

Inflammatory responses and inflammation-associated diseases in organs

Linlin Chen^{1,*}, Huidan Deng^{1,*}, Hengmin Cui^{1,2}, Jing Fang^{1,2}, Zhicai Zuo^{1,2}, Junliang Deng^{1,2}, Yinglun Li^{1,2}, Xun Wang^{1,2} and Ling Zhao^{1,2}

¹College of Veterinary Medicine, Sichuan Agricultural University, Wenjiang, Chengdu 611130, China

²Key Laboratory of Animal Diseases and Environmental Hazards of Sichuan Province, Sichuan Agriculture University, Wenjiang, Chengdu 611130, China

*These authors contributed equally to this work

Correspondence to: Hengmin Cui, **email:** cui580420@sicau.edu.cn

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ABSTRACT

Inflammation is a biological response of the immune system that can be triggered by a variety of factors, including pathogens, damaged cells and toxic compounds. These factors may induce acute and/or chronic inflammatory responses in the heart, pancreas, liver, kidney, lung, brain, intestinal tract and reproductive system, potentially leading to tissue damage or disease. Both infectious and non-infectious agents and cell damage activate inflammatory cells and trigger inflammatory signaling pathways, most commonly the NF- κ B, MAPK, and JAK-STAT pathways. Here, we review inflammatory responses within organs, focusing on the etiology of inflammation, inflammatory response mechanisms, resolution of inflammation, and organ-specific inflammatory responses.

INTRODUCTION

Inflammation is the immune system's response to harmful stimuli, such as pathogens, damaged cells, toxic compounds, or irradiation [1], and acts by removing injurious stimuli and initiating the healing process [2]. Inflammation is therefore a defense mechanism that is vital to health [3]. Usually, during acute inflammatory responses, cellular and molecular events and interactions efficiently minimize impending injury or infection. This mitigation process contributes to restoration of tissue homeostasis and resolution of the acute inflammation. However, uncontrolled acute inflammation may become chronic, contributing to a variety of chronic inflammatory diseases [4].

At the tissue level, inflammation is characterized by redness, swelling, heat, pain, and loss of tissue function, which result from local immune, vascular and inflammatory cell responses to infection or injury [5]. Important microcirculatory events that occur during the inflammatory process include vascular permeability changes, leukocyte recruitment and accumulation, and inflammatory mediator release [2, 6].

Various pathogenic factors, such as infection, tissue injury, or cardiac infarction, can induce inflammation by causing tissue damage. The etiologies of inflammation can be infectious or non-infectious (Table 1). In response to tissue injury, the body initiates a chemical signaling cascade that stimulates responses aimed at healing affected tissues. These signals activate leukocyte chemotaxis from the general circulation to sites of damage. These activated leukocytes produce cytokines that induce inflammatory responses [7].

INFLAMMATORY RESPONSE MECHANISMS

The inflammatory response is the coordinate activation of signaling pathways that regulate inflammatory mediator levels in resident tissue cells and inflammatory cells recruited from the blood [8]. Inflammation is a common pathogenesis of many chronic diseases, including cardiovascular and bowel diseases, diabetes, arthritis, and cancer [9]. Although inflammatory response processes depend on the precise nature of the initial stimulus and its location in the body, they all

Table 1: Etiology of inflammation

Non-infectious factors	Infectious factors
Physical: burn, frostbite, physical injury, foreign bodies, trauma, ionizing radiation	Bacteria
Chemical: glucose, fatty acids, toxins, alcohol, chemical irritants (including fluoride, nickel and other trace elements)	viruses
Biological: damaged cells	other microorganisms
Psychological: excitement	

share a common mechanism, which can be summarized as follows: 1) cell surface pattern receptors recognize detrimental stimuli; 2) inflammatory pathways are activated; 3) inflammatory markers are released; and 4) inflammatory cells are recruited.

Pattern recognition receptor activation

Microbial structures known as pathogen-associated molecular patterns (PAMPs) can trigger the inflammatory response through activation of germline-encoded pattern-recognition receptors (PRRs) expressed in both immune and nonimmune cells [10, 11]. Some PRRs also recognize various endogenous signals activated during tissue or cell damage and are known as danger-associated molecular patterns (DAMPs) [11]. DAMPs are host biomolecules that can initiate and perpetuate a non-infectious inflammatory response [12]. Disrupted cells can also recruit innate inflammatory cells in the absence of pathogens by releasing DAMPs [13].

Classes of PRR families include the Toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and NOD-like receptors (NLRs) [5]. TLRs are a family of highly conserved, mammalian PRRs that participate in the activation of the inflammatory response [14]. More than ten members of the TLR family have been identified, and TLRs are the most well-studied of the known PRRs [15]. Transmission of PAMPs and DAMPs is mediated by myeloid differentiation factor-88 (MyD88) along with TLRs. Signaling through TLRs activates an intracellular signaling cascade [16, 17] that leads to nuclear translocation of transcription factors, such as activator protein-1 (AP-1) and NF- κ B or interferon regulatory factor 3 (IRF3) (Figure 1). DAMPs and PAMPs share receptors, such as TLR4, suggesting similarities between infectious and noninfectious inflammatory responses [18, 19].

