PHYSIOLOGY 40: 4–25, 2025. First published July 30, 2024; doi:10.1152/physiol.00021.2024

Low-Grade Chronic Inflammation: a Shared Mechanism for Chronic Diseases

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Inflammation is an important physiological response of the organism to restore homeostasis upon pathogenic or damaging stimuli. However, the persistence of the harmful trigger or a deficient resolution of the process can evolve into a state of low-grade, chronic inflammation. This condition is strongly associated with the development of several increasingly prevalent and serious chronic conditions, such as obesity, cancer, and cardiovascular diseases, elevating overall morbidity and mortality worldwide. The current pandemic of chronic diseases underscores the need to address chronic inflammation, its pathogenic mechanisms, and potential preventive measures to limit its current widespread impact. The present review discusses the current knowledge and research gaps regarding the association between low-grade chronic inflammation and chronic diseases, focusing on obesity, cardiovascular diseases, digestive diseases, and cancer. We examine the state of the art in selected aspects of the topic and propose future directions and approaches for the field.

cancer; cardiovascular disease; chronic disease; inflammation; obesity

Introduction

Inflammatory processes are crucial for the organism to respond to pathogens and other damaging stimuli to restore homeostasis. However, when inflammation persists because of a continuous trigger, or if the resolution stage is not achieved, it can evolve into a low-grade, chronic inflammation. This condition is implicated in the onset of a wide array of illnesses, including cancer and cardiovascular diseases, and it is a significant factor in overall mortality (1). Such diseases are now the predominant cause of global morbidity and mortality. The spread of Western lifestyle habits to developing countries is exacerbating what is termed the “invisible epidemic” of chronic diseases (2). This trend poses a significant threat to global health, underscoring the need to address the root causes of chronic inflammation and its widespread impact. The present review aims to critically discuss the current knowledge and research gaps regarding the association between low-grade chronic inflammation and chronic diseases, focusing on cardiovascular diseases (CVDs), obesity, and cancer. By understanding the state of the art in selected aspects of the topic, we discuss future directions and approaches for the field.

Inflammation: a Double-Edged Sword in Health and Disease

Inflammation occurs as a physiological response to damaging stimuli. This mechanism consists of an initial fast-acting response elicited by a complex interaction between cells from the innate immune system and the production of proinflammatory mediators that amplify the process. This response is followed by a resolution phase, in which tissue function and structure are actively restored through a series of events that include changes in the cellular composition at the inflammation site and the production of specialized proresolving mediators (SPMs) (3). SPMs are lipid-derived molecules grouped into lipoxins, resolvins, protectins, and maresins. They contribute to closing the inflammation process by stimulating the clearance of apoptotic neutrophils, cellular debris, and microbes, together with limiting neutrophil infiltration and proinflammatory cytokine production (4). What was previously considered a passive process reliant on the dilution of inflammatory factors is now recognized as a highly regulated and complex mechanism, offering groundbreaking therapeutic potential.

Permanent failure of the resolution process results in chronic inflammation (5). This persistent state of

inflammation can be triggered by various lifestyle factors, including smoking; consuming a low-quality diet rich in ultraprocessed foods, saturated and trans fats, and refined sugars; excessive alcohol intake; stress; sleep disorders; and a sedentary lifestyle (6, 7). Furthermore, chronic inflammation can also result from the continuous presence of infectious organisms or exposure to certain environmental pollutants (7–10). At the molecular level, these triggers lead to oxidative stress, mitochondrial dysfunction, and cell damage, which in turn releases inflammation-inducing signals, such as metabolism-associated molecular patterns (MAMPs), including free fatty acids, advanced glycation end products (AGEs), cholesterol, mitochondrial DNA, glucose, uric acid, and other compounds like free radical species and oxidized lipoproteins. These substances activate various inflammatory pathways, exacerbating and sustaining the inflammatory response (11).

Low-grade chronic inflammation refers to conditions where the inflammatory process exists, albeit at a subclinical level, i.e., clear symptoms such as pain, fever, fatigue, and other functional alterations are not present (1, 12). Most chronic diseases have a common pathophysiological basis involving systemic low-grade inflammation. Initially manifesting at a localized level, chronic inflammation can escalate to a systemic condition, as observed in obesity (13), metabolic-associated fatty liver disease (MAFLD) (14), and diseases induced by microorganisms such as chronic gastritis induced by *Helicobacter pylori* infection (8, 9) and periodontitis (10). In this context, the term "low-grade" denotes a subtle inflammatory process that remains below the threshold for triggering overt clinical symptoms (1). However, the prolonged systemic presence of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, along with increased expression of adhesion molecules, can have harmful effects. These include alterations such as reduced insulin signaling, hypoxia, oxidative stress, fibrosis, cellular senescence, endoplasmic reticulum stress, mitochondrial dysfunction, and elevated activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which is key in controlling the expression of numerous proinflammatory factors (15).

Sustained chronic inflammation is associated with oxidative stress from excessive reactive oxygen species (ROS) production and sustained inflammation. ROS and proinflammatory factors act reciprocally in a positive feedback loop; the activation of inflammatory cells leads to the production of ROS, which contributes to the accumulation of cytokines and the activation of inflammatory transcription factors. In this loop, ROS stimulate the accumulation of cytokines, which in turn stimulate inflammatory cells to generate more ROS that stimulate the release of further cytokines. Intracellular ROS may reach toxic levels that can induce cell death, provoking the recruitment of more inflammatory cells (16). Such cascading effects lead to significant organ dysfunction and systemic metabolic disturbances, underlining the critical impact of chronic low-grade inflammation on metabolic health and disease progression.

Fibrosis occurs when the body's response to tissue damage involves the excessive deposition of collagens and other extracellular matrix components. Although initially reparative, this process becomes problematic when it is dysregulated, leading to disruptions in normal tissue architecture and function (17). This pathological process often occurs in response to low-grade chronic inflammation (18).

The link between fibrosis and low-grade chronic inflammation involves several key factors: the initiation of the inflammatory response, the role of immune cells, and the activation of specific signaling pathways associated with fibrosis development (19, 20). Inflammation typically begins as a response to tissue injury or infection, involving the release of cytokines, chemokines, and other signaling molecules that attract immune cells to the injury site. Immune cells such as neutrophils, macrophages, and lymphocytes are recruited to the affected tissue, with macrophages playing a crucial role in the fibrotic response. During inflammation, cytokines like transforming growth factor-beta (TGF-β) promote the differentiation of fibroblasts into myofibroblasts, which deposit collagen and other extracellular matrix components, leading to the formation of fibrotic tissue. Fibrosis is a significant factor in the progression and complications of various noncommunicable chronic diseases (18).

The clinical expression of the unregulated fibrotic process accompanying low-grade chronic inflammation depends on the tissues affected. For instance, in obesity chronic inflammation leads to increased macrophage infiltration of the adipose tissue, and altered cytokine secretion contributes to tissue remodeling and insulin resistance in obese individuals (21). Fibrous connective tissue accumulates abnormally within adipose tissue, significantly affecting metabolic health and fat tissue function (22); managing obesity through lifestyle changes and medical interventions can help reduce the risk of fibrosis and its complications (23, 24). In chronic liver diseases such as alcoholic liver disease and nonalcoholic fatty liver disease, fibrosis leads to cirrhosis, characterized by excessive collagen deposition that disrupts liver architecture and impairs function. This can progress to liver failure and increase the risk of hepatocarcinoma (25). Cardiac fibrosis, caused by conditions like hypertension, myocardial infarction, and cardiomyopathies, involves the replacement of healthy myocardial tissue with nonfunctional scar tissue, reducing cardiac output and potentially causing arrhythmias (26). The same risk factors leading to CVD also cause chronic kidney diseases, including diabetic and hypertensive nephropathy, resulting in fibrosis that disrupts kidney function and impairs filtration and waste removal (27).

In cancer, the body's fibrotic response to tumor growth, termed desmoplasia, involves the deposition of

collagen and other extracellular matrix proteins around the tumor. This response can promote tumor progression by fostering angiogenesis and enhancing tumor cell survival (28). Studies have shown that factors such as SPARC (Secreted Protein, Acidic and Rich in Cysteine), a mediator of fibrosis, can promote tumor cell survival by upregulating signaling pathways like p38 MAPK/MAPKAPK2/HSP27 and pAKT (29, 30). The fibrotic microenvironment can also promote epithelial-mesenchymal transition, giving cancer cells invasive and metastatic properties; this transition is facilitated by various factors in the tumor microenvironment, such as cytokines like IL-8 and TGF-β (31–33). Paradoxically, radiation therapy and specific chemotherapeutic agents can induce fibrosis in surrounding normal tissues (34).

