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Review

Molecular and cellular crosstalk between atherosclerosis and cancer: Mechanistic insights and therapeutic opportunities

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Abstract

Atherosclerosis and cancer are among the leading causes of morbidity and mortality worldwide and are increasingly recognized as biologically interconnected diseases rather than independent pathological conditions. Accumulating evidence indicates that these disorders share a complex molecular landscape characterized by chronic inflammation, oxidative stress, immune dysregulation, metabolic reprogramming, endothelial dysfunction, and age-related cellular alterations. This review integrates current knowledge on the molecular and cellular mechanisms underlying the bidirectional relationship between atherosclerosis and malignancy, with particular emphasis on inflammatory signaling pathways, NLRP3 inflammasome activation, macrophage polarization, clonal hematopoiesis of indeterminate potential (CHIP), cellular senescence, and gut microbiota-mediated immune modulation. We further discuss how these shared mechanisms contribute to disease initiation, progression, and therapeutic responses, highlighting the influence of cardiovascular medications on cancer biology and the cardiovascular toxicities associated with anticancer therapies. By synthesizing emerging evidence from cardiovascular biology, oncology, and immunology, this review proposes a unified molecular framework in which atherosclerosis and cancer represent interconnected manifestations of common pathogenic processes. Recognizing this molecular crosstalk provides new opportunities for the identification of shared biomarkers, improved risk stratification, and the development of mechanism-based therapeutic strategies, thereby advancing precision medicine at the interface of cardiovascular disease and cancer.

Keywords: Atherosclerosis; malignant tumors; chronic inflammation; oxidative stress; tumor microenvironment; clonal hematopoiesis; statins; cardio-oncology

1. Introduction

Cardiovascular disease and cancer together account for more than half of all deaths in industrialized nations, and atherosclerosis and malignancy stand as the principal pathological substrates underlying each category, respectively [1,2]. For decades the two conditions were viewed through separate clinical and research lenses: atherosclerosis as a lipid-driven degenerative disease of the arterial wall, and cancer as a disorder of uncontrolled cellular proliferation governed by genetic and epigenetic alterations. This dichotomy has progressively dissolved as it has become clear that both diseases share a common biological substrate rooted in chronic inflammation, oxidative injury, aberrant immune surveillance and tissue remodeling [3-5].

Atherosclerosis is now recognized not as a passive accumulation of lipid within the arterial intima but as an active, chronic inflammatory disease initiated by the retention of apolipoprotein B-containing lipoproteins in the subendothelial space, followed by their oxidative modification, monocyte recruitment, foam-cell formation, smooth-muscle-cell migration and fibrous-cap formation [3,4]. In parallel, the hallmarks-of-cancer framework has expanded beyond genomic instability and sustained proliferative signaling to include tumor-promoting inflammation, immune evasion and metabolic reprogramming as central, enabling features of malignant transformation [6]. The convergence of these two conceptual frameworks around inflammation provided the initial rationale for investigating a mechanistic link between atherosclerotic disease and carcinogenesis, an idea traceable to Virchow's nineteenth-century observation that leukocytes infiltrate neoplastic tissue [7].

Clinically, the relationship between atherosclerosis and cancer is bidirectional. Cancer and its treatments (radiotherapy, anthracyclines, tyrosine-kinase inhibitors, immune-checkpoint inhibitors) accelerate atherosclerotic disease, while pre-existing atherosclerotic burden and its associated inflammatory milieu appear to promote tumor

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development and more aggressive tumor biology. This review focuses specifically on the less extensively discussed direction of this relationship: how atherosclerosis, through its systemic and local biological consequences, may contribute to the initiation, growth and dissemination of malignant tumors. We examine the epidemiological evidence for this association, the shared risk factors that create a "common soil" for both diseases, and the specific molecular and cellular mechanisms that mechanistically link the atherosclerotic plaque and the tumor microenvironment, concluding with a discussion of the therapeutic implications of this converging pathobiology. Although numerous studies have independently investigated atherosclerosis and cancer, a comprehensive molecular framework integrating their shared pathogenic pathways and therapeutic interactions remains lacking. This review addresses this gap by synthesizing recent evidence from molecular biology, immunology, and cardio-oncology.

2. Epidemiological Evidence Linking Atherosclerosis and Malignancy

The global burden of both diseases has been rising in parallel. GLOBOCAN estimates for 2022 documented approximately 20 million new cancer cases and 9.7 million cancer deaths worldwide, with incidence projected to increase substantially over the coming decades as populations age [1]. Over the same period, the Global Burden of Disease Study 2019 reported that the burden of atherosclerosis, measured by disability-adjusted life-years, has continued to rise globally despite improvements in risk-factor control in high-income countries [2]. Because both diseases share advancing age as their single strongest risk factor, some of the observed epidemiological association is attributable to simple co-occurrence in an aging population. However, several lines of evidence suggest that the relationship extends beyond coincidental co-occurrence.

