Leading Edge
Overview Essay

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Inflammation 2010: New Adventures of an Old Flame

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Inflammation is an essential immune response that enables survival during infection or injury and maintains tissue homeostasis under a variety of noxious conditions. Inflammation comes at the cost of a transient decline in tissue function, which can in turn contribute to the pathogenesis of diseases of altered homeostasis.

Inflammation has been known to humankind for at least a few thousand years, in part because it accompanied two major scourges of the past, wounds and infections, and in part because it is rather conspicuous. Although references to inflammation can be found in ancient medical texts, apparently the first to define its clinical symptoms was the Roman doctor Cornelius Celsus in the 1st century AD. These symptoms came to be known as the four cardinal signs of inflammation: *rubor et tumor cum calore et dolore* (redness and swelling with heat and pain). Celsus mentions these signs in his treatise *De medicina*, while describing procedures for treating chest pain, and in so doing became an oft-quoted medical celebrity (Majno, 1975).

The physiological basis of the four cardinal signs of inflammation was revealed much later by Augustus Waller (1846) and Julius Cohnheim (1867), who discovered leukocyte emigration from the blood vessels and other vascular changes characteristic of an acute inflammatory response. Analyzing living tissues under the microscope, Cohnheim observed vasodilation, leakage of plasma, and migration of leukocytes out of blood vessels and into the surrounding tissue (Majno and Joris, 2004).

The fifth cardinal sign, *functio laesa* (disturbance of function), was added by Rudolph Virchow in 1858 in his book *Cellularpathologie* (Majno, 1975). Notably, although the four cardinal signs of Celsus only apply to acute inflammation accompanying wounds and infections, *functio laesa* is the only universal sign that accompanies all inflammatory processes. Virchow's main contribution to inflammation research was to establish the cellular basis of pathology, a dramatic departure from the traditional view of disease as an imbalance of the four humors, which had dominated medicine since the time of Hippocrates.

Another major milestone was the discovery of phagocytosis by Elie Metchnikoff and his theory of cellular immunity developed in 1892. Metchnikoff emphasized the beneficial aspects of inflammation and pointed out the key role of macrophages and microphages (neutrophils) both in host defense and in the maintenance of tissue homeostasis (Tauber, 2003). We now appreciate the importance of these concepts, as we learn more about the biological functions of inflammation and the roles of macrophages in diseases of impaired homeostasis, such as obesity and atherosclerosis. Meanwhile, Paul Ehrlich was busy developing the humoral theory of immunity following the discovery of serum therapy against diphtheria and tetanus toxins by Emil von Behring and Shibasaburo Kitasato in 1890. The role of serum components in immunity was further supported by the discovery of complement by Jules Bordet in 1896. Finally, the establishment of the germ theory of disease in the late 19th century by Robert Koch and Louis Pasteur was crucial for appreciating microbial agents as major inducers of the acute inflammatory response.

Subsequent advances included the identification of different classes of inflammatory mediators, the pathways that control their production, and their mechanisms of action. We now know that inflammation comes in many different forms and modalities, which are governed by different mechanisms of induction, regulation, and resolution. In the past few decades, the spectrum of prevailing inflammatory conditions has shifted from acute inflammatory reactions in response to wounds and infections to chronic inflammatory states that accompany, for example, type 2 diabetes, atherosclerosis, asthma, neurodegenerative diseases, and cancer. It is as if surviving wounds and infections early in life almost guarantees encountering chronic inflammatory diseases at an advanced age. It is therefore hard to overestimate the role of inflammatory processes in human health and disease. And as we cannot completely escape from inflammation, we should at least try to understand it well enough to be able to avoid its more unpleasant aspects.

