



Immunotherapeutic Strategies in Cancer and Atherosclerosis—Two Sides of the Same Coin

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The development and clinical approval of immunotherapies has revolutionized cancer therapy. Although the role of adaptive immunity in atherogenesis is now well-established and several immunomodulatory strategies have proven beneficial in preclinical studies, anti-atherosclerotic immunotherapies available for clinical application are not available. Considering that adaptive immune responses are critically involved in both carcinogenesis and atherogenesis, immunotherapeutic approaches for the treatment of cancer and atherosclerosis may exert undesirable but also desirable side effects on the other condition, respectively. For example, the high antineoplastic efficacy of immune checkpoint inhibitors, which enhance effector immune responses against tumor cells by blocking co-inhibitory molecules, was recently shown to be constrained by substantial proatherogenic properties. In this review, we outline the specific role of immune responses in the development of cancer and atherosclerosis. Furthermore, we delineate how current cancer immunotherapies affect atherogenesis and discuss whether anti-atherosclerotic immunotherapies may similarly have an impact on carcinogenesis.

Keywords: tumor, atherogenesis, cardiovascular disease, immunotherapy, immunity, T cell, checkpoint inhibition, co-stimulatory molecule

INTRODUCTION

Although prevention strategies and therapeutic opportunities have been significantly improved during the past decades, atherosclerotic cardiovascular diseases (CVD) and cancer still represent the two most common causes of death worldwide (1). As already recognized by Rudolph Virchow in the nineteenth century (2, 3), the critical role of inflammatory processes in atherogenesis and carcinogenesis is now well-established and has prompted investigation of strategies to combat these deadly diseases by modulating underlying immune responses (4–10). Several anti-cancer immunotherapies, such as cytokines, antibodies targeting immune cell receptors, or immune checkpoints, dendritic cell therapy, and chimeric antigen receptor (CAR) T cell therapy, already found their way into clinical practice and thereby revolutionized cancer treatment (9, 11). In stark contrast, clinically approved immunotherapies for CVD are still not available [except for antibodies targeting proprotein convertase subtilisin/kexin 9 (PCSK9) to lower low-density lipoprotein (LDL) cholesterol, representing an immunotherapeutic approach in a broader sense (12, 13)]. In 2017, the CANTOS trial demonstrated that administration of an antibody directed

against the pro-inflammatory cytokine interleukin-1 β (IL-1 β) reduced cardiovascular events in patients with coronary artery disease (CAD), thereby providing first evidence for effectiveness of an immunotherapy in CVD (14). Yet, this therapy increased the risk of fatal infections and did not reduce mortality, which consequently prevented its approval for treatment of CVD (14). CANTOS illustrated the central dilemma of many immunomodulatory strategies: Broad interventions in the immune system can have detrimental side effects. In general, anti-atherosclerotic strategies are geared toward suppression of vascular inflammation (5, 8, 15), whereas immune-based cancer treatments aim at enhancing immune responses against tumor cells (7, 9). The therapeutic efficacy of several anti-cancer immunotherapies is constrained by their proimmunogenic (and thus proatherogenic) properties, increasing the risk to develop CVD in patients (16). Particularly, immune checkpoint inhibitors directly aggravate atherosclerotic plaque growth in patients (17). Whereas, cancer survival has dramatically improved over the past few decades (18), the exposure of cancer survivors to therapy-induced cardiovascular risk represents an emerging problem, which leads to excess cardiovascular mortality and thus significantly affects long-term prognosis (19–22). This problem is relevant, as the global cancer burden is expected to increase by ~47% within the next 20 years and to reach more than 28 million cases in 2040 (23).

In recent years, vaccination strategies aiming to either induce immune responses against tumor-specific neoantigens (4) or to suppress immunity against atherosclerosis-related autoantigens (6) have emerged. Immunization strategies are promising as they enable specific immunomodulation without impairing host defense responses or accelerating progression of atherosclerosis. Whereas, anti-atherosclerotic vaccination strategies are still in their infancy (6), therapeutic cancer vaccines are already being investigated in clinical trials (4).

In this review, we will provide an overview of current immunomodulatory concepts for treatment of cancer and atherosclerosis with a focus on their reciprocal interactions and consequences. Finally, we will highlight the potential of immunization strategies against cancer and CVD that enable targeted, antigen-specific immunity without affecting the immune system.

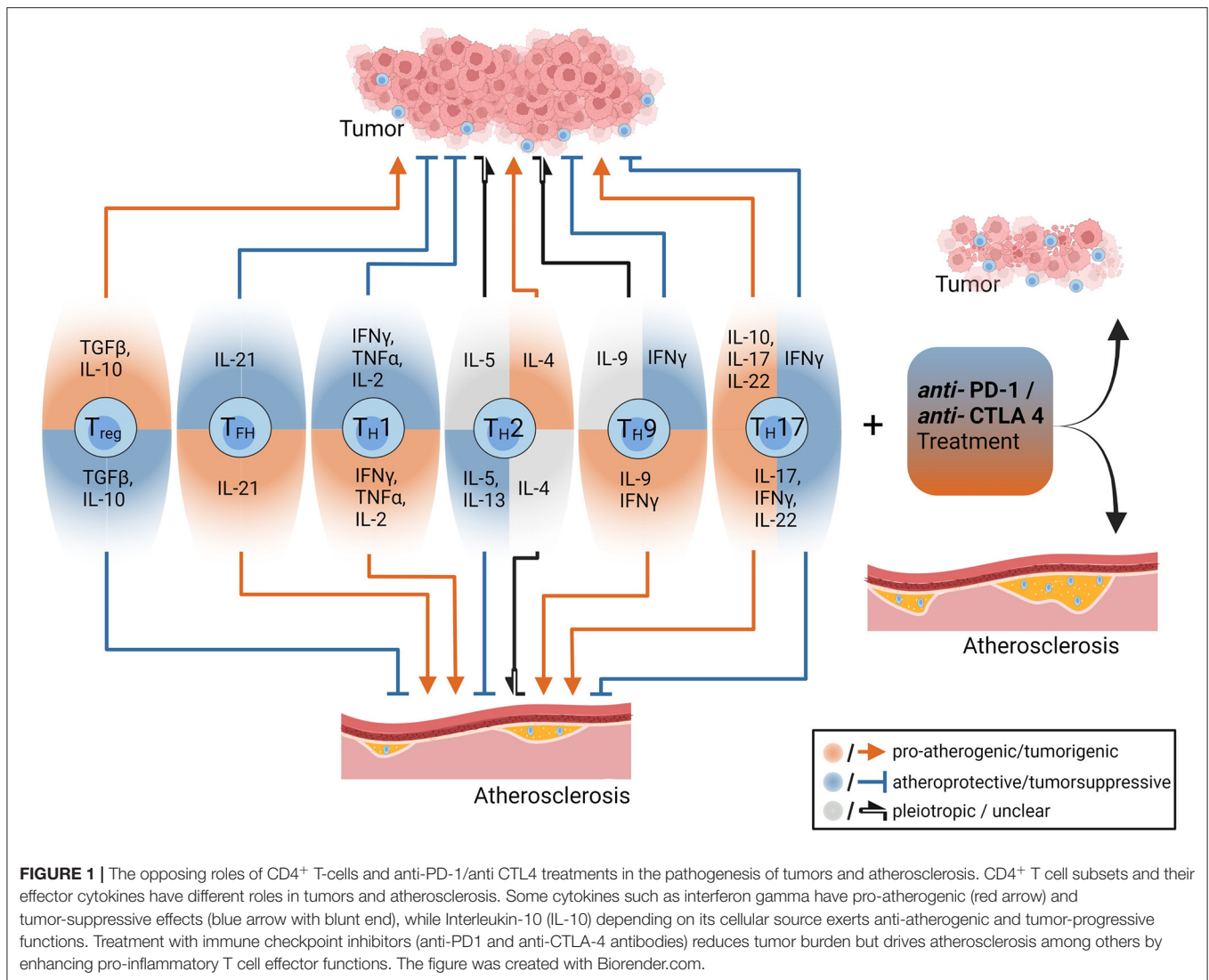
INFLAMMATION AND ADAPTIVE IMMUNITY IN ATHEROGENESIS

Atherosclerosis involves formation of lipid-laden plaques in large and medium-sized arteries (24), which may rupture or erode and give rise to acute thrombotic vessel occlusion (25). Plaque formation primarily occurs in regions with disturbed blood flow and low endothelial shear stress (26). Such hemodynamic alterations induce a cascade of endothelial dysfunction, subendothelial accumulation and subsequent oxidation of lipoproteins, and finally an inflammatory response that is characterized by monocyte infiltration and foam cell formation (25, 26). Extensive research during the past decades has indicated that plaque-related inflammation is not simply a

passive process but is rather orchestrated by an adaptive immune response involving T cells and humoral immunity (27).

