Review Article

Interlinking pathways: a narrative review on the role of IL-6 in cancer and atherosclerosis

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Background and Objective: Interleukin-6 (IL-6) plays multifaceted roles in cancer and atherosclerosis. Initially recognized for its role in immune response and inflammation, IL-6 promotes tumor progression via the JAK-STAT and MAP kinase pathways and is associated with poor cancer prognoses. In atherosclerosis, IL-6 contributes to endothelial dysfunction and plaque formation. This review highlights the shared inflammatory mechanisms of IL-6 in both diseases and explores the regulatory dynamics of IL-6 signaling, including gene polymorphisms and epigenetic modifications.

Methods: Google Scholar, Scopus, and PubMed were searched for English-language articles on IL-6 and those reporting shared pathogenic mechanisms of IL-6 in cancer and atherosclerosis from their inception through June 2024.

Key Content and Findings: The investigation into IL-6's mechanisms in cancer and atherosclerosis reveals the intricate and interconnected nature of inflammatory processes in chronic diseases. The role of IL-6 in both conditions underscores its centrality in disease pathology, particularly through its involvement in inflammation, immune modulation, and cellular proliferation. This commonality highlights IL-6 as a key player linking these seemingly distinct diseases.

Conclusions: Given the shared pathogenic mechanism of IL-6 in cancer and atherosclerosis, this narrative review concludes by emphasizing the therapeutic potential of modulating IL-6 in treating both cancer and atherosclerosis. It advocates for personalized treatment strategies that combine targeted therapies with lifestyle modifications. This holistic approach is considered crucial for effective disease management, given the diverse and complex roles IL-6 plays in these widespread conditions.

Keywords: Cancer; atherosclerosis; cardiovascular disease; inflammation

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Introduction

Interleukin-6 (IL-6), a multifaceted cytokine, assumes a central role in the pathophysiology of various diseases, particularly cancer and atherosclerosis. These conditions represent major societal, public health, and economic challenges in the 21st century due to their high mortality and morbidity worldwide (1-3).

Over time, its known role has expanded beyond being a regulator in immune responses and inflammation, encompassing diverse physiological and pathological domains (4,5).

In oncology, IL-6 has been identified as a crucial element in tumor progression and metastasis. It promotes the proliferation and survival of cancer cells, aiding in the development of a conducive microenvironment for tumor

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growth. Its signaling through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) and mitogen-activated protein (MAP) kinase pathways demonstrates its importance in cancer cell survival and proliferation (6,7).

Furthermore, elevated IL-6 levels have been linked to poor prognosis in various types of cancer, marking it as a potential target for therapeutic intervention (8).

Atherosclerosis, a leading cause of cardiovascular diseases, also exhibits a significant involvement of IL-6 in its pathogenesis (9). IL-6 contributes to endothelial dysfunction and fosters a pro-inflammatory state within the vascular system (10). Its role in promoting human endothelial cell and monocyte adhesion further elucidates its contribution to the development of atherosclerotic lesions. Recent studies have highlighted the therapeutic potential of IL-6R antagonism in mitigating atherosclerosis, particularly in cases linked to clonal hematopoiesis associated with Tet2 deficiency (11).

The interplay between IL-6 pathways in both cancer and atherosclerosis suggests shared mechanisms underlying these diseases. Both conditions are characterized by chronic inflammation, with IL-6 playing a pivotal role as a mediator. This commonality points to potential overlapping pathways in their pathogenesis, offering a rationale for targeted strategies that modulate IL-6 activity.

Moreover, due to significant advances in oncological diagnostics and therapy, the number of cancer survivors has grown substantially (12). However, this positive trend is tempered by an increasing risk of cardiovascular complications among cancer patients. Today, the majority of cancer patients die from non-cancer causes, with cardiovascular disease significantly contributing to mortality and morbidity in cancer survivors (12-14). Additionally, cancer chemotherapy has been associated with the induction of atherosclerosis, further exacerbating cardiovascular risks (12-14).

Exploring the role of IL-6 in these conditions also involves understanding its regulatory mechanisms. IL-6 signaling is modulated by various factors, including soluble IL-6 receptors (IL-6R) and the trans-signaling system. The balance between classic signaling and trans-signaling pathways determines the cytokine's functional outcomes in different contexts. Moreover, the genetic and epigenetic regulation of IL-6 expression adds another layer of complexity to its role in disease. Gene polymorphisms and epigenetic modifications can influence IL-6 levels, thereby affecting disease susceptibility and progression.

Rationale and knowledge gap

The multifaceted nature of IL-6 in disease pathogenesis highlights several existing research gaps. Despite significant advances, many aspects of IL-6 signaling, its interactions with other molecular pathways, and the shared mechanisms in atherosclerosis and cancer remain poorly understood.

Objective

This review comprehensively analyzes the multifaceted roles of IL-6, a versatile cytokine, in the contexts of cancer and atherosclerosis. It explores the shared pathogenic mechanisms mediated by IL-6 in both diseases, emphasizing their common root in chronic inflammation. Additionally, the review examines the regulatory dynamics of IL-6 signaling, including the impact of gene polymorphisms and epigenetic modifications. Finally, it underscores the therapeutic implications of modulating IL-6 in treating both conditions, advocating for personalized treatment approaches that integrate targeted therapies with lifestyle modifications. We present this article in accordance with the Narrative Review reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-344/rc).