Population-based cohort studies have repeatedly demonstrated that individuals with documented coronary, carotid or peripheral atherosclerotic disease carry an elevated subsequent risk of incident cancer compared with age- and sex-matched controls, and that markers of subclinical atherosclerosis, such as coronary artery calcium score, carotid intima-media thickness and ankle-brachial index, are independently associated with future cancer incidence and cancer mortality, even after adjustment for shared risk factors such as smoking, obesity and diabetes. Similarly, elevated high-sensitivity C-reactive protein, a systemic biomarker of the low-grade inflammatory state that accompanies atherosclerosis, predicts not only cardiovascular events but also incident cancer and cancer-related mortality, reinforcing the notion that the two diseases share a common inflammatory trajectory rather than merely coexisting by chance [3,5].

The bidirectionality of this relationship is further supported by the observation that many malignancies, in turn, accelerate atherosclerotic disease through tumor-derived pro-inflammatory and pro-thrombotic factors, and that cancer survivors face an elevated long-term risk of cardiovascular events independent of the cardiotoxic effects of specific therapies. Taken together, the epidemiological data support a model in which atherosclerosis and cancer are not independent comorbidities but interacting components of a shared chronic-disease continuum, best explained by overlapping biological mechanisms rather than by chance co-occurrence in an aging, high-risk population.

3. The Common-Soil Hypothesis: Shared Risk Factors

The "common soil" hypothesis proposes that atherosclerosis and cancer arise from a shared substrate of modifiable and non-modifiable risk factors that independently damage vascular and epithelial tissues while simultaneously fostering a systemic pro-inflammatory, pro-oxidant and metabolically dysregulated state permissive to both diseases. Cigarette smoking is the paradigmatic example: tobacco combustion products directly injure the vascular endothelium, promote lipid oxidation and plaque formation, and simultaneously act as potent mutagens and tumor promoters in the respiratory epithelium, explaining why smoking-related atherosclerosis and lung cancer frequently coexist in the same patients and why smoking cessation reduces the incidence of both conditions.

Obesity and the associated adipose-tissue dysfunction represent another shared driver. Expansion of visceral adipose tissue is accompanied by adipocyte hypertrophy, hypoxia and a phenotypic switch of resident macrophages toward a pro-inflammatory state, with consequent overproduction of interleukin-6, tumor necrosis factor-alpha, leptin and other adipokines that simultaneously promote endothelial dysfunction, insulin resistance and atherogenesis while providing a pro-tumorigenic milieu that favors angiogenesis, cellular proliferation and resistance to apoptosis in nascent tumor clones. Type 2 diabetes mellitus and the broader metabolic syndrome compound these effects through chronic hyperglycemia, hyperinsulinemia and activation of the insulin-like growth factor axis, mechanisms that accelerate atherosclerotic plaque progression while also stimulating proliferative and anti-apoptotic signaling in epithelial and hematopoietic cells.

Age itself deserves particular emphasis as a unifying risk factor, since the aging process is accompanied by mitochondrial dysfunction, accumulation of senescent cells, chronic low-grade "inflammaging," and the progressive acquisition of somatic mutations in multiple tissues, all of which independently promote both atherosclerotic plaque formation and neoplastic transformation. Diet, physical inactivity, chronic psychosocial stress and environmental exposures such as air pollution and ionizing radiation further contribute to this shared risk architecture. This overlapping constellation of risk factors establishes the epidemiological plausibility for a mechanistic link between the two diseases, which the remainder of this review addresses in detail.

4. Chronic Inflammation as the Central Unifying Mechanism

Chronic, low-grade, non-resolving inflammation is widely regarded as the principal mechanistic bridge between atherosclerosis and cancer [3,8,9]. In the arterial wall, the initiating event is the subendothelial retention of apolipoprotein B-containing lipoproteins, which undergo oxidative and enzymatic modification and are subsequently recognized by pattern-recognition and scavenger receptors on resident and recruited myeloid cells. This recognition activates the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, triggering caspase-1-dependent maturation and release of interleukin-1beta, which in turn induces hepatic and local production of interleukin-6 and downstream acute-phase reactants such

as C-reactive protein, sustaining a self-amplifying inflammatory loop within the plaque [10,11].

