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Review Article

A Comprehensive Overview of Organ Inflammatory Responses: Genesis, Possible Mechanisms, and Mediators of Inflammation

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Abstract

An immune system response known as inflammation can be carried on by a variety of things, such as infections, damaged cells, and noxious substances. These factors may cause acute or chronic inflammatory responses in the heart, pancreas, liver, kidney, lungs, brain, colon, and reproductive system, which may cause disease or tissue damage. Inflammatory cells and signaling pathways are activated by both pathogenic and non-pathogenic agents, cell injury, and infectious agents. The most ubiquitous types of these include tumor necrosis factor-alpha (TNF-α), nuclear factor kappa B (NF-κB), High mobility group box 1 protein (HMGB1), mitogen-activated protein kinase (MAPK), monocyte chemoattractant protein (MCP1), interleukin 1 beta (IL1β), and Janus kinase-signal transducer and activator of transcription (JAK-STAT). Severe inflammation has the potential to cause systemic inflammatory response syndrome. The most severe forms of this condition are characterized by hyperinflammation and can cause organ damage, shock, and even death. We concentrate on the origin of inflammation, all conceivable inflammatory mechanisms, and organ-specific inflammatory responses in this study on inflammatory reactions inside organs.

Introduction

Inflammation, the immune system's response to harmful stimuli like pathogens, damaged cells, poisonous substances, or radiation, works by removing dangerous stimuli and starting the healing process. Therefore, one important defense mechanism for maintaining good health is inflammation.[1,2] Cellular and molecular activity and interactions typically serve to successfully control potential damage or infection during acute inflammatory responses.[3, 4] Acute inflammation is reduced as a result of this mechanism, and tissue homeostasis is also restored. However, if acute inflammation is left untreated, it can lead to several chronic inflammatory disorders.[5-7] Redness, swelling, heat, discomfort, and a loss of tissue function are signs of tissue-level inflammation. Local immune, vascular, and inflammatory cell reactions to infection or injury cause this illness. Leukocyte recruitment and accumulation, alterations in vascular permeability, and the release of inflammatory mediators are all significant microcirculatory processes that occur during the inflammatory phase. Inflammation can be caused by a variety of pathogenic events that cause tissue damage, including infection, tissue injury, or myocardial infarction.[8,9] The body starts a chemical signaling cascade in response to tissue damage, which leads to actions intended to restore the damaged tissues. Leukocytes move to the injured sites as a result of these signals. These cytokines are produced by these activated leukocytes and cause inflammatory reactions.[10-12]

Cytokines and Chemokines as Chemical Mediators

White blood cells and other cells release cytokines, which are tiny glycoproteins with a molecular weight of 30 kDa, in response to a variety of internal and external stimuli. While certain cytokines have specific purposes, others act as regulatory proteins to support the growth of immune effector cells. According to the Watford group in 2003, depending on their function, secretion, or target of the action, cytokines include interleukins (IL), chemokines, interferons, tumor necrosis factor-alpha (TNF-α), and lymphokines; however, hormones and growth factors are typically ignored. The cytokine family includes chemoattractant chemokines, which are released proteins that control the immune system.[13] Cytokines are produced and secreted by a wide range of cells, including immune

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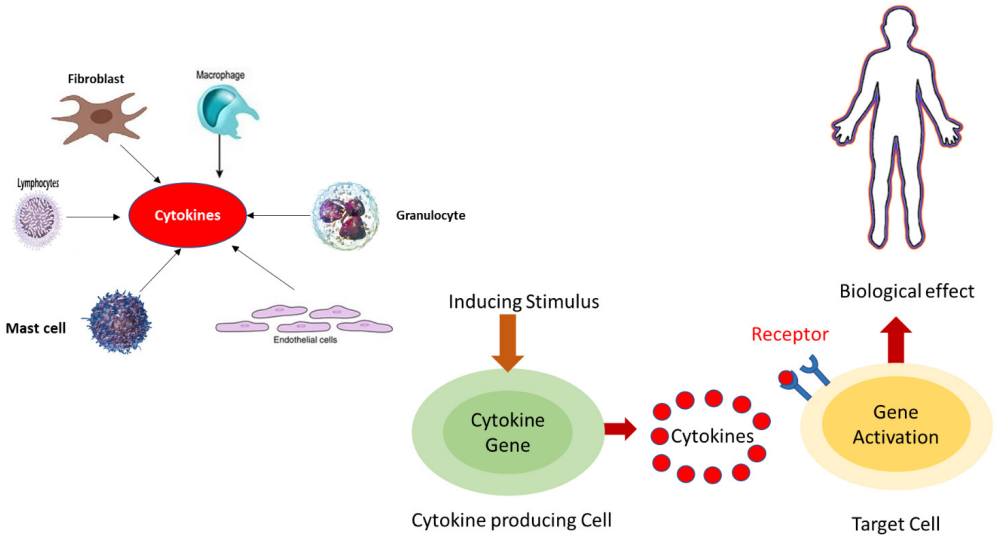

Figure 1. The schematic diagram shows how macrophages, lymphocytes, mast cells, endothelial cells, and lymphocytes induce the production of cytokines. When cytokines connect to receptors, a biological reaction occurs.

cells such as macrophages, T and B lymphocytes, mast cells, fibroblasts, endothelial cells, and other stromal cells.[14] In a signal induction cascade, numerous genes and the transcription factors that regulate them may be activated or inhibited, leading to the generation of further cytokines. The surface receptors of other molecules are consequently enhanced by these additional cytokines, which might cause feedback inhibition. When cytokines attach to a target cell's membrane receptor and activate signaling pathways at the same time, the altered gene expression on the targeted cells causes a variety of biological reactions. Cytokines serve a critical role in coordinating and orchestrating normal immunological homeostasis, development, and protection against a variety of infectious disease situations.[15] The presence of more cytokines is assumed to signal the activation of cytokine-related pathways involved in the development of inflammatory reactions or illness. Numerous illnesses, including severe depression and Alzheimer's disease, as well as many cancers whose intensity fluctuates from their physiological state, have been related to the unexpected consequences of cytokine release. Analyzing cytokine levels can help us understand the inflammatory processes that lead to autoimmune diseases. They are thought to be ideal therapeutic targets and agents for particular cytokine antagonists in a variety of inflammatory and immune disorders[16] (Figure 1).

Chemokines play a role in a number of biological processes, including chemotaxis, leucocyte degranulation, hematopoiesis, and angiogenesis. They interact with cell surface G-protein coupled receptors GPCRs) and contribute to the onset of atherosclerosis, cancer, and infectious illnesses.[17] Based on the distance between disulfide bridges connecting peptides, the four subfamilies are CXC subfamily, CC subfamily, C or XC subfamily, and CX3C subfamily. It is possible to use CXCL12 and CXCL8, also known as IL-8, as markers of vascular dysfunction.[18] Through its interactions with endothelial cells and vascular smooth muscle cells, CXCL8 might play a part in uremia-related vascular calcification. In all phases of chronic kidney disease (CKD), the scavenger receptor for oxidized LDL, CXCL16, has been linked to a decline in renal function. In type 2 diabetes patients, it also seems to be a marker of renal impairment because it is independently associated with microalbuminuria, and its levels in the urine may indicate the severity of interstitial fibrosis and other issues.[19]

Plasma CCL2 commonly referred to as monocyte chemoattractant protein 1 (MCP-1), rises with deteriorating renal function but does not appear to represent a separate risk factor for death in CKD patients. But dyslipidaemia has been linked to CCL2 levels in haemodialysis patients. Chronic kidney disease's onset has also been linked to CCL2 baseline values. Additionally, patients with diabetic nephropathy have greater CCL2 levels, which suggests tubular damage. Studies on gene polymorphisms have shown that CCL2 polymorphisms increase the risk of developing CKD.[20] Paediatric CKD patients' blood and urine levels of CCL2 were assessed, and the results were contrasted with those of controls. Although urine levels varied among CKD etiologies, glomerular disease patients had greater urine levels than those with renal and urinary tract abnormalities. Furthermore, it was discovered that the inflammatory marker CCL2 fractional excretion could forecast tubular dysfunction in children with CKD. In patients with ANCA-associated crescentic glomerulonephritis, CCL18, also known as the pulmonary and activation-regulated chemokine, may serve as a biomarker for disease activity and recurrence. A thorough analysis revealed that CCL2 may contribute to renal fibrosis and declining renal function. In mice, it has been demonstrated that CCL2 protects the kidneys against acute inflammation after renal ischemia/reperfusion injury. Additionally, it has been demonstrated that CCL5, which is well known for its function in the attraction of macrophages and T lymphocytes to wounded tissues, protects mice against kidney damage by inhibiting CCL2's

proinflammatory effects.[21]

Interleukins

Leukocytes are where the interleukins family of cytokines was initially identified. Based on receptor complexes that interact with different interleukins, they have been categorized into 16 categories, including the IL-1 superfamily, IL-6 family, IL-10 family, IL-12 family, and IL-17 family.[22]

Interleukin-6

Vascular pulse wave velocity reveals a relationship between IL-6 and elevated central aortic stiffness. Higher IL-6 levels were linked to advanced carotid plaques in South African CKD patients, and the IL-6 gene's -174G/C polymorphism was discovered to be widespread.[23] Despite this, a recent meta-analysis found no link between the -174G/C polymorphism and the risk of renal failure. Increased fibroblast growth factor 23 (FGF23) transcription in acute kidney injury (AKI) and CKD, which is linked to higher morbidity and mortality, is another potential role for IL-6. It has also been found to play a role in erythropoiesis in adults.[24,25] A poor response to erythropoiesis-stimulating agent (ESA) therapy in hemodialysis patients has been associated with higher levels of IL-6. Additionally, animal studies point to a role for it in the emergence of hypertension and end-organ damage, indicating therapeutic opportunities.

