The Biology of Inflammation

The Biology of Inflammation:

A Comprehensive Guide

By

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This book is dedicated to all the hard-working, dedicated students I have had the privilege to teach.

I want to thank my wife, Megan, for her suggestion to write about inflammation, and Albert Mensah, MD, and Judith Bowman, MD, for their continued support of my research.

TABLE OF CONTENTS

PART 1

THE BIOLOGY OF INFLAMMATION

INTRODUCTION

Overview of Inflammation

Inflammation is a fundamental biological process that serves as the body's first line of defense against various harmful stimuli, such as pathogens, damaged cells, or irritants (1-3). It is a protective response that involves immune cells, blood vessels, and molecular mediators (3). The inflammatory response is non-specific, meaning it occurs similarly regardless of the pathogen or injury (4), and is part of the innate immune system, which acts quickly and is the initial reaction to an insult (5,6).

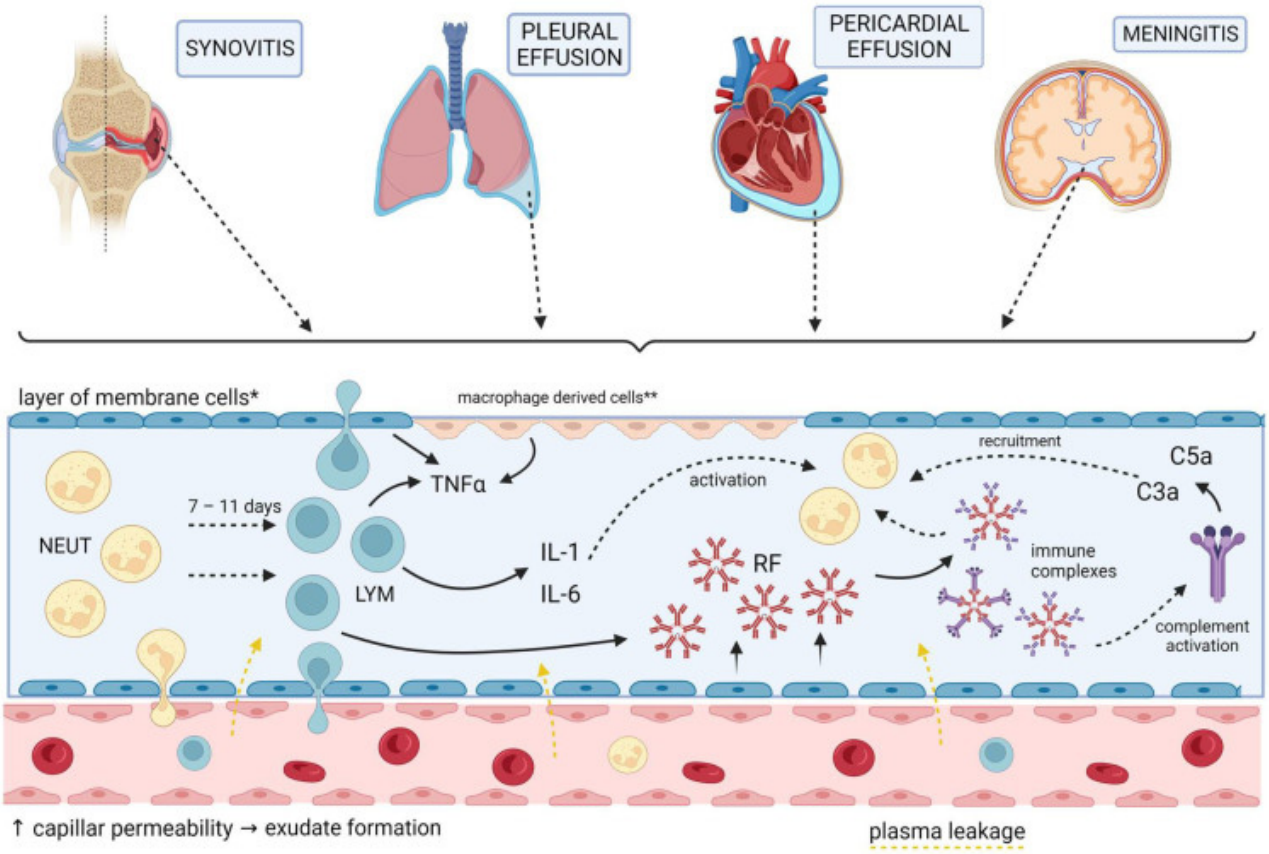


Fig. Intro – 1 Illustration showing proposed common mechanisms of local inflammation in RA-related membrane involvement including similarities in the development of synovitis, pleural and pericardial effusion, and meningitis. NEUT—neutrophils, LYM—lymphocytes, RF—rheumatoid factor, and C3a and C5a—complement components, * synoviocytes/pleural and pericardial mesothelial/leptomeningeal cells, ** replacement of mesothelial cells with macrophage-derived cells. Joško Mitrović, Stela Hrkač, Josip Tečer, Majda Golob, Anja Ljilja Posavec, Helena Kolar Mitrović, Lovorka Grgurević https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10216027/ (Creative Commons – free usage).

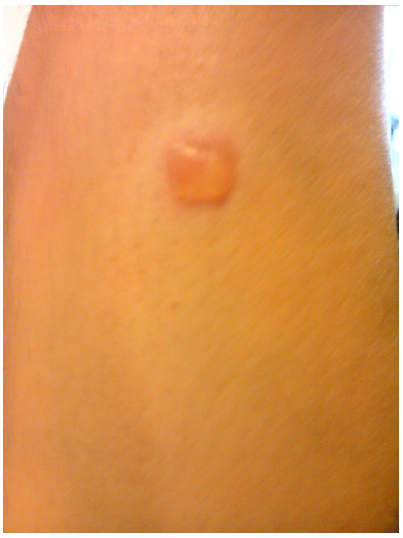
Inflammation often initiates and signals the longer-lasting, specific immune response designed to recognize foreign pathogens.

