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Origin and physiological roles of inflammation

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Inflammation underlies a wide variety of physiological and pathological processes. Although the pathological aspects of many types of inflammation are well appreciated, their physiological functions are mostly unknown. The classic instigators of inflammation — infection and tissue injury — are at one end of a large range of adverse conditions that induce inflammation, and they trigger the recruitment of leukocytes and plasma proteins to the affected tissue site. Tissue stress or malfunction similarly induces an adaptive response, which is referred to here as para-inflammation. This response relies mainly on tissue-resident macrophages and is intermediate between the basal homeostatic state and a classic inflammatory response. Para-inflammation is probably responsible for the chronic inflammatory conditions that are associated with modern human diseases.

Inflammation is an adaptive response that is triggered by noxious stimuli and conditions, such as infection and tissue injury[1,2]. Considerable progress has been made in understanding the cellular and molecular events that are involved in the acute inflammatory response to infection and, to a lesser extent, to tissue injury. In addition, the events that lead to localized chronic inflammation, particularly in chronic infections and autoimmune diseases, are partly understood. Much less is known, however, about the causes and mechanisms of systemic chronic inflammation, which occurs in a wide variety of diseases, including type 2 diabetes and cardiovascular diseases. These chronic inflammatory states do not seem to be caused by the classic instigators of inflammation: infection and injury. Instead, they seem to be associated with the malfunction of tissue: that is, with the homeostatic imbalance of one of several physiological systems that are not directly functionally related to host defence or tissue repair (Fig. 1).

It is generally thought that a controlled inflammatory response is beneficial (for example, in providing protection against infection), but it can become detrimental if dysregulated (for example, causing septic shock). Thus, the pathological inflammatory state is assumed to have a physiological counterpart. However, whereas the physiological rationale of infection-induced inflammation is clear, many other types of inflammatory response are only known in pathological settings, and there is no clear understanding of their physiological counterparts. It is not even clear whether there is any physiological counterpart for some inflammatory conditions, such as gout and obesity. Whether or not there are physiological counterparts for all inflammatory conditions, an important piece of the puzzle is missing from the current understanding of the inflammatory process. The standard view of inflammation as a reaction to infection or injury might need to be expanded to account for the inflammatory processes induced by other types of adverse conditions.

Regardless of the cause, inflammation presumably evolved as an adaptive response for restoring homeostasis. Therefore, the origin of inflammatory responses is perhaps best understood in this broader context. Here I discuss some of the physiological roots of inflammation as an adaptive response to tissue malfunction or homeostatic imbalance. Different types of inflammatory inducer, including altered cellular and tissue states, are discussed in this context.

Overview of the inflammatory response

At a basic level, the acute inflammatory response triggered by infection or tissue injury involves the coordinated delivery of blood components (plasma and leukocytes) to the site of infection or injury[1,2]. This response has been characterized best for microbial infections (particularly bacterial infections), in which it is triggered by receptors of the innate immune system, such as Toll-like receptors (TLRs) and NOD (nucleotide-binding oligomerization-domain protein)-like receptors (NLRs)[3]. This initial recognition of infection is mediated by tissue-resident macrophages and mast cells, leading to the production of a variety of inflammatory mediators, including chemokines, cytokines, vasoactive amines, eicosanoids and products of proteolytic cascades. The main and most immediate effect of these mediators is to elicit an inflammatory exudate locally: plasma proteins and leukocytes (mainly neutrophils) that are normally restricted to the blood vessels now gain access, through the postcapillary venules, to the extravascular tissues at the site of infection (or injury). The activated endothelium of the blood vessels allows selective extravasation of neutrophils while preventing the exit of erythrocytes. This selectivity is afforded by the inducible ligation of endothelial-cell selectins with integrins and chemokine receptors on leukocytes, which occurs at the endothelial surface, as well as in the extravascular spaces (where newly deposited plasma proteins form a provisional matrix for the binding of leukocyte integrins)[4]. When they reach the afflicted tissue site, neutrophils become activated, either by direct contact with pathogens or through the actions of cytokines secreted by tissue-resident cells. The neutrophils attempt to kill the invading agents by releasing the toxic contents of their granules, which include reactive oxygen species (ROS) and reactive nitrogen species, proteinase 3, cathepsin G and elastase[5]. These highly potent effectors do not discriminate between microbial and host targets, so collateral damage to host tissues is unavoidable[6].

A successful acute inflammatory response results in the elimination of the infectious agents followed by a resolution and repair phase, which

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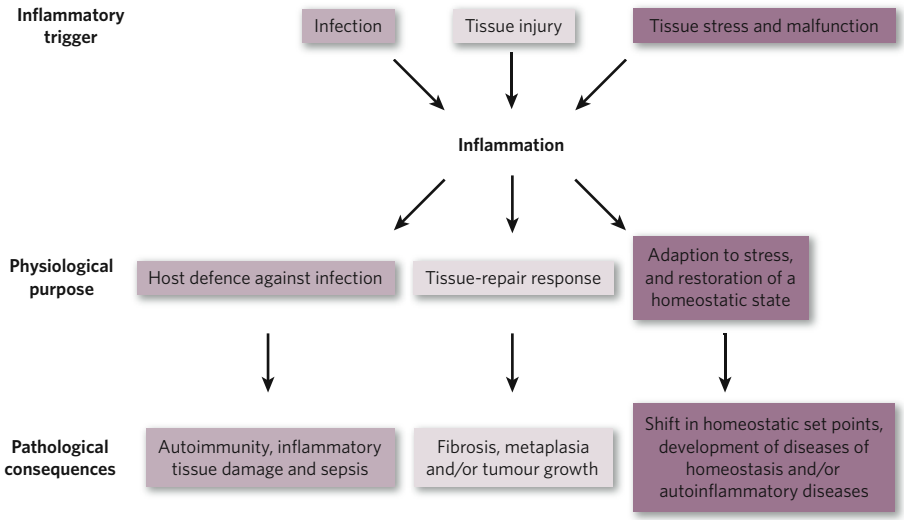

