A guiding map for inflammation

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Biologists, physicians and immunologists have contributed to the understanding of the cellular participants and biological pathways involved in inflammation. Here, we provide a general guide to the cellular and humoral contributors to inflammation as well as to the pathways that characterize inflammation in specific organs and tissues.

Inflammation is viewed as the driving factor in many diseases, including atherosclerosis, cancer, autoimmunity and infections[1], and it is a major contributor to age-related conditions[2]. The classical definition of inflammation—comprising *rubor* (redness), *calor* (warmth), *dolor* (pain) and *tumor* (swelling), as described by Celsus (30 BC–38 AD), and *functio laesa* (loss of function), as added by Galen (129–210 AD)—has persisted in modern times. Functionally, inflammation is broadly defined as a protective response of the organism to stimulation by invading pathogens or endogenous signals such as damaged cells, thus resulting in the elimination of the initial cause of injury, the clearance of necrotic cells and tissue repair. However, owing to the complex and often simultaneous molecular, immunological and physiological processes involved in the inflammatory response, clearly defining inflammation presents a challenge. Here, we provide a guide to the sequence of events initiated during inflammation (**Fig. 1**) and the main mechanisms leading to the resolution of inflammation (**Fig. 2**), and we include an overview of the most important characteristics of the inflammatory process in various tissues and diseases (**Table 1**).

Basic elements of inflammation

Inflammation is induced when host cells sense evolutionarily conserved structures on pathogens (pathogen-associated molecular patterns) or endogenous stress signals (danger-associated molecular patterns) through germline-encoded pattern-recognition receptors (PRRs)[3]. PRRs are mainly expressed by myeloid cells, such as monocytes, macrophages, neutrophils and dendritic cells, but are also expressed by lymphocytes, fibroblasts and epithelial cells[4]. Cellular stimulation triggers inflammatory processes through the release of proinflammatory cytokines and chemokines. The cytokines TNF and IL-1β have autocrine and paracrine effects leading to the local activation of macrophages and neutrophils, but when these cytokines are released in large amounts, they can exert endocrine effects, such as induction of acute-phase proteins in the liver, platelet activation, fever, fatigue and anorexia. Cytokines activate endothelial cells, thus increasing vascular permeability and facilitating entrance of immune cells into tissues at the site of infection, but they can also lead to capillary leakage, vasodilation and hypotension[5,6] (**Fig. 1**). The main function of chemokines is to recruit additional immune cells to the site of infection[7]; these cells include neutrophils, which exert a crucial role in the phagocytosis and killing of pathogens[8,9]. The cytokine IFN-γ, derived from type 1 helper T cells (T_H1 cells), activates neutrophils, whereas the cytokine IL-22, derived from IL-17-producing helper T cells (T_H17 cells) and innate lymphoid cells, acts on epithelial cells and subsequently stimulates the production and release of antimicrobial peptides, including defensins[10].

In the bloodstream, activated monocytes and neutrophils release cytokines, which in turn stimulate the release of prostaglandins, molecules that mediate the signs and symptoms of illness (somnolence, fatigue and fever) by acting on the hypothalamus[11]. An important aspect of mediators of inflammation in the circulation is the activation of the complement system, which mediates microbial opsonization and killing, and generates inflammatory peptides such as C3a and C5a[12].

Basic elements of resolution

Mechanisms that shut down the inflammatory response have paramount importance in the return to homeostasis (**Fig. 2**). Resolution is not simply the elimination of the stressing agent but instead is an active process involving functional reprogramming of cells through *ad hoc* production of mediators. Several mechanisms inhibit inflammation. The cytokine IL-10 suppresses the production of proinflammatory cytokines[13] and is mainly derived from regulatory T cells. IL-37, a member of the IL-1 family, broadly suppresses inflammation, as does the cytokine TGF-β, which is released from monocytes and platelets[14]. Cleaved extracellular domains of cytokine receptors, such as soluble TNFR and IL-1R, serve as decoy receptors and limit inflammation by binding and neutralizing their respective cytokines. Receptor antagonists, such as IL-1Ra, bind IL-1R without inducing an intracellular signal, thus inhibiting the biological activity of the interleukins IL-1α and IL-1β (ref. 15). Complement inhibitors also modulate inflammation[16], and prostaglandins and lipid mediators such as resolvins

A full list of affiliations can be found at the end of the paper.