Types of Inflammation

Inflammation can be categorized into acute and chronic (7-9). Acute inflammation is a short-term, rapid response that begins within minutes to hours after the harmful event and tends to resolve upon the removal of the stimulus (10-12). Chronic inflammation, on the other hand, is a long-term response that can last for months or even years and is often associated with the inability of the body to eliminate the cause of inflammation (13-15). Chronic inflammation is implicated in the development of numerous diseases, such as rheumatoid arthritis, cardiovascular disease, and certain types of cancer (16,17).

Signs and Symptoms

The classic signs of acute inflammation include redness, heat, swelling, pain, and loss of function. Chronic inflammation can lead to a variety of symptoms, including body pain, fatigue, mood disorders, gastrointestinal issues, and frequent infections (18).



Fig, Intro-2 Serous inflammation on the skin. Hanabishi (Creative Commons – free usage)

Cellular and Vascular Components

The cellular component of inflammation involves the migration of leukocytes, especially neutrophils, from the bloodstream to the site of injury or infection (19,20). The vascular component includes the movement of plasma fluid and proteins like fibrin and immunoglobulins into the inflamed tissue, which helps to isolate the affected area and prevent the spread of infection (21).

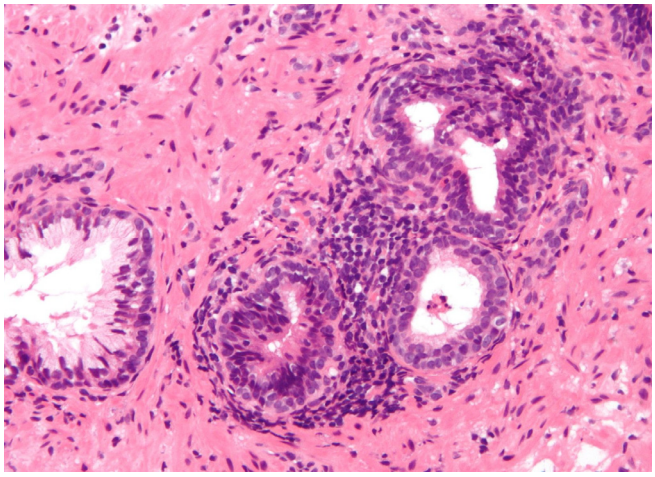


Fig. Intro – 3 Prostatic inflammation is the pathologic correlate of prostatitis. Prostatitis is a benign cause of PSA elevation, i.e. a high PSA value prompts a biopsy, as cancer is a possibility, yet the cause of the elevated PSA is prostatitis. Blue spots are stained nuclei of white blood cells that have migrated to the place of inflammation. Nephron (Creative Commons – free usage)

Role of Cytokines and Chemokines

Cytokines are crucial in inducing and suppressing the inflammatory response (22, 23). They are produced in response to pathogens and are responsible for stimulating, recruiting, and proliferating immune cells (24). Pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α, play a significant role in promoting inflammation (25). Chemokines, a subset of cytokines, have chemotactic activities that guide immune cells to the site of inflammation (26).

Inflammatory Pathways and Mediators

The complement and coagulation systems are key pathways activated during inflammation. The complement system promotes opsonization, chemotaxis, and the formation of the membrane attack complex (MAC), while the coagulation system forms a protective mesh over injury sites (27).

Regulation of Inflammation

Proteins like POP2 can inhibit key inflammatory pathways, preventing the inflammatory response from becoming destructive (28). This regulation is essential, as uncontrolled or excessive inflammation can disrupt normal bodily functions and contribute to disease (29,30).

Consequences of Chronic Inflammation

When inflammation fails to subside, it can contribute to a wide range of chronic diseases (16). Chronic inflammatory response promotes disease through various mechanisms, including inflammasomes, senescent cells, and microglia activation (31). A loss of immune regulation can lead to severe conditions like COVID-19 (32).

Treatment and Management

Anti-inflammatory drugs such as NSAIDs, corticosteroids, and antihistamines can manage inflammation (33). However, these drugs can have adverse effects, including an increased risk of stroke, kidney problems, heart attacks, and gastrointestinal issues (34). Due to these risks, there is a growing interest in natural anti-inflammatory products (35). Additionally, reducing the activity of pro-inflammatory cytokines can alleviate disease symptoms (36).

Recent Discoveries

Recent research has identified a central inflammation program that is significant in various inflammatory conditions and autoimmune diseases (37). This discovery emphasizes the importance of measuring inflammation in the body and could lead to new approaches for tackling infections and chronic inflammation (38).

Inflammation is a complex and vital immune system response that protects the body from harm. While acute inflammation is generally beneficial, chronic inflammation can lead to numerous health issues. Understanding the mechanisms and regulation of inflammation is crucial for developing effective treatments and managing inflammatory diseases.

CHAPTER 1

THE PROCESS OF INFLAMMATION

Inflammation is a complex biological response of the body's immune system to harmful stimuli such as pathogens, damaged cells, or irritants. It is a protective mechanism that removes injurious stimuli and initiates healing.

