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MOLECULAR MECHANISMS OF INFLAMMATION IN DISEASE PROGRESSION AND THERAPEUTIC TARGETING

Dr. Karthika Padmavathy[1*], Dr. Minnath Beevi[2], Dr. Ajab Singh Choudhary[3], Poonam Kumari[4], Prianka Kishore Aedla[5], Anuneet Kaur[6]

[1*]Professor, Department of Pathology, Sri Lalithambigai medical college and hospital, Dr. MGR Educational and Research Institute, Chennai, Email Id: karthika.path@drmgrdu.ac.in.
[2]Assistant Professor, Department of Pharmacy Practice, Yenepoya Pharmacy College and Research Centre, Yenepoya, Deemed to be University, Derlakatte, Karnataka, Email Id: drminnathbeevi@gmail.com, Orcid Id: 0009-0006-7844-8309.
[3]Assistant Professor, Medical Laboratory Technology, SOAHS, Noida International University, Sector 17 A Yammuna Expressway Greater Noida, UP, Email Id: ajab.singh@niu.edu.in, Orcid Id: https://orcid.org/0000-0002-2338-9106.
[4]Assistant Professor, Department of Pharmacology, Himachal Pharmacy College, Majhauli (Nalagarh) Himachal Pradesh-174101, India, Email Id: poonamthkr5@gmail.com, Orcid Id: 0009-0000-3069-8102,
[5]Student, The International School Bangalore, Karnataka-562125, India, Email Id: priankakishoreaedla@gmail.com.
[6]Assistant Professor, Department of Pharmacology, Himachal Pharmacy College, Majhauli (Nalagarh) Himachal Pradesh-174101, India, Email Id: kauranunit145@gmail.com, Orcid Id: 0009-0005-1964-752X.
*Corresponding Author: Dr. Karthika Padmavathy, Email Id: karthika.path@drmgrdu.ac.in.

ABSTRACT
Inflammation is a fundamental biological response required for host defense, tissue repair, and maintenance of homeostasis. Although acute inflammation is protective and self-limiting, persistent or dysregulated inflammation contributes to the initiation and progression of many chronic diseases. This review aims to examine the molecular mechanisms through which inflammation influences disease progression and to discuss major therapeutic targets and emerging anti-inflammatory strategies. Inflammatory responses are coordinated by immune and non-immune cells, including macrophages, neutrophils, lymphocytes, endothelial cells, epithelial cells, and stromal cells. These cells communicate through cytokines, chemokines, prostaglandins, reactive oxygen species, and damage-associated molecular patterns. Key signaling pathways, including NF-κB, JAK/STAT, MAPK, Toll-like receptor signaling, and inflammasome activation, regulate inflammatory gene expression, immune-cell recruitment, and tissue remodeling. When inflammation fails to resolve, sustained cytokine production, oxidative stress, immune dysregulation, fibrosis, angiogenesis, and extracellular matrix remodeling promote disease progression in cancer, autoimmune disorders, cardiovascular disease, metabolic dysfunction, neurodegeneration, and chronic infections. Therapeutic targeting of inflammatory pathways has advanced substantially through corticosteroids, non-steroidal anti-inflammatory drugs, biologics, cytokine blockade, JAK inhibitors, COX inhibitors, and emerging inflammasome inhibitors. Understanding the molecular basis of inflammation is essential for developing precise and effective therapies. Future strategies should focus on biomarker-guided treatment, resolution-based therapies, RNA-based approaches, microbiome modulation, and personalized interventions that suppress pathological inflammation while preserving protective immunity.

KEYWORDS: Inflammation; Cytokines; Inflammasome; Targeted therapy.

1. INTRODUCTION
Inflammation is a basic biological reaction, which helps organisms to sense, contain, and remove harmful stimuli and recover tissue integrity subsequent to injury. It is traditionally linked with infection and tissue damage, yet modern immunology expands the definition of inflammation to a coordinated program of protection and encompasses the immune-activation processes, vascular response, metabolic and tissue-repair processes. Inflammation, in this sense, is not a pathology but is a significant part of host defence and physiological adjustment. Medzhitov (2008) pointed out that inflammation has extensive evolutionary foundations and plays vital physiological functions of facilitating resistance to infection, healing of damaged tissues and environmental adaptation. Nevertheless, the same processes that safeguard the host may turn out to be detrimental when they are too many, too long or triggered improperly.
The process of inflammation is closely intertwined with homeostasis. Homeostasis is the process or power of tissues and organisms to maintain functional stability despite external and internal stresses. In response to a perturbation of homeostatic balance by infection, trauma, toxins, metabolic stress, or tissue injury, inflammatory signaling is triggered to eliminate the cause of the perturbation and recover normal tissue function. Kotas and Medzhitov (2015) suggested that inflammation could be viewed as a subset of a larger system of homeostatic control, where the tendency to become diseased is determined by the effectiveness with which the organism perceives change, generates an adaptive response, and restores homeostasis. This perspective matters as it changes the perspective on inflammation as a merely defensive response to a sophisticated regulatory mechanism that shapes health, resilience and susceptibility to disease.

Infectious and non-infectious stimuli may cause the inflammatory response. In the case of infection, the immune cells identify the pathogen-associated molecular patterns and trigger antimicrobial responses. Nevertheless, the inflammation may take place without the presence of pathogens. Endogenous danger signals are released by harmed, strained, or dying cells and cause sterile inflammation. These damage-related molecular patterns trigger innate immune receptors and cytokine production, leukocyte recruitment and tissue repair processes (Chen & Nuñez, 2010). Sterile inflammation is particularly applicable to chronic conditions like atherosclerosis, cancer, metabolic dysregulation, neurodegeneration, and ischemic injury, where cell damage, metabolic imbalance, crystals, oxidative stress, or extracellular matrix disruption can be the trigger of inflammation instead of microbial infection.

