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It's time to redefine inflammation

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ABSTRACT: Inflammation has been defined for many years as the response to tissue injury and infection. We are now forced to reconsider this definition by the avalanche of reports that molecules and cells associated with inflammation are activated or expressed in high concentration in a large variety of states in the absence of tissue injury or infection. Modest increases in concentration of C-reactive protein, a circulating marker of inflammation, have been reported to be associated with an astounding number of conditions and lifestyles felt to be associated with poor health; these conditions represent or reflect minor metabolic stresses. In recent years we have learned that inflammation is triggered by sentinel cells that monitor for tissue stress and malfunction—deviations from optimal homeostasis—and that molecules that participate in the inflammatory process play a role in restoring normal homeostasis. Accordingly, we suggest that inflammation be redefined as the innate immune response to potentially harmful stimuli such as pathogens, injury, and metabolic stress.—Antonelli, M., Kushner, I. It's time to redefine inflammation. FASEB J. 31, 1787–1791 (2017). www.fasebj.org

KEY WORDS: C-reactive protein · unfolded protein response · homeostasis · Claude Bernard · innate immunity

It is becoming nearly impossible to pick up a medical or scientific journal and not find a report that inflammation is implicated in yet another pathologic process. Gerald Weissmann, in an essay published in *The FASEB Journal* a few years ago appropriately entitled "It's complicated," listed 12 conditions not accompanied by the classic signs of inflammation, for which inflammation has been held responsible (1), including atherosclerosis, obesity, depression, Alzheimer's disease, schizophrenia, and osteoporosis. Among the conditions that can be added to this list are asthma (2), insulin resistance (3), and type 2 diabetes (4). What are we to make of this?

Inflammation has always been a somewhat fuzzy, loosely defined concept. As we suggested nearly 2 decades ago, it is time to redefine the term "inflammation" (5). A current textbook of pathology defines inflammation as "a response…to infections and damaged tissues that bring cells and molecules of host defense from the circulation to the sites where they are needed in order to eliminate the offending agents" (6). This definition defines inflammation in terms of its stimulus and a limited view of its function. Clearly, this definition is inadequate; many conditions currently regarded as inflammatory, including those mentioned in our first paragraph, occur without obvious infection, damaged tissue, or an apparent "offending agent." The inflammation seen in acute gout is not triggered by tissue injury or infection; nor are the autoinflammatory or autoimmune diseases.

We review the findings, as they have evolved throughout history, which have led physicians to conclude that inflammation is present; briefly survey some of the immense variety of conditions that are currently felt to be associated with inflammation; and discuss possible mechanisms that trigger inflammation in these conditions as well as the presumed short and long term purposes of the inflammatory process in different circumstances. We conclude that there is a great variety of inflammatory processes, if judged by stimuli, triggering mechanisms, and functions. They differ enough that one might think it best if they were regarded as separate entities, but it is probably too late for that, in view of the ubiquitous use of the term "inflammation" in recent years. Finally, we propose a definition of inflammation, modified from that of Orozco *et al.* (7), that reflects our current understanding.

HOW HAS INFLAMMATION BEEN RECOGNIZED OVER TIME?

The term "inflammation," derived from "flame," owes its name to the presence of warmth and redness, two of the cardinal signs observed by Aulus Cornelius Celsus (*ca.* 25 BC to *ca.* 50 AD)—rubor (redness), tumor (swelling), calor (warmth), and dolor (pain)—in people with acute inflammation. Subsequently, varieties of what were called inflammation began to be differentiated. We have long been aware that inflammation did not always resolve, that chronic inflammation might go on indefinitely, and that it

ABBREVIATIONS: CREBH, cyclic AMP response element-binding protein-H; CRP, C-reactive protein; ER, endoplasmic reticulum; TLR, Toll-like receptor; UPR, unfolded protein response