Figure 1 | Causes, and physiological and pathological outcomes, of inflammation. Depending on the trigger, the inflammatory response has a different physiological purpose and pathological consequences. Of the three possible initiating stimuli, only infection-induced inflammation is coupled with the induction of an immune response.

is mediated mainly by tissue-resident and recruited macrophages[7]. The switch in lipid mediators from pro-inflammatory prostaglandins to lipoxins, which are anti-inflammatory, is crucial for the transition from inflammation to resolution. Lipoxins inhibit the recruitment of neutrophils and, instead, promote the recruitment of monocytes, which remove dead cells and initiate tissue remodelling[7]. Resolvins and protectins, which constitute another class of lipid mediator, as well as transforming growth factor-β and growth factors produced by macrophages, also have a crucial role in the resolution of inflammation, including the initiation of tissue repair[7,8].

If the acute inflammatory response fails to eliminate the pathogen, the inflammatory process persists and acquires new characteristics. The neutrophil infiltrate is replaced with macrophages, and in the case of infection also with T cells. If the combined effect of these cells is still insufficient, a chronic inflammatory state ensues, involving the formation of granulomas and tertiary lymphoid tissues[2,9]. The characteristics of this inflammatory state can differ depending on the effector class of the T cells that are present. In addition to persistent pathogens, chronic inflammation can result from other causes of tissue damage such as autoimmune responses (owing to the persistence of self antigens) or undegradable foreign bodies. Unsuccessful attempts by macrophages to engulf and destroy pathogens or foreign bodies can lead to the formation of granulomas, in which the intruders are walled off by layers of macrophages, in a final attempt to protect the host[1,2].

It should be noted that the mechanisms of infection-induced inflammation are understood far better than are those of other inflammatory processes. It is unclear how applicable knowledge of infection-induced inflammation is to other types of inflammation. Indeed, although infection-induced inflammation is vital, it might be a special case. The mechanisms of systemic chronic inflammatory states in general are poorly understood, but it is clear that they do not seem to fit the classic pattern of transition from acute inflammation to chronic inflammation.

The inflammatory 'pathway'

The inflammatory response is coordinated by a large range of mediators that form complex regulatory networks. To dissect these complex networks, it is helpful to place these signals into functional categories and to distinguish between inducers and mediators of inflammation. Inducers are the signals that initiate the inflammatory response. They activate specialized sensors, which then elicit the production of specific sets of mediators. The mediators, in turn, alter the functional states of tissues and organs (which are the effectors of inflammation) in a way that allows them to adapt to the conditions indicated by the particular inducer of inflammation. Thus, a generic inflammatory 'pathway' consists of inducers, sensors, mediators and effectors, with each component determining the type of inflammatory response (Fig. 2a and Table 1). In the following sections, these four pathway components are discussed in turn.

Inducers and sensors of inflammation

Inducers of inflammation can be exogenous or endogenous (Fig. 2b).

Exogenous inducers of inflammation

Exogenous inducers can be classified into two groups: microbial and non-microbial. There are, in turn, two classes of microbial inducer: pathogen-associated molecular patterns (PAMPs) and virulence factors. The first class of microbial inducer, PAMPs, is a limited and defined set of conserved molecular patterns that is carried by all microorganisms of a given class (whether pathogenic or commensal)[10]. PAMPs are defined in the sense that the host has evolved a corresponding set of receptors (known as pattern-recognition receptors) that detect their presence.

The second class of microbial inducer comprises a variety of virulence factors and is therefore restricted to pathogens. In contrast to PAMPs, they are not sensed directly by dedicated receptors. Instead, the effects of their activity, particularly their adverse effects on host tissues, are responsible for triggering the inflammatory response. Typical activities of virulence factors can be detected by specialized sensors. For example, the pore-forming exotoxins produced by Gram-positive bacteria are detected by the NALP3 (NACHT-, leucine-rich-repeat- and pyrin-domain-containing protein) inflammasome, which is sensitive to the efflux of K^+ ions that results from pore formation[11]. Similarly, the proteolytic activity of proteases produced by helminths is sensed by basophils by an unknown sensor[12]. Notably, this sensing mechanism can be inadvertently activated by functional mimics, so allergens that are proteases can trigger the pathway that is usually induced by helminths[12]. An alternative way of sensing virulence activity is non-specific and even more indirect, through detecting the effects on cell death and tissue damage. In this case, the actual inducers of the inflammatory response are endogenous products of damaged cells and tissues. Importantly, the inflammatory responses that are induced by these two sensing mechanisms of virulence activity differ in their specificity, because the former is characteristic of pathogens (and in some cases, pathogen classes), but the latter is not. These inflammatory responses are likely to have different characteristics, and it will be interesting to investigate whether they result in distinct physiological and pathological outcomes.

It should be emphasized that microbial inducers of inflammation are not necessarily derived from pathogens. Commensal bacteria provide an important source of inflammation inducers that are detected by TLRs[13]. The activation of TLRs by these bacteria is actively suppressed by multiple mechanisms. An example of this is the lethal TLR-dependent inflammation that develops in mice that lack A20, one of the crucial negative regulators of TLR signalling[14].

Exogenous inducers of inflammation that are of non-microbial origin include allergens, irritants, foreign bodies and toxic compounds[1]. Certain allergens are detected because they mimic the virulence activity of parasites (as mentioned earlier); others can act as irritants on the mucosal epithelia. The inflammatory response induced by both types of allergen is largely similar because defence against parasites and environmental irritants relies on expulsion and clearance mediated by the mucosal epithelia. The sensors for allergens are largely unknown.