T cells derive from hematopoietic progenitor cells and undergo a complex maturation and selection process in the thymus, which is characterized by development of a unique, antigen-specific T cell receptor (TCR) through random genetic recombination (28) and elimination of cells that are either non-functional or bind self-antigens with too high-affinity, which are potentially dangerous for the host (29). The high prevalence of autoimmune disorders indicates the insufficiency of this process. Eventually, the TCR and one of its co-receptors CD4 or CD8 are expressed on the T cell surface, which is released into the periphery and circulates through the body to encounter its cognate antigen (30). Activation of a naïve T cell requires two signals. First, the TCR must be bound by its cognate antigen: CD4⁺ T cell activation requires presentation of an antigenic peptide-sequence, the so-called epitope, on major histocompatibility complex class II (MHC-II) molecules, which are exclusively expressed by professional antigen-presenting cells (APCs), such as dendritic cells, macrophages and B cells. CD8⁺ T cells recognize antigens presented on MHC-I molecules, which are expressed by all nucleated cells (31). Second, the T cell must simultaneously receive a proper co-stimulatory signal, that is binding of a specific receptor (such as CD28) by its ligand expressed on the APC (32). Once activated, T cells proliferate and CD8⁺ T cells become cytotoxic, whereas CD4⁺ T cells can differentiate into a variety of different subtypes, which are characterized by expression of specific surface markers, transcription factors (TFs) and cytokines (33). For example, T helper 1 (T_H1) cells, which are characterized by expression of the TF T-box expressed in T cells (T-bet), exert pro-inflammatory effects through production of interferon gamma (IFN- γ) (**Figure 1**). In contrast, regulatory T cells (T_{regs}), which are characterized by expression of the TF forkhead box protein P3 (FoxP3), produce the anti-inflammatory cytokines IL-10 and transforming growth factor beta (TGF- β) and thus ensure immune tolerance. For a thorough overview of different T cell subtypes and their role in atherosclerosis the interested reader is referred to Saigusa et al. (34).

Presence of T cells in atherosclerotic plaques was firstly described by Hansson and colleagues more than 30 years ago (35). T cells within the plaques were activated (36) and *in vitro* work showed lesional CD4⁺ T cells responding to oxidized low-density lipoprotein (oxLDL), which established the theory of T cells contributing to plaque formation (37). By now, CD4⁺ and CD8⁺ T cell responses against plaque-associated autoantigens have been identified to modulate atherogenesis (34, 38, 39). Whereas, T cell reactivity against LDL was originally thought to be induced by oxidation-dependent generation of neoepitopes representing “altered self” (37), more recent work has identified CD4⁺ T cells responding to peptides of native Apolipoprotein B (ApoB), the core protein of LDL, chylomicrons, and other lipoprotein particles. Several unmodified ApoB-peptides have been found to bind murine and human MHC-II molecules with high affinity and thereby evoke a CD4⁺ T cell response (40–43). Such ApoB-reactive (ApoB⁺) CD4⁺ T cells mainly comprise T_{regs}, which confer atheroprotective properties in



healthy humans, but coexpress TFs typical of proatherogenic TH1 or TH17 cells in individuals with subclinical atherosclerosis as determined by carotid ultrasound (42). Preclinical studies further elucidated that CD4⁺ Tregs, particularly those reactive to ApoB, gradually acquire proatherogenic TH1/TH17, TH1/Treg or T follicular helper (TFH) phenotypes during atherogenesis (43–45). Whereas, therapeutic interventions that aim to stabilize and/or expand ApoB⁺ Tregs hold promise for atherosclerosis prevention and treatment, immunomodulatory therapies causing destabilization of Tregs naturally aggravate progression of atherosclerotic lesions (46).

Besides T cells, humoral immune responses against plaque-associated autoantigens have been implicated in atherogenesis (38, 47). Antibodies directed against oxLDL are detectable in human plaques (48) and in plasma samples of humans with or without atherosclerotic CVD (49, 50). Accordingly, B cells can be found in healthy and atherosclerotic vessels, especially in arterial tertiary lymphoid organs located in the adventitia (51).

Autoantibodies against oxLDL were shown to block uptake of oxLDL by macrophages (52, 53) and to confer atheroprotection (54). Genetic B-cell depletion aggravated atherosclerosis in LDL-receptor-deficient (*Ldlr*^{-/-}) mice (55). Yet, depletion of mature B cells through administration of a CD20 monoclonal antibody was unexpectedly atheroprotective in Apolipoprotein E-deficient (*Apoe*^{-/-}) and *Ldlr*^{-/-} mice (56, 57). This treatment preserved the production of natural IgM antibodies directed against oxLDL but reduced anti-oxLDL IgG antibodies (56). Adoptive transfer of B2 B cells, but not B1 B cells, to lymphocyte or B cell deficient *Apoe*^{-/-} mice was proatherogenic (57). B cells mainly consist of B2 B cells (which are thus termed conventional B cells) that undergo maturation in the spleen and can produce high-affinity IgG antibodies after receiving T cell help (58). B1 B cells represent a specialized B cell subpopulation: They develop in the fetal and neonatal period, harbor the capability of self-renewal, mainly reside in body cavities and are characterized by the production of so called “natural” IgM antibodies (59).

Taken together, different B cell subsets and antibody subtypes may exert diametral functions in atherogenesis and therapeutic modulation of humoral immune responses could represent an attractive anti-atherosclerotic strategy but also promote atherosclerosis progression.

INFLAMMATION AND ADAPTIVE IMMUNITY IN CANCER

In the nineteenth century, the German physicians Rudolph Virchow, Wilhelm Busch and Friedrich Fehleisen independently hypothesized that inflammation may affect carcinogenesis (2, 60). Whereas, Virchow assumed that leukocyte infiltrates represented an underlying cause of cancer (2), Busch and Fehleisen suggested that inflammation may reverse tumorigenesis (60). After independently observing involution of malignancies in patients with erysipelas, they demonstrated tumor regression in cancer patients upon intentional infection with bacteria isolated from erysipelas (61, 62). Later, the American surgeon William Coley reported disappearance of tumors in patients with inoperable sarcoma or other types of cancer after treatment with heat-inactivated bacteria which was termed “Coley’s Toxin” (63). In 1909, Paul Ehrlich suggested that cellular immunity may recognize neoplastic cells and protect from tumor development, although he was not able to experimentally substantiate this hypothesis (64). First experimental proof for anti-tumor immune responses was provided by Gross and Foley around 1950 (65, 66) and Paul Ehrlich’s concept was adopted by Lewis Thomas and Sir Frank Macfarlane Burnet who proposed that lymphocytes recognize and target cancer cells through their expression of tumor-specific antigens, similar to homograft rejection (known as immunosurveillance) (7, 67). Yet, this theory was abandoned after immunologically impaired animals, such as athymic nude mice, showed similar susceptibility to experimentally induced tumors (68, 69). Several limitations of these experiments became evident: Nude mice—despite lack of T and B cells—are not completely immunocompromised and especially susceptible to 3-methylcholanthrene, the chemical carcinogen which was used for tumor induction (due to expression of highly active enzyme isoforms involved in biotransformation of the chemical) (68). Novel immunocompromised mouse models with pure genetic backgrounds demonstrated that lymphocyte deficiency (70), lack of perforin (an important component of cytotoxic T lymphocyte granules) (71, 72), and ablation of proinflammatory cytokine signaling (70–73) increased tumor susceptibility in mice, which led to the renaissance of the immunosurveillance theory (68). This preclinical evidence was supported by studies reporting an increased cancer risk in immunocompromised patients (74–76) and that tumor lymphocyte infiltration predicts better outcome (77, 78). Despite overall proof in support of the immunosurveillance theory was provided, subsequent work demonstrated that immunity may also exert tumor-sculpting effects (68): Tumors derived from immunocompromised mice were rejected more frequently when transplanted into immunocompetent recipients than tumors derived from wild-type controls (70, 72, 79, 80). Thus, the

immune system of the wild-type donors must have shaped tumors to become less immunogenic and more resistant to the hosts (uncompromised) immune response.