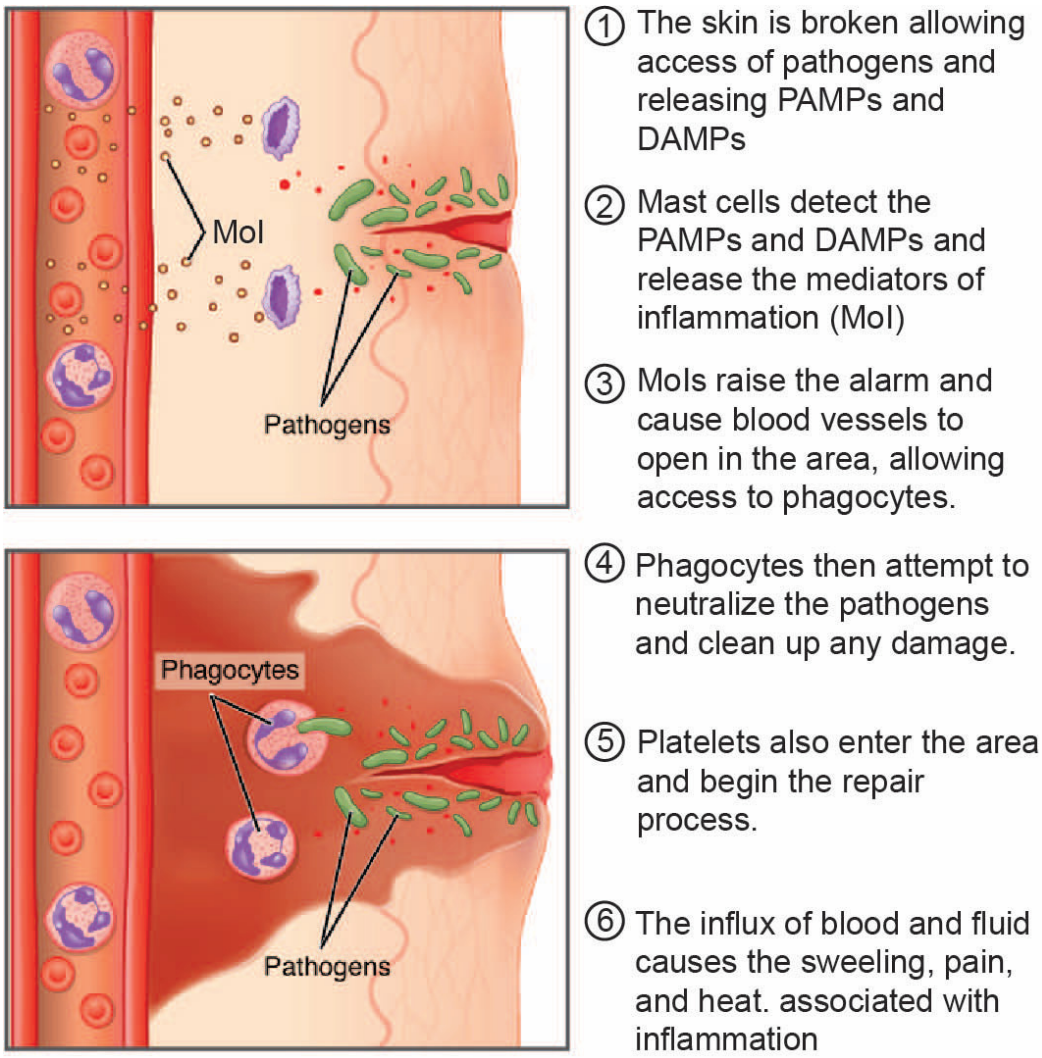


Fig. 1-1 Inflammatory Process Illustration from OpenStax College, Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013. (Creative Commons – free usage)

Inflammatory Response

The inflammatory response is triggered when tissues are injured by factors such as bacteria, trauma, toxins, or heat (1). This response involves immune cells, blood vessels, and molecular mediators (2). Damaged cells release chemicals such as histamine, bradykinin, and prostaglandins, which cause blood vessels to leak fluid into the tissues, leading to swelling (3). These chemicals also attract white blood cells, particularly phagocytes, to consume germs and dead or damaged cells (4).

Acute vs. Chronic Inflammation

Inflammation can be classified as either acute or chronic. Acute inflammation is a short-term response that typically appears within minutes to hours after injury and begins to subside once the harmful stimulus is removed (5). Chronic inflammation, on the other hand, is a prolonged inflammatory response that can last for months or years (6).

Signs and Symptoms

The classic signs of acute inflammation include redness, swelling, heat, pain, and loss of function (7,8). These are the body's mechanisms to increase blood flow and immune cell migration to the affected area. The loss of function is a later addition to the classical signs, believed to have been noted by Galen, Thomas Sydenham, or Rudolf Virchow (9).

Cellular and Vascular Components

The cellular component of inflammation involves leukocytes moving into the inflamed tissue via a process called extravasation (10). The vascular component includes the movement of plasma fluid, which contains proteins like fibrin and immunoglobulins, into the inflamed tissue (11).

Molecular Mediators

Several molecular systems are activated during inflammation, including the complement system, which promotes opsonization, chemotaxis, and agglutination, and the coagulation system, which forms a protective protein mesh over injury sites (12). Phagocytes express cell-surface receptors that recognize microbial patterns, leading to the destruction of microbes within the phagolysosomes (13).

Systemic Effects

Severe inflammation can lead to systemic inflammatory response syndrome (SIRS), characterized by hyperinflammation that can cause organ injury, shock, and even death (14). Chronic inflammation is associated with various diseases, including cardiovascular diseases, atherosclerosis, pancreatitis, liver and kidney inflammation, and intestinal tract diseases (15).

Lifestyle and Chronic Inflammation

Poor nutrition, pesticides, stress, and lack of sleep can contribute to chronic inflammation (16). Lifestyle changes, such as a healthy diet and adequate sleep, may help reduce chronic inflammation (17).

Treatment

Treatment for inflammation may include non-steroidal anti-inflammatory drugs, steroids, and regenerative medicine approaches like PRP injections or bone marrow stem cell therapy (18).

Inflammation is a vital immune response that protects the body from infection and injury. While acute inflammation is generally beneficial, chronic inflammation can lead to a range of health issues. Understanding the mechanisms of inflammation can help develop treatments and manage inflammatory diseases effectively.

