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Infectious–Immune Triggers of Atherosclerosis

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Abstract:
Atherosclerosis is considered a chronic inflammatory process in which infectious agents, infection-induced systemic inflammation, disturbances of innate and adaptive immunity, as well as microbial metabolites may play a role in its development and progression. This paper summarizes data on the association between chronic infections—including periodontitis, viral hepatitis, herpesvirus infections, and other inflammatory conditions—and an increased risk of atherosclerotic cardiovascular complications. Key pathogenetic mechanisms are discussed, including endothelial dysfunction, activation of Toll-like receptor (TLR) signaling, foam cell formation, involvement of the NLRP3 inflammasome, trained immunity, and the influence of the gut microbiota through trimethylamine N-oxide (TMAO) and metabolic endotoxemia. Particular attention is paid to the limited evidence of a causal relationship, as interventional studies on infection eradication have not yet demonstrated a convincing reduction in cardiovascular events. Promising therapeutic directions, including anti-inflammatory strategies, gut microbiota modulation, and targeting the NLRP3/IL-1β/IL-6 axis, are also outlined.

Keywords: *atherosclerosis; infections; inflammation; endothelial dysfunction; NLRP3 inflammasome; trained immunity; microbiota; TMAO; periodontitis; cardiovascular risk.*

Introduction

For many decades, interest in the hypothesis of a causal role of infections in the development of atherosclerosis has persisted. Although definitive evidence remains lacking, infections may influence traditional risk factors, such as hypercholesterolemia, through a variety of mechanisms. Numerous studies demonstrate an association between chronic infections and the risk of atherosclerosis and its complications.

Meta-analyses have shown that in the presence of periodontitis, the risk of major adverse cardiovascular events (MACE) and coronary heart disease increases by approximately 20–25% [1,2]. Similar associations have been observed in chronic viral infections; for example, in hepatitis C, the prevalence of subclinical atherosclerosis (measured by carotid intima-media thickness) is higher than in uninfected populations [3].

Chronic inflammation associated with infections such as *Helicobacter pylori*, HBV, CMV, HIV,

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and others also correlates with an increased incidence of myocardial infarction and stroke [4]. These findings indicate a strong epidemiological association between infections and atherosclerotic cardiovascular disease (ASCVD), although it remains unclear to what extent this reflects a direct causal relationship.

Extravascular infectious processes may also significantly influence the course of atherosclerosis and its clinical manifestations. Circulating cytokines and bacterial components produced in response to distant infectious foci can induce activation of endothelial cells and leukocytes within existing atherosclerotic plaques, forming a type of "systemic inflammatory response" of the vascular wall.

The acute-phase response during infection is accompanied by alterations in hemostatic balance, including increased levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1), contributing to a shift toward a prothrombotic state. Such changes may determine the likelihood of progression from subclinical plaque damage to clinically significant thrombotic events.

In addition, acute infectious conditions are associated with hemodynamic and metabolic changes, such as tachycardia and increased myocardial oxygen demand, which may provoke myocardial ischemia in patients with pre-existing atherosclerotic lesions of the coronary arteries [5,6,7].

Methods

This work was conducted as a narrative review and analytical study. The preparation of the manuscript was based on data from modern clinical-epidemiological, experimental, and interventional studies investigating the role of infections, chronic inflammation, immune mechanisms, and microbial metabolites in the pathogenesis of atherosclerosis.

The review includes data from meta-analyses, prospective cohort studies, randomized clinical trials, preclinical animal models of atherogenesis, as well as studies analyzing molecular pathways of endothelial activation, foam cell formation, NLRP3-mediated inflammation, trained immunity, and the influence of the gut microbiota.

The selection and interpretation of materials were aimed at systematizing current knowledge about the potential causal role of infectious–immune factors in atherosclerosis and identifying promising therapeutic targets.

Results and descussion

Significant doubt regarding causality arises from the lack of effect of infection eradication. For example, a prospective randomized study in patients after acute coronary syndrome (ACS) demonstrated that long-term administration of the antibiotic gatifloxacin (effective against *Chlamydia pneumoniae*) did not reduce the incidence of cardiovascular events [8,9].

Similarly, large-scale trials of macrolides (CLAIRCOR) and penicillin therapy failed to confirm any clinical benefit of antibiotics in coronary heart disease. This suggests that associated infections may modify the inflammatory background rather than serve as the sole cause of plaque formation.

Only a few small studies have shown improvement in biomarkers following periodontal treatment (reduction of CRP, IL-6, and improvement in flow-mediated dilation) [10]; however, to date, no large randomized controlled trials (RCTs) have demonstrated a reduction in myocardial infarction or stroke following treatment of periodontitis.