Effective fibrosis management requires addressing the underlying causes of tissue injury, reducing inflammation, and sometimes employing specific antifibrotic therapies to slow its progression (18). Early detection and intervention are crucial to prevent irreversible organ damage and improve patient outcomes (35).

Chronic Diseases: the XXI Century Pandemic

Chronic diseases are lifelong conditions that in many cases develop over time, given the continuous exposure to risk factors. They are a group of medical conditions conventionally defined as not caused by infectious agents and not spreadable through the transmission of microorganisms between individuals. In the last decade, the relevance of their association with lifestyle, environmental and social conditions (36), and host determinants modulating the susceptibility to environmental triggers has been highlighted (37). Genetic susceptibility plays a crucial role in the development of inflammation-related conditions. Several studies have highlighted the role of genetic loci in influencing the levels of inflammatory markers like C-reactive protein (CRP), which is a sensitive biomarker of chronic low-grade inflammation and is linked to the development of complex diseases (38, 39). Several examples are available in the context of specific diseases. For instance, it is estimated that 40–60% of the interindividual variation in coronary artery disease (CAD) susceptibility is attributable to heritability, with specific genetic variants playing a pivotal role in CAD pathogenesis (40, 41). The association between particular genetic variants and cardiovascular diseases (CVDs) has been consistently replicated across numerous studies and diverse populations. However, the risk conferred by these variants varies depending on the genetic background of the population (42). Single-nucleotide polymorphisms (SNPs) at the 9p21.3 locus are among the most consistently associated with CAD and myocardial infarction (MI) across various populations (43, 44). Genetic susceptibility has also been significantly linked to conditions such as inflammatory bowel disease (IBD), a complex disorder associated with chronic relapsing intestinal inflammation. The interplay between genetic mutations encoding aspects of innate immunity and mucosal homeostasis, along with environmental triggers, leads to a sustained inflammatory response (45, 46). In the context of chronic obstructive pulmonary disease (COPD), genetic variance has been associated with susceptibility to cigarette smoke-induced damage-associated molecular pattern (DAMP) release (47), emphasizing the role of genetic factors in inflammatory responses to environmental triggers like tobacco smoke. Genetic susceptibility to inflammation has also been studied in cancer; for instance, variations in inflammation-related genes can affect tumor susceptibility and severity of skin tumor progression (48), underscoring the impact of genetic architecture on cancer development.

Chronic diseases are characterized by their complex, multifactorial causes and prolonged course often leading to disability or functional impairment and typically have limited options for cure (2). The burden of mortality associated with chronic diseases poses a significant challenge worldwide, impacting both high-income and low- to middle-income countries. Notably, the latter group accounts for approximately three-quarters of global deaths annually, totaling over 41 million fatalities (2).

It is interesting to note that the concept of noncommunicability in chronic diseases is somewhat misleading. Behavioral risk factors such as tobacco use, alcohol misuse, sedentarism, and unhealthy diets are important modifiable lifestyle elements with great influence on disease incidence and are highly dependent on environmental determinants. Familiar networks and social contexts are an important source of "communication" of risk factors for chronic diseases (49).

As mentioned above, one common aspect of many chronic diseases is the persistence of an underlying chronic low-grade inflammation, triggered by multiple factors including lifestyle elements, environmental contaminants, microbial infections, or other underlying disease states. On the other hand, several inflammatory mediators and altered proinflammatory pathways and signals are shared among these diseases. The role of inflammation in selected chronic disease development is further discussed below.

Low-Grade Chronic Inflammation in the Development and Persistence of Chronic Diseases

Inflammation in Obesity and Obesity-Related Metabolic Disorders

Obesity is associated with the development of numerous chronic metabolic disorders such as type 2 diabetes mellitus (T2DM) and MAFLD. At the mechanistic level, the link between obesity and these conditions is primarily attributed to the adverse effects of excess

dysfunctional adipose tissue. Inflammatory processes within this tissue are considered a primary driver of these diseases, highlighting the critical role of inflammation in mediating the relationship between obesity and metabolic disorders.

Fat expansion in obesity, particularly in the visceral depot (50), is accompanied by numerous changes in adipose insulin sensitivity and overall tissue composition and function, eventually leading to changes in the profile of proinflammatory versus anti-inflammatory adipokine and cytokine secretion (1). Obesity is associated with increased levels of adipose tissue-derived free fatty acids, proinflammatory cytokines, such as TNF-α and IL-6, and adipokines, like leptin and resistin. Concurrently, there is a reduction in adiponectin, an anti-inflammatory and insulin-sensitizing hormone (51). This imbalance can induce ectopic lipid deposition, insulin resistance, and inflammation in other metabolically relevant tissues, sustaining the chronic inflammatory state observed in individuals with obesity (50, 52).

Adipocyte hypertrophy, cell damage, and death, together with elevated chemokine production, lead to the infiltration of immune cells. Notably, the emergence of phagocytic macrophages forming "crownlike structures" around ruptured adipocytes constitutes a histological hallmark of dysfunctional and inflamed adipose tissue (52). These dying adipocytes secrete numerous damage-associated molecular patterns, which activate the multiprotein complex NOD-, LRR- and pyrin domain-containing protein 3IL (NLRP3) inflammasome, mainly through toll-like receptor (TLR)4 in macrophages and adipocytes (53). Other NLRP3 inflammasome activators elevated in obesity include saturated fatty acids and ceramides. NLRP3 inflammasome activation induces the production and secretion of active IL-1β, which mediates the activation of inflammatory pathways and dysfunction in distant organs such as the liver, pancreas, and skeletal muscle (54).

As discussed above, chronic adipose tissue inflammation induces several alterations that promote systemic inflammation and metabolic dysregulation. Chronic inflammation in adipose tissue and the ensuing alterations in its endocrine function have been related to the development of numerous disorders, such as T2DM (13), MAFLD (55), CVD, and cancer. For instance, inflammation plays a critical role in heart failure with preserved ejection fraction (HFpEF), a prevalent ailment in patients with obesity (56). A number of cancers whose risk are elevated in obesity also have adipose tissue-induced low-grade inflammation as a common etiopathogenic mechanism (57).

Recently, an additional source of obesity-induced systemic inflammation, which involves alterations in the intestinal microbiota, has been proposed. The gut microbiota is crucial in maintaining gut integrity and contributing to the host immune response. The microbiota exhibits high sensitivity to changes in diet, with dysbiosis or microbial imbalance capable of occurring within a few hours. This dysbiosis can impact on the intestinal barrier, allowing the entry of allergens, toxic substances, and Gram-negative bacteria-derived lipopolysaccharides (LPS) into the bloodstream. LPS, in turn, initiates low-grade inflammation, increasing the risk of metabolic disorders (58).

Individuals with obesity have a gut microbiota composition distinct from their lean counterparts, characterized by reduced richness (59) that can improve with weight loss (60). As mentioned above, mechanisms proposed for the dysbiosis-induced inflammation in obesity involve a leaky intestinal barrier, whereby the epithelial barrier that separates the intestinal lumen from the circulation is altered, allowing the translocation of LPS and MAMPs into the bloodstream, particularly under conditions of a high-fat diet (61). Experiments in mice have shown that those colonized with microbiota from humans with obesity gained more weight and had elevated levels of circulating proinflammatory cytokines compared to those with lean donors (62). Interestingly, in this study, where animals were fed a regular (not high fat) diet, increased intestinal permeability was not observed in recipients of obese microbiota, suggesting that in this case mechanisms independent from a leaky gut may be involved in the development of systemic inflammation. The results indicate that microbiota from donors with obesity promoted increased bacterial adherence to the epithelial layer, triggering IL-1β production. This process resulted in an intensified immune response within the intestinal tract and led to the accumulation of inflammatory immune cells in both the small intestine and adipose tissue.

T2DM, highly associated with obesity, is also linked to chronic, low-grade inflammation mediated by various factors, including adipose tissue dysfunction, oxidative stress, and immune dysregulation (63). As expected, dysfunctional adipose tissue in individuals with diabetes releases proinflammatory cytokines, such as TNF-α and IL-6, contributing to systemic inflammation (64). Oxidative stress, resulting from increased production of ROS, can activate inflammatory pathways and promote inflammation in diabetes (65). Immune dysregulation, including altered function of immune cells and increased production of inflammatory mediators, as well as dysregulation of adipokines, such as adiponectin and leptin, further contributes to chronic inflammation and insulin resistance in diabetes (66). Furthermore, other factors, such as AGEs, formed as a result of prolonged exposure to high blood glucose levels (described in more detail below), can activate inflammatory pathways and promote the production of proinflammatory cytokines (67), contributing to the inflammatory state of diabetes (68, 69).