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might take the form of persisting purulence, fibrosis, or tissue destruction, as in abscesses or tuberculous cavities. Thus, in a 1794 posthumous publication, *A Treatise on the Blood, Inflammation and Gunshot Wounds*, the surgeon John Hunter (1728–1793) divided inflammation into 3 main groups based on their gross appearance: adhesive, suppurative, and ulcerative (8). Microscopy was introduced into medicine in the middle of the 19th century, permitting inflammation to be diagnosed histologically. It became apparent that polymorphonuclear leukocytes were the predominant cells involved in the early stages of acute inflammation, whereas cellular infiltrates largely consisted of monocytes/macrophages and lymphocytes in chronic inflammation. A major change in our understanding of inflammation occurred during that era, when Rudolph Virchow (1821–1902), the father of modern pathology, concluded that there was not a single entity named "inflammation" but rather that there were various inflammatory processes. He differentiated 4 kinds of inflammation—exudative, infiltrative, parenchymatous, and proliferative—and stressed the importance of the inflammatory stimulus. He unsuccessfully wrestled with the definition of inflammation throughout his life and even considered used a different term, but apparently none came to mind (9).

Our understanding of the mechanisms that mediate inflammation has expanded and accelerated markedly since then, most notably in the last half century, and the criteria for concluding that inflammation is present have changed accordingly. A large number of ancient innate immune mechanisms—the pattern recognition molecules that signal the need to initiate an inflammatory response—have been recognized. Some, such as Toll-like receptors (TLRs), recognize microorganisms (pathogen-associated molecular patterns), and some recognize tissue injury (damage-associated molecular patterns). Additionally, TLRs have been found to play a role in other pathologic conditions such as gout, in which TLR4 recognizes urate crystals. After engagement of their ligands, an extraordinarily complex process ensues—the innate immune response—culminating in the activation of many genes that encode the proteins that mediate and regulate inflammation. An army of mediators may participate, including multiple cytokines, histamine, bradykinin, prostaglandins, leukotrienes, platelet-activating factor, complement components, inflammasomes, and a family of cell adhesion–promoting molecules. In addition, circulating markers of inflammation—acute phase proteins, most notably C-reactive protein (CRP)—are produced by hepatocytes in response to circulating cytokines (10).

LOW-GRADE INFLAMMATION

As a result, we now regularly conclude that inflammation is present when increased concentrations of the elements of the innate immune response are found (*i.e.*, extracellular mediators, such as inflammatory cytokines, or activation of intracellular mediators, such as the transcription factor NF-κB). In addition, it is now commonly concluded that inflammation is present when concentrations of the acute phase protein CRP are elevated, even if only modestly. Indeed, CRP elevation, variously defined (11), is today regarded virtually as a synonym for inflammation. As a result, a new, not quite official entity has arisen, variously referred to as "low-grade inflammation," "subclinical inflammation," or "microinflammation." Low-grade inflammation is not a consequence of tissue injury or infection, Celsus's classic signs of inflammation are not found, and CRP levels are minimally elevated compared with those that accompany acute inflammation after tissue injury or infection. Such modest CRP elevations (between 3 and 10 mg/L) are found in about 30% of the American population (12).

What explains such a high prevalence of so-called low-grade inflammation? Low-grade inflammation has been reported to be associated with an astounding number of conditions and lifestyles felt to be associated with poor health; these conditions represent or reflect minor metabolic stresses. The lengthy (partially cited here) list includes exposure to environmental irritants such as cigarettes, secondhand smoke, sleep deprivation, low levels of physical activity, atrial fibrillation, hypertension, low birth weight, lumbar disc herniation, impaired cognition, low grip strength, polycystic ovary syndrome, living at high altitude (12, 13), prehypertension (14), obstructive sleep apnea (15), premenstrual symptoms (16), a large variety of unhealthy diets (17), hypoxia (18), social isolation (19, 20), being unmarried (21), and aging (22, 23).

QUALITY CONTROL IS ESSENTIAL TO MAINTAIN HOMEOSTASIS

Human beings were not intelligently designed. Rather, we were put together incrementally, building on preexisting parts, by mutations, gene flow, genetic variation and recombination, in multiple steps, one might say haphazardly, over the course of millions of years. As the great French biologist François Jacob pointed out, "Nature is a tinkerer and not an inventor": new sequences are adapted from preexisting sequences rather than invented (24). As one might expect in organisms that developed this way, things do not always work smoothly. Very many quality control mechanisms are required to prevent things from going awry as a result of the minor perturbations, which are part of daily life, that affect homeostasis. Thus, we have a multitude of feedback loops, inhibitory molecules, the unfolded protein response, heat shock proteins, *etc*.