Interleukins 1 and 18

The IL-1 family consists of four anti-inflammatory antagonists (IL-1RA, IL-36Ra, IL-37, and IL-38) and seven pro-inflammatory agonists (IL-1, IL-18, IL-36, IL-36, and IL-33) that promote inflammation.[26] They play a part in the initiation and control of innate immune responses like complement activation, activation of innate immune receptors, and nondirected phagocytosis, where an imbalance can lead to excessive inflammatory responses. IL-1, which binds to the IL-1 receptor and activates the immune system, is one of the substances that has generated the most research. Additionally, it promotes the development of T helper 17 cells, which are important in the pathophysiology of autoimmune diseases like psoriasis and rheumatoid arthritis. Its transcription is triggered by the toll-like receptor (TLR), IL-1 receptor activation, or TNF-α, and the inflammasome caspase-1 is required to cleave it into the mature form.[27] There has been a previous study on how IL-1 suppression affects renal function. The use of the recombinant human IL-1 receptor antagonist anakinra led to the conclusion that IL-1 may be a significant mediator of inflammation in Heart failure (HF) and CKD.[28]

Similar to how caspase-1 activates IL-1, IL-18 activates NF-κB and generates inflammatory mediators by using the same mechanism. Because it is produced by myeloid cells and attaches to the IL-18 receptor increases Interferon (IFN) production, and autoimmune illnesses such as lupus erythematosus, psoriasis, and inflammatory bowel disease have high levels of it. Particularly in diabetic nephropathy, where its expression is linked to albuminuria and disease progression, it seems to be primarily focused on renal pathology. Inhibiting it could be a therapeutic target because of its importance in diabetic nephropathy.[29]

Interleukin-1β (IL-1β)

IL-1β is a proinflammatory cytokine with a reputation for regulating pain sensitivity. TNF-α and IL-1β are frequently involved in the inflammatory response after central nervous system (CNS) injury. The CNS is exposed to IL-1β, which results in mechanical autonomic dysfunction and thermal hyperalgesia. In mutant mice with impaired IL-1β signaling, there is no atypical neuronal activity, no neuropathic pain, and almost no self-mutilation.[30,31] Furthermore, the mice's thermal hyperalgesia following nerve injury was decreased by a rat antibody to the IL-1 receptor. Bumetanide therapy has been demonstrated to decrease inflammation by suppressing IL-1 expression. Thiazolidinediones (TZDs), powerful synthetic agonists of the transcription factor peroxisome proliferator-activated receptor-gamma (PPAR gamma), have also been demonstrated to produce neuroprotection following cerebral ischemia by lowering IL-1 levels. Additionally, it is thought that IL-1 is what causes matrix metalloproteinases (MMPs) to be upregulated.[32]

Other Interleukins

In the combat against bacterial and fungal skin diseases, the IL-17 family, which consists of IL-17A through IL-17F, contributes to tissue inflammation. It recently came to light that it blocks the interstitial fibrosis brought on by transforming growth factor (TGF) in the kidney. IL-10, which is a member of the IL-10 family along with IL-19, IL-20, IL-22, IL-24, and IL26, is one of the anti-inflammatory mediators. The primary producers are tissue epithelial cells and immune cells.[33] Its role in tissue fibrogenesis, which includes renal fibrosis, has been thoroughly explored. As a potential antifibrotic therapy, the interaction of IL-10 with other signaling molecules is being researched. In preclinical hypertension investigations, its anti-inflammatory properties improve vascular and renal function. A new meta-analysis of IL-10 gene polymorphisms suggests that some single nucleotide polymorphisms (SNPs) may shield type 2 diabetics from developing diabetic nephropathy.[34]

Interferons

A class of cytokines known as IFNs was first recognized for their capacity to stop viral replication in the host. They are divided into three groups. Interferons of type I, including interferon-alpha (INF-α) and interferon-beta (IFN-β), are produced by innate immune cells; interferons of type II, also known as interferon-gamma (IFN-γ), are produced by natural killer cells and T lymphocytes; and interferons of type III, also known as interferon lambda (IFN- λ), or initially IL-28 and IL-43.[35,36] Tyrosine kinase 2 (TYK2) and

JAK1 are activated when type I IFNs bind to IFN alpha and beta receptor subunits 1 and 2 (IFNAR1 and IFNAR2). The identical signal cascade is activated by IFN- type III signaling, but IFN binds to IL28-R and IL-10R2. When IFN- binds to IFN-λ receptors 1 and 2, it activates JAK1 and JAK2 to send signals. (IFNGR1 and IFNGR2). But it was also noted in IgAN, lupus nephritis, and renal vasculitis. IFN- γ has a significant impact on a number of extrarenal viral diseases, including hepatitis C infection, which may culminate in membranoproliferative glomerulonephritis.[28] Plasma IFN-γ levels in hemodialysis patients are independently related to survival and are related to a better hepatitis B virus (HBV) vaccine response. Interferon has been utilized as a therapy option in a few case reports, typically for ailments other than renal disease.[37]

Immunity and Inflammation

Two interconnected pathways make up the host defensive systems. The innate immune system acts fast to heal wounds. It recognizes a broad range of pathogen-associated molecular patterns (PAMPs), which are frequently observed on pathogens but are absent in mammals and lack the precise structural specificity of the adaptive immune response.[38] PAMPs are ligands for macrophage pattern recognition receptors and comprise lipopolysaccharides, surface phosphatidylserine, and aldehyde-derivatized proteins. Low-density lipoproteins (LDL), a traditional risk factor for atherosclerosis, are also a part of them in modified forms.[39] NF-κB and mitogen-activated protein kinase (MAPK) pathways are stimulated when TLR are activated, but bound ligands may be endocytosed and destroyed by lysosomes when scavenger receptors combine. Additionally, TLR activation can accelerate phagocytosis, produce more reactive oxygen species (ROS), and release cytokines, glucocorticoids, and lipid mediators, all of which help to coordinate and exaggerate the local inflammatory response. The adaptive immune response, the other major element of host defenses, develops more slowly and has a more specialized response mechanism.[40] Th2 cells can enhance humoral immunity by secreting a range of cytokines that encourage B-cell maturation into antibody-producing plasma cells and B-cell class switching, which enhances the synthesis of IgE antibodies.[41] Mast cells, another cause of allergic reactions and a factor in chronic inflammation in some tissues and disease states, can be drawn to and activated by Th2 cells. Along with these specific pro-inflammatory responses, Th2 cells can inhibit inflammation by generating anti-inflammatory cytokines such as IL-10.[42]

To protect the host from pathogens, viruses, toxins, and diseases, inflammation is an effector process that involves the activation of immune and non-immune cells. It also facilitates tissue repair and recovery.[43] To maintain metabolic energy and provide the active immune system with more resources, metabolic and neuroendocrine changes may occur depending on the scope and severity of the inflammatory response, including whether it is systemic or local.[44] Sadness, persistent depression, tiredness, reduced libido, and food intake, disrupted sleep, social withdrawal, elevated blood pressure, insulin resistance, and dyslipidemia are some of the specific bio-behavioral effects of inflammation.[45] In conditions of physical damage or microbiological threat, these behavioral adjustments may be vital for survival. The hallmark of a typical inflammatory response is a brief spike in inflammatory activity that occurs in response to a threat, dissipates once the threat has passed, and then returns to normal.[46] Changes from a short-lived to a long-lived inflammatory response can impair immunological tolerance and result in significant changes to all tissues and organs as well as to normal cellular physiology, which can raise the risk of different non-communicable diseases in both young and old people.