Foreign bodies are indigestible particles that either are too large to be phagocytosed or cause phagosomal membrane damage in macrophages. Silica and asbestos particles are notorious examples of foreign bodies that elicit an inflammatory response. Their large size and resistance to removal, as well as a lack of self markers (such as CD47) that are normally present on autologous cells and prevent their phagocytosis (by engaging inhibitory receptors), point to an abnormal occurrence in the tissues. The 'missing self' recognition presumably triggers a 'phagocytic reflex' in macrophages, but the large size or the shape of foreign particles results in 'frustrated phagocytosis': that is, a phagocytic cup is formed but cannot close to form a phagosome. If a foreign body is too large for a phagocytic cup to be formed, the macrophage forms a granuloma around this body instead. The sensor that triggers this reaction in macrophages is unknown. In some cases, macrophages can fuse with each other to form 'giant cells' that encapsulate the foreign body. The encapsulation of foreign objects is an ancient defensive strategy, which is also found in *Drosophila melanogaster*, in which lamellocytes (macrophage-like cells) encapsulate parasitoid wasp eggs to protect the host[15]. Regardless of whether a foreign body is too large to be phagocytosed or disrupts the phagosomal membrane, when a macrophage encounters foreign bodies, the NALP3 inflammasome (a sensor) is activated[16].

Endogenous inducers of inflammation

Endogenous inducers of inflammation are signals produced by stressed, damaged or otherwise malfunctioning tissues (discussed later). The identity and characteristics of these signals are poorly defined. But they probably belong to various functional classes according to the nature and the degree of tissue anomalies on which they report.

One common (but not universal) theme in detecting acute tissue injury is the sensing of the desequestration of cells or molecules that are normally kept separate in intact cells and tissues. The sequestration of these components (for example, ligands and their receptors, or enzymes and their activators or substrates) is afforded by the various types of compartmentalization that occur in normal tissues. Important examples are sequestration bounded by cellular membranes (especially the plasma membrane), basement membranes, the surface epithelium and the vascular endothelium.

During necrotic cell death, for example, the integrity of the plasma membrane is disrupted, resulting in the release of certain cellular constituents, including ATP, K^+ ions, uric acid, HMGB1 (high-mobility group box 1 protein) and several members of the S100 calcium-binding protein family (S100A8, S100A9 and S100A12)[17,18]. ATP binds to purinoceptors (including $P2X_7$) at the surface of macrophages, resulting in K^+ ion efflux, and can cooperate with other signals to activate the NALP3 inflammasome[11]. ATP also activates nociceptors (which are sensory receptors), thereby reporting tissue injury to the nervous system[19]. HMGB1 and S100A12 engage the receptor RAGE (advanced glycation end-product-specific receptor; also known as AGER), which (at least in the case of HMGB1) cooperates with TLRs to induce an inflammatory response[20,21]. S100A8 and S100A9 signal through TLR4 (ref. 22). It should be noted that, although intracellular proteins are thought to be passively released when the plasma membrane of necrotic cells is disrupted, numerous intracellular proteins can be secreted by way of a non-canonical (endoplasmic-reticulum–Golgi-independent) pathway. A recent study has shown that this non-canonical secretion is mediated by activated caspase 1, implying that the secretion is regulated by inflammasomes[23]. In light of this finding, it will be necessary to examine whether inflammatory intracellular proteins are passively released from necrotic cells or secreted by way of this caspase-1-dependent mechanism. These two possibilities are mutually exclusive for a given cell, because necrotic cells are metabolically inactive, whereas caspase-1-dependent secretion is an ATP-driven process. If caspase 1 is responsible for the secretion of intracellular proteins with inflammatory activities, this will shed a different light on the role of intracellular inflammatory proteins in initiating inflammation, as well as on the role of necrotic cell death. The prime example in this case is HMGB1, which has been shown to be secreted by macrophages stimulated with the TLR4 ligand lipopolysaccharide[24], apparently in the absence of necrotic cell death, suggesting that the non-canonical caspase-1-dependent secretory pathway might be involved.

In intact tissues, epithelial cells and mesenchymal cells are normally separated from each other by the basement membrane, and the disruption of this barrier results in 'unscheduled' epithelial–mesenchymal interactions. These interactions indicate the presence of tissue damage and consequently initiate tissue-repair responses, but how these abnormal interactions are sensed is poorly understood. The surface epithelia separate the internal compartments from the external environment. In organs, such as the intestine, that are colonized by commensal microorganisms, the disruption of the epithelial barrier gives commensal microorganisms access to the TLRs on macrophages that reside in the lamina propria, resulting in TLR-mediated induction of tissue-repair responses in the intestine[13,25]. In sterile organs with an epithelial lining, the desequestration of some non-microbial luminal components might have a similar role. Another remarkable example of the use of a desequestration strategy is the separation of the growth factor heregulin (also known as neuregulin 1) from its receptors (ERBB2, ERBB3 and ERRB4) in the airway epithelium[26]. The tight junctions of the intact polarized epithelium separates heregulin, which is apically expressed, from its receptors, which are basolaterally expressed, thereby preventing their interaction. On epithelial injury, heregulin gains access to its receptors and initiates a tissue-repair response[26].

Finally, damage to the vascular endothelium allows plasma proteins and platelets to gain access to extravascular spaces[4]. A key plasma-derived regulator of inflammation, the Hageman factor (also known as factor XII), becomes activated by contact with collagen and other components of the extracellular matrix (ECM). Activated Hageman factor acts as a sensor of vascular damage and initiates the four proteolytic cascades that generate inflammatory mediators: the kallikrein–kinin cascade, the coagulation cascade, the fibrinolytic cascade and the complement cascade[1]. Platelets are also activated by contact with collagen and produce various inflammatory mediators, including thromboxanes and serotonin[1].

