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COMMON THERAPEUTIC TARGETS OF ATHEROSCLEROSIS AND CROHN DISEASE: A NARRATIVE REVIEW

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ABSTRACT

Atherosclerosis and Crohn disease have long been regarded as unrelated disorders, yet a growing body of epidemiological and mechanistic evidence places them on a shared inflammatory continuum. Patients with inflammatory bowel disease, and Crohn disease in particular, carry an independent excess risk of ischemic heart disease and myocardial infarction that is most pronounced during periods of active intestinal inflammation. Both conditions are chronic, immune-mediated diseases in which an aberrant interaction between innate and adaptive immunity, the vascular or mucosal endothelium, lipid handling, and the gut microbiota perpetuates tissue injury. This narrative review synthesizes the molecular and cellular targets that the two diseases hold in common and the therapeutic developments that have grown out of them. The targets discussed include tumor necrosis factor-alpha, the interleukin-12 and interleukin-23 to T-helper-17 axis, the interleukin-1-beta and NLRP3 inflammasome pathway, interleukin-6 signaling, the Janus kinase and signal transducer and activator of transcription cascade, leukocyte adhesion and trafficking molecules, endothelial dysfunction with oxidative stress, and the gut microbiota and its metabolite trimethylamine N-oxide. We show how agents engineered for one disease inform or directly treat the other: anti-tumor-necrosis-factor and anti-interleukin-12 and 23 biologics control intestinal inflammation and may favorably influence vascular risk, while interleukin-1-beta blockade and low-dose colchicine reduce cardiovascular events by dampening the same inflammasome pathway that drives intestinal disease. We also highlight where target biology diverges and where safety signals demand caution. Two summary tables compare the shared targets and catalogue the corresponding therapeutic developments. A common-target framework supports rational drug repurposing, biomarker-guided therapy, and integrated cardiovascular and gastrointestinal risk management, but dedicated outcome trials in inflammatory bowel disease populations remain necessary to confirm cross-disease benefit.

KEYWORDS: Atherosclerosis; Crohn disease; Inflammation; Therapeutic targets; Cytokines; Gut microbiota

INTRODUCTION

Atherosclerosis is no longer viewed as a passive, lipid-storage disorder of the arterial wall but as a chronic inflammatory disease in which immune cells and cytokines participate at every stage, from the earliest endothelial activation to plaque rupture and thrombosis [1,2,3,4,5]. It underlies most ischemic heart disease and stroke and remains the leading cause of death worldwide. Decades of work have shown that low-density lipoprotein retention in the intima triggers an immune response in which monocyte-derived macrophages, T lymphocytes, and a network of pro-inflammatory mediators sustain lesion growth, so that residual cardiovascular risk persists even when lipids are aggressively lowered [6].

Crohn disease is one of the two principal forms of inflammatory bowel disease. It is a chronic, relapsing, frequently transmural inflammation of the gastrointestinal tract that arises when genetically susceptible individuals mount a dysregulated immune response to the intestinal microbiota under the influence of environmental triggers [7,8]. As in atherosclerosis, the disease process is driven by an imbalance between pro-inflammatory and regulatory signaling, with innate immune activation, T-helper-1 and T-helper-17 polarization, and a self-amplifying cytokine cascade as central features.

Although the two diseases affect different organs and have traditionally been studied in isolation, several lines of evidence connect them. Meta-analyses and large national cohorts show that inflammatory bowel disease is independently associated with ischemic heart disease, myocardial infarction, and ischemic stroke, with relative risks that are not explained by the classical cardiovascular risk-factor profile, which in these patients is often comparatively favorable [9,10,11,12,13,14]. The excess risk is most evident during disease flares and among young patients with

severely active disease, pointing to systemic inflammation rather than to a shared exposure as the operative mechanism. Detailed reviews of the epidemiology and pathophysiology have concluded that atherosclerosis and inflammatory bowel disease share substantial ground in genetics, immunology, environmental exposures, and the gut microbiome [15,16].