Methods

In this paper, literature retrieval was conducted using Google Scholar, Scopus, and PubMed to find articles published in English that are related to IL-6 and report on the shared pathogenic mechanisms of IL-6 in cancer and atherosclerosis, covering studies from their inception through June 2024.

The search strategy is summarized in *Table 1*.

Section 1: IL-6 and its biological significance

IL-6 is a cytokine that plays a significant role in immune regulation and inflammation, acting as both a pro-inflammatory and anti-inflammatory mediator (15) (*Table 2*).

Its role in the immune system is complex and multifaceted, influencing various aspects of innate and adaptive immunity.

IL-6 in immune system regulation

IL-6 is important in regulating the immune system, and its functions are diverse and complex. Produced by a variety of cell types, including macrophages, T-cells, and endothelial

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Table 1 The search strategy summary

Items	Specification
Date of search	1 June 2024
Databases and other sources searched	PubMed, Scopus, and Google Scholar
Search terms used	((IL-6 OR "interleukin-6" OR "IL6" OR "IL6 pathways" OR "IL-6 signaling") AND (atherosclerosis OR "vascular disease" OR "arteriosclerosis" OR "plaque formation" OR "endothelial dysfunction" OR "Atherosclerosis"(MeSH))) OR ((IL-6 OR "interleukin-6" OR "IL6" OR "IL6 pathways" OR "IL-6 signaling") AND (cancer OR "malignant neoplasm" OR "tumor" OR "carcinoma" OR "oncology" OR "neoplasia" OR "Neoplasms"(MeSH)))
Timeframe	From inception until June 2024
Inclusion and exclusion criteria	Inclusion criteria: original research, technical notes, review articles, and guidelines/expert written in English
	Exclusion criteria: documents not written in English, case reports, and publications from non-academic sources (such as websites, newspapers, and magazines)
Selection process	R.C. analyzed the scientific literature to extract relevant data for this narrative review

cells (16), IL-6 is a key responder to physiological stimuli such as infections or tissue injuries. This multifunctional cytokine activates several immune response mechanisms, illustrating its central function in both innate and adaptive immunity.

In the context of innate immunity, IL-6 is pivotal during the acute phase response (17), a rapid inflammatory reaction to tissue injury or infection. This response involves the liver's production of acute phase proteins, such as C-reactive protein (CRP), which are critical for enhancing the body's ability to prevent infection and promote healing. IL-6 acts as a signaling molecule that alerts the liver to increase the synthesis of these proteins, thus serving a vital role in modulating the inflammatory response.

Regarding adaptive immunity, IL-6 significantly influences the differentiation and function of B and T cells (18). It promotes the differentiation of B cells into plasma cells, the antibody-producing cells crucial for humoral immunity (19). This process involves IL-6 binding to its receptor on B cells, triggering signaling pathways that lead to their proliferation and differentiation. The antibodies produced by plasma cells are essential for targeting and neutralizing pathogens (20).

IL-6 also aids in T-cell activation and differentiation (NO_PRINTED_FORM). It influences the fate of T cells, particularly affecting the differentiation of naïve T cells into various subsets, including Th17 cells and regulatory T cells (Tregs) (21). Th17 cells, known for their role in promoting inflammation, are involved in the defense against certain pathogens and in the pathogenesis of autoimmune diseases. Tregs, on the other hand, are crucial for maintaining immune tolerance and preventing excessive immune responses. The balance between these different T cell subsets, influenced by IL-6, is vital for the immune system's proper functioning and for preventing autoimmune conditions.

IL-6 in inflammation

In the context of inflammation, IL-6 functions as a pro-inflammatory cytokine (22). It is crucial in the pathogenesis of several inflammatory diseases, including rheumatoid arthritis and inflammatory bowel disease. One of the pivotal mechanisms through which IL-6 enhances inflammation is by inducing VEGF (22), a signaling protein instrumental in angiogenesis—the formation of new blood vessels. In inflammatory settings, IL-6-induced VEGF expression serves two primary purposes: it increases vascular permeability, facilitating the migration of immune cells to the inflamed site, and it promotes angiogenesis, which can sustain and exacerbate chronic inflammation by supplying necessary nutrients and oxygen to the inflamed tissues (18,23).

Furthermore, IL-6 acts as a catalyst in the inflammatory response by stimulating the production of other pro-inflammatory cytokines. It activates cells like macrophages and T-cells, which then release additional cytokines such as TNF-α and IL-1 (18,24). This results in a cascade of cytokine activity, amplifying the inflammatory response and contributing to the persistence and severity of chronic inflammatory diseases.