An effective inflammatory response involves initiation and resolution. The acute inflammation is often short-lived. It is characterized by vasodilation, vascular permeability, neutrophil and monocyte recruitment, cytokines and lipid mediators, and tissue repair. When the damaging stimulus is no longer present, the resolution mechanisms inhibit the additional recruitment of leukocytes, eliminate apoptotic cells, reinstatement of barrier functioning and tissue remodeling. Fullerton and Gilroy (2016) defined resolution as a process that is active and well-regulated, as opposed to a passive decrease in inflammatory activity. The therapeutic implications of this concept are significant since the encouragement of resolution can regulate inflammation without suppressing protective immunity in general.

Conversely, nonresolving inflammation occurs when inflammation reactions are not resolved properly. Nathan and Ding (2010) termed nonresolving inflammation as one of the key processes underlying chronic tissue injury and disease. To sustain a pathological cycle of injury and repair, long-lasting production of cytokines, leukocyte infiltration, oxidative stress, and immune-cell activation are perpetuated in this state. The inflammatory process, which is supposed to achieve homeostasis, turns into a cause of tissue dysfunction. This shift in protective inflammation to chronic inflammatory pathology is core to most of the major diseases, such as autoimmune diseases, cardiovascular disease, cancer, chronic infections, metabolic syndrome, and neurodegenerative disease.

The applicability of chronic inflammation throughout the life span has become more and more evident. Furman et al. (2019) demonstrated that chronic inflammation is a factor in the development of diseases that start in early life up to old age by affecting the immune system, metabolism, tissue performance, and physiology of the body in general. Persistent inflammation of low grade may overtime build up and predispose to various disorders such as diabetes, heart disease, frailty, cancer and cognitive decline. The relevance of this disease implies that the phenomenon of inflammation does not exist in the traditional diseases of inflammation; it is a universal biological process that ties together the various pathological processes.

The contemporary concept of inflammation thus needs to consider both the protective and pathogenic aspects of the concept. Medzhitov (2010) emphasized the fact that inflammation is a growing area of study due to its overlaps with immunity, metabolism, tissue biology, microbiology, and chronic disease studies. The inflammatory response depends on molecular pathways that define whether the response will be resolved successfully or the pathologic process will develop. The knowledge of these pathways is critical in determination of therapeutic targets that can help in reducing the destructive inflammation without compromising on host defense and tissue repair. To this end, this review will explore the cellular and molecular inflammation mechanisms, the key signaling pathways that govern inflammatory responses, the contribution of chronic inflammation to disease pathogenesis, and the current and emerging therapeutic targeting strategies.

2. Cellular and Molecular Basis of Inflammation

The complex network of immune and non-immune cells works to coordinate the inflammation by perceiving tissue damage, infection, or cellular stress and converting these signals into molecular responses. Macrophages are the key regulators of the immune system since they combine environmental signals and shape up context-specific phenotypes. They help in the clearance of pathogens, the removal of apoptotic cells, tissue repair, and resolution, although chronic activation of the macrophages can also aid chronic inflammation, fibrosis, and tissue destruction (Murray & Wynn, 2011). The tissue-resident macrophages are of particular relevance as they are developed by specific developmental programs and they protect local immune surveillance and tissue homeostasis in organs, including liver, brain, lung, and skin (Ginhoux & Guilliams, 2016).

The other key cellular component of the inflammatory response is neutrophils. They are rapidly recruited into injured or infected tissues using chemotactic gradients, endothelial adhesion and transmigration. After activation, neutrophils can eliminate pathogens by the process of phagocytosis, degranulation, reactive oxygen species, and neutrophil extracellular traps. Nonetheless, over- or prolonged activation of neutrophils may hurt host tissues and increase inflammatory pathology (Kolaczkowska & Kubes, 2013). Lymphocytes also influence inflammation, connecting innate and adaptive immunity. Inflammatory intensity is regulated by T cells using effector and regulatory subsets and B cells using antibody production, antigen presentation and cytokine release.

Structural cells that are non immune also actively contribute to inflammation. Endothelial cells control leukocyte recruitment through the expression of adhesion molecules and vascular permeability. Epithelial cells serve as sentinel cells that reveal the presence of microbial products and tissue injury, secrete cytokines and chemokines, and trigger the recruitment of immune cells. Pathological signaling, tissue remodeling, and disease progression may be maintained in chronic inflammatory environments by stromal and epithelial cells. This communication between inflammatory cells and tissue-resident cells is especially obvious in cancer, where inflammatory mediators have the potential to promote angiogenesis, matrix remodelling, tumor-cell survival and immune evasion (Coussens & Werb, 2002).

At the molecular level, cytokines, chemokines, lipid mediators, reactive oxygen species, and danger signals mediate inflammation. The immune-cells are controlled by cytokines like tumor necrosis factor, interleukins, and interferons,

which regulate the activation, differentiation, and survival of immune-cells, yet dysregulated networks of cytokines play a role in autoimmune, metabolic, infectious, and degenerative diseases (Kany et al., 2019). Chemokines control the movement of leukocytes and define the spatial structure of inflammatory infiltrates, thus bridging the relationship between cell migration and tissue injury associated with diseases (Turner et al., 2014). Prostaglandins and other lipid mediators regulate vascular tone, pain, fever, and leukocyte activity, and reactive oxygen species play a role as antimicrobial effectors and as mediators of oxidative tissue damage. Damage-associated molecular patterns released by injured or stressed cells activate pattern-recognition receptors in sterile inflammation to trigger inflammatory cascades without infection (Zindel & Kubes, 2020). Inflammation, therefore, is an expression of a combined cellular and molecular program, which is protective under normal conditions but pathogenic under abnormal conditions, such as exaggerated, unresolved, or maladaptive. The predominant immune and structural cells in inflammatory reactions are displayed in Table 1 and represented in Figure 1.