Interestingly, even though inflammatory processes have long been recognized as a main trigger for obesity-related disorders, a study from 2014 highlighted the essential role of inflammation in the physiological adaptation and remodeling of adipose tissue (70). This

research demonstrated that mouse models with inhibited proinflammatory signaling exhibited metabolic impairment. It proposed that a proper inflammatory response is required to trigger inflammation resolution rather than proceed toward chronicity. Subsequent research from the same group confirmed these results (71), concluding that a certain level of adipocyte inflammation is necessary for adequate insulin sensitivity and adipose tissue functionality. Inflammatory processes in adipose tissue are thus part of its physiology, which becomes pathological when the injury is permanent (e.g., due to lifestyle factors), leading to its unchecked chronicity.

Inflammation and Cardiovascular Diseases

In recent years, there has been a growing body of evidence linking inflammation to CVD. Multiple studies have demonstrated that inflammatory markers, such as C-reactive protein (CRP), IL-6, and fibrinogen, are associated with an increased risk of CVD in healthy populations (72, 73). Inflammation has been shown to participate centrally in all stages of atherosclerosis, from the initial lesion to the end-stage thrombotic complications (74), contributing to the chronicity, progression, and morbidity of many CVDs (75). Although the mechanisms linking traditional risk factors with inflammation are not completely elucidated, a large body of evidence supports this claim since most of the major risk factors for CVD are associated with chronic, low-grade inflammation.

Hypertension is a significant determinant of CVD onset and development. Inflammation and its associated oxidative stress and endothelial dysfunction play essential roles in the development of hypertension (76–78). Inflammation can activate the renin-angiotensin system, which is a key regulator of blood pressure, and it can also modulate the production of cytokines and other inflammatory mediators that contribute to the development of hypertension (79, 80). In addition, chronic peripheral inflammation promotes sympathetic outflow and may serve as a feedforward mechanism in the development of neurogenic hypertension (81, 82).

Recent research has increasingly recognized the critical role of the immune system in hypertension development and progression, with evidence pointing to the activation of both innate (83) and adaptive immune responses, extensively reviewed elsewhere (84). A novel role of the immune system in hypertension lies in its interaction with the autonomous nervous system (85). The sympathetic nervous system, known for its significant contribution to hypertension, extends its influence to the bone marrow, spleen, and peripheral lymphatic system, exerting a proinflammatory effect (86, 87). Conversely, the parasympathetic nervous system mitigates inflammatory responses (88) through the action of α7-nicotinic acetylcholine receptors (89). This neuro-immune interaction is characterized by bidirectional communication, where cytokines (90) and vasoactive peptides can augment sympathetic nervous activity via effects on the central nervous system (91). This enhancement in sympathetic activity subsequently promotes the mobilization, migration, and infiltration of immune cells into target organs. Notably, the kidneys can become infiltrated with immune cells, including mesangial cells originating from the bone marrow, which further contribute to renal damage by releasing proinflammatory cytokines (92, 93). There is also a notable infiltration of the adventitia and perivascular adipose tissue by inflammatory immune cells, such as macrophages. TLR4 (94) and possibly TLR2 (83) on both resident cells as well as infiltrating immune cells are activated by DAMPs such as angiotensin II (95) to synthesize and secrete cytokines. The escalated production of cytokines by these cells leads to myogenic and structural alterations in the resistance vessels, culminating in increased blood pressure.

Similar to the changes observed in obesity, dysregulated microbiota seems to play a role in the pathogenesis of hypertension (96, 97). Deviations in the composition and functional dynamics of the gut microbiota are closely associated with both the onset and progression of hypertension (97–101). The gut microbiota acts as a key regulator of blood pressure through various mechanisms, including the production of gut-derived metabolites such as trimethylamine *N*-oxide (TMAO) (101), modulating the renin-angiotensin system (102) and engaging in intricate interactions with the immune, vascular, and inflammatory systems (98, 103). The reciprocal relationship between the gut microbiota and host immune responses has been increasingly acknowledged as a pivotal factor in the pathogenesis of hypertension (104, 105), with the microbiota's effect on T lymphocyte-mediated inflammatory responses further driving the progression of hypertension (105).

Interestingly, the phenomenon of dysbiosis is not confined to the gut but also extends to the salivary microbiota, linking it to hypertension and demonstrating associations with metabolic syndrome biomarkers. This connection highlights the broader implications of microbiome imbalance on hypertension and related health conditions (106). In line with these observations, numerous studies have pointed to the therapeutic potential of targeting gut microbiota in managing hypertension. Specifically, interventions with probiotics and prebiotics have been found effective in preventing hypertension that may be programmed by high fructose consumption during prenatal and lactation periods (107).

As discussed above, the altered endocrine dysfunction of adipose tissue in obesity is closely linked to chronic inflammation, playing a pivotal role in the pathogenesis of hypertension through the secretion of proinflammatory and vasoactive factors. Adipose tissue contributes to hypertension by producing

angiotensinogen, which affects both local and systemic circulation (108). Moreover, the activation of the adipose renin-angiotensin system is implicated in metabolic imbalances and CVD (109), with leptin highlighted as a key factor in obesity-induced hypertension (110). The role of visceral fat, particularly intra-abdominal fat, in hypertension is well established, showing a strong link to the condition independent of body weight or subcutaneous fat (111–113). Notably, reducing visceral fat correlates with lower blood pressure, especially in individuals with overweight or obesity (114). The impact of epicardial and pericardial fat, given their proximity to cardiac structures and influence on blood flow, is also significant. These fat depots are associated with early hypertension and a range of cardiovascular risks, including impaired left ventricular function and diastolic dysfunction, even in patients with normal ejection fractions, suggesting a critical role in the progression from cardiometabolic risk to heart failure (115–119).

Although available evidence underscores the role of inflammation in hypertension, its clinical significance remains a topic of debate. This ambiguity arises because chronic inflammation is also linked to prevalent co-occurring conditions, such as obesity and chronic kidney disease (CKD) (120, 121). In some patients, lifestyle modifications (122, 123) or weight loss strategies(124–126) lead to a reduction in inflammatory markers and reduced cardiovascular events (127, 128). These findings imply that inflammation associated with hypertension might partially act as an indicator of the overall health impact of these comorbid conditions, rather than being a direct causative factor.

Sedentary behavior, or physical inactivity, has consistently been associated with chronic inflammation and an increased risk of CVD in individuals with or without obesity (129–131). Physical inactivity leads to low-grade systemic inflammation characterized by elevated levels of proinflammatory cytokines, such as IL-6 and TNF-α (132). Sedentary behavior also contributes to the accumulation of visceral fat, which releases proinflammatory adipokines, such as leptin and resistin, further promoting inflammation and contributing to insulin resistance and atherosclerosis (130, 133). In addition to its direct effects on inflammation, sedentary behavior can interact with other risk factors to exacerbate the inflammatory response. For example, sedentary behavior combined with obesity has a synergistic effect on increasing the risk of chronic inflammation and subsequent development of CVD and T2DM (134). Similarly, physical inactivity and exposure to secondhand smoke exhibit a synergistic effect, significantly increasing the risk of T2DM (135).

Smoking, another major CVD risk factor, is strongly associated with chronic inflammation and has detrimental effects on the immune system (136, 137). Cigarette smoke contains numerous toxic compounds that can trigger an inflammatory response in the respiratory system and throughout the body (138). The inhalation of cigarette smoke leads to the activation of immune cells, such as macrophages and neutrophils, which release proinflammatory cytokines and chemokines (138, 139). These inflammatory mediators contribute to the development and progression of various diseases, including chronic obstructive pulmonary disease (COPD), CVD, and cancer (136, 138).

Nontraditional risk factors, such as exposure to air pollution and periodontitis, play a significant role in contributing to the proinflammatory backdrop associated with CVD. Air pollutants including particulate matter (PM), nitrogen dioxide (NO_2), and ozone (O_3) are known to incite inflammation both in the respiratory system and systemically (140–142). Such exposure is connected to increased levels of inflammatory markers like CRP and IL-6, further elevating the risk for CVD, respiratory ailments, and metabolic dysfunctions (140, 143). Similarly, periodontitis has been identified as a contributor to elevated CVD risk, with systemic inflammation induced by periodontal disease posited as a connecting mechanism between these two conditions (144–146).

