = interleukin; JNJ = Johnson & Johnson; KY = Kymab; LAG-3 = lymphocyte-activation gene 3; MMP = matrix metalloproteinase; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; REGN = Regeneron Pharmaceuticals; SIRP = signal regulatory protein; SRF = Surface Oncology; Sym = Symphogen; TIM-3 = T-cell immunoglobulin and mucin-domain-containing-3; TNF = tumor necrosis factor; T_{reg} = regulatory T cell; VCAM = vascular cell adhesion molecule; VSMCs = vascular smooth muscle cells.

FIGURE 2 **Atherogenesis and Effects of T-Cell Activation**



Damaged endothelial cells express platelet endothelial cell adhesion molecules (PECAM), intracellular adhesion molecules (ICAM), vascular cell adhesion protein (VCAM), and selectins that recruit monocytes to the subendothelium. Monocytes are activated into macrophages that consume oxidized low-density lipoproteins (ox-LDLs) and produce inflammatory cytokines, leading to foam cell and necrotic core formation. T cells are recruited to the subendothelium and activated by APCs. Activation of T helper 1 (T_h1) cells leads to tumor necrosis factor (TNF)-α secretion that promotes monocyte recruitment and endothelial damage, and interferon (IFN)-γ secretion that promotes macrophage activation. T-cell activation decreases the function of regulatory T cells (T_{reg}) that normally decrease T-cell and monocyte recruitment via transforming growth factor (TGF)-β secretion and reduces T_h1 differentiation via interleukin (IL)-10 secretion. T-cell activation is enhanced by immune checkpoint altering antibodies. Created with BioRender.

T_{reg} cells' atheroprotective role has been well studied, and their effects are primarily mediated through secretion of TGF-β and IL-10 (Figure 2). TGF-β inhibits recruitment and activation of T cells and macrophages, and increases plaque stability by promoting VSMC proliferation.[41] Mice with defective TGF-β receptors have larger atherosclerotic lesions with increased T-cell and macrophage composition, increased IFN-γ expression, and more vulnerable plaque phenotype.[42] IL-10 reduces T_h1 differentiation and prevents the recruitment and cytokine secretion of T cells and macrophages.[43] A study with IL-10-deficient mice demonstrated increased susceptibility to atherosclerosis, and higher T-cell infiltration and IFN-γ expression compared with controls.[44] In addition, T_{reg} secretion of IL-10 promotes the transformation of macrophages from the proinflammatory to the anti-inflammatory phenotype, potentiating its atheroprotective effect.[45] Ait-Oufella et al[46] demonstrated that deficiency in T_{reg} was associated with increased plaque size and more advanced plaque phenotype in mice, and that subsequent cotransference of T_{reg} reduced inflammatory cell infiltration and plaque size. In addition, the number of T_{reg} cells was inversely correlated with plaque vulnerability in human carotid arteries.[47]

The roles of the remaining T-cell subtypes in atherosclerosis are less well defined. T_h2 cells oppose

the production of IFN-γ, which suggested a potentially atheroprotective role. This was further supported because deficiency in IL-5, one of the primary T_h2 secreted cytokines, was shown to accelerate atherosclerosis development in mice.[48,49] However, the deletion of another T_h2 cytokine, IL-4, has been shown to decrease plaque lesion size in mice.[50] Thus, the role of T_h2 cells in atherogenesis remains unclear.

T_h17 cells have received considerable attention in atherosclerosis in recent years, although its definitive role is still controversial. A study analyzing human coronary atherosclerotic plaques demonstrated that IL-17, the principal cytokine released by T_h17, worked synergistically with IFN-γ to promote inflammation by increasing secretion of IL-6.[51] However, cytokine secretion of T_h17 cells relies on environmental context, and subsets secrete IL-17 in conjunction with the anti-inflammatory IL-10, making the role of T_h17 cells in atherosclerosis difficult to define.[52] Several studies have indicated an atherogenic role to IL-17,[53] whereas others suggest an atheroprotective role and promotion of plaque stability via Type I collagen production.[54,55] Despite these inconclusive findings, the ratio between T_h17 and T_{reg} cells have been implicated in atherosclerosis progression, with increased T_h17 and decreased T_{reg} levels observed in patients with coronary atherosclerosis. Recent data suggest that inhibition of CD69, a key molecule expressed on early T lymphocytes regulating T-cell differentiation, leads to elevated T_h17/T_{reg} ratios and exacerbation of atherosclerosis in mice.[56] Indeed, the delicate balance between T_h17 and T_{reg} cells has important implications on autoimmune conditions and off-target adverse events related to ICI therapy, including myocarditis.[57,58]