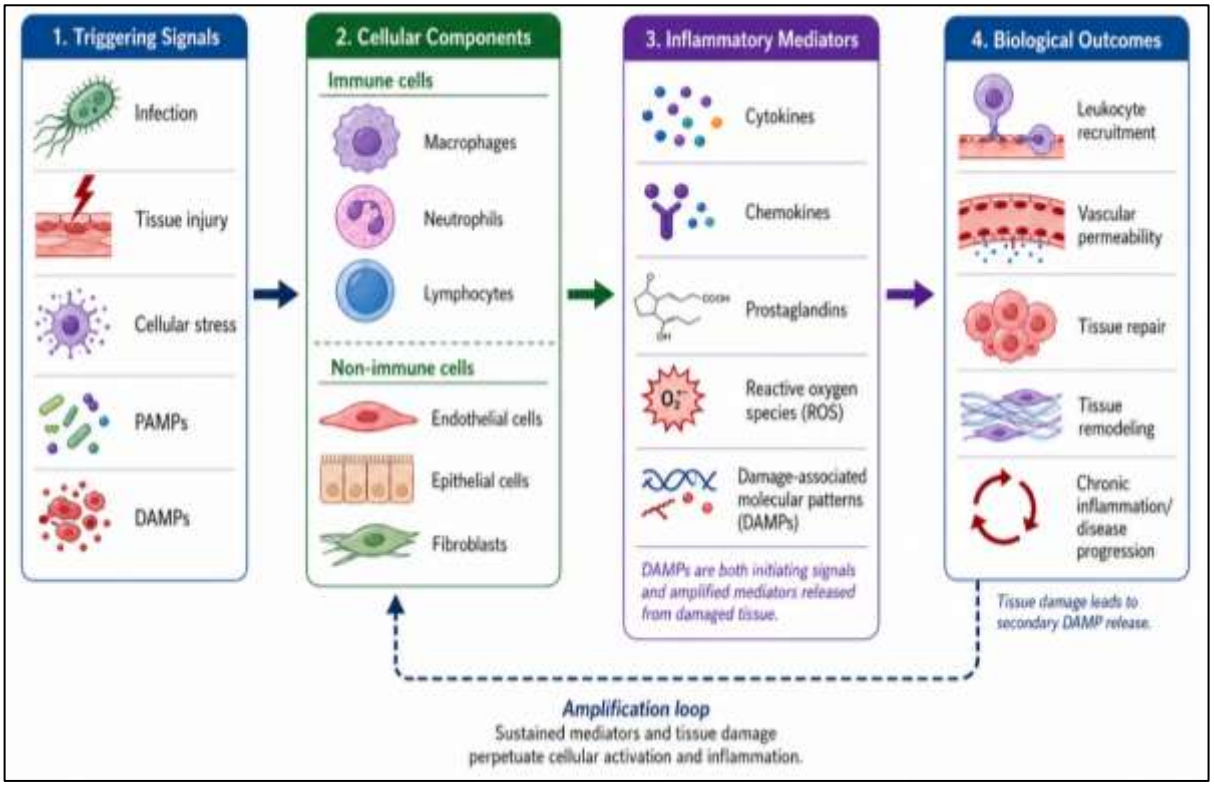

Figure 1. Cellular and Molecular Network of Inflammation

Table 1. Major Cellular Contributors to Inflammation

Cell type	Major inflammatory role	Key mediators/functions	Disease relevance
Macrophages	Coordinate innate immunity, phagocytosis, tissue repair, and chronic inflammation	TNF-α, IL-1β, IL-6, ROS, growth factors	Autoimmune disease, fibrosis, cancer, metabolic inflammation
Neutrophils	Rapid response to infection and tissue injury	Phagocytosis, degranulation, ROS, neutrophil extracellular traps	Acute inflammation, chronic tissue injury, autoimmune pathology
T lymphocytes	Regulate adaptive immune responses and inflammatory memory	IFN-γ, IL-17, IL-4, IL-10, cytotoxic activity	Autoimmunity, allergy, chronic infection, cancer
B lymphocytes	Antibody production, antigen presentation, cytokine release	Antibodies, immune complexes, IL-6, TNF-α	Autoimmune disease, chronic inflammation
Endothelial cells	Control leukocyte adhesion, vascular permeability, and angiogenesis	Adhesion molecules, chemokines, nitric oxide, VEGF	Atherosclerosis, tumor angiogenesis, inflammatory vascular injury
Epithelial cells	Barrier defense and immune sensing	Cytokines, chemokines, antimicrobial peptides, DAMP responses	Asthma, inflammatory bowel disease, infection, cancer
Fibroblasts/stromal cells	Matrix remodeling, fibrosis, immune-cell retention	Collagen, matrix metalloproteinases, chemokines, growth factors	Fibrosis, rheumatoid arthritis, cancer microenvironment

3. Major Inflammatory Signaling Pathways

The interdependent signaling pathways that translate extracellular danger signals into coordinated transcriptional, metabolic and cellular programs control inflammatory responses. Nuclear factor-κB (NF-κB) is one of the most important mediators of inflammation among these pathways. It is triggered by the presence of microbial products, pro-inflammatory cytokines, oxidative stress, and tissue injury signals, which results in the transcription of genes that regulate cytokine production, leukocyte recruitment, cell survival, and immune activation (Hayden and Ghosh, 2011). NF-KB signaling Canonical NF-kB entails a rapid response that is especially critical to innate immune responses by promptly activating mediators include interleukins, tumor necrosis factor, chemokines, and adhesion molecules. Nevertheless, chronic inflammation may be maintained by incessant stimulation of NF-kB and lead to autoimmune disease, cancer, and tissue degeneration (Liu et al., 2017). Its extensive applicability to human disease is due to the capacity to bridge inflammatory signaling and cell proliferation, resistance to apoptosis, immune control, and stress response (Zhang et al., 2017).