A Spectrum of Inflammatory Responses

A typical inflammatory response consists of four components: inflammatory inducers, the sensors that detect them, the inflammatory mediators induced by the sensors, and the target tissues that are affected by the inflammatory mediators (Figure 1). Each component comes in multiple forms and their combinations function in distinct inflammatory pathways. The type of pathway induced under given conditions depends on the nature of the inflammatory trigger. Thus, bacterial pathogens are detected by receptors of the innate immune system, such as Toll-like receptors (TLRs),

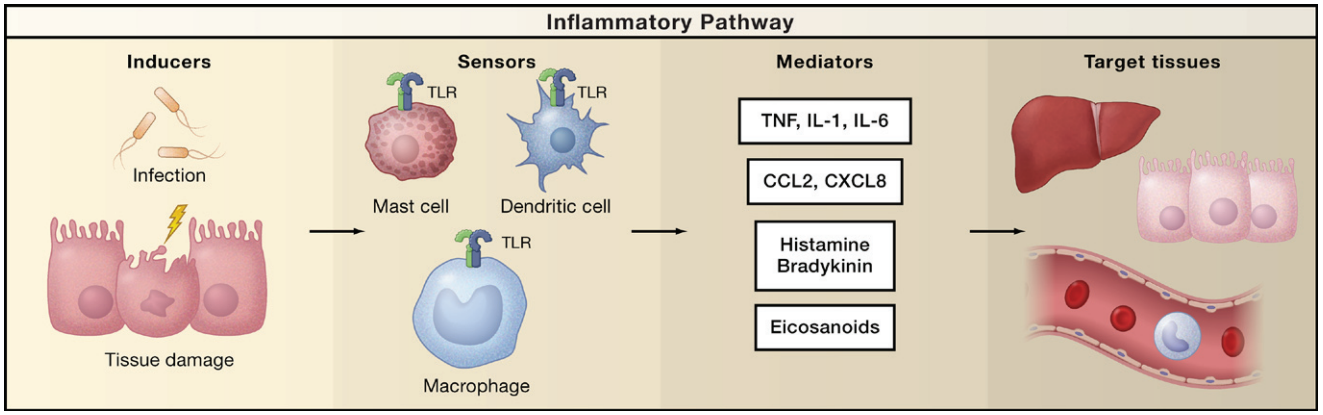

Figure 1. Inflammatory Pathway Components

The inflammatory pathway consists of inducers, sensors, mediators, and target tissues. Inducers initiate the inflammatory response and are detected by sensors. Sensors, such as Toll-like receptors (TLRs), are expressed on specialized sentinel cells, such as tissue-resident macrophages, dendritic cells, and mast cells. They induce the production of mediators, including cytokines, chemokines, bioactive amines, eicosanoids, and products of proteolytic cascades, such as bradykinin. These inflammatory mediators act on various target tissues to elicit changes in their functional states that optimize adaptation to the noxious condition (e.g., infection or tissue injury) associated with the particular inducers that elicited the inflammatory response. The specific components shown represent only a small sample of the myriad different sensors, mediators, and target tissues involved in the inflammatory response.

which are expressed on tissue-resident macrophages and induce the production of inflammatory cytokines (e.g., TNF, IL-1, IL-6) and chemokines (e.g., CCL2 and CXCL8), as well as prostaglandins. These inflammatory mediators then act on target tissues, including local blood vessels, to induce vasodilation, extravasation of neutrophils, and leakage of plasma into the infected tissue. Neutrophils recruited from the circulation, tissue-resident macrophages, and mast cells seek and destroy invading pathogens. This process is aided by plasma components, including antibodies and complement. In addition, IL-1, TNF, and IL-6 can have systemic effects when secreted in sufficient amounts. They induce liver cells (hepatocytes) to produce acute phase proteins such as C-reactive protein and coagulation factors, and they activate brain endothelium to produce prostaglandins, including the major proinflammatory prostaglandin, PGE2. Locally produced PGE2, in turn, induces specific populations of neurons in the central nervous system to promote so-called sickness behavior: fever, anorexia, fatigue, sleepiness, and social withdrawal (Pecchi et al., 2009).

