Mechanisms of inflammation associated with chronic diseases: A brief review

Abstract:

Inflammation is a vital immune response that protects the body from infections, damaged cells, and harmful stimuli. It can be acute (rapid and short-term, aiding tissue repair) or chronic (persistent, causing tissue damage and contributing to diseases like cancer and autoimmune disorders). Pattern recognition receptors activate inflammation through signaling pathways like JAK/STAT, MAPK, and NF-kB. Inflammatory mediators, such as cytokines, reactive oxygen species, and acute-phase proteins, attract immune cells (e.g., neutrophils and macrophages) to the damage site. Diagnostic markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) assess inflammation levels. Chronic inflammation is linked to conditions like rheumatoid arthritis and cardiovascular disease. NSAIDs, which block cyclooxygenase enzymes, are commonly used to manage inflammation. Understanding inflammation mechanisms is key to improving treatments and clinical outcomes.

Keywords: Immune response, inflammation, erythrocyte sedimentation rate, C-reactive protein

Introduction:

Inflammation is a vital response required for the successful recovery from injury, trauma (surgically induced), sepsis and infections. Inflammation is body's natural protection mechanism that is essential to healthiness [1]. The term ‘inflammation’ derived from the Latin word inflammare, which means to ignite [2]. This process is quite intricate and is a component of the immune response that includes an initial natural phase followed by a subsequent adaptive phase [3].

According to visual assessments, ancient scholars identified five primary signs of inflammation: redness (rubor), swelling (tumour), heat (calor; only relevant to the body's extremities), pain (dolor), and altered function (functiolaesa). In more contemporary terms, inflammation has been defined as the sequence of changes that occurs in living tissue following an injury, as long as the injury does not immediately compromise its structure and

vitality, or the reaction of the living microcirculation along with associated tissues to injury [4].

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Causes:

1. **Physical agents** -Mechanical injuries, alteration in temperatures and pressure, radiation injuries.
2. **Chemical agents**-Including the increasing lists of drugs and toxins.
3. **Biologic agents (infectious)**-Bacteria, viruses, fungi, parasites
4. **Immunologic disorders**-Hypersensitivity reactions, autoimmunity, immunodeficiency states etc
5. **Genetic/metabolic disorders**-Gout, Diabetes Mellitus [5]

Types of Inflammation:

1. Acute Inflammation:

Duration	Short term
Trigger	PAMPs (infection), DAMPs (cellular stress, trauma)
Magnitude	High-grade
Outcome(s)	Healing, trigger removal, tissue repair
Age-related	No
Biomarkers	IL-6, TNF-α, IL-1β, CRP

Table 1: Acute Inflammation

2. Chronic Inflammation:

Duration	Persistent, non-resolving
Trigger	DAMPs (‘exposome’, metabolic dysfunction, tissue damage)
Magnitude	Low-grade
Outcome(s)	Collateral damage
Age-related	Yes
Biomarkers	Silent-no canonical standard biomarkers

Table 2: Chronic Inflammation [6]

Acute and Chronic Inflammation in mammals:

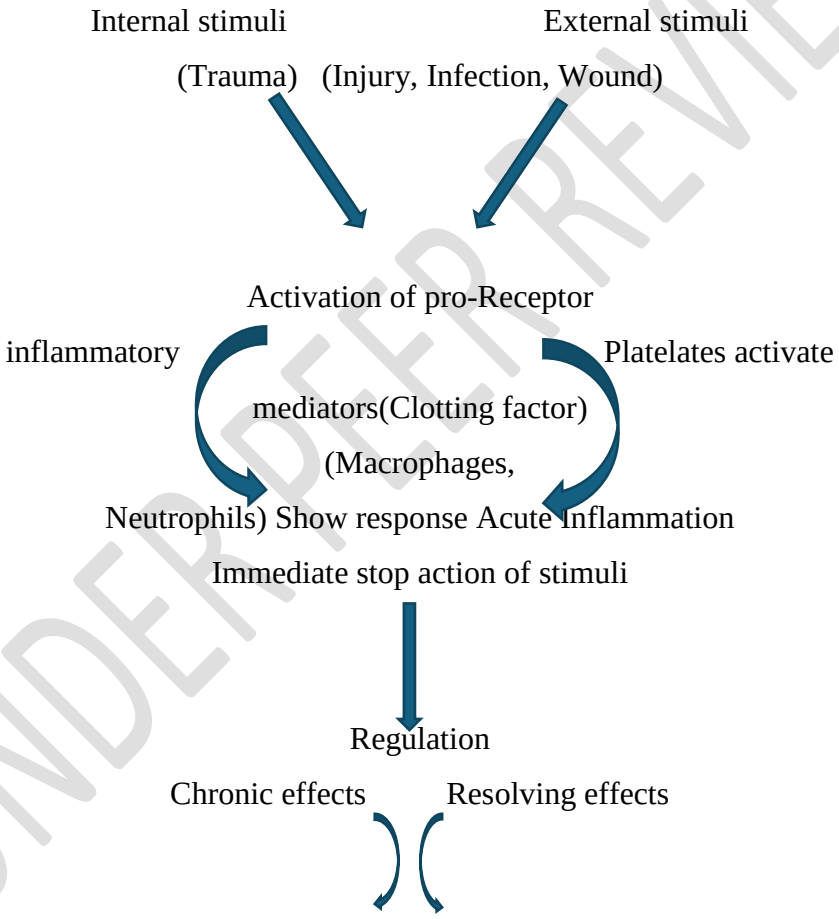

Fig 1: Acute and Chronic Inflammation in Mammals [7]

Mechanism: [8, 9]

1. Cell surface pattern receptors recognize detrimental stimuli:

When pattern recognition receptors (PRRs) detect environmental stimuli, the innate immune system initiates an inflammatory response. In addition to danger-associated molecular patterns (DAMPs), PRRs also identify pathogen-associated molecular patterns (PAMPs). Membrane-bound TLRs, which detect extracellular or endosomal signals, and intracellular receptors, such NLRs and AIM2-like receptors (ALRs), are examples of these receptors [10]. An intracellular complex called the inflammasome assembly, which is facilitated by a subset of cytosolic PRRs, activates the proinflammatory cytokines IL-1β and IL-18 [11]. For caspase-1 activation to occur, the inflammasome which is made up of caspase-1, ASC and NLRs is essential [12]. IFN-α and IFN-β are examples of Type I interferons (IFNs) that also control inflammation and are crucial for immunological defense, apoptosis, antiviral responses, and hematopoietic stem cell turnover [13].

2. Inflammatory pathways are activated:

In chronic disorders, inflammatory mediators and regulatory mechanisms are important. Microbial products and cytokines (IL-1β, IL-6, and TNF-α) are examples of inflammatory stimuli that activate receptors such TLRs, IL-1R, IL-6R, and TNFR [14]. This sets off intracellular signaling pathways that drive inflammation, such as NF-κB, MAPK, and JAK-STAT [15–17].

The NF-kappaB pathway:

NF-kB is a transcription factor composed of five subunits: p65 (RelA), RelB, c-Rel, p105/p50, and p100/p52. These subunits regulate genes involved in cell survival, inflammation, and immunity. NF-kB is inactive in the cytoplasm, bound by inhibitors (IkBs), and is activated through two pathways. The canonical pathway is triggered by surface receptors like BCR and TLRs, leading to IkB degradation and nuclear translocation of the p50/RelA complex. The non-canonical pathway, activated by receptors like BAFF-R and CD40, processes p100 into p52, leading to RelB/p52 complex translocation. NF-kB activation increases cytokine, chemokine, and adhesion molecule production, driving inflammation and regulating cell processes like proliferation and differentiation. [18,19,20,21,22,23]

MAPK pathway:

Enzymes known as MAPKs (Mitogen-Activated Protein Kinases) are triggered by outside stimuli and phosphorylate effector proteins to control cellular processes. The three main MAPK subgroups in mammals are ERK, p38s, and JNK [24]. MEK1/2 activates ERKs, MKK3/6 activates p38s, MKK4/7 activates JNKs, and MKK4 also activates p38s. These six primary MAP2Ks are responsible for different subgroups of MAPKs, which are activated through phosphorylation by MAP2Ks (MAPK kinases) [25-27]. Growth factors, cytokines,

hormones, and stressors like oxidative or endoplasmic reticulum stress can all set off these MAPK cascades, which impact survival, apoptosis, differentiation, and proliferation [28].