This same interleukin-1beta/interleukin-6/nuclear factor-kappa B (NF-kB) signaling axis is a well-established driver of carcinogenesis. Interleukin-6 activates the Janus kinase-signal transducer and activator of transcription 3 (JAK-STAT3) pathway in epithelial and stromal cells, promoting cellular proliferation, resistance to apoptosis, angiogenesis and epithelial-to-mesenchymal transition, while also polarizing myeloid cells toward an immunosuppressive, tumor-permissive phenotype [11,12]. A recent narrative review specifically dedicated to interleukin-6 signaling concluded that this cytokine functions as a genuine "interlinking pathway" between atherosclerosis and cancer, given its central role in endothelial dysfunction and plaque progression on one hand and tumor growth and poor prognosis on the other [12]. NF-kB, activated downstream of both the interleukin-1 receptor and Toll-like receptors, functions as a master transcriptional regulator in both diseases, driving expression of adhesion molecules and chemokines in the atherosclerotic endothelium while simultaneously promoting survival, proliferation and invasive gene-expression programs in transformed cells.

The concept of chronic inflammation as a shared disease driver is further supported by the "inflammaging" model, which frames the systemic elevation of circulating inflammatory mediators observed with advancing age as a unifying etiological factor across multiple chronic diseases, including atherosclerosis, cancer, neurodegeneration and metabolic disease [13]. Consistent with this framework, elevated high-sensitivity C-reactive protein predicts adverse outcomes in both conditions, and pharmacological interruption of this inflammatory axis produces measurable effects on both vascular and neoplastic endpoints.

The most direct clinical evidence for a causal inflammatory link between atherosclerosis and cancer comes from the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). This randomized, placebo-controlled trial enrolled over ten thousand patients with prior myocardial infarction and residual inflammatory risk, defined by elevated high-sensitivity C-reactive protein, and tested selective interleukin-1beta inhibition with canakinumab. While the trial was designed to assess recurrent cardiovascular events, a pre-specified exploratory analysis revealed a dose-dependent reduction in incident and fatal lung cancer among canakinumab-treated patients, with the highest dose associated with a substantial reduction in lung cancer incidence and mortality compared with placebo [14]. This finding, obtained in a population selected exclusively for atherosclerotic disease, provided the first randomized clinical evidence that an anti-inflammatory intervention targeting the atherosclerosis-associated NLRP3-interleukin-1beta axis can modify cancer risk, offering strong support for a causal, rather than merely correlative, relationship between vascular inflammation and tumorigenesis [9,15].

5. Oxidative Stress and Lipid-Driven Mechanisms

Oxidative modification of low-density lipoprotein (LDL) is the initiating molecular event of atherogenesis and represents a second major mechanistic bridge to malignancy. Oxidized LDL (oxLDL) and its constituent oxidized phospholipids are recognized by scavenger receptors, including CD36 and the lectin-like oxidized LDL receptor-1 (LOX-1), on macrophages, endothelial cells and, notably, on tumor and tumor-infiltrating immune cells [16]. Within the atherosclerotic plaque, oxLDL uptake drives foam-cell formation, endothelial activation and generation of reactive oxygen species (ROS) that cause further lipid peroxidation, protein oxidation and DNA damage, perpetuating a self-sustaining cycle of oxidative injury.

The same oxidized lipid species that accumulate within atherosclerotic lesions have been shown to accumulate within the tumor microenvironment, where they exert direct pro-tumorigenic effects. Oxidized phosphatidylcholines have been demonstrated to promote epithelial-to-mesenchymal transition and enhance the migratory and invasive capacity of hepatocellular carcinoma and breast cancer cells through activation of the AMPK-mTOR autophagy axis, with elevated tissue concentrations of these oxidized phospholipids correlating with more advanced tumor stage in patient-derived samples [17]. In the tumor microenvironment, myeloid-derived oxidized lipids accumulate within dendritic cells, macrophages and myeloid-derived suppressor cells, where they impair antigen presentation, promote an immunosuppressive phenotype and thereby facilitate tumor immune evasion [18,19]. Elevated oxLDL signaling through CD36 and LOX-1 has additionally been linked to activation of NF-kB, phosphoinositide 3-kinase (PI3K)-Akt and mitogen-activated protein kinase (MAPK) pathways within the tumor microenvironment, expanding regulatory T-cell and myeloid-derived suppressor-cell populations while suppressing cytotoxic T-cell function, an effect of particular relevance to resistance against immune-checkpoint inhibitor therapy [20].

Beyond oxLDL itself, dysregulated cholesterol and fatty-acid metabolism, hallmarks of both the atherosclerotic plaque and the malignant cell, provide substrate for membrane biogenesis, steroid-hormone signaling and lipid second-messenger production required for sustained proliferative signaling. Tumor cells frequently upregulate LDL-receptor and CD36 expression to satisfy this heightened lipid demand, effectively co-opting the same lipoprotein-uptake machinery that drives macrophage foam-cell formation in the atherosclerotic plaque [21]. Reactive oxygen species generated during fatty-acid oxidation further shape the polarization and phagocytic capacity of tumor-associated myeloid cells, mirroring the ROS-dependent phenotypic plasticity long described in plaque macrophages [22]. These convergent lipid-handling and redox pathways position dyslipidemia and lipid peroxidation as mechanistic, and not merely epidemiological, links between atherosclerotic and neoplastic disease.