The clinical relevance of the inflammatory hypothesis of atherosclerosis was firmly established when anti-inflammatory therapy was shown to reduce cardiovascular events independently of lipid lowering [17]. Interleukin-1-beta blockade with canakinumab lowered recurrent vascular events in the CANTOS trial [18], and low-dose colchicine produced similar benefits in the LoDoCo, COLCOT, and LoDoCo2 trials [19,20,21]. Strikingly, the cytokines and pathways targeted by these cardiovascular interventions are the very ones that have been blocked for years to treat Crohn disease. The purpose of this review is to synthesize the molecular and cellular targets that atherosclerosis and Crohn disease hold in common and the therapeutic developments that have emerged from them, and to consider the opportunities and limitations of a common-target strategy for drug repurposing and integrated patient management.

SHARED PATHOPHYSIOLOGY OF ATHEROSCLEROSIS AND CROHN DISEASE

A common-target framework is meaningful only because the two diseases share an underlying architecture. Their shared ground extends to genetic susceptibility: susceptibility genes for Crohn disease such as NOD2 [22] sit within innate-immune pathways highlighted by genome-wide studies of inflammatory bowel disease [23], several of which converge conceptually on the inflammatory genetics of coronary artery disease [24]. Four interconnected functional domains then link the diseases: endothelial dysfunction with leukocyte recruitment, innate immune activation centered on the inflammasome, adaptive immunity dominated by the T-helper-17 axis, and the gut microbiota together with the metabolic consequences of barrier failure.

Endothelial dysfunction and leukocyte recruitment

Endothelial activation is an early and unifying event. In the arterial wall, oxidized low-density lipoprotein and disturbed flow induce endothelial cells to express adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, which capture circulating monocytes and direct them into the intima, where they differentiate into foam cells. In Crohn disease, chronic mucosal inflammation produces a parallel state of systemic endothelial dysfunction: patients show impaired flow-mediated dilation and evidence of endothelial activation even in the absence of overt cardiovascular disease [25]. Increased aortic stiffness, a recognized surrogate of cardiovascular risk, has been documented in inflammatory bowel disease and tracks with the inflammatory burden, falling toward normal values when inflammation is controlled with anti-tumor-necrosis-factor therapy [26]. The same adhesion and trafficking machinery that recruits leukocytes into the gut wall therefore operates, with organ-specific accents, in the artery.

Innate immunity and the NLRP3 inflammasome

Macrophages sit at the center of both diseases. In atherosclerosis, cholesterol crystals and other danger signals activate the NLRP3 inflammasome [27], leading to caspase-1-dependent maturation of interleukin-1-beta and interleukin-18; interleukin-1-beta then drives interleukin-6 production and, downstream, hepatic synthesis of C-reactive protein [6]. This axis defines the principal druggable inflammatory pathway in cardiovascular medicine. In Crohn disease, inflammasome activation in mucosal macrophages and dendritic cells likewise amplifies interleukin-1-beta and interleukin-18, contributing to epithelial injury and to the recruitment and activation of effector lymphocytes. The shared dependence on the inflammasome explains why agents that interrupt it, whether by neutralizing interleukin-1-beta or by interfering with microtubule-dependent inflammasome assembly, have effects relevant to both organs.

Adaptive immunity and the T-helper-17 axis

Adaptive immunity provides a second point of convergence. Interleukin-12 promotes T-helper-1 responses, while interleukin-23 stabilizes and expands pathogenic T-helper-17 cells that secrete interleukin-17 and other effector cytokines. The interleukin-23 to T-helper-17 axis is firmly implicated in the chronic, treatment-refractory phenotype of Crohn disease and is also detectable within atherosclerotic plaque, where interleukin-17 modulates the balance of plaque-stabilizing and plaque-destabilizing processes [7]. The cytokine biology is nonetheless context-dependent: the precise role of interleukin-17 in the artery is more nuanced than in the gut, a divergence that has direct therapeutic consequences.