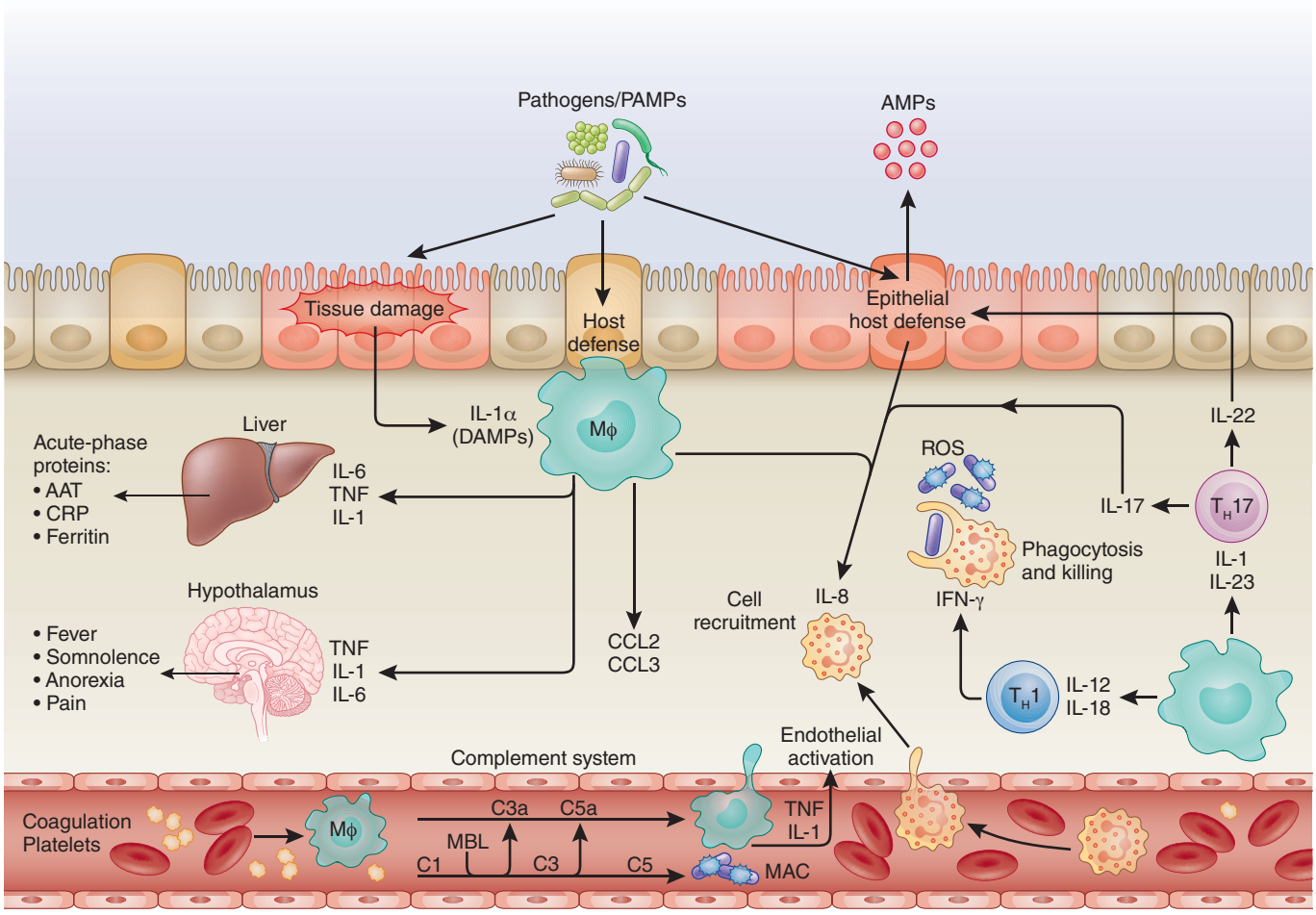

Figure 1 The immunological mechanisms leading to the induction of inflammation during the first stages of host defense against invading pathogens. AAT, a1-antitrypsin; PAMPs, pathogen-associated molecular patterns; AMPs, antimicrobial peptides; DAMPs, danger-associated molecular patterns; MAC, membrane attack complex; ROS, reactive oxygen species; CRP, C-reactive protein; MBL, mannose-binding lectin; Mϕ, macrophage or monocyte; CCL, C-C-motif chemokine ligand.