JAK/STAT Pathway:

The JAK/STAT signalling pathway, activated by growth factors and cytokines like IL-6, regulates key cellular functions such as survival, migration, differentiation, and proliferation. JAK2 phosphorylates STAT proteins upon ligand binding, triggering gene transcription. STAT proteins dimerize and enter the nucleus with the help of nucleoprotein interactor 1 (NP-1). The JAK/STAT pathway also influences other signalling pathways, including RAS/MAPK, PI3, and AKT.[29,30]

3. Inflammatory mediators are released

- Reactive oxygen species (ROS) and reactive nitrogen oxide species (RNOS)
- Formation of DNA adducts
- Cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha, and chemokines
- Acute-phase proteins, such as C-reactive protein or CRP
- Prostaglandins
- Cyclooxygenase (COX)-related metabolites
- Inflammation-related growth factors and transcription factors, such as NF-kappaB
- Major immune cell types [31]

4. Inflammatory cells are recruited;

Macrophages respond by releasing cytokines that draw other inflammatory cells, including neutrophils [32], to the infection site. Leukocyte migration, also known as recruitment [33], is the movement of cells such as neutrophils and eosinophils along the vascular endothelium. Leukocytes and endothelium selectins first engage in modest interactions (rolling) [34], which lack the strength to stop blood flow-induced cell migration. Leukocytes' corresponding receptors (LFA-1, Mac-1) and endothelium's ICAM-1 [35] are expressed in response to chemokines (e.g., Eotaxin, IL-8) generated at the site of inflammation. Tight binding is induced, enabling leukocyte extravasation (diapedesis) into tissues. As the first responders, neutrophils phagocytose infections and release hydrogen peroxide and lysosomes, which can harm tissue in addition to killing the pathogen [36].

Diagnosis of Inflammation:

1. C – Reactive Protein (CRP):

Inflammation, infection, and injury cause a sharp rise in C-reactive protein levels. CRP is an acute indicator of inflammation. CRP is mostly produced by IL-6-dependent hepatic biosynthesis. The activation of the C1q molecule in the complement pathway, which results

in the opsonization of pathogens. CRP can trigger the host defines fluid phase pathways by triggering the complement system, it can also trigger cell-mediated pathways by binding to IgG's Fc receptors and activating complement [37]. CRP binds to Fc receptors with the resulting interaction leading to the release of pro-inflammatory cytokines. [38]

2. Erythrocyte Sedimentation Rate:

It is haematological test that can detect and track an increase in the body's inflammatory activity [39]. Growing levels of alpha globulins and fibrinogen, the primary clotting protein, have an impact on the sedimentation rate during an inflammatory reaction. By evaluating the propensity of red blood cells to cluster and "fall" through the variable viscous plasma, the test primarily determines the viscosity of the plasma [40]. Because of its low cost and reproducibility, the ESR has been employed as a "sickness indicator" for a long time. [41].

3. Serum Protein Electrophoresis:

The electrophoresis method evaluates blood protein distribution, including alpha globulins, a diverse class of liver-produced transport proteins like macroglobulin, haptoglobin, lipoproteins, and ceruloplasmin. Alpha globulins are useful for diagnosing and monitoring chronic viral infections and inflammatory conditions. [42].

4. Molecular Imaging of Inflammation:

Traditional imaging techniques like CT and MRI show structural changes in inflamed tissues, such as edema, contrast enhancement, and organ injury. Recently, advanced molecular imaging methods, including PET, SPECT, and MRI, have been used for more precise imaging of the inflammatory response. [43]

Organ-specific Inflammatory Responses:

Brain:

Inflammatory reactions in the central nervous system (CNS) are linked to disorders like epilepsy, autoimmune diseases, Alzheimer's, and Parkinson's. These inflammations can damage cells, increase neuronal excitability, and compromise the blood-brain barrier. [44, 45] CNS inflammation arises from activated immune cells and microglia releasing pro-inflammatory signals. Endogenous ligands, such as DAMPs (e.g., heat-shock proteins), can trigger inflammation, especially when the blood-brain barrier is breached. Both infections and brain injuries, like ischemic, traumatic, or excitotoxic events, can elicit robust CNS inflammatory responses. [46, 47, 48]

Lung:

Lung inflammation is primarily caused by environmental pollutants, infections, and tissue exposure. Persistent inflammation and unresolved lung injury are associated with conditions like asthma, cystic fibrosis, COPD, and acute respiratory distress syndrome. [49, 50]

Cigarette smoking, a major COPD risk factor, promotes immune cell infiltration (macrophages, neutrophils, T lymphocytes) and increases lung production of chemokines, oxygen radicals, proteases, and cytokines such as TNF-α, IL-6, and IL-8. [51]

Kidney:

Growing renal injury can lead to conditions such as glomerulonephritis, end-stage renal disease, acute or chronic kidney disease (CKD), and kidney inflammation. Kidney inflammation is typically caused by infections, ischemia/reperfusion, immune complex formation or deposition, and dysregulation of the complement system [52]. Various harmful stimuli, including growth factors, cytokines, DAMPs, PAMPs, TLRs, NLRs, and metabolic and immunological mediators (such as high glucose and advanced glycosylation end products), activate transcription factors like NF-kB or MAPK, contributing to kidney damage. [53].