Gut microbiota, barrier failure, and metabolic endotoxemia

The gut microbiota is increasingly recognized as a shared driver. Both atherosclerosis and inflammatory bowel disease are characterized by reduced microbial diversity and a relative loss of butyrate-producing members of the Firmicutes phylum, such as Faecalibacterium prausnitzii [28], together with impaired intestinal barrier integrity. Barrier failure permits translocation of bacterial products such as lipopolysaccharide into the circulation, initiating a low-grade systemic inflammatory response that promotes atherogenesis. In addition, gut microbes convert dietary choline, phosphatidylcholine, and L-carnitine into trimethylamine, which the liver oxidizes to trimethylamine N-oxide, a metabolite mechanistically linked to foam-cell formation, platelet hyperreactivity, and accelerated atherosclerosis

[29,30,31,32]. The gut-vascular axis thus connects the organ of primary injury in Crohn disease to the vascular consequences that the two diseases share.

COMMON MOLECULAR AND CELLULAR THERAPEUTIC TARGETS

Building on this shared architecture, several molecular and cellular nodes qualify as common therapeutic targets, in the sense that intervening on them is biologically rationalized, and in some cases clinically validated, in both diseases. Table 1 compares these targets and their roles in each condition; the subsections that follow discuss them in turn.

Table 1. Common therapeutic targets of atherosclerosis and Crohn disease and their roles in each disease.

Shared target / pathway	Role in atherosclerosis	Role in Crohn disease	Selected references
TNF-alpha	Activates endothelium, promotes adhesion-molecule and chemokine expression, foam-cell formation and a pro-atherogenic, insulin-resistant state.	Pivotal effector cytokine; sustains mucosal inflammation and is the long-standing first-line biologic target.	[26,16]
IL-12 / IL-23 - Th17 axis	IL-17 and Th17 cells are present in plaque and modulate plaque stability; role more context-dependent than in gut.	Drives pathogenic Th17 responses and treatment-refractory disease; central validated target.	[7,33]
IL-1-beta / NLRP3 inflammasome	Cholesterol-crystal-activated inflammasome generates IL-1-beta; blockade reduces cardiovascular events.	Inflammasome activation in mucosal macrophages amplifies epithelial injury and effector immunity.	[27,18]
IL-6 signaling	Downstream of IL-1-beta; drives C-reactive protein; IL-6 response predicts residual cardiovascular risk.	Elevated in active disease; contributes to systemic inflammatory burden and acute-phase response.	[34]
JAK-STAT signaling	Transduces multiple pro-inflammatory cytokines; class-level cardiovascular cautions apply.	Intracellular hub effectively blocked by oral JAK inhibitors in moderate-to-severe disease.	[35]
Leukocyte adhesion / trafficking	Adhesion molecules recruit monocytes into the intima during early atherogenesis.	Integrin alpha-4-beta-7 and MAdCAM-1 direct lymphocyte homing to gut; gut-selective blockade is effective.	[36] [25]
Gut microbiota / TMAO	Dysbiosis and TMAO promote foam-cell formation, platelet reactivity and atherogenesis.	Dysbiosis and barrier failure are core to pathogenesis; source of systemic inflammatory signals.	[29,32]
Endothelial dysfunction / oxidative stress / lipids	Initiating and propagating events; statins exert pleiotropic anti-inflammatory effects.	Systemic endothelial dysfunction and increased arterial stiffness accompany active disease.	[25] [37]

Tumor necrosis factor-alpha

Tumor necrosis factor-alpha is the most established shared target. In Crohn disease it is a pivotal effector cytokine, and monoclonal antibodies against it have been first-line biologic therapy for moderate-to-severe disease for more than two decades. In the artery, tumor necrosis factor-alpha activates endothelial cells, induces adhesion molecules and chemokines, drives macrophage activation and foam-cell formation, and promotes a pro-atherogenic, insulin-resistant metabolic state. Direct evidence that anti-tumor-necrosis-factor therapy reduces hard cardiovascular endpoints in inflammatory bowel disease is still limited, but surrogate data are encouraging: long-term anti-tumor-necrosis-factor therapy reduced aortic stiffness in inflammatory bowel disease patients to levels comparable with healthy controls [26], and observational data in related immune-mediated diseases suggest a reduction in cardiovascular events. The relationship is not uniformly favorable, however; tumor necrosis factor-alpha inhibition can worsen pre-existing heart failure, which tempers enthusiasm in patients with established cardiac disease [16].