Despite CD8+ T cells comprising about 50% of lymphocytes in atherosclerotic lesions,[59] fewer studies have addressed the role of CD8+ cells. Cytotoxic CD8+ T cells have been shown to promote atherosclerosis in mouse models through IFN-γ secretion[60] and necrotic core formation by perforin and granzyme B-mediated apoptosis of macrophages.[61] However, another mouse model suggests an atheroprotective role by promoting cytolysis of APCs.[62]

IMMUNE CHECKPOINT THERAPIES AND ATHEROSCLEROSIS

B7-1/B7-2 AND CD28/CTLA-4 PATHWAY. The immunoregulatory effects of CTLA-4 and B7-1/B7-2 binding suggests an atheroprotective role for this pathway. The use of abatacept, a synthetic analog of CTLA-4, prevented CD4+ cell activation and reduced atherosclerosis development in murine femoral arteries by 78%, whereas the administration of CTLA-4 blocking antibodies increased atherosclerotic lesion sizes.[63] Similarly, mice with elevated homocysteine levels had larger atherosclerotic plaque sizes associated with decreased membrane expression of CTLA-4, and pretreatment of these mice with abatacept ameliorated plaque development with reduced IFN-γ and IL-2 production and decreased macrophage content.[64] Matsumoto et al[16] demonstrated that transgenic mice with constitutive CTLA-4 overexpression exhibited a significant reduction in atherosclerotic lesion size at the aortic root. In this study, CTLA-4 overexpression appeared to reduce atherosclerosis by decreasing plaque inflammation, as evidenced by a 38% decrease in macrophage accumulation and a 42% decrease in CD4+ T-cell infiltration, and down-regulation of T-cell proliferative capacity and proinflammatory cytokine production.[16]

Modeling the role of ICIs in atherosclerosis, Poels et al[65] evaluated the role of antibody-mediated CTLA-4 inhibition on atherogenesis. They demonstrated a 2-fold increase in the size of atherosclerotic lesions in mice treated with CTLA-inhibiting antibodies, which was primarily mediated by a transition to an activated T-cell profile without significant alterations in the macrophage inflammatory profile. CTLA-4 inhibition was also associated with plaque progression to more advanced phenotypes, with decreased collagen content and increased intimal thickening and necrotic core areas.

PD-1 AND PD-L1/PD-L2 PATHWAY. PD-1 has been shown to suppress T_h1 cytokine production and promote the development of T_{reg} cells, suggesting a potentially atheroprotective role for this pathway.[66] In hyperlipidemic mice, both PD-L1/PD-L2 deficiency and PD-1 receptor inhibition have been associated with increased atherosclerotic lesion size, increased plaque T-cell activation, and enhanced TNF-α secretion.[67,68] In contrast to CTLA-4 inhibition, PD-1 inhibition also exhibited increased lesion macrophage content, and enhanced the cytotoxicity of lesion CD8+ T cells.[68] PD-1 deficiency has been shown to activate both CD4+ T cells and regulatory T cells, but the net effect was still exacerbated atherosclerotic lesion growth and increased plaque T-cell infiltration.[69]

In humans, several studies have observed decreased expression of PD-1 or its ligands in patients with coronary artery disease (CAD) and acute coronary syndrome, suggesting its protective role in atherogenesis and progression to advanced plaque phenotype.[70,71] At baseline, human atherosclerotic

plaque T cells express high levels of PD-1 as a marker of T-cell exhaustion in chronic inflammation.[72] Thus, the delicate co-existence of PD-1–expressing T cells with activated T cells within human plaques raises concern that PD-1 inhibition would lead to exacerbation of atherosclerosis.