Another key inflammatory signaling axis is the Janus kinase/signal transducer and activator of transcription. JAK proteins are activated by cytokines and interferons and lead to phosphorylation of STAT transcription factors and gene expression related to immune-cell differentiation, antiviral response, hematopoiesis, and the amplification of the inflammatory response (O'Shea et al., 2015). Unregulated JAK/STAT signaling is implicated in multiple immune-mediated and inflammatory diseases due to its role in the polarization of T-cells, the activation of macrophages, the sensitivity to cytokines, and immune damage at the tissue level. Recent studies have also implicated JAK/STAT signaling in stress-induced inflammatory conditions, which is why it is an important disease pathway and treatment target (Sarapultsev et al., 2023).

The inflammatory signaling is also regulated by mitogen-activated protein kinase pathways such as p38, ERK and JNK which are activated by cytokines, pathogen-associated molecules and cellular stress. These kinases affect transcription factor activation, cytokine production, mRNA stability and the activity of inflammatory cells. MAPK signaling, in innate immunity, works together with NF-kB to either up-regulate or down-regulate the extent and duration of inflammatory gene expression (Arthur and Ley, 2013). These pathways have an upstream sensing system in the form of toll-like receptors and other pattern-recognition receptors. They identify pathogen-associated and damage-associated molecular patterns and initiate adaptor proteins that induce NF-KB, MAPK, and interferon-regulatory factor signaling, thus connecting molecular recognition to the production of cytokines and recruitment of immune-cells (Takeuchi and Akira, 2010).

Another level of control of inflammation is inflammasome signaling. Inflammasomes are multiprotein complexes present in the cytosol that sense the microbial products, cellular damage, and metabolic stress. Their activation facilitates caspase-1-dependent interleukin-18 and interleukin-12 maturation and may lead to pyroptotic cell death, which exacerbates local and systemic inflammation (Lara-Reyna et al., 2022). NF- 0 -JAK / STAT- MAPK - Toll-like receptor as well as inflammasome pathways constitute a networked signaling network. These pathways orchestrate the expression of inflammatory genes, activation of immune-cells, vascular and epithelial responses, and tissue remodeling. Under tight control, they aid host defense and repair; in excess or unregulated, they fuel chronic inflammatory pathology and disease progression. The main inflammatory signaling pathways and their outcomes in relation to the disease are shown in Table 2.

Table 2. Major Inflammatory Signaling Pathways and Their Functional Outcomes

Pathway	Main triggers	Core molecular components	Major inflammatory outcomes	Disease relevance
NF-κB	TNF-α, IL-1β, TLR ligands, oxidative stress, DAMPs	IKK complex, IκB, RelA/p65, p50	Cytokine transcription, cell survival, leukocyte recruitment	Autoimmunity, cancer, chronic inflammation
JAK/STAT	Cytokines and interferons	JAK1, JAK2, JAK3, TYK2, STAT proteins	Immune-cell differentiation, cytokine response, antiviral defense	Rheumatoid arthritis, inflammatory bowel disease, psoriasis
MAPK	Cytokines, stress signals, microbial products	p38, ERK, JNK	Cytokine synthesis, transcription factor activation, inflammatory amplification	Innate immune activation, tissue injury
Toll-like receptor signaling	PAMPs and DAMPs	TLRs, MyD88, TRIF, IRFs, NF-κB	Innate immune sensing, cytokine and interferon production	Infection, sterile inflammation, chronic immune activation
Inflammasome signaling	Cellular stress, crystals, microbial toxins, metabolic danger signals	NLRP3, ASC, caspase-1	IL-1β and IL-18 maturation, pyroptosis	Autoinflammation, metabolic disease, neuroinflammation

4. Chronic Inflammation and Disease Progression

Chronic inflammation occurs when inflammatory responses to protect against the bodily damage is unable to heal but becomes chronic, self-perpetuating and tissue destructive. In contrast to acute inflammation, which tends to be time-limited and helps to eliminate the pathogen or repair tissue damage, chronic inflammation is characterized by persistent cytokine release, the recruitment of immune-cells, the oxidative stress, and the gradual loss of tissue homeostasis. This unresolved inflammatory condition aids in diseased development since it sustains pathological microenvironment in which immune, stromal, endothelial, and parenchymal cells are continually in a state of activation.

Sustained cytokine and chemokine signaling via an extensive process is a significant key factor between chronic inflammation and disease progression. Continuous activity of tumor necrosis factor, interleukins, interferons, and chemokines stimulates leukocyte infiltration, cellular stress, insulin resistance and metabolic dysfunction. This has been referred to as metaflammation in metabolic disorders, which is a low grade chronic inflammatory condition caused by nutrient excess, dysfunction of adipose tissue and immune-metabolic imbalance (Hotamisligil, 2017). On the same note, the process of aging is linked to inflammaging, a low-grade, chronic, systemic inflammatory response, which links to age-related disorders by means of impaired immune metabolism, senescence of cells, mitochondrial malfunction, and innate immune activation (Franceschi et al., 2018).