The interleukin-12 and interleukin-23 to T-helper-17 axis

Blockade of the interleukin-12 and interleukin-23 axis is a validated strategy in Crohn disease. Ustekinumab, which neutralizes the shared p40 subunit of interleukin-12 and interleukin-23, is effective for induction and maintenance of remission [33], and selective interleukin-23 p19 inhibitors such as risankizumab have since demonstrated efficacy and a favorable safety profile [38]. Because interleukin-23 and interleukin-17 are also active within atherosclerotic plaque, this axis is a plausible shared target, and interleukin-23 inhibitors have shown low cardiovascular event rates in clinical programs. A crucial cautionary lesson comes from interleukin-17 itself: although anti-interleukin-17 therapy is highly effective in psoriasis, it paradoxically worsened Crohn disease in a controlled trial [39], underscoring that a cytokine beneficial to target in one tissue may be harmful to block in another. The shared target must therefore be defined at the level of the specific node, not the pathway as a whole.

Interleukin-1-beta and the NLRP3 inflammasome

The interleukin-1-beta and NLRP3 inflammasome pathway is the clearest example of a target validated by outcomes in one disease that is mechanistically central to the other. In CANTOS, the interleukin-1-beta-neutralizing antibody canakinumab reduced recurrent major cardiovascular events independently of lipid levels, and the magnitude of benefit tracked with the reduction in C-reactive protein achieved [18,40]. Low-dose colchicine, which interferes with microtubule-dependent inflammasome assembly and neutrophil function, reduced cardiovascular events across the LoDoCo, COLCOT, and LoDoCo2 trials [19,20,21] and is now an approved anti-inflammatory option for atherosclerotic disease. The same inflammasome operates in the inflamed intestine, so interventions that constrain interleukin-1-beta generation are attractive candidates for dual benefit, even though dedicated Crohn disease outcome data for these specific agents remain to be generated.

Interleukin-6 signaling

Interleukin-6 lies immediately downstream of interleukin-1-beta and is the principal driver of the hepatic acute-phase response, including C-reactive protein. Secondary analyses of CANTOS showed that patients whose interleukin-6 response was most suppressed derived the greatest cardiovascular benefit, identifying interleukin-6 signaling as a target in its own right [34]. Interleukin-6 is also elevated in active Crohn disease and contributes to the systemic inflammatory burden that links intestinal activity to vascular risk. Direct interleukin-6 pathway inhibition is being explored on the cardiovascular side and has an established place in other immune-mediated diseases, making it a logical, if not yet fully realized, shared target.

Janus kinase and signal transducer and activator of transcription signaling

Many of the cytokines implicated in both diseases signal through the Janus kinase and signal transducer and activator of transcription cascade, making this intracellular hub an appealing target. Oral Janus kinase inhibitors such as tofacitinib and upadacitinib are effective in inflammatory bowel disease [35,41]. Here the shared-target logic meets an important safety divergence: a dedicated safety trial in rheumatoid arthritis raised concerns about major adverse cardiovascular events and thromboembolism with tofacitinib [42], so Janus kinase inhibition carries class-level cardiovascular warnings and must be used cautiously in patients at elevated vascular risk [16]. This illustrates that a shared molecular target does not guarantee a shared safety profile.

Leukocyte adhesion and trafficking molecules

Adhesion and trafficking molecules are mechanistically central to both diseases but offer an instructive contrast in selectivity. In atherogenesis, endothelial adhesion molecules recruit monocytes into the intima. In Crohn disease, the integrin alpha-4-beta-7 and its endothelial ligand MAdCAM-1 direct lymphocyte homing specifically to the gut, and the gut-selective antibody vedolizumab exploits this to control intestinal inflammation with minimal systemic immunosuppression [36]. The very gut selectivity that makes vedolizumab safe limits its expected systemic vascular effect, demonstrating that organ-restricted targeting can be a feature rather than a limitation when the goal is to avoid off-target consequences.