Depending on the type of infection (bacterial, viral, or parasitic), the sensors, mediators, and target tissues vary such that the appropriate type of inflammatory response is induced. For example, viral infections induce the production of type-I interferons (IFN-α, IFN-β) by infected cells and the activation of cytotoxic lymphocytes, whereas infections with parasitic worms lead to the production of histamine, IL-4, IL-5, and IL-13 by mast cells and basophils. The latter response can also be triggered by allergens, resulting in allergic inflammation that affects primarily the mucosal epithelium, smooth muscles, and vasculature.

In the case of sterile tissue injury in the absence of infection, acute inflammation promotes tissue repair and helps to prevent colonization of the damaged tissues by opportunistic pathogens. The molecular identities of the triggers and sensors involved in the inflammatory response to tissue injury are incompletely understood, although molecules released from dying cells, breakdown products of the extracellular matrix, and products of the proteolytic cascades activated by vascular damage are thought to be involved. Tissue damage is detected by both tissue-resident macrophages, which induce inflammatory and reparative responses, and by pain receptors (nociceptors) that enable pain sensation in the affected area. Interestingly, both types of tissue damage sensors can be activated by some of the same signals that are produced upon injury, for example, extracellular ATP released from dying cells and bradykinin generated by a proteolytic cascade induced by vascular damage (Basbaum et al., 2009). Inflammation and nociception are functionally linked at multiple levels: exudate formation, tissue swelling, and inflammatory mediators are responsible for "inflammatory pain," and nociception complements inflammatory sensors in monitoring tissue homeostasis. In addition, prostaglandins can lower the threshold of pain sensation by increasing the sensitivity of nociceptors. Notably, sensing of the inflammatory milieu by the vagus nerve triggers an "inflammatory reflex," which is involved in the negative control of inflammation (Tracey, 2002).

The acute inflammatory response is normally terminated once the triggering insult is eliminated, the infection is cleared, and damaged tissue is repaired. Termination of the inflammatory response and transition to the homeostatic state is an active and highly regulated process known as the resolution of inflammation. Several key regulatory mechanisms of resolution have been identified including the switch from proinflammatory prostaglandins to anti-inflammatory, resolution-inducing lipoxins. This switch, in turn, orchestrates a transition from neutrophil to monocyte recruitment that results in clearance of the dead cells and other debris and initiation of tissue repair at the affected site (Serhan and Savill, 2005). If the inflammatory trigger is not eliminated by the acute inflammatory response or persists for any other reason, the resolution phase may not be appropriately induced and a chronic inflamma-

tory state may ensue. This state can be caused by chronic infections, unrepaired tissue damage, persistent allergens, undigestable foreign particles, or endogenous crystals, such as monosodium urate (Kumar et al., 2003; Majno and Joris, 2004). The chronic inflammatory response in these cases is typically localized to the site where the inflammatory inducer is present and often results in different types of local tissue remodeling. For example, persistent infection can lead to the formation of granulomas and the generation of tertiary lymphoid organs at the site of infection. Similarly, persistent airway inflammation induced by allergens can lead to respiratory epithelial tissue remodeling resulting in asthma.

In addition, a growing number of chronic inflammatory conditions have been described where the initiating trigger is not well defined but does not seem to involve infection or tissue damage. These inflammatory conditions are of particular interest because they accompany many diseases of industrialized countries, including obesity and type 2 diabetes, atherosclerosis, neurodegenerative diseases, and cancer. Interestingly, in these cases of chronic inflammation there appear to be vicious cycles connecting inflammation and the pathological process it accompanies. Thus, obesity can lead to inflammation, whereas chronic inflammation can promote obesity-associated diabetes in part by inducing insulin resistance (Hotamisligil, 2006). Similar positive feedback loops are present in atherosclerosis, cancer, and other chronic inflammatory diseases. Indeed, this type of reciprocal relationship may be responsible, at least in part, for the chronic nature of these inflammatory conditions and distinguishes them from the first type of chronic inflammation, which is caused by persistence of the inflammatory inducer. To understand the origin of these inflammatory processes we need to take a broader view of inflammation and its relationship with other systems of homeostatic control.

