<PE-AT>Future of Preventing and Managing Common Chronic Inflammatory Diseases

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One-sentence summary: Elevated low-grade systemic inflammation, driven by specific cytokines, influences some chronic diseases, including cardiovascular disease, and may inform how periodontal disease influences certain common chronic diseases.

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Disclaimer: Kenneth Kornman is an officer of Sitokine Ltd, London. Sitokine has patents covering genetic patterns that increase production of IL-1β and increase risk for various chronic diseases but has no patents related to periodontal disease.

Abstract

Chronic inflammation has emerged as a key factor that contributes to some common chronic diseases and reduces lifespan. Studies have identified multiple types of chronic inflammation ranging from autoimmune disease, which attacks specific tissues, to autoinflammatory diseases, which cause low-grade systemic inflammation and contribute to several common chronic diseases. This article highlights new perspectives on the role of chronic inflammation in cardiovascular disease. Such information is being leveraged to develop new treatment strategies for cardiovascular disease and may inform how periodontal disease influences cardiovascular disease.

<PE-FRONTEND>

Chronic Inflammation as a Factor in Chronic Diseases and Reduced Lifespan

A major change in the understanding of chronic inflammatory diseases occurred in the late 1990's. Fundamental to this change was research focused on the association between levels of low-grade systemic inflammation and cardiovascular disease (CVD) clinical outcomes.[1-5] These studies used high sensitivity C-reactive protein (hsCRP) analysis of blood samples as the indicator of systemic inflammation. CRP is one component of the acute phase responses that are produced by the liver in response to circulating cytokines, most commonly interleukin-6 (IL-6), IL-1β, and tumor necrosis factor alpha (TNFα). The concentration of hsCRP in the blood is an effective indicator of circulating pro-inflammatory cytokines arising from any inflamed tissue at the time of hsCRP measurement. Most hsCRP studies focused on prediction of cardiovascular disease outcomes in response to interventions that reduced inflammation, as measured by changes in hsCRP.

Low density lipoprotein cholesterol (LDL-C) is accepted as a major causal factor for CVD and determinant of atherosclerotic events, although several modifying risk factors certainly influence disease expression. The systemic inflammation studies in recent years challenged the concept that CVD was primarily caused by LDL-C driven lipid accumulation on the arterial wall, which ultimately produced symptoms that required medication, surgical interventions, or both.[6] The early inflammation studies in CVD intervention provided evidence that reducing systemic inflammation was as protective against recurrent or initial major atherosclerotic events as was lowering LDL-C.[3,4,7]

During the same period, evidence emerged, primarily from genetic studies, to support the causality of another lipid factor, lipoprotein(a) [Lp(a)] in CVD.[8-11] The *LPA* gene, encoding Lp(a), is highly polymorphic, and its expression determines plasma levels of Lp(a) that vary among populations. Consequently, and in contrast to LDL-C, Lp(a) blood levels are not influenced by diet, exercise, or statins.

In parallel to the inflammation clinical trials, researchers were identifying a key role for IL-1β as a major driver of vascular inflammation and trigger of atherosclerotic events.[5,6,12-14] In a clinical study of patients with CVD, the risk of coronary artery disease increased with blood levels of Lp(a) that were above the median, but primarily in patients with *IL1B* genetic patterns that lead to high expression of IL-1β protein. The subjects without genetic patterns that led to high IL-1β levels had minimal increased risk of coronary artery disease regardless of elevated Lp(a) level.[9,10,15-17]

On the basis of many studies implicating systemic inflammation and the role of IL-1β in CVD,[18-22] a 10,000-person randomized controlled trial tested if blocking inflammation with canakinumab, an

antibody specifically targeting IL-1β, reduced the risk of cardiovascular events in a high-risk patient population.[5,22] The results were striking. Not only did blocking inflammation reduce the incidence of recurrent major cardiovascular events, but it also reduced the number of hospitalizations in patients with heart failure,[23] the incidence of lung cancer,[24] and the occurrence of major renal events in patients with chronic kidney disease.[25]

Another study implicated chronic systemic inflammation as a risk factor that prevents healthy aging. The "Hawaii Lifespan Study" is a longitudinal study of Japanese-American men born and living in Hawaii.[26] Survival analysis of this cohort of men found that indicators of low-grade chronic inflammation, such as higher concentrations of circulating fibrinogen or increased numbers of white blood cells, were associated with reduced survival. This chronic inflammation was one of only 7 primary factors that prevented healthy aging. Thus, chronic inflammation is a key factor that contributes to both chronic disease risk and healthy aging.

