Cellular and molecular mechanisms of inflammation: A modern perspective


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Abstract
Inflammation is a fundamental immunological response triggered by tissue damage, poisoning, or infection. Although unchecked or persistent inflammation can develop into chronic inflammation, which may lead to various serious diseases such as diabetes, cardiovascular disease, autoimmune disorders, and neurodegenerative conditions, acute inflammation serves as a protective mechanism essential for healing and re-establishing homeostasis. Complex signalling pathways are involved in the inflammatory process, including the activation of downstream signalling molecules like MAPKs and NF-kB, as well as cytokines (such as IL-1β, IL-6, and TNF-α) and their receptors. Immune cell recruitment and activation result from these coordinated interactions. Numerous factors contribute to chronic inflammation, such as immunological reactions, infections, poor diet, stress, obesity, and environmental pollutants. While inflammation is vital for survival, its dysregulation necessitates the use of specific management strategies. These include pharmaceutical treatments (e.g., biologics, NSAIDs), anti-inflammatory diets, stress reduction, exercise, and emerging treatments like Semaglutide, Dupixent, and NLRP3 inflammasome inhibitors.

Keywords: Cytokines, immune response, inflammation, NF-kB signalling

1. Introduction
The body has several defense mechanisms, one of which is inflammation. It is an immunologic reaction of the body to harmful stimuli. The process of inflammation may be triggered by poisons, toxic chemicals, tissue damage, or various infections (bacteria, viruses). TNF-α, interleukin-1β (IL-1β), interleukin-6, and other inflammatory cytokines are released when leukocytes are activated by such harmful stimuli, which set off a series of signalling events. TLR4, GM-CSFR, TNFR-1, TNFR-2, IL-6R, and other receptors are activated and coupled with these cytokines. The activation of receptors causes the phosphorylation of numerous signalling molecules, including nuclear factor kappa-B (NF-kB), Janus kinase, and mitogen-activated protein kinase (MAPK), which in turn activate transcription factors. This coordinated activation of signalling molecules not only recruits inflammatory cells from the blood but also regulates the levels of inflammatory mediators in resident tissue cells. The body uses acute inflammation as a defensive mechanism to eliminate harmful stimuli and initiate the healing process, thereby restoring the body's homeostasis (1).

However, failure to control acute inflammation may lead to chronic inflammation, which can serve as a

foundation for several serious chronic diseases, including cancer, multiple sclerosis, lateral disease, autoimmune diseases, diabetes, cardiovascular diseases, Parkinson's disease, Alzheimer's disease, and fibrillation.Although aetiology varies, the inflammatory mediators, as well as those involved in control and signalling, are typically the same. To register and transmit signals through the plasma membrane into the cell interior, receptors must be located on the cell membrane and internalized. The components of the signalling cascade, including transcription factors and various kinases, must gather in a location known as “signalling organelles/endosomes”, where they become activated. Activated transcription factors must migrate into the nucleus to regulate inflammatory genes, resulting in the synthesis and release of inflammatory cytokines into the environment. Inflammation can be classified as either acute or chronic. Acute inflammation is temporary and typically advantageous because it promotes the body's ability to recover from wounds like cuts and sprains. The redness, swelling, and warmth at the injury site are signs that the immune system is actively working. Chronic inflammation is a long-lasting inflammation that occurs due to the action of the immune response without any threat. This chronic inflammation continues, which affects the healthy tissues also and may lead to many infections like cancer, heart disease, Diabetes, arthritis, and also neurological disorders like Alzheimer’s disease (2).

The detection of infections or tissue injury by immune cells like neutrophils and macrophages triggers cellular inflammation. The cytokines and prostaglandins that these cells release encourage blood flow to the afflicted location and draw in additional immune cells. This leads to the characteristic signs of inflammation, which include pain, swelling, redness, heat, and loss of function. These reactions provide short-term protection, but long-term inflammation can harm healthy tissues. Persistent infections, prolonged exposure to irritants, autoimmune reactions, or lifestyle factors, including smoking, stress, poor food, and lack of exercise, can all lead to chronic inflammation. In contrast to acute inflammation, which goes away as soon as healing starts, chronic inflammation can go unnoticed for years and subtly advance a disease. Excessive inflammation is the starting point for systemic inflammation, including sepsis, which results in a protracted immunosuppressed condition. It uses functional assays and single-cell transcriptomics to show that the immunosuppression is caused by decreased type I interferon signalling and poor monocyte maturation, both of which can be restored by interferon-β therapy. According to a recent study, GZMK was created by the majority of immunological CD8+ T cells in rheumatoid arthritis patients' joints (3). Furthermore, it was discovered that people with a variety of chronic inflammatory disorders have higher levels of these GZMK-secreting immune cells in their inflammatory tissues. Additionally, the study has looked into how this pathway affects different diseases and is currently working on creating inhibitors that target GZMK in the hopes of providing patients with autoimmune and inflammatory diseases with new, focused treatments.