Infiltration of Inflammatory Cells

The pathophysiology of many chronic diseases is influenced by the inflammatory pathway, which includes common inflammatory mediators and regulatory systems.[47] Inflammatory triggers activate intracellular signaling pathways, which in turn trigger the creation of inflammatory mediators. The main causes of inflammation include cytokines and microbial compounds; such as TNF-α, which interacts with NF-κB, interleukin-6, interleukin-8, and interleukin-1 beta to produce inflammation.[48] The recruitment of inflammatory cells to the site of injury is a vital step in wound healing once the wound heals after the completion of repair and recovery. Inflammation persists and does not go away and becomes a powerful catalyst for the onset of fibrotic illness. Therefore, fibrosis typically occurs before inflammation. Endocytosis and phagocytosis mediated by cytokines are the primary causes of inflammation.[49] Neutrophils are the first cells to be recruited and activated. The activation of T cells is also the main process that initiates fibrogenesis and encourages the release of fibrogenic cytokines. As soon as neutrophils and T cells are activated, macrophages enter damaged tissues and release fibrogenic cytokines. In the fibrotic tissues, macrophages are primarily responsible for producing transforming growth factor beta1 (TGF-β1). IFN-γ activates macrophages and increases NF-κB activity. Additionally, macrophages produce a variety of chemokines and ROS, have a distinctive pro-inflammatory tendency, and contribute to tissue fibrosis and destruction. Macrophage adoption worsens the fibrotic lesions, while macrophage depletion lowers fibrosis after injuries.[50] And therefore, the initiation and progression of fibrotic disease may be caused by the infiltration and activation of inflammatory cells. Targeting inflammatory signaling reduces fibrosis overall.

Inflammatory cytokines such as chemokines, TNFs, IFNs, TGFs, and colony-stimulating factors (CSF) are produced by cells to induce leukocytes to the site of an infection or injury.[51] Through a tangled series of interactions, cytokines control inflammation and modify the immune system's

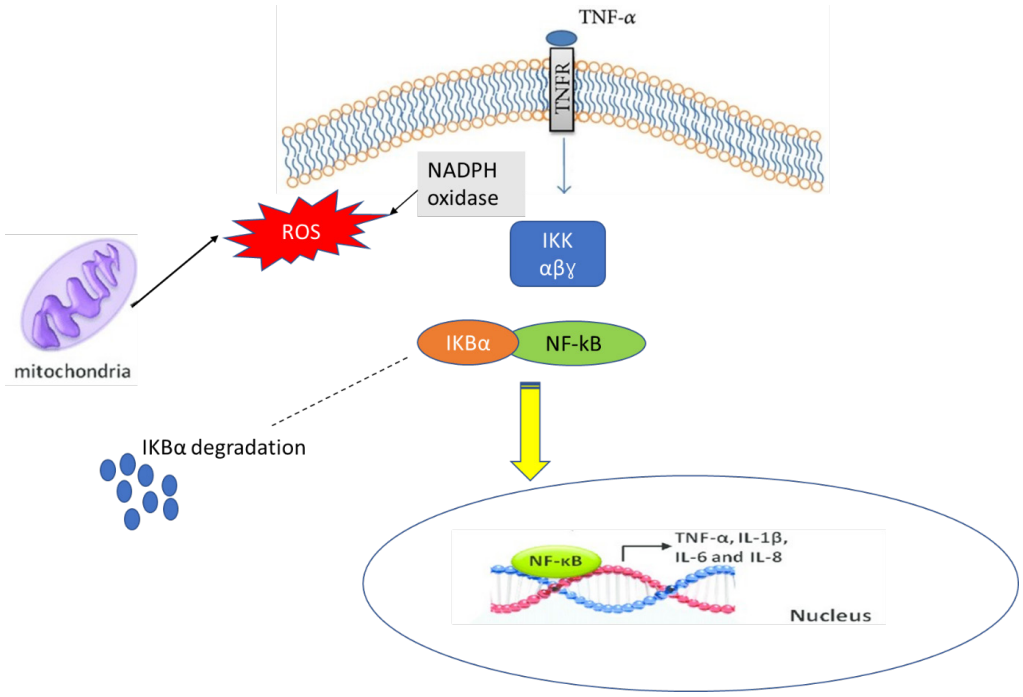

Figure 2. Signaling mechanisms via which reactive oxygen species (ROS) activate nuclear factor kappa-B (NF-κB). These kinase pathways are triggered by proinflammatory cytokines, oxidative stress, and other inflammatory stimuli, as well as by ROS generated by mitochondria and NADPH oxidase. Tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 are just a few of the target genes that NF-κB, which translocate to the nucleus, can boost transcription of (IL-8).

response to infection or inflammation. However, excessive synthesis of inflammatory cytokines can cause organ failure, tissue damage, hemodynamic abnormalities, and even death. Greater awareness of how cytokine pathways are regulated may lead to more accurate agent-mediated inflammation diagnosis and inflammation illness treatment.[52]

The abnormal activation of several enzymes, including high-mobility group box 1 (HMGB1), superoxide dismutase (SOD), glutathione peroxidase (GPx), NADPH oxidase (NOX), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2, is a significant factor in the emergence of inflammatory diseases like cancer and cardiovascular disease. (COX-2).[53] As a result, inflammatory cytokines including TNF-α and IL-1 are released. In medicine, inflammatory proteins and enzymes have been used as biomarkers for injury, infection, and inflammation. Oxidative stress is influenced by antioxidant defense systems, which include antioxidant enzymes. Increased oxidative stress can result in the production of malondialdehyde (MDA), 8-hydroxy-2-deoxyguanosine (8-OHdG), and ROS, which all trigger NF-κB, Activator protein 1(AP-1), and p53. The expression of genes that produce growth factors, inflammatory cytokines, and chemokines may rise as a result (Figure 2).

Markers of Inflammation

In therapeutic settings, inflammation markers are used to differentiate between healthy and unhealthy biological processes and to evaluate the effectiveness of treatment. The origins and effects of inflammatory diseases such as cardiovascular disease, endothelial dysfunction, and infection are all correlated with inflammatory indicators, which may be used to predict inflammatory disorders.[54]

Tumour necrosis factor-α (TNF-α)

TNF-α is a key stimulus that triggers inflammation by interacting with the TNF receptor, IL-1 receptor, IL-6 receptor, and toll-like receptors (TLRs). The three most important intracellular signaling pathways produced by receptor activation are NF-κB, MAPK, and Janus kinase (JAK)-signal transducer and activator of transcription (STAT).[55] TNF-α plays a crucial role in the cascade of inflammatory reactions at both the local and systemic levels and exhibits direct involvement in the etiology of many systemic diseases. Because normal cells require TNF to maintain essential homeostatic processes including cell division, necrosis, and apoptosis, TNF is more important. TNF-α causes edema and immune cell infiltration by increasing the synthesis of lipid mediators on vascular epithelial cells through the activation of leukocyte adhesion molecules. Various studies have shown that anti-TNF-α medications are beneficial in treating inflammatory diseases.[56]

By triggering apoptosis and ECM build-up in glomerular and tubular regions, TNF-α is known to change glomerular filtration, tubular permeability, and reabsorption. The synthesis of cardiac-actin and a myosin-heavy chain may also be inhibited by TNF-α, which is linked to a loss in ventricular systolic function in heart failure (HF).[57] Furthermore, long-term high TNF- α levels in vivo could change the architecture of the heart by promoting

cardiomyocyte enlargement, raising cardiomyocyte mortality, and resulting in myocardial fibrosis. Additionally, rodents' lungs exhibit mild fibrosis and inflammation due to TNF-overexpression. In airway epithelial cells, TNF-α promotes fibroblast growth, epithelial cell hyperplasia, cell recruitment, and cell death.[58]