Types of Chronic Inflammatory Disease

Although the CVD studies increased awareness of chronic inflammatory diseases, such diseases are not a single entity. The most prevalent chronic inflammatory diseases, obesity and periodontitis, involve chronic continuing challenges. The chronic inflammation of obesity is driven by an overnutrition challenge, and a chronic interproximal bacterial challenge leads to most cases of periodontitis. Substantial new understanding about autoinflammatory and autoimmune diseases has emerged due in large part to classification of such diseases as a biologic continuum (Figure 1).[27,28]

The classic chronic inflammatory disease is often activated by an autoimmune process, such as in rheumatoid arthritis. These diseases have high levels of systemic inflammation, with circulating CRP concentrations that often exceed 10 mg/L.[29] Not only is there autoimmune destruction of local tissues, but there is also tissue damage that results from secondary inflammation caused by the autoimmune attack. There are more than 80 autoimmune diseases, which exhibit great variation among patients in terms of their severity. In all of these, the underlying issue is dysregulated immune tolerance to one's own tissues and subsequent inflammatory damage to local tissues. TNFα blocking agents, such as etanercept, have been very effective with several autoimmune diseases including rheumatoid arthritis, Crohn's Disease, psoriasis, and others.[30]

Autoinflammatory diseases represent another dimension of chronic inflammatory diseases. They were originally identified in patients that had unpredictable flares that produced symptoms, including fever, skin rashes, or joint swelling that were known to be initiated by innate immune mechanisms. Clinicians recognized that these presentations were rare and were ultimately identified as being caused by genetic mutations in biological mechanisms that regulated the innate immune response. It became clear that these rare autoinflammatory diseases were not autoimmune diseases involving antibodies that attacked the patient's healthy body tissues.

Some of these autoinflammatory diseases are rare monogenic diseases and others are quite common. Among the rare monogenic diseases are FMF (Familial Mediterranean Fever), NOMID (Neonatal Onset Multisystem Inflammatory Disease), and DIRA (Deficiency of Interleukin-1 Receptor Antagonist). These diseases are associated with rare mutations in inflammasome genes that lead to a dysregulated active caspase-1 that converts pro-IL-1β to active IL-1β. Such mutations result in high levels of IL-1β released to cause the symptom patterns associated with the rare monogenic

autoinflammatory diseases. Anti-TNFα drugs are less effective for the autoinflammatory diseases as opposed to the autoimmune diseases.

In contrast to the rare autoinflammatory diseases, there is emerging recognition and interest in more prevalent chronic inflammatory diseases that are in part driven by an imbalance of key cytokines, including IL-1β and IL-6, that drive innate immunity. These more common diseases driven by an imbalance of innate immunity do not display the intense episodes of acute inflammation, as described above for rare autoinflammatory diseases.[30] Both the rare forms of autoinflammatory disease and the more common forms are defined by increased inflammation involving cytokines of the innate immune system, more specifically IL-1β.

Atherosclerotic cardiovascular disease is the most well-studied common disease in which increased risk for major clinical events is found in patients with persistent elevations of systemic inflammation, as defined by blood hsCRP, despite various drugs that produce substantial reductions in LDL cholesterol levels.[31] The systemic inflammatory challenge in chronic diseases can be from dysregulated metabolism as occurs in cancer and metabolic disorders, genetic factors, respiratory and skin irritants, and unresolved infections. These common autoinflammatory diseases are typically associated with excessive production of cytokines that activate amplifying cascades, in particular IL-1β or IL-6.[13,31,32] It is well established that once released, IL-1β self-activates its own gene expression through the IL-1 receptor I. The auto-stimulation has been shown in some clinical situations to be the result of an imbalance between the IL-1β agonist and the natural antagonist IL-1Ra, which has been demonstrated in Type 2 diabetes[33] and in progressive knee osteoarthritis.[34] The pathologic outcomes arise from amplifying cascades driven by cytokine-activated pathways.