2. What causes inflammation?

Several factors can trigger inflammation in the body. These include (4):

2.1. Infections

Harmful microorganisms like bacteria, fungi, and viruses can enter the body, the immune system gets activated immediately to fight off inflammation. With the effect of microbes, white blood cells move to the site and affect the release of chemicals, which are responsible for swelling, redness, and pain. This is used to remove the pathogen.

2.2. Physical injuries

Wounds such as cuts, sprains, and bruises can cause inflammation. This is known as localized inflammation. Due to the body’s mechanism, the affected area can receive increased blood flow and immunological activity. This initiates tissue regeneration and helps to prevent infection.

2.3. Chemical and environmental irritants

Exposure to chemicals, tobacco smoke, and other air pollutants may cause irritation to the lungs and

other organs, prompting an inflammatory response. People who work in these environments with harmful substances may be at a higher risk of chronic inflammatory diseases.

2.4. Autoimmune disorders

The immune system incorrectly perceives the body's tissues as dangerous and launches attacks on them in autoimmune disorders such as lupus and rheumatoid arthritis. This can cause chronic inflammation that will affect organs, joints, and other tissues.

2.5. Obesity

Adipokines are a type of pro-inflammatory chemical released by fat cells, particularly those found in abdominal fat. Throughout the body, these chemicals encourage chronic, low-grade inflammation. This gives clarification on why obesity is a major risk factor for Type 2 diabetes and heart disease.

2.6. Stress

Emotional and psychological stress can lead to increased cortisol levels, which causes the disruption of immune function and promotes inflammation. Long-term stress can lead to ongoing inflammation, contributing to a number of medical conditions, including as depression and hypertension.

2.7. Poor diet

Inflammatory reactions can be brought on by a diet heavy in sugar, bad fats, and processed foods. It is also identified that the processed foods that contain more carbohydrates and trans fats can also lead to inflammation. Eating foods with high nutrients, like almonds, oily salmon, and green leafy vegetables, helps in decreasing inflammation.

3.How inflammation affects the body

Although inflammation is meant to protect the body, long-term inflammation can do the opposite, causing damage instead of healing (5). This has occurred due to various reasons, which include:

3.1. Development of chronic diseases

Chronic inflammation has been linked to neurological diseases, cancer, heart disease, and Type 2 diabetes. For example, blood vessel inflammation raises the risk of heart attacks and strokes by promoting plaque accumulation.

3.2. Damage to the joints and tissue

In autoimmune diseases, inflammation can attack and destroy healthy tissues. In rheumatoid arthritis, for example, the joints become inflamed and painful, eventually leading to erosion of cartilage and bone.

3.3. Pain and swelling

Inflammation increases blood flow and causes fluid buildup at the site of injury, leading to swelling. Chemicals like prostaglandins and histamines also irritate nerves, resulting in pain. This is why inflamed areas often feel tender and sore (6).

3.4. Suppressed immunity

Ironically, chronic inflammation can weaken the immune system. When the body is always on alert, it may start misfiring, causing immune fatigue or making the body more susceptible to infections and illnesses.

4. Managing inflammation naturally and medically

Fortunately, inflammation is manageable and even reversible with the correct techniques. Some useful strategies to deal with it are as follows (7):

4.1. Medications

- NSAIDs (e.g., ibuprofen, aspirin): These over-the-counter drugs help reduce inflammation and relieve pain.