6. Endothelial Dysfunction, Angiogenesis and the Tumor Vascular Niche

Endothelial dysfunction, characterized by reduced nitric-oxide bioavailability, increased expression of adhesion molecules, enhanced vascular permeability and a pro-thrombotic surface phenotype, is both an early initiating event in atherogenesis and a permissive condition for tumor growth and dissemination [3,4]. The dysfunctional endothelium overlying an atherosclerotic plaque secretes vascular endothelial growth factor (VEGF), basic fibroblast growth factor and other angiogenic mediators as part of the plaque's own neovascularization response, a process that closely parallels the "angiogenic switch" that permits avascular tumor nodules to progress toward a vascular-

ized, invasive phenotype [23,24].

Intraplaque neovascularization, arising predominantly from the adventitial vasa vasorum, is now recognized as a hallmark of unstable, rupture-prone atherosclerotic lesions. These newly formed microvessels are structurally immature, hyperpermeable and prone to intraplaque hemorrhage, sharing striking morphological and functional similarities with the chaotic, leaky vasculature characteristic of solid tumors. Chronic systemic exposure to circulating pro-angiogenic factors elaborated by an atherosclerotic vascular bed may thus prime distant tissues for tumor neovascularization, while local endothelial activation facilitates the adhesion, transmigration and extravasation of circulating tumor cells, a critical early step in metastatic seeding. Adhesion molecules upregulated on inflamed, atherosclerotic endothelium, including vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and E-selectin, which normally mediate monocyte recruitment into the plaque, have also been implicated in facilitating circulating tumor-cell arrest and extravasation at distant vascular beds, suggesting that the same endothelial activation program that sustains atherogenesis may simultaneously promote metastatic colonization.

Furthermore, circulating microparticles and extracellular vesicles shed from activated, atherosclerotic endothelium and from platelets carry pro-angiogenic microRNAs and growth factors capable of modulating gene expression in distant endothelial and tumor cells, providing an additional systemic mechanism by which vascular disease may support tumor angiogenesis at sites remote from the primary atherosclerotic lesion. Together, these observations position the dysfunctional, atherosclerosis-associated endothelium not as a passive bystander but as an active participant in creating a pro-angiogenic and metastasis-permissive vascular environment.

7. Myeloid Cell and Macrophage Crosstalk: From Foam Cells to Tumor-Associated Macrophages

Perhaps the most compelling cellular parallel between atherosclerosis and cancer lies in the shared biology of the monocyte-macrophage lineage. In the atherosclerotic plaque, circulating monocytes are recruited to the subendothelial space, differentiate into macrophages, and internalize oxLDL through scavenger receptors to become lipid-laden foam cells. These plaque macrophages exhibit remarkable phenotypic plasticity, ranging from a classically activated, pro-inflammatory M1-like state that promotes plaque instability, to an alternatively activated M2-like state associated with tissue repair and inflammation resolution, with numerous intermediate and plaque-specific phenotypes now recognized [25,26].

An essentially identical spectrum of polarization states characterizes tumor-associated macrophages (TAMs), which typically constitute the most abundant immune-cell population within the tumor stroma. Early in tumorigenesis, TAMs may adopt a pro-inflammatory, tumoricidal phenotype; however, as tumors progress, the microenvironment increasingly favors polarization toward an M2-like, immunosuppressive and pro-angiogenic phenotype that secretes VEGF, matrix metalloproteinases, interleukin-10 and transforming growth factor-beta, thereby facilitating tumor angiogenesis, extracellular-matrix remodeling, invasion and suppression of anti-tumor cytotoxic T-cell responses [27,28]. High TAM density and a predominantly M2-skewed polarization state are consistently associated with more aggressive tumor behavior and worse prognosis across multiple cancer types.

The mechanistic overlap between plaque macrophages and TAMs extends to shared recruitment pathways, notably the C-C chemokine receptor 2 (CCR2)-C-C motif chemokine ligand 2 (CCL2, also known as monocyte chemoattractant protein-1) axis, which drives monocyte recruitment into both the atherosclerotic intima and the tumor stroma, and the colony-stimulating factor-1 receptor (CSF1R) pathway, which sustains macrophage survival and M2 polarization in both tissues [27]. Oxidized-lipid handling further unites the two cell populations: myeloid cells within the tumor microenvironment accumulate oxidized lipids through mechanisms analogous to foam-cell formation, and this lipid loading similarly promotes an immunosuppressive, reactive-oxygen-species-dependent phenotype that favors tumor immune escape [18,29]. Fatty-acid oxidation and reactive-oxygen-species generation shape macrophage polarization, recruitment and phagocytic capacity in both settings, reinforcing the conceptual model that the atherosclerotic foam cell and the tumor-associated macrophage represent tissue-specific manifestations of a single, evolutionarily conserved myeloid-cell response to chronic lipid and inflammatory stress [29].