To account for the dual role of the immune system in tumor development, G.P. Dunn and R.D. Schreiber proposed the groundbreaking “immunoediting” or “three E’s” theory in 2002 (68), which is the current explanation of tumor-related immune responses (81). The theory involves three processes: (1) In the elimination phase, which conforms to the original immunosurveillance theory, tumor cells are targeted by innate and, subsequently, adaptive immune cells including tumor antigen-specific CD4⁺ and CD8⁺ T cells. If the immune system is successful in destroying all tumor cells, progression to subsequent phases is prevented. (2) In the equilibrium phase, that may last for years, tumor cells that have survived the initial elimination process and the ongoing immune response are in balance. Although tumor growth is still under immunological control, the immune system fails in eliminating all tumor cells, and thus causes selection pressure on the surviving variants. (3) In the escape phase, tumor cells that have undergone extensive immunoediting, evade immunological control, and expand rapidly, resulting in development of clinically apparent disease (68).

More recently, immunological processes underlying the three phases of immunoediting have been characterized in greater detail, which has led to development of immunotherapies that efficiently enhance anti-tumor immune responses (82, 83). Modern technologies have enabled identification of tumor-specific, MHC-I and -II restricted neoantigens and detection of CD8⁺ and CD4⁺ T cells responding to such neoantigens (82, 83). These technologies include deep-sequencing approaches to determine the “mutanome,” that is the entirety of tumor-specific mutations, followed by *in-silico* prediction algorithms to identify mutation-specific epitopes capable of binding to MHC-I or -II molecules (84–88). In a second step, immunogenicity of identified epitopes is verified through T cell restimulation assays of peripheral blood mononuclear cells from the sequenced patient (84, 86–89) or MHC-I (85, 90) and -II (91, 92) tetramers or multimers detecting tumor-neoantigen-specific CD8⁺ and CD4⁺ T cells, respectively. Finally, multimer-selected neoepitope-specific CD8⁺ and CD4⁺ T cells can be phenotyped by flow-cytometry or (single-cell) RNA-sequencing approaches (90–92). Whereas, initial studies were focused on the role of CD8⁺ T cells in mediating anti-tumor immunity (85, 87, 93), subsequent work established that the immunogenic mutanome—against former expectations—predominantly induced a CD4⁺ T cell response in mice and humans (86, 89–91, 94). Tumor neoepitope-reactive CD4⁺ T cells were crucially involved in generation of potent anti-tumor CD8⁺ T cell responses (92, 95). This T cell help is mainly mediated by interactions of CD40 ligand (CD40L), which is expressed on the surface of activated CD4⁺ T cells, and CD40 on the surface of APCs (96). Additionally, CD4⁺ T cells may exert direct anti-neoplastic activity through production of pro-inflammatory cytokines or execution of cytotoxic signals on tumor cells and aid in B cell mediated humoral anti-tumor responses through CD40L signaling (97).

Neopeptide-specific CD4⁺ T cells of the T_H1 subtype are involved in anti-tumor responses (92). Adoptive transfer of neopeptide-specific CD4⁺ T_H1 cells led to tumor regression in a patient with metastatic cholangiocarcinoma (98). In line with this, high levels of circulating tumor-antigen-specific T_H1 CD4⁺ T cells and low levels of CD4⁺ cells co-expressing the immune-checkpoints programmed cell death protein 1 (PD-1) and T cell immunoglobulin and mucin-domain containing-3 (Tim-3) predict better survival in lung cancer patients (99). In contrast, high levels of tumor-infiltrating T_{regs}, which can be found in various cancer types, are associated with poor prognosis (100, 101). Animal studies identified tumor-induced conversion of CD4⁺ non-T_{regs} into T_{regs} as an important mechanism of immune escape (102) and, accordingly, circulating tumor-antigen-specific T_{regs} can be detected in cancer patients but not in healthy individuals (103). Other T helper cell subsets, such as T_H2 and T_H17 cells, can also be found in the tumor microenvironment, but their specific role in tumor immunity and prognostic importance are still under debate (104, 105).

In conclusion, CD4⁺ T cells responding to tumor-specific neopeptides play an important role in mediating anti-tumor immune responses. Yet, tumor cells may engage various escape mechanisms to acquire resistance to this response, which include induction of CD4⁺ T cell phenotype switching from proinflammatory anti-neoplastic T_H1 cells into immunosuppressive and thus tumor growth-promoting T_{regs} (105).

EFFECTS OF CLINICALLY APPROVED CANCER IMMUNOTHERAPIES ON ATHEROGENESIS

Several immunotherapeutic strategies aim at preserving or restoring anti-tumor immune responses. Yet, the opposing roles of adaptive immunity in atherosclerosis and cancer development (Figure 1) implicate that such therapeutic approaches might involve proatherogenic side effects (17), especially if they are not antigen-specific but affect the immune system as a whole. In contrast, B cell depleting antibodies and antibodies targeting growth factor receptors overexpressed by tumor cells may confer atheroprotection. In the following section we will discuss effects of clinically approved cancer immunotherapies on atherogenesis and delineate their mechanistic background (an overview of these effects is given in Table 1).

Immune Checkpoint Inhibitors (ICIs)

Immune checkpoints refer to a variety of regulatory pathways that exert inhibitory actions on adaptive immune cells and beyond and are thus critical for preservation self-tolerance and prevention of exaggerated immune responses (130). The Nobel prize winning discoveries of James P. Allison and Tasuku Honjo, who unraveled that tumor cells may engage immune-checkpoint pathways to escape from anti-tumor immune responses, have paved the way for the development of monoclonal antibodies against these molecules—immune checkpoint inhibitors (ICIs)

(131, 132). Ipilimumab inhibits the cytotoxic T lymphocyte antigen 4 (CTLA-4) and was shown to improve overall survival in patients with metastatic melanoma (133), which made it the first ICI approved by the Food and Drug Administration (FDA) in 2011 (134). Subsequently, four antibodies (pembrolizumab, nivolumab, cemiplimab, and dostarlimab) targeting the co-inhibitory programmed cell death protein 1 (PD-1) and three antibodies (atezolizumab, durvalumab, and avelumab) directed against the programmed cell death ligand 1 (PD-L1) were demonstrated to effectively improve survival in several malignancies (134, 135) which led to the FDA-approval for treatment of 19 different cancer types and two tissue-agnostic conditions [that is a tumor with a specific genetic alteration regardless of the cancer type and location (136)]. ICIs have become a cornerstone of modern cancer therapy and nowadays more than 40% of cancer patients are eligible for ICI treatment (137).

Given that immune checkpoints represent important regulators of physiological immune responses, ICI therapy can naturally involve inflammatory side effects, which are referred to as immune-related adverse events (IRAEs) (138). Although the precise pathomechanisms of such IRAEs are not yet fully clear, unconstrained activation of autoreactive T cells is suggested to play a dominant role (138). CTLA-4 and PD-1 are co-inhibitory molecules expressed on the cell surface of CD4⁺ and CD8⁺ T cells (139, 140). When bound by their ligands—CD80/CD86 and PD-L1/PD-L2—CTLA-4- and PD-1 suppress activation of T cells (140). As mentioned above, T cell activation requires simultaneous engagement of the TCR by its cognate antigen and proper costimulatory signals (32). Activation of CD28, the prototype co-stimulatory molecule, by its ligands CD80 or CD86 induces high T cell surface expression of the co-inhibitory molecule CTLA-4 (141). CTLA-4 binds CD80/CD86 with much higher affinity than CD28. However, in contrast to CD28, CTLA-4 does not exert stimulatory but inhibitory signals and thus attenuates T cell activation (141). Given that CD80/CD86 are expressed on the surface of APCs, CTLA-4 inhibits T cell activation mainly in the priming phase. Prolonged TCR stimulation during an ongoing immune response induces PD-1 expression on the cell surface of T cells (141). When bound by its ligands PD-L1 or PD-L2, which can be expressed by tumor cells, PD-1 attenuates TCR-signaling and thus reduces T cell proliferation and cytokine production. Thus, PD-1 mediates T cell inhibition in the effector phase and is used as a marker of T cell exhaustion (141). Consequently, antibody-mediated inhibition of CTLA-4, PD-1 and PD-L1 enhances T cell activation. IRAEs can affect almost every organ and mostly occur within 2–16 weeks after treatment initiation (138, 142). According to a recent meta-analysis including 36 phase II and III randomized controlled trials (RCTs), the pooled incidence of all IRAEs ranges between 54 and 76% (143). Whereas, the incidences of specific IRAEs depend on the ICI used and several other factors, the integumentary, gastrointestinal, endocrine, hepatic, and pulmonary systems are overall most commonly affected (143, 144). In a meta-analysis of 112 trials including 19,217 patients, IRAE-associated fatality rates ranged between 0.36% for anti-PD-1 mono-therapy and 1.23% for PD1/PD-L1

TABLE 1 | Pro-atherogenic and athero-protective effects of current cancer immunotherapies.