Atherosclerosis, characterized by the deposition of lipids in the arterial wall, leading to CAD and stroke, is a well-known process with a significant inflammatory component that has been extensively reviewed (147). Although CAD and stroke risk can be reduced by lowering lipid levels, existing therapies do not adequately address inflammation's equally essential contribution (148). However, preclinical data support that inhibition of innate immunity's NLRP3/IL-1β/IL-6/CRP pathway is a potent target for atheroprotection (149). The links between inflammation and cardiovascular disease have inspired clinical trials to test whether drugs that target inflammation primarily can reduce cardiovascular events (150). The Cardiovascular Inflammation Reduction Trial (CIRT) evaluated whether low-dose methotrexate, compared to placebo, reduced major vascular events among a group of post-myocardial infarction patients with either diabetes or metabolic syndrome, known to have high cardiovascular risk on the basis of a persistent proinflammatory response (151). Methotrexate causes nitric oxide synthase uncoupling and increases T-cell apoptosis, diminishing immune responses. Although the results of CIRT were neutral, methotrexate failed to reduce IL-6 levels, evidencing the difficulties of targeting a complex, redundant response as inflammation. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), using an IL-1β inhibitor, significantly reduced major adverse cardiovascular events with a benefit directly related to the magnitude of reduction in downstream IL-6 and CRP (152).

Interestingly, IL-1β inhibition did not reduce the development of incident hypertension or modify the relationship between hypertension and cardiovascular events, suggesting that the cardiovascular benefit of canakinumab was directly due to a reduction in inflammation, not hypertension. Similarly, colchicine, an

NLRP3 antagonist, has been used extensively as an inflammation-modulating medication in CVD. In the Low-Dose Colchicine (LoDoCo) trial, patients with stable coronary disease treated with low-dose colchicine had fewer cardiovascular events than those not receiving colchicine (153). The results of the LoDoCo 2 trial, a larger placebo-controlled study on patients with chronic coronary disease, confirmed that colchicine significantly reduced the incidence rates of spontaneous myocardial infarction, ischemia-driven coronary revascularization, and cardiovascular death. However, the study also found a higher incidence of death from noncardiovascular causes in the colchicine group compared to the placebo group (0.7 vs. 0.5 events per 100 person-years) (154). Similarly, in the context of acute myocardial infarction, the Colchicine Cardiovascular Outcomes Trial (COLCOT) demonstrated a reduction in cardiovascular events, including stroke (155). Nonetheless, an increased rate of pneumonia was observed in the colchicine group, highlighting the potential risks of unintended adverse events when targeting inflammation.

Recently, research has focused on targeting IL-6 as a common pathway linking inflammation and CVD, based on murine models with high IL-6 levels that show increased susceptibility to atherogenesis (156) as well as Mendelian randomization studies that suggest that genetic variants in the IL-6 signaling pathway associate with lifelong coronary risk (157). The RESCUE II trial evaluated the safety of ziltivekimab, a fully human monoclonal antibody directed against the IL-6 ligand in individuals with elevated levels of high-sensitivity C-reactive protein (hs-CRP) and CKD. The trial primary end point showed a robust reduction of hs-CRP (158). The upcoming ZEUS clinical trial using ziltivekimab on individuals with CKD and elevated hs-CRP will prove whether targeting inflammation beyond conventional CVD risk factor management and lipid-lowering therapy is a valuable tool for reducing cardiovascular risk (149).

In the intricate web of signaling pathways linking inflammation to CVD, NF-κB emerges as a pivotal mediator. Inflammatory cytokines such as IL-1β, IL-6, IL-18, and TNF-α are recognized for their role in activating NF-κB, thereby contributing to the inflammatory processes associated with CVD (15, 159). This pathway's activation is notable in various conditions, including diabetes (63), obesity (160), smoking (136), and hypertension (161), that perpetuate the production of inflammatory mediators and sustain the chronic, uncontrolled inflammation characteristic of CVD.

Further downstream, the NLRP3 inflammasome is implicated in the nexus between chronic inflammation and cardiovascular risk, activated by danger signals, such as oxidized low-density lipoprotein (LDL) and cholesterol crystals found in atherosclerotic plaques. The activation of NLRP3 facilitates the adhesion of immune cells to the endothelium and impairs nitric oxide (NO) production, exacerbating endothelial dysfunction associated with atherosclerosis and CVD (162). The significance of NLRP3 signaling is also highlighted by associations between NLRP3 gene polymorphisms and hypertension during pregnancy (163) and evidence that deletion of the NLRP3 gene reduces angiotensin II-induced vascular inflammation and attenuates vascular remodeling and hypertension in experimental models (164).

Inflammation and Cancer

Low-grade inflammation is associated with a myriad of chronic diseases, with cancer having the most severe impact on public health. Among these, breast cancer and gastrointestinal (GI) tumors not only exhibit the highest mortality rates but also serve as prime examples of neoplastic transformation driven by low-grade inflammation. Therefore, and given space limitations, this discussion focuses specifically on these cancer types.

Breast cancer. Breast cancer ranks among the most common cancers globally, primarily impacting women, though it can also occur in men at a rate ~100 times lower. The development of this disease may be linked to specific mutations in genes, like *BRCA1* and *BRCA2*. However, such genetic variants only account for ~5–10% of all cases. Instead, for most patients, disease development is linked to environmental factors, such as hormonal changes, exposure to ionizing irradiation, and alcohol consumption. In this context, factors that induce inflammation, now recognized as a hallmark of cancer, are also deemed relevant (165–167).

The acute-phase protein and inflammation marker C-reactive protein (CRP), identified in the nipple aspirate fluid of healthy women, is associated with a heightened risk of breast cancer (166). Furthermore, multiple immune cells, such as CD4+ and CD8+ T lymphocytes, macrophages, and dendritic cells found in normal breast tissue samples from healthy women, may contribute to the onset of chronic inflammatory changes (168). The link between metabolic disorders, resultant inflammation, and increased cancer risk is further supported by the presence of macrophages forming crownlike structures in the breast adipose tissue of women with obesity, indicative of chronic inflammation and a higher disease risk (169). Moreover, preventive treatments for healthy women with anti-inflammatory agents, like acetylsalicylic acid, decrease the risk for developing breast cancer (170, 171). Taken together, these findings underscore that low-grade inflammatory changes in normal breast tissue may increase the risk for developing breast cancer.

Metastasis is the primary cause of ~80–90% of deaths in patients initially diagnosed with breast cancer. The most prevalent initial sites of breast cancer metastasis are bone (65%) followed by lung (31%), liver (26%), and brain (9%) (172). Thus, beyond the role of inflammation in the initial genesis of the disease, it is important to consider how this factor may also promote

dissemination to other sites in the body. The mechanisms by which inflammation favors cancer development involve activation of epithelial-to-mesenchymal transition (EMT), chemokine-mediated homing of tumor cells, and a positive feedback amplification of the protumorigenic inflammation loop between tumor and resident cells (173). One of the most-studied and best-understood mechanisms connecting inflammation to cancer development involves the NF-κB pathway. This transcription factor is activated by a large number of mechanisms and signaling pathways induced by carcinogens and regulates many target genes implicated in tumor formation. Moreover, it is constitutively active in protumorigenic inflammatory cells and most human cancers, including breast cancer. Additionally, signaling pathways involving NF-κB, such as those interacting with STAT3 and downstream effector molecules, are among the key culprits of tumorigenesis (174). The activation of the IL-1β/IL-1R signaling axis often occurs downstream of NF-κB and is associated with a wide range of effects (175). In particular, the proinflammatory cytokine IL-1β is considered a key mediator of inflammation in the tumor microenvironment, where it is produced by several cell types, including fibroblasts, adipocytes, tumor-associated macrophages, and the tumor cells themselves (175, 176), including breast cancer cells (177). Other important proinflammatory effectors include cyclooxygenase 2 (COX2), an enzyme that generates prostaglandins from arachidonic acid. COX2 is induced in inflamed and cancerous tissues by proinflammatory cytokines, including IL-1β and TNF-α, and is implicated in several steps of tumorigenesis relevant also in breast cancer (178, 179), where it promotes tumor growth and suppresses immunity (180). Thus, therapeutic approaches targeting these different proinflammatory pathways constitute valuable options for the treatment of late-stage breast cancer and metastasis (181, 182).

Exosomes, a distinct subtype of extracellular vesicles (EVs) released by nearly all cells, have recently been recognized as key players in intercellular communication in cancer. These vesicles play significant roles in the interaction between tumor cells and the tumor microenvironment, critically influencing the development and progression of breast cancer, including therapy resistance. Interestingly, EVs derived from more aggressive breast cancer cells are recognized as mediators of inflammation. For instance, recent research has shown that MDA-MB-231, a metastatic breast cancer cell line, exhibits increased migration and invasion after CAV1 phosphorylation at tyrosine-14 (183, 184). CAV1 in exosomes transfers these traits to less aggressive cells (185). There are several other mechanisms linking exosome biology, inflammation, and cancer. For instance, exosomes derived from cancer cells can modulate the host immune response, leading to immune escape mechanisms that promote tumor progression (186, 187). Tumor-derived exosomes can activate angiogenesis, a process crucial for tumor growth and metastasis, by modulating the immune system and promoting the formation of new blood vessels (188–191). Exosomes also facilitate the remodeling of the tumor microenvironment by modulating immune responses, promoting inflammation, and influencing stromal cells to support tumor growth and progression (192–194); tumor-derived exosomes can inhibit the response of immune effector cells and induce immune suppressor cells, leading to the modulation of the tumor microenvironment and the development of chemoresistance in cancer cells (195). Finally, exosomes can trigger chronic inflammation in cancer, leading to immune evasion and tumor progression by transferring noncoding RNAs and modulating molecular signaling pathways (196–198). These findings exemplify how exosome mechanisms participate in critical events in cancer by amplifying inflammation. The versatility of exosomes is leading to the development of promising new clinical applications (199).