INVESTIGATIONAL IMMUNE CHECKPOINT TARGETS AND ATHEROSCLEROSIS

CD40-CD40L PATHWAY. CD40 is a T-cell costimulatory molecule and a member of the TNF receptor family that is present on APCs as well as nonimmune cells such as endothelial cells, VSMCs, and platelets.[73] Its classic ligand, CD40L, is expressed on activated CD4+ T cells. The binding of CD40 to CD40L promotes B-cell proliferation and improves dendritic cell antigen presentation and T-cell activation.[74] CD40/CD40L ligation leads to recruitment of TNF receptor-associated factors that lead to downstream increases in atherogenic cytokines including IL-1β, IL-6, TNF-α, and IFN-γ, which enhances the activities of macrophages.[73]

Activation of the CD40/CD40L pathway has been shown to enhance antitumor immune response and promote tumor cell apoptosis and has been explored in cancer immunotherapy.[75] Several ongoing Phase 1 and 2 clinical trials are evaluating the effect of anti-CD40 agonist antibodies, such as elicrelumab and dacetuzumab, in various hematologic and solid tumor malignancies.[76]

Several studies have explored role of the CD40/CD40L pathway in atherosclerosis. CD40L ligation to CD40 promotes thrombosis due to its activating effects on endothelial cells and platelets and its promotion of tissue factor production.[77,78] Endothelial cells exposed to CD40L exhibit increased expression of adhesion molecules such as VCAM-1 and P-selectin that enhance leukocyte recruitment, a key process in atherosclerosis initiation.[79] CD40L has also been shown to promote foam cell formation in atherosclerotic plaques.[80] Bruemmer et al[81] observed that, in human iliac arteries, the expression of CD40 increased with atherosclerotic stage, and the largest increases occurred in the early stages of atherosclerosis. In later stages of atherosclerosis, the CD40/CD40L pathway stimulation increased secretion of matrix-degrading metalloproteinases that increase plaque rupture vulnerability.[78]

Several preclinical studies have explored the inhibition of CD40/CD40L in reducing atherosclerosis. Blockade of CD40L either via antibodies or knock out models resulted in decreased leukocyte composition in the atherosclerotic plaque and phenotypic evidence of increased plaque stability.[82-85] However, CD40L blockade was inconsistent in achieving plaque size reduction, where studies by Bavendiek et al[85] and Mach et al[82] observed reduced plaque size, whereas 2 studies from Lutgens et al[83,84] did not. In addition, CD40L inhibitory antibodies have been shown to increase the risk of thromboembolic events via platelet activation, limiting its systemic use in atherosclerosis treatment.[86] Recent data from Lacy et al[87] demonstrated differing roles for CD40L depletion on atherosclerosis depending on cell source, with T-cell CD40L inhibition leading to reduced T_h1 polarization and IFN-γ secretion, whereas platelet-CD40L inhibition led to reduced atherothrombosis. These data hold promise for the development of cell-specific CD40L inhibition in the treatment of atherosclerosis.

With further research, CD40L/CD40 blockade may be pursued as a treatment for atherosclerosis. Conversely, with CD40/CD40L agonists being studied in clinical trials for cancer immunotherapy, their possible implications on cardiovascular disease must be carefully considered.

GITR-GITRL PATHWAY. Similar to CD40, glucocorticoid-induced TNF receptor-related protein (GITR) is a T-cell costimulatory molecule present on T and NK cells and it binds to its ligand, GITRL, expressed on APCs and endothelial cells.[88] GITR-GITRL signaling promotes macrophage activity, increases CD8+ T-cell cytotoxicity, and enhances effector T-cell activation by increasing IFN-γ and IL-2 secretion.[89,90] Simultaneously, T_{reg} cells experience a decrease in immunosuppressive effect downstream of GITR-GITRL interaction.[89] The efficacy of tumor inhibition by GITR agonists was directly correlated with intratumor CD4+ and CD8+ levels, suggesting its therapeutic potential in NSCLC, renal cell carcinoma, and melanoma.[91] Several Phase 1 clinical trials have shown limited therapeutic response as monotherapy, but possible synergistic activity in combination with anti-PD-1 agents.[92]