Type of immunotherapy	Specific approach/substance	Compounds	Effect on atherosclerosis in clinical trials	Effect on atherosclerosis in animal studies	Potential mechanisms
Immune checkpoint inhibitors	Anti-CTLA4-Abs	Ipilimumab	↑ (17, 106)	↑ (107–111)	<ul style="list-style-type: none"> - Increased plaque-infiltration by CD4⁺ and CD8⁺ T cells - Higher expression of proinflammatory cytokines (IFN-γ and TNF-α) by T cells - Enhanced T cell activation
	Anti-PD1-Abs	Pembrolizumab, Nivolumab, Cemiplimab, Dostarlimab			
Monoclonal antibodies	Anti-PD-L1-Abs	Atezolizumab, Durvalumab, Avelumab			
	Anti-CD20-Abs	Rituximab, Obinutuzumab, Ofatumumab	↓ (112–114)	↓ (56, 57)	<ul style="list-style-type: none"> - Depletion of mature B cells and reduction of anti-oxLDL IgG antibodies
	VEGF inhibitors	Bevacizumab, Ramucirumab	↑ (115–117)	↑ (118)	<ul style="list-style-type: none"> - Induction of an inflammatory endothelial cell phenotype and impairment of endothelial function - Reduction and functional impairment of T_{regs} and induction of proinflammatory T_H1 cells
	EGFR targeting Abs	Cetuximab, Nectinumab, Panitumumab	–	↓ (119–121)	<ul style="list-style-type: none"> - Reduced accumulation of macrophages in plaques - Reduced lipid uptake by macrophages and reduced foam cell formation - Reduced CD4⁺ T cell activation, proliferation and plaque infiltration - Reduced pro-inflammatory cytokine production - Reduced SMC proliferation
Cytokines	IFN- α	Interferon alfa	↑ (122, 123)*	↑ (124)	<ul style="list-style-type: none"> - Increased plasma cholesterol and triglyceride levels - Induction of lipid uptake by macrophages and increased foam cell formation - Inhibition of T_{reg} activation and proliferation - Direct stimulation of cytotoxic CD4⁺ T cell function - Sensitization of antigen-presenting cells toward pathogen-derived TLR4 ligands
	IL-2	Aldesleukin	High-dose: ↑ (125) Low-dose: ?**	High-dose: ↑ (126) Low-dose***: ↓ (127)	<ul style="list-style-type: none"> - High-dose: unspecific expansion of T cells - Low-dose: selective expansion of functional T_{regs}
Antifolate	DHFR inhibition	Methotrexate	- (128)	↓ (129)****	<ul style="list-style-type: none"> - Attenuation of monocyte maturation and recruitment - Modulation of lipoprotein transcellular transport - Reduction of pro-inflammatory cytokine production

↑ = proatherogenic effect. ↓ = atheroprotective effect. *These studies demonstrated an association between plasma IFN- α levels and atherosclerosis. A direct effect of IFN- α administration on atherosclerosis has not yet been shown in clinical trials. **Currently investigated in the "Low-dose interleukin-2 in patients with stable ischemic heart disease and acute coronary syndromes (LILACS)" trial. ***and complexed with a specific anti-IL2-mAb (JES6-1A12).****delivered via nanoparticles.
 Abs, monoclonal antibodies; CTLA4, cytotoxic T lymphocyte antigen 4; DHFR, dihydrofolate reductase; EGFR, epidermal growth factor receptor; IFN- α , interferon alpha; IFN- γ , interferon gamma; IL2, interleukin 2; mAb, monoclonal antibody; oxLDL, oxidized low density lipoprotein; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SMC, smooth muscle cell; TLR4, toll-like-receptor 4; TNF- α , tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

plus CTLA-4 combinational therapy and were most commonly caused by colitis, pneumonitis, hepatitis, myocarditis and neurotoxic effects (145). Cardiovascular IRAEs, which include myocarditis, pericardial diseases, heart failure, dyslipidemia,

myocardial infarction, and cerebral arterial ischemia, are, overall, relatively rare with an incidence ranging between ~3 and 20 per 1,000 patients (146). Yet, cardiovascular toxicities are severe in over 80% of cases (147) and myocarditis, which carries the

highest fatality risk of all IRAEs (40–50%), is of particular prognostic relevance (145, 147).

Besides acutely occurring cardiovascular IRAEs, recent evidence has suggested that ICI therapy may promote atherogenesis (148, 149). In a retrospective analysis of 1,215 patients treated with ICIs, atherosclerotic cardiovascular events (CVE) occurred in 1% within a follow-up period of 6 months (150). In three meta-analyses, the ICI-related incidence of myocardial infarction and stroke ranged from 0.4 to 1.0% and 1.1 to 2.0%, respectively (149). Yet, the majority of studies included in these meta-analyses were not specifically designed to assess CVE and may thus underestimate incidences (149). To evaluate the ICI-related risk of atherosclerotic CVE (defined as the composite of myocardial infarction, coronary revascularization, and ischemic stroke), Drobni et al. analyzed event-rates in 2,842 patients treated with ICIs and matched controls (17). Additionally, a case-crossover analysis was performed, in which event rates within the 2 years before (control period) and the 2 years after (at-risk period) initiation of ICI therapy were compared. ICI therapy was associated with a 3-fold and almost 5-fold higher risk of atherosclerotic CVE in the matched-control study and case-crossover analysis, respectively (17). In a nested imaging substudy including 40 patients, a 3-fold increase in aortic atherosclerotic plaque volume progression from 2.1%/year before to 6.7%/year after ICI initiation could be detected (17). Another recent study retrospectively analyzed 2-[¹⁸F]fluorodeoxyglucose (FDG) positron emission tomography/computed tomography scans, which had been performed in 20 melanoma patients before and during ICI treatment (mean time interval: 4.4 months) (106). A significantly increased FDG uptake in large arteries after ICI treatment initiation could be detected, pointing toward an ICI-related induction of arterial inflammation (106). In accordance to these clinical findings, a series of animal studies reported enhanced plaque inflammation and accelerated atherogenesis in *LDLr*^{-/-} mice genetically deficient for or treated with inhibitory antibodies against PD-1, PD-L1 and CTLA-4 (148, 149). This was accompanied by an increased number of plaque-infiltrating CD4⁺ and CD8⁺ T cells (107–111), higher expression of proinflammatory cytokines [IFN- γ and tumor necrosis factor alpha (TNF- α)] by T cells (107, 111), and enhanced T cell activation (108, 110, 111).

Collectively these data emphasize that ICI therapy promotes atherogenesis and substantially increases the risk of atherosclerotic CVE. Presumably, ICIs exert their proatherogenic effects—at least in part—through disinhibition of T cells responding to plaque-associated autoantigens. Atherosclerosis is a slowly progressing disease and all above-mentioned clinical studies were limited by relatively short follow-up periods. As indications for ICI therapy are rapidly expanding and cancer-survival has dramatically improved in recent years, the detrimental impact of ICIs on atherogenesis will, therefore, likely become a more relevant health issue in the future.

Antibody Therapy

Since the FDA approval of muromonab-CD3, a monoclonal antibody targeting the T cell co-receptor CD3, for the prevention of transplant rejection in 1986, more than 100 therapeutic

antibodies have been included in clinical practice (135). Rituximab, a monoclonal antibody targeting the B cell receptor CD20, was approved for treatment of follicular lymphoma in 1997, which opened the door for the use of antibodies in cancer therapy (151). Cancer has emerged as the most common condition for antibody therapy with currently over 40 FDA-approved antibodies (including ICIs) for treatment of several cancer types (135). Antibodies can target cancer through several mechanisms, including direct tumor cell killing, immune-mediated tumor cell-killing, and inhibition of neovascularization or stroma cells (152, 153). Direct tumor cell killing can be achieved through eliciting agonistic activity to apoptosis-promoting receptors, inhibiting growth factor receptor signaling, neutralizing key enzymes, or delivering cytotoxic agents into the cell (152, 153). Mechanisms of immune-mediated tumor cell killing include induction of phagocytosis, complement-activation and cellular toxicity (152, 153). Besides ICIs, the use of several other monoclonal antibodies in cancer therapy is constrained by their cardiovascular side effects, which include myocarditis, heart failure, arrhythmia, orthostatic dysregulation and atherosclerotic cardiovascular events (16). Fortunately, the latter complication is rare and some antibodies can even confer atheroprotective effects.