Claude Bernard, the founder of experimental medicine, brilliantly perceived that our cells live in a fairly constant internal environment—the *milieu intérieur* (25). Late in his life, he came up with this sweeping but valid statement: "All of the vital mechanisms, however varied they may be, have always but one goal, to maintain the uniformity of life in the internal environment." At first glance, it would seem that inflammation is an exception to Bernard's sweeping statement because acute inflammation is accompanied by putting aside the normal homeostatic settings and their replacement by new set points, the acute phase response in the broad sense. On reflection, "all of the vital mechanisms" does indeed include inflammation. It is apparent that the ultimate purpose of inflammation in response to tissue injury or infection is to ultimately return tissues to their normal state, including tissue repair and regeneration, which are the anatomic equivalent of metabolic homeostasis; cytokines actively participate in tissue repair (26).

It is now clear that inflammation can also be induced by tissue stress and malfunction in the absence of infection or overt tissue damage (27). Low-grade inflammation occurs when changes from the optimal internal environment lead to stressed cells. Such deviations are recognized by macrophages, dendritic cells, and a variety of sentinel cells that monitor tissue homeostasis. It has recently been found that innate lymphoid cells also play a role in assuring tissue homeostasis, although the mechanisms by which they recognize metabolic or dietary stress and how they affect homeostasis are poorly defined (28). Adjustments are then made so that the normal homeostatic state is restored. We now know that the inflammatory response in these instances participates in the return to the optimal homeostatic state.

INFLAMMATION PARTICIPATES IN RESTORING HOMEOSTASIS

The unfolded protein response (UPR), an essential adaptive intracellular signaling pathway, is an instructive example of the quality control mechanisms that respond to metabolic stress in order to restore homeostasis (29). The endoplasmic reticulum (ER) is the location in the cell where one third of all newly synthesized proteins are folded, modified, sorted, and transported to their ultimate location. Alterations in ER homeostasis trigger UPR pathways with the goal of restoring homeostasis. Many metabolic stressors can create ER stress, including glucose deprivation, perturbations of intraluminal calcium levels, cytokines, altered cellular redox state, hypoxia, toxins, viruses, increased protein trafficking, and nutrient excess or deficiency (30). In response, general protein translation is reduced and expression of proteins that mark the targeted proteins for degradation is increased. Once homeostasis is restored, global mRNA translation resumes normally to allow cell survival.

Recent studies reveal connections between the UPR and inflammation at multiple levels (31). The UPR results in induction of many inflammation-associated genes, including cytokines capable of acute-phase protein induction. NF-κB, a master transcriptional regulator of inflammation, can be activated by all 3 UPR pathways. ER stress can activate the nod-like receptor family, pyrin domain-containing-3 complex (NLRP3) (29). Obese adipose tissue demonstrates up-regulation of inflammatory pathways leading to increased expression of TNF-α and IL-6 as well as other mediators (32). Cyclic AMP response element-binding protein-H (CREBH), a transcription factor similar to activating transcription factor-6 (ATF-6; one of 3 sensors lodged in the ER membrane that trigger the UPR), acts in an especially liver-mediated acute phase response, resulting in transcription of the acute-phase proteins CRP and hepcidin (33–35). In addition, in response to metabolic stress, CREBH plays a key role in maintaining lipid homeostasis by regulating expression of the genes involved in hepatic lipogenesis, fatty acid oxidation, and lipolysis (36). Finally, calcium released from the ER augments the production of mitochondrial reactive oxygen species (37).