The endogenous inducers that have been discussed so far are involved in acute inflammatory responses to tissue injury. Another class of endogenous inducer is more relevant to chronic inflammatory conditions. This class of inducer includes crystals of monosodium urate and calcium pyrophosphate dihydrate, AGEs (advanced glycation end products) and oxidized lipoproteins (such as high-density lipoproteins and low-density lipoproteins). The formation of such crystals is facilitated in certain connective tissues, which provide an appropriate surface for crystal nucleation[17]. The formation of monosodium urate and calcium pyrophosphate dihydrate crystals in the joints and periarticular tissues, for example, is responsible for the inflammatory conditions known as gout and pseudogout, respectively[17]. When these crystals reach a certain size, they are detected by macrophages and treated in essentially the same way as foreign bodies (discussed earlier). Phagocytosis of these particles triggers the activation of the NALP3 inflammasome and subsequently the production of caspase-1 substrates, including members of the interleukin 1 (IL-1) family[16,27].

AGEs are products of the non-enzymatic glycation of long-lived proteins, such as collagen[28]. These products can result in the crosslinking of the proteins they are attached to, leading to gradual deterioration of the function of these proteins. In addition, AGEs are recognized by their receptor, RAGE, which has inflammatory activity either alone[21] or in combination with TLRs[29]. AGEs can accumulate under hyperglycaemic and pro-oxidative conditions, including type 1 and type 2 diabetes, and ageing[28]. ROS, produced by phagocytes, also have a role in converting

high-density lipoproteins and low-density lipoproteins into inflammatory signals by oxidizing their lipid and protein components[30].

Another group of endogenous inducers of inflammation consists of breakdown products of the ECM that are generated during tissue malfunction or damage. The best-studied component of the ECM in this context is the glycosaminoglycan hyaluronate. In normal conditions, hyaluronate is present as an inert high-molecular-weight polymer. Tissue injury promotes its breakdown into low-molecular-weight fragments, which are inflammatory, activating TLR4 and promoting a tissue-repair response[31]. This conversion is also thought to be ROS dependent[32]. Thus, several endogenous pathways that initiate the inflammatory response depend on ROS.

The list of endogenous inducers of inflammation is growing, but the scientific literature on this subject contains many discrepancies. This is largely due to the technical difficulties that are associated with characterizing this class of signal. A common reason for incorrectly identifying a factor as an inducer results from contamination of recombinant proteins with traces of microbial ligands for TLRs or NOD proteins. More importantly, many endogenous inducers of inflammation presumably exert the appropriate activity *in vivo* only when present in certain combinations and perhaps only in the context of malfunctioning or damaged tissues. For example, ischaemia (local lack of blood supply), hypoxia, increased concentrations of ROS and altered ECM components are all commonly associated with tissue damage or malfunction but are not reproduced in tissue-culture conditions, which are commonly characterized by supra-physiological nutrient and oxygen concentrations.

In addition to the inducers associated with infection and tissue damage, there is probably another, currently unidentified, class of inducer that triggers the inflammatory response in tissues that are malfunctioning or are under stress. These signals report on the homeostatic status of tissues and induce adaptive changes that involve some hallmarks of the classic inflammatory response (discussed later).

Mediators and effectors of inflammation

Inducers of inflammation trigger the production of numerous inflammatory mediators, which in turn alter the functionality of many tissues and organs — the downstream effectors of the inflammatory pathway. Many of these inflammatory mediators have effects in common on the vasculature and on the recruitment of leukocytes. These mediators can be derived from plasma proteins or secreted by cells[1,2]. The cellular mediators can be produced by specialized leukocytes (particularly tissue-resident macrophages and mast cells) or by cells present in local tissues. Some mediators (such as histamine and serotonin) are preformed and stored in the granules of mast cells, basophils and platelets. Others are preformed and circulate as inactive precursors in the plasma. The plasma concentration of these mediators can increase markedly as a result of increased secretion of the precursors by hepatocytes during the acute-phase response. Other mediators are produced directly in response to appropriate stimulation by inducers of inflammation.

Inflammatory mediators can be classified into seven groups according to their biochemical properties[1,2]: vasoactive amines, vasoactive peptides, fragments of complement components, lipid mediators, cytokines, chemokines and proteolytic enzymes.

First, vasoactive amines (histamine and serotonin) are produced in an all-or-none manner when mast cells and platelets degranulate. They have complex effects on the vasculature, causing increased vascular permeability and vasodilation, or vasoconstriction, depending on the context. The immediate consequences of their release by mast cells can be highly detrimental in sensitized organisms, resulting in vascular and respiratory collapse during anaphylactic shock.

Second, vasoactive peptides can be stored in an active form in secretory vesicles (for example, substance P) or generated by proteolytic processing of inactive precursors in the extracellular fluid (for example, kinins, fibrinopeptide A, fibrinopeptide B and fibrin degradation products). Substance P is released by sensory neurons and can itself cause mast-cell degranulation. Other vasoactive peptides are generated through proteolysis by the Hageman factor, thrombin or plasmin and cause vasodilation and increased vascular permeability (either directly or by inducing the release of histamine from mast cells). As mentioned earlier, the Hageman factor has a key role in coordinating these responses, and it functions as both a sensor of vascular damage and an inducer of inflammation. The Hageman factor activates the kallikrein–kinin cascade, and the main product of this cascade, bradykinin, affects the vasculature, as well as having a potent pro-algesic (pain-stimulating) effect. Pain sensation has an important physiological role in inflammation by alerting the organism to the abnormal state of the damaged tissue.

Third, the complement fragments C3a, C4a and C5a (also known as anaphylatoxins) are produced by several pathways of complement activation. C5a (and to a lesser extent C3a and C4a) promote granulocyte and monocyte recruitment and induce mast-cell degranulation, thereby affecting the vasculature.