TNF-α is an essential pro-inflammatory cytokine that is involved in all phases of the growth of breast cancer and is found in the tumor microenvironment (TME). It affects metastasis, recurrence, and the epithelial-to-mesenchymal transition (EMT), as well as the survival and proliferation of tumor cells.[59] TNF-α is one of the most important pro-inflammatory cytokines found in the TME of breast tumors and is secreted by both stromal cells, especially M1 TAMs, and cancer cells. A type II transmembrane protein belonging to the cytokine TNF/TNFR superfamily, TNF-α is produced by the TNF gene.[60] However, it can function as both a membrane-integrated protein and a soluble molecule at the beginning of numerous signaling cascades by interacting with its two different receptors, TNFR1 and TNFR2. TNFR1 is expressed by a variety of cell types, including tumor epithelial cells, whereas TNFR2 is largely expressed by hematopoietic cells as a transmembrane protein.[61] The recent discovery of TNFR2 expression in breast cancer tissues may have prognostic consequences. As such, TNF-α was considered one of the most promising anti-cancer cytokines. Since then, two main mechanisms for its anti-cancer action have been proposed. First, it was found that the local administration of exogenous TNF-α promotes the destruction of the tumor vasculature, thus causing indirect necrosis of tumor cells.[62] In addition, TNF-α appeared to synergize with liposome-mediated chemotherapy by increasing blood vessel permeability and, thereby, facilitating drug accumulation at the tumor site. Secondly, it was found that high levels of exogenous TNF-α administration may act directly on malignant cells by inducing apoptosis, but that the cytotoxic effects may emerge only in the presence of other metabolic inhibitors.[63] TNF activity has been linked to NP reaction development due to a NO-mediated mechanism that induces glial and neuronal death. It is suggested that it protects against excitotoxic amino acids and aids in the maintenance of intracellular Ca^{2+} levels.[64]

Nuclear factor-kappa B (NF-κB)

The transcription of genes implicated in the inflammatory and anti-apoptotic responses is strongly encouraged by NF-κB. NF-κB is crucial for a variety of features of immune responses. Through two key signaling pathways, NF-κB is activated in response to immunological and stress stimuli.[65] Additionally, NF-κB is essential for healthy immune responses to infections, but aberrant NF-κB activation is a significant contributor to inflammatory disorders. Blocking this pathway is a viable strategy for the prevention of unfavorable cardiac remodeling because activation of NF-κB is closely associated with the emergence of heart expansion and hypertrophy.[66]

The processes of inflammation, immunological response, survival, and apoptosis all require the transcription factor NF-κB. Members of the NF-κB family of transcription factors include p50, p52, and p65. Numerous enzymes, intercellular inflammatory cytokines, pathogen-derived compounds, and other triggers can all cause NF-B to become active.[51] Under normal circumstances, NF-κB is inhibited by IB proteins in the cytoplasm. When IB is phosphorylated, the proteasome breaks it down, releasing NF-κB for nuclear translocation and gene transcription activation. The inflammatory response depends on the production of pro-inflammatory cytokines and the recruitment of inflammatory cells, both of which are regulated by this pathway. One of the most potent signaling pathways in the early immune response, the NF-κB route coordinates and controls a variety of immune system defense responses in response to potentially harmful stimuli such as viral infections.[67]

The NF-κB pathway initiates a strong and immediate immunological response as the first line of defense. Negatively regulating NF-κB transcriptional activity properly and quickly is essential to prevent immune system hyperactivation. Therefore, NF-κB pathway dysregulation is intimately associated with autoimmune illnesses, neurological diseases, allergies, and the emergence of various cancers, among other maladies.[68] Therefore, in addition to numerous genes involved in inflammation and cell survival, active NF-κB frequently causes the powerful expression of proteins involved in negative feedback loops, such as IκB. IκB is primarily in charge of keeping NF-κB (p65-p50) dimers in the cytoplasm in an unstimulated condition, but it is also in charge of bringing DNA-bound NF-κB subunits from the cell nucleus to the cytoplasm, which prevents the transcriptional response and returns the pathway to its resting state.[69]

Monocyte chemoattractant protein (MCP-1)

MCP-1 is responsible for triggering the production of pro-inflammatory cytokines and the attraction of macrophages and inflammatory cells.[70] It suggests that MCP-1 is a crucial mediator in the emergence of cardiac fibrosis.[71] According to several studies, the MCP-1 axis disruption reduces fibrosis in experimental models of myocardial infarction and ischemic cardiomyopathy, attenuating unfavorable cardiac remodeling. Since the level of renal damage in both inflammatory and non-inflammatory models of glomeruli coincides with the glomerular production of MCP-1, it also contributes to the advancement of glomerular lesions.[72]

High mobility group box 1 protein (HMGB1)

HMGB1, a member of the high mobility group nuclear protein family, is one of the most evolutionarily conserved proteins. Mammalian cells always contain HMGB1, which is then released into the extracellular media in response to the right stimuli. The inflammasome is crucial to this process.[73] The release occurs both actively and passively after inflammatory cells like dendritic cells and monocyte/

macrophages are stimulated by an inflammatory stimulus. HMGB1 enters the secretory lysosome after being transported from the nucleus to the cytoplasm and is then expelled from the cell by exocytosis. The damage signal is transmitted to nearby cells when it is released from necrotic or burst cells. HMGB1 controls cellular processes like autophagy and apoptosis in the cytoplasm. After being sequestered inside double-membrane delimited vacuoles, intracellular organelles undergo a process known as autophagy that results in their destruction. HMGB1 is essential for oxidative stress-mediated autophagy, making it a new target for the treatment of stress-related disorders.[74] HMGB1 aids in cell proliferation through autophagy, but it also activates endonuclease G and DNA fragmenting factor (DFF) to encourage apoptosis. As a damage-associated molecular pattern molecule (DAMP), HMGB1 released into extracellular fluid mediates the non-infectious inflammatory response.[75] Macrophage antigen-1, chemokine (C-X-C motif) receptor 4, receptor advanced glycation end product (RAGE), TLR2, TLR4, and mucin domain proteins are a few examples of surface molecules that extracellular HMGB1 can interact with. To stop metastasis and invasive migration, HMGB1's COOH-terminal motif is where RAGE and HMGB1 interact.[76] HMGB1 interacts with TLR2/4 receptors to promote the translocation of cytoplasmic NF-κB into the nucleus and start an inflammatory response. It binds to the chemokine (C-X-C motif) ligand 12 and interacts with CXCR4 to promote monocyte and fibroblast movement (CXCL12). As a result of HMGB1 activation, which is dependent on the IL-6/Stat3 signaling axis, miR-21 is overexpressed[77] (Figure 3).

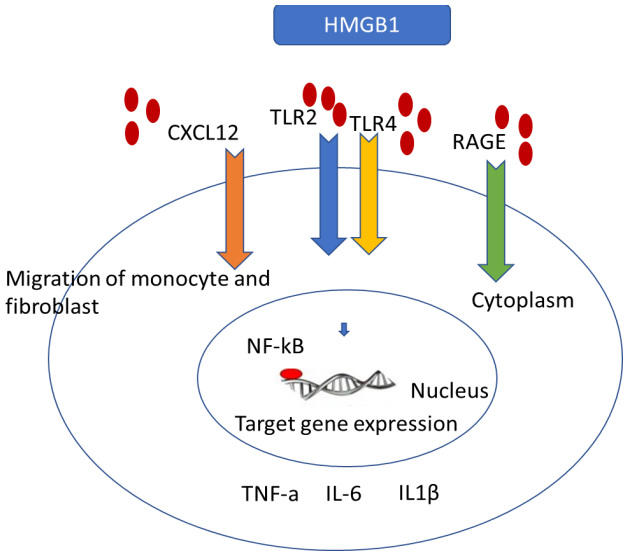

Figure 3. Interaction of extracellular HMGB1 released from inflammatory and necrotic cells with cell surface receptors. (**a**) HMGB1 binds to RAGE which induces nuclear transcription of NF-κB, leading to transcription and expression of target genes of cytokines and chemokines; (**b**) HMGB1 causes inflammation by interacting with TLR2/TLR4 (**c**) the heterocomplex formed by binding of HMGB1 and CXCL12 promotes the migration of monocytes and fibroblasts.