Macrophage and effector T-cell activation and T_{reg} suppression by the GITR/GITRL pathway suggests a proatherogenic role. GITR+ macrophages, T cells, and endothelial cells have been identified within atherosclerotic plaques.[93,94] Moreover, Shami et al demonstrated increased GITR expression in carotid artery plaques in patients with symptomatic cerebrovascular disease, which correlated with increased plaque vulnerability.[94] Kim et al[95] showed that GITR agonist antibodies promoted macrophage production of proatherogenic cytokines, plaque-destabilizing metalloproteinases, and intracellular cell adhesion

molecule 1. Conversely, GITR deficiency has been associated with decreased plaque size and increased plaque stability in mice.[94] Thus, GITR agonism may be beneficial in combination with other ICIs such as PD-1 in cancer immunotherapy, but may worsen atherosclerosis, although studies of the direct effect of GITR agonistic monoclonal antibody on atherosclerosis are needed.

OTHER COSTIMULATORY PATHWAYS: CD27/CD70 AND INDUCIBLE COSTIMULATOR. Agonism of several other costimulatory pathways are being explored as immunotherapy. CD27 is a transmembrane glycoprotein that is part of the TNF superfamily that binds to CD70 (also known as CD27L) expressed on activated T cells. Its agonism enhances T-cell expansion and promotion of memory T cells, with a predilection toward IFN-γ production.[96] It has gained interest as a target for immunotherapy, with ongoing Phase 1/2 trials for anti-CD27 agonists such as varlilumab.[97] With its promotion of IFN-γ production, initial studies postulated that CD27/CD70 agonism would worsen atherogenesis. Surprisingly, chronic inflammation from CD70 overexpression was atheroprotective, as the CD27/CD70 pathway has shown important roles in macrophage efferocytosis, oxLDL clearing, and promotion of atheroma T_{reg} survival.[98,99]

Inducible costimulator (ICOS) is a protein involved in CD4+ and CD8+ differentiation, survival, and proliferation, promoting activation of cytotoxic T cells, enhancing effector T-cell production of IL-4, IL-5, IL-10, and TNF-α, as well as promoting T_{reg} activity.[100] Given its prominent role in the survival of both protumor and antitumor T cells, both ICOS agonists and antagonists are in early-phase cancer immunotherapy trials.[100] In preclinical studies, ICOS inhibition was associated with aggravated atherosclerosis via a reduced T_{reg} population, as well as enhanced IFN-γ production and diminished IL-10 production.[101,102] Thus, contrary to CD40 and GITR, further study of CD27/CD70 and ICOS agonism may one day prove beneficial in atherosclerosis.

INVESTIGATIONAL COINHIBITORY MOLECULES: TIM-3 AND LAG-3. T cell immunoglobulin and mucin domain-containing protein (TIM-3) is a negative regulatory immune checkpoint present on effector T cells, T_{reg} cells, and dendritic cells. It binds to 4 separate ligands, most notably to galectin-9 that triggers T_h1 and CD8+ T-cell death.[103,104] Ongoing clinical trials are studying anti-TIM-3 antibodies such as cobolimab both as monotherapy or in combination with anti-PD-1 inhibitors.[24]

Several preclinical studies have suggested that TIM-3 is a negative regulator of atherosclerosis. Foks et al[105] found that TIM-3 expression was increased in mice fed with an atherogenic diet, and that TIM-3 antibody blockade was associated with larger atherosclerotic plaque size, increased lesion macrophage content, and decreased lesion T_{reg} cells. In atherosclerotic lesions, CD8+ T cells exhibit co-expression of PD-1 and TIM-3, and inhibiting both immune checkpoints was associated with an increase TNF-α and IFN-γ and a decrease in IL-10 and IL-4 when compared with singular PD-1 or TIM-3 blockade.[106] Thus, the development of anti-TIM-3 checkpoint inhibitors poses theoretical risks of exacerbating atherosclerosis.