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Table 2 Multifaceted function of IL-6 in human biology

Aspect	Description	Cell types and factors involved	Mechanisms and pathways	Biological and clinical implications
Role in immune system	Central in mediating responses in both innate and adaptive immunity	Macrophages, T-cells, B-cells, endothelial cells	Responds to infections, tissue injuries	Facilitates communication between innate and adaptive immune systems; critical in immune response modulation
Innate immunity functions	Pivotal in acute phase inflammatory response	Liver cells	Produces acute phase proteins like CRP and fibrinogen	Enhances pathogen defense, regulates inflammation, aids in tissue repair and healing
Adaptive immunity functions	Modulates differentiation and function of B and T cells	B cells, T cells	Promotes B cell differentiation; affects T cell subsets	Key in antibody production, influences balance between pro-inflammatory and regulatory T cell responses
Role in inflammation	Acts as a pro-inflammatory cytokine in various diseases	Macrophages, T-cells	Induces VEGF, stimulates cytokines like TNF-α, IL-1	Involved in chronic inflammatory diseases pathogenesis; impacts disease progression and severity
Transcriptional regulation	Controls IL-6 gene expression at transcriptional level	NF-κB, AP-1	Activated by stress, cytokines, antigens	Critical in rapid IL-6 production in response to inflammatory stimuli; influences cellular responses to inflammation
Post-transcriptional regulation	Involves mRNA stability and miRNA-mediated regulation	–	Affects mRNA degradation, translation inhibition	Allows for nuanced control of IL-6 levels; adapts IL-6 expression to specific cellular environments
Regulatory feedback mechanisms	Involves complex feedback loops for homeostasis	Various immune cells, endothelial cells	Interactions between IL-6, its receptor, and signaling pathways	Maintains immune homeostasis; prevents overactivation of immune responses
Role in autoimmune diseases	Contributory factor in autoimmune pathologies	Immune cells	Promotes autoantibody production, T cell activation	Linked to diseases like rheumatoid arthritis, systemic lupus erythematosus; potential target for therapeutic interventions
Impact on tissue repair and regeneration	Influences healing processes	Fibroblasts, endothelial cells	Stimulates growth factors, collagen synthesis	Important in wound healing, tissue regeneration; excessive levels can lead to fibrosis
Interactions with other cytokines	Works in conjunction with or in opposition to other cytokines	Immune cells	Synergistic or antagonistic interactions	Determines the nature of immune response, e.g., synergizing with IL-1 or antagonizing IL-10
Clinical implications in cancer	Role in cancer progression and metastasis	Cancer cells, immune cells	Promotes tumor growth, immune evasion	Target for cancer therapy; IL-6 blockers may reduce tumor progression and improve survival

CRP, C-reactive protein; AP-1, activator protein 1; IL, interleukin; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

IL-6 signaling

IL-6 signaling can proceed through either the classical or trans-signaling pathways. In the classical pathway, IL-6 binds to membrane-bound IL-6R, leading to the formation of a trimeric complex with gp130, which forms dimers and triggers intracellular signaling through pathways including JAK/STAT, rat sarcoma proto-oncogene (RAS)/mitogen-activated protein kinase (MAPK), and phosphoinositide-3 kinase (PI3K). Conversely, the trans pathway involves soluble IL-6R (sIL-6R), which activates cells lacking membrane-bound IL-6R, initiating downstream IL-6 signaling and inducing inflammatory responses in these cells (20).

Importantly, the IL-6 trans-signaling pathway is responsible for many of IL-6's detrimental effects in chronic inflammatory diseases and cancer (25).

Recently, a third IL-6 signaling pathway was described, namely IL-6 cluster signaling. In this pathway, IL-6 forms

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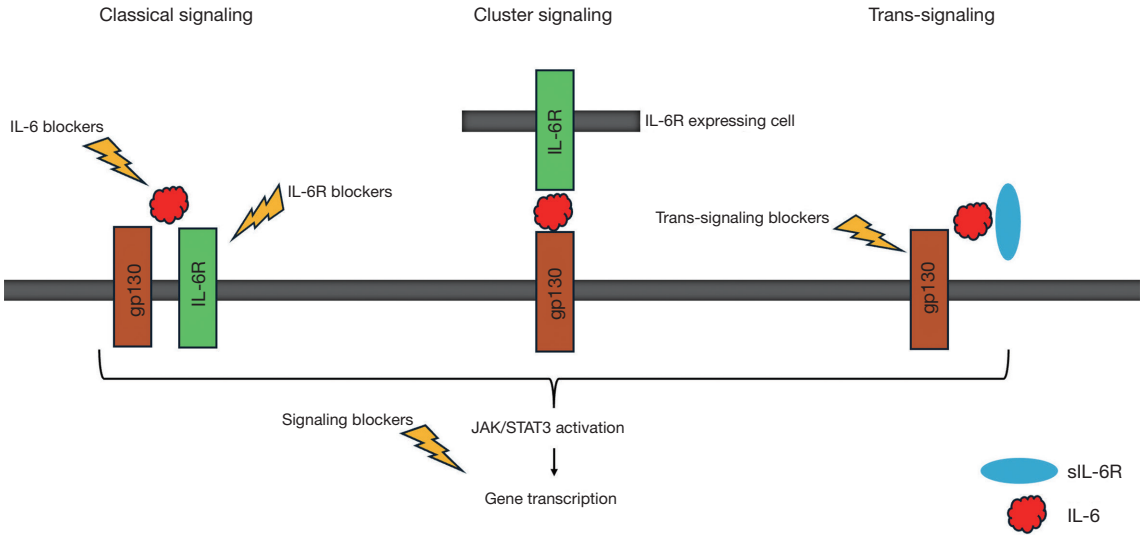

Figure 1 IL-6 signaling and potential therapeutic treatments in both cancer and atherosclerosis. IL-6, interleukin-6; IL-6R, interleukin-6 receptor; sIL-6R, soluble interleukin-6 receptor; JAK/STAT, Janus kinase/signal transducers and activators of transcription.

complexes with membrane-bound IL-6R α-subunits on transmitting cells, which subsequently activate gp130 subunits on adjacent receiving cells (23) (*Figure 1*).