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- Corticosteroids (e.g., prednisone): Often prescribed for more serious inflammation, especially in autoimmune diseases, to suppress the immune system.
- Biologic drugs: These target specific parts of the immune system and are used in cases like rheumatoid arthritis or inflammatory bowel disease.
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4.2. Anti-Inflammatory diet

Adopting a diet that fights inflammation is one of the best long-term strategies. This includes:

- Fruits and vegetables rich in antioxidants (e.g., berries, spinach, broccoli)
- Healthy fats like omega-3s found in fish (salmon, sardines) and flaxseeds
- Whole grains instead of refined grains
- Spices like turmeric, ginger, and cinnamon which have natural anti-inflammatory effects

4.3. Exercise

Moderate physical activity helps regulate immune function and reduce the production of inflammatory chemicals. Activities like brisk walking, cycling, and yoga not only improve fitness but also reduce stress and inflammation.

4.4. Stress management

Mindfulness practices like meditation, journaling, and deep breathing help lower stress hormones. Chronic stress is a major contributor to inflammation, so learning to manage it is crucial for overall health.

4.5. Quality sleep

Lack of sleep is strongly linked to increased inflammatory markers in the body. In order to promote immunological balance and recuperation, try to get 7 to 9 hours of adequate sleep per night.

4.6. Supplements

The following natural substances may aid in reducing inflammation:

- Omega-3 fatty acids
- Curcumin, Vitamins D, C, and E

Always get medical advice before beginning a supplement regimen.

4.7. Changes in lifestyle

- Reduce alcohol intake and stop smoking. Weight should be managed to ease the strain on the inflammatory reactions.
- Whenever possible, stay away from recognized poisons like pesticides and air pollutants.

As per the anti-inflammatory therapies, new drugs targeting disorders have been developed from recent studies. Here is a summary of a few noteworthy treatments:

Table 1. Emerging and novel anti-inflammatory drugs (8-10**)**

Drug	Mechanism	Efficacy
Dupixent (Dupilumab)	Reduces lung inflammation by focusing on the IL-4 and IL-13 pathways.	In clinical trials, it was shown to enhance lung function and reduce exacerbations by 30–34% when taken in conjunction with traditional inhalation therapy.
Semaglutide (Ozempic, Wegovy)	Glucagon-like peptide-1 mimics the natural hormone GLP-1's activities.	According to recent research, it may decrease biological ageing and reduce inflammation markers by 43%

Duvakitug	Prevents tumour necrosis factor-like ligand 1A (TL1A) from attaching itself to death receptor 3 (DR3).	In phase 2 trials, ulcerative colitis patients experienced remission rates of 36.2% and 47.8%, while placebo patients experienced remission rates of 20.5%.
Velsipity (Etrasimod)	Reduces inflammation by altering sphingosine-1-phosphate receptors to stop T-cell migration.	Shown effectiveness in ulcerative colitis induction and maintenance treatments.
Vamorolone (Agamree)	Working in conjunction with the glucocorticoid receptor (GR) to provide immunosuppressive and anti-inflammatory effects	Demonstrated a notable improvement in linear growth and the persistence of improvements in motor outcomes.
Nibrozetone (RRx-001)	Reduces neuroinflammation by inhibiting the NLRP3 inflammasome.	Reduced inflammasome activation and better motor deficit were observed in animal experiments.

5. Conclusion

Inflammation is an important immune pathway that increases the healing process and keeps the body safe from harmful situations. Acute inflammation is mainly associated with benign and transient conditions, but chronic inflammation may lead to other diseases, such as Cancer, Diabetes, Heart disease and Neurological disorders. Chronic inflammation is triggered by Infections, Trauma, Stress, Obesity, autoimmune disorders. and poor eating habits. NF-κB and MAPKs signalling pathways and cytokines are the essential mediators for the inflammatory processes. Anti-inflammatory diet, regular exercise, adequate sleep, and stress management are all helpful in the management of inflammation. Along with this, the medical agents like Corticosteroids, NSAIDs, and novel therapeutic agents also play an important role in the management of inflammation. Novel agents mainly target the inhibition of GZMK and also modify the action of cytokines, thereby showing anti-inflammatory activity. Understanding the mechanism and the unwanted effects of inflammation is very essential for further development of new drug entities for the treatment of inflammation and also for the maintenance of health and prevention of diseases.