Neutrophils, mast cells and myeloid-derived suppressor cells expanded systemically as a consequence of chronic atherosclerotic inflammation may likewise seed distant tumor microenvironments, contributing pre-metastatic niche formation and further linking the systemic myeloid response to atherosclerosis with the establishment of a tumor-permissive immune landscape at distant organ sites.

8. Clonal Hematopoiesis of Indeterminate Potential: A Shared Somatic Driver

One of the most significant recent advances connecting atherosclerosis and cancer at the genomic level is the discovery of clonal hematopoiesis of indeterminate potential (CHIP), defined as the age-related clonal expansion of hematopoietic stem cells harboring somatic driver mutations, most commonly in the epigenetic regulators DNMT3A and TET2 and, less frequently, in ASXL1 and JAK2, occurring at a variant allele frequency of at least 2% in individuals without overt hematologic malignancy, dysplasia or cytopenia [30,31]. CHIP was originally identified through large-scale sequencing studies designed to characterize the genomic origins of hematologic malignancy, which unexpectedly revealed that CHIP carriers face not only a 0.5-1.0% per-year risk of progression to overt leukemia but also a substantially increased risk of cardiovascular disease and all-cause mortality that could not be explained by hematologic transformation alone [30,31].

Subsequent human genetic and experimental studies established that CHIP is an independent, causal risk factor for atherosclerotic cardiovascular disease. Individuals carrying CHIP-associated mutations have been shown to have a markedly increased risk of coronary heart disease and early-onset myocardial infarction, and murine models of Tet2-deficient clonal hematopoiesis demonstrate accelerated atherosclerotic plaque development, driven by exaggerated NLRP3 inflammasome activation and interleukin-1beta/interleukin-6 production within mutant macrophages, directly linking a hematopoietic somatic-mutation state to vascular inflammation and plaque pro-

gression [32,33]. Tet2-mutant clonal hematopoiesis has further been shown to accelerate the transition to heart failure through this same interleukin-1beta/NLRP3 inflammasome mechanism, underscoring the centrality of this pathway [34].

CHIP therefore occupies a unique position at the intersection of atherosclerosis and cancer: it is, by definition, an early, pre-malignant clonal state of the hematopoietic system that simultaneously predisposes to both hematologic malignancy and, through its pro-inflammatory macrophage progeny, to accelerated atherosclerotic disease [35]. This dual risk illustrates in the most direct possible way how a shared somatic driver, acting through a common inflammatory effector pathway, can promote the development of both a cardiovascular and a neoplastic phenotype in the same individual. Because CHIP prevalence rises steeply with age, exposure to genotoxic stressors such as cytotoxic chemotherapy and radiotherapy, and tobacco use, it also provides a plausible molecular explanation for the shared risk-factor architecture of atherosclerosis and cancer discussed in Section 3, and has emerged as a promising biomarker for the integrated risk stratification of cardio-oncologic disease.

9. Gut Microbiota and Metabolic Crosstalk

The gut microbiome has emerged as an additional systemic link between atherosclerosis and malignancy, principally through the generation of bioactive metabolites capable of influencing both vascular and neoplastic tissue. Dietary phosphatidylcholine and L-carnitine, abundant in red meat and other animal products, are metabolized by specific gut bacterial taxa to trimethylamine, which is subsequently oxidized in the liver by flavin-containing monooxygenase 3 to trimethylamine N-oxide (TMAO). Circulating TMAO promotes macrophage foam-cell formation, platelet hyperreactivity and vascular inflammation, and has been mechanistically and epidemiologically linked to accelerated atherosclerosis and adverse cardiovascular outcomes [36].

The same gut microbial ecosystem, and several of its metabolic products, has been implicated in colorectal and other gastrointestinal malignancies through mechanisms that include the generation of genotoxic and pro-inflammatory bacterial metabolites, disruption of the intestinal epithelial barrier, and induction of chronic low-grade mucosal inflammation that promotes epithelial proliferation and neoplastic transformation [37]. Dysbiosis characterized by an expansion of pro-inflammatory, TMAO-producing bacterial taxa may therefore simultaneously drive vascular inflammation and provide a tumor-permissive intestinal microenvironment, positioning the gut microbiome as a modifiable, shared upstream determinant of both diseases. Diet-based and microbiome-targeted interventions capable of reducing TMAO generation are consequently of interest not only for cardiovascular risk reduction but also as a potential strategy for mitigating shared inflammatory drivers of malignancy.