Likewise, the role of vaccination (e.g., influenza vaccination) in the primary prevention of ASCVD has been studied epidemiologically, but evidence of its specific effect on atherosclerosis remains insufficient.

It is important to note that the available data do not satisfy all Bradford Hill criteria for establishing causality: most associations are weak to moderate, and a clear dose–response relationship is not consistently demonstrated. Thus, at present, evidence of causality remains limited [11,12].

Molecular Mechanisms

Endothelial activation. Infectious agents and their products (lipopolysaccharide (LPS), viral

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proteins) induce endothelial dysfunction. Elevated levels of systemic cytokines such as IL-1β, TNF-α, and IL-6 during infection enhance the expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin) on the endothelium [13,14]. Thus, in chronic hepatitis C, increased levels of soluble ICAM-1 and VCAM-1 have been observed, correlating with markers of endothelial dysfunction [15]. This promotes the recruitment of monocytes and lymphocytes into the vascular wall—representing the first step of atherogenesis.

Macrophages and Foam Cells. Infection-induced inflammation enhances foam cell formation. Pathogens and pathogen-associated molecular patterns (PAMPs) (e.g., LPS, components of periodontal pathogens) activate Toll-like receptors (TLRs) on monocytes, increasing the uptake of oxidized LDL and cholesterol accumulation. Activated macrophages secrete IL-1β, IL-18, and other cytokines, promoting the M1 phenotype and accelerating inflammation within the atherosclerotic plaque [16]. In particular, activation of the NLRP3 inflammasome in macrophages is directly associated with their transformation into foam cells. NLRP3-derived products (IL-1β, IL-18) enhance oxidative stress and antiproliferative responses, thereby reducing plaque stability.

NLRP3 Inflammasome. The NLRP3 complex plays a central role at the intersection of infection and atherosclerosis. It is activated not only by cholesterol crystals but also by various infectious signals, including bacteremia, viral proteins (e.g., SARS-CoV-2 ORF3a/E), and microbial metabolites. Activation of NLRP3 leads to the maturation of IL-1β and IL-18 and induces pyroptosis in vascular cells. This results in increased expression of adhesion molecules and chemokines in the endothelium, disruption of the endothelial barrier, and formation of microthrombi [17]. At the macrophage level, NLRP3 enhances M1 polarization and promotes foam cell breakdown, releasing damage-associated molecular patterns (DAMPs) and amplifying inflammation (see figure).

Modern concepts of atherogenesis consider it a chronic inflammatory process based on the complex interaction between innate and adaptive immunity. Macrophages recruited to the vascular wall at early stages of lesion formation not only accumulate lipids but also actively regulate inflammatory responses by producing a wide range of cytokines, chemokines, and lipid mediators. Furthermore, these cells generate reactive oxygen species, intensifying oxidative stress within the atherosclerotic plaque microenvironment.

Alongside innate mechanisms, the adaptive immune response also plays a crucial role. Dendritic cells and macrophages present antigens to T lymphocytes, leading to their activation and subsequent cytokine secretion, which modulates the course of atherosclerosis. Potential antigens include modified lipoproteins, heat shock proteins, and components of infectious agents. Th1-type helper T cells produce proinflammatory cytokines, including interferon-γ and TNF-α, which contribute to plaque destabilization. In contrast, Th2-associated cytokines and regulatory T cells exert anti-inflammatory effects, limiting disease progression. Thus, the balance between proinflammatory and anti-inflammatory immune mechanisms is a key determinant of atherosclerotic progression.

Trained Immunity. Chronic infections can "train" the innate immune system—a phenomenon known as trained immunity. Experimental studies have shown that periodontal infections and other inflammatory conditions (such as arthritis and hyperglycemia) induce epigenetic reprogramming of bone marrow stem cells. As a result, hyperresponsive monocytes and neutrophils with enhanced proinflammatory potential circulate in the blood for months. These "trained" cells exhibit an increased metabolic response upon secondary stimulation, thereby accelerating atherosclerosis during repeated infectious exposures. IL-1β-dependent signaling in the bone marrow is considered a key mechanism underlying central trained immunity. This phenomenon may explain the cumulative effect of recurrent infections and unhealthy lifestyles on the progression of atherosclerosis.

Microbial Metabolites. Microbiota-derived metabolites represent a new link in pathogenesis. For example, trimethylamine N-oxide (TMAO), a product of choline/carnitine metabolism by gut microbiota, correlates with the risk of atherosclerosis (elevated TMAO levels are associated with increased incidence of cardiovascular events and mortality). TMAO induces reactive oxygen species and

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activates the NLRP3 pathway (via TXNIP and MAPK/NF-κB), leading to endothelial damage and reduced plaque stability. In addition, dysbiosis may contribute to metabolic dis endotoxemia is associated with increased intestinal permeability, allowing lipopolysaccharides (LPS) of Gram-negative bacteria to enter the bloodstream. Experimental studies have demonstrated the presence of LPS within atherosclerotic plaques, where it sustains local inflammation and promotes thrombogenesis. Thus, the gut microbiota and its products (both pro-inflammatory and anti-inflammatory) exert a direct influence on the atherosclerotic process.