Lymphocyte-activation gene 3 (LAG-3) is a cell surface protein analogous to CD4 present on T cells and dendritic cells that binds MHC class II molecules and serves as an inhibitory signal. It directly competes with TCR and CD4 binding to MHC class II, suppresses T-cell expansion, and promotes CD4+ T-cell differentiation into T_{reg}.[107] LAG-3-targeting ICIs, such as relatlimab, are being investigated in Phase 2 and 3 clinical trials.[108] One observational study of the Multiethnic Study of Atherosclerosis (MESA) cohort demonstrated that patients with CAD had higher LAG-3 levels, and LAG-3 was a significant CAD risk predictor.[109] Despite this positive correlation, no causal relationship between LAG-3 and atherosclerosis has been established. Preclinical studies are needed to evaluate whether increased LAG-3 expression is a contributory or compensatory mechanism in atherosclerosis.

CD47-SIRP$_\alpha$ (CD47 SIGNAL REGULATORY PROTEIN ALPHA PATHWAY). In addition to T-cell–mediated ICIs, novel classes of immune check therapies being explored include the macrophage-mediated immune checkpoint CD47. CD47 is an Ig-like molecule that binds to signal regulatory protein alpha (SIRPα) and impairs phagocytosis. In areas with high rates of apoptosis and cell turnover, such as within tumors and atherosclerotic necrotic cores, effective clearance of apoptotic cellular debris helps prevent further inflammatory response.[110] This process, known as "efferocytosis" refers to programmed cell removal by which macrophages detect cell surface markers that signal phagocytosis, collectively termed "eat me" signals.[111] By contrast, cells may express markers that impair phagocytosis, termed "don't eat me" signals, such as CD47.

Kojima et al[112] demonstrated an up-regulation of CD47 in both murine and human atherosclerotic plaque, particularly in the necrotic core. Treatment of atherosclerotic models with CD47 inhibitory antibodies markedly reduced atherosclerosis by restoring

efferocytosis, evidenced by the enhanced removal of diseased vascular smooth muscles and macrophages in vivo.[112,113] In addition, CD47 inhibition was shown to down-regulate genes implicated in macrophage response to IL-1 and IFN-γ, leading to significant reduction in atherosclerotic inflammation in positron emission tomography/computed tomography imaging of mouse models.[113] CD47 has also been suggested to reduce the ability of macrophages to remove opsonized targets, including the removal of opsonized clonal smooth muscle cells thought to give rise to the majority of cells in atherosclerotic plaques.[114]

In recent years, CD47 inhibitor therapies have been used in clinical trials aimed at increasing tumor cell recognition and phagocytosis by macrophages. Magrolimab, the first-in-class anti-CD47 antibody, showed promising results in Phase 1B trials of relapsed and refractory non-Hodgkin's lymphoma.[115] It recently gained breakthrough therapy designation by the U.S. Food and Drug Administration, and ongoing trials are evaluating its efficacy in various hematologic and solid tumor malignancies. Interestingly, a small retrospective analysis on the non-Hodgkin's lymphoma trial participants demonstrated a reduction of fluorodeoxyglucose (FDG) uptake in the carotid arteries after 9 weeks of Magrolimab treatment, implying that CD47 inhibition reduces vascular inflammation.[116] Thus, CD47 inhibition may be a shared pathway against both oncogenesis and atherogenesis.

Macrophage efferocytosis has also been shown to be influenced by T_{reg} cell activity. Proto et al[117] showed that T_{reg} cell expansion enhanced efferocytosis via expression of IL-13, which in turn increased IL-10 production in macrophages and led to apoptotic cell engulfment and clearance. Since existing PD-1 and CTLA-4 targeted ICI therapies have been suggested to suppress T_{reg} activity, decreased efferocytosis may be another avenue by which other classes of immune checkpoint therapies may exacerbate atherosclerosis. However, extensive research is needed to substantiate this potential link.