Regulation of IL-6 and epigenetic changes

The intricate regulation of IL-6 production involves a multifaceted interplay of various signaling pathways and transcription factors. At the transcriptional level, NF-κB and AP-1 emerge as pivotal players orchestrating the fine-tuning of IL-6 gene expression. Triggered by diverse stimuli like stress, cytokines, and environmental factors, NF-κB translocates to the nucleus, binding to specific sequences in the IL-6 gene promoter and initiating the transcriptional cascade (26-28).

Simultaneously, AP-1, responsive to growth factors and inflammatory cytokines, collaborates with NF-κB to enhance the transcription of the IL-6 gene (29). This collaborative effort forms part of a larger regulatory network, where these transcription factors interact with upstream signaling pathways and other transcriptional regulators, creating a sophisticated system for IL-6 expression (20,23,30,31).

Aberrant epigenetic modifications can dysregulate genes involved in chronic inflammation. The IL-6 pathway is affected by DNA methylation, which alters the patterns of related genes and promotes tumorigenesis (32-34).

Moving beyond transcriptional control, post-transcriptional mechanisms add another layer of complexity to IL-6 regulation. The stability of IL-6 mRNA emerges as a critical factor determining the quantity of IL-6 protein produced. Various cellular signals come into play, influencing the delicate balance between mRNA degradation and stabilization, thereby modulating the overall IL-6 protein synthesis.

Along with DNA methylation, microRNA (miRNA)-mediated regulation introduces another epigenetic mechanism implicated in the control of gene expression. These small, non-coding RNAs target the mRNA of the IL-6 gene, leading to either degradation or inhibition of translation. This dynamic interplay of miRNAs provides an additional layer of fine-tuning, allowing for precise modulation of IL-6 expression in response to a diverse array of internal and external stimuli (35-37).

In essence, the regulation of IL-6 is a dynamic and sophisticated process, influenced by an extensive range of factors. This complexity not only enables precise control of IL-6 levels in various physiological and pathological conditions but also underscores the adaptability of the regulatory mechanisms governing this crucial cytokine.

Section 2: IL-6 in cancer

The role of IL-6 in the pathogenesis of cancer has garnered significant attention in recent years (38). IL-6 is involved in various aspects of cancer development, including cell proliferation, survival, angiogenesis, and metastasis, and

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Table 3 Previous studies that evaluated the role of IL-6 in various aspects of cancer development, including cell proliferation, survival, angiogenesis, and metastasis, have linked to a poor prognosis in several cancer types

References	Aspect	Relevant cancer	Signaling pathways involved	Detailed description	Clinical observations
Kumari *et al.*, 2016 (8), Guo *et al.*, 2012 (43)	Role in tumor growth	Breast and lung cancer	JAK/STAT pathway	IL-6 promotes cancer cell proliferation and survival	Linked to tumor progression in various cancers, particularly breast and lung cancer
Kumari *et al.*, 2016 (8), Masjedi *et al.*, 2018 (44)	Tumor microenvironment	Breast and lung cancer	–	IL-6 levels are elevated in the tumor microenvironment	High IL-6 levels are associated with resistance to chemo- and radiotherapy
Kumari *et al.*, 2016 (8), Chen *et al.*, 2010 (42)	Cell resistance	Breast, lung, and pharyngeal cancer	Counter-signalling pathways (anti-apoptotic/pro-survival)	IL-6 protects cancer cells from therapy-induced damage	IL-6 linked to reduced sensitivity of cancer cells to conventional anticancer therapies
Masjedi *et al.*, 2018 (44), Manore *et al.*, 2022 (31)	Cell survival and invasiveness	Breast and lung cancer	–	High IL-6 levels in breast cancer contribute to tumor growth and therapeutic resistance	Targeting IL-6 and/or its receptor may potentiate anticancer therapies in breast cancer treatment
Chen *et al.*, 2010 (42)	Tumor microenvironment and cell resistance	Pharyngeal cancer	p-STAT3 pathway, EGFR nuclear translocation	IL-6 signaling contributes to resistance to irradiation and EGFR inhibitors	Blocking IL-6 signaling sensitizes cancer cells to treatments
Berger *et al.*, 2023 (40)	Tumor microenvironment and cell resistance	Breast and lung cancer	Sortilin-progranulin axis	IL-6 promotes breast cancer stem cell propagation	Targeting IL-6 could inhibit breast cancer progression, especially in estrogen receptor-negative models
Nenu *et al.*, 2023 (41)	Cell survival and invasiveness	Hepatocellular cancer	–	Dual role in promoting and inhibiting HCC progression	IL-6's complex role in HCC underlines the need for tailored therapeutic strategies
Florescu *et al.*, 2023 (39)	Cell survival and invasiveness	Colorectal cancer	–	Correlation of IL-6 with diagnosis and prognosis of colorectal cancer	Elevated IL-6 levels associated with advanced tumor stages and short survival in patients

EFGR, epidermal growth factor receptor; HCC, hepatocellular carcinoma; IL, interleukin; JAK/STAT, Janus kinase/signal transducers and activators of transcription; pSTAT3, phosphorylated transducer and activator of transcription-3.

has been linked to a poor prognosis in several cancer types (8,31,39-44) (*Table 3*).