The critical role of adenosine A2A receptors (A2AR) in the control of inflammation

Low quantities of adenosine, an endogenous purine nucleoside, are detected in the extracellular space; nevertheless, ischemia, hypoxia, inflammation, and trauma are situations that cause an increase in extracellular adenosine.[78] Following the release, adenosine binds to particular adenosine receptors on the cell surface. Adenosine has four different receptor subtypes: A1, A2A, A2B, and A3 adenosine receptors. In particular, Gs-protein-coupled A2A and A2B adenosine receptors can raise intracellular cAMP levels by activating adenylate cyclase, which is a type of G-protein-coupled receptor. The majority of people think that adenosine's anti-inflammatory effect is primarily mediated by adenosine A2A receptors (A2ARs). A2AR activation on macrophages can increase the secretion of IL-10 in response to lipopolysaccharide (LPS) while decreasing the production of TNF-α and Nitric oxide (NO).[79, 80]

Although A2ARs are present throughout the body, the immune system and the striatopallidal system in the brain have the highest levels of A2AR expression. Adenosine activates immune cells' A2AR, which raises intracellular cAMP levels. An intracellular off signal called cAMP blocks intracellular signal pathways, which stops immune cells' pro-inflammatory activities. Using sub-threshold dosages of inflammatory stimuli, A2AR-deficient animals developed considerably worse liver damage and sepsis, revealing the crucial role of A2ARs in the regulation of inflammation and protection from tissue harm.[81]

Jun N-terminal kinase (JNK) pathway

Both leukocytes and non-leukocytes can be stimulated by JNK to produce an inflammatory response. The transcription factor AP-1 is a key method by which the JNK pathway induces inflammation, even though the stimuli that activate JNK can differ depending on the type of cell and kind of tissue injury.[82,83] TNF-α, CCL2, and leukocyte adhesion molecules like Vascular cell adhesion protein 1(VCAM-1) are just a few of the many genes that are regulated by JNK's ability to phosphorylate c-Jun and facilitate dimerization with c-Fos.[84] Therefore, JNK activation in endothelial cells can encourage leukocyte adhesion and transmigration by increasing adhesion molecules and chemokines, whereas JNK activation in epithelial cells (like those in the injured kidney, lung, or liver) can attract and activate leukocyte populations by producing chemokines and cytokines.[85] JNK also phosphorylates activating transcription factor 2 (ATF-2), which is involved in the transcription of genes involved in the inflammatory response. JNK signaling also contributes to the activation of the Th1 and Th2 T cell subsets. TNF-α, IL-1, LPS, and oxidative stress are among the triggers that might cause inflammation by activating JNK/AP-1 and NF-κB.[86] In addition, JNK can promote IκB degradation to directly activate NF-κB. Thus, NF-κB controls JNK-dependent cell death whereas JNK/AP1 and NF-κB can

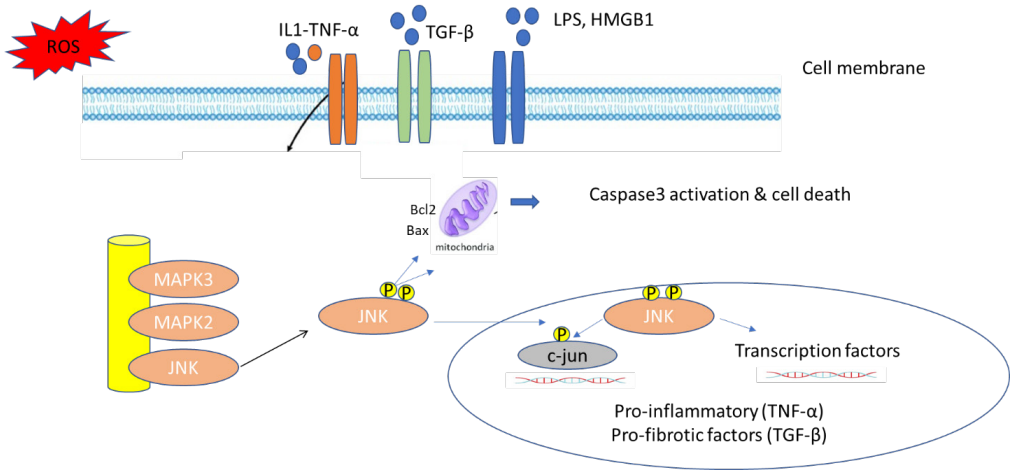

Figure 4. Schematic diagram of the JNK signaling pathway; The JNK signaling pathway is shown schematically. Members of the mitogen-activated protein kinase kinase kinase (MAP3K) family can be triggered by pro-fibrotic growth factors and inflammatory cytokines. MAP3K activation may also be caused by other elements including osmotic stress and reactive oxygen species (ROS). The scaffold protein (JNK-interacting protein-1) maintains the individual members of the MAP3K and MAP2K families as well as JNK close and supports a quick succession of phosphorylation events leading to phosphorylation of the activation site of JNK. B cell lymphoma (Bcl-2) and Bcl-2 associated x-protein are two molecules that the activated JNK can use to drive mitochondria-dependent apoptosis after dissociating from this complex (Bax). JNK activation can encourage fibrosis, inflammation, and cell death.

coordinate the inflammatory response. Therefore, by its pro-apoptotic and pro-inflammatory effects, activation of the JNK pathway may aid in the promotion of renal fibrosis. There is also proof that JNK signaling can directly enhance the fibrotic response[87] (Figure 4).

The Janus kinase-signal transducer and activator of transcription (JAK-STAT)

The JAK-STAT pathway is a signaling mechanism that allows external stimuli to impact gene expression. It is made up of cytokines, growth factors, interferons, and related molecules including leptin and growth hormone.[51] When ligands bind to JAKs attached to receptors, they become active and phosphorylate one another, creating docking sites for STATs, latent cytoplasmic transcription factors. Before being sent to the nucleus, STATs recruited from the cytoplasm are phosphorylated and then dimerized. Phosphorylation of tyrosine is necessary for STAT dimerization and DNA binding.[88] The direct translation of an external stimulus into a transcriptional response is made possible by JAK/STAT signalling. The JAK-STAT proteins are activated when members of the IL-6 family engage with plasma membrane receptors. Target genes' promoters are bound by translocated STAT proteins in the nucleus. NF-κB, MAPK, or JAK-STAT activity dysregulation has been linked to autoimmune, metabolic, inflammatory, and cancer illnesses. When receptors are active, crucial intracellular signalling pathways like the MAPK, NF-κB, and JAK-STAT are activated.[89] In response to various stimuli, such as osmotic stress, mitogens, heat shock, and inflammatory cytokines (such as IL-1, TNF-α, and IL6), the MAPK pathway is a collection of serine/threonine protein kinases that regulates cell proliferation, differentiation, survival, and apoptosis (Figure 5).

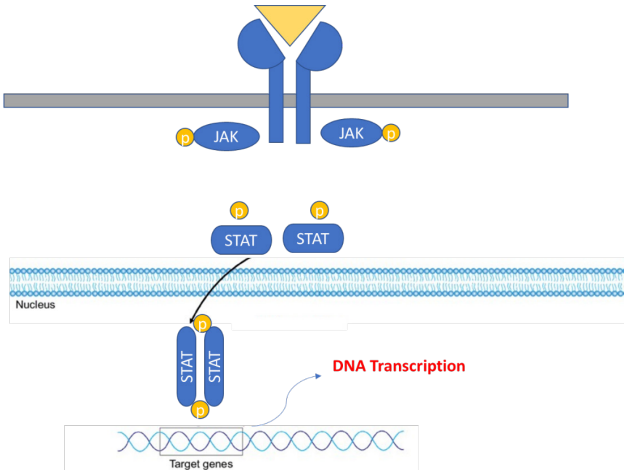

Figure 5. JAK-STAT signaling pathway illustration. Notes: Particular ligands bind to their associated receptors to activate the JAK component. To activate its kinase function, JAK phosphorylates its tyrosine component, which then phosphorylates the STAT component. STATs that have been activated go into the nucleus to encourage DNA transcription. JAK: Janus kinase, and STAT: signal transducer and activator of transcription.

Matrix metalloproteases (MMPs)

Many different cell surface proteins, including adhesion molecules, receptors, growth factors, and cytokines, are degraded by a family of extracellular proteases called zinc-dependent matrix metalloproteases.[90] By supporting growth and regeneration activities in healthy conditions, MMP-9, which is produced in migrating growth cones, is thought to mediate the cellular extracellular environment. During the inflammatory response in injured tissue, ROS, mechanical stimulation, and the MAPK pathway activate transcription factors including AP-1 and NF-B, which affects how neuropathic pain manifests. MMP-2 and MMP-9 also play a crucial part in this process. These factors have a direct impact on MMPs and other strong

inflammatory mediators like IL-1 and TNF-α. It is thought that MMPs, which are overexpressed in injured spinal cord tissue, mediate NP by cleaving IL-1. The fact that NP related to MMP-9 production is frequently linked to microglia activation, whereas NP associated with MMP-2 expression appears to be a substantial difference between these two MMP profiles.[91] MMP-9 overexpression after spinal cord injury (SCI) has a significant unfavourable impact on the blood-spinal cord barrier disintegration. As a result of this breakdown, immune cells like neutrophils and inflammatory substances can enter the area of injury, adding to further tissue damage and interacting with nearby astrocytes and microglia to produce more inflammatory cytokines.[92] Through necrotic processes including the formation of ROS, proteases, and nitric oxide, invading neutrophils will contribute to the lesion's expansion. The invasion of the injury site by macrophages and the surrounding astrocytes help to induce MMP-2. After SCI, animals lacking MMP-9 exhibited improved blood-spinal cord barrier integrity and decreased neutrophil and macrophage infiltration. This shows that blocking MMP-9 plays a neuroprotective effect after SCI.[93]