10. Cellular Senescence and the Senescence-Associated Secretory Phenotype

Cellular senescence, a state of stable cell-cycle arrest triggered by DNA damage, oncogene activation, oxidative stress or telomere attrition, contributes to both atherosclerosis and cancer through a shared secretory program known as the senescence-associated secretory phenotype (SASP). Senescent cells, while themselves incapable of proliferation, secrete a complex mixture of pro-inflammatory cytokines (including interleukin-6 and interleukin-1beta), chemokines, matrix metalloproteinases and growth factors that remodel the surrounding tissue microenvironment and, paradoxically, can promote the proliferation and invasive behavior of neighboring non-senescent, potentially pre-malignant cells [38].

Within the atherosclerotic plaque, senescent vascular smooth-muscle cells, endothelial cells and, notably, lipid-laden "senescent foam cells" accumulate progressively with plaque age and contribute to plaque instability; selective clearance of these senescent cells in murine models reduces plaque burden and improves features of plaque stability at every stage of disease, directly implicating senescent cell accumulation as a driver, rather than a mere consequence, of atherosclerotic progression [39,40]. The SASP elaborated by these senescent plaque cells shares its principal cytokine constituents, interleukin-6, interleukin-1beta and various matrix metalloproteinases, with the SASP described in senescent stromal cells found in the vicinity of premalignant and malignant epithelial lesions, where it can create a field of chronic inflammation, extracellular-matrix degradation and paracrine growth-factor signaling permissive to malignant transformation.

Given that senescent cell burden increases with chronological age, with genotoxic exposures common to atherosclerosis risk (smoking, hyperglycemia, oxidative stress) and with prior exposure to cytotoxic cancer therapies, cellular senescence provides a further unifying, age-associated mechanism linking the two diseases and represents an active area of investigation for senolytic and senomorphic pharmacological strategies with potential dual cardiovascular and oncologic benefit.

Collectively, these interconnected molecular and cellular mechanisms establish a common pathogenic network linking atherosclerosis and cancer, as illustrated in Figure 1.

The major molecular pathways shared between atherosclerosis and cancer, together with their biological functions and potential therapeutic targets, are summarized in Table 1.

11. Therapeutic Crosstalk: Statins, Anti-Inflammatory Agents and Repurposed Oncologic Drugs

The mechanistic overlap between atherosclerosis and cancer has direct therapeutic implications, most prominently illustrated by the pleiotropic, cholesterol-independent effects of statins. Beyond inhibition of hepatic HMG-CoA reductase and consequent LDL-cholesterol lowering, statins inhibit the mevalonate pathway broadly, reducing the synthesis of isoprenoid intermediates required for the post-translational prenylation and membrane localization of Ras and Rho-family GTPases that drive proliferative and invasive signaling in malignant cells [41]. This mechanistic rationale is supported by large population-based studies demonstrating reduced cancer-specific mortality among statin users, and multiple retrospective cohort analyses in patients with underlying cardiovascular or hepatic disease have reported reduced incidence of hepatocellular, prostate, breast and other malignancies among statin users compared with non-users, although randomized evidence specifically powered for cancer endpoints remains limited

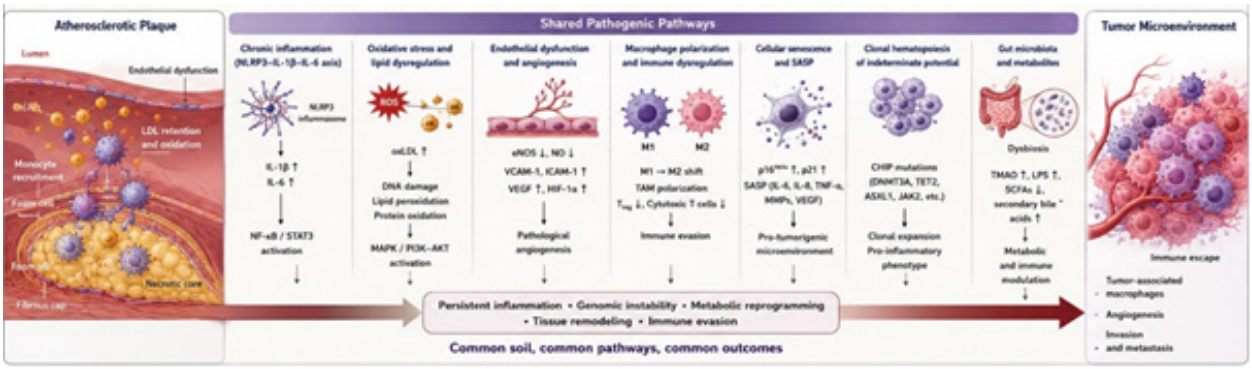


Fig. 1. Shared molecular and cellular mechanisms linking atherosclerosis and cancer. Schematic illustration of the principal molecular and cellular pathways shared between atherosclerosis and cancer. Chronic inflammation, oxidative stress, endothelial dysfunction, macrophage polarization, cellular senescence, clonal hematopoiesis of indeterminate potential (CHIP), and gut microbiota dysbiosis collectively promote immune dysregulation, metabolic reprogramming, angiogenesis, and tissue remodeling, thereby contributing to the initiation and progression of both diseases.