exert negative feedback loops by suppressing the transcription and release of cytokines. Acute-phase proteins induced during inflammation, such as α-1 antitrypsin, have broad anti-inflammatory properties[17]. Additional anti-inflammatory mechanisms involve stress hormones, particularly corticosteroids and catecholamines; negative regulators of Toll-like-receptor signaling, such as IRAK-M and A20; and microRNAs, such as miR-146 or miR-125. Neuroimmunoregulatory mechanisms (the so-called immunological reflex) provide anti-inflammatory negative feedback, which is triggered by peripheral sensory input transmitted through the afferent vagus nerve to the brainstem and is followed by activation of the efferent vagus and splenic nerve[18], release of norepinephrine in the spleen and secretion of acetylcholine by a subset of $CD4^+$ T cells, thereby inhibiting production of proinflammatory cytokines by macrophages. However, an anti-inflammatory response that is too pronounced or persistent may render the host vulnerable to secondary infections[19].

Here, we provide an up-to-date guide to inflammation and summarize the main features of acute or chronic inflammation in specific human diseases (**Table 1**).

Sepsis

In sepsis, the release of danger-associated molecular patterns or alarmins from injured host cells activates PRRs, which also recognize pathogen-associated molecular patterns, thus giving rise to a vicious cycle of sustained hyperinflammation[20]. However, an ineffective antimicrobial host defense often accompanies this condition. Proinflammatory cytokines produced after recognition of the invading pathogens by PRRs[21] can help protect the host but also can promote tissue injury during overwhelming sepsis. Unrestrained activation of complement contributes to organ failure, and C5a blockade improves the outcome of experimental sepsis. Local activation of the coagulation system in sepsis helps to confine pathogens to the primary site of infection, whereas systemic activation may result in disseminated intravascular coagulation, microvascular thrombosis and bleeding[22] (**Table 1**). Enhanced adherence of leukocytes and platelets to the endothelial surface, and subsequent transmigration, results in vascular inflammation and disruption of the endothelial-cell barrier, thus causing leakage of intravascular proteins into the extravascular space, tissue edema and decreased microvascular perfusion. When severe, these abnormalities may lead to organ dysfunction and even death[23].

Acute intestinal inflammation

Acute intestinal inflammation is protective by eliminating infectious, toxic and other injurious agents, while initiating the process of repair. Chronic inflammation in the gastrointestinal tract results from repeated acute injury and/or impaired resolution of inflammation, thus leading to conditions such as chronic gastritis and peptic ulcer disease, chronic pancreatitis,

celiac disease and inflammatory bowel disease. In Crohn's disease and ulcerative colitis, although the precise etiology is unknown, treatment aims to dampen inflammation and its consequences[24]. Corticosteroids decrease inflammatory flares but in most cases do not maintain remission. Immunosuppressants are also effective but do not represent a definitive cure. Such immunosuppressants include azathioprine and methotrexate, monoclonal antibodies against TNF, IL-12 or IL-23, and monoclonal antibodies against $\alpha_4\beta_7$ integrin, a protein complex that promotes leukocyte trafficking specifically into the gastrointestinal tract.

Rheumatoid arthritis

Rheumatoid arthritis, an autoimmune disease involving severe joint inflammation, cartilage and bone destruction, is strongly associated with the presence of autoantibodies, such as rheumatoid factor and anti-citrullinated-peptide antibodies[25]. Monocytes, neutrophils, macrophages and dendritic cells promote chronic joint inflammation. Proinflammatory cytokines produced by these cells, such as TNF, IL-1β, IL-6, IL-12, IL-18 and IL-23, promote the generation of pathogenic B and T cells. IFN-γ^+IL-17$^+$CD4$^+$ T cells mediate destruction of cartilage and bone[26]. IL-1β and IL-23 expand these IFN-γ^+IL-17$^+$ IL-22$^+$ T_H17 cells[27]. IL-1β and IL-17A induce destruction of cartilage and bone, the latter through the activation of osteoclasts by the cytokine RANKL (**Table 1**). Anti-TNF monoclonal antibodies or IL-1Ra, anti-IL-6R, anti-IL-12p40 or anti-IL-17A can treat rheumatoid arthritis[26]. Small-molecule inhibitors of the Jak–STAT signaling pathway downstream of inflammatory-cytokine receptors have shown efficacy in subsets of patients.