Inflammation: An Adaptive Response to Noxious Conditions

Despite the diversity of inflammatory phenomena, fundamentally, inflammation is an adaptive response to noxious conditions. Both beneficial and detrimental aspects of inflammation can be explained from this perspective. To better understand inflammation and inflammatory diseases, we need to consider how inflammation is related to other adaptive processes that operate at different levels in metazoan organisms.

The notion of homeostasis was first proposed in 1865 by Claude Bernard, who described the constancy of the internal environment as a "condition of free and independent life." The idea of homeostasis was further developed by Metchnikoff. He viewed this process as being controlled and maintained by phagocytes (Metchnikoff, 1892) and proposed the concept of "physiological inflammation" to describe the role of phagocytes in the active maintenance of "harmony" (i.e., homeostasis). These concepts are important because inflammation is essentially an adaptive response that aims to restore homeostasis. But if this is so, then why is inflammation associated with, and sometimes rightfully blamed for, so many diseases, particularly the very diseases that are caused by a loss of homeostasis? The usual answer to this question is that inflammation is beneficial in appropriate amounts but can easily become detrimental when excessive because of its tissue-damaging potential. This is certainly true, but at least two other reasons may account for the pathological potential of inflammatory processes.

The first reason is the consequence of a general feature of any adaptive response to noxious conditions: it always occurs at the expense of normal function. For example, cells deal with various types of noxious conditions by inducing appropriate stress responses that ensure adaptation and survival in the face of an abnormal cellular environment. A number of dedicated sensors have evolved to detect different stressors and to induce appropriate adaptive responses. Thus, heat shock, hypoxia, high levels of reactive oxygen species, and glucose and amino acid deprivation are sensed by HSF-1, HIF-1α, NRF-2, AMPK, and ATF4, respectively, resulting in alterations in cellular physiology that allow for adaptation to abnormal conditions. These adaptations occur at the expense of normal cellular functions and, if persistent, may have detrimental consequences. At the level of the organism, unfavorable environmental conditions, such as cold temperature, nutrient deprivation (caloric restriction), or dehydration, affect the switch between antagonistic physiological processes that promote either reproductive fitness or somatic maintenance. This switch is controlled by the IGF-1-FOXO pathway, with activation of the transcription factor FOXO leading to increased stress resistance. In some animals, this transition is taken to an extreme by triggering entry into a state of suspended animation such as the dauer state in nematodes or hibernation in certain mammals. However, this transition occurs at the expense of normal functions, principally reproduction. Similarly, the inflammatory response (excessive or not) invariably occurs at a temporary cost to normal tissue function and therefore is universally accompanied by *functio laesa*.

The second reason for the detrimental potential of inflammation concerns a particular mode of adaptation to certain types of persistent or extreme conditions. Specifically, one can envision two types of adaptation strategies: One promotes the restoration of homeostasis by returning the regulated variables to homeostatic set points. The second strategy is to switch the homeostatic set points to different values that are better suited to deal with the extreme or persistent abnormal conditions. The inflammatory response can engage in both modes of adaptation, although the second mode has been underappreciated. Nevertheless, changes in homeostatic set points may be particularly important in chronic inflammatory diseases, such as obesity and type 2 diabetes. Indeed, inflammation can induce a switch in metabolic homeostatic set points, for example, through its effect on insulin sensitivity, which may be intended for the reallocation of nutrients under conditions of stress or infection. This intended and beneficial mechanism can, however, become detrimental not because inflammation is excessive, but because the changes in homeostatic set points can become maladaptive in, and perpetuated by, the "unnatural" environment of industrialized countries. In other words, the intended, beneficial role of this mode

of adaptation can become detrimental because of the mismatch between the current environment and the evolutionary pressures of the past (Gluckman and Hanson, 2004).