CHOLESTEROL METABOLISM AND T-CELL–MEDIATED IMMUNITY IN CANCER

Clinically, obesity and metabolic syndrome have been clearly linked with increased cancer risk, mediated by many shared risk factors.[118] One shared link is energy metabolism, where alterations in lipid metabolism can shape the immune system's response to tumor activity. Cholesterol metabolism is essential for cancer progression, including the formation of cellular membranes during rapid proliferation and in tumor migration and invasion.[119]

The features of metabolic syndrome, including hypertriglyceridemia, hyperglycemia, and hypercholesterolemia, promote a chronic inflammatory state that paradoxically blocks physiologic immune function.[120] Chronic inflammation and hypercholesterolemia promote an increase in the production of myeloid-derived suppressor cells through a process termed "emergency myelopoiesis."[121] Myeloid-derived suppressor cells inhibit T-cell functions through alterations in TCR receptors that impair downstream signaling, secretion of TGF-β, IL-10, and cytokines that decrease effector T-cell function, and overexpression of PD-L1.[122] In addition, Ma et al[123] used an $Apoe^{-/-}$ mouse model traditionally used to study atherosclerosis to demonstrate negative regulatory effect of hypercholesterolemia on IL-9 levels, which impair CD8+ T-cell differentiation and antitumor response. The enriched cholesterol content of the tumor microenvironment induces T-cell exhaustion and the expression of immune checkpoints such as PD-1, TIM-3, and LAG-3 on CD8+ T cells.[124]

Given the intricate relationship of hypercholesterolemia and repressed T-cell function, it is anticipated that cholesterol levels modulate patient response to immunotherapy. Perrone et al[125] found that among patients receiving ICIs, baseline hypercholesterolemia was associated with improved overall survival rates. Other studies have established improved prognosis in obese patients treated with ICIs.[126,127] Thus it can be postulated that patients with cancer with higher cholesterol levels may have worse T-cell dysfunction by the mechanisms described, and subsequently exhibit a more pronounced response to the restoration of T-cell function by immune checkpoint inhibition. However, these data are limited to date, and whether hypercholesterolemia is a causative factor in improved ICI response or simply a biomarker of chronic inflammation rendering patients more susceptible to immune restoration has yet to be established.

Cholesteryl esters are a storage form of cholesterol that are observed in increased numbers in the tumor microenvironment. One of the key enzymes in this process is Acetyl-coenzyme A acetyltransferase (ACAT1), which promotes cholesterol esterification into the storage form and facilitates cholesterol transport in blood,[128] has been studied in antitumor therapy and atherosclerosis. ACAT1 inhibition has been shown to decrease cancer cell migration and tumor progression in breast cancer and glioblastomas.[129,130] In the early stages of atherosclerosis, ACAT1 expression is increased in macrophages to

enhance their ability to store free cholesterol, and the use of ACAT inhibitors had been shown to promote cell death.[131] The ACAT1 inhibitor avasimibe has been studied in animals and humans with hyperlipidemia, however, its effects on plasma cholesterol and atherosclerotic plaque size were inconsistent.[132-134] Yang et al[135] applied ACAT inhibition to cancer immunotherapy, and demonstrated that the addition of avasimibe to anti-PD-1 therapy was more effective in the treatment of melanoma in mice, with demonstrated enhancement in CD8+ T-cell antitumor activity. Together, these findings imply an important relationship between hypercholesterolemia, a major driver of atherosclerosis, and tumor progression.

CLINICAL IMPLICATIONS OF ICI THERAPY ON ASCVD

Recent clinical data have emerged to suggest an association between ICI use and accelerated atherosclerosis and atherosclerotic cardiovascular events. Initially, a case series of 11 patients suggested that PD-1 blockade may actually improve complicated plaque burden, because PD-1 blockade was associated with regression of atherosclerotic plaque in 3 patients (27%), no change in 7 (64%), and an increase in 1 (9%). However, this study was limited by a short computed tomography scan follow-up period and imaging protocols that were not intended for vascular imaging.[136] Since, 2 case reports have linked PD-L1 and PD-1 inhibitors with rapid interval progression of CAD on left heart catheterization and fatal acute coronary syndrome in metastatic lung and giant bone cell cancer, respectively.[137,138]

Several single-center studies have documented the incidence of ASCVD in ICI therapy. In a retrospective analysis of ICI clinical trials where PD-1 and PD-L1 inhibitors including nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab were tested in patients with NSCLC, Hu et al[139] reported a 1% incidence of myocardial infarction and a 2% incidence of stroke. In a single-center registry by Oren et al[140] of 3,326 patients with any malignancy on ICI therapy including atezolizumab, avelumab, ipilimumab, nivolumab, and pembrolizumab, there was a 7% incidence for both myocardial infarction and stroke within a 16-month period.