Antibody-Mediated B Cell Depletion

During the past two decades, B cell depleting strategies have been used for treatment of B cell lymphoma and several autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus (SLE) and multiple sclerosis (MS) (151, 154). In addition to rituximab and other antibodies targeting CD20 (e.g., obinutuzumab and ofatumumab), antibodies directed against the B cell surface proteins CD19 (blinatumomab), CD22 (inotuzumab ozogamicin and moxetumomab pasudotox), CD38 (daratumumab and isatuximab) and CD319 (elotuzumab) have been approved to treat these conditions (153).

As mentioned above, depletion of B cells through administration of a CD20-specific antibody ameliorated atherogenesis in *Apoe*^{-/-} and *Ldlr*^{-/-} mice (56, 57). In line with this, treatment of *Apoe*^{-/-} mice with a monoclonal antibody targeting B cell activating factor-receptor (BAFFR) to selectively deplete mature B2 cells while sparing B1 cells conferred atheroprotection (155). Similarly, antibody-mediated inhibition of the cytokine B cell-activating factor (BAFF) reduced atherosclerosis in *Apoe*^{-/-} and *Ldlr*^{-/-} mice (156). These findings were recently confirmed in a clinical study: Patients who received rituximab therapy after kidney transplantation had a significantly lower rate of atherosclerotic CVE during 8 years of follow-up as compared to propensity-matched controls (112). Accordingly, rituximab therapy was shown to reduce carotid intima media thickness (113) and to improve flow mediated dilation of the brachial artery, a non-invasive marker of endothelial function (114). The effect of other B-cell-depleting antibodies (including those targeting receptors predominantly expressed on antibody-secreting plasma cells, such as CD39 and CD319) on atherosclerosis has not yet been investigated and the role of plasma cells in atherogenesis is not yet clear (157). Depletion of IgG-producing plasma cells reduced atherosclerotic

plaque development in *ApoE*^{-/-} and *Ldlr*^{-/-} mice (158, 159) but associated with plaque instability, which may have deleterious consequences in patients with preexisting atherosclerosis (158). Evidence from preclinical and clinical studies indicate that antibodies targeting CD20 may confer atheroprotection, but these early findings will have to be confirmed in larger clinical trials.

Antibodies Targeting Vascular Endothelial Growth Factor

Bevacizumab was the first clinically approved monoclonal antibody targeting vascular endothelial growth factor (VEGF) (160). Originally thought to exert antineoplastic actions exclusively via inhibition of tumor angiogenesis, VEGF-targeted therapies have been demonstrated to arrest tumor growth through a variety of mechanisms, which are not yet fully understood (160). In addition to bevacizumab, an antibody targeting VEGF receptor 2 (ramucirumab) and small-molecules inhibiting VEGF receptor tyrosine kinases (sorafenib and sunitinib) have been FDA-approved (153). A major drawback of VEGF inhibitors is their tendency to induce atherosclerotic CVE. Recent meta-analyses including up to 22 studies reported a \approx 1.4- to 2.5-fold higher risk of arterial ischemia in patients treated with bevacizumab (115–117). High-dose bevacizumab therapy was even associated with a 4.4- and 6.7-fold higher risk of cardiac and cerebral ischemia, respectively (115). A preclinical study confirmed and mechanistically substantiated these findings by demonstrating that administration of a VEGF-targeting antibody impaired endothelial function and increased atherosclerotic lesions by 33% in *ApoE*^{-/-} mice (118). Accordingly, VEGF inhibitors were shown to induce an inflammatory phenotype in cultured human coronary artery endothelial cells (161). Besides affecting endothelial function, VEGF inhibitors may decrease the number of T_{regs} and impair their suppressive capacity, reduce expression of co-inhibitory T cell molecules, and thus induce proinflammatory T_H1 responses (162). Although experimental proof is missing, these immunological effects might contribute to the proatherogenic properties of VEGF-inhibiting antibodies (162).

Antibodies Directed Against Epidermal Growth Factor Receptors

Receptors of the epidermal growth factor receptor family, such as epidermal growth factor receptor (EGFR) or human epidermal growth factor receptor 2 (HER2/neu), may be overexpressed by tumor cells of several cancer types which can thus acquire the capability of autonomous and uncontrolled proliferation (163, 164). Overexpression of EGFR or HER2/neu is a strong predictor of a negative prognosis in a variety of malignancies (165, 166) and the development of monoclonal antibodies targeting such receptors has advanced cancer treatment. Early clinical studies and large-scale phase 3 trials showed improved outcome in patients with metastatic breast cancer and gastric cancer treated with trastuzumab (targeting HER2/neu) and patients with metastatic colorectal cancer and head and neck cancer treated with cetuximab (directed against EGFR) (167–170). Further HER2/neu and EGFR targeting antibodies have been clinically

approved (153). A major drawback of growth factor receptor targeting antibodies (especially trastuzumab) is their potential to induce heart failure, which occurs in up to 20% of all cases (167, 171) and is 1.7 to 4 times more frequently compared to standard chemotherapy (172–174). Accordingly, mice lacking Her2/neu were demonstrated to develop dilated cardiomyopathy (175).

Direct effects of antibodies targeting growth factor receptors on atherogenesis have not yet been reported in clinical trials. Nevertheless, EGFR was detected in human atherosclerotic plaques (176) and increased HER2/neu plasma levels were shown to be associated with a higher risk of CAD (177). In line with this, evidence from preclinical studies indicated that inhibition of growth factor signaling may confer atheroprotection (119–121). In two elegant studies, Zeboudj, Ait-Oufella and colleagues demonstrated that cell-specific depletion of EGFR either in myeloid cells (119) or in CD4⁺ T cells (120) protected *Ldlr*^{-/-} mice from atherosclerosis. EGFR deficiency in myeloid cells limited macrophage accumulation within plaques and lipid uptake by macrophages, whereas CD4⁺ T cell-specific depletion of EGFR reduced CD4⁺ T cell activation, proliferation and infiltration in atherosclerotic lesions. Both cell-specific EGFR deletions were accompanied by reduced pro-inflammatory cytokine production (119, 120). Despite these promising findings, some uncertainties regarding the mechanistic implication of EGFR and its ligands in atherogenesis remain (178), beyond EGFR's profound immunomodulatory role systems-wide must be taken into account (179). Whether atheroprotective effects of growth factor receptor targeting antibodies also apply to humans is still unclear.

Cytokine Therapy

A variety of cytokines may exert significant anti-neoplastic effects either by directly inhibiting proliferation and inducing apoptosis of tumor cells or by stimulating anti-tumor immune responses (180, 181). Despite promising findings in early preclinical studies, utilization of cytokines as cancer therapeutics was later demonstrated to involve several limitations which hindered broad translation of this treatment approach into clinical practice (180, 181). Nevertheless, IFN- α and IL-2 were clinically approved for the treatment of different malignancies such as hairy cell leukemia, follicular non-Hodgkin lymphoma, melanoma, and Kaposi's sarcoma (IFN- α) or renal cell carcinoma and melanoma (IL-2) (180, 181).

Interferon Alpha (IFN- α)

Clinical application of IFN- α is particularly limited by its proatherogenic properties (182, 183). *Ldlr*^{-/-} mice treated with IFN- α had accelerated atherosclerosis and increased plasma cholesterol and triglyceride levels (124). Several other proatherogenic effects of IFN- α have been reported, such as induction of lipid uptake by macrophages and foam cell formation (184, 185), inhibition of T_{reg} activation and proliferation (186, 187), direct stimulation of cytotoxic CD4⁺ T cell function (188), and sensitization of antigen-presenting cells toward pathogen-derived toll-like receptor 4 (TLR4) ligands (189). Clinical studies demonstrated that plasma type I IFN (IFN- α and - β) levels are associated with atherosclerosis development

in patients with SLE (122) and human immunodeficiency virus-1 (HIV-1) infection (123). Experimental evidence suggested that IFN- α directly promotes atherogenesis by impairing vascular repair (190, 191) or inducing endothelial dysfunction (192) and may thus causally contribute to the highly increased risk of atherosclerotic CVE in SLE patients, which is not adequately explained by traditional risk factors (193). For a thorough review on the impact of IFN- α on different atherosclerosis-associated cell types and clinical implications the interested reader is referred to Chen et al. (182).