CHAPTER 2

TISSUE INJURY THAT LEADS TO INFLAMMATION

Inflammation is a complex biological response to harmful stimuli such as pathogens, damaged cells, or irritants. It is a protective mechanism that involves immune cells, blood vessels, and molecular mediators. Inflammation aims to eliminate the initial cause of cell injury, clear out damaged cells and tissues, and establish repair. The inflammation process is tightly linked to tissue injury, where the body's immune system responds to restore the affected tissues.

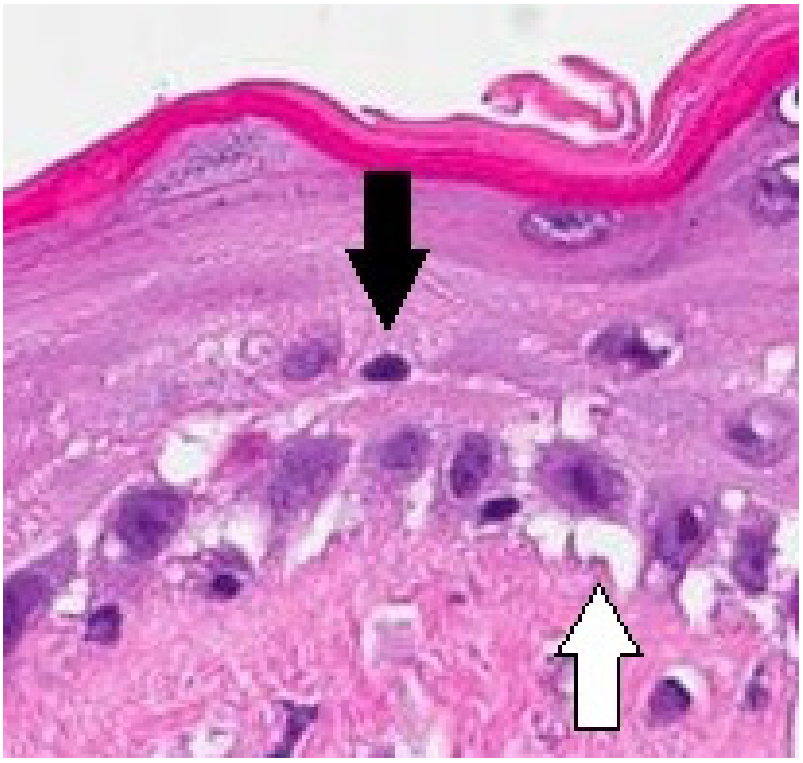
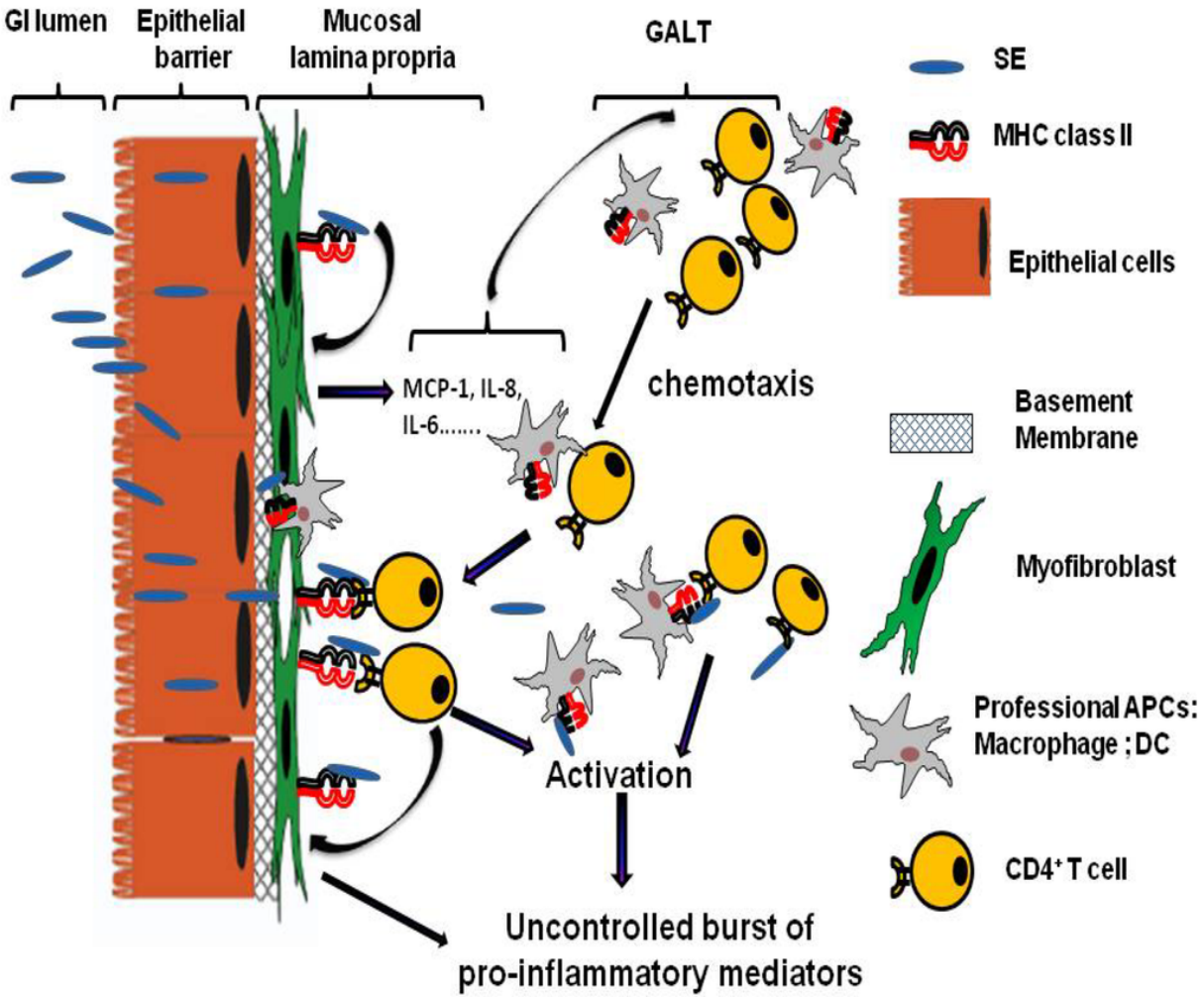