In the largest single-center study to date, Drobni et al[7] compared 2,842 patients on any ICIs (the majority of which being PD-1 inhibitors) with controls matched for age, cancer type, and cardiovascular history on their risk of ASCVD-related events over a 2-year follow-up period. ICI use was associated with >4-fold greater risk for composite cardiovascular events (HR: 4.7; 95% CI: 3.5-6.2; $P < 0.001$), >7-fold greater risk of myocardial infarction (HR: 7.2; 95% CI: 4.5-11.5; $P < 0.001$), 3-fold greater risk of coronary revascularization (HR: 3.3; 95% CI: 2.0-5.5; $P < 0.001$), and 4-fold greater risk of stroke (HR: 4.6; 95% CI: 2.9-7.2; $P < 0.001$).

Small-scale human imaging and histologic studies have attempted to substantiate the possibility that ICI therapy increases atheromatous inflammation and atherosclerosis. In Calabretta et al,[141] positron emission tomography scans from 20 patients with melanoma treated with ICIs (80% PD-1 inhibitors, 5% CTLA-4 inhibitors, and 15% combination) showed significant elevation in FDG uptake of all aortic segments about 6 months post-treatment, particularly in noncalcified and mildly calcified segments ($P < 0.001$). However, in a study by Poels et al,[142] 10 patients with melanoma treated with pembrolizumab or combination nivolumab/ipilimumab showed no absolute change in overall vascular FDG-positive inflammation after 6 weeks. These discrepant results may be due to small sample sizes and varying follow-up periods. In a substudy by Drobni et al,[7] 40 patients with melanoma were evaluated via computed tomography at 3 different time points, and ICI treatment was shown to accelerate the rate of atherosclerotic plaque progression 3-fold (from 2.1%/y pre-ICI to 6.7%/y after ICI; $P = 0.02$). In an autopsy study of 11 patients on ICI therapy, although the absolute number of T cells was unchanged, there was an increased ratio of CD3+ cells to CD68+ cells leading to a shift from macrophage- to lymphocyte-predominant inflammation.[143] Future large-scale, long-term imaging and histologic studies will be needed to further clarify the role of ICI on atheromatous plaque progression and immune response.

ROLE OF PHARMACOTHERAPY IN CARDIOVASCULAR RISK REDUCTION IN PATIENTS RECEIVING ICIs

Growing clinical data signaling increased atherosclerosis in ICI therapy invite consideration of pharmacotherapies to reduce cardiovascular events in this patient population. In addition to lipid lowering, statins have been associated with plaque stabilization, endothelial dysfunction reversal, and inflammation reduction. How statins reduce inflammation are not fully understood, but may involve inhibition of beta-2 integrin leukocyte function antigen-1, an adhesion molecule with a role in T cell activation.[144] In Drobni et al[7] the markedly increased rate of aortic

plaque progression associated with ICI therapy was attenuated by the use of statins, although no direct comparisons of cardiovascular events based on statin use were performed. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are an increasingly popular class of monoclonal antibodies that reduce serum low-density lipoprotein (LDL) and atherosclerotic events in higher-risk patients.[145] In contrast to statins, there is much less known about potential anti-inflammatory effects of PCSK9 inhibitors.