Interleukin 2 (IL-2)

IL-2 was originally termed T cell growth factor as it was first identified as a component of T cell culture fluids that induced proliferation of antigen-activated T cells (194, 195). It was thought to act as a crucial mediator in T cell immune responses and to play an important role in host response and tumor control, which led to test high-dose IL-2 as a novel cancer treatment in the mid 1980s (196). Although limited by toxicities such as capillary leak syndrome, fever, chills, malaise and arthralgias, this approach facilitated significant tumor regression and emerged as the first effective immunotherapy for human cancer (196). Yet, IL-2 deficient mice developed severe lymphoproliferation and autoimmunity which pointed toward an additional important role of the cytokine in maintaining self-tolerance (197, 198). Subsequent studies revealed that T_{reg} generation is dependent on IL-2 (195). T_{regs} express increased levels of the high-affinity IL-2 receptor alpha chain (IL-2R α , also known as CD25) compared to effector T cells (T_{eff} cells) and are thus more sensitive for IL-2 (199). Accordingly, daily low-dose IL-2 therapy stimulated selective expansion of functional T_{regs} through increased proliferation, thymic export and resistance to apoptosis (while only minimally affecting conventional CD4⁺ T cells) and thus led to a substantial clinical improvement in patients with active chronic graft-vs.-host disease (200, 201).

The specific role of IL-2 in atherogenesis has not yet been fully clarified. Increased IL-2 serum levels were shown to be associated with carotid artery intima-media thickness (202), a sonographic marker of atherosclerosis, and CAD (203). An early clinical study reported atherosclerotic CVE in 3.8% (angina or ischemic changes in 2.6% and myocardial infarction in 1.2%) of patients who received IL-2 for cancer therapy (125). Accordingly, IL-2 administration (2 × 10⁴ units twice weekly for a period of 6 weeks) accelerated atherogenesis in *ApoE*^{-/-} mice, whereas administration of an antibody targeting IL-2 was atheroprotective (126). Treatment of *Ldlr*^{-/-} (204) and *ApoE*^{-/-} mice (127) with low-dose IL-2 complexed with a specific IL-2 monoclonal antibody (JES6-1A12) conferred significant atheroprotection by inducing a substantial expansion of T_{regs} in atherosclerotic lesions and several other tissues. Neither IL-2 nor the anti-IL2 antibody alone affected atherogenesis (127) and the observed anti-atherogenic efficacy depended on the antibody clone used. Administration of IL-2 complexed with another IL-2 antibody clone (SAB6) induced expansion of natural killer (NK) and CD8⁺ T cells (205). A subsequent study unraveled the mechanism by which the two different antibody complexes selectively induce expansion of T_{regs} or T_{eff} cells: (1) JES6-1

sterically blocks the interaction of IL-2 with IL-2R β and IL-2R γ and allosterically disrupts binding of IL2 to IL-2R α , thereby favoring activation of T_{regs} with high IL-2R α expression; (2) SAB6 sterically hinders IL-2/IL-2R α interaction and enhances IL-2/IL-2R β interaction, thus stimulating all IL-2-responsive T cells (206). More recently, a human anti-IL2-antibody (F5111.2) was developed that selectively promotes T_{reg} expansion when complexed with human IL-2 by inducing similar conformational changes (207). Administration of IL2-F5111.2 complexes yielded substantial therapeutic efficacy in humanized animal models of different autoimmune diseases, such as type 1 diabetes, autoimmune encephalomyelitis or xenogeneic graft-vs.-host disease (207). Whether such approach might be translatable into clinical practice has not yet been determined. The randomized, double-blind, placebo-controlled LILACS trial (NCT03113773) examined whether solely administering low-dose IL-2 is safe and effective in patients with stable ischemic heart disease and acute coronary syndrome (208). The study has been completed and its results are awaited for publication.

In conclusion, current evidence suggests that high-dose IL-2 therapy promotes atherogenesis through induction of pro-inflammatory T_{eff} cell responses, whereas administration of low-dose IL-2 might confer atheroprotection by selectively stimulating expansion of T_{regs}. Complexing IL-2 with specific anti-IL-2 antibodies might even enhance the latter effect through augmenting the selectivity to IL-2R α , which is highly expressed on T_{regs}.

Methotrexate

Methotrexate (MTX) is a structural analog of folic acid (Vitamin B9) that inhibits enzymes involved in folate metabolism, such as dihydrofolate reductase (DHFR), and thus limits cellular division (209). DHFR catalyzes conversion of dihydrofolate to tetrahydrofolate, which acts as an important coenzyme in synthesis of pyrimidine and purine. In 1948 Farber et al. firstly reported that treatment with the folate analog aminopterin enabled temporary remission in childhood leukemia (210). Subsequently, MTX (initially termed amethopterin) was found to have better pharmacological properties than aminopterin (211) and thus emerged as one of the most extensively used chemotherapy agents for a variety of cancer types (209, 212). Besides anti-neoplastic properties, MTX exerts potent anti-inflammatory actions (213). Several studies reported efficacy of low-dose MTX in the treatment of rheumatoid arthritis (RA) (214, 215). The compound has become a mainstay in therapy of RA and other autoimmune diseases, although its immunosuppressive mechanisms of action have not yet been fully clarified (213). Observational data revealed that low-dose MTX therapy associated with a lower risk for CVD and cardiovascular mortality (216, 217). The Cardiovascular Inflammation Reduction Trial (CIRT) included 4,786 patients with CAD and additional metabolic risk factors (type 2 diabetes or metabolic syndrome) randomly assigned to receive low-dose MTX or placebo (128). After a median follow-up of 2.3 years, MTX neither reduced pro-inflammatory biomarkers [IL-1 β , IL-6, and C-reactive protein (CRP)] nor CVE. MTX was associated with modest elevations in liver enzymes, reductions

in leukocyte counts and hematocrit levels, and an increased incidence of non-basal-cell skin cancers. Although the study had some methodical limitations (e.g., patients were not screened for an increased inflammatory risk), the data overall discouraged further investigations on MTX therapy for CVD prevention. In a recent murine study, nanoparticle-formulated MTX conferred substantial atheroprotection through modulating lipoprotein transcellular transport, reducing expression of pro-inflammatory cytokines and attenuating monocyte maturation and recruitment (129).

Although several immunotherapeutic approaches have yielded promising results in preclinical CVD models, only few of these strategies have proven beneficial in clinical studies (8, 218). Canakinumab (14), a monoclonal antibody targeting IL-1 β , and colchicine (219, 220), an ancient drug traditionally used for gout therapy which exerts anti-inflammatory effects (among other potential mechanisms) through inhibition of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome in leukocytes (221), were demonstrated to reduce cardiovascular events in large-scale clinical trials. Although not targeting inflammatory pathways, monoclonal antibodies [evolocumab (13) and alirocumab (12)] or a siRNA-based compound [inclisiran (222, 223)] targeting PCSK9 to lower LDL cholesterol levels have proven clinically beneficial.

Considering that a pro-inflammatory immune response is critically involved in early elimination of mutated cells (68), immunotherapies exerting systemic anti-inflammatory effects may mitigate anti-tumor immunity and thus increase the risk of cancer development. In the following section we discuss recent evidence on the impact of above-mentioned immunotherapeutic strategies for CVD on cancer incidence (an overview is given in **Table 2**).