Activation of inflammatory pathways

Inflammatory pathways impact the pathogenesis of a number of chronic diseases, and involve common inflammatory mediators and regulatory pathways. Inflammatory stimuli activate intracellular signaling pathways that then activate production of inflammatory

mediators. Primary inflammatory stimuli, including microbial products and cytokines such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α), mediate inflammation through interaction with the TLRs, IL-1 receptor (IL-1R), IL-6 receptor (IL-6R), and the TNF receptor (TNFR) [20]. Receptor activation triggers important intracellular signaling pathways, including the mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF- κ B), and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways [21–23].

NF- κ B pathway

The NF- κ B transcription factor plays important roles in inflammatory, immune response, survival, and apoptosis processes [24]. The NF- κ B family includes five related transcription factors: P50, p52, RelA (p65), RelB, and c-Rel [25, 26]. NF- κ B activity is induced by a range of stimuli, including pathogen-derived substances, intercellular inflammatory cytokines, and many enzymes [27, 28]. Under physiological conditions, I κ B proteins present in the cytoplasm inhibit NF- κ B [29]. PRRs use similar signal transduction mechanisms to activate I κ B kinase (IKK), which is composed of two kinase subunits, IKK α and IKK β , and a regulatory subunit, such as IKK γ . IKK regulates NF- κ B pathway activation through I κ B phosphorylation [8]. I κ B phosphorylation results in its degradation by the proteasome and the subsequent release of NF- κ B for nuclear translocation and gene transcription activation [30]. This pathway regulates pro-inflammatory cytokine production and inflammatory cell recruitment, which contribute to the inflammatory response (Figure 2).

MAPK pathway

MAPKs are a family of serine/threonine protein kinases that direct cellular responses to a variety of stimuli, including osmotic stress, mitogens, heat shock, and inflammatory cytokines (such as IL-1, TNF- α , and IL-6), which regulate cell proliferation, differentiation, cell survival and apoptosis [31, 32]. The mammalian MAPKs include extracellular-signal-regulated kinase ERK1/2, p38 MAP Kinase, and c-Jun N-terminal kinases (JNK) [33]. Each MAPK signaling pathway comprises at least

three components: a MAPK, a MAPK kinase (MAPKK), and a MAPK kinase kinase (MAPKKK). MAPKKKs phosphorylate and activate MAPKKs, which in turn phosphorylate and activate MAPKs [33, 34]. ERKs are generally activated by mitogens and differentiation signals,

while inflammatory stimuli and stress activate JNK and p38 [35]. MKK1 and MKK2 activate ERK1/2, MKK4 and MKK7 activate JNK, and MKK3 and MKK6 activate p38. Activation of the MAPKs, including Erk1/2, JNK, leads to phosphorylation and activation of p38 transcription factors

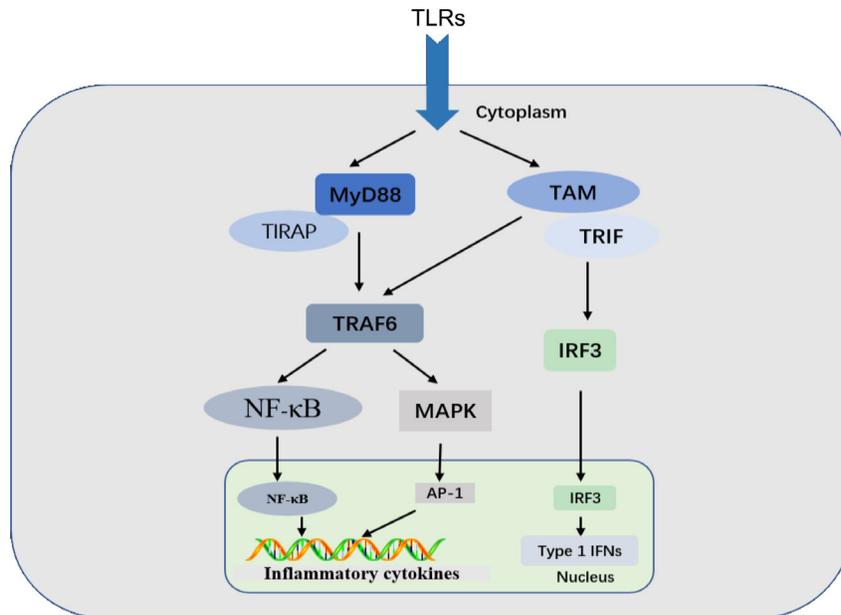


Figure 1: TLR signaling. MyD88-dependent and TRIF-dependent pathways are shown. Signaling through TLRs activates intracellular signaling cascades that lead to nuclear translocation of AP-1 and NF-κB or IRF3, which regulates the inflammatory response.