Fig. 2-1 Vacuolar interface dermatitis, a type of inflammation, with lymphocytes in the dermis and epidermis (black arrow indicates one) and vacuolization (white arrow) at the dermoepidermal junction. In this case, the cause was toxic epidermal necrolysis. Brandon T. Beal, Taryn Blaha, David D. Xiong, Sarah H. Schneider, Steven D. Billings, Anthony P. Fernandez, Shilpi Khetarpal (2018). "A Rare Presentation of Toxic Epidermal Necrolysis – Like Acute Systemic Lupus Erythematosus". *SKIN The Journal of Cutaneous Medicine* **2** (2): 144. DOI:10.25251/skin.2.2.9. ISSN 2574-1624. (Creative Commons – free usage)

Immune System Activation

The immune system is among the first to respond when tissues are injured due to infection, toxic, or mechanical damage (1). This response is characterized by the activation and recruitment of various immune cells, such as neutrophils, macrophages, natural killer (NK) cells, B cells, T cells, fibroblasts, and endothelial cells (2). These cells play a crucial role in initiating and resolving the inflammatory process.



Fig, 2-2 Model of the role of mucosal lamina professional and nonprofessional APCs in SE-associated Gastro-Intestinal (GI) inflammatory injury. GI inflammatory injury during staphylococcal enterotoxigenic disease is mediated mostly through the SE superantigenic effect on MHC class II expressing mucosal professional (macrophages and dendritic cells, DC) and nonprofessional (such as myofibroblasts) APCs and TCR expressing CD4+ T cells. SE can cross the intestinal epithelial barrier and bind to class II MHC molecules expressed on subepithelial myofibroblast. These processes will lead to a strong production of the proinflammatory cytokines and chemokines, including IL-6, IL-8, and MCP-1. The last one may lead to the increased chemotaxis of professional immune cells (CD4+ T cells, Macrophages, DC) from gut-associated lymphoid tissue (GALT) to the site of SE-associated inflammation in GI mucosa. Those MHC class II:SEs: TCR interactions may, in turn, result in hyperactivation of the APCs and the T cells, leading to the excessive proliferation of T cells and the uncontrolled burst of various proinflammatory cytokines and chemokines, causing the superantigen-mediated acute inflammation and shock. Pinchuk, I.V.; Beswick, E.J.; Reyes, V.E. https://www.mdpi.com/2072-6651/2/8/2177 (Creative Commons – free usage)

Cellular Mechanisms

The process of inflammation involves several cellular mechanisms. For instance, tissue injury leads to smooth muscle contraction, which facilitates the infiltration of white blood cells into the damaged tissue (3). Fibroblasts, which are pivotal in initiating inflammation and tissue repair, induce chemokine synthesis that activates the chemotaxis of immune cells (4). Macrophages release proinflammatory factors that cause vasodilation and increased permeability of blood vessels, aiding in the migration of neutrophils to the site of injury (5).

Neutrophils and Macrophages

Neutrophils are often the first inflammatory cells to respond to tissue injury (6). They can resolve the cause of the issue through various strategies, including the generation of neutrophil extracellular traps, phagocytosis, or the release of soluble antimicrobial agents (7). Macrophages are also critical in regulating all stages of tissue repair and fibrosis (8). They follow neutrophils to the site of injury, where they mature and exert their effects (9).

Molecular and Cellular Regulators

A network of molecular and cellular regulators supports antimicrobial functions and tissue repair throughout the healing process (10). This includes the release of anti-inflammatory mediators and growth factors that suppress inflammation and initiate the proliferative phase of healing (11). Cytokines and growth factors released by inflammatory cells, such as macrophages, orchestrate the regulation of the proliferation phase (12).

Complement System and Trauma

The complement system, part of the innate immune response, can have detrimental effects after trauma, leading to complement-mediated tissue damage (13). Trauma activates complement both locally and systemically, which can contribute to the pathogenesis of trauma-induced sequelae (14). For example, traumatic brain injury induces a profound inflammatory response, with the complement cascade playing a pivotal role in the development of secondary brain injury (15).

Inflammasomes

Inflammasomes are involved in the innate responses to traumatic injuries and contribute to the development of conditions such as acute respiratory distress syndrome (ARDS) (16). They promote an exaggerated systemic and organ-specific inflammatory response, which can lead to tissue damage (17). Inflammasomes also play a role in post-trauma immunosuppression mediated by dysregulated monocyte functions (18).

Inflammation and Tissue Healing

Acute Inflammation

Acute inflammation is essential for pathogen clearance and the activation of reparative events (19). It involves the recognition of danger/damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) by innate receptors on tissue-resident cells, triggering an acute inflammatory reaction (20). This reaction is mediated by the activation of pathways such as nuclear factor-kB (NF-κB) and mitogen-activated protein kinase (MAPK) (21).

Cytokines and Mediators

Cytokines like IL-6 and IFN-γ play diverse roles in inflammation and tissue repair. IL-6 promotes the resolution of inflammation, enhances fibroblast proliferation, and stimulates angiogenesis (22). IFN-γ, on the other hand, activates macrophages to produce proinflammatory cytokines and enhances phagocytosis, but it can inhibit angiogenesis and collagen deposition (22). Other mediators, such as histamine, prostaglandins, and leukotrienes, also contribute to the inflammatory and reparative responses (23).