Fourth, lipid mediators (eicosanoids and platelet-activating factors) are derived from phospholipids, such as phosphatidylcholine, that are present in the inner leaflet of cellular membranes. After activation by intracellular Ca^{2+} ions, cytosolic phospholipase A_2 generates arachidonic acid and lysophosphatidic acid, the precursors of the two classes of lipid mediator listed above, from phosphatidylcholine. Arachidonic acid is metabolized to form eicosanoids either by cyclooxygenases (COX1 and COX2), which generate prostaglandins and thromboxanes, or by lipoxygenases, which generate leukotrienes and lipoxins[2]. The prostaglandins PGE_2 and PGI_2, in turn, cause vasodilation, and PGE_2 is also hyperalgesic and a potent inducer

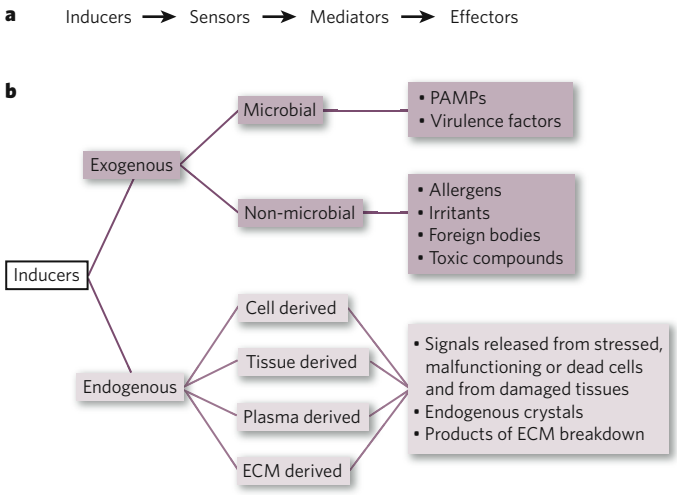

Figure 2 | The inflammatory pathway. a, A generic inflammatory pathway consists of inducers, sensors, mediators and effectors. Table 1 provides examples of each component for several inflammatory pathways. **b**, Inducers of inflammation can be classified as exogenous or endogenous, and these two groups can be further classified as shown. ECM, extracellular matrix; PAMP, pathogen-associated molecular pattern.

Table 1 | Examples of inflammatory pathways

Inducer	Sensor	Mediator	Effectors
Lipopolysaccharide	TLR4	TNF-α, IL-6 and PGE_2	Endothelial cells, hepatocytes, leukocytes, the hypothalamus, and others
Allergens	IgE	Vasoactive amines	Endothelial cells and smooth muscle cells
Monosodium urate crystals and calcium pyrophosphate dihydrate crystals	NALP3	IL-1β	Endothelial cells, hepatocytes, leukocytes, the hypothalamus, and others
Collagen	Hageman factor	Bradykinin	Endothelial cells and smooth muscle cells

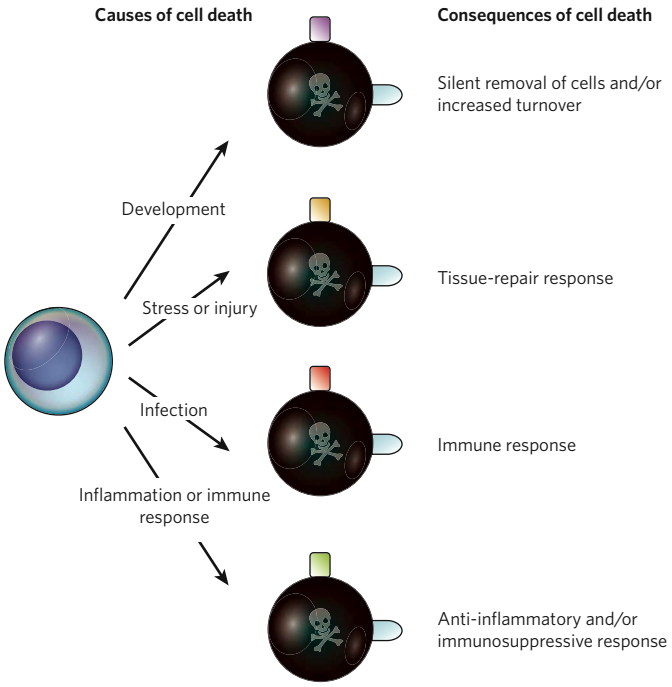

Figure 3 | Cell death and its consequences. Apoptotic cells display the lipid phosphatidylserine (blue) at the plasma membrane, resulting in their recognition and, subsequently, phagocytosis by macrophages. In addition, apoptotic cells probably produce other signals (coloured rectangles) that determine the outcome of their recognition by macrophages, but the type of signal is likely to depend on the cause of cell death.

of fever[33]. Lipoxins (and dietary ω3-fatty-acid-derived resolvins and protectins) inhibit inflammation and promote resolution of inflammation, and tissue repair[8]. The second class of lipid mediator, platelet-activating factors, are generated by the acetylation of lysophosphatidic acid and activate several processes that occur during the inflammatory response, including recruitment of leukocytes, vasodilation and vasoconstriction, increased vascular permeability and platelet activation[1,2].

Fifth, inflammatory cytokines (tumour-necrosis factor-α (TNF-α), IL-1, IL-6 and many others) are produced by many cell types, most importantly by macrophages and mast cells. They have several roles in the inflammatory response, including activation of the endothelium and leukocytes and induction of the acute-phase response.

Sixth, chemokines are produced by many cell types in response to inducers of inflammation. They control leukocyte extravasation and chemotaxis towards the affected tissues.

Seventh, several proteolytic enzymes (including elastin, cathepsins and matrix metalloproteinases) have diverse roles in inflammation, in part through degrading ECM and basement-membrane proteins. These proteases have important roles in many processes, including host defence, tissue remodelling and leukocyte migration.

It should be noted that it is unclear to what extent the nature of an inflammatory trigger dictates the type of mediator induced. In addition, many (but not all) mediators not only have direct effects on target tissues but also themselves induce the production of additional mediators. It will be important to understand the logic underlying this hierarchy of mediators.

The effectors of an inflammatory response are the tissues and cells, the functional states of which are specifically affected by the inflammatory mediators. Responsiveness to certain inflammatory mediators (such as TNF-α and IL-1) is almost ubiquitous, although these mediators have distinct effects in different tissue and cell types. Although the most obvious effect of inflammatory mediators is to induce the formation of an exudate (through their effects on the vasculature and on leukocyte migration), many inflammatory mediators have other, equally important, effects on neuroendocrine and metabolic functions and on the maintenance of tissue homeostasis in general[34]. These functions of inflammatory mediators reflect a more general role for inflammation in the control of tissue homeostasis and in adaptation to noxious conditions.