Matrix metalloprotease tissue inhibitors (TIMPs)

Matrix metalloprotease tissue inhibitor activity is critical to maintaining a healthy balance of extracellular matrix (ECM) turnover in a healthy state because it prevents the rampant breakdown of ECM proteins by constitutively active MMPs.[94] The most common mechanism of TIMP inhibition of MMP activity involves the binding of the N-terminal amino acid of the TIMP protein and the zinc ion coordinated to the MMP. This interaction between TIMPs and the catalytic domain of MMPs results in conformational changes that prevent MMP proteolytic activity. TIMP-1 was discovered to inhibit MMP-9 activity, suggesting that its activation may have a neuroprotective role in CNS injury. MMP control is correlated with MAPK activity. Activating the c-Jun and c-Fos binding domains also contributes to TIMP overexpression.[95]

Nitric oxide (NO)

One of the most powerful inflammatory mediators is nitric oxide (NO). Vasodilation, a rise in the production of free radicals, and the mediating of important cellular processes are all results of the stimulation of cyclic guanosine monophosphate (cGMP). NO concentrations above a specific point can be neurotoxic. NO synthase activity is typically the best predictor of NO-induced inflammation since NO has such a short half-life. The three types of nitric oxide synthases that are active during chronic inflammation are endothelial, neuronal, and inducible nitric oxide synthase (iNOS). TNF- α and IL-1 are believed to be the main cytokines that cause iNOS to be upregulated. Both of these cytokines are active a few hours to many days after injury and work through the nuclear transcription factor NF-κB.[96] Because they are released by wounded cells, overexpressed forms of NOS like neuronal and endothelial play a higher role in the inflammatory response just after the injury. In chronic constrictive models of SCI, iNOS inhibitors have been proven to improve function and reduce NP.[97] A generic NOS inhibitor has also been shown to lessen swelling, hyperalgesia, and allodynia following excitotoxic SCI. Research has unexpectedly suggested that specific endogenous NO activity may have neuroprotective effects in the years after SCI. Although the mechanism is unclear, rats given a new gabapentin derivative that releases NO showed reduced pain behaviour following injury. The multiple effects that NO mediates must be taken into account in treatment efforts aimed at blocking NO's role in NP formation.[98]

Transforming growth factor beta (TGF-β)

The control of cell proliferation is mediated by the cytokine TGF-β. Whatever the name, it is essential for maintaining the balance of immune cells and can either stimulate or inhibit cell proliferation. Additionally, it has been linked to the start of other illnesses, such as connective tissue problems, fibrosis, and cancer.[99] Genomic sequence analysis has led to the identification of 33 proteins that are members of the TGF family. Smad proteins are intracellular receptors and effectors that control target gene expression and mediate intracellular signaling.[100] TGF regulation and release of gene mutations have been linked to connective tissue diseases and skeletal disorders. Renal fibrosis is a typical side effect of several kidney conditions, including diabetic and membranous nephropathy. One of the important regulators appears to be TGF-β, which promotes the transition from epithelial to mesenchymal tissue, increases matrix protein synthesis, prevents matrix breakdown, and alters cell-to-cell communication.[101] One of the TGF-regulated pathways, TGF/Mothers against decapentaplegic homolog 3 (SMAD 3), is associated with tissue fibrosis through myofibroblast scar formation. The fibrosis process is also aided by non-canonical pathways like p53, JAK/STAT3, and the epidermal growth factor receptor (EGFR). TGF serum levels were found to be greater in diabetics by meta-analysis. As a result, pyrrole-imidazole (PI) polyamide, a promoter inhibitor of TGF-1, was studied in a mouse model, and it was found to minimize podocyte injury.[102] A phase 2 trial examined the impact of TGF-β1 monoclonal antibody therapy on renin-angiotensin-aldosterone system (RAAS) inhibitor therapy in individuals with diabetic nephropathy. Treatment has not reduced the decline of renal function. The long non-coding ribonucleic acids (lnc-RNA) Erbb4-IR and lnc-TSI are potential therapeutic targets for progressive renal fibrosis linked to the recently identified TGF/SMAD3 pathway. Obstructive nephropathy also has a pathophysiologic foundation in TGF/SMAD3-induced fibrosis.[103,104] The nuclear factor erythroid 2-like 2 (Nrf2)/SMAD7 pathways are one more molecular mechanism. Recently, the NRF-2 activator bardoxolone helped mice with tubular necrosis and interstitial fibrosis.[105]

Inflammation and Diseases

Chronic inflammation and infection are thought to be the primary causes of 15% of all human malignancies. Acute and chronic inflammation-mediated tissue injury is present in many organ systems, including the heart, pancreas, liver, kidney, lung, brain, digestive tract, and reproductive system.[106,107] Inflammation is an essential response to microbial invasion or tissue damage in order to preserve tissue homeostasis. An inflammatory pathway has been recognized as a significant molecular basis in the aetiology of many chronic diseases.[108] A growing amount of research suggests that excessive inflammation may have a significant role in the development and/or onset of stress-related illnesses. A significant amount of evidence points to the inflammatory response as the "common soil" of numerous diseases, including cancer, neurodegenerative disorders, psychotic diseases, and cardiovascular and metabolic diseases.[109]

Numerous disorders, including atherosclerosis, cancer, diabetes, cancer, and cardiovascular disease are linked to oxidative stress. As a result, the metabolites of oxidative stress can serve as indicators of an inflammatory response. Inflammatory reactions involve various cell types.[110] Macrophages are significant mononuclear phagocyte system members who contribute significantly to the development, maintenance, and resolution of inflammation.[111] Macrophages have a variety of roles, including delivering antigens, participating in phagocytosis, and regulating the immune response during inflammation by generating cytokines and growth factors. Mast cells are inflammatory effector cells that are present on the surfaces of epithelial cells and connective tissue matrices. Inflammatory mediators such as cytokines, chemokines, histamine, proteases, prostaglandins, leukotrienes, and serglycin proteoglycans are released by activated mast cells.[112]

Inflammation role in neuropathy (NP)

Inflammation is required for the production of NP. The development of NP has been associated with the accumulation and recruitment of inflammatory cytokines, chemokines, and prostaglandins, as well as changes in extracellular proteins, transmembrane receptor expression, immune cell infiltration, and intracellular adjustments regulated by ion channel activity and receptor signalling.[113] Despite the fact that most body tissues swell up after damage, the central nervous system differs from other body tissues in some ways. The only cells identified in the central nervous system are neurons, astrocytes, oligodendrocytes, and microglia. It is also understood that neurons have a finite ability to repair themselves. The absence of a lymphatic drainage system prevents the CNS from growing, which places restrictions on other surrounding tissues such the dura, spinal canal, and skull.[114] In addition, the blood-brain barrier triggers an inflammatory reaction unique to the CNS. The healing process is aided by growth factors and endogenous neurochemical mediators that are produced as a result of injury. Leukocytes are attracted to the site of inflammation in the CNS, infections are eradicated, necrotic tissue is phagocytized, and some types of injured tissues can facilitate repair mechanisms.[115] Additionally, it has been shown that neuroprotective properties of neurotrophic substances generated by microglia and astrocytes in response to cytotoxic factors produced by injured cells exist. On the other hand, it's hypothesized that the inflammatory response helps NP illnesses develop.[116] Numerous neurotrophic substances, including TNF-α, which have been shown to have neuroprotective characteristics, also increase the inflammatory response. Secondary damage is mediated by acute increases in proteases, nitric oxide, bradykinins, prostaglandins, and TNFα.[117]

The CNS's resident immune cells, known as microglia, are also constantly scanning their environment for foreign signals. They are a component of the innate immune response that is quickly activated in response to injury or infection, and they resemble the macrophage, the main immune cell of the peripheral nervous system (PNS), in many ways. Due to their greater levels of CD45 expression, diminished ability to deliver antigens, and reduced inflammatory response, microglia differ from macrophages.[118] Microglia express TLRs, allowing them to detect bacterial and viral molecular patterns. After a nerve injury, microglial cells in the ventral horn of the spinal cord form dense clusters surrounding the cell bodies of wounded motor neurons, much like how macrophages surround injured sensory neurons in the PNS. TNF-α, IL-1, IL-6, and NO are examples of inflammatory cytokines that are released after activation and can start an immune response.[119] Local spinal microglia and circulating monocytes reach the dorsal horn at the lesion site via three signalling pathways. TLR, a chemokine that activates on the CX3CR1 receptor, and CCL2 signalling through CCR2 are all involved. Microglial stimulation in the spinal cord reduces KCC2 expression, which helps to explain the mechanical hyperalgesia and spinal neuronal hyperactivity caused by diabetes. As a result of chemicals released by activated microglia in SCI, more inflammatory mediators are produced by the microglia. This increases dorsal horn hyperresponsiveness. The possibility for NP to develop even further is offered by this positive feedback loop. Through pathways including TNF-α and IL-1, as well as IL-6 in chronic conditions, microglial activation is necessary for the emergence and maintenance of below-level allodynia following SCI.[120]