Atherosclerosis

Atherosclerosis is characterized by a strong activation of endothelial cells in the inner lining of the arterial lumen; these cells recruit monocytes via the expression of adhesion molecules. Monocytes mature into macrophages that replicate[28] and engulf modified lipoprotein particles, thus forming inflammatory foamy macrophages. Excessive deposition of cholesterol in the subintimal space can cause precipitation of cholesterol crystals, which trigger the NLRP3 inflammasome and consequently the release of active IL-1β (ref. 29) (**Table 1**). Cells mediating the adaptive immune response, including T and B cells, also enter the arterial wall during atherogenesis, where they regulate pathogenic functions of innate immune cells in the plaque[30]. In clinical practice, biomarkers of inflammation, such as high-sensitivity C-reactive protein, indicate vascular inflammation. Statins (inhibitors of HMG-CoA reductase, an enzyme involved in cholesterol synthesis) have proven remarkably successful in preventing first and recurrent cardiovascular events and in decreasing levels of both cholesterol and high-sensitivity C-reactive protein. Clinical trials are currently evaluating whether anti-inflammatory agents such as low-dose methotrexate and canakinumab (a monoclonal antibody targeting IL-1β) could prevent atherosclerotic events.

Neurodegenerative diseases

Innate immunological mechanisms are emerging as crucial components of normal brain aging as well as major contributors to neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis[31,32]. Several mutations in genes encoding immune proteins increase the risk of developing Alzheimer's disease (*TREM2*, *CD33* and *PLCG2*), amyotrophic lateral sclerosis (*C9orf72*, *TBK1* and *CHCHD10*) and Parkinson's disease (*LRRK2*) (**Table 1**). Activation of microglia in response to β-sheet-structured proteins, misfolded proteins, neuronal debris or aberrant nucleic acids[33] triggers neuronal dysfunction, structural damage and ultimately cell death. β-amyloid fibrils, a major pathological hallmark of Alzheimer's disease, induce the activation of the NLRP3 inflammasome and the generation of IL-1β in microglia through activation of various PRRs[34]. Microglia express receptors for neurotransmitters and neurotrophins in a brain-region-specific manner. Norepinephrine and acetylcholine suppress excess inflammation in the brain[35].

Liver diseases

Mediators of inflammation, particularly cytokines such as IL-1 family cytokines, IL-6 and TNF, are associated with acute liver failure, the hepatic acute-phase response, steatosis, cholestasis, hypergammaglobulinemia and the development of fibrosis[36]. In acute injury, hepatic inflammatory cytokines induce necrosis of hepatocytes but also mediate hepatocyte regeneration. Hepatocyte necrosis releases IL-1α, which recruits bone-marrow-derived monocytes and macrophages. Macrophages are also rapidly recruited from the peritoneum, and they appear to have protective effects. Fibrosis and the release of TGF-β play crucial roles in chronic liver disease. Alcoholic and nonalcoholic fatty liver disease are characterized by sterile inflammation with massive lipid accumulation. Anti-inflammatory strategies have not yet been adequately developed in the management of these disorders.

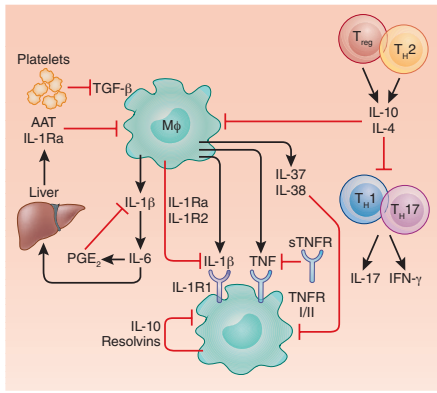

Figure 2 The regulatory mechanisms that modulate inflammation and lead to resolution after the elimination of invading pathogens. AAT, a1-antitrypsin; IL-1R1 and IL-1R2, IL-1R type I and type II, respectively; sTNFR, soluble TNFR; TNFR I/II, TNFR types I and II; PGE_2, prostaglandin E2; Mϕ, macrophage or monocyte; T_{reg}, regulatory T cell.

