

# Inflammation and Factors That May Regulate Inflammatory Response

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The concept of inflammation has a long history. Although an inflammatory response to injury or another trigger is necessary, chronic diseases, such as coronary heart disease and diabetes, may develop because of unchecked inflammatory responses that have maladapted over decades. For example, the earliest changes in atherosclerosis occur in the endothelium, leading to a cascade of inflammatory responses, such as accumulation of monocytes and T cells, migration of leukocytes into the intima, monocyte differentiation and proliferation, and lesion and fibrous cap development. Inflammatory markers, such as C-reactive protein, may allow clinical insight into these decades-long processes, adding value to predictive measures of disease outcomes. Anti-inflammatory factors, such as adiponectin, may provide further understanding of the inflammatory pathways involved. Greater understanding of the complex pathways involved in inflammation may provide alternative therapeutic strategies to combat inflammation and chronic diseases potentially arising from it. *J Periodontol* 2008;79:1503-1507.

## KEY WORDS

Adiponectin; atherogenesis; chemokines, CC; chemokines, CXC; C-reactive protein; cytokines.

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Inflammation has long been studied. As documented by Celsus, the ancients understood that, as a result of irritation, injury, or infection, the tissue gave rise to redness (rubor), swelling (tumor), heat (calor), and pain (dolor). From a pathologic perspective, inflammation is a process driven by inflammatory cells responding to signals and is “the reaction of blood vessels leading to the accumulation of fluid and leukocytes in extravascular tissues.”<sup>1</sup> The extravasation of inflammatory cells from the bloodstream starts a cascade of relevant reactions. Central to this is the understanding that atherosclerosis, diabetes, and most chronic inflammatory disorders arise over decades. What is of concern is the environmental set-up for the development of chronic diseases that might arise from predominately inflammatory processes in response to injury. In addition, there is the question of whether chronic, low-grade inflammation marks, exacerbates, or instigates chronic inflammatory diseases. Research is needed to determine whether the mechanisms involved in the inflammatory process can be used to predict, diagnose, or treat inflammation.

## THE IMMUNE SYSTEM

In response to an infectious or inflammatory trigger, two distinct, yet intricately linked, immune responses occur: innate and adaptive.

The innate immune system<sup>2,3</sup> is an older evolutionary defense mechanism that provides immediate protection

against infection or inflammation. It acts through the recruitment of immune cells, activation of the complement system, identification and removal of foreign substances, and activation of the adaptive immune system. Phagocytic cells, such as polymorphonuclear neutrophils, monocytes, and macrophages, trigger the release of chemical mediators, such as cytokines (e.g., tumor necrosis factor [TNF] and interleukins [IL]), that ultimately activate systems such as the complement system and acute phase response. These systems assist antibodies in clearing pathogens or mark them for destruction by other cells.

In addition to the non-specific innate immune response, the body is able to acquire more specific adaptive<sup>4</sup> responses to injury or inflammation. These recognize pathogens, thereby allowing a stronger response should the pathogen present again in the future. The adaptive immune response is able to distinguish the body's own cells from unwanted invaders. Its major functions are recognizing antigens during antigen presentation, tailoring a response to eliminate specific pathogens, and remembering the pathogen's antigen signature in case subsequent infections occur. When an injury occurs, there is a proliferation of antigen-specific T and B cells. T cells recognize the foreign antigen and specifically target it, which stimulates B cells to produce antibodies against the antigen. T and B cells assist macrophages and help generate killing cells that mount a response.

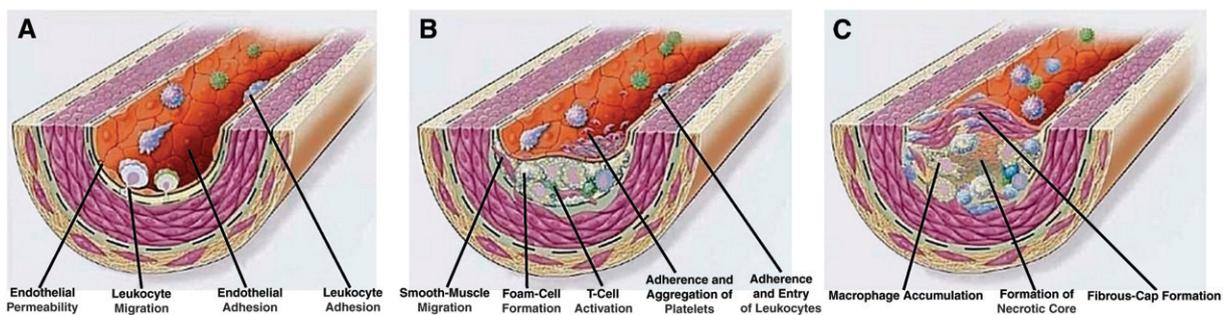
The immune system is essential; the body must be able to marshal the innate and adaptive responses to stave off infection. However, in inflammatory disease, the responses become chronic, and tissues do not return to homeostasis. In this article, the inflammatory aspects of atherosclerosis and diabetes are discussed as examples where these events may be maladaptive.<sup>4</sup>