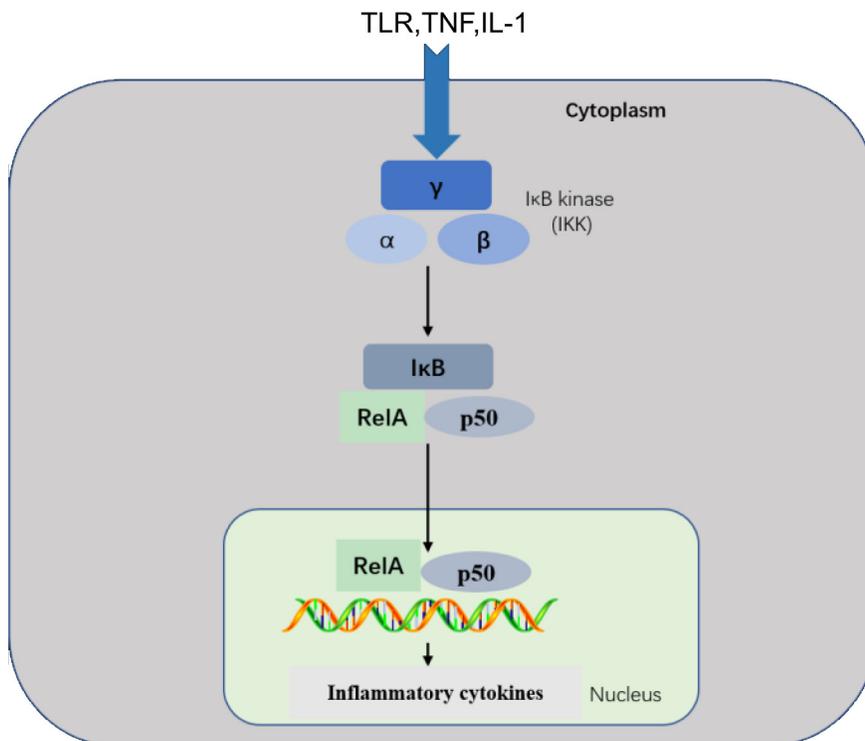


Figure 2: NF-κB pathway. This pathway is triggered by TLRs and inflammatory cytokines, such as TNF and IL-1, leading to activation of RelA/p50 complexes that regulate expression of inflammatory cytokines. NF-κB signaling requires IKK subunits, which regulate pathway activation through IκB phosphorylation.

present in the cytoplasm or nucleus, which initiates the inflammatory response [32, 36] (Figure 3).

JAK-STAT pathway

The highly conserved JAK-STAT pathway involves diverse cytokines, growth factors, interferons, and related molecules, such as leptin and growth hormone, and is a signaling mechanism through which extracellular factors can control gene expression [37]. Receptor-associated JAKs are activated by ligands and phosphorylate one other, creating docking sites for STATs, which are latent, cytoplasmic transcription factors. Cytoplasmic STATs recruited to these sites undergo phosphorylation and subsequent dimerization before translocation to the nucleus [38]. Tyrosine phosphorylation is essential for STAT dimerization and DNA binding [39]. Therefore, JAK/STAT signaling allows for the direct translation of an extracellular signal into a transcriptional response. For example, binding of IL-6 family members to plasma membrane receptors activates the JAK-STAT proteins. STAT proteins translocated into the nucleus bind target gene promoter regions to regulate transcription of inflammatory genes (Figure 4) [40].

Dysregulation of NF- κ B, MAPK, or JAK-STAT activity is associated with inflammatory, autoimmune, and metabolic diseases, and cancer [41]. Signaling through transcription factors results in secretion of cytokines [42, 43]. Multiple transcription factors regulate a variety of inflammatory genes, such as IL-1, TNF- α , IL-6 [44], colony stimulating factor (CSF), interferons, transforming growth factor (TGF), and chemokines.

Inflammatory markers

Markers are used in clinical applications to indicate normal versus pathogenic biological processes, and assess responses to therapeutic interventions. Inflammatory markers may be predictive of inflammatory diseases [45–50], and correlate with the causes and consequences of various inflammatory diseases, such as cardiovascular diseases, endothelial dysfunctions, and infection [51, 52]. Stimuli activate inflammatory cells, such as macrophages and adipocytes, and induce production of inflammatory cytokines, such as IL-1 β , IL-6, TNF- α , and inflammatory proteins and enzymes. These molecules can potentially serve as biomarkers for diseases diagnosis, prognosis, and therapeutic decision making [53–57].