In particular, classical IL-6 signaling is regarded as crucial for maintaining homeostatic processes, while trans-signaling has been shown to specifically amplify inflammation and promote inflammation-induced carcinogenesis (18,45).

One of the mechanisms through which IL-6 exerts this effect is by activating the JAK/STAT pathway. This pathway is crucial in transmitting signals from the cell surface to the nucleus, leading to the expression of genes that drive cell growth and survival. Excessive activation of STAT3 due to an overabundance of IL-6, coupled with oncogenic driver mutations, facilitates the development of malignant tumors (46-48).

IL-6 also plays a role in angiogenesis, the process of new blood vessel formation, which is essential for tumor growth and metastasis (38). It does so by upregulating vascular endothelial growth factor (VEGF) and other angiogenic factors (49). Furthermore, IL-6 can promote metastasis by enhancing the invasive capabilities of cancer cells and by modifying the tumor microenvironment to favor cancer cell migration and invasion (24).

Therapeutic implications

Research using IL-6-deficient mice has demonstrated that IL-6 plays a significant role in the pathogenesis of various

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inflammatory conditions (50,51).

Consequently, inhibiting IL-6 has become a promising therapeutic approach worthy of clinical translation. In principle, IL-6 signaling can be achieved by using antibodies targeting any component of the receptor signaling complex—whether IL-6 itself, IL-6R, or gp130. The initial clinical trial of an IL-6-specific inhibitor was conducted in patients with plasma cell leukemia, demonstrating suppression of myeloma cell proliferation in the bone marrow and a decrease in CRP levels (52).

Subsequently, humanized monoclonal antibodies to IL-6R, such as tocilizumab, sarilumab, and satralizumab, were developed to prevent IL-6 from binding to its receptor. Notably, none of these IL-6 signaling inhibitors can differentiate between classical signaling and trans-signaling; they block both pathways simultaneously. To address this, a selective inhibitor of IL-6 trans-signaling that does not interfere with classical signaling, sgp130Fc (olamkicept), was developed. Another therapeutic strategy for targeting IL-6 is linked to JAK/STAT pathway (53-56). In cancer, IL-6's role in tumor growth, survival, and immune evasion makes it a compelling therapeutic target (57-69).

Previous studies focusing on IL-6 inhibitors are summarized in *Table 4*.

Generally, the primary adverse effects of anti-IL-6/IL-6R antibodies are associated with bacterial infections, likely because IL-6 coordinates innate and adaptive immune responses and activating the acute phase response. Inhibiting IL-6 trans-signaling could offer significant advantages as it does not interfere with the classical IL-6 signaling pathway, thus preserving the immune response against infections. Additionally, the major detrimental pro-inflammatory effects of IL-6 are mediated through trans-signaling (20,70).

Effectively treating cancer and enhancing the efficacy of current therapies, including immunotherapy, requires overcoming the immunosuppression caused by cancer-promoting inflammation. Immunotherapy often shows limited success in certain solid tumors due to the immune system's suppression driven by chronic inflammation. This inflammation is highly complex, regulated by multiple interactive pathways, and involves numerous compensatory mechanisms, making it a difficult target. These challenges likely explain why cytokine-targeting drugs have not been effective as monotherapies in halting tumor progression. However, robust preclinical evidence suggests that combining inhibitors of IL-6 family cytokine signaling with immune checkpoint blockade (ICB) could be a promising therapeutic strategy (7).

Several clinical trials are testing the efficacy of combining immunotherapy and blockade of IL-6 family cytokines (e.g., NCT03866239, NCT03821246, NCT04191421, etc.).

Section 3: IL-6 in atherosclerosis

Atherosclerosis is the primary cause of cardiovascular and cerebrovascular diseases and a major contributor to human mortality and morbidity (71-75). Numerous studies have shown that atherosclerosis is a chronic inflammatory condition with IL-6 has a crucial role (76). The pathogenesis of atherosclerosis involves multiple steps, beginning with the deposition of low-density lipoproteins (LDLs) in the arterial intima, along with local oxidative stress and immune and inflammatory activation. IL-6 sustains vascular inflammation by promoting smooth muscle cell (SMC) proliferation and migration, endothelial dysfunction, and the recruitment and activation of inflammatory mediators (76). These processes lead to the development and destabilization of atherosclerotic plaques (77).

Endothelial dysfunction represents the primary stage of atherosclerosis formation. IL-6 promotes the expression of adhesion molecules on endothelial cells, such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin. This expression facilitates not only endothelial permeability but also the attachment and infiltration of the vascular wall by circulating immune cells, including neutrophils, lymphocytes, and macrophages, thereby enhancing the level of inflammatory molecules (76,78).

Schuett *et al.* confirmed this data in atherosclerosis-prone mice by using a fusion protein of the IL-6 trans-signaling inhibitor soluble gp130 to block trans-signaling in LDL receptor-deficient mice, demonstrating that treatment with this fusion protein was effective. They found that treatment with this fusion protein reduced the progression of atherosclerotic lesions, which was accompanied by decreased expression of adhesion molecules on the endothelium and reduced macrophage infiltration in the aorta, underscoring the significance of trans-signaling in the pro-atherogenic properties of IL-6 (79).