Current evidence suggests that the gut microbiome should be considered not only as a source of metabolites but also as a regulator of systemic inflammation. Even moderate disruption of the intestinal barrier may lead to the translocation of microbial components into the bloodstream, thereby enhancing vascular inflammation and contributing to atherogenesis.

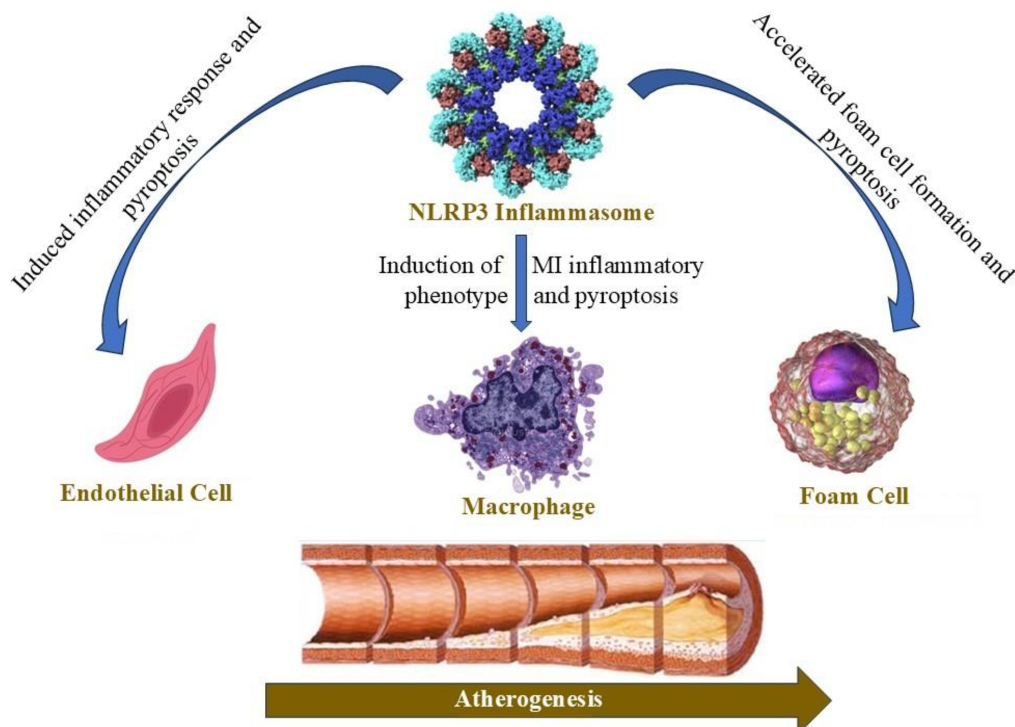

Figure 1. *Activation of the NLRP3 inflammasome in vascular wall cells promotes increased release of IL-1β/IL-18, endothelial activation (ICAM, VCAM), pyroptosis, as well as macrophage polarization toward the M1 phenotype and the formation of foam cells.*

Clinical and Experimental Approaches, Markers, and Causality

To assess the causal role of infections, the following approaches are proposed:

Causality criteria. The Bradford Hill criteria should be applied, including evaluation of temporal relationships (infection precedes atherosclerosis), biological gradient (e.g., severity of infection or antibody titers correlate with risk), consistency of data (interaction with known mechanisms), and experimental evidence. Currently, temporal association and biological plausibility (inflammatory mechanisms) are the most convincingly supported. However, the "dose–response" relationship (infection severity versus ASCVD risk) has not always been demonstrated, and intervention trials have yielded inconsistent results.

It is important to incorporate advanced statistical methods, such as genetic randomization approaches (e.g., Mendelian randomization using polymorphisms of immune receptors such as TLR, HLA, or coagulation factors during infection), to distinguish the effect of infection from confounding risk factors.

Experimental models. Transgenic mice ($ApoE^{-/-}$ or $LDLR^{-/-}$) are commonly used to model infection-induced atherosclerosis. For example, infection with *P. gingivalis*, HSV, or respiratory viruses

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such as SARS-CoV-2 may accelerate atherosclerosis progression in these models. Bone marrow transplantation from infected donors into non-infected recipients can be used to assess the contribution of trained immunity.