Homeostatic control through stress response and adaptation

Homeostatic control mechanisms ensure that internal environmental parameters (such as glucose and oxygen concentrations) are maintained within an acceptable range near a certain set point[35]. Abnormal conditions can cause a deviation in some parameters beyond the normal homeostatic range, resulting in either an acute stress response that affords a transient adaptation to the new conditions or a more sustained adaptive change that involves a shift in the relevant set points. In a general sense, acute inflammation and chronic inflammation are different types of adaptive response that are called into action when other homeostatic mechanisms are either insufficient or not competent.

The inflammatory response is commonly thought to operate during severe disturbances of homeostasis, such as infection, tissue injury and the presence of foreign bodies or irritants. However, infection and injury are at the extreme end of a spectrum of conditions that can trigger inflammation, and they trigger responses of the highest magnitude (which is why these are the best known and characterized inflammatory responses). More generally, an inflammatory response is presumably engaged whenever tissue malfunctions are detected. These types of inflammatory response are likely to be more common but of lower magnitude than the classic inflammatory responses induced by infection or injury. The nature and the degree of tissue malfunction will influence whether the inflammatory responses is detectable using common biomarkers. Such tissue alterations can range from mild tissue-specific malfunctions to massive injury. Accordingly, the magnitude of the inflammatory response can differ markedly. Very mild stress might be handled by tissue-resident cells (mainly macrophages and mast cells), whereas more extensive malfunctions or damage might require additional leukocytes to be recruited and plasma proteins to be delivered locally. These latter effects (in response to extensive malfunction or damage) are those of a classic inflammatory response. Unlike the signals that report infection and injury, the signals that report tissue stress and malfunction, and the molecular sensors that detect these signals, are largely unknown.

Whatever the cause of the inflammatory response, its 'purpose' is to remove or sequester the source of the disturbance, to allow the host to adapt to the abnormal conditions and, ultimately, to restore functionality and homeostasis to the tissue. If the abnormal conditions are transient, then a successful acute inflammatory response returns the system to the basal homeostatic set points. If, by contrast, the abnormal conditions are sustained, then an ongoing inflammatory state shifts the system to different set points, as occurs during chronic inflammation. An adaptive change often provides short-term benefits; however, in a chronic phase, it can become maladaptive, as exemplified by a sustained decline in insulin sensitivity of the skeletal muscle or by squamous metaplasia of the respiratory epithelium. More specifically, a transient decrease in insulin sensitivity during acute inflammation would allow the redistribution of glucose from one of its major consumers (for example, skeletal muscle) to leukocytes and other cell types that can have an increased energy demand during infection and tissue repair. However, sustained insulin resistance in skeletal muscle can lead to type 2 diabetes. Likewise, squamous metaplasia can have a short-term benefit by protecting the respiratory tract from damage by irritants, but it results in a decline in respiratory function in the long term. Indeed, inducible adaptive changes generally occur at the expense of many other physiological processes and therefore cannot be sustained without adverse side effects caused by the decline in the affected functions. For example, the acute-phase response and oedema both have adaptive values during bacterial infections but occur at the expense of the normal functioning of many tissues. The marked increase in plasma protein concentration that occurs during the acute-phase response alters the oncotic pressure, which has many potential adverse effects on the circulatory system, and oedema causes local hypoxia by increasing the

distance between parenchymal cells and capillaries. The potential for adverse effects is intrinsic to any adaptive changes, whether these changes occur at the cellular, tissue or organismal level.

Because any tissue malfunction is initiated by changes at the cellular level, I now discuss the cellular alterations that might be associated with the initiation of an inflammatory response.

Cell states

Any cell can be in one of four possible states: basal, stressed, apoptotic or necrotic. A cell is in a basal state when conditions are normal, and this state is maintained by the availability of nutrients, oxygen and growth factors, and by attachment to other cells and/or the ECM. A change in any of the vital internal environmental parameters (temperature, osmolarity, oxygen, and so on) induces a stress response, which is in essence a cellular adaptation to the abnormal condition. If the change in a parameter is greater than the stress response can handle, the cell undergoes apoptosis. If the change is greater still, the cell undergoes necrosis. Developmentally controlled apoptosis occurs for reasons unrelated to tissue maintenance and is not discussed here.

Each of the four cellular states is regulated by specialized signalling pathways. Recent evidence indicates that even necrosis, previously considered to be an accidental and unplanned form of cell death, is regulated by dedicated genetic programs[36]. Importantly, the pathways that induce or maintain each of the states are 'wired' so that they inhibit the transition to the next state, as shown by the following examples. The basal state can be maintained by a prototypical insulin-like growth factor 1 (IGF1)-dependent cell-survival pathway, which inhibits the generic stress response regulated by FOXO transcription factors[37]. The stress-inducible nuclear factor-κB pathway inhibits apoptosis by engaging multiple mechanisms[38]. The key effectors of apoptosis — caspase 3, caspase 6 and caspase 7 — cleave and inactivate PARP (which is involved in DNA repair), thereby blocking PARP-dependent necrosis[36] (which results from the depletion of cytosolic NAD, a substrate of PARP[36,39]). Thus, the more desirable cellular state (which in descending order is basal, stressed, apoptotic, then necrotic) inhibits the transition to the next, less desirable, state until the transition is unavoidable. This fundamental property of cell-fate decisions has two important implications. First, it ensures that the transition occurs in a switch-like manner rather than gradually. This is important because it enables the cells to exhaust their attempts to stay in a more preferable state before making the transition to the next, less preferable, state. Second, each cellular state can express distinct sets of signals that report the cellular state, and the switch-like transition prevents the generation of mixed messages.