## ATHEROGENESIS

Atherogenesis leading to atherosclerosis involves highly specific cellular and molecular responses that can be described as an inflammatory disease.<sup>5,6</sup> Classic cardiovascular risk factors can be viewed as an injury or insult to which the body adapts, setting in motion a decades-long response. Regardless of the cause, the earliest changes in atherosclerosis occur in the endothelium (Fig. 1A). These lead to increased permeability and adhesiveness, particularly to leukocytes, as well as increased procoagulant properties that result in activation of vasoactive molecules, cytokines, and growth factors.<sup>5,6</sup>

In the development of atherosclerosis, antigen presentation occurs in response to injury, leading to accumulation of monocytes and T cells at the injury site because of the presence of adhesion molecules. T cells are then activated, releasing mediators, such as cytokines and chemokines. Chemokines, a class of cytokines that mediate chemoattraction (chemotaxis) between cells, attract leukocytes to the site. Through a cascade of signals, the process leading to entry of leukocytes into the endothelium involves the rolling, activation, and adherence of leukocytes. One particular adhesion molecule, vascular cell adhesion molecule-1, is of importance in the adherence process because it binds precisely with monocytes and T lymphocytes.<sup>7,8</sup> Once adhered to the endothelium, leukocytes transmigrate into the intima (Fig. 1B).

During inflammation, there is a dramatic increase in chemokine secretion resulting in selective recruitment of leukocytes to the injured tissue. Early proinflammatory cytokines, such as IL-1 and TNF- $\alpha$  stimulate chemokine production.<sup>9</sup> Another cytokine, interferon-gamma (IFN- $\gamma$ ), is secreted by T lymphocytes (specifically, T-helper cell type 1); this induces



**Figure 1.**

**A)** The earliest changes that precede the formation of atherosclerosis lesions occur in the endothelium. These changes include increased endothelial permeability to lipoproteins and other plasma constituents, upregulation of leukocyte and endothelial adhesion molecules, and migration of leukocytes into the artery wall. **B)** Fatty streaks initially consist of lipid-laden monocytes and macrophages (foam cells) together with T lymphocytes that are subsequently joined by migrating smooth muscle cells. **C)** As fatty streaks progress to advanced lesions, they tend to form a fibrous cap representing a type of healing or fibrous response to the injury.<sup>5</sup> Copyright 1999 Massachusetts Medical Society. All rights reserved.

chemokine production directly and by acting with IL-1 and TNF- $\alpha$ .<sup>10,11</sup>

Two groups of chemokines associated with IFN- $\gamma$  are CC and CXC. CC chemokines induce the migration of monocytes. For example, monocyte chemoattractant protein-1, a CC chemokine, seems to be responsible for migration of monocytes from the bloodstream into the surrounding tissue by binding to and activating CC chemokine receptors, in this case, CCR2.<sup>12-14</sup> Depending on their structural characteristics, CXC chemokines can induce migration of neutrophils or attract lymphocytes. Research suggests that the differential expression of three IFN- $\gamma$ -inducible CXC chemokines (IFN-inducible protein 10, monokine induced by IFN- $\gamma$ , and IFN-inducible T-cell alpha chemoattractant) by atheroma-associated cells plays a role in the recruitment and retention of activated T lymphocytes within vascular wall lesions during atherogenesis.<sup>15</sup> This study also found increased expression of the receptor for these chemokines, CXCR3, by T lymphocytes within human atherosclerotic lesions.