Cancer-associated fibroblasts (CAFs) are another new addition to the complex mechanisms underlying oncogenesis. These cells, integral to the tumor microenvironment, significantly contribute to cancer progression by facilitating tumor growth, invasion, and metastasis through various mechanisms involving inflammation. CAFs are instrumental in forming the tumor stroma and interact directly with cancer cells to promote their proliferation and invasion (200).

In breast cancer, CAFs are implicated in the metabolic reprogramming of the tumor microenvironment, therapy resistance, and the establishment of a supportive niche for cancer cells (201). They secrete growth factors, chemokines, and extracellular matrix components that enhance cancer cell proliferation, migration, and invasion (202, 203). Furthermore, studies have demonstrated that CAFs can undergo phenotypic changes, such as senescence, which leads to the acquisition of a protumorigenic phenotype that influences cancer behavior, including tumor cell growth and metastasis (204).

CAFs also modulate immune cell function within the tumor microenvironment, impacting cancer progression. Their interactions with cancer cells are crucial for tumor development, as they support tumor epithelial growth, invasion, and therapeutic resistance (205). Additionally, CAFs secrete factors that enhance cancer cell motility and aggressiveness, thereby contributing to tumor progression (205).

Gastrointestinal tumors. Gastrointestinal (GI) tumors, particularly colorectal, gastric, and hepatocellular carcinomas, also rank among the most common cancers globally in both men and women. In most of these organs, tumors emerge in the context of low-grade inflammation, as is the case for Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) (207), *Helicobacter pylori*-associated chronic gastritis and stomach adenocarcinoma (STAD), as well as IBD and colorectal carcinoma. In the accessory organs of the GI system, similar phenomena can be observed

(i.e., liver cirrhosis—hepatocellular carcinoma; chronic cholecystitis—gallbladder carcinoma; chronic pancreatitis—pancreatic carcinoma) (208).

In BE, the squamous cell epithelium is replaced by a metaplastic columnar epithelium with gastric or intestinal features (209) as a consequence of chronic acid reflux-induced DNA damage and cytokine-mediated injury (210, 211). BE affects 1% of the worldwide population and has a cumulative annual rate of 0.2–0.5% of risk for developing EAC (207). A proinflammatory genotype based on polymorphisms in the IL-10 and -12B cytokines contributes to the development of BE (212). Interestingly, the progression from BE to EAC is mediated by the IL-6/STAT3 pathway involved in cell proliferation and apoptosis resistance (213).

In the stomach, persistent infection by *H. pylori* induces multiple inflammatory pathways, involving TLR, JAK-STAT, and c-MEt-PI3K/Akt-mTOR. This inflammatory state results in the loss of functional glands in the gastric mucosa, which are replaced by fibrotic tissue in combination with intestinal epithelium (214–216). This state, known as gastric interstitial metaplasia, is a recognized risk condition for the development of STAD, with a hazard rate of 37.9 [95% confidence interval (CI): 4.5–317] (217). Virulence factors from *H. pylori* such as CagA, VacA, and urease are examples that contribute to the onset and maintenance of this chronic inflammatory state (218).

Inflammatory bowel disease (IBD) exemplifies chronic low-grade inflammation and encompasses both ulcerative colitis and Crohn's disease. Ulcerative colitis primarily causes ulcerative inflammation in the colon and rectum, whereas Crohn's disease mainly affects the small intestine. IBD is associated with an increased risk of developing colorectal carcinoma (CRC), with a standardized incidence ratio of 1.7 (95% CI: 1.2–2.2) (219). During the ulcerative inflammatory process, reactive oxygen and nitrogen species induce cell-derived cytokines, which in turn promote both innate and adaptive immune responses (220, 221). Additionally, an imbalance in the gut microbiota, commonly observed in IBD, contributes to the carcinogenic process by increasing the production of carcinogenic metabolites (222). This chronic low-grade inflammation plays a crucial role in promoting carcinogenesis through oncogenic signaling pathways (223).

Liver cirrhosis arises from various inflammatory conditions, with viral hepatitis B (HBV) and C (HCV) infections being the predominant causes (224). The neoplastic outcome of liver cirrhosis is hepatocellular carcinoma (HCC), a tumor with a poor prognosis where incidence and mortality rates are closely aligned (225). Both HBV and HCV infections induce oxidative stress, which disrupts oncogenic cellular signaling pathways critical to HCC development (226). HBV-related tumors frequently exhibit chromosomal alterations, p53 inactivation, and activation of the WNT/β-catenin pathway (227). Coinfection with hepatitis D virus (HDV) exacerbates liver damage and significantly increases the risk of HCC (228).

The gallbladder is another organ where chronic inflammation, primarily due to gallstones, leads to gallbladder cancer (GBC). GBC exhibits a geographically heterogeneous distribution, with the highest mortality rates reported in southern Chile (229–231). Gallstones (GS) affect 20% of the global population, with 2% of these cases leading to incidental GBC (232). The prevalence of GS and the rate of cholecystectomy are increasing, affecting younger individuals and even children.

Diet is the main preventable factor for GS, GBC, and hepatobiliary diseases. Current understanding suggests that westernized diets, high in sugars and saturated fats, disrupt the intestinal barrier. This disruption facilitates the translocation of gut microbiota to the liver, affecting the metabolism of biliary acids (BAs). The interaction between BAs and the microbiota is reciprocal, with each influencing the other and further enhancing intestinal barrier permeability. Primary bile acids (BAs), such as chenodeoxycholic and cholic acid, are synthesized from cholesterol in the liver and stored in the gallbladder. These BAs are then released into the intestine, where gut microbiota convert them into secondary BAs, including deoxycholic and lithocholic acid. Approximately 95% of BAs are reabsorbed in the ileum and returned to the liver, while the remaining 5% are transformed into secondary BAs. These secondary BAs act as signaling molecules for receptors that mediate interactions between the immune system and intestinal microbiota, influencing metabolism, inflammation, and immunity (233–236).

The removal of the gallbladder significantly alters lipid metabolism and the enterohepatic circulation of bile. The gallbladder typically accumulates and concentrates bile, releasing it in pulses into the intestines during eating. Postcholecystectomy, there is a continuous flux of diluted BAs into the intestines, which become the primary BA reservoir. This increases intestinal-liver recycling and secondary BA formation (237). Such changes contribute to dysbiosis, steatotic liver diseases, and elevated risks of digestive and hepatobiliary cancers.

Reducing the risk of hepatobiliary disorders involves adopting a diet low in animal products, enriched with anti-inflammatory and low-glycemic load foods, and maintaining a healthy body weight. Additionally, understanding and manipulating microbiota-derived metabolites and their pathways may offer new therapeutic strategies for managing digestive diseases.

Similar to breast cancer, in GI oncology tumor-derived exosomes are emerging as promising markers for diagnosis, prognosis, and monitoring of treatment responses because of their specific content and presence in body fluids (238). Additionally, exosomes are being explored as natural drug delivery systems, offering a novel approach to treating inflammatory and neoplastic conditions in the GI tract (239, 240).

EMERGING ROLES OF EPIGENETICS IN THE DEVELOPMENT OF LOW-GRADE INFLAMMATION AND CANCER IN THE GASTROINTESTINAL SYSTEM. For many years, it was believed that only a small fraction of the human genome regulated cell function and development through protein-coding genes. We now know that this fraction represents merely 2% of the human genome, whereas the remaining 98% was initially dismissed as "junk DNA" or more recently termed "spam DNA" (241). However, subsequent studies revealed that most of this DNA is transcribed into a broad array of non-protein-coding RNAs, ranging in size from 20 nucleotides (microRNAs or miRs) to larger than 200 nucleotides (long noncoding RNAs or lncRNAs) (242). These novel families of genes play essential roles in regulating protein-coding genes in low-grade inflammation and cancer through diverse molecular mechanisms (243). The most relevant mechanisms include DNA hypermethylation at the DNA level, competing endogenous (ceRNA) networks at the RNA level, and ribonucleoprotein (RNP) complexes at the protein level (244). Dysregulation of any of these layers significantly contributes to the progression from low-grade inflammation to cancer (245).