Inflammation pathway in the gastrointestinal tract

The use of biological medicines that target cytokines is one of the most important types of therapy that is particularly helpful in the current treatment of IBD.[121] Exaggerated release of cytokines originating from innate immune cells, which are both proinflammatory and hence major drivers of adaptive T-cell function, is thought to be related to the development of IBD. Both TNF-α and IL-6 are key

therapeutic targets in the treatment of IBD. Antibodies targeting the TNF-α or IL-6 receptor signalling pathways have emerged as promising potential treatments for this condition. Similarly, cytokines produced by innate immune cells, such as IL-12 and IL-23, have been proven to be important therapeutic targets for Crohn's disease(CD). These cytokines are closely connected and encourage the growth of inflammatory T cells while inhibiting regulatory T cells.[122] There appears to be an abnormal Th2-like cytokine response in ulcerative colitis (UC), which may be connected with natural killer T (NKT) cells and is characterized by excessive IL-13 synthesis through a less well-understood pathway, making IL-13 an intriguing therapeutic target. Similarly, by the release of TGF-β, IL-10, and IL-35, some subsets of dendritic cells and macrophages can drive T cells into a regulatory phenotype that reduces inflammation. Thus, the final determinant of whether chronic inflammation or homeostasis will occur is the balance between regulatory T cells and proinflammatory T-helper cells.[123]

Myocardial inflammation

The underlying cause of myocarditis, myocardial infarction (MI), ischemia-reperfusion injury (I/R) injury, heart failure (HF), aortic valve problems, atherosclerosis, and hypertension is excessive or chronic myocardial inflammation that leads to significant myocardial injury.[124] Myocardial inflammation causes many substances, such as pro-inflammatory cytokines, cell surface molecules, and chemokines, to be produced by cardiac myocytes, which aid neutrophil infiltration into the heart. Additionally, myocardial inflammation is regulated by several mechanisms.[125] Inflammation is brought on by pattern recognition receptors (PRRs), crucial components of the innate immune system. PRRs can identify and respond to damage-associated molecular patterns (DAMPs), including exogenous pathogen-associated molecular patterns (PAMPs), which are conserved structures of pathogenic bacteria, and endogenous alarmins, which are created in response to stress or tissue damage.[126] The first line of innate host defense is cardiac myocyte inflammation, which is stimulated by TLR activation by DAMPs. This inflammation also controls adaptive immunological responses.[127] TLR4, a vital member of the TLR family, has been linked to inflammatory bowel illness, autoimmune disorders, neuronal degeneration, metabolic diseases brought on by obesity, and cardiovascular disease.[128] TLR4 has a critical role in myocardial inflammation, which includes myocarditis, MI, I/R damage, HF, aortic valve problems, atherosclerosis, and hypertension. TLR4 has the greatest levels in the heart when compared to other TLRs. TNF-α, IL-6, IL-1, IL-18, and immunological antigens were among the inflammatory mediators that were found to be higher in the plasma of HF patients. These results validated the "cytokine theory," which postulated that inflammation contributed to HF development.[129] Proinflammatory cytokines and chemokines that are abundantly generated and released in HF include TNF-α, IL-1, IL-6, IL-18, and MCP-1, and their plasma levels are inversely correlated with organ damage.[130] These cytokines may originate from the heart's cardiomyocytes, endothelial cells, or fibroblasts as well as from extracardiac tissues or invading inflammatory cells like macrophages. TNF-α, IL-1, and IL-6 levels have been found to rise, but some studies that support this finding have small sample sizes or lack adequate adjustment. Numerous studies have found elevated levels of TNF receptors (TNFR1 and TNFR2) or molecules connected to the TNF receptor superfamily, such as Fas or osteoprotegerin (OPG).[131]

HF is caused by structural and functional cardiac changes. The structural modifications include structural alterations, myofibroblast transformation of cardiac fibroblasts, and cardiomyocyte hypertrophy. This remodelling impairs both the systolic and diastolic functions of the heart and increases the risk of proarrhythmia.[132] Many of the pathogenic effects at the tissue level are caused by angiotensin II, which causes lung fibrosis and low-level pulmonary clearance via ERK1/2 kinases. Angiotensin II induces MAPK in cardiac fibroblasts, resulting in myocardial hypertrophy, and upregulates COX-2.[133] Angiotensin II also enhanced IL-6 and TNF-synthesis in the heart and kidneys, according to *in vivo* studies. Proinflammatory cytokine release is maintained by increased endothelin 1 expression and decreased natriuretic peptide levels, which are connected to increased NO synthesis by iNOS and decreased myocardial contractility.[134] TNF- and IL-1 infusion weakens left ventricular contractility and prolongs operative end-diastolic volume. By altering the myocardial calcium current and Na^+/Ca^{2+} exchange, TNF and IL-6 also lower the peak intracellular Ca^{2+} levels. TNF-α also makes myofilaments less sensitive to calcium. Cardiovascular depressants TNF-α, IL-1, and IL-6 can have both immediate and delayed effects.[135] Through their influence on constitutive nitric oxide synthase, they generate baseline levels of NO (cNOS). In animal experiments, they activate iNOS quickly (30 min), increasing NO levels and generating ROS, particularly peroxynitrite. The adrenergic receptors' decreased responsiveness, which is NO-dependent, is another mechanism that decreases contractility. Animal studies have demonstrated that mitochondrial Ca^{2+} is a crucial regulator of energy use and controls mitochondria-induced cell death. The extremely adaptable organelles known as cardiomyocyte mitochondria are responsible for the production of adenosine triphosphate (ATP), which is necessary for cell integrity and contractility.[136] Another warning indicator is the ATP released by apoptotic cells, which changes the expression patterns of numerous cytokines, including IL-1, IL-6, chemokine C-X-C motif ligand 1 (CXCL-1), and MCP-1.[137]

Fibrosis is brought on by macrophage activation and infiltration and impairs contractility. Cardiomyocyte death and heart failure are brought on by calcium influx brought on by BCL2/adenovirus E1B interacting protein 3 (BNIP3) overexpression or leakage *via* ryanodine receptor type 2

(RYR2) mutant channels.[130] Two defensive mechanisms that stop mitochondrial breakdown include mitophagy and the mitochondrial unfolded protein response. Urolithin A, a mitophagy inducer, enhances mitochondrial activity by lowering cardiac depression brought on by systemic inflammation.[138] In mice, deletion of the regulatory FUN14 domain-containing protein 1 (FUNDC1) blocks calcium input from the cytoplasm via IP3R2, maintaining mitochondrial integrity. Pharmacological intervention can improve mitochondrial function. It has been demonstrated that anti-inflammatory medications enhance mitochondrial function.[139]

Inflammation's role in kidney injury

Inflammation in the kidneys can send cytokines and chemokines into the bloodstream, leading organs further away, such as the heart and lungs, to malfunction.[140] As a result, renal TLR4 activation triggers a critical signalling cascade that affects nearby and distant organs, causing systemic inflammation that significantly worsens the clinical state. TLR4 inhibition or inactivation is a promising target for the prevention or treatment of AKI. NLRs (Nod-like receptors) are intracellular sensors found throughout the kidney and have been linked to several AKI models, in contrast to TLRs, which are situated on the surfaces of cells and endosomes.[141] PAMPs and DAMPs are recognized by immune cells resident in the body as well as renal parenchymal cells that express TLRs and NLRs.[142] Proinflammatory cytokines and chemokines are released when these receptors are activated *via* intracellular pathways like JNK, MAPK, and NF-κB. When TLR4 and/or TLR2 were absent, along with their adaptor protein MyD88, IRI-exposed mice suffered less kidney damage. According to the evidence now available, alarmins generated after cell damage and/or death bind to these receptors, activating them and causing the development of downstream inflammatory processes. TLR4 is required for the development of renal injury in mice with cisplatin-induced AKI.[143] One way it might affect the condition is by increasing FGF23, which regulates phosphate homeostasis, causes problems with minerals and bones, and has been connected to all-cause mortality in CKD patients. According to a study, TNF-α levels rise as diabetic nephropathy worsens and are higher in diabetic patients than in healthy individuals. Additionally, higher soluble TNFR levels have been linked to diabetic renal disease, where they have been shown to independently predict incident cardiovascular disease.[144]

The significance of TNF in diabetic nephropathy led researchers to examine additional kidney conditions. Higher levels of circulating TNFR have been linked to poor renal function and histopathologic abnormalities in Immunoglobulin A Nephropathy (IgAN) patients. Additionally, starting points indicated eventual renal impairment. According to the Heart and Soul study, TNFR affects deteriorating renal function. TNF-α levels were associated with proteinuria and impaired renal function, indicating that it may be used as a biomarker to assess the severity of illness[145] (Figure 6).