Tissue Repair Phases

Tissue repair is a complex biological reaction to injury that includes hemostasis, inflammation, proliferation, and remodeling to restore damaged tissues (24). Fibroblasts construct granulation tissue to fill the wound gap while keratinocytes migrate to cover the wound surface (25). The balance between protection and the potential for collateral tissue damage is crucial (26).

CHAPTER 3

IMMUNE CELLS IN INFLAMMATION

Inflammation is a complex biological response of the body's immune system to harmful stimuli such as pathogens, damaged cells, or irritants. It is a protective mechanism that involves immune cells, blood vessels, and molecular mediators. The primary purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair.

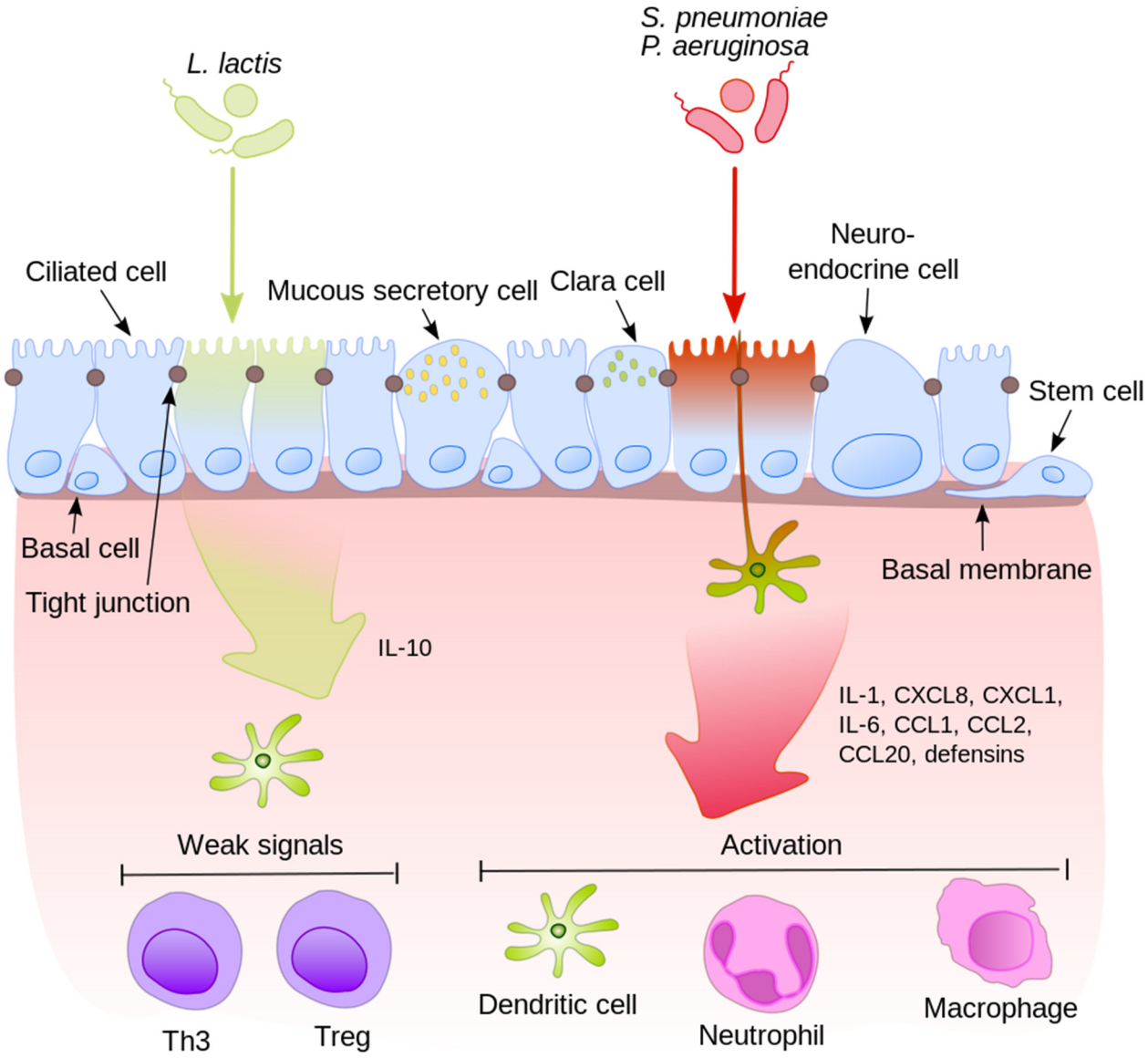


Fig. 3-1 Mechanisms underlaying the inflammation in COPD. The airway epithelium has a complex structure: it consists of at least seven diverse cell types that interact with each other through tight junctions. Moreover, epithelial cells can deliver the signals into the underlying tissues, participating in innate and adaptive immune defense mechanisms. The key transmitters of the signals are dendritic cells. Once pathogenic bacterium (e.g., S. pneumoniae, P. aeruginosa) has activated particular pattern recognition receptors on/in epithelial cells, the proinflammatory signaling pathways are activated. This results mainly in IL-1, IL-6, and IL-8 production. These cytokines induce the chemotaxis to the site of infection in its target cells (e.g., neutrophils, dendritic cells, and macrophages). On the other hand, representatives of standard microbiota cause only weak signaling, preventing inflammation. The mechanism of distinguishing between harmless and harmful bacteria on the molecular and physiological levels is not entirely understood. БИОлогиня (Creative Commons – free usage)

Cytokines and Chemokines

Cytokines are small proteins crucial in controlling the growth and activity of other immune system cells and blood cells (1). When released, they signal the immune system to do its job. Cytokines can be pro-inflammatory and upregulate inflammatory reactions (2).