Inflammatory cytokines

Cytokines (Table 2) are predominantly released from immune cells, including monocytes, macrophages, and lymphocytes. Pro- and anti-inflammatory cytokines facilitate and inhibit inflammation, respectively. Inflammatory cytokines are classified as ILs, colony stimulating factors (CSF), IFNs, TNFs, TGFs, and chemokines, and are produced by cells primarily to

recruit leukocytes to the site of infection or injury [58]. Cytokines modulate the immune response to infection or inflammation and regulate inflammation itself via a complex network of interactions. However, excessive inflammatory cytokine production can lead to tissue damage, hemodynamic changes, organ failure, and ultimately death [59, 60]. A better understanding of how to regulate cytokine pathways would allow for more accurate identification of agent-mediated inflammation and the treatment of inflammatory diseases [58].

Inflammatory proteins and enzymes

Inflammatory proteins in the blood, including C-reactive protein (CRP), haptoglobin, serum amyloid A, fibrinogen, and alpha 1-acid glycoprotein [61], help restore homeostasis and reduce microbial growth independently of antibodies during trauma, stress, or infection [62]. Abnormal activation of certain enzymes, including high-mobility group box 1 (HMGB1), superoxide dismutase (SOD), glutathione peroxidase (GPx), NADPH oxidase (NOX), inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2, play key roles in the development of inflammation-related diseases, such as cardiovascular disease and cancer [63–66]. For example, extracellular HMGB1 effects may be mediated by activation of TLR-coupled signaling pathways [67]. The primary target of extracellular HMGB1 is TLR4 [68], which triggers MyD88-dependent intracellular signaling cascades involved in activation of the NF- κ B and MAPK pathways. This leads to release of such inflammatory cytokines as TNF- α and IL-1 β [67]. Inflammatory proteins and enzymes have been used as inflammation, infection, and trauma biomarkers in medicine.

Other inflammatory markers

Antioxidant defense systems, including antioxidant enzymes, influence oxidative stress. Elevated oxidative stress can induce production of reactive oxygen species (ROS), malondialdehyde (MDA), 8-Hydroxy-2-deoxyguanosine (8-OHdG) and isoprostanes [64, 69], each of which can activate various transcription factors, including NF- κ B, AP-1, p53, and STAT. Thus, this cascade can increase expression of genes encoding growth factors, inflammatory cytokines, and chemokines [70]. Oxidative stress is associated with the pathogenesis of multiple diseases, such as cardiovascular disease, cancer, diabetes, hypertension, aging, and atherosclerosis. Therefore, oxidative stress products can also be used as markers of the inflammatory response.

Cell types in inflammatory responses

The inflammatory response involves a highly coordinated network of many cell types. Activated

Table 2: Summary of cytokines and their functions

Cytokine	Family	Main sources	Function
IL-1 β	IL-1	Macrophages, monocytes	Pro-inflammation, proliferation, apoptosis, differentiation
IL-4	IL-4	Th-cells	Anti-inflammation, T-cell and B-cell proliferation, B-cell differentiation
IL-6	IL-6	Macrophages, T-cells, adipocyte	Pro-inflammation, differentiation, cytokine production
IL-8	CXC	Macrophages, epithelial cells, endothelial cells	Pro-inflammation, chemotaxis, angiogenesis
IL-10	IL-10	Monocytes, T-cells, B-cells	Anti-inflammation, inhibition of the pro-inflammatory cytokines
IL-12	IL-12	Dendritic cells, macrophages, neutrophils	Pro-inflammation, cell differentiation, activates NK cell
IL-11	IL-6	Fibroblasts, neurons, epithelial cells	Anti-inflammation, differentiation, induces acute phase protein
TNF- α	TNF	Macrophages, NK cells, CD4 ⁺ lymphocytes, adipocyte	Pro-inflammation, cytokine production, cell proliferation, apoptosis, anti-infection
IFN- γ	INF	T-cells, NK cells, NKT cells	Pro-inflammation, innate, adaptive immunity anti-viral
GM-CSF	IL-4	T-cells, macrophages, fibroblasts	Pro-inflammation, macrophage activation, increase neutrophil and monocyte function
TGF- β	TGF	Macrophages, T cells	Anti-inflammation, inhibition of pro-inflammatory cytokine production

macrophages, monocytes, and other cells mediate local responses to tissue damage and infection. At sites of tissue injury, damaged epithelial and endothelial cells release factors that trigger the inflammatory cascade, along with chemokines and growth factors, which attract neutrophils and monocytes. The first cells attracted to a site of injury are neutrophils, followed by monocytes, lymphocytes (natural killer cells [NK cells], T cells, and B cells), and mast cells [71–73]. Monocytes can differentiate into macrophages and dendritic cells and are recruited via

chemotaxis into damaged tissues. Inflammation-mediated immune cell alterations are associated with many diseases, including asthma, cancer, chronic inflammatory diseases, atherosclerosis, diabetes, and autoimmune and degenerative diseases.