Table 1. Shared molecular pathways linking atherosclerosis and cancer and their therapeutic implications.

Molecular pathway	Role in atherosclerosis	Role in cancer	Potential therapeutic targets
Chronic inflammation	Promotes plaque initiation, progression, and instability	Supports tumor initiation, progression, and metastasis	IL-1β inhibitors, IL-6 inhibitors, anti-inflammatory therapies
NF-κB signaling	Induces inflammatory cytokines and endothelial activation	Enhances proliferation, survival, angiogenesis, and metastasis	NF-κB inhibitors
NLRP3 inflammasome	Activates IL-1β and vascular inflammation	Promotes tumor-promoting inflammation	NLRP3 inhibitors, colchicine
Oxidative stress (ROS)	Oxidized LDL formation, endothelial injury	DNA damage, genomic instability, tumor evolution	Antioxidants, NRF2 modulators
Endothelial dysfunction	Leukocyte adhesion and plaque formation	Tumor angiogenesis and vascular remodeling	Statins, ACE inhibitors, VEGF-targeted therapy
Macrophage polarization	Foam cell formation (M1/M2 imbalance)	Tumor-associated macrophages promote immune suppression	CSF1R inhibitors, macrophage-targeted therapies
Clonal hematopoiesis (CHIP)	Accelerates vascular inflammation and plaque progression	Increases cancer susceptibility and therapy-related malignancies	Anti-inflammatory strategies, precision monitoring
Gut microbiota	Produces proatherogenic metabolites (e.g., TMAO)	Regulates immune responses and cancer progression	Microbiota modulation, probiotics, dietary interventions
Cellular senescence (SASP)	Promotes chronic vascular inflammation	Creates a tumor-promoting microenvironment	Senolytics, senomorphics
PI3K/AKT/mTOR signaling	Regulates vascular cell survival and proliferation	Drives tumor growth and metabolic reprogramming	PI3K, AKT, and mTOR inhibitors

[42].

The most direct and clinically compelling evidence for a therapeutic bridge between atherosclerosis and cancer, however, derives from the exploratory oncologic findings of the CANTOS trial discussed in Section 4, in which selective interleukin-1beta blockade with canakinumab, administered specifically to reduce recurrent atherosclerotic cardiovascular events, produced a dose-dependent reduction in lung cancer incidence and mortality [14]. This finding has stimulated broader interest in repurposing anti-inflammatory agents developed for atherosclerotic disease, including colchicine and interleukin-6 pathway inhibitors, as adjunctive anti-cancer strategies, and has conversely prompted investigation of established oncologic agents, including tyrosine-kinase inhibitors and mTOR inhibitors, for their potential to modulate vascular smooth-muscle proliferation, macrophage polarization and neoangiogenesis within the atherosclerotic plaque, given the substantial overlap in the dysregulated proliferative, angiogenic and inflammatory pathways operative in both diseases.

Taken together, these observations support an integrated, "cardio-oncologic" pharmacological paradigm in which agents targeting the shared inflammatory, lipid-metabolic and proliferative pathways described throughout this review may confer simultaneous benefit across both atherosclerotic and neoplastic disease, an approach that