In the esophagus, DNA methylation plays a critical role in the pathogenesis of EAC (246). Epigenetic studies have identified various subtypes of EAC, particularly noting genomic alterations in the EGFR/ERBB2 pathway, which occur through the aberrant methylation of the protein tyrosine phosphatase non-receptor type 13 (PTPN13) gene (247). In the stomach, *Helicobacter pylori*–induced gastritis is associated with the DNA methylation of tumor suppressor genes, with an increased number of methylated genes observed in normal, inflamed, and neoplastic tissues (248). In these scenarios, upregulation of DNA methyltransferase 1 (DNMT1) at the transcript and protein levels has been observed (249).

In IBD, increased DNA methylation is noted in the colorectal mucosa, particularly in tumor suppressor genes (250). Expression profiling analyses of ceRNA networks have revealed potential cross talk between IBD and CRC (251). In the liver, various low-grade inflammatory conditions promote genomic and epigenomic alterations and the upregulation of inflammatory cytokines, mediating the progression of HCC (252). These alterations are associated with a field effect in liver cirrhosis (253, 254). Clonal analyses of epigenetic and genetic changes in the progression to HCC have demonstrated that these changes evolve independently (254).

Clinical Management: Is Inflammation Resolution Where the Future Should Focus?

The clinical management of inflammation focuses on curbing proinflammatory pathways and fostering the resolution phase of the process. Primarily, this involves modifying the identified risk factors that elevate disease risk. Secondarily, it includes employing medications with anti-inflammatory properties that minimize adverse effects or toxicity. Emerging research emphasizing the importance of the inflammation resolution stage offers new insights into addressing inflammation-related diseases, suggesting a shift toward strategies that not only prevent but also actively resolve inflammation.

The traditional anti-inflammatory therapy, focused on blocking the inflammation phase, has the downside of generating an impaired or suppressed immune state, which is associated with undesired side effects. Instead, the focus on inflammation resolution as a therapeutic strategy can provide a more effective means to tackle the pernicious feedback loop of inflammatory signals and metabolic dysfunctions in chronic low-grade inflammation. Specialized proresolving mediators (SPMs) have been described during the last two decades (255). These are lipids derived from essential polyunsaturated fatty acids (PUFAs) that have potent effects leading to self-resolution of inflammation (256). There is active ongoing research to elucidate the cellular mechanisms and potential of SPMs in chronic low-grade inflammatory disorders. The novel so-called resolution therapy also incorporates biological drugs, such as the secreted products of specific cells and cell-based therapies, e.g., the use of apoptotic cells (257). The latter approach is based on the fact that apoptotic cells may induce macrophage reprogramming to an anti-inflammatory phenotype, via the release of soluble immunosuppressive factors, the presence of certain surface molecules, or other metabolites derived from apoptotic cell digestion after efferocytosis (the process whereby phagocytes remove apoptotic cells). This anti-inflammatory reprogramming in macrophages manifests itself by the release of proresolving factors such as IL-10, PGE-2, RvD5, and TGF-β. A drug candidate for resolution therapy based on factors secreted by efferocytic macrophages was thoroughly discussed in a recent review (257). This drug has been reported to limit peritoneal cancer cell dissemination (258), decrease disease scores, and promote wound healing in a colitis mouse model (259) and abrogated chronic inflammation in mice with collagen-induced arthritis that presented moderate/high symptom score (260).

In the context of atherosclerotic disease, statins play a pivotal role, recognized not only for their LDL-lowering effects but also for their anti-inflammatory properties. Statins have shown benefits in the primary prevention of cardiovascular disease beyond merely reducing LDL levels. For secondary prevention, particularly in acute coronary syndromes, high doses of statins are often prescribed, leading to a demonstrated decrease in morbidity and mortality in the postinfarction phase (261). Statins inhibit the formation of intracellular isoprenoids, which subsequently reduces the activation of the small GTPase Rho protein (262). This

Table 1. ***Upcoming clinical trials targeting inflammation in CVD, cancer, and obesity***

Clintrials.gov ID	Condition	Intervention	Mechanism	Phase
NCT00764270	Atherosclerosis	R-alpha lipoic acid	ROS scavenging?	2/3
NCT02898610	Stroke	Colchicine	NLPR3 inflammasome inhibition	3
NCT03699293	CAD, rheumatoid arthritis	NSAIDs vs. COXIBs	COX inhibition	4
NCT03260881	T2DM, CAD	Liraglutide	GLP-RA	4
NCT04181996	T2DM with vascular complications	Colchicine	NLPR3 inflammasome inhibition	3
NCT04478500	Hypertension	Minocycline	Inhibition of neutrophil migration and degranulation	4
NCT05021835	CKD	Ziltivekimab	IL-6 inhibition	3
NCT05797376	CAD, carotid stenosis	Aspirin/rivaroxaban	COX inhibition/factor Xa inhibition	4
NCT04774159	Peripheral arterial disease	Colchicine	NLPR3 inflammasome inhibition	3
NCT05956145	CAD	Colchicine	NLPR3 inflammasome inhibition	3
NCT05162742	Aortic stenosis	Colchicine	NLPR3 inflammasome inhibition	3
NCT06158698	Myocarditis	Colchicine	NLPR3 inflammasome inhibition	3
NCT05459974	Atrial fibrillation	Colchicine	NLPR3 inflammasome inhibitor	3
NCT05427084	Stable CAD	Canagliflozin	SGLT2 inhibitor	3
NCT05618353	CABG	Colchicine	NLPR3 inflammasome inhibition	2/3
NCT05850091	High-risk CAD	Rosuvastatin, colchicine	HMGCoA reductase inhibitor/NLPR3 inhibitor	4
NCT05739929	CAD	Colchicine	NLPR3 inflammasome inhibition	4
NCT05597202	T2DM, atherosclerosis	Semaglutide	GLP-RA	3
NCT05476991	Stroke	Colchicine	NLPR3 inflammasome inhibition	4
NCT05420012	Heart failure	Vericiguat	Soluble guanylate cyclase stimulator	3
NCT06078904	CAD	Colchicine	NLPR3 inflammasome inhibition	4
NCT04762472	CAD, air pollution	Montelukast	Leukotriene inhibitor	3
NCT05809011	Acute heart failure	Dexamethasone	Glucocorticoid	4
NCT05803759	CAD	Allicor (*Allium sativum* extract)	Cytokine modulation	2/3
NCT06076824	Aortic stenosis	Methylprednisolone	Glucocorticoid	4
NCT06200207	Heart failure	Ziltivekimab	IL-6 inhibition	4
NCT05855746	Myocarditis	Colchicine	NLPR3 inflammasome inhibition	3
NCT06217120	Heart failure	Colchicine	NLPR3 inflammasome inhibition	3
NCT06095765	CAD	Colchicine	NLPR3 inflammasome inhibition	3
NCT06217120	Heart failure	Colchicine	NLPR3 inflammasome inhibition	2/3
NCT04534075	Pelvic cavity tumors—radiotherapy	Dietary fiber	Improved gut microbiome	3
NCT04106999	Intraperitoneal chemotherapy	Dexmedetomidine	α2-Adrenergic receptor agonist	2/3

(*Continued*)

Table 1.–*Continued*

Clintrials.gov ID	Condition	Intervention	Mechanism	Phase
NCT03875690	Digestive cancer surgery	Dexamethasone	Glucocorticoid	3
NCT06016400	Oral squamous cell carcinoma	Vitamin D	Cytokine modulation	2/3
NCT05327751	Capecitabine-induced hand and foot syndrome	Celecoxib	COX inhibition	3
NCT05624138	Oxaliplatin-induced peripheral neuropathy	Ketotifen	COX inhibition	3
NCT05384431	Obesity	MUSCLE 5/TRIM 7 dietary supplements	Cytokine modulation	3
NCT06164860	Obesity, psoriasis	Mediterranean diet	Cytokine modulation	4
NCT04578652	Obesity, insulin resistance	Metformin, dietary fiber	Improved gut microbiome	3
NCT05574439	Early-onset obesity	Semaglutide	GLP-RA	4
NCT05870462	Obesity, T2DM	Semaglutide	GLP-RA	4
NCT04979130	Obesity, T2DM	Semaglutide	GLP-RA	4

Data aggregated from ClinicalTrials.gov to provide insights into current research directions and potential treatments involving anti-inflammatory strategies across different stages of cardiovascular disease (CVD), cancer, and obesity, highlighting the diversity of approaches and the emphasis on novel therapeutic targets. CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COX, cyclooxygenase; COXIB, cyclooxygenase-2 inhibitor; GLP-RA, glucagon-like peptide-1 receptor agonist; HMGCoA, 3-hydroxy-3-methylglutaryl-coenzyme A; IL-6, interleukin-6; NLPR3, NLR family pyrin domain-lcontaining 3; NSAID, nonsteroidal anti-inflammatory drug; ROS, reactive oxygen species; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

reduction leads to increased expression of the eNOS gene (263) and enhanced stabilization of eNOS mRNA through polyadenylation (264, 265). Furthermore, statins enhance eNOS gene expression by stimulating the PI3-Akt pathway (266), an effect that may be further augmented by the upregulation of Hsp90 induced by statins (267). In the failing myocardium, the increased generation of ROS is dependent on NADPH oxidase and Rac1-GTPase activity, which can be inhibited by statins (268). In aortic smooth muscle cells, atorvastatin inhibits the thrombin-mediated increase in proinflammatory cytokine synthesis by preventing the membrane translocation of RhoA (269). As a result, statins modulate the redox state in vascular and myocardial tissues, improve the bioavailability of nitric oxide, and suppress inflammation in both the vascular system and the myocardium.