Neutrophils, which target microorganisms in the body, can also damage host cells and tissues [74]. Neutrophils are key mediators of the inflammatory response, and program antigen presenting cells to activate T cells and release localized factors to attract monocytes and

dendritic cells [7]. Macrophages are important components of the mononuclear phagocyte system, and are critical in inflammation initiation, maintenance, and resolution [75]. During inflammation, macrophages present antigens, undergo phagocytosis, and modulate the immune response by producing cytokines and growth factors. Mast cells, which reside in connective tissue matrices and on epithelial surfaces, are effector cells that initiate inflammatory responses. Activated mast cells release a variety of inflammatory mediators, including cytokines, chemokines, histamine, proteases, prostaglandins, leukotrienes, and serglycin proteoglycans [76].

Multiple groups have demonstrated that platelets impact inflammatory processes, from atherosclerosis to infection. Platelet interactions with inflammatory cells may mediate pro-inflammatory outcomes. The acute phase response (APR) is the earliest response to infection or injury, and some studies have indicated that platelets induce the APR [77]. After being recruited by inflammatory stimuli, immune cells amplify and sustain the APR by releasing local inflammatory mediators at the site of recruitment.

RESOLUTION OF INFLAMMATION

To prevent progression from acute inflammation to persistent, chronic inflammation, the inflammatory response must be suppressed to prevent additional tissue damage. Inflammation resolution is a well-managed process involving the spatially- and temporally-controlled production of mediators, during which chemokine gradients are diluted over time.

Circulating white blood cells eventually no longer sense these gradients and are not recruited to sites of injury. Dysregulation of this process can lead to uncontrolled chronic inflammation [78]. Inflammation resolution processes that rectify tissue homeostasis include reduction or cessation of tissue infiltration by neutrophils and apoptosis of spent neutrophils, counter-regulation of chemokines and cytokines, macrophage transformation from classically to alternatively activated cells, and initiation of healing [79, 80].

Chronic inflammation occurs when acute inflammatory mechanisms fail to eliminate tissue injury [81], and may lead to a host of diseases, such as cardiovascular diseases, atherosclerosis, type 2 diabetes, rheumatoid arthritis, and cancers [82]. Understanding the common mechanisms that orchestrate dysfunction in the various organ systems will allow for development and production of improved targeted therapies.

ORGAN-SPECIFIC INFLAMMATORY RESPONSES

Inflammation has long been recognized as a major cause of disease. It is estimated that some 15% of human cancers are associated with chronic infection and inflammation [83]. Acute and chronic inflammation-mediated tissue injury is observed in many organ systems, including the heart, pancreas, liver, kidney, lung, brain, intestinal tract, and reproductive system.

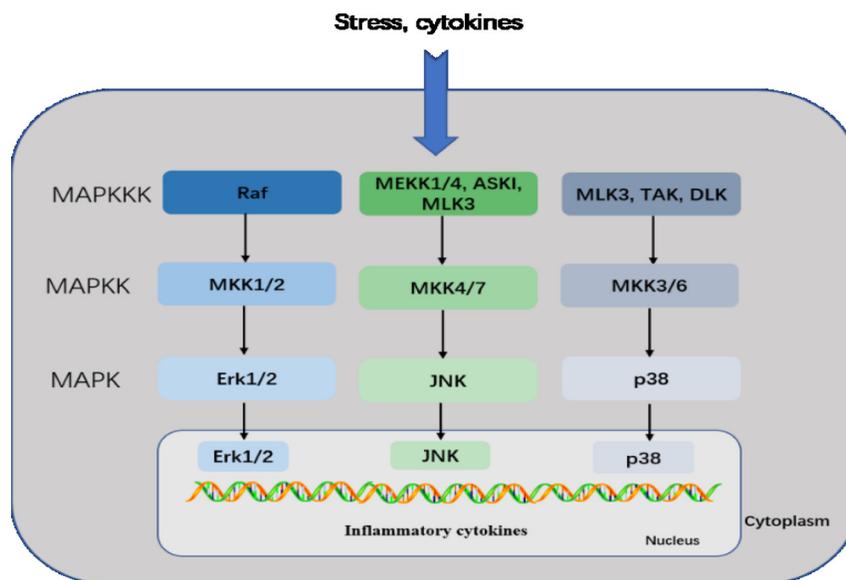


Figure 3: MAPK pathway. This pathway mediates intracellular signaling initiated by extracellular stimuli, such as stress and cytokines. MAPKKKs phosphorylate and activate MAPKKs, which in turn phosphorylate and activate MAPKs. The mammalian MAPK family includes Erk1/2, JNK, and p38. In the Erk1/2 pathway, Erk1/2 is activated by MKK1/2, which is activated by Raf. In the JNK pathway, JNK is activated by MKK4/7, which is activated by MEKK1/4, ASK1, and MLK3. In the p38 pathway, p38 is activated by MKK3/6, which is activated by MLK3, TAK, and DLK. Activated MAPKs phosphorylate various proteins, including transcription factors, resulting in regulation of inflammatory responses.