Canakinumab

Although canakinumab reduced CVE in patients with CAD, several limitations, such as a significant impairment of host defense and high costs, prevented its clinical approval for secondary prevention of CVD (14). Recent evidence suggests that IL-1 β has a dual role in cancer development: On the one hand, it initiated pro-inflammatory anti-tumor immune responses by activating tumor antigen-specific T_H1 and T_H17 cells and facilitated tumor regression (233). On the other hand, IL-1 β can promote carcinogenesis by inducing chronic inflammation, endothelial cell activation, angiogenesis, or development of immunosuppressive cells, such as tumor-associated macrophages and myeloid-derived suppressor cells (233). In contrast to anti-tumor immunity, which is critically involved in cancer elimination, chronic inflammation may drive tumorigenesis through several mechanisms including inhibition of antineoplastic immune responses, modulation of the tumor microenvironment to become more tumor-permissive, and direct tumor-promoting actions on epithelial and cancer cells (234). In line with this, IL-1 β -deficient mice transplanted with melanoma cells were protected from development of local tumor and metastases (225) and canakinumab significantly reduced incidence of fatal cancer in the CANTOS trial (14). An exploratory analysis further revealed

that canakinumab treatment especially reduced the incidence of lung cancer and lung cancer mortality (224). These findings motivated the initiation of three randomized phase III trials, CANOPY-A (NCT03447769), CANOPY-1 (NCT03631199), and CANOPY-2 (NCT03626545) (235), and a phase II trial, CANOPY-N (NCT03968419) (236) to investigate the potential of canakinumab in the treatment of non-small cell lung cancer (NSCLC). Although most trials are still ongoing, the CANOPY-2 study, which evaluated canakinumab in a second- or third-line treatment setting (that is in patients with locally advanced or metastatic NSCLC and tumor progression after or during platinum-based chemotherapy and PD-(L)1 inhibitor therapy) failed to meet the primary endpoint of overall survival (237).

Colchicine

Colchicine is derived from the autumn crocus, which has been used for gout therapy since ancient times (238). Until today, colchicine represents a first-line drug for gout treatment (239). More recently, the compound has emerged as a promising candidate for secondary prevention of CVD. In two large-scale RCTs, the COLCOT (219) and LoDoCo 2 (220) trials, collectively enrolling more than 10,000 patients with recent myocardial infarction or chronic coronary syndrome, low-dose colchicine therapy significantly reduced the incidence of CVE. In contrast to canakinumab, colchicine did not increase the risk of fatal infections, although in COLCOT non-fatal pneumonia occurred more often in colchicine-treated patients. Nevertheless, colchicine therapy did not significantly reduce cardiovascular mortality in these trials and was associated with an almost significant increase in non-cardiovascular mortality in LoDoCo2 (220). A smaller RCT, enrolling 795 patients, reported a significantly higher rate of all-cause mortality (mainly due to non-cardiovascular deaths) in patients with acute coronary syndrome when colchicine was added to standard therapy (240). Recent meta-analyses confirmed that low-dose colchicine therapy in patients with CAD was associated with a significantly reduced risk of CVE (myocardial infarction, stroke, and the need for coronary revascularization) and a non-significant reduction of cardiovascular deaths, which was counterbalanced by a non-significant increase in non-cardiovascular deaths (241, 242). Considering the robust reduction of CVE observed in these studies as well as the low price and wide availability of the compound, low-dose colchicine might become an option for secondary prevention in high-risk CVD patients, but the increased non-cardiovascular death rates need further investigation.

Despite the increase in non-cardiovascular mortality, colchicine was not associated with higher rates of cancer in any of the above-mentioned studies (219, 220, 240). Preclinical evidence showed that colchicine may reduce tumor growth of several cancer types, such as prostate (229), hypopharyngeal (230) and liver cancer (231) as well as tumor implantation of pressure-activated colon carcinoma cells (232). The incidence of all-cause cancers was significantly reduced in 13,679 male gout patients (at least temporarily) treated with colchicine compared with 10,371 control gout patients (228). Besides reducing tumor cell proliferation and inducing apoptosis (243),

TABLE 2 | Effects of anti-atherosclerotic immunotherapies (with clinically proven efficacy) on cancer.

Type of immunotherapy	Target	Compounds	Effect on cancer in clinical trials	Effect on cancer in animal studies	Potential mechanisms
Monoclonal antibodies	IL-1 β	Canakinumab	↓ (224)	↓ (225)*	- Reduction of tumor-promoting chronic inflammation
	PCSK9	Alirocumab	–	↓ (226)	- Increased MHC I expression on tumor cell surface and enhanced tumor infiltration by cytotoxic T cells
		Evolocumab			
Natural anti-tubulin agent	CD3	Teplizumab	–	↓ (227)	- Induction of leukemic cell apoptosis
		Foralumab			
		Colchicine	↓ (228)	↓ (229–232)	- Direct antiproliferative effects on tumor cells and induction of apoptosis - Enhancement of CD4 ⁺ and CD8 ⁺ T-cell-mediated anti-tumor immunity

↑ = pro-carcinogenic effect. ↓ = anti-carcinogenic effect. * In this study IL-1 β knockout mice were shown to be protected from tumor development, but antibody-mediated IL-1 β depletion was not investigated. **besides other anti-inflammatory mechanisms.

IL-1 β , interleukin 1 beta; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; PCSK9, proprotein convertase subtilisin/kexin 9.

colchicine enhances CD4⁺ and CD8⁺ T-cell-mediated anti-tumor immunity by promoting dendritic cell maturation and antigen presentation (244). Colchicine toxicity at high doses prevents its application as anti-tumor drug (243). Whether low-dose colchicine might confer clinically relevant anti-cancer effects has yet to be determined.

PCSK9 Inhibitors

PCSK9, a protein which is primarily expressed in the liver, counteracts clearance of LDL cholesterol by inducing degradation of internalized LDL receptor in hepatocytes leading to increased plasma LDL cholesterol levels (245). Inhibition of PCSK9 has emerged as a highly effective second-line cholesterol lowering strategy, which has received class I recommendations by current guidelines (246). Two monoclonal antibodies targeting PCSK9, evolocumab (13) and alirocumab (12), and a siRNA-based compound, inclisiran (222, 223), are approved for clinical use in selected high-risk patients.

Cholesterol is a driving force in atherogenesis, yet its role in cancer is less clear: Both positive and negative correlations as well as absence of any associations between cholesterol levels and cancer development have been reported by clinical studies (247). Likewise, several meta-analyses concluded that statin therapy reduces cancer incidence or improves prognosis (248–250), whereas others found no such correlations (251, 252). PCSK9 inhibitors have not been reported to affect cancer incidence in clinical trials (12, 13). However, in a recent study PCSK9 inhibition could potentiate anti-tumor immune responses and thus substantially reduced tumor growth in murine cancer models (226), which was independent of cholesterol-lowering. PCSK9 induced lysosomal degradation of MHC-I and disrupted its recycling to the cell surface. PCSK9 inhibition, either through genetic deletion or administration of monoclonal antibodies, increased MHC-I expression on the tumor cell surface and thus enhanced tumor infiltration by cytotoxic T cells. Besides limiting tumor growth when administered alone, anti-PCSK9 antibodies significantly enhanced anti-tumor

efficacy of ICI therapy (anti-PD-1) (226). Another recent study demonstrated that a nanoliposomal anti-PCSK9 vaccine limited tumor progression and improved survival in a murine model of colon carcinoma (253). Concluding, these preclinical data warrant further exploration of PCSK9 inhibitors as cancer therapeutics in clinical trials.

Anti-CD3 Antibody Therapy

Anti-CD3 monoclonal antibodies bind to the CD3-TCR complex on the surface of T cells and thus induce disappearance by shedding or internalization of the receptor complex (254). This process, which is termed antigenic modulation, renders T cells temporarily blind to their cognate antigen and leads to anergy or apoptosis of activated T cells (254). Anti-CD3 antibody therapy induced long-lasting T_{reg}-mediated immune tolerance through increased TGF- β production by apoptotic T cells and phagocytes involved in clearance of apoptotic T cells (255, 256). Clinical application of the murine muromonab-CD3 is limited by high immunogenicity and resulting side effects (e.g., nausea, fever, headaches) (254). Humanized anti-CD3 antibodies (e.g., teplizumab, and oteelixumab) and a fully human anti-CD3 antibody (foralumab) have been developed, that were well-tolerated in initial clinical studies (254). Early clinical evidence suggests reasonable efficacy of such novel anti-CD3 antibodies in the treatment or prevention of autoimmune diseases, such as multiple sclerosis (257), type 1 diabetes (258–261), and inflammatory bowel disease (262). In several preclinical studies, intravenous or oral administration of anti-CD3 antibodies conferred substantial atheroprotection by enhancing TGF- β production and thereby inducing anti-atherogenic T_{regs} (263–265). Muromonab-CD3 was reported to significantly decrease CD3⁺ tumor cells in a patient with refractory T cell acute lymphoblastic leukemia (266), but was ineffective in enhancing immune activation in patients with solid tumors when administered in combination with high- or low-dose IL-2 (267, 268). However, a recent preclinical study demonstrated high anti-tumor efficacy of teplizumab and

foralumab in murine models of T cell acute lymphoblastic leukemia (227). To date, the potential of humanized or fully human anti-CD3 antibodies in the treatment of CVD or cancer has not yet been investigated in clinical trials. Considering the promising data from animal studies these compounds merit further investigation into their clinical application.