In addition to its various effects on the endothelium, IL-6 significantly impacts vascular smooth muscle by inducing proliferation, migration, and hypertrophy (76). Both endothelial and SMCs respond to these conditions by expressing chemical mediators and recruiting macrophages. These macrophages accumulate intracellular lipids,

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Table 4 Previous studies focusing on IL-6 inhibitors in cancer therapy

Authors, year	Number of patients	Country	Relevant cancer	Study design	Phase	Study focus	Role of IL-6	Outcome data	Key findings related to IL-6
Kim *et al.*, 2020 (63)	39	USA	Biliary tract cancer	Multi-center	Phase II	Efficacy of regorafenib	Association with overall survival	Overall survival, progression-free survival, and objective response rates	Elevated baseline IL-6 was associated with shorter overall survival
Heath *et al.*, 2019 (65)	58	USA	Prostate cancer	Multi-center	Phase II	Efficacy of cediranib in combination with docetaxel and prednisone	Predictive of progression	Overall survival and progression-free survival	Increased baseline levels of IL-6 were significantly associated with an increased risk of progression
Haldar *et al.*, 2018 (67)	38	Israel	Breast cancer	Multi-center	Phase II	Perioperative inhibition of β-adrenergic and COX2 signaling	Serum cytokine levels	Level of systemic inflammation and pro-metastatic/pro-growth biomarkers	Treatment reduced pro-inflammatory cytokines including IL-6 in the serum
Puchalski *et al.*, 2010 (66)	68	UK	Metastatic renal cell carcinoma	Single-center	Phase I/II	Pharmacodynamics of siltuximab	Pharmacokinetic and pharmacodynamic modeling	Level of systemic inflammation biomarkers	IL-6 levels were used as a pharmacodynamic marker to assess the efficacy of siltuximab
Meyerhardt *et al.*, 2012 (64)	27	USA	Metastatic colorectal cancer	Multi-center	Phase I	Efficacy of vandetanib combined with cetuximab and irinotecan	Biomarker analysis	Overall survival and progression-free survival	IL-6 was monitored as a potential biomarker for treatment efficacy, although no significant changes in IL-6 levels were observed during therapy
Henry *et al.*, 2006 (62)	19	USA	Prostate cancer	Multi-center	Phase II	Copper depletion with tetrathiomolybdate	Serum cytokine levels	Level of systemic inflammation and angiogenesis factors	IL-6 levels were elevated compared to normal controls prior to therapy but did not change significantly during treatment

COX2, cyclooxygenase-2; IL, interleukin.

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leading to pathologic intimal thickening with lipid pools. Exogenously administered IL-6 significantly accelerated the development of fatty lesions in mice, increasing the size of the fatty streak by up to 5.1-fold (80).

In the prospective population-based Cardiovascular Health Study (CHS), the role of circulating IL-6 levels in the prediction carotid plaque severity, vulnerability, and progression was evaluated in 4,334 patients with carotid atherosclerosis. The authors demonstrated that IL-6 predicted plaque severity (β=0.09, P=1.3×10^{-3}), vulnerability [odds ratio (OR), 1.21; 95% confidence interval (CI), 1.05–1.40; P=7.4×10^{-3}, E-value =1.71], and progression (OR, 1.44; 95% CI, 1.23–1.69; P=9.1×10^{-6}, E-value =2.24). Moreover, a cut-off of 2.0 pg/mL may suggest the selection of individuals that would benefit from anti-IL-6 drugs (81).

The association between plaque progression and IL-6 was demonstrated in a study by Okazaki *et al.*, which prospectively followed 210 patients with carotid atherosclerosis over a median of 9.0±1.0 years. Baseline levels and progression of carotid mean-maximal intima-media thickness were positively correlated with IL-6 levels (P<0.001 for both). This significant association remained even after adjusting for age, sex, traditional risk factors, and baseline carotid mean-maximal intima-media thickness, suggesting that chronic elevation of serum IL-6 is associated with the progression of atherosclerosis (82).

IL-6 not only accelerates the formation of atherosclerotic plaques but also contributes to plaque instability and cardiovascular events. Mossmann *et al.* investigated the role of increased serum IL-6 as a predictive marker of cardiovascular events in 100 consecutive patients undergoing coronary angiography, with a median follow-up of 297 weeks (95% CI: 266.95–327.16). They found that an IL-6 level higher than 0.44 pg/mL was associated with a worse prognosis (83).

Moreover, IL-6 contributes to vascular calcifications in chronic inflammation (84,85), a well-known imaging biomarker of plaque instability (86-90).

Given the significant and growing global burden of atherosclerosis, it is essential to identify the cellular mechanisms underlying its pathogenesis. This knowledge can lead to the discovery of novel therapeutic targets for preventing or mitigating its clinical consequences.

Therapeutic implications

In 2017, the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) provided compelling evidence supporting the inflammation hypothesis of atherothrombosis. This study, involving 10,000 participants, demonstrated that targeting IL-1β significantly reduces rates of major cardiovascular events, independent of effects on cholesterol, blood pressure, or coagulation. Importantly, the degree of risk reduction observed in CANTOS correlated directly with the reduction in IL-6 levels achieved by participants. Among those treated with canakinumab who experienced greater than median reductions in IL-6 after the first dose, a 36% decrease in major adverse cardiovascular events was observed with long-term therapy [hazard ratio (HR) 0.64, 95% CI: 0.54–0.77; P<0.0001] (91). Conversely, among patients who did not experienced IL-6 reduction, Canakinumab showed marginal improvement over placebo (92). This trial emphasized IL-6 as a potential therapeutic target.