The gut microbiota and trimethylamine N-oxide axis

The gut microbiota and the trimethylamine N-oxide pathway constitute an emerging shared target that sits upstream of the immune cascade. Strategies under investigation include non-lethal inhibition of the microbial choline trimethylamine-lyase enzymes that generate trimethylamine, dietary modulation of trimethylamine N-oxide precursors, and broader microbiome-directed approaches such as restoration of butyrate-producing taxa [29,30,32]. Because dysbiosis and barrier dysfunction are integral to Crohn disease and also feed atherogenesis, interventions that repair the barrier or reshape the microbiota could, in principle, act on both diseases at once.

Endothelial dysfunction, oxidative stress, and lipids

Finally, the endothelium, oxidative stress, and lipid handling are shared targets approached most successfully through statins. Beyond lowering low-density lipoprotein, statins exert pleiotropic anti-inflammatory and endothelium-stabilizing effects, and the JUPITER trial showed that targeting inflammation, indexed by C-reactive protein, identifies patients who benefit even at conventional lipid levels [37]. In inflammatory bowel disease, where endothelial dysfunction and arterial stiffness accompany active disease [25], the same endothelial-protective principles apply, and the appropriate, guideline-based use of lipid-lowering and endothelium-protective therapy is part of integrated risk management.

THERAPEUTIC DEVELOPMENTS BASED ON SHARED TARGETS

Translating shared targets into therapy proceeds along two complementary routes. In the first, agents developed for Crohn disease define the inflammatory nodes whose blockade might also benefit the artery; in the second, anti-inflammatory agents validated by cardiovascular outcome trials suggest interventions that could be repurposed for intestinal disease. Table 2 catalogues the principal therapeutic developments organized by shared target, together with their regulatory status in Crohn disease and the available evidence on the cardiovascular side.

Table 2. Therapeutic developments based on targets shared by atherosclerosis and Crohn disease.

Agent (class)	Molecular target	Status in Crohn disease	Evidence and considerations in atherosclerosis / cardiovascular disease
Infliximab, adalimumab (anti-TNF mAbs)	TNF-alpha	Approved, long-standing first-line biologics.	Reduce arterial stiffness in inflammatory bowel disease [26]; observational signals of lower cardiovascular events in immune-mediated disease, but caution in heart failure [16].
Ustekinumab (anti-IL-12/23 p40); risankizumab (anti-IL-23 p19)	IL-12 / IL-23	Approved for moderate-to-severe disease [33,38].	IL-23 inhibitors show low cardiovascular event rates; biologically rational given Th17 activity in plaque; dedicated outcome data pending.
Canakinumab (anti-IL-1-beta mAb)	IL-1-beta	Not approved for Crohn disease; mechanistically relevant.	Reduced recurrent cardiovascular events in CANTOS independently of lipids [18]; proof of concept for inflammasome targeting.
Colchicine (oral anti-inflammatory)	NLRP3 inflammasome / microtubules	Used in related autoinflammatory conditions; investigational in IBD.	Reduced cardiovascular events in COLCOT and LoDoCo2 [20,21]; an approved anti-inflammatory option for atherosclerotic disease.
Tofacitinib, upadacitinib (JAK inhibitors)	JAK-STAT	Approved / effective in moderate-to-severe disease [35,41].	Class-level cardiovascular and thromboembolic warnings [42]; require careful use in high-risk patients.
Vedolizumab (anti-alpha-4-beta-7 mAb)	Integrin alpha-4-beta-7 / MAdCAM-1	Approved; gut-selective [36].	Favorable cardiovascular safety; gut selectivity limits expected systemic vascular effect.
Statins (HMG-CoA reductase inhibitors)	Lipids, endothelium, inflammation	Adjunctive for cardiovascular risk management.	Cornerstone of atherosclerosis prevention; pleiotropic anti-inflammatory and endothelial effects (JUPITER) [37].
Microbiome / TMAO-directed approaches	Gut microbiota; TMA-lyase; barrier	Investigational (diet, FMT, engineered strains).	TMA-lyase inhibition and microbiome modulation reduce atherogenesis experimentally [32]; early-stage for both diseases.