A newer concept in chronic inflammatory diseases is that some common conditions do not have overt characteristics of inflammation and generally do not respond predictably to non-specific anti-inflammatory drugs,[5,21,31,35] yet these conditions have an essential inflammatory component that drives the pathology.[5,23,24,36] These are often common diseases in which low-grade chronic inflammation may be evident, but disease-initiating factors become the focus of preventing or managing the disease. Examples include diet-influenced saturated fats or high blood pressure as initiating factors in CVD;[5,6] smoking in lung cancer;[24] and physical trauma to a joint in osteoarthritis.[34,37] In those examples of common chronic diseases, there are activating factors that trigger inflammation control points, such as IL-1β, that drive multiple cascades that amplify or resolve inflammation at various stages. The inflammatory response is essential to health but depends on tightly controlled regulation. If the inflammation activators are too potent or prolonged, the downstream inflammatory mediators that make prostaglandins, vascular adhesion molecules, chemotaxins, hematopoietic factors, lymphocyte and tissue cell growth factors, and other cytokines, such as IL-6 and IL-8, can lead to disease and tissue damage. The evolving concepts of common autoinflammatory diseases are well characterized by extensive work on the role of low-grade systemic inflammation in cardiovascualr disease events.[1,4,5]

These downstream inflammatory mediators then drive damage to arterial vessels in CVD, amplify destruction of pulmonary tissue in lung cancer, and destroy both connective tissue and bone in osteoarthritis. These common diseases with a chronic inflammatory component generally do not have an autoimmune component and are associated with low-grade circulating CRP (less than 10

mg/L). Indeed, in CVD, the increased risk for cardiovascular events has been associated with hsCRP levels exceeding 2 mg/L.[36]

Common chronic diseases also have an imbalance in inflammation that is evident as elevated hsCRP and, combined with inflammation activators, such as lipoprotein(a) or low-density lipoprotein cholesterol, produce a low-grade chronic inflammation. Such conditions have been recently validated in a randomized controlled clinical trial involving an IL-1β inhibitor (canakinumab).[5] Thus, chronic inflammation can contribute to common chronic diseases, such as CVD,[5] cancer,[24] and chronic kidney disease.[25] Both a secondary inflammatory response to tissue injury or the presence of an autoinflammatory condition can contribute to common chronic diseases that impact healthy aging, quality of life, and ultimately lifespan.

Targeting the Inflammatory Component of Cardiovascular Disease

The evolution of observations and technologies that drove various concepts of pathogenesis of atherosclerosis since the 1800's has been richly described by Libby and Hansson.[6] The clinical evidence supports that at least two blood lipids, LDL-C and Lp(a), along with inflammatory mechanisms, produce atherosclerotic CVD that, in some individuals, results in Major Adverse Cardiovascular Events (MACE).

Recent clinical trials demonstrated that PCSK9 inhibitors achieved dramatic lowering of LDL-C beyond that attainable with intensive statin therapy and, as a result, strongly enhanced prevention of recurrent MACE.[38,39] An antisense drug targeting Lp(a) is also under investigation.[40] However, it will be a few years before the results will show if this drug lowers Lp(a) sufficiently to reduce MACE. The development of MACE in individuals with elevated Lp(a) was conditional on the presence of an IL-1β genetic pattern that leads to high production of IL-1β protein.[16,17] In high risk CVD patients, drugs that specifically block IL-1β, but not less specific anti-inflammatory drugs, reduced MACE.[35]

With this appreciation of the role of inflammation as a key driver of CVD events, new treatment options have been and are being developed (**Figure 2**). These include blocking the lipids that trigger atherosclerosis and vascular inflammation. Such agents include inhibitors of PCSK9, a liver protein that promotes the degradation of LDL receptors which leads to higher cholesterol. The PCSK9 inhibitors block degradation of LDL receptors which reduces blood cholesterol. Even in patients already taking statins, PCSK9 inhibitors have dramatically reduced LDL-cholesterol and the risk of cardiovascular disease events. [18,19] An antisense drug designed to specifically reduce Lp(a) is in Phase III clinical trials.[40]

If the initiating factors are not reduced or the patient fails to respond to such treatments, MACE can be reduced by blocking the key drivers of arterial inflammation, most prominently IL-1β. IL-1β must be activated by molecular complexes called inflammasomes. Thus, there are several points at which IL-1β signaling can be inhibited: Drugs can target IL-1β itself, as with canakinumab,[22,24] drugs can inhibit the assembly of the inflammasome to block processing and release of IL-1β, or drugs can inhibit the induction of IL-1β by either blocking the intracellular signaling pathway or by preventing activation of the receptors that initiate IL-1β expression.