Therapeutic strategies for targeting IL-6 can be categorized into three interconnected approaches: direct inhibition of IL-6, targeting receptors like IL-6R or gp130, and focusing on downstream kinases or transcription factors within the JAK-STAT pathway (93).

Existing clinical trials focusing on IL-6 inhibitors in atherosclerosis are summarized in *Table 5*.

Section 4: common pathways and mechanisms in IL-6-driven cancer and atherosclerosis

Cancer and atherosclerosis are interconnected through shared risk factors and a fundamental pathophysiological mechanism involving chronic inflammation, also mediated through IL-6 signaling. The intersection of these two diseases is crucial, as it highlights not only their biological similarities but also the possibility of overlapping therapeutic strategies. This section delves into the common pathways and mechanisms through which IL-6 influences both cancer and atherosclerosis, underscoring the potential for overlapping therapeutic strategies.

Cancer and atherosclerosis: common risk factors

Diabetes, smoking, dyslipidemia, obesity, hypertension, sedentary behavior, unhealthy diets, physical inactivity, alcohol abuse, impaired immune response are risk factors common to both atherosclerosis development and progression and cancer. The presence of shared risk factors between cancer and atherosclerosis implies the existence of common pathogenetic mechanisms, prominently involving chronic inflammation (94).

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Table 5 Ongoing clinical trials focusing on IL-6 inhibitors in atherosclerosis

Clinical trial (NCT number)	Country	Study design	Target	Conditions	Interventions	Phase	Outcome measure
NCT03926117	USA	Multicenter	IL-6 ligand	Individuals with elevated high-sensitivity CRP and chronic kidney disease	Ziltivekimab	II	Level of systemic inflammation biomarkers
NCT05485961	United States, Canada, Belgium, Germany and Australia	Multicenter	IL-6 ligand	Adults with cardiovascular disease and/or diabetes receiving maintenance dialysis With high-sensitivity CRP ≥2 mg/L at baseline	Clazakizumab	IIb	Level of systemic inflammation biomarkers
NCT04626505	Japan	Multicenter	IL-6 ligand	Individuals with elevated high-sensitivity CRP and chronic kidney disease	Ziltivekimab	II	Level of systemic inflammation biomarkers
NCT06447701	China	Multicenter	IL-6 receptor	Patients having an ischemic stroke or a TIA prior to randomization with symptomatic intracranial atherosclerosis (50–99%)	Tocilizumab	I	Newly diagnosed ischemic stroke
NCT05021835	USA	Multicenter	IL-6 ligand	Individuals with elevated high-sensitivity CRP and chronic kidney disease	Ziltivekimab	III	Major adverse cardiovascular event
NCT03004703	Norway	Multicenter	IL-6 receptor	Patients with ST-segment elevation myocardial infarction	Tocilizumab	II	Myocardial salvage index
NCT01491074	Norway	Multicenter	IL-6 receptor	Patients with acute non-ST-segment elevation myocardial infarction	Tocilizumab	II	Level of systemic inflammation biomarkers
NCT05350592	Denmark	Single-center	IL-6 receptor	Patients with acute myocardial infarction	Tocilizumab	II	Level of systemic inflammation biomarkers and adverse cardiovascular outcomes

CRP, C-reactive protein; IL-6, interleukin 6; TIA, transient ischemic attack.

Cancer and atherosclerosis: IL-6 a common mediator

Several biological processes have been identified that share mechanisms between cancer and atherosclerosis, with IL-6 serving a common role in both (95,96).

IL-6's role as a pro-inflammatory cytokine is crucial in both diseases. In cancer, inflammation promotes tumor initiation, progression, and metastasis, while in atherosclerosis, chronic inflammation drives the development and progression of atherosclerotic plaques (95).

One of the primary mechanisms through which IL-6 exerts its effects in both cancer and atherosclerosis is the JAK/STAT pathway. Upon binding to its receptor, IL-6 activates JAK, which in turn phosphorylates and activates STAT proteins. These activated STATs translocate to the nucleus and modulate the expression of genes involved in cell proliferation, survival, and inflammation. Dysregulation of the JAK/STAT pathway is a hallmark of several cancers, contributing to uncontrolled cell growth and survival. Similarly, in atherosclerosis, the JAK/STAT pathway promotes the inflammatory processes that underpin plaque development. Activation of this pathway sustains inflammation, facilitating both tumor growth in cancer and plaque formation in atherosclerosis (97).

The IL-6 amplifier (IL-6 Amp) is another mechanism by which IL-6 perpetuates chronic inflammation in both diseases. This positive feedback loop involves the

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synergistic activation of STAT3 and NF-κB, which leads to the production of various pro-inflammatory cytokines and chemokines. In cancer, this mechanism sustains an inflammatory tumor microenvironment, promoting tumor growth and metastasis. In atherosclerosis, the IL-6 Amp enhances the recruitment of immune cells to the arterial wall, driving plaque progression and instability (50).

Angiogenesis, the formation of new blood vessels, is another shared process between cancer and atherosclerosis, with IL-6 playing a critical role. By stimulating the production of VEGF and other angiogenic factors, IL-6 enhances blood vessel formation. In cancer, angiogenesis is essential for tumor growth and metastasis, providing the tumor with the blood supply needed to sustain rapid cell proliferation. In atherosclerosis, angiogenesis contributes to the formation of vulnerable plaques, which are prone to rupture and lead to acute cardiovascular events (55,98,99).