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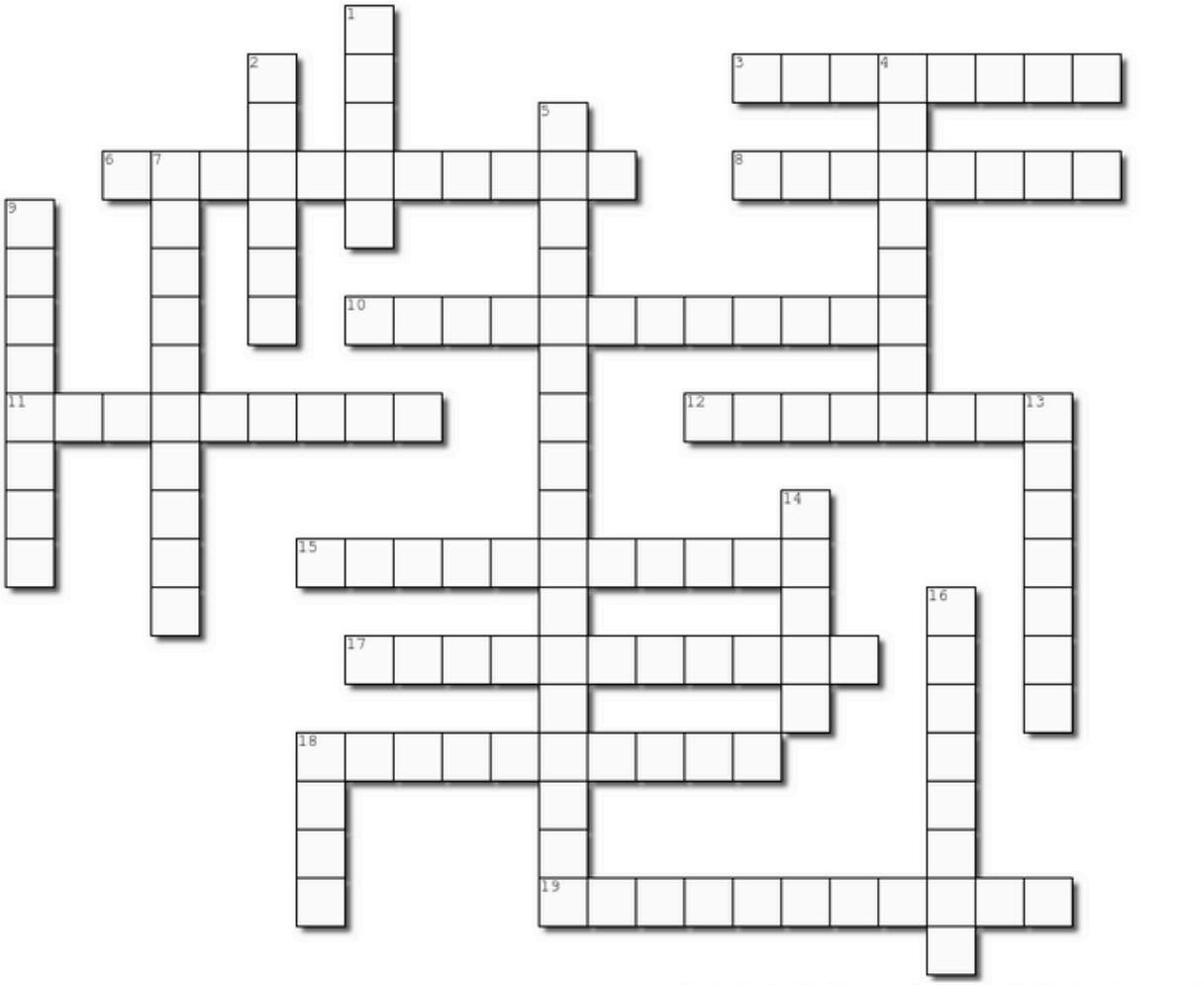

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Across

3. Type of fat releasing cytokines
6. First responders to inflammation, a type of white blood cell
8. Tissue death from inflammation
10. Signaling molecules in inflammation
11. Nuclear receptor with anti-inflammatory roles
12. Inflammatory cytokine from macrophages
15. DNA mutation process caused by inflammation
17. Anti-inflammatory hormone from fat
18. Age-related brain inflammation
19. Inflammation with pus

Down

1. Sign of inflammation that causes redness
2. Lung condition with airway inflammation
4. Natural hormone mimicked by corticosteroids
5. Chronic inflammatory bowel disease
7. TNF-alpha blocker biologic
9. Signaling pathway for inflammation
13. Immune-triggering molecule
14. Pain-relieving and anti-inflammatory drug (abbr.)
16. Tissue scarring from chronic inflammation
18. Advanced glycation end products (abbr.)

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