Diabetes

Type I diabetes (10% of people with diabetes) is caused by immunologically mediated selective beta-cell destruction triggered by unknown environmental factors in individuals with a polygenetic predisposition. Inflammation plays a crucial role in this process, whose first step—the appearance of inflammatory macrophages and proinflammatory cytokines, particularly IL-1β and TNF, in the islet-cell infiltrate—contributes to beta-cell toxicity. Subsequently, a lymphocytic infiltrate develops, including populations of CD8$^+$ and CD4$^+$ T cells displaying autoreactivity against specific islet antigenic peptides. The T cells are often accompanied by an influx of CD20$^+$ B cells. Despite the promising initial results found in small studies, the use of antagonists of IL-1 or TNF to improve insulin secretion in people with new-onset type I diabetes has not been successful in phase II trials[37,38]. Type II diabetes (T2D; 90% of cases) is characterized by defective insulin secretion as well as a decreased response to insulin. IL-1β-driven inflammation plays an important role in the beta-cell loss in T2D. Insulin resistance in T2D is also due to inflammation of liver and fat tissues through general inflammatory pathways as described above, and activation of the IL-1β–inflammasome pathway plays a crucial role (**Table 1**). Clinical trials using IL-1Ra, antibodies to IL-1β and salsalate[39,40] have offered a proof of concept of a beneficial effect of dampening inflammation in T2D.

Lung disease

Innate inflammation and adaptive immunity are essential to lung defense; however, if unchecked, they result in lung disease. Air pollutants with inflammatory effects, including