Once migration has occurred, monocytes differentiate into macrophages and proliferate. Fatty streaks develop; these consist of lipid-laden monocytes and macrophages as well as T lymphocytes, which eventually are joined by migrating smooth muscle cells (Fig. 1C). If the cascade of events goes unchecked, the fatty streaks develop into advanced lesions whereby macrophages accumulate, a necrotic core is developed, and a fibrous cap is formed that blocks the lesion from the lumen.<sup>5</sup> This fibrous cap, which is characteristic of late-stage atherosclerosis, is of concern; rupture of this fibrous cap is believed to underlie the vast majority of myocardial infarctions that may derive from these inflammatory processes.<sup>16-18</sup> Cytokines, such as INF- $\gamma$ , are involved in the destabilization of the plaque because they lead to a decrease in matrix synthesis as well as matrix degradation.<sup>19</sup> In addition to these cytokines, matrix metalloproteinase (MMP) enzymes are involved in controlling degradation;<sup>16</sup> macrophages express MMPs, further contributing to degradation. Ultimately, the integrity of the fibrous cap is compromised. Under these conditions, matrix degradation may be maladaptive as the fibrous cap becomes thinner and ruptures more readily.

### MARKERS OF INFLAMMATION: C-REACTIVE PROTEIN (CRP)

To what extent can a clinician use measurement of markers of inflammation to investigate the decades-long process of atherosclerosis and obtain information on outcomes? CRP is an important cardiovascular risk predictor<sup>20-22</sup> and is produced by macrophages, endothelial cells, and smooth muscle, leading to a

host of effects. It has been proposed that CRP may not be just a marker, but an active player in the inflammatory process by mediating the uptake of native low-density lipoproteins by macrophages.<sup>23</sup> This suggests a possible role of CRP in foam cell formation during atherogenesis.

Research has also attempted to elucidate whether inflammatory markers, such as CRP, can predict long-term cardiovascular outcomes. In healthy men followed for 8 years from the first Monitoring Trends and Determinants in Cardiovascular Disease Augsburg survey<sup>24</sup> (1984 to 1985), there was a positive relationship between CRP and first major coronary heart disease (CHD) event. In addition, using prospective data from the Physician's Health Study, baseline CRP levels in apparently healthy males were found to add predictive value to the lipid parameters (total cholesterol and high-density lipoprotein cholesterol) in determining the risk for first myocardial infarction.<sup>25</sup> Among those with high levels of CRP and total cholesterol, the relative risks (RR = 5.0;  $P = 0.0001$ ) were greater than the individual risk associated with the elevation of CRP (RR = 1.5) or total cholesterol (RR = 2.3). Therefore, inflammatory markers, such as CRP, may add value beyond the traditional lipid profile for cardiovascular disease.

### METABOLIC DISORDERS

What is the relationship among inflammatory pathways in metabolic diseases, such as type 2 diabetes or insulin resistance? Some studies<sup>26-28</sup> demonstrated a positive association between insulin resistance and CRP, which suggests that inflammation may be part of diabetes and its processes.

An active area of current research is the effect of adipose tissue on inflammatory pathways in metabolic diseases. Adipose tissue is now recognized as a biologically active endocrine organ and not a site of inert lipid storage. Adipocytes were shown to secrete a variety of bioactive proteins, collectively known as adipokines, into the circulation, including TNF- $\alpha$ ,<sup>29</sup> plasminogen activator inhibitor type 1,<sup>30</sup> resistin,<sup>31</sup> and adiponectin.<sup>32</sup> This helps to explain why obesity and central adiposity are important and often associated with diabetes and atherosclerosis. Evidence suggests that inflammatory cells may be found within adipose tissue; perhaps the fat itself is actively involved in inflammatory processes, contributing through the release of inflammatory mediators.

Adiponectin is synthesized by white adipose tissue. It has a variety of effects in muscle, liver, and blood vessel walls and is believed to play an important role in modulating glucose and lipid metabolism. Although adipose tissue may release a host of proinflammatory cells, adiponectin is of interest because it seems to be anti-inflammatory<sup>33</sup> and, therefore,

protective. For example, lower levels of plasma adiponectin are found in patients with diabetes and CHD compared to patients with diabetes and without CHD, suggesting that adiponectin may be antiatherogenic.<sup>34</sup> Humans in insulin-resistant states also had lower levels of adiponectin;<sup>35</sup> this could be reversed by the administration of thiazolidinedione,<sup>36-39</sup> an insulin-sensitizing compound. There also seems to be a negative relationship between adiponectin and CRP,<sup>40,41</sup> again suggesting that adiponectin has an anti-inflammatory role.

## CONCLUSIONS

The concept of inflammation is long established. Immune responses to injury and infection are necessary; however, they cause problems when inflammatory processes are maladaptive, leading to chronic diseases, such as diabetes and CHD. Innovative research is needed to elucidate the intricate pathways involved in chronic inflammation. Clearly, many mechanisms are involved; ultimately, the question is how these can be used to better diagnose or treat the late-stage sequelae that many lines of evidence argue are driven by inflammatory processes.

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