Pro-Inflammatory Cytokines

Pro-inflammatory cytokines are secreted by immune cells such as Th1 cells, CD4+ cells, macrophages, and dendritic cells (3). These cytokines include IL-1, IL-6, and TNF-α, key players in the inflammatory process (4). IL-1β, for instance, is a potent pro-inflammatory cytokine induced mainly by lymphocytes, macrophages, and monocytes in response to microbial molecules (5). IL-6 acts not only on the immune system but also affects other biological systems and many physiological events (6). TNF-α is particularly important for triggering the expression of vascular endothelial cells and enhancing leukocyte adhesion, which stimulates immune cell infiltration (7).

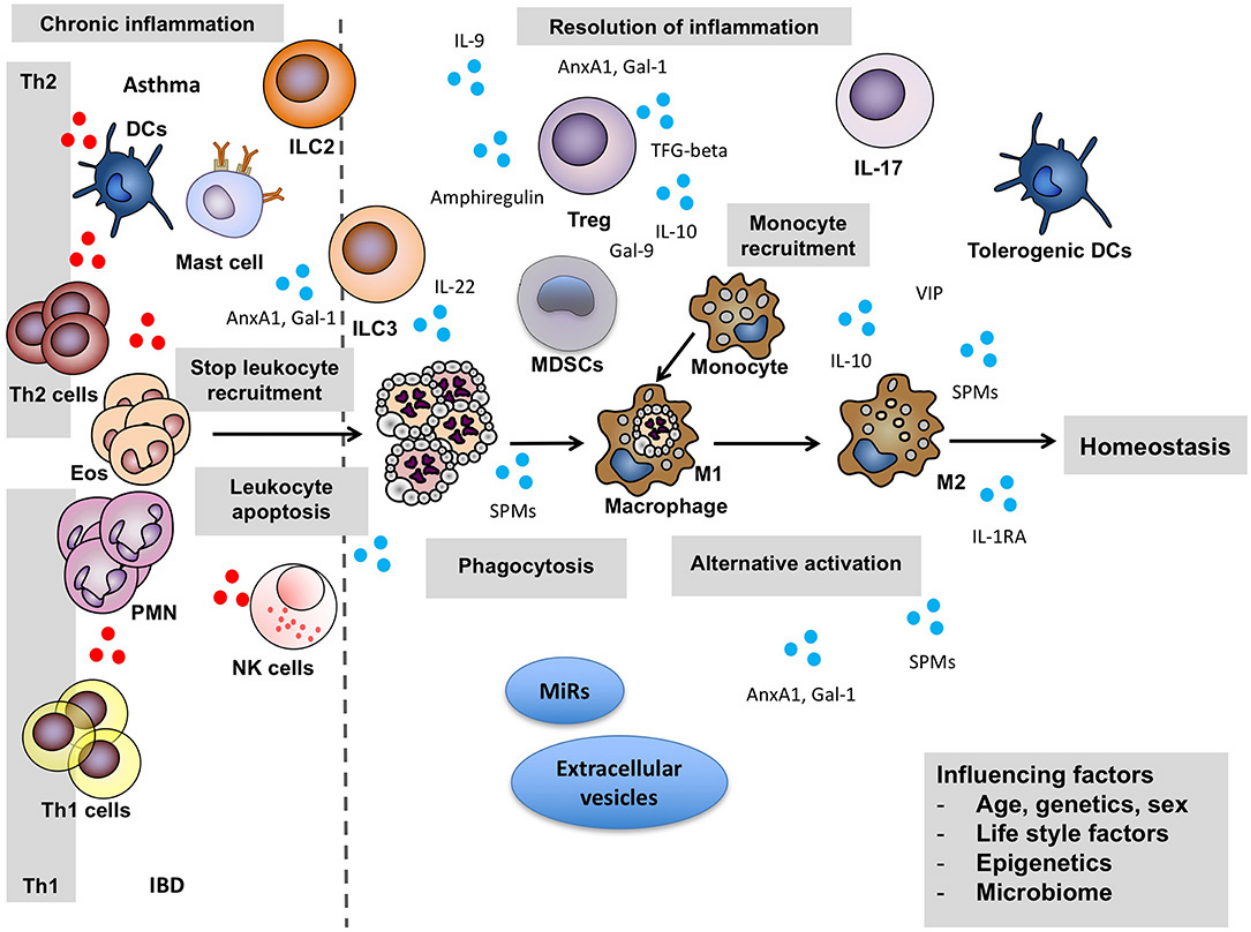


Fig. 3-2 Key cellular actors of resolution. For effective resolution of inflamed tissues and for tissue homeostasis to occur and be restored, specific cellular mechanisms under the control of pro-resolving mediators are enlisted. They promote the termination of the inflammatory response and initiate tissue repair and healing. Pro-inflammatory mediators are red circles, and pro-resolving mediators are blue circles. Anx, annexin; DCs, Dendritic cells; Eos, eosinophils; Gal, Galectin; IBD, inflammatory bowel disease; IL, interleukin; ILC2, Type 2 innate lymphoid cells; ILC3, Type 3 innate lymphoid cells; MDSCs, Myeloid-derived suppressor cells; MiRs, MicroRNAs; NK, Natural killer; PMN, polymorphonuclear cells; TGF-beta, Transforming growth factor beta; Th1, Type 1 T helper cells; Th2, Type 2 T helper cells; Treg, regulatory T cells; SPMs, specialized pro-resolution lipid mediators; VIP, vasoactive intestinal peptide. Cindy Barnig, Tjitske Bezema, Philip C. Calder, Anne Charloux, Nelly Frossard, Johan Garssen, Oliver Haworth, Ksenia Dilevskaya, Francesca Levi-Schaffer, Evelyne Lonsdorfer, Marca Wauben, Aletta D. Kraneveld and Anje A. te Velde https://www.frontiersin.org/articles/10.3389/fimmu.2019.01699/full (Creative Commons - free usage)

Chemokines

Chemokines are a subset of cytokines with chemotactic activities that guide the movement of immune cells to the sites of inflammation, infection, or trauma (8,9). They are classified into four main subfamilies: CXC, CC, CX3C, and XC, each with structural and functional differences.