Table 1 Specific characteristics of inflammation in various tissues and diseases

Disease/tissue	Main characteristics of inflammation	Main pathways/markers	Specific complications	Immunotherapy
Sepsis	• Exaggerated inflammation and inappropriate endothelial activation combined with immunoparalysis	• Increased cytokines/acute-phase proteins • Activation of complement, coagulation and endothelial cells	• Septic shock • Multiple-organ failure • Opportunistic infections	• Personalized immunotherapy: in hyperinflammation, IL-1Ra, anti-C5a; in immunoparalysis, rIFN-γ, GM-CSF, anti-PD1, rIL7
Inflammation of the gastrointestinal tract	• Permanent structural and functional alterations • Ulcers, strictures, fistulas • Disturbed motility and barrier function	• Increased circulating cytokines and acute-phase proteins • Decreased neutrophil function	• Peptic ulcer disease • Chronic pancreatitis • Celiac disease • Crohn's disease • Ulcerative colitis	• Corticosteroids • Antibodies to TNF, IL-12, IL-23 or integrin $\alpha_4\beta_7$
Rheumatoid arthritis	• Autoantibodies/immune complexes • Proinflammatory cytokines • Macrophage influx • Pathogenic T and B cells	• TNF, IL-1β, IL-6, IL-12, IL-18 and IL-23 • IFN-γ^+IL-17^+IL-22^+ T_H17 cells • RANKL • Anti–citrullinated peptides	• Joint inflammation • Cartilage destruction	• Anti-TNF, IL-1Ra, Anti-IL-6R, Anti-IL-12p40, Anti-IL-17A • JAK–STAT inhibitors
Atherosclerosis	• Dyslipidemia and cholesterol deposition • Monocyte and lymphocyte influx in intima • Activation of inflammasomes and cytokines	• Inflammasome and cytokines • hsCRP	• Angina pectoris • Acute myocardial infarction • Stroke	• Statins, including methotrexate and anti-IL-1β (canakinumab) currently in trials
Neurodegenerative diseases	• Peripheral infection/inflammation–induced activation of microglial cells • β-amyloid fibrils	• *TREM2*, *CD33*, *PLCG2* • *LRRK2*, *C9orf72*, *TBK1*, *CHCHD10* • Activation of inflammasomes and IL-1β	• Alzheimer's disease • Parkinson's disease • Amyotrophic lateral sclerosis	• Not yet available
Liver disease	• Acute liver failure • Hepatic acute-phase response • Steatosis • Cholestasis, hypergammaglobulinemia, fibrosis	• IL-1α and other proinflammatory cytokines • TGF-β for fibrosis	• Acute and chronic hepatitis • Nonalcoholic fatty liver disease • Cirrhosis	• Not yet available
Diabetes	• Infiltration of pancreatic islets with innate and adaptive immune cells and beta-cell apoptosis in T1D • Low-grade innate inflammation in adipose tissue, liver and islets; insulin resistance and beta-cell apoptosis in T2D	• Proinflammatory cytokines IL-1β and TNF • In T1D, also T cell–mediated beta-cell killing	•Macrovascular complications (myocardial infarction, stroke, claudication) •Microvascular complications (kidney, ocular, neuronal)	• Anti-IL-1 (anakinra, canakinumab) • Anti-TNF
Lung disease	• Inflammation and hyper-reactivity • Fibrosis	• T_H2 and IL-4/IL-5/IL-13 allergic responses (asthma) •Polymorphonuclear leukocyte and macrophage infiltrate, cytokines (COPD) • TGF, integrin $a_v\beta_6$, platelet-derived growth factor β (idiopathic pulmonary fibrosis)	• Asthma • COPD • Idiopathic pulmonary fibrosis	• Corticosteroids • Anti-IL5
Chronic kidney disease	• Low-grade inflammation	• NLRP3 inflammasome, IL1β, IL-6, PGE2, TGF-β	• Kidney insufficiency	• IL-1Ra (anakinra) • IL-1 soluble receptor (rilonacept)
Inflammatory skin diseases	• Inflammation with exaggerated T_H2 (Alzheimer's disease) or T_H17 (psoriasis) • Inflammation in apocrine glands (HS)	• T_H17, T_H2, antimicrobial peptides • T_H2, filaggrin • IL-1β and TNF (HS)	• Psoriasis • Atopic dermatitis • HS	• Antibodies to TNF, IL-17, IL-17R, IL-23 (psoriasis) • Anti-TNF and anti-IL-1 (HS)
Autoinflammatory syndromes (e.g., deficiency of IL-1Ra, FMF, HIDS, cryopyrin-associated periodic syndrome)	• Sterile inflammation in joints and peritoneum, fever, systemic inflammation	• Inflammasome/IL-1β pathway IL-1/IL-1Ra balance • NF-κB perturbations • Type I IFN production	• Amyloid deposition (FMF)	• Anti-IL-1 therapies (anakinra, canakinumab, gevokizumab, rilonacept) • TNF inhibitors • JAK–STAT inhibitors
Cancer-related inflammation	• Infiltration of tumor-associated macrophages with strong immunosuppressive activity	• M2 macrophage phenotype • Checkpoint proteins PD-1, PD-L1 and CTLA-4 • IL-1β, IL-6, TNF, IL-4, IL-10 and TGF-b • Pentraxin-3	• T cell exhaustion and anergy • Tumor progression	• Checkpoint blockade: antibodies to PD-1, PD-L1 and CTLA-4 • Immunostimulatory: BCG, muramyl dipeptide (mifamurtide), β-glucan

FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D and periodic fever syndrome; HS, hidradenitis suppurativa; hsCRP, high-sensitivity C-reactive protein; T1D, type I diabetes; COPD, chronic obstructive pulmonary disease; BCG, *Mycobacterium bovis* bacillus Calmette–Guerin; GM-CSF, granulocyte-macrophage colony-stimulating factor; r, recombinant.

endotoxin, can exacerbate asthma but can also initiate the disease. Whereas IL-4 and dendritic cells promote inflammation mediated by type 2 helper T cells (T_H2 cells), airway epithelia produce IL-1α, IL-1β, IL-25, IL-33 and thymic stromal lymphopoetin, each of which recruits and activates ILC2 cells, eosinophils and basophils, thereby enhancing inflammation and remodeling of the airway[41]. The cytokines IL-4 and IL-13 contribute to the interaction between innate and adaptive immunological mechanisms that promote inflammatory airway disease. IL-5 promotes differentiation and activation of eosinophils, and clinical trials targeting the IL-5 pathway by blocking the cytokine or its receptor in asthma have indicated benefits in people with high T_H2 profiles.