Implications for Treating Periodontal Disease

Much of the clinical focus has been on systemic inflammation as a contributor to chronic disease. However, chronic diseases can also contribute to systemic inflammation, thereby connecting multiple chronic diseases through an inflammatory component. These inflammatory diseases include periodontitis, type 2 diabetes, obesity, and others. Indeed, obesity and periodontitis are among the most prevalent chronic inflammatory diseases and are risk factors for other chronic diseases (**Figure 3**).

Although periodontitis, as with CVD, does not exhibit the classic signs of rare autoinflammatory diseases including unpredictable fevers, skin rashes, and joint damage, severe periodontitis is characterized by increased levels of IL-1β[41-45] and CRP,[46-48] which are consistent with other common autoinflammatory diseases.[49]

In recent years, investigators have used large clinical databases to ask whether the presence of a specific disease that increases systemic inflammation also increases the risk for future cardiovascular disease or type 2 diabetes. One of the most impressive studies of this type used the UK clinical practice research database and identified more than 100,000 patients with diagnoses of specific types of chronic inflammatory diseases. They asked whether the presence of one or more of the chronic inflammatory diseases increased the risk for future coronary artery disease, stroke, or type II diabetes. They compared the frequency of these three diseases in individuals who had a chronic inflammatory disease and those that did not. There were greater than 370,000 individuals who had no prior history of chronic inflammatory diseases and served as the reference population.[50] The investigators reported that individuals with a history of chronic inflammatory disease and increased systemic inflammation had a 30 to 35% greater incidence of coronary artery disease, stroke, or type 2 diabetes compared to the reference group.

The studies of inflammation in chronic disease, which have used hsCRP as the indicator, have revealed many factors that influence systemic inflammatory burden (**Figure 3**). These factors include ethnicity, gender, smoking, polymorphisms in genes involved in inflammation, diet, and other environmental factors. These factors increase systemic inflammatory burden, which then contributes to chronic diseases, including rheumatoid arthritis, Alzheimer's disease, type 2 diabetes, coronary artery disease, obesity, and moderate to advanced periodontitis. The current challenge is identifying which individuals with chronic inflammatory diseases, such as periodontitis, have increased systemic inflammation that alters the course of other chronic diseases including cardiovascular disease and Type 2 diabetes. Systemic inflammation is a central player that connects periodontitis to multiple chronic diseases of aging.

Conclusion

Although there are many studies that show an independent association between moderate to severe periodontitis and coronary artery disease and strokes, there are no direct intervention studies that show treatment of specific cases of periodontitis reduce MACE. It is reasonable, however, to propose establishing salivary and blood biomarkers to objectively assess treatment outcomes of periodontitis that may include decreases in systemic biomarkers that have been shown to reduce both first and recurrent cardiovascular disease events as a first step. It is likely that the knowledge gained from the study of systemic inflammation in cardiovascular disease and other chronic diseases will inform new treatment strategies for periodontal disease.

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Figure 1. Inflammatory and autoimmune diseases are a continuum. Examples of rare monogenic autoinflammatory diseases include FMF (Familial Mediterranean Fever), CAPS (Cryopyrin-Associated Periodic Syndrome) and NOMID (Neonatal Onset Multisystem Inflammatory Disease). Examples of polygenic autoinflammatory diseases include Crohn's disease, ulcerative colitis, psoriatic arthritis, CVD. Examples of polygenic autoimmune diseases include Systemic Lupus Erythematosus, Type 1 diabetes, and rheumatoid arthritis. An example of a rare monogenic autoimmune disease is ALPS (autoimmune lymphoproliferative syndrome. Reprinted with permission from Journal of Leukocyte Biology.[28]