Inflammation: A Tissue Stress Response

The analogy between inflammation and stress responses is illustrative for an additional reason: local inflammation can be thought of as a tissue stress response, whereas systemic inflammation is clearly a specialized type of stress response that occurs at the level of the whole organism. In fact, in some cases it is not obvious where to draw the line between the classical cellular stress response and inflammation. The main distinction may be that cellular stress responses are largely cell-autonomous adaptations, whereas inflammation typically operates at the tissue or organismal level. However, the origin of the inflammatory response may become clearer if we consider that even classical stress responses have non-cell-autonomous components. For example, hypoxia is sensed by HIF-1α and induces cellular adaptation to a shortage of oxygen, but it also results in production of vascular endothelial growth factor, which induces tissue adaptation through angiogenesis. Viral infections induce cell-autonomous antiviral responses but also lead to production of IFN-β, which induces tissue level adaptation to the virus by inducing an antiviral state in the surrounding cells. Indeed most, if not all, cellular stress responses, in addition to cell-autonomous adaptive changes, produce secreted factors that affect other cells in the tissue, including resident macrophages. In fact, tissue-resident macrophages may be specialized sentinel cells that sense not only injury and infection but also other types of noxious conditions such as hypoxia and metabolic stress. Indeed, macrophages have many trophic functions that are essential for tissue maintenance and homeostasis (Pollard, 2009), and presumably for stress adaptation as well. Depending on the nature and extent of the problem, the tissue-resident macrophages may recruit additional cells (e.g., different types of monocytes) to the affected tissue even when the problem is not associated with infection or injury. Thus, macrophages infiltrate the adipose tissue of obese animals, a phenomenon with well-appreciated pathological consequences (insulin resistance) but an unknown physiological purpose (Schenk et al., 2008). The tissue stress response orchestrated by macrophages and mast cells is intermediate between the cell-autonomous stress response and the bona fide inflammatory response and can be referred to as "parainflammation" (Medzhitov, 2008) (Figure 2).

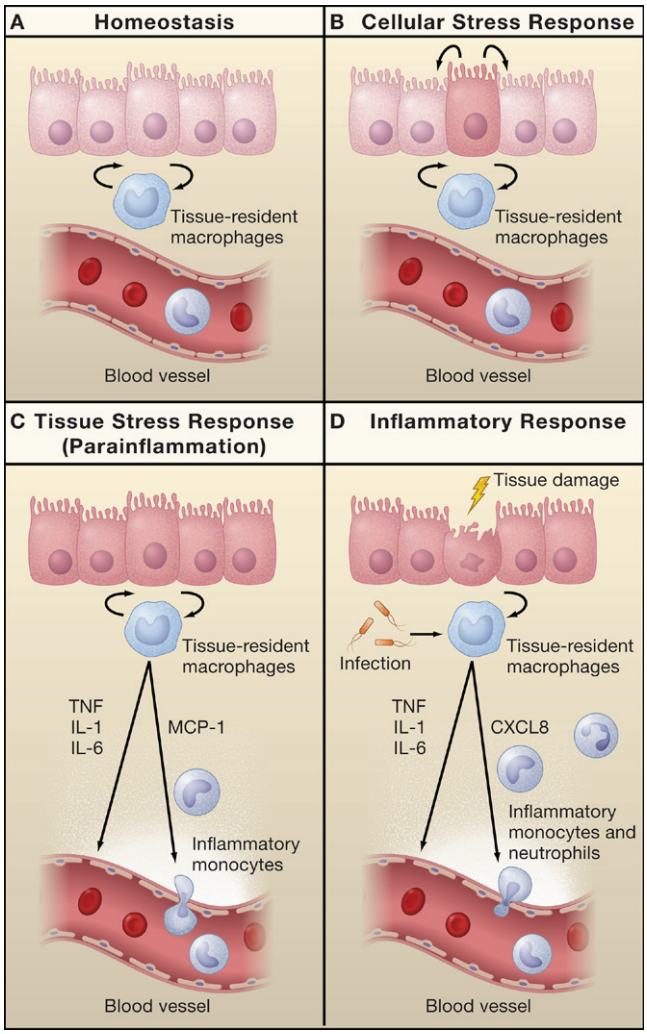

Figure 2. Inflammation and the Stress Response

Inflammation is an adaptive response to noxious conditions.