The state of cells and tissues is probably monitored mainly by tissue-resident macrophages (and, in some tissues, also by mast cells). When tissues are in the basal state, tissue-resident macrophages maintain tissue homeostasis by a variety of tissue-specific mechanisms. Tissue-resident macrophages constitute 10–15% of most tissues, and their functions extend beyond host defence and the removal of apoptotic cells[40,41]. Examples are control of the turnover of epithelial cells, regulation of the metabolic activity of adipocytes and remodelling of bone (which is carried out by osteoclasts)[40,41]. When tissues are in conditions of stress, or when they malfunction for other reasons, they might send a different set of signals to tissue-resident macrophages than those sent by tissues in the basal state. The tissue-resident macrophages, in turn, produce increased amounts, or different sets, of growth factors and other signals that are relevant for the particular tissue. When the stress or malfunction is extreme, the help provided by local macrophages might be insufficient, and the tissues might 'call for' the recruitment of additional macrophages. Thus, malfunctioning adipocytes in obese animals secrete the chemokine CC-chemokine ligand 2 (CCL2), which recruits more macrophages to the adipose tissue[42]. Hypoxic tissues produce the chemokine CXC-chemokine ligand 12 (CXCL12), which can also recruit macrophages[43]. There are also many other cases in which macrophages are recruited in a tissue-specific or condition-specific manner[44]. Furthermore, tissue-derived signals can control the activation state and type of recruited macrophage[44,45]. The main purpose of these interactions is to help the tissues to adapt to the stressful conditions and to restore their functionality. However, when these interactions are sustained or excessive, they can become maladaptive, as is evident from macrophages that have been recruited to sites of inflammation contributing to insulin resistance in adipose tissue. Moreover, the accessory function of macrophages (assisting the adaptation of tissues to stress conditions) can be exploited by tumour cells, which can recruit macrophages and use them as a source of growth factors, angiogenic factors and chemokines. Several examples of such exploitation by tumour cells have been documented and shown to have a crucial role in tumour progression and metastasis[46].

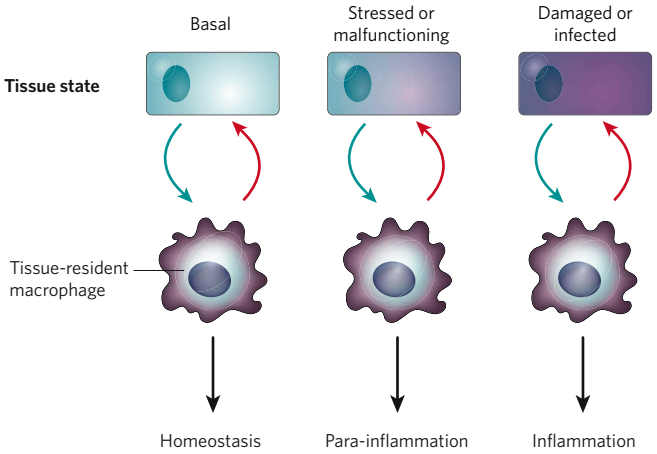

Figure 4 | Three modes of adaptation and maintenance of tissue homeostasis. The state of a tissue can range from basal, to stressed or malfunctioning, to damaged or infected, and each state is graded (as indicated by shading). The state affects the mode of maintenance of tissue homeostasis or adaptive response that is engaged by tissue-resident macrophages and, in some tissues, by other types of leukocyte. Blue arrows indicate signals that report the tissue state to macrophages; red arrows indicate macrophage-derived signals that control tissue adaptation. At one extreme of the range of responses is inflammation, which follows infection or tissue damage. By contrast, tissue stress or malfunction induces para-inflammation, which helps a tissue to adapt to the noxious conditions and restore tissue functionality. Dysregulated para-inflammation might be responsible for the chronic inflammatory states that are associated with many modern human diseases, such as type 2 diabetes and atherosclerosis.

If tissue malfunction or stress is excessive and adaptation is no longer possible, the cells die by apoptosis or necrosis. Infection and tissue injury are the most common contributors to this transition, but other insults also have this effect. These insults can be classified as 'inflammation inducers' (discussed earlier). In these cases, cell death is again monitored and interpreted by macrophages. In addition to the removal of apoptotic and necrotic cells, macrophages make one of several possible 'decisions', ranging from the silent removal of dead cells to the induction of an inflammatory response. Because necrotic cell death is generally associated with tissue damage, the outcome of necrotic-cell recognition by macrophages is usually an inflammatory response[17,36,47]. Apoptosis, by contrast, can occur for several reasons, and macrophages therefore need to be able to decipher the cause of death to take the appropriate actions. In this way, for each of the four (or more) situations in which apoptosis occurs, a different outcome is possible (Fig. 3).

First, during developmentally programmed apoptosis, dead cells are removed by macrophages without any additional consequences. Because this form of apoptosis is a normal part of development or cell turnover, no further action is needed (although in the case of cell turnover, macrophages might produce growth factors that promote cell proliferation, in order to replace dead cells).

Second, apoptosis induced by excessive stress or injury results in unscheduled cell loss, which needs to be compensated for by the generation of new cells of the same type. Therefore, on recognition of cells that have died prematurely, macrophages should (in general) induce a tissue-repair response.

Box 1 | Evolution of adaptive traits

Why is the inflammatory response closely associated with pathological conditions? To answer this question, it is worthwhile considering some basic principles of the evolution of adaptive traits[56].

It is often assumed that any given physiological process, as a product of evolution, has an adaptive value. However, some traits can evolve without being adaptive, owing to chance or constraints of an organism's history[57]. Similarly, evolution does not necessarily produce an optimal solution to every problem.