Vaccination or antigen-based treatment in animal models followed by assessment of atherosclerotic plaque changes (via MRI or histology) can help establish causal links. Molecular markers are also evaluated in vitro—for instance, stimulation of endothelial cells with LPS or viral proteins with subsequent measurement of VCAM/ICAM expression and reactive oxygen species (ROS) production.

For clinical studies, important markers include indicators of inflammation and endothelial dysfunction: high-sensitivity CRP, IL-6, IL-1β, IL-18, TNF-α, platelet activation markers (D-dimer, tissue factor), as well as sICAM-1/sVCAM-1 and endothelin-1.

Specific serological markers of infection (antibody titers or antigens such as *C. pneumoniae*, herpesviruses, HCV) and detection of pathogen DNA in plasma or atherosclerotic plaques are also essential. Markers of innate immune activation (e.g., increased $CD14^{+}CD16^{+}$ monocytes, levels of sCD14/sCD163) may indicate trained immunity. Functional tests (e.g., flow-mediated dilation, circulating foam cell density) provide additional insights.

Robust clinical approaches should include prospective cohort studies with comprehensive data integration (genomics, metagenomics, inflammatory markers) to correlate infection history and immune status with atherosclerosis development.

Perspective therapeutic targets

Prevention and treatment of infections may reduce the pro-inflammatory burden. For example, successful eradication of *H. pylori* may decrease inflammatory markers and improve lipid profiles. Intensive treatment of periodontitis (scaling, antibiotics, surgery) reduces CRP levels and improves vascular elasticity. However, direct evidence of their impact on ASCVD clinical outcomes remains limited, necessitating further research.

NSAIDs and anti–IL-1 therapy. Randomized trials (e.g., CANTOS) have shown that IL-1β blockade (canakinumab) reduces the incidence of myocardial infarction in patients with elevated CRP, confirming the role of inflammation in coronary artery disease. Colchicine, which partially inhibits NLRP3, has demonstrated efficacy in several randomized controlled trials in stable coronary artery disease (reducing complications by approximately 20%).

These findings highlight the NLRP3–IL-1 pathway as a promising therapeutic target. Selective NLRP3 inhibitors (MCC950, OLT1177, etc.) are currently under development. In preclinical models, MCC950 directly inhibits NLRP3 and prevents atherosclerosis progression. Other modulators, including vaccines targeting IL-1β, TNF antagonists, and TLR blockers, are also being investigated.

Diet, probiotics/prebiotics, and physical activity can modify gut microbiota composition, reducing TMAO-producing bacteria and intestinal permeability. In both animal and human studies, inhibitors of microbial enzymes responsible for trimethylamine production (e.g., DMB, 3,3-dimethylbutyramine) have been proposed to reduce TMAO levels and slow atherosclerosis progression.

Improvement of intestinal barrier function using agents such as L-glutamine, pectin, or other therapies may theoretically reduce systemic LPS burden. Although promising, clinical evidence remains insufficient. Given the role of trained immunity, drugs that reprogram innate immune responses are of particular interest.

For example, statins and metformin exhibit immunomodulatory effects beyond lipid control, partially inhibiting NLRP3 and IL-1β pathways. Epigenetic modulators (e.g., histone deacetylase inhibitors, miRNA mimetics) also represent potential strategies for reprogramming inflammatory monocytes.

Clonal Hematopoiesis of Indeterminate Potential as a Risk Factor

Clonal hematopoiesis of indeterminate potential (CHIP) is an age-associated condition characterized by the emergence of hematopoietic cell clones carrying somatic mutations affecting genes involved in proliferation and inflammatory responses. CHIP is associated with an increased risk of

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cardiovascular diseases independently of traditional risk factors.

One of the key mechanisms linking CHIP to atherogenesis is the усиление inflammatory signaling pathways, particularly activation of the "inflammasome–interleukin-1β–interleukin-6" cascade. Mutations in the *TET2* gene enhance the production of pro-inflammatory cytokines, whereas *JAK2* mutations are associated with increased thrombotic activity, partly due to enhanced formation of neutrophil extracellular traps (NETs).

Incorporating CHIP into the pathophysiological model of atherosclerosis expands our understanding of immune system involvement and opens promising avenues for precision anti-inflammatory therapeutic strategies targeting key inflammatory pathways.

Conclusion

In conclusion, the modern paradigm of atherosclerosis increasingly incorporates infectious and inflammatory factors alongside traditional risk factors. Although definitive proof of causality is still lacking, accumulating molecular and clinical evidence suggests that chronic infection and immune responses play a significant role in the initiation and progression of atherosclerotic plaques.

Future research should adopt an integrated approach, combining large prospective cohorts, experimental models, and novel biomarkers (including NLRP3 activity, trained immunity triggers, and microbial metabolites), as well as targeted interventions to identify critical points within inflammatory pathways and reduce residual ASCVD risk.

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