Inflammasomes also have a role in pyroptosis, mitochondrial regulation, and myofibroblast differentiation in CKD patients. They also control the inflammatory response. The inflammasomes' nucleotide oligomerization domain (NOD), leucine-rich repeat (LRR), and pyrin domain-containing protein 3 both activate IL-1 and IL-18 (NLRP3). Inflammation develops in CKD patients as a result of its activation, which encourages renal phagocytes and podocytes to produce IL-1 and IL-18.[146] Renal fibrosis, diabetic nephropathy, obesity-related kidney disease, chronic glomerulonephritis, IgAN, and renal damage brought on by crystal-related nephropathy have all been linked to NLRP30 in studies. Current research indicates

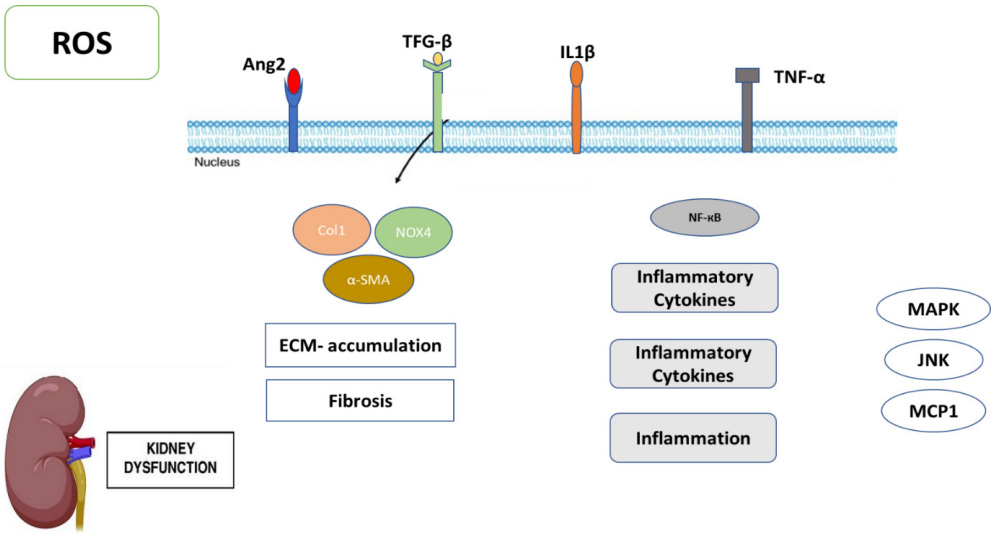

Figure 6. Schematic diagram of induction of Kidney injury. Reactive oxygen species (ROS) induce the activation of angiotensin II(Ang2), transforming growth factor-beta (TGF-β), Interleukin 1 beta (IL1β), nuclear factor-kappa B (NF-κB), Jun N terminal kinase (JNK), monocyte chemoattractant protein 1 (MCP1). Continuous activation of these inflammatory markers will increase the expression of alpha-smooth muscle actin (α-SMA), and ECM accumulation and increase the incidence of fibrosis.

that reducing plasma oxalate levels may help prevent or treat CKD because elevated plasma oxalate levels trigger the activation of inflammasomes. Allopurinol, which has been demonstrated to reduce renal inflammation by blocking the NLRP3 inflammasome, has been linked to similar findings.[147] Controlling cell apoptosis, tissue remodeling, and mitochondrial function are only a few of NLRP3's inflammasome-independent roles in the pathophysiology of CKD. Nephron-calcinosis and hyperoxaluria, two diseases associated with NLRP3, are influenced by TGF receptor signaling and macrophage polarization. With implications for renal function, renal fibrosis, hypertension, atherosclerosis, and diabetes mellitus, NLRP3 suppression has also been shown to be a potential therapeutic target in numerous studies.

Inflammation's role in lung injury

Inflammation plays a crucial role in lung injury.[148] When the lungs are exposed to harmful substances, such as viruses bacteria, or environmental pollutants, the immune system responds by triggering an inflammatory response. This response is designed to protect the body from further harm, but it can also lead, to tissue damage and lung injury if it becomes too severe or prolonged. In the case of lung injury, inflammation can cause several different effects. In summary, inflammation is a necessary response to lung injury, but it can also cause tissue damage and contribute to the progression of lung disease if it becomes too severe or prolonged. Managing inflammation is an important aspect of treating lung injury and preventing further damage to the lungs[149] (Table 1).

Inflammation's role in liver injury

Inflammation plays a key role in liver injury by activating immune cells, producing cytokines, and promoting tissue damage and fibrosis.[150] Managing inflammation is an important aspect of treating liver injury and preventing further damage to the liver[151] (Table 2).

Inflammation's role in pancreas injury

The pancreas is a glandular organ that produces digestive enzymes and hormones such as insulin and glucagon.[152] Inflammation of the pancreas, also known as pancreatitis, can be caused by a variety of factors, including alcohol abuse, gallstones, and high levels of triglycerides in the blood.[153] During pancreatitis, inflammation causes the release of enzymes and cytokines that can damage the pancreatic tissue.[154] The enzymes can also leak out of the pancreas and into surrounding tissues, causing further damage and inflammation. In severe cases, pancreatitis can lead to the formation of cysts or abscesses within the pancreas, which can be life- threatening. Chronic inflammation of the pancreas can also lead to the development of pancreatic cancer.[155] Inflammation can cause changes in the DNA of pancreatic cells, leading to mutations that can result in cancerous growth. Overall, inflammation is a key factor in pancreatic injury and disease. Managing inflammation through lifestyle changes, such as avoiding alcohol and maintaining a healthy diet, can help reduce the risk of developing pancreatic problems.

Table 1. Role of inflammation on lung disease.

Role of inflammation in lung injury	Effects
Production of ROS	ROS can damage lung tissue and impair lung function.[156]
Increased permeability of blood vessels	Allows fluid and immune cells to leak into the lung tissue, causing edema and further damage.[157]
Recruitment of immune cells	Neutrophils and macrophages can release toxic substances that further damage the lung tissue.[158]
Necessary response	Inflammation is a necessary response to lung injury.[159]
Potential for tissue damage	Inflammation can cause tissue damage and contribute to the progression of lung disease if it becomes too severe or prolonged.[160]
Importance of managing inflammation	Managing inflammation is an important aspect of treating lung injury and preventing further damage to the lungs.[160]

Table 2. Role of inflammation in liver injury.

Role of inflammation in liver injury	Effects
Activation of immune cells	In response to liver injury, immune cells such as macrophages and neutrophils are activated and recruited to the site of injury.[161]
Production of cytokines	These immune cells produce cytokines, which can further activate other immune cells and promote inflammation.[162]
Tissue damage	Inflammatory cells and cytokines can directly damage liver cells, leading to liver dysfunction and impaired liver function.[163]
Fibrosis	Chronic inflammation can also lead to the development of liver fibrosis, which is characterized by the buildup of scar tissue in the liver.[164]
Importance of managing inflammation	Managing inflammation is a critical component of treating liver injury and preventing further liver damage.[165]

Conclusion

According to clinical investigations, inflammatory pathways, which include common pro-inflammatory mediators and regulatory pathways, play a significant role in the etiology of several chronic disorders connected to aging. When organ illness advances in a harmful way, inflammation is usually a primary factor. There are three crucial factors to consider. The pathways NF-κB, MAPK, TNF-α, TGF-β, and JAK-STAT all play important roles. Inflammation has a role, and dysregulation of one or more of them can lead to disease. Inflammation-related diseases may be caused by one or more of these aforementioned mechanisms. Briefly, our understanding of the inflammatory response has improved. New routes and molecular mechanisms will definitely lead to improvements in cancer prevention and the treatment of inflammatory diseases.

Author Contributions

Samar A. Antar: Conceptualization, Investigation, Writing - Original Draft. Ayman M. Mahmoud: Investigation, Writing - Review & Editing. Walied Abdo: Investigation, Writing - Review & Editing. Cherry Gad: Investigation, Writing - Review & Editing. Ahmed A. Al-Karmalawy: Conceptualization, Methodology, Investigation, Supervision, Writing - Original Draft.

Conflict of Interest

The authors report no conflicts of interest.

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