ADOPTIVE T CELL TRANSFER IN CANCER AND ATHEROSCLEROSIS

Chimeric antigen receptor (CAR) T cell therapy represents an innovative cancer treatment strategy, in which circulating T cells are isolated and genetically modified *in vitro* to express a synthetic tumor-antigen-specific receptor (269), which are subsequently expanded and infused back into the patient to attack tumor cells (269). In 2017, CAR T cells directed against CD19 (tisagenlecleucel and axicabtagene ciloleucel) showed substantial anti-tumor activity in patients with refractory large B cell lymphoma and follicular lymphoma (270, 271), which led to their FDA approval. Subsequently, anti-CD19 CAR T cells brexucabtagene autoleucel and lisocabtagene maraleucel were approved for treatment of mantle cell lymphoma and diffuse large B cell lymphoma, respectively (272, 273). Idecabtagene vicleucel targets B cell maturation antigen (BCMA) and is the first clinically approved CAR T cell therapy for multiple myeloma treatment (274). A major drawback of CAR T cell therapy is its association with severe and potentially fatal side effects (275). Cytokine-release syndrome (CRS), that can potentially develop into fulminant haemophagocytic lymphohistiocytosis (HLH), and CAR-T-cell-related encephalopathy syndrome (CRES), are the two most common adverse reactions (275). A recent study reported that CVE, such as new onset of heart failure or arrhythmias, occurred in 12% of 137 patients who received CAR T cell therapy (all events were associated with CRS) (276). Whether CAR T cells affect atherogenesis and increase the cardiovascular risk in the long-term, is unknown.

Adoptive transfer of autologous *ex vivo* expanded polyclonal T_{regs} has emerged as a promising strategy to treat autoimmune diseases and is currently investigated in clinical trials (277). First evidence suggested safety and efficacy of this approach for the treatment of type 1 diabetes (278, 279), prevention of graft-vs.-host-disease (280, 281), or transplant rejection (282). Therapeutic potency may be enhanced by utilization of antigen-specific rather than polyclonal T_{regs}. Administration of ovalbumin-specific T_{regs}, which respond to a major component of chicken egg white, was demonstrated to be safe and effective in patients with refractory Crohn's disease (283). Adoptive transfer of both polyclonal (284) and antigen-specific T_{regs} (responding to heat-shock protein 60) (285) conferred atheroprotection in *ApoE*^{-/-} mice fed with a WD for 6–8 weeks. Yet, administration of ApoB⁺ T_{regs} to WD-fed *ApoE*^{-/-} mice failed to limit plaque progression during a more extended period of observation (12 weeks) (43). In this study, more than half of all transferred cells lost expression of T_{reg} markers and converted into conventional T cells, which likely accounted for treatment failure. Clarification of the mechanisms underlying such phenotypic conversion and

development of strategies to ensure T_{reg} stability are essential for clinical translation of this approach.

VACCINATION STRATEGIES IN THE TREATMENT OF CANCER AND ATHEROSCLEROSIS

Vaccination strategies aiming to induce pro-inflammatory immune responses against tumor-specific antigens or immune tolerance to plaque-associated autoantigens hold great promise for the treatment of cancer and atherosclerosis, respectively (4, 6). Through eliciting antigen-specific immunity, such approaches are highly effective without impairing the host defense against infectious agents and cancer cells or enhancing atherogenesis.

A series of animal studies have indicated the great potential of immunization against ApoB-related antigens for the treatment of atherosclerosis (6). The underlying idea originates from the observation that administration of oxLDL to hypercholesterolemic rabbits reduced atherosclerotic lesions (286). Subsequent studies identified an expansion of ApoB⁺ T_{regs} (42, 287, 288) and a humoral immune response against LDL (289) to account for the observed atheroprotection. Despite these promising preclinical data, several unknowns, such as optimal epitopes, adjuvants, administration route and vaccination scheme, stability of the atheroprotective immune response, and criteria for patient selection, have hitherto hindered translation of anti-atherosclerotic vaccination strategies into clinical practice (6). Recently, utilization of nanoparticle-formulated, nucleoside-modified messenger RNA (mRNA) without addition of adjuvants was demonstrated to enable sustained immune tolerance to MS-related autoantigens through induction of functional T_{regs} in mice (290). Considering that mRNA-based vaccines are already in clinical use, this approach has high translational potential for development of a vaccine against atherosclerosis.

Therapeutic cancer vaccines aim to induce a sustained effector immune-response against tumor-specific antigens (291). Initial approaches used self-antigens, which exist in non-malignant tissues, but are abnormally expressed or overexpressed by tumor cells, or applied non-self-antigens of viral origin (4, 291). Technological advances, such as next-generation sequencing, enabled identification of tumor-specific epitopes resulting from mutations (4, 291). These so-called neoepitopes or neoantigens are then evaluated for their capacity to bind human MHC-I or -II molecules. Candidates with high binding capacity can finally be utilized for development of personalized cancer vaccines or *in vitro* expansion of tumor-antigen specific CD4⁺ and CD8⁺ T cells, which are then transferred into the patient (4, 291). Vaccination with neoepitopes predicted to bind MHC-II or -I was shown to elicit strong CD4⁺ and/or CD8⁺ responses and thereby facilitate tumor rejection in animal models (292). In 2015, Carreno et al. firstly demonstrated the capability of a neoantigen-based vaccine strategy using dendritic cells as vaccine platform to induce a tumor-specific CD8⁺ T cell response in three patients with advanced melanoma (293). Subsequently peptide- and mRNA-based neoantigen vaccines were shown to induce strong CD4⁺ and CD8⁺ T cell responses

alongside with significant tumor regression in melanoma patients (90, 91). Despite the promising results of these early clinical trials, several open questions on how to improve efficacy and feasibility of neoantigen-based tumor vaccines remain, that include identification of optimal antigens, delivery platforms, adjuvants, and routes of administration (4). Several clinical trials investigating the efficacy of neoantigen-based vaccine approaches in different cancer types are underway and will likely help to find answers to these questions (4, 291).

CONCLUSION

Adaptive immunity is critically involved in the pathogenesis of atherosclerotic cardiovascular diseases and cancer, which represent the two most common causes of death worldwide. During the past few decades, novel treatment strategies enhancing anti-tumor immune responses have already found their way into clinical practice, whereas successful translation of strategies targeting atherogenesis-related immune responses into the clinic has not yet been accomplished. Given that some immunotherapies (e.g., CD20-, EGFR-, IL-1 β - or PCSK9-targeting antibodies) were shown to protect from both cancer and atherosclerosis, inflammatory processes and immunity underlying carcinogenesis and atherogenesis may be closely interconnected. Further characterization of tumor-promoting and proatherogenic immune responses may help to identify novel pharmacological targets that allow simultaneous treatment of both disease entities. Further characterization of tumor-promoting and proatherogenic immune responses may help to identify novel pharmacological targets that allow simultaneous treatment of both disease entities. In that regard, multimodal sequencing approaches, such as Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-Seq),

which allow combined measurement of gene and surface-protein expression on a single-cell level, will be valuable tools. Active immunization represents a novel, promising approach for the treatment of cancer and atherosclerosis. Preclinical studies have underscored the great anti-atherosclerotic potential of vaccination against plaque-related autoantigens. Further research is required to optimize this promising approach. Major objectives in this context include identification of optimal vaccine delivery platforms, adjuvants and administration routes. Furthermore, development of clinically feasible approaches to identify eligible patients, to determine expression of target antigens within an individual patient, and to monitor treatment responses will be crucial for broad implementation of this approach into clinical practice. If these obstacles can be overcome, active immunization may prospectively take cancer and atherosclerosis therapy to the next level.

AUTHOR CONTRIBUTIONS

FN wrote the manuscript. FP prepared the figure. FN and HW conceptualized the work. HW and FH supervised the work and provided funding. All authors substantially contributed to data research, critically discussed the content, reviewed the manuscript before submission, and have read and agreed to the published version of the manuscript.

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