Chronic inflammation is also a contributor to cardiovascular disease, especially atherosclerosis. The presence of modified lipoproteins, endothelial dysfunction, macrophage activation and production of cytokines in atherosclerotic lesions provide a sustained inflammatory state in the arterial wall. This mechanism leads to the development of plaque, progression, instability and thrombotic complications, making inflammation a prime mechanism in atherosclerotic disease and not a by-product (Libby, 2021). Chronic inflammatory signals in the nervous system that involve microglia, astrocytes, cytokines and oxidative mediators are involved in neuronal dysfunction and degeneration. They are involved in neurodegenerative diseases, in which sustained immune response may exacerbate synaptic damage, protein deposition and neuronal death (Glass et al., 2010).

Inflammation aids various processes of tumor growth and progression in cancer. Inflammation induced by cancer facilitates genomic instability, angiogenesis, survival of tumor-cells, invasion, metastasis and inhibition of anti-tumor immunity (Mantovani et al., 2008). Such inflammatory activities are increasingly being coupled with broadened paradigms of cancer biology, in which tumor-promoting inflammation has become a hallmark facilitating characteristic of malignancy (Hanahan, 2022). Tissue architecture is also remodelled by chronic inflammatory cues via fibrosis, extracellular matrix remodelling, and dysregulated repair responses, which may also promote tumor growth and organ dysfunction.

The importance of trained immunity in chronic inflammatory disease and cancer is also highlighted in recent evidence. The progenitors and the innate immune cells can be reprogrammed by repeated or persistent inflammatory exposures leading to long-term hyperresponsive states that worsen the inflammation and progression of diseases (Hajishengallis et al., 2025). Therefore, chronic inflammation is not only a disease symptom, but a mechanistic contributor to pathological remodelling, immune dysregulation and progressive organ damage in a variety of disease settings. Table 3 provides examples of disease-specific mechanisms that chronic inflammation facilitates progression.

Table 3. Chronic Inflammation in Major Disease Categories

Disease category	Major inflammatory mechanisms	Pathological consequences	Representative examples
Cancer	Cytokine production, angiogenesis, immune suppression, oxidative stress, stromal activation	Tumor initiation, survival, invasion, metastasis, immune evasion	Colorectal cancer, liver cancer, lung cancer
Cardiovascular disease	Endothelial dysfunction, macrophage activation, lipid-driven inflammation, plaque cytokines	Atherosclerotic plaque formation, plaque rupture, thrombosis	Atherosclerosis, myocardial infarction
Metabolic disorders	Low-grade adipose inflammation, insulin resistance, immune-metabolic dysfunction	Type 2 diabetes, obesity-related inflammation, metabolic syndrome	Obesity, diabetes, fatty liver disease
Neurodegenerative disease	Microglial activation, cytokine release, oxidative injury, protein aggregation-associated inflammation	Synaptic dysfunction, neuronal injury, progressive degeneration	Alzheimer's disease, Parkinson's disease
Autoimmune disease	Loss of immune tolerance, autoreactive lymphocytes, cytokine amplification	Chronic tissue destruction and systemic inflammation	Rheumatoid arthritis, lupus, psoriasis
Aging-related disease	Inflammaging, cellular senescence, mitochondrial dysfunction, innate immune activation	Frailty, vascular dysfunction, metabolic decline, cognitive impairment	Age-related chronic diseases

5. Inflammation, Immune Dysregulation, and Tissue Microenvironment

Although inflammation is not a systemic immune response, it also restructures the local tissue microenvironment, which dictates tissue reversion to homeostasis or chronic disease progression. The role of inflammatory mediators during acute

injury is to promote host defense, clearance of damaged cells, and repair. But as inflammatory signaling continues, the same events may give rise to a pathological microenvironment with accumulation of immune cells, stromal stimulation, vascular pathology, extracellular matrix remodeling, and feedback. In cancer, e.g., inflammatory cues have the potential to transform local tissue niches into tumor-initiation, tumor-survival, tumor-angiogenic, tumor-invasive, and tumor-immune-evasive environments (Greten & Grivennikov, 2019).

One of the critical aspects of this process of remodeling is the recruitment of immune-cells. The chemokines and chemokine receptors direct the movement of leukocytes into the inflamed tissue and also determine the spatial arrangement of the local niches. It is this trafficking that dictates the presence of neutrophils, monocytes, macrophages, T cells or other immune populations in the inflammatory infiltrate (Griffith et al., 2014). These cells generate cytokines, growth factors, proteases and reactive mediators which change the tissue structure and functions once recruited. The macrophages are particularly significant as they exhibit significant heterogeneity and can transition into inflammatory, regulatory, reparative, and tissue-destructive phenotype in response to local signals. Macrophage variety plays a role in synovial inflammation, cytokine generation, cartilage erosion, and unpredictable treatment results in rheumatoid arthritis (Udalova et al., 2016).

Stromal cells also play an active role in the development of inflammatory diseases. Inflammatory cytokines induce the reaction of fibroblasts, endothelial cells and epithelial cells to produce chemokines, matrix components and survival factors that augment immune-cell recruitment and tissue remodeling. Reparative inflammation is desirable as it re-establishes tissue integrity in response to injury but sustained activation may promote abnormal repair, fibrosis, and pathological remodelling (Karin and Clevers, 2016). The fibroblasts are of particular importance since they have a two-way interaction with the macrophages that influence the immune activation and deposition of the extracellular matrix. Such fibroblast-macrophage interactions aid wound healing in a regulated setting, yet they foster fibrosis and cancer development when stimulated on a sustained basis (Buechler et al., 2021).