Several themes emerge from these developments. Drug repurposing is the most immediate opportunity: an agent that is already approved and whose safety is characterized in one disease can be evaluated for the other with a lower barrier than a wholly new molecule. Combination strategies that pair lipid lowering with a validated anti-inflammatory agent are being actively explored in cardiology and have conceptual appeal in patients who carry both atherosclerotic and intestinal disease. Biomarker-guided therapy is a unifying thread, because high-sensitivity C-reactive protein on the vascular side and fecal calprotectin on the intestinal side both index the inflammatory activity that the shared targets address, offering a practical means to select patients and monitor response. Finally, microbiome-based and metabolite-directed therapeutics represent a frontier in which a single intervention might modify the shared upstream driver of both diseases.

DISCUSSION

The convergence of targets reviewed here supports a common-soil interpretation of atherosclerosis and Crohn disease, in which a shared inflammatory architecture, rather than coincidence, links intestinal and vascular disease. The strongest single piece of evidence is the interleukin-1-beta and NLRP3 inflammasome pathway: validated by cardiovascular outcome trials and mechanistically active in the gut, it shows that dampening a cytokine circuit central to Crohn disease can reduce hard cardiovascular endpoints [18,20,21]. The practical implications are threefold. First, drug repurposing across the two indications is biologically justified and, for several agents, already feasible. Second, integrated care that recognizes the cardiovascular consequences of intestinal inflammation, and treats inflammation to a target, may yield benefits beyond symptom control. Third, shared biomarkers permit a unified, inflammation-centered approach to patient selection and monitoring.

These opportunities are bounded by important caveats. The biology of individual cytokines is context-dependent, and a target that is beneficial to block in the gut may be neutral or harmful in the artery, and vice versa. The contrast between the success of interleukin-23 blockade and the deterioration of Crohn disease under interleukin-17 blockade, and the divergent cardiovascular safety of Janus kinase inhibitors despite their efficacy in intestinal disease, both make this point forcefully [39,42,16]. Not every anti-inflammatory strategy succeeds, either: low-dose methotrexate, effective in some immune-mediated diseases, failed to reduce cardiovascular events in the CIRT trial, demonstrating that target choice within the inflammatory network is decisive [43]. Moreover, dedicated cardiovascular outcome trials in inflammatory bowel disease populations are largely lacking, so much of the cross-disease inference rests on surrogate endpoints and on extrapolation from related conditions. Residual inflammatory risk persists even with optimal therapy, indicating that no single node fully captures the shared pathology.

Future research should therefore prioritize prospective trials that measure cardiovascular endpoints directly in patients with Crohn disease treated with target-specific agents, mechanistic studies that resolve the tissue-specific roles of interleukin-17, interleukin-23, and the Janus kinase isoforms, and translational work on the gut-vascular axis, including trimethylamine N-oxide and barrier-directed interventions. Precision approaches that use inflammatory biomarkers and, ultimately, genetic and microbial profiles to match patients to the target most relevant to their disease biology are the logical endpoint of a common-target strategy.

CONCLUSION

Atherosclerosis and Crohn disease, long treated as separate entities, share a core inflammatory architecture that gives rise to a set of common therapeutic targets spanning tumor necrosis factor-alpha, the interleukin-12 and interleukin-23 to T-helper-17 axis, the interleukin-1-beta and NLRP3 inflammasome, interleukin-6, Janus kinase signaling, leukocyte trafficking, the gut microbiota and its metabolites, and the endothelium. Therapies developed against these targets in one disease illuminate and, in several cases, may directly benefit the other, making rational drug repurposing, biomarker-guided treatment, and integrated cardiovascular and gastrointestinal risk management realistic goals. Realizing this potential will require careful attention to the context-specific biology and safety of each target and, above all, dedicated outcome trials that test cross-disease benefit directly rather than by inference.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed Consent

The authors declare that no patients were used in this study.

Availability of data and material

Not applicable.

Authors' contributions
All authors had equal roles in study design, work, statistical analysis and manuscript writing.

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