Liver:

Microorganisms such as bacterial products, hepatitis B virus (HBV), and hepatitis C virus (HCV) are major causes of infectious liver inflammation [54]. Additionally, sterile inflammation (SI) contributes significantly to the development of various liver diseases, including ischemia/reperfusion, drug-induced liver injury, and alcoholic or non-alcoholic steatohepatitis [55-57]. In sterile inflammation, immune cells are activated by endogenous Damage-Associated Molecular Patterns (DAMPs), which are released from damaged tissues [58].

Gastrointestinal tract:

An overactive inflammatory response to gut lumen microbial flora is a hallmark of the complicated, polygenetic inflammatory bowel disorders (IBDs) [59].Inflammatory Bowel Diseases (IBDs) include non-infectious inflammation of the intestine, with ulcerative colitis (UC) and Crohn's disease (CD) being the most common types [60, 61]. These idiopathic IBDs are driven by cytokine-mediated inflammation. For example, UC is associated with excessive production of IL-13, while CD is linked to high levels of IFN-γ/IL-17 and IL-12/IL-23 [61].

Inflammation Associated Diseases:

1.Rheumatoid arthritis (RA):

Arthritis may be defined as inflammation of joints causing pain, swelling, and stiffness. The broad category of arthritis includes diseases that can be categorized as inflammatory, degenerative, metabolic, or infectious. Rheumatoid arthritis (RA) is the commonest form of chronic inflammatory arthritis, characterized by synovial inflammation and subsequent tissue damage [62].

2. Cancer:

In the past decade, evidence has shown that inflammation plays a key role in tumorigenesis. Chronic inflammation, if prolonged, can lead to disease and increase cancer risk. Triggers include infections (e.g., Helicobacter pylori for gastric cancer, papillomavirus for cervical cancer, and hepatitis viruses for liver cancer), autoimmune diseases (e.g., inflammatory bowel disease for colon cancer), and unexplained inflammatory conditions (e.g., prostatitis for prostate cancer).[63]

3. Cardiovascular diseases:

Atherosclerosis is a low-grade, sterile inflammatory disease central to cardiovascular disease (CVD) development and progression. Inflammation, triggered by factors like endothelial dysfunction, stress, autoimmune diseases, infections, and aging, drives the vascular inflammatory response and atherosclerosis progression. Inflammatory biomarkers can predict CVD independently of traditional risk factors. Inflammation links traditional and emerging cardiovascular risk factors to conditions such as coronary artery disease (CAD), thrombotic stroke, and cerebral aneurysms.[64,65]

4. Inflammatory Bowel Disease:

Inflammatory bowel disease (IBD) has been a global healthcare problem with a sustained increasing incidence. It includes two major forms, Crohn's disease (CD) and ulcerative colitis (UC), which are distinct chronic bowel-relapsing inflammatory disorders. CD can cause transmural inflammation and affect any part of the gastrointestinal tract (most commonly, the terminal ileum or the perianal region) in a non-continuous type [66].

5. Inflammatory Airway Diseases:

Asthma, or bronchial asthma (BA), is a chronic inflammatory airway disease causing coughing, shortness of breath, wheezing, airway narrowing, and chest tightness. Chronic obstructive pulmonary disease (COPD) is a common lung condition with inflammation and breathing difficulty. COPD includes chronic bronchitis (long-term mucus-laden cough) and emphysema (progressive lung destruction).[67]

Conclusion:

To sum up, inflammation is a vital biological reaction that is necessary for tissue repair and immunological protection. There are two main phases to it: acute inflammation, which happens quickly in reaction to an injury or illness, and chronic inflammation, which lasts longer and may cause long-term health issues. Numerous physical, chemical, and immune system stimuli can initiate the inflammatory process. These stimuli activate pattern recognition receptors, which then release mediators to draw in immune cells like neutrophils and macrophages for tissue healing and pathogen removal. On the other hand, chronic

illnesses including cancer, heart disease, and autoimmune disorders can be exacerbated by dysregulated inflammation.

In addition to sophisticated imaging methods that offer organ-specific information, biomarkers such as C-reactive protein and erythrocyte sedimentation rate are essential for the accurate diagnosis of inflammation. Addressing the root causes of chronic inflammatory illnesses and limiting its harmful effects require effective inflammation control. In order to provide innovative medications that target inflammation and give patients with a variety of inflammatory disorders hope for better outcomes and treatments, ongoing research is essential.

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