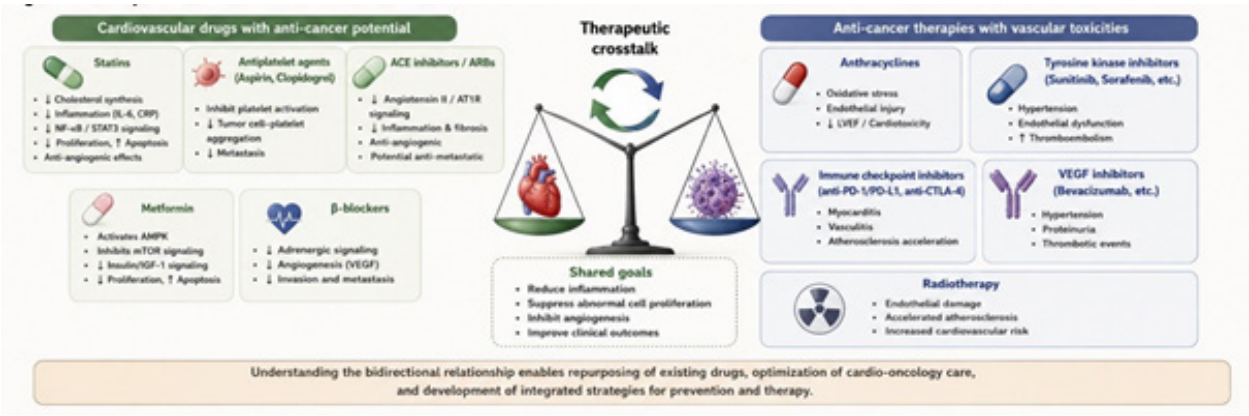


Fig. 2. Therapeutic crosstalk between atherosclerosis and cancer. Overview of the bidirectional therapeutic interactions between cardiovascular disease and cancer. Cardiovascular drugs, including statins, antiplatelet agents, ACE inhibitors/ARBs, metformin, and β-blockers, exhibit potential anticancer properties, whereas anticancer therapies such as anthracyclines, tyrosine kinase inhibitors, immune checkpoint inhibitors, VEGF inhibitors, and radiotherapy may induce vascular injury, endothelial dysfunction, accelerated atherosclerosis, and cardiovascular toxicity. Understanding these interactions provides opportunities for integrated cardio-oncology and mechanism-based therapeutic strategies.

warrants further evaluation in prospective, dual-endpoint clinical trials.

The bidirectional interactions between cardiovascular and anticancer therapies are summarized in Figure 2.

12. Clinical and Translational Implications

The recognition that atherosclerosis and cancer share a substantial mechanistic overlap carries several practical implications for clinical practice and future research. First, markers of subclinical atherosclerosis and systemic inflammation, including coronary artery calcium score, carotid intima-media thickness and high-sensitivity C-reactive protein, may hold value not only for cardiovascular risk stratification but also as adjunctive biomarkers of cancer risk, particularly in populations with heavy shared risk-factor burden such as long-term smokers. Second, the emergence of CHIP as a common, age-related somatic driver of both diseases raises the possibility that clonal hematopoiesis screening, already under investigation in cardiovascular risk assessment, could eventually be integrated into combined cardio-oncologic risk models. Third, lifestyle and pharmacological interventions that reduce chronic inflammation, oxidative stress and dyslipidemia, including smoking cessation, weight management, physical activity, statin therapy and, prospectively, targeted anti-inflammatory therapy, may offer simultaneous benefit in the primary prevention of both atherosclerotic cardiovascular disease and malignancy. Finally, the growing field of cardio-oncology, initially focused predominantly on the cardiotoxic effects of cancer therapy, should be expanded conceptually to encompass the reciprocal contribution of pre-existing atherosclerotic disease to cancer risk and tumor biology, supporting closer integration of cardiology and oncology in both clinical management and translational research programs.

13. Conclusions and Future Perspectives

The growing body of evidence indicates that atherosclerosis and cancer are not independent diseases but interconnected pathological conditions driven by overlapping molecular and cellular mechanisms. Chronic inflammation, oxidative stress, endothelial dysfunction, immune remodeling, clonal hematopoiesis, gut microbiota dysbiosis, and cellular senescence collectively establish a shared biological network that contributes to the initiation and progression of both disorders. These convergent pathways provide a compelling rationale for integrating cardiovascular biology and oncology into a unified mechanistic framework.

Recent advances in molecular medicine are transforming our understanding of this complex crosstalk. High-throughput multi-omics technologies, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics, together with single-cell sequencing and spatial transcriptomics, are enabling unprecedented characterization of cellular heterogeneity and intercellular communication within both atherosclerotic plaques and the tumor microenvironment. In parallel, artificial intelligence and machine learning approaches are accelerating the discovery of shared biomarkers, improving risk prediction, and facilitating the identification of novel therapeutic targets.

These emerging technologies are expected to accelerate the transition from conventional disease-specific management toward precision medicine, in which molecular profiling will enable individualized prevention, early diagnosis, prognostic stratification, and personalized therapeutic interventions. Furthermore, the rapid expansion of cardio-oncology underscores the importance of interdisciplinary collaboration to optimize cardiovascular health while improving cancer outcomes.

Future investigations should prioritize integrated systems biology approaches, longitudinal clinical studies, and mechanism-driven translational research to validate shared molecular targets and evaluate innovative therapeutic strategies. A deeper understanding of the molecular crosstalk between atherosclerosis and cancer will not only clarify their common pathogenesis but also pave the way for precision cardio-oncology, ultimately improving patient outcomes across both diseases.

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Conflict of Interest

The authors declare no conflict of interest.

Generative AI Statement

The author declares that generative AI (artificial intelligence) tools, including Grammarly & QuillBot, were used to enhance the language & clarity of this work. The author takes full responsibility for the accuracy & integrity of the content.

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