Stromal activation in tumors and other chronically inflamed tissues is characterized by endothelial dysfunction, angiogenesis, hypoxia, and matrix remodeling. One example of stromal cells creating a disease-supportive microenvironment is cancer-associated fibroblasts, which regulate the architecture of the extra-cellular matrix, immune exclusion, growth factor signaling, and therapeutic resistance (Sahai et al., 2020). The chronic inflammation may thus form a feed-forward mechanism whereby immune cells, stromal cells and parenchymal cells mutually activate each other. Such loops can repress the effective anti-tumor immunity, and enhance tumor growth in cancer, and the inflammatory microenvironment is a potential therapeutic target (Coussens et al., 2013). Therefore, inflammation remodels tissue ecologies by restructuring cellular composition, molecular signaling, vascular activity, and matrix architecture, transforming local injury responses into systems of long-term disease pathogenesis.

6. Molecular Targets for Anti-inflammatory Therapy

Molecular targeting has revolutionized the management of inflammatory diseases by changing the approach of treating the diseases by the general immunosuppression to a specific inhibition of disease promoting pathways. Among the most significant is the tumor necrosis factor-alpha (TNF-alpha), a cytokine that enhances the activation of macrophages, expression of adhesion molecules on the endothelium, recruitment of leukocytes, and tissue-destructive cytokine cascades. The discovery of TNF as a therapeutic target in rheumatoid arthritis was a good indication that inhibition of a single inflammatory signal can inhibit multifaceted autoimmune pathology, and improve clinical outcomes (Feldmann and Maini, 2003). Since then, this has been the guiding principle of therapeutic approaches in a number of immune-mediated diseases.

Another key target is Interleukin-1B since it connects the innate immune activation with fever, leukocyte recruitment, endothelial activation and tissue injury. The IL-1 blocking is of special interest in autoinflammatory disorders, where the overaction of the inflammasome is responsible for the unregulated production of IL-1b (Dinarello, 2011). Very similar to this strategy is direct targeting of the inflammasome components and more specifically the NLRP3 inflammasome. NLRP3 combines various danger signals, such as cellular stress, crystals, metabolic disturbance and microbial products and triggers caspase-1 activation, IL-1b and IL-18 maturation, and pyroptotic cell death. The NLRP3 inhibitor could thus disrupt the upstream processes that perpetuate inflammatory amplification in metabolic, cardiovascular, neurodegenerative, and autoimmune diseases (Mangan et al., 2018).

Interleukin-6 also has a pivotal role in inflammatory disease as it controls the acute phase reaction, maturation of B-cells, differentiation of T-cells, hematopoiesis, and systemic inflammatory symptoms. The persistent IL-6 signaling is also involved in autoimmunity, chronic inflammation, and tissue damage, and thus IL-6 and its receptor are important therapeutic targets (Tanaka et al., 2014). Cytokine-directed therapy has shown in rheumatoid arthritis to be successful as well as to demonstrate broader principles of inflammatory pathogenesis. Autoimmune inflammation has been shown to be sustained by interlinked circuits of immune cells instead of being single cell type or a mediator alone by treatments that target TNF, IL-6, T-cell costimulation, B cells, and intracellular signaling pathways (McInnes & Schett, 2017).

Another significant group of anti-inflammatory targets are intracellular signaling molecules. Janus kinase inhibitors inhibit cytokine signaling in part by inhibiting JAK-stimulated activation of STAT transcription factors, inhibiting expression of inflammatory genes and activation of immune-cells. Cyclooxygenase enzymes, in specific COX-2, are still relevant therapeutic targets since they control the activity of the production of prostaglandins, which is involved in pain, fever, vascular alterations, and local symptoms of inflammation. The chemokine receptors are also appealing targets as they regulate the leukocyte movement in inflamed tissues, but the redundancy of chemokine networks can complicate the efficacy of therapy.

Type 2 immunity and immune checkpoint regulation inflammatory pathways are becoming more and more relevant in allergic, dermatologic, pulmonary, and cancer-related inflammation. Cytokines and epithelial-derived mediators Type 2 cytokines and epithelial-derived mediators influence inflammation in the skin and lungs, and support cytokine-targeted therapies, including IL-4, IL-5, and IL-13, and associated pathways (Akdis et al., 2020). Altogether, the idea of blocking TNF-alpha, IL-1-beta, IL-6, COX-2 enzymes, JAK-kinases, inflammasomes, chemokine receptors, and immune-regulatory mechanisms can break the loop of inflammation, decrease tissue damage, and enhance disease control when combined with the predominant molecular mediators of pathology. The list of key inflammatory signaling pathways and their respective therapeutic targets are described in Figure 2.