It should not surprise us that molecules that participate in the inflammatory process play a role in restoring normal homeostasis. As we stated in 1998: "We often forget that boundaries between various organ systems and between categories of functional activity are merely man-made; an attempt to impose conceptual order on biologic phenomena. There is no a priori reason why nature should respect these boundaries" (5). As Okin and Medzhitov (38) point out, "Inflammatory mediators…act on target tissues and alter their functional states, promoting …restoration of tissue homeostasis." Inflammatory signals can mediate numerous variables in homeostasis systems *via* cytokines, chemokines, biogenic amines, and eicosanoids (39), thus influencing metabolism. For example, the inflammatory cytokines TNF-α and IL-1β activate lipolysis and inhibit gluconeogenesis; TNF-α makes fat, liver, and skeletal muscle less sensitive to insulin; and TNF-α and IL-1β suppress expression of GLUT2 and glucokinase in pancreatic β cells, thus making them less sensitive to blood glucose levels (39).

THE INFLAMMATORY PROCESSES AND A PROPOSED DEFINITION

Acute and low-grade inflammation differ both phenotypically and in being triggered by different mechanisms (**Table 1**). Acute inflammation is accompanied by the

TABLE 1. *Comparison of acute, low-grade, and autoinflammatory inflammation*

Parameter	Infection	Tissue injury	Low-grade inflammation	Autoinflammatory diseases
Cause	Pathogens	Trauma, tissue infarction	Metabolic malfunction	Usually spontaneous
Mediators	Molecules and cells of the innate immune response	Molecules and cells of the innate immune response	Molecules and cells of the innate immune response	Molecules and cells of the innate immune response
Classic signs of inflammation	+++	+++	None	+++
CRP response	+++	+++	+	+++
Purpose	Defense healing and repair	Healing and repair	Restoration of homeostasis	None apparent
Triggering mechanism	Pattern recognition molecules, notably for PAMPs and DAMPs	Pattern recognition molecules, notably for DAMPs	Sentinel cells that monitor for tissue stress, notably the UPR	Genetically based dysregulation

DAMP, damage-associated molecular patterns; PAMP, pathogen-associated molecular pattern. Plus symbols indicate magnitude.

classic signs of rubor, calor, tumor, dolor, and a substantial acute phase protein response and has the immediate goal of removing offending agents, removing necrotic tissue, and restoring tissue integrity. Acute inflammation in response to infection and tissue injury is triggered by pattern recognition molecules. In contrast, low-grade inflammation is not accompanied by the classic signs of inflammation and manifests a modest (at best) acute phase protein response. Low-grade inflammation is triggered by sentinel cells that monitor for tissue stress and malfunction, which are deviations from the optimal homeostatic state. What do acute and low-grade inflammation have in common? They share many of the same effector molecules and cells and have the same ultimate goal of restoring the normal, optimal homeostatic state. We now know that acute gouty attacks are triggered by binding of urate crystals to TLR4 (40). Yet another species of inflammation, that seen in autoinflammatory diseases, results from genetically based dysregulation of suppressive components of the inflammatory response that result in purposeless episodes of inflammation. Acute flares of autoinflammatory diseases are usually not precipitated by external stimuli. Autoimmune diseases may be regarded as a variety of tissue injury in which the stimulus persists for extended periods.

The boundary between normal adaptive homeostatic adjustments and inflammation is indistinct. It appears that there is no sharp boundary between normal, quotidian adaptive, homeostasis-restoring processes and inflammation. At what point do we conclude that it is pathologic—that it is "inflammation" as we have understood it?

In light of these significant differences, perhaps it would be best if acute inflammation and low-grade inflammation were regarded as separate entities. Indeed, the differences between these entities are striking enough so that two leading investigators in the field have suggested a distinct nomenclature for the latter state; both "para-inflammation" and "metaflammation" (metabolically triggered inflammation) have been proposed (30, 41). But it is probably too late; the proverbial train seems to have already left the station. We recognize that words have a range of meanings that change with the times. In any case, if "low-grade inflammation" is to be accepted as belonging in the "inflammation" category, then a redefinition of inflammation is called for. We propose a formulation modified from that used by Orozco *et al.* (7): "Inflammation is the innate immune response to harmful stimuli such as pathogens, injury and metabolic stress." The ultimate function of inflammation, in any case, is to restore the optimal homeostatic state, as, per Claude Bernard, is true of all the body's mechanisms. FJ

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AUTHOR CONTRIBUTIONS

M. Antonelli and I. Kushner wrote and edited the manuscript.

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