(A) Under normal conditions, tissue-resident macrophages maintain tissue homeostasis by removing dead cells and other debris and by producing growth factors.

(B) Under noxious conditions, the cellular stress response is activated and results in a cell-autonomous adaptation. But it may also involve communication between stressed cells and other cells in the tissue environment, including resident macrophages.

(C) If the nature or the extent of stress is such that it affects not only individual cells but the entire tissue (e.g., hypoxia or hyperthermia), then a tissue-level stress response, or parainflammation, is elicited by the resident macrophages (and in some tissues by mast cells). Depending on the degree of the noxious condition, this response can involve the recruitment of different types of inflammatory monocytes from the circulation. Parainflammation may also involve low-level release of plasma components into the affected tissue.

(D) Finally, if the condition is severe enough (e.g., infection or injury), an acute inflammatory response ensues. This is characterized by the recruitment of neutrophils and specialized subsets of monocytes from the circulation that help to protect the host from infection and promote tissue repair and restoration of homeostasis. (Only a few examples of inflammatory mediators are shown.)

Regulation of the Inflammatory Response

The inflammatory response can be controlled at multiple levels (Nathan, 2002), but the regulatory principles are still incompletely understood, in part due to the complexity of the inflammatory response and the multitude of components involved. One way to deconvolute this complexity is to distinguish among different checkpoints in the inflammatory response and to consider the different modes of action of regulatory signals.

In principle, the inflammatory response can be controlled at four levels, corresponding to the four components of the inflammatory pathway: inducers, sensors, mediators, and target tissues. One key control point, which is regulated by major anti-inflammatory signals (e.g., IL-10,

TGF-β, glucocorticoids), is production of inflammatory mediators. However, anti-inflammatory signals could also act on the target tissue itself. First, the responsiveness of the target tissue to inflammatory mediators can be regulated at the level of receptors and signaling pathways activated by the mediators. This mode of regulation affords an extra level of specificity by controlling which tissues respond, as well as the extent and duration of the response, to a given mediator. Notably, many inflammatory mediators, for example PGE2, can signal through multiple receptor subtypes that may have opposite effects on target tissues. In other cases, the action of inflammatory mediators can be dampened by decoy receptors, again providing specific control of target tissues. Switching the expression of different types of receptors may contribute to this mode of regulation. Second, anti-inflammatory signals can act by reversing the effects of the mediators on the target tissue. For example, noradrenaline can reverse the effects of histamine and bradykinin on bronchiole smooth muscle by inducing bronchodilation. Vasoconstriction and vasodilation can also be controlled by pro- and anti-inflammatory signals without affecting the production of inflammatory mediators. The advantage of this type of control mechanism is that it can selectively regulate responsiveness of different target tissues without affecting the overall strength or duration of the inflammatory response.

Regulatory mechanisms are often specific for a particular component of the inflammatory response. Thus, rather than shutting down the response completely, many anti-inflammatory signals selectively inhibit certain aspects of the response. Examples include the effects of IL-10 and glucocorticoids on TLR-induced inflammatory responses in macrophages. These anti-inflammatory signals inhibit expression of only 10% to 15% of TLR-inducible target genes. The same appears to be true for many other anti-inflammatory signals. The reason for this selectivity of regulation is that the response induced by inflammatory sensors, such as TLRs, typically has multiple functional components. Thus, in addition to inflammatory mediators, TLRs induce expression of antimicrobial, tissue repair, and metabolic genes. These components may need to be regulated independently of each other, which presumably explains why major anti-inflammatory signals act in a component-specific manner. Mechanistically, this type of control is commonly performed at the level of gene transcription. Elucidating the physiological rationale underpinning this specificity of regulation is an important challenge for future studies.