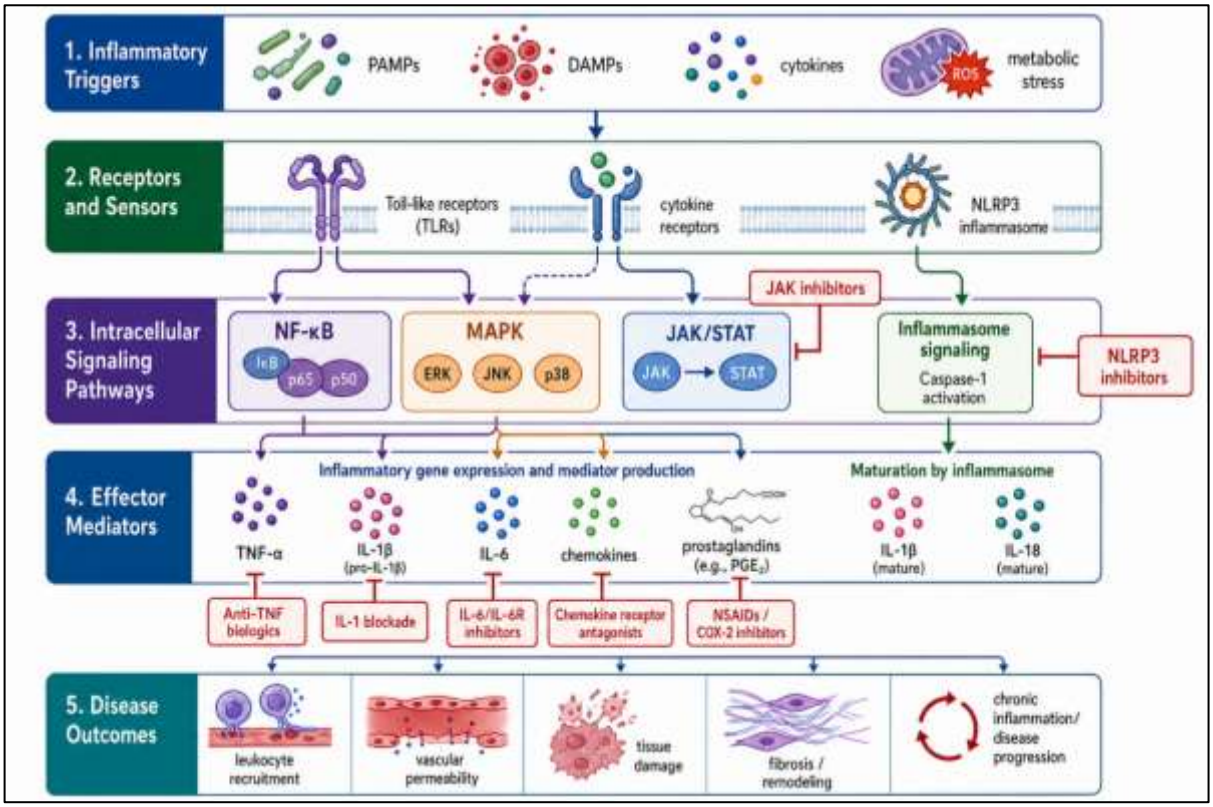

Figure 2. Inflammatory Signaling Pathways and Therapeutic Targeting

7. Current and Emerging Therapeutic Strategies

The contemporary anti-inflammatory treatment consists of the traditional agents and mechanism-guided targeted therapies. Corticosteroids continue to be among the most popular anti-inflammatory medications as they inhibit many transcriptional programs of cytokine production, leukocyte activation, vascular permeability and production of inflammatory mediators. Their use is, however, restricted by cardiovascular, skeletal, infectious, and metabolic complications in the long run. Non-steroidal anti-inflammatory drugs are also quite popular, especially in pain and fever, as well as inflammatory symptoms. Their actions are primarily mediated by suppressing cyclooxygenase enzymes and decreased production of prostaglands. Even more selective COX-2 inhibitors were produced to enhance anti-inflammatory effects and decrease part of gastrointestinal toxicity but cardiovascular safety is a significant issue in the long-term administration (Ju et al., 2022).

Biologic therapies are a significant improvement since it is specific to cytokines, receptors, or immune-cell pathways. The use of cytokine blockade has become the main focus of the treatment of various immune-mediated diseases. Interleukin-1 blocking has been shown to be effective in diseases that involve innate immune activation and autoinflammation, and that the broader concept that inhibiting a single upstream cytokine can alter the activity of inflammatory diseases in a wide range of clinical contexts is valid (Dinarello et al., 2012). Likewise, disease management in rheumatoid arthritis demonstrates the capacity of combination of targeted therapy with early disease detection, disease activity, and treat-to-target methods to prevent joint destruction and systemic complications (Aletaha and Smolen, 2018). The use of anti-cytokine therapies is also under investigation in inflammatory bowel disease, such as clinical trials of interleukin-6 blockade in Crohn's disease, but efficacy and safety need to be carefully balanced in the complex mucosal immune disorders (Danese et al., 2019).

Small-molecule inhibitors have been used to increase the number of therapeutic options by addressing intracellular signaling pathways that are challenging to inhibit using antibodies. One notable example is JAK inhibitors, which inhibit the downstream signaling of various cytokine receptors, and prevent expression of inflammatory genes, lymphocyte-activation and tissue inflammation. They are orally available and have a wide range of cytokine-modulating activities, which has made them valuable in various immune and inflammatory disorders but the risk of infection, hematologic and patient selection should be closely monitored (Schwartz et al., 2017).

A promising emerging therapeutic group is inflammasome inhibitors. Various danger signals trigger the NLRP3 inflammasome, which facilitates interleukin-1β maturation, interleukin-18 release and pyroptosis. Selective NLRP3 inhibitors can thus inhibit upstream inflammatory amplification and not just downstream cytokines. The NLRP3 ATP-hydrolysis motif, e.g., is directly targeted by MCC950, which supports the development of inflammasome-targeted drugs in a mechanistic way (Coll et al., 2019). There are other selective NLRP3 inhibitors which, too, have demonstrated potentially healing inflammatory conditions by directly disrupting inflammasome activation (Jiang et al., 2017).

New approaches such as RNA-based therapy, microbiome-targeted therapy, and precision medicine are becoming part of the emerging strategies. RNA therapeutics can provide an opportunity to selectively silence or regulate inflammatory mediators, whereas microbiome-based interventions can be used to restore homeostasis between the host and the microbiome and decrease mucosal or systemic inflammation. It is likely that precision medicine will be of particular significance since the inflammatory diseases are heterogeneous, and therapeutic responses are dependent on overriding cytokine networks, genetic background, tissue context, biomarkers, and disease stage. Therefore, the future of anti-inflammatory treatment is likely to be an integration of conventional medicines, directed biologics, small molecules, inflammasome blockage and biomarker-based therapy to attain longer-lasting and personalized disease management. Table 4 summarizes the current and emerging anti-inflammatory therapeutic strategies.