As discussed above, colchicine, a cost-effective anti-inflammatory medication traditionally used for gout treatment, has proven effective in managing acute pericarditis and certain cardiovascular conditions, including postpericardiotomy syndrome, and in preventing atrial fibrillation following cardiac surgery and atrial fibrillation ablation (270). Colchicine's action mechanism includes inhibiting neutrophil migration, reducing neutrophil adhesion to endothelium, downregulating tumor necrosis factor receptors on macrophages and endothelial cells, diminishing monocyte/macrophage secretion of tumor necrosis factor, and suppressing NLRP3 inflammasome assembly and activation. This leads to a decrease in IL-1β and IL-18 production mediated by the inflammasome (271). A low dose of colchicine is suggested for managing stable coronary artery disease and post-acute coronary syndrome in high-risk patients, despite concerns about potential long-term effects like an increased risk of infections (271). Therapeutic strategies based on monoclonal antibodies targeting IL-1β (canakinumab), IL-1 (anakinra), or IL-6 (tocilizumab) are currently not recommended because of a lack of significant benefits or safety concerns (272).

Hypoglycemic drugs have shown potential anti-inflammatory effects. Metformin, a biguanide introduced in the 1950s, is one of the most widely used antidiabetic medications. It lowers fasting plasma glucose by decreasing hepatic glucose production and enhancing muscle insulin sensitivity (273). Beyond its glucose-lowering capabilities, metformin has been proven to restore endothelial function in high fat-fed diabetic rats by increasing nitric oxide (NO) bioavailability, reducing oxidative stress, and lowering CCL2 levels in the aorta (274). This is achieved through the activation of AMP-activated protein kinase (AMPK), which boosts NO synthesis and reduces reactive oxygen species (ROS) production by inhibiting NAD(P)H oxidase (275, 276). Metformin also inhibits nuclear factor κB (NF-κB) activation, leading to lower serum C-reactive protein (CRP) levels (277), and suppresses cytokine-induced NF-κB activation via AMPK in human umbilical vein endothelial cells (HUVECs) (278). Furthermore, metformin's anti-inflammatory actions involve the AMPK-phosphatase and tensin homolog (PTEN) pathway, regulation

of inflammatory mediators by dissociating PARP-1 from Bcl-6, and upregulation of the SIRT1/LKB1/AMPK pathway (279), thus mitigating ROS/PARP signaling in diabetic models. However, despite these promising effects, there remains uncertainty about whether metformin reduces cardiovascular disease risk among T2DM patients (280).

Conversely, in patients with HFpEF and obesity, semaglutide, a glucagon-like protein (GLP)-1 receptor agonist (GLP-1 RA), produced large improvements in HF-related symptoms, physical limitations, exercise function, inflammation (as indicated by CRP levels), body weight, and NT-proBNP (281). The exact mechanism behind GLP-1 RA beneficial effects remains unclear, but the reductions in NT-proBNP suggest that factors beyond weight loss contribute to its efficacy. The limited evidence available suggests two major pathways by which GLP-1 RAs exert their anti-inflammatory effects: reducing inflammatory cytokine levels and modulating immune system activity. Semaglutide suppresses the release of proinflammatory cytokines such as IL-6, TNF-α, and IL-1β by modulating signaling pathways including the NLRP3 inflammasome, p38 MAPK, and c-Jun-NF-κB p65 in brain tissues of animal models, leading to neuroprotection and improved cognitive function (282, 283). In clinical studies, semaglutide reduced circulating inflammatory cytokines in patients with T2DM, contributing to decreased systemic inflammation and potentially lowering cardiovascular risk (284). Semaglutide also reduces inflammation in epicardial fat by decreasing neutrophil activity and adhesion to endothelial cells (285). Additionally, GLP-1 RAs inhibit immune cell recruitment, reducing atherogenic plaque formation (286). Indirectly, semaglutide mitigates inflammation associated with oxidative stress and obesity by downregulating inflammatory mediators like S100a8, S100a9, and Cxcl2 in neutrophils (287) and reducing ROS production via an AMPK-dependent pathway (288). These multifaceted actions highlight GLP-1 RA potential in modulating immune responses and reducing inflammation across various tissues. However, the broader application of GLP-1 RA in treating obesity faces challenges, including high costs and possible serious adverse effects such as depression. Furthermore, contraindications exist for patients with a history of pancreatitis and those with multiple endocrine neoplasia syndrome type 2 (MEN2) or with a history of thyroid cancer, because of an increased risk of developing thyroid carcinomas (289).

Anti-inflammatory therapy in cancer has garnered significant attention because of the intricate relationship between inflammation and cancer progression. As discussed above, tumor microenvironments are rich in inflammatory cells and mediators, and targeting these factors has shown promise in reducing cancer development, growth, and spread (290). Strategies involving anti-inflammatory agents, blockade of myeloid cell mobilization, and immunostimulatory adjuvants have been explored to modulate the tumor microenvironment and enhance anti-tumor immune responses (291). Chronic inflammation has been associated with resistance to cancer immunotherapy, emphasizing the importance of controlling inflammation to improve treatment outcomes (292); combining immunotherapy with drugs that modulate chronic inflammation has been proposed to counteract oxidative stress, correct metabolic derangements, and enhance anti-tumor immune reactivity (293). Senescence, characterized by irreversible cell cycle arrest, can be triggered by genotoxic stress and oncogenic signaling pathways. Senescent cells release various cytokines known as the senescence-associated secretory phenotype (SASP), which can impact immune responses and inflammation within the tumor microenvironment (294, 295). In the realm of cancer therapy, therapy-induced senescence (TIS), such as is observed in subjects treated with immune checkpoint inhibitors, can have dual effects. TIS can enhance immunosurveillance to eliminate tumor cells, but it can also lead to chronic inflammation and drug resistance, contributing to cancer recurrence (296) or progression (297) by fostering chronic inflammation, immune evasion, and tumor cell proliferation (298). Targeting senescent cells through senolytics or senomorphics shows promise in developing innovative therapeutic approaches to modulate the inflammatory response in cancer (299). For instance, metformin has been demonstrated to alleviate SASP secretion and inflammation in senescent cells, suggesting a potential therapeutic strategy to counteract the proinflammatory consequences of senescence in cancer (300). The interconnected pathways involving DNA damage, senescence, and inflammation underscore the complexity of cancer development and the potential for targeting these processes to enhance cancer outcomes (290).

The therapeutic potential of modulating inflammation in CVD represents a significant focus of current research. Table 1 outlines the ongoing phase 3 and 4 clinical trials aimed at addressing inflammation within the context of CVD, cancer, and obesity. These studies are exploring various strategies to mitigate the inflammatory processes that contribute to the development and progression of these conditions, highlighting the importance of inflammation as a therapeutic target.

Nanoparticles are a novel approach in low-grade inflammation. The strategic targeting of inflammation is crucial for diagnosing and treating diseases linked to inflammation, pinpointing relevant cell types involved in pathogenesis, or achieving selective drug delivery (291). Nanomaterials have emerged as effective vehicles for drug administration, enhancing the efficacy and bioavailability of therapeutic agents. Furthermore, nanoparticles enhance the accuracy of molecular imaging techniques, such as in the diagnosis of Alzheimer's disease through gold nanoparticles in X-ray tomography (292–295, 301–304).