For the purpose of this discussion, it is useful to consider two situations. The first is that a particular characteristic (or a trait) can be adaptive (that is, beneficial) if it was selected for because it had a positive effect on the organism's fitness (and, ultimately, on the organism's reproductive success). It is important to note that such traits are adaptive in the conditions that were present when they evolved. If these conditions change sufficiently, the same traits can be maladaptive. Obesity and allergy are examples of maladaptive traits. The second situation is that a trait can be non-adaptive when it exists as a consequence of another (adaptive) trait but has no positive value of its own. Anaphylactic shock and tissue destruction by activated neutrophils are examples of non-adaptive traits. These non-adaptive traits were not selected for, because they are either neutral or detrimental with respect to an organism's fitness (in the conditions in which they evolved) but exist as an unavoidable consequence of an adaptive trait. The second situation is common and constitutes an evolutionary trade-off between the beneficial effects of adaptive traits and the detrimental effects of non-adaptive traits with which they are coupled. In the conditions in which the traits evolved, the beneficial effects must have outweighed the detrimental effects. But, again, a change in conditions can shift the balance in this trade-off, making the non-adaptive traits a substantial burden to the organism. This situation is particularly characteristic of young species, such as humans, that have not yet reached an evolutionary equilibrium. Many modern human diseases are the result of unbalanced trade-offs caused by marked changes in environmental conditions and lifestyles.

When considering the inflammatory process, there are many examples of adaptive and non-adaptive traits. However, for many chronic inflammatory processes, only the pathological (maladaptive) aspects are evident, and there is no understanding of their physiological (adaptive) counterparts, which are presumed to exist. Distinguishing between adaptive and non-adaptive characteristics is essential not only for gaining a deeper understanding of inflammation but also for developing efficient therapeutic strategies. For example, both adaptive and non-adaptive processes can contribute to disease symptoms (owing to inherent trade-offs), but interfering with the adaptive processes can, ultimately, make matters worse, whereas blocking the non-adaptive processes should be beneficial and should not cause adverse side effects.

Third, apoptosis induced by infection (including the caspase-1-dependent process, known as pyroptosis[48]) should switch the macrophages to a host-defence mode, thereby promoting the generation of an immune response.

Fourth, apoptosis induced by inflammatory or immune responses should have the opposite effect to infection-induced apoptosis. The recognition of apoptotic cells by macrophages, in this case, should result in the induction of anti-inflammatory and immunosuppressive pathways. This is exemplified by the recently described anti-inflammatory pathway controlled by the TAM family of receptor tyrosine kinases[49].

Macrophages recognize all apoptotic cells (regardless of how apoptosis is induced) by detecting phosphatidylserine at the surface of these cells[50,51]. The outcome of the various forms of apoptosis is probably determined, however, by additional signals, which are likely to be differentially produced by apoptotic cells that have died from different causes.

Para-inflammation

Cell states are discrete rather than graded, and transitions between these states occur in an all-or-none manner (as discussed earlier). By contrast, tissue states are graded: tissues can contain different numbers of dead cells, for example, or they can malfunction to different degrees. Accordingly, the adaptive response elicited by the tissues can take different forms depending on the degree of the problem that is experienced. Thus, in basal conditions, the tissues are maintained in a homeostatic state, in many cases with the help of the tissue-resident macrophages. In noxious conditions, tissues undergo stress and can malfunction. If the changes are considerable, then adaptation to the conditions requires the help of tissue-resident or recruited macrophages and might require small-scale delivery of additional leukocytes and plasma proteins, depending on the extent of the problem. This adaptive response has characteristics that are intermediate between basal and inflammatory states. It could be termed para-inflammation (*para-* being the Greek prefix for near).

Para-inflammatory responses are graded: at one extreme, they are close to the basal state, whereas, at the other, they start to transition into inflammation (Fig. 4). The induction of a para-inflammatory response does not require overt tissue injury or infection; instead, it is switched on by tissue malfunction, in order to restore tissue functionality and homeostasis. If tissue malfunction is present for a sustained period, para-inflammation can become chronic. Sustained malfunction can result from mutations or environmental factors. It can also be caused by the maladaptive traits that are responsible for modern human diseases (Box 1). Indeed, many chronic inflammatory diseases that are not caused by infection or injury seem to be associated with conditions that were not present during the early evolution of humans, including the continuous availability of high-calorie nutrients, a low level of physical activity, exposure to toxic compounds, and old age. The human diseases that are associated with these conditions — including obesity, type 2 diabetes, atherosclerosis, asthma and neurodegenerative diseases — are all characterized by chronic low-grade inflammation (para-inflammation), which might not have any physiological counterparts. Furthermore, the chronic para-inflammation that persists in these conditions can, in turn, contribute to further disease progression, in part because of changes in homeostatic set points (such as insulin sensitivity or blood pressure).

The inflammatory range proposed here is consistent with inflammation having a general physiological role in maintaining tissue homeostasis, monitoring tissue malfunction, and promoting adaptation to adverse conditions and dysfunctional states that the tissues cannot resolve by themselves. This idea is in accordance with the fact that many inflammatory mediators (including TNF-α, IL-6, CCL2 and prostaglandins) also have important homeostatic functions, for example in repair of tissues, control of metabolism, and regulation of the hypothalamus–pituitary axis[52–54]. Thus, inflammatory processes can extend the homeostatic capacity of the organism and complement the homeostatic controls provided by the endocrine system and the autonomic nervous system.

Conclusions

Inflammation is exceedingly complex and equally fascinating. It has a crucial role in mammalian physiology. Many components of the inflammatory response have been found in all vertebrates studied so far, and some forms of adaptive response to adverse conditions (including infection and injury) occur in all animals and plants. However, the complexity of vertebrates — which are characterized by having multiple renewable tissues — perhaps necessitated the development of a specialized adaptive and protective capacity that is provided by the inflammatory response.

This invention came at a price, however. The pathological potential of inflammation is unprecedented for a physiological process[55]. Although the destructive ability of infection-induced inflammation is understandably unavoidable, the pathogenic capacity of other types of inflammation is puzzling. A major unresolved problem is defining the normal physiological counterpart of the systemic chronic inflammatory state. The idea of para-inflammation might provide part of the answer. In a broader context, it will be necessary to understand better which pathological aspects of inflammation are the results of trade-offs with beneficial traits and which are maladaptive for other reasons. ■

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