Heart

Cardiovascular disease, and its underlying pathology, atherosclerosis, is the major cause of death and disability worldwide [84, 85]. By 2030, almost 23.6 million people are projected to die annually from cardiovascular disorders [86, 87]. Inflammatory mediators play key roles in atherosclerosis, from initial leukocyte recruitment through rupture of the atherosclerotic plaque [88–91]. Inflammation is also an early event in cardiac stress. Elevated levels of endothelial adhesion molecules and increased inflammatory cytokine and chemokine production and release are observed in affected cardiac tissues [92].

The innate immune system is the primary cardiac defense against pathogens and tissue damage [93]. Myocardial infarction, which commonly results from coronary atherosclerosis and involves acute loss of many myocardial cells, is the most common cause of cardiac injury [94]. Necrotic cardiac cells initiate an inflammatory cascade to clear dead cells and debris from the infarct [95, 96]. Cell death releases intracellular components that activate innate immune mechanisms to initiate an inflammatory response. Endogenous ligands released following injury are recognized as danger signals by cell surface receptors, and activate inflammation [97, 98]. TLR-mediated pathways trigger post-infarction inflammatory responses by activating NF- κ B signaling [98–103]. Chemokines recruit inflammatory leukocytes to the infarct, and cytokines promote leukocyte-endothelial cell adhesions [104, 105]. Moreover, TGF- β and IL-10 promote cardiac repair by suppressing inflammation, enhancing myofibroblast phenotypic modulation, and promoting extracellular matrix deposition [106, 107].

Cardiovascular disease is the main cause of death and disability in patients with diabetes mellitus, especially those with type 2 diabetes (T2D), in whom cardiovascular disease occurs 14.6 years earlier on average [108]. About two-thirds of deaths in people with diabetes are due to

cardiovascular disease; among these, approximately 40% die from ischemic heart disease, 15% from other forms of heart disease, principally congestive heart failure, and about 10% from stroke [109]. Recent global estimates indicate that over 422 million adults currently live with diabetes, of which over 90% have T2D.

Diabetes is a group of metabolic disorders characterized by sustained high blood sugar levels, and is a major global health challenge, both to individuals and their families, and to healthcare systems [110]. Diabetes complications include heart attack, stroke, kidney failure, limb amputation, blindness, and nerve damage. Diabetes results from either impaired insulin production in the pancreas or body cells not responding to produced insulin [111]. Insulin resistance is defined as decreased insulin-stimulated glucose uptake, and is associated with inactivity, obesity, and aging. Pancreatic islet cells respond to insulin resistance by enhancing insulin secretion and cell mass. However, when islet β -cells are unable to compensate for insulin resistance, insulin deficiency develops, followed by T2D [112], which is increasingly being characterized as an inflammatory disease [113, 114]. Elevated circulating levels of acute-phase proteins, including CRP, fibrinogen, serum amyloid A, plasminogen activator inhibitor, and haptoglobin, along with sialic acid, cytokines, and chemokines, have been observed in patients with T2D. Elevated IL-1 β , IL-6, TNF- α , and CRP levels are also predictive of T2D. IL-1 receptor antagonist (IL-1RA) is elevated in obesity and prediabetes prior to T2D onset. Excessive nutrient levels, including those of glucose and free fatty acids, promote insulin resistance. T2D also activates the NF- κ B, MAPK, and JAK-STAT pathways, which can each promote tissue inflammation [110, 114, 115]. Metabolic stressors also negatively impact pancreatic islet cells and insulin-sensitive tissues, including adipose tissue, promoting local cytokine and chemokine production and release. At the same time, immune cells, such as mast cells and macrophages, are recruited and contribute to

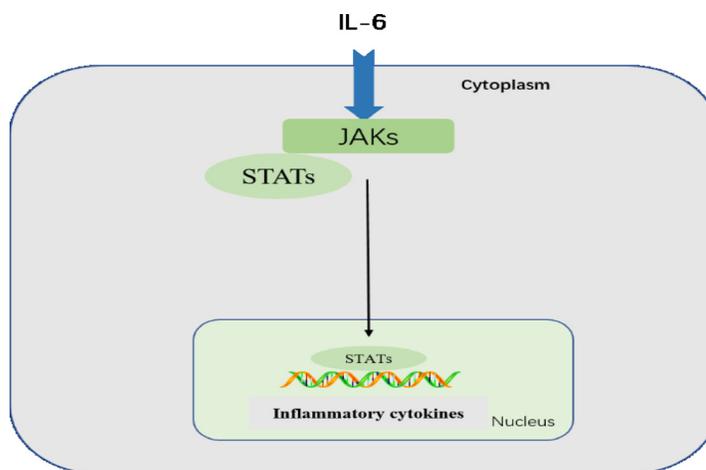


Figure 4: JAK-STAT pathway. Following IL-6 binding, signal is transduced by a receptor to activate the JAKs, which then activate STATs. STATs are dephosphorylated in the nucleus, leading to activation of downstream cytokines.

tissue inflammation. Similarly, cytokine and chemokine release from adipose tissues into the circulation promotes further inflammation in other tissues [116].