Nanoparticles offer promising clinical applications for the diagnosis and treatment of inflammation-

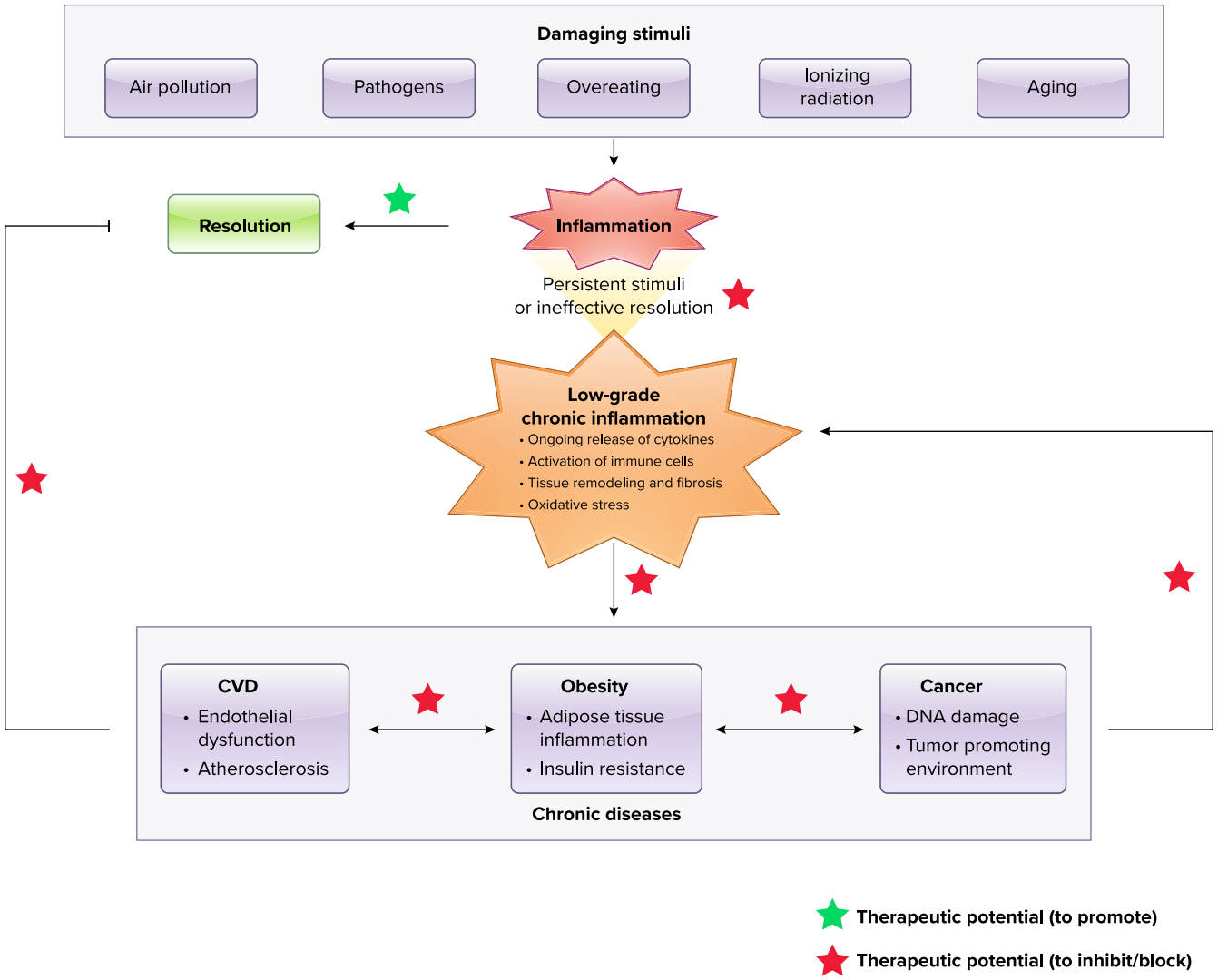

FIGURE 1. **Low-grade Inflammation and chronic diseases**
Upon the appearance of a damaging stimulus, an acute physiological inflammatory response is triggered. Homeostasis is reestablished when the resolution mechanisms are activated. However, inflammation turns chronic if the damaging stimulus persists or the resolution process is impaired. This chronic inflammation is associated with numerous events that favor the development of cardiovascular disease (CVD), obesity, and different types of cancer. In turn, these disorders generate signals reinforcing the inflammatory process and each other, generating a feedforward loop that further perpetuates the damaging stimuli and impairs the resolution process. As discussed in the text, red and green stars represent therapeutic opportunities for inhibiting and favoring specific processes, respectively.

related conditions. One notable example is the use of ultrasound-assisted mapping of carbon nanoparticle suspensions that provides good diagnostic results in breast cancer-associated inflammation (305), currently undergoing clinical trial. Because of the size of carbon nanoparticles in the suspension, they can easily penetrate lymphatic vessels for the detection of the sentinel lymph node. Additionally, curcumin, known for its anti-inflammatory properties, has been encapsulated in nanoparticles to enhance its solubility, stability, and permeability. This innovative formulation, administered orally, has shown to increase the therapeutic effectiveness and minimize side effects when treating moderate-to-severe psoriasis, a condition marked by complex inflammatory pathways (306). Another example is dextran nanoparticles containing mycophenolic acid, a commonly used immunosuppressant in systemic lupus erythematosus treatment because of its ability to promote M2-like macrophage polarization. This leads to decreased surface expression of CD80 and CD4 and reduced TNF-α production. The dextran nanoparticles address the drug's traditional limitations of short half-life and poor biodistribution (307). Furthermore, proresolving mediators can also be targeted for delivery using nanotechnology. A preclinical study in a pulmonary fibrosis mouse model utilized nanoparticles containing fish oil, rich in omega-3 fatty acid metabolites. Administered via inhalation, this formulation improved anti-inflammatory status and pulmonary function in fibrotic lungs (308).

Although the applications of nanoparticles in medical science hold vast potential, challenges such as potential cytotoxicity and the exacerbation of inflammation present significant hurdles. However, advances in nanotechnology have led to the engineering of nanoparticles

capable of early detection of pathological inflammation as well as theranostic applications, combining therapy and diagnosis within the same nanomaterial. The critical challenge lies in developing formulations that not only offer high-resolution detection but also can distinguish between physiological and pathological inflammation, ensuring targeted and effective treatment strategies.

Conclusions and Perspectives

For a summary, see FIGURE 1.

- Inflammation plays a key role in the organism's response to damaging stimuli to restore homeostasis. However, it evolves to low-grade chronic inflammation if it persists or its resolution is not achieved.
- The main drivers of chronic inflammation today are westernized diet, low physical activity, insufficient sleep, and environmental pollution, all of which are preventable. However, prevention strategies based on individual lifestyle changes would take decades. Changing the enabling conditions through legislation is also a long-term goal. The focus should be on decreasing the current damage associated to chronic inflammation, while educating people on how to prevent this condition.
- Low-grade chronic inflammation has been associated with the onset and progression of chronic diseases, including cardiovascular diseases, diabetes mellitus, obesity, and cancer.
- Recent research has recognized the roles of aging, dysregulated gut microbiota, innate and adaptive immune responses, and epigenetics in the genesis of low-grade chronic inflammation and its association with chronic diseases.
- Addressing lifestyle patterns and environmental pollutants while minimizing exposure to inflammatory triggers remains an urgent task for mitigating chronic inflammation. Prevention requires a comprehensive approach to modify environmental determinants, facilitating population access to healthy foods, physical activity, and health education.
- To address low-grade chronic inflammation comprehensively and discover novel risk and protective factors associated with the development of chronic diseases, multifaceted approaches that consider the complex interplay of genetic, environmental, lifestyle, and physiological factors in epidemiological cohorts are required through the use of novel tools such as genomics and others that escaped the scope of this review, such as artificial intelligence, bioinformatics, and single-cell analysis.
- Ongoing research continues to unravel the complexity of low-grade chronic inflammation and its participation in chronic disease development. Future directions that target key components of low-grade chronic inflammation using tools such as those based on nanotechnology should contribute to paving the way for more innovative, targeted treatments that would significantly improve patient outcomes in chronic disease. ■

This work was supported by ANID-FONDAP (15130011) and ANID-FONDAP APOYO 1523A0008 (M.C., H.E.V., P.F.C., A.H.C., C.F., A.F.G.Q., M.J.K., S.L.), FONDECYT (1211477) (M.C.), FONDECYT (1211270) (H.E.V), FONDECYT (1210644) (A.F.G.Q.), FONDECYT 1240444 (S.L.), anillo act210068 (M.J.K.), and FONDECYT 1231773 (A.H.C.).

S. L. is an editor of *Physiology* and was not involved and did not have access to information regarding the peer-review process or final disposition of this article. An alternate editor oversaw the peer-review and decision-making process for this article. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

M.C., H.E.V., and S.L. conceptualized review; M.C., H.E.V., P.F.C., A.H.C., C.F., A.F.G.Q., M.J.K., and S.L. analyzed data; M.C., H.E.V., A.H.C., A.F.G.Q., M.J.K., and S.L. prepared figures; M.C. and H.E.V. drafted manuscript; M.C., H.E.V., and S.L. edited and revised manuscript; M.C., H.E.V., P.F.C., A.H.C., C.F., A.F.G.Q., M.J.K., and S.L. approved final version of manuscript.

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