Both cancer and atherosclerosis are characterized by oxidative stress and endothelial dysfunction, with IL-6 playing a central role in exacerbating these processes. In cancer, oxidative stress contributes to DNA damage and mutation, promoting carcinogenesis. In atherosclerosis, it leads to the dysfunction of endothelial cells, a critical early step in plaque formation. IL-6, through its pro-inflammatory effects, exacerbates oxidative stress and endothelial dysfunction in both diseases (100-102).

IL-6 modulates the immune system, impacting both cancer and atherosclerosis. In cancer, IL-6 contributes to the creation of an immunosuppressive tumor microenvironment, which allows tumors to evade immune surveillance. By promoting the differentiation of M2 macrophages and myeloid-derived suppressor cells (MDSCs), IL-6 enhances tumor growth and metastasis by suppressing anti-tumor immune responses (50).

In atherosclerosis, IL-6 influences the immune response within plaques, affecting the balance between pro-inflammatory and anti-inflammatory cells. By promoting the recruitment and activation of macrophages, IL-6 drives the inflammatory processes that lead to plaque formation and progression (96).

Recent research has highlighted genomic instability, such as clonal hematopoiesis of indeterminate potential, as a potential linking mechanism between cancer and atherosclerosis, with IL-6 playing a central role. Clonal hematopoiesis, the expansion of blood cell clones with certain genetic mutations, is associated with an increased risk of both hematological malignancies and atherosclerotic cardiovascular disease (95,103).

Discussion

The exploration of IL-6's mechanism in cancer and atherosclerosis shows the complexity and interconnectedness of inflammatory processes in chronic diseases (18,70). The function of IL-6 in both cancer and atherosclerosis highlights the cytokine's centrality in disease pathology. Its involvement in inflammation, immune modulation, and cellular proliferation provides a common thread linking these two seemingly disparate conditions (7).

The exploration of IL-6 as a therapeutic target in the realms of cancer and atherosclerosis is marked by its significant potential, albeit accompanied by intricate challenges and implications for future research and clinical practice.

The systemic nature of IL-6's role in the body implies that its modulation as a treatment strategy must be approached with a nuanced understanding of its widespread effects. Particularly, there is a need to balance the therapeutic benefits of targeting IL-6 against the potential risks, such as impaired immune responses or heightened susceptibility to infections (7,38). This consideration is crucial, given IL-6's integral role in immune regulation and inflammation.

Looking ahead, the path to fully leveraging IL-6's therapeutic potential is paved with several key research directions. A deeper molecular understanding of IL-6's role across different diseases is essential. This knowledge will facilitate the development of more effective, targeted treatments, particularly by shedding light on IL-6's interactions with other significant signaling pathways in cancer and atherosclerosis. Alongside this, the identification of biomarkers predictors of treatment response to IL-6 targeted therapies represents a critical frontier (104,105).

Such biomarkers could guide patient selection, ensuring that those most likely to benefit from these treatments are accurately identified, thereby enhancing the precision and efficacy of therapy.

In terms of treatment strategies, the exploration of combination therapies involving IL-6 targeting agents is particularly promising. These combinations, which might include traditional chemotherapy, targeted agents, or immunotherapies in cancer, and statins or other anti-inflammatory drugs in atherosclerosis, as well as lifestyle changes, hold the potential for synergistic effects. Such strategies could not only amplify therapeutic efficacy but also counteract the development of resistance (106).

From a clinical perspective, the insights into IL-6's

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function have immediate and significant implications. They herald new approaches to diagnosis and treatment, emphasizing the need for comprehensive, holistic management of chronic diseases. This approach should ideally integrate targeted IL-6 therapies with lifestyle interventions and traditional treatments, addressing the multifaceted nature of these conditions. Furthermore, patient education about IL-6's role and the importance of comprehensive management strategies is pivotal. This includes a focus on adherence to therapy and lifestyle changes.

Clinicians must also be proactive in managing potential adverse effects of IL-6 targeted therapies and vigilant in monitoring for signs of immune suppression or other systemic impacts. Regular patient monitoring is essential to ensure the safety and effectiveness of these treatments (107).

Strengths and limitations

The main strength of this narrative review lies in its comprehensive scope. It offers a detailed technical background on IL-6 pathophysiology and highlights its shared pathogenic mechanisms through chronic inflammation in both cancer and atherosclerosis. Additionally, it synthesizes potential therapeutic options targeting IL-6 pathways in both diseases.

The primary limitation is that, despite our best efforts to include the most relevant research, the field of IL-6 is continuously evolving, as evidenced by several ongoing clinical trials. As a result, newer findings may not be reflected in this review. Other limitations include potential biases from the selection of included studies and the reliance on subjective interpretations of the literature. Nonetheless, every effort has been made to present a balanced, informative, and rigorous perspective on the topic.

Conclusions

While targeting IL-6 offers a promising avenue for treating cancer and atherosclerosis, it requires a comprehensive, individualized approach that considers the unique challenges and intricacies inherent in its modulation. Ongoing research in this area is vital, not only to enhance our understanding of IL-6's diverse roles but also to develop more effective and personalized treatment strategies.

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