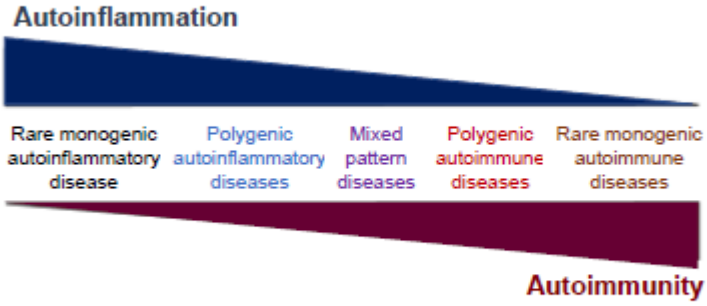

Figure 2. New therapeutics from CVD studies that are poised to address common chronic inflammatory diseases. The left side represents drugs that specifically reduce CVD by targeting "residual cholesterol risk." The right side represents drugs that could reduce CVD and other chronic diseases associated with increased systemic inflammation by reducing "residual inflammatory risk." [Credit: Heather McDonald, BioSerendipity, LLC]

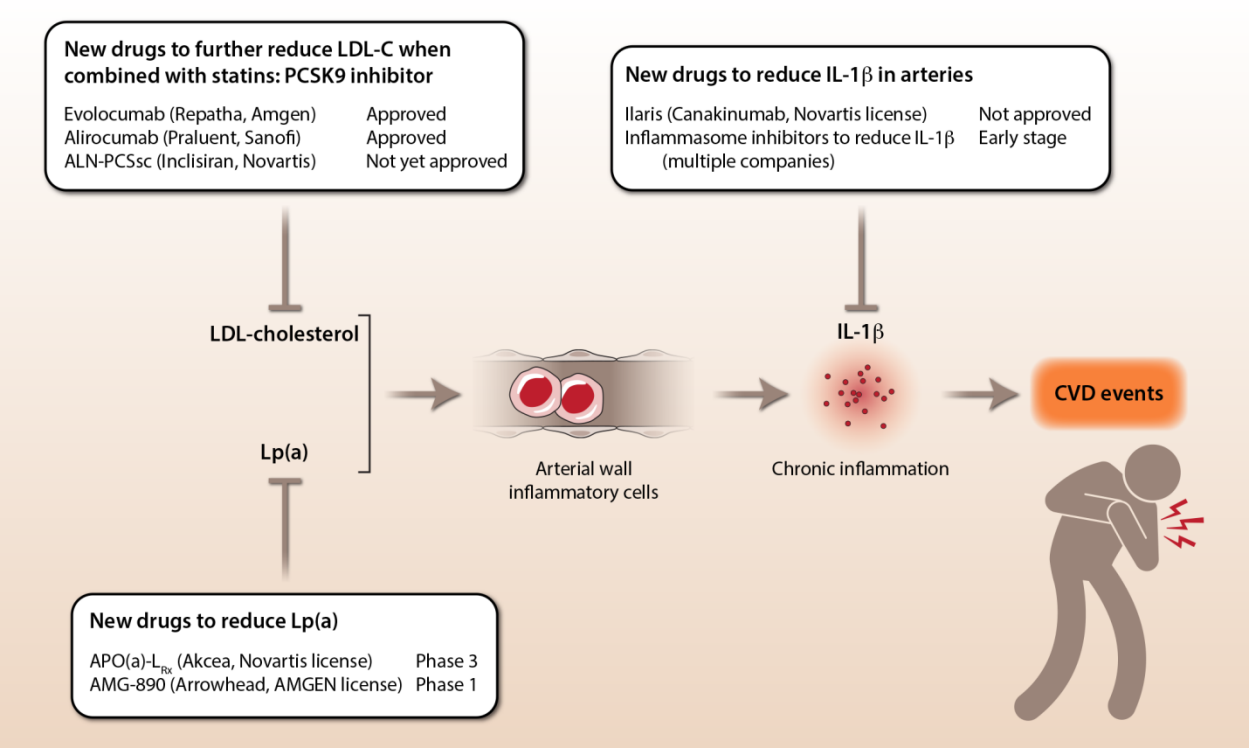

Figure 3. Multiple factors contribute to an individual's systemic inflammatory burden. Studies using hsCRP as an indicator of systemic inflammation revealed that gender, ethnicity, genetics, smoking, diet, and lifestyle contribute to systemic inflammatory burden. Systemic inflammatory burden contributes to multiple chronic diseases and diseases associated with aging. Periodontal disease and obesity are common inflammatory diseases. By causing systemic inflammation, chronic inflammatory diseases contributed to increased risk of other chronic diseases. [Credit: Heather McDonald, BioSerendipity, LLC]