Table 4. Therapeutic Targets and Anti-inflammatory Treatment Strategies

Therapeutic target/strategy	Mechanism of action	Examples of therapeutic approach	Clinical relevance
TNF-α blockade	Reduces cytokine amplification, endothelial activation, and leukocyte recruitment	Anti-TNF biologics	Rheumatoid arthritis, inflammatory bowel disease, psoriasis
IL-1 blockade	Suppresses innate immune activation and fever-associated inflammatory responses	IL-1 receptor antagonists, anti-IL-1 antibodies	Autoinflammatory diseases, gout, systemic inflammation
IL-6 pathway inhibition	Reduces acute-phase response, B-cell activity, and T-cell differentiation	Anti-IL-6 or anti-IL-6 receptor therapy	Rheumatoid arthritis, systemic inflammatory disorders
JAK inhibition	Blocks intracellular cytokine signaling through JAK/STAT pathways	Small-molecule JAK inhibitors	Rheumatoid arthritis, psoriasis, inflammatory bowel disease
NLRP3 inflammasome inhibition	Reduces caspase-1 activation, IL-1β maturation, IL-18 release, and pyroptosis	Selective NLRP3 inhibitors	Autoinflammation, metabolic inflammation, neuroinflammation
COX inhibition	Reduces prostaglandin synthesis involved in pain, fever, and inflammation	NSAIDs and selective COX-2 inhibitors	Pain, fever, arthritis, inflammatory symptoms
Chemokine receptor targeting	Limits immune-cell trafficking into inflamed tissues	Chemokine receptor antagonists	Autoimmune and inflammatory diseases
RNA-based and precision therapies	Modulates disease-specific inflammatory mediators or pathways	siRNA, antisense oligonucleotides, biomarker-guided therapy	Emerging personalized anti-inflammatory treatment

8. Challenges and Future Perspectives

Even though key progress has been made on the concept of inflammatory processes, there are still a number of obstacles that restrict the efficacy of an anti-inflammatory treatment. The biological complexity of inflammation is one of the major problems. The same signaling pathways, immune cells and cytokines can play protective effects in host defense and tissue repair and pathological effects when excessive or persistent. As such, general inhibition of inflammation can suppress disease activity, but can also predispose to infection, worsen wound healing, or disrupt immune surveillance. This is especially in the case of corticosteroids, biologics, JAK inhibitors, and any other targeted immunomodulators.

Heterogeneity of diseases is another challenge. Inflammatory drivers, tissue-specific immune responses, genetic background, and response to therapy among patients with the same clinical diagnosis may vary. This means that an effective treatment in one subgroup may not be effective or safe in another. A significant obstacle to precision anti-inflammatory medicine is still the unreliability of biomarkers to stratify the patient, monitor the disease, and predict the response to therapy. There is also therapy resistance, relapse following drug withdrawal, adverse effects, and high costs of treatment which also make long-term management of the disease difficult.

The future research suggests the definition of disease-specific inflammatory signatures by using multi-omics technologies, single-cell analysis, spatial profiling, and systems biology. These methods can be used to recognize prevailing cytokine networks, pathogenic cell states and tissue-specific signaling networks. Inflammasome, RNA, microbiome-targeted, and combination regimens are emerging therapies that could have more selective and long-lasting control of inflammation. The therapeutic approaches in the future must focus not only on the inhibition of inflammation, but on immune balance, resolution, and inhibition of pathological remodelling of tissues. The further evolution of safer, more specific and patient-

specific interventions in inflammatory, metabolic, autoimmune, neurodegenerative, cardiovascular and malignant diseases will thus require a deeper molecular understanding of inflammation.

9. CONCLUSION

Inflammation is an inherent biological reaction, which safeguards the host against infection, injury, and cellular stress but may also persist or become dysregulated, making it a potent pathogenic force. On a cellular level, there are complex networks of intercellular interactions between macrophages, neutrophils, lymphocytes, endothelial cells, epithelial cells and stromal cells involving cytokines, chemokines, lipid mediators, reactive oxygen species and danger signals. These molecular mediators stimulate key signaling pathways like NF-KB, JAK/STAT, MAPK, Toll-like receptor signaling, and inflammasome pathways, which together control the expression of inflammatory genes, recruitment of immune-cells, tissue repair, and pathological remodelling. The acute to chronic inflammatory switch-over is at the core of numerous diseases, such as autoimmune diseases, cancer, cardiovascular disease, metabolic syndrome, neurodegeneration and chronic infections. Prolonged inflammatory signaling enhances oxidative stress, fibrosis, angiogenesis, immune dysregulation, extracellular matrix remodeling, and tissue destruction. These mechanisms redefine the local microenvironment and form feedback mechanisms that sustain disease activity despite the decreasing original trigger. Targeting of inflammation in therapy has greatly improved the management of diseases. Biologics against TNF-α, IL-1β, and IL-6, small-molecule JAK inhibitors, COX inhibitors, corticosteroids, and emerging inflammasome inhibitors demonstrate the clinical value of interrupting specific inflammatory pathways. Nevertheless, there is still little treatment due to the heterogeneity of patients, adverse effects, immune suppression, resistance, and biomarker inadequacy. Any future approach has to transition to specific suppression instead of a generalized one, towards the narrow-band modulation of inflammatory pathways. Molecular profiling, biomarker-driven therapy, RNA-based therapies, microbiome interventions, and resolution-based therapies can be integrated to allow safer and more long-term results. In general, the explanation of the molecular pathways of inflammation is a key to finding specific treatment that would regulate the disease and maintain the protection immunity.

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