Pancreas

Pancreatitis, caused by pancreatic duct obstruction, trypsinogen gene mutation, or alcoholism, is an inflammatory disease of the pancreas [117]. Acute pancreatitis (AP) incidence ranges from 4–45 per 100,000 patients per year and increases annually by approximately 1.3–4.0% in most developed countries. AP is one of the most common gastrointestinal causes for hospitalization in the US, and chronic pancreatitis (CP) is less common than AP. However, CP patients experience chronic abdominal pain and exocrine and/or endocrine insufficiency, leading to reduced quality of life [118]. Pancreatitis is characterized by acinar cell destruction and activation of inflammatory cells, including macrophages, neutrophils, and granulocytes, which secrete inflammatory cytokines [117, 119]. These cytokines further activate pancreatic stellate cells (PSCs) to promote CP [120]. Pancreatitis development requires various molecular pathways, such as NF- κ B, MAPK, and JAK-STAT, which play critical roles in inflammatory cell activation during pancreatitis [117].

Pancreatic cancer (PC) remains one of the most lethal of malignancies and a major health burden [121], and is the fourth most common cause of death from cancer in the US [118]. There is a strong link between antecedent CP and PC [122]. CP leads to fibrosis, which is a common pathological feature and major risk factor for PC [123]. Pancreatic cancer results from dysregulation of oncogenes and tumor suppressor genes, as well as growth factors and their receptors, including epidermal growth factors, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and many cytokines, such as TGF- β , IL-1, IL-6, TNF- α , and IL-8, which modulate pathways involved in growth and differentiation [124, 125]. Shi, *et al.* has showed that VEGF is upregulated by low extracellular PH (acidosis), which occurs frequently around necrotic regions in tumors, and that acidosis activates IL-8 [126]. VEGF and IL-8 are important angiogenic factors in PC [126], and acidosis-promoted upregulation of these genes can be mediated through NF- κ B and AP-1 transactivation and cooperation [127].

Liver

Inflammation in the liver protects this organ from infection and injury, but excessive inflammation may lead to extensive loss of hepatocytes, ischemia-reperfusion injury, metabolic alterations, and eventually permanent hepatic damage [128]. Inflammation can destroy hepatic parenchymal cells, increasing the risk of chronic liver diseases, such as non-alcoholic fatty liver disease (NAFLD) or viral hepatitis. Chronic liver diseases are a leading cause of morbidity and mortality in the US [129].

The liver is the largest solid organ in the body [130], and is a target of both infectious and non-infectious inflammatory pathologies. Infectious inflammation of the liver is mainly caused by microorganisms, such as bacterial products, hepatitis B virus (HBV), or hepatitis C virus (HCV) [131, 132]. Sterile inflammation (SI) is also important in the pathology of many liver diseases, such as alcoholic or nonalcoholic steatohepatitis, drug-induced liver injury, and ischemia/reperfusion [133–135]. In SI, endogenous DAMPs are released to injured tissues and activate immune cells [136]. While pathogen-driven inflammation and SI differ, they share several functional characteristics. Many receptors and pathways can be activated by both PAMPs and DAMPs [137]. TLR4, for example, can be activated by bacterial LPS and cellular HMGB1. Because of the liver's unique vascular supply, PAMPs of intestinal origin and DAMPs from hepatocytes both contribute to inflammation in a variety of diseases. For example, PRR activation by DAMPs and PAMPs can induce production of pro-inflammatory cytokines and immune cell localization to sites of injury. Recognition of DAMPs and PAMPs results in assembly of the inflammasome, a cytosolic protein complex that activates the serine protease caspase-1, followed by activation and secretion of IL-1 β and other cytokines. At the same time, Kupffer cell activation and inflammatory cell recruitment leads to production of cytokines and chemokines that promote long-term inflammation, hepatocyte damage, and/or cholestasis [138].

Lung

Lung inflammatory diseases involve complex interactions among and between structural and immune cells [139]. Lung inflammation results predominantly from tissue exposure to bacterial and viral pathogens, and/or environmental pollutants. Excessive acute inflammation and subsequent lung injury can cause pulmonary fibrosis and impair gas exchange. Unresolved lung injury and chronic inflammation are frequently observed in acute respiratory distress syndrome, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma [140–142]. Approximately 90% of COPD cases are associated with cigarette smoking-induced inflammation in small airways and lung parenchyma [143]. Cigarette smoking is a major risk factor for COPD, which involves both systemic and pulmonary inflammation. Long-term smoking can cause macrophage, neutrophil, and activated T lymphocyte infiltration into airways, and promote production of chemokines, oxygen radicals, proteases, and cytokines, including that of TNF- α , IL-6 and IL-8, in the lung [144].