The potential for cholesterol levels to modulate ICI response raises important considerations for the effects of these cholesterol-lowering agents on ICI efficacy. Despite the correlation between hypercholesterolemia and improved outcomes of ICI therapy, statins and PCSK9 inhibitors have shown preliminary evidence of synergistic benefit when paired with ICI therapy independent of their cholesterol-lowering effects. In particular, statins have been shown to inhibit protein prenylation leading to enhanced antigen presentation that may be synergistic with immunotherapy.[146] Several clinical studies in patients with advanced NSCLC and malignant pleural mesothelioma treated with ICIs demonstrated that statins were associated with increased response rate, improved time to treatment failure, and progression-free and overall survival.[147,148] Liu et al[149] showed that PCSK9 inhibition with evolocumab synergized with anti-PD-1 therapy to suppress tumor growth by increasing the expression of MHC I proteins and enhancing lymphocyte proliferation into the tumor. These findings highlight the complex interplay between cholesterol metabolism and the immune system that requires further research, but demonstrate that statins and PCSK9 inhibitors have the potential to both enhance ICI efficacy and treat ICI-related atherosclerosis. However, Drobni et al[150] recently demonstrated increased risk of myopathy in patients treated concurrently with statins and ICIs. Thus, further study is needed to confirm the safety of existing therapies and identify novel therapeutics in the treatment of ASCVD in the context of ICI use.

CONCLUSIONS

Numerous studies have demonstrated the role of various immune checkpoint pathways in atherogenesis, and emerging clinical studies have begun describing an association between ICI use and increased risk of ASCVD. Taken together, these reports indicate that the cardiovascular effects of immune checkpoint therapies extend beyond the rare incidences of myocarditis. Because ASCVD is one of the most prominent causes of morbidity and mortality worldwide, if further clinical studies confirm this association, the risk of major adverse cardiovascular events in patients receiving ICIs must be carefully considered.

The current level evidence linking ICI therapy to atherogenesis and atherosclerotic events is not without its limitations. Preclinical studies thus far have not clearly delineated how immune checkpoint alteration will impact each stage of atherosclerosis. It has become increasingly recognized that the microenvironmental context of cell death and apoptosis is important in determining whether the net effect is atherogenic or atheroprotective.[111] Thus, the effect of ICIs on atherosclerosis may prove to be more heterogeneous and evolve as clinical disease progresses. Careful mechanistic understanding of the effect of ICI at each stage of atherosclerosis is needed to determine the timing and need of interventions.

On a clinical level, the linkage between ICI use and atherosclerosis has only been suggested by smaller observational studies, and extensive further evidence with larger sample sizes and longer study duration are needed to confirm this association and estimate the rate of adverse cardiovascular events in this population. If future studies continue to demonstrate significant ASCVD burden in patients receiving ICIs, effort must be taken to identify atherosclerotic development and control reversible atherosclerosis risk factors. In this effort, integration of baseline and routine atherosclerotic imaging in these patients may help to quantify atherosclerotic burden.

Patients who develop ASCVD from ICI therapy represent a unique patient population that warrants our investigation of potential pharmacotherapeutic options. The role of statins, PCSK9 inhibitors, and other pharmacotherapies should be explored in animal models, and randomized controlled trials are needed to prove their effectiveness and safety in this population.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Drs Stein-Merlob and Nayeri are supported by the National Institutes of Health Cardiovascular Scientist Training Program (grant T32HL007895). Dr Sallam is supported by the American Heart Association Transformational Project Award and the National Institutes of Health grant HL149766. Dr Neilan is supported by a gift from A. Curt Greer and Pamela Kohlberg, and grants from the National Institutes of Health/National Heart, Lung, and Blood Institute grants R01HL130539, R01HL137562, and K24HL150238. Dr Yang is supported by a grant from CSL Behring. Dr Neilan has been a consultant to and received fees from Amgen, H3-Biomedicine, and AbbVie outside of

the current work; has received consultant fees from Bristol Myers Squibb for a Scientific Advisory Board focused on myocarditis related to immune checkpoint inhibitors; and has received grant funding from AstraZeneca on atherosclerosis with immune checkpoint inhibitors. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Eric H. Yang, UCLA Cardiovascular Center, 100 Medical Plaza, Suite 630, Los Angeles, California 90095, USA. E-mail: ehyang@mednet.ucla.edu. Twitter: @datsunian.

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KEY WORDS **atherosclerosis, cardio-oncology, cardiovascular disease, immunology, inflammation**