Chronic kidney disease

Chronic kidney disease is a low-grade inflammatory process. Inflammatory macrophages infiltrate the kidney and induce the release of proinflammatory cytokines and mediators such as IL-1β, TNF, IL-6, IL-23, reactive oxygen species, nitric oxide and inducible nitric oxide synthase. Cytokines such as TNF or TGF-β1 produced locally during kidney inflammation decrease kidney expression of the nephroprotective proteins Klotho and PGC-1α and lead to suboptimal induction of these proteins. Circulating IL-1β, IL-1Ra, IL-6 and C-reactive protein are elevated in people with advanced stages of chronic kidney disease[42], thus predicting a decline in kidney function[43]. IL-1β contributes to tubular interstitial fibrosis, promotes tubular epithelial–myofibroblast transdifferentiation, cytokine gene expression, production of prostaglandin E2 by mesangial cells and interstitial fibrosis mediated by TGF-β (ref. 44). Treatment with the IL-1 soluble receptor trap (rilonacept) decreases concentrations of C-reactive protein, improves dilation mediated by brachial artery flow and decreases vascular oxidative stress in people with chronic kidney disease[45].

Inflammatory skin diseases

In atopic dermatitis, penetration of external stimuli (for example, allergens) through an impaired skin barrier leads to an exaggerated T_H2 response[46]. Local immunological imbalance causes further skin-barrier deterioration as IL-4 and IL-13 downregulate the expression of major skin-barrier genes such as filaggrins, thus leading to a vicious circle. In psoriasis, a T cell–driven disease with contributions of innate and adaptive immunity, inflammation is driven by signaling through NF-κB and T_H17- and T_H1-type cytokines, and therapies targeting TNF, IL-12/IL-23 and IL-17 have been found to be effective (**Table 1**). Psoriasis involves systemic inflammatory responses, and frequent comorbidities are rheumatological or cardiovascular in nature[47]. In hidradenitis suppurativa, also known as acne inversa, a devastating skin disorder bearing characteristics of both autoinflammatory and autoimmune disorders, histopathology reveals heavy lesional deposits of TNF, IL-1β, IL-23 and IL-17, as well as activation of both $CD4^+$ and $CD8^+$ T cells[48].

Autoinflammatory syndromes

Autoinflammatory syndromes can be defined as disorders with abnormally increased inflammation, which are mediated predominantly by the cells and molecules of the innate immune system, with a substantial host predisposition. The enhanced inflammatory state encompasses the production of proinflammatory pyrogenic cytokines, particularly IL-1β, and hence fever and acute-phase responses are common prominent signs. From a theoretical viewpoint, autoinflammatory syndromes result from excessive production and/or biological activity of inflammatory mediators, or from a lack of endogenous inhibition. The prototypical condition associated with the latter is deficiency of IL-1Ra, in which a lack of inhibition of IL-1 bioactivity leads to excessive inflammation[49]. Other important syndromes are familial Mediterranean fever, cryopyrinopathies, and hyperimmunoglobulinemia D and periodic fever syndrome. An exaggerated IL-1β response is a hallmark of many autoinflammatory disorders, for which interference with IL-1 action is the preferred therapy[50].

Cancer

All the usual components of the inflammatory response reside in the tumor microenvironment but often exhibit 'corrupted' functions. Cancer-related inflammation is a key component of the tumor microenvironment[51,52] and includes inflammatory cells, especially tumor-associated macrophages, which affect all aspects of cancer including growth, genetic instability, angiogenesis and metastasis[53]. Tumor-associated macrophages contribute to cancer immunosuppression by producing prostaglandins, products of tryptophan metabolism, and by expressing checkpoint-blockade triggers (such as PD-L1). T and B cells, neutrophils, mast cells and eosinophils are also cellular components of cancer-related inflammation. Inflammatory cytokines such as TNF, IL-6 and IL-1 are important mediators of intercellular communication in cancer-related inflammation, along with many other members of the chemokine family[51,52]. The humoral arm of innate immunity also participates in cancer-related inflammation. Pentraxin-3, a fluid-phase PRR, interacts with complement components and functions downstream of IL-1 in mouse models of carcinogenesis (**Table 1**). The type of inflammatory reaction determines the clinical severity of cancer. T cell–driven inflammation, characterized by an interferon signature, is associated with a better prognosis[54], whereas high macrophage infiltration is generally associated with poorer prognosis, especially when markers of type 2 polarization are considered[53].

Conclusions and future perspectives

The heterogeneous nature of the inflammatory response depends on the type of disease and the organ in which it occurs, and inflammation can have both protective effects and collateral deleterious consequences for the host. The examples of successful therapies targeting inflammation underscore the importance of understanding inflammatory pathways to enable further therapeutic advances.

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