Kidney

Kidney inflammation contributes to progressive renal injury, which may lead to glomerulonephritis, end-stage renal disease, or acute or chronic kidney disease (CKD)

[145–147]. Approximately 10–12% of the population suffers from CKD, and some 50% of elderly patients show signs of kidney dysfunction, which is associated with high morbidity and mortality [52]. Kidney inflammation is most commonly induced by infection, ischemia/reperfusion, *in situ* immune-complex formation/deposition, or complement pathway dysregulation [145]. CKD and acute kidney injury (AKI) are the most severe types of kidney disease [148]. Interstitial inflammation and tubular injury are commonly observed in acute and chronic kidney injury cases. Renal tubular epithelial cells are likely important promoters of kidney inflammation, secreting a variety of inflammatory cytokines in response to both immune and non-immune factors, and leukocyte infiltration depends on the local presence of these cytokines [146]. Stimuli that can induce kidney injury activate transcription factors (NF- κ B or MAPK). These stimuli include cytokines, growth factors, DAMPs, and PAMPs, TLRs, Nod-like receptors (NLRs), and metabolic (high glucose, advanced glycosylation end products) and immune mediators [147].

Intestinal tract

Acute and chronic inflammatory diseases of the intestine can cause various health issues, and decrease patient quality of life worldwide [149, 150]. The complex, polygenetic inflammatory bowel diseases (IBDs) are characterized by an excessive inflammatory response to gut lumen microbial flora [151]. IBDs mainly include ulcerative colitis (UC) and Crohn disease (CD), but also noninfectious inflammation of the bowel [152, 153]. Idiopathic IBDs, such as CD and UC, are caused by cytokine-driven, non-infectious inflammation of the gut. For example, CD is associated with excessive IFN- γ /IL-17 and IL-12/IL-23 production, while UC is associated with excess IL-13 [153]. Thus, IBD appears to be the result of a dysfunctional interaction between gut bacteria and the mucosal immune system [154]. A key process in the immune system's response to microbes is the recognition of microbial agents via PRRs, including TLRs and nucleotide-binding oligomerization domain containing NLRs, which sense evolutionarily conserved PAMPs [155]. Upon PAMP detection, PRRs activate intracellular signaling pathways that induce production of cytokines and chemokines to promote host resistance to infection. TLR (mainly TLR4) signaling induces NF- κ B and MAPK transcription. At the same time, NLRs are also activated through ligand detection [154], in turn activating caspase-1, followed by activation and secretion of IL-1 β , interleukin-18 and other cytokines [154].

Reproductive system

The hallmarks of inflammation are observed during many normal reproductive processes, including menstruation, ovulation, implantation, and parturition [156]. Injury and healing caused by menstruation,

ovulation, and parturition trigger the inflammatory cascade. However, initiation and maintenance of inflammatory processes are also important components of many reproductive tract diseases. Damaged tissues locally release inflammatory interleukins, growth factors, cytokines, and prostaglandins, which activate signaling pathways and recruit immune cells (e.g. neutrophils and macrophages) to the site of injury. This process synergistically controls tissue remodeling and repair, but can also induce inflammatory diseases [7]. Inflammatory cytokines, including IL-6, are the primary mediators of inflammation-related reproductive tract diseases, and act via signal transduction pathways such as the MAPK pathway [157, 158].

Brain

Inflammatory responses occur in the brain in many central nervous system (CNS) diseases, including autoimmune diseases, neurodegenerative diseases like Alzheimer's (AD) and Parkinson's disease (PD), and epilepsy. Inflammatory responses in the brain can enhance neuronal excitability, injure cells, and increase blood-brain barrier permeability to various molecules [159–161]. Inflammation-associated CNS diseases result from activation of the brain's resident immune cells and microglia, which produce pro-inflammatory markers [162]. These inflammation processes also involve both the innate and adaptive immune systems and resemble immune responses to systemic infection. Cytokines and TLRs are major inflammatory mediators in the transition between innate and adaptive. Inflammatory responses in the CNS may also be triggered by endogenous ligands recognized by TLRs. DAMPs, such as heat-shock proteins and extracellular matrix degradation molecules, entering the brain through a damaged blood-brain barrier may initiate inflammatory responses. The CNS inflammatory response is strong in reaction to both infectious agents and brain injury, such as tissue damage observed following ischemic, traumatic, or excitotoxic brain injury, or seizure [160, 163, 164].

CONCLUSIONS

Inflammation is frequently a key element in the pathological progression of organ disease. Three main pathways, NF- κ B, MAPK, and JAK-STAT, play major roles in inflammation, and dysregulation of one or more of these pathways may lead to inflammation-associated disease. A better understanding of inflammatory response pathways and molecular mechanisms will undoubtedly contribute to improved prevention and treatment of inflammatory diseases.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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