Another important aspect of the control of the inflammatory response is the way in which anti-inflammatory signals are produced. For example, IL-10 is produced as a result of an inflammatory response and is a component of an activity-dependent negative-feedback loop. IL-10 typically inhibits the response that initiated its own production and acts on cells that produce inflammatory mediators, such as macrophages or T cells. Although glucocorticoids can be induced by inflammation (Besedovsky and del Rey, 2000), they also can be produced in response to signals unrelated to the inflammatory response (psychological stress, the circadian clock) and can act on almost any cell, including cells that are targets of the inflammatory response. Thus, IL-10 and glucocorticoids (and several nuclear receptors) act in a manner that is intrinsic or extrinsic to the inflammatory pathway, respectively. Not surprisingly, IL-10 and glucocorticoids have nonredundant roles in the control of inflammation, and it would be useful to compare their distinct regulatory functions under different inflammatory conditions.

Challenges and Perspectives

Inflammation comprises a diverse range of processes that affect every aspect of normal physiology and pathology. The field has become too large and amorphous to fit into a single discipline, let alone to be covered in a brief overview. Although individual branches of inflammation research have proceeded at different paces and in ever more divergent directions, there are still some common principles that remain to be elucidated. For example, there is no satisfactory theory that explains the chronic inflammatory states associated with diseases of homeostasis. The inflammatory inducers responsible for many chronic inflammatory states are not clearly defined, although recent advances have implicated certain stress response components (Hotamisligil, 2006). Connections between cellular stress and inflammation warrant further study. In particular, little is known about the non-cell-autonomous aspects of cellular stress responses. Analyses of cell communication during stress responses are likely to reveal new principles of tissue homeostasis and adaptation to noxious conditions. Although many molecules have been implicated as inflammatory inducers during tissue injury, their relative contributions are poorly defined and which of them, if any, are essential for the induction of the inflammatory response is unclear.

The relationship between inflammatory and adaptive immune responses is also incompletely understood. Although inflammation is likely to be required for the induction of adaptive immune responses, it is clearly not sufficient. It is important to note that inflammatory responses to infection and to sterile tissue injury have different purposes: the former aims to protect the host from infection and can be coupled with the induction of adaptive immunity, whereas the latter primarily serves to promote tissue repair. A detailed analysis of the inflammatory mediators induced under the two conditions should help to elucidate the distinct features of inflammation induced by infection and injury.

An excessive inflammatory response is detrimental due to its negative effect on tissue function and, when extreme, results in overt tissue damage. Apart from the acute phase of the inflammatory response, however, other stages of the inflammatory process can also become dysregulated. A dysregulated tissue repair response with accompanying tissue remodeling, fibrosis, and persistent tissue metaplasia can lead to the decline or complete loss of normal tissue function as happens, for example, in asthma. One can imagine that dysregulation of the resolution of inflammation may similarly contribute to tissue pathology. It would also be interesting to investigate whether pathogens that establish chronic infections, such as the bacterium *Mycobacterium tuberculosis*,

may trigger a dysregulated resolution response as part of their immune evasion strategy.

Inflammatory tissue damage and immunopathology incur high fitness costs, and the fact that they have been maintained during evolution may reflect a trade-off with the beneficial, often life-saving, functions of the inflammatory response. The question remains, however, of whether specialized mechanisms exist that have evolved to minimize inflammatory tissue damage. If so, these mechanisms may operate without affecting the protective aspects of inflammation, for example, by controlling target tissue responsiveness to inflammatory mediators, or by increasing tissue resistance to inflammatory damage through induction of cytoprotective mechanisms (Seixas et al., 2009).

One of the most daunting aspects of studying inflammation is the diversity and complexity of the inflammatory mediators and their effects on target tissues. Although mechanistic aspects of their effects are relatively well understood, their coordinate functions in the context of intact tissues and their multiple modes of regulation are poorly defined.

Inflammation research has come a long way from the first description of its cardinal signs by Celsus almost two millennia ago. Although much time has been spent studying inflammation in pathological contexts, increasingly, inflammation occupies a central position in many branches of biology. This is reflected by the broad range of subjects discussed in the Reviews and Essays in this *Cell* special issue on inflammation.

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