Macrophages

Macrophages are key players in initiating and resolving inflammation, a process known as polarization (10). In the lungs, for example, alveolar macrophages (AMs) and interstitial macrophages (IMs) contribute to the development and progression of inflammatory responses (11). During the acute phase of inflammation, M1-type macrophages are activated and release pro-inflammatory cytokines (12). As the inflammation resolves, M1 macrophages can transition into M2 macrophages, which release anti-inflammatory molecules and contribute to tissue repair (13).

T Cells

T cells are another group of immune cells involved in the inflammatory response. Th1 and Th17 cells differentiated from CD4+ T cells promote inflammation, while Th2 and Treg cells inhibit it (14). CD8+ T cells also contribute to inflammation and are directly involved in the development of metabolic diseases (15). Activated T cells secrete cytokines such as TNF and IL-17, which can recruit macrophages and produce IFN-γ to activate macrophages (16).

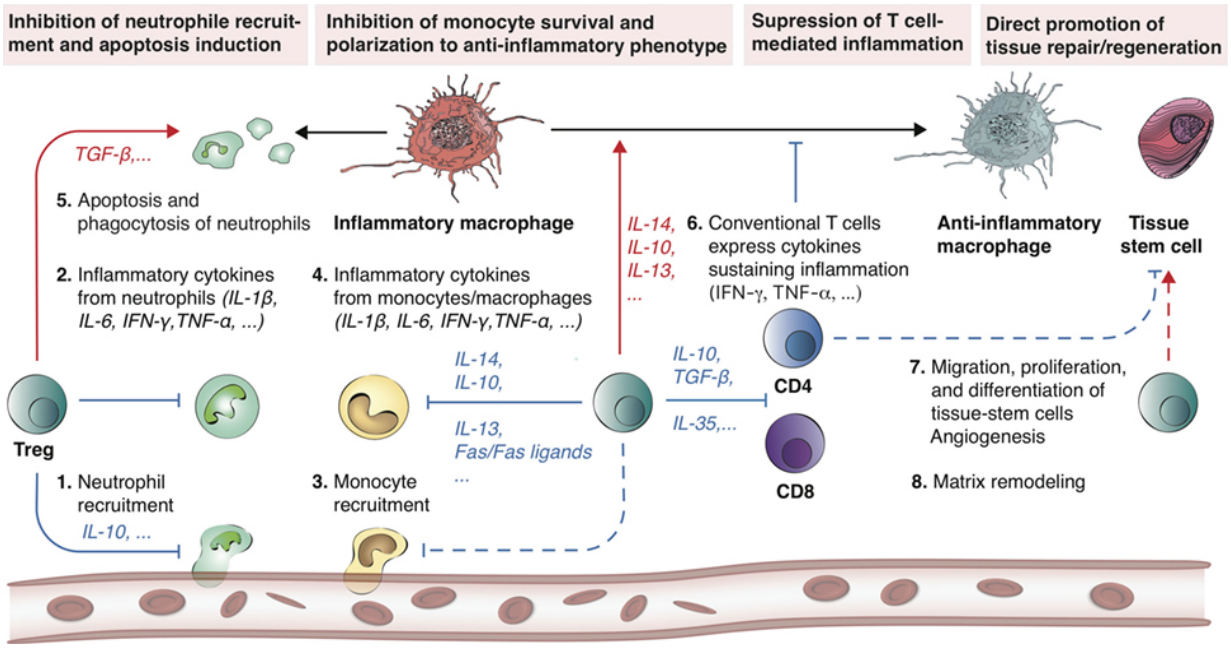


Fig 3-2 Treg promotes tissue repair and regeneration by modulating inflammation. Tregs have demonstrated the ability to promote tissue repair and regeneration by controlling innate and adaptive immune systems. Following tissue injury, a cascade of immune events is triggered (steps 1–6) until a new tissue is formed (steps 7–8). Tregs are involved in all these different steps. At the onset of inflammation, Treg can neutralize inflammatory cytokine secretion (e.g., IL-6, IFN-γ, TNF-α, and IL-1β) by inhibiting neutrophil extravasation via IL-10. In addition, Tregs can promote the apoptosis of neutrophils and encourage phagocytosis of dead neutrophils by macrophages. Concomitantly, Treg further inhibit monocyte activity and survival and stimulate macrophage polarization toward an anti-inflammatory phenotype (M2) via the release of anti-inflammatory cytokines (e.g., IL-4, IL-10, IL-13). Similarly, Treg can naturally suppress CD4 and CD8 T cell-mediated inflammation (via IL-10, TGF-β, and IL-35). Overall, these Treg-mediated mechanisms result in the inhibition of neutrophil, inflammatory macrophage, as well as CD4 and CD8 T-cell activity, which is generally favorable for tissue repair and regeneration. Dashed lines indicate a hypothetical mechanism. Red arrows indicate induction, while blue arrows indicate inhibition. Jiatao Li, Jean Tan, Mikaël M. Martino and Kathy O. Lui https://www.frontiersin.org/articles/10.3389/fimmu.2018.00585/full (Creative Commons – free usage)

Inflammatory Diseases and Conditions

Chronic inflammatory cytokine production can contribute to various diseases, such as atherosclerosis, cancer, and autoimmune disorders (17). In rheumatoid arthritis (RA), macrophages drive chronic inflammation and tissue destruction (18). In allergic asthma, macrophage polarization affects the pathogenesis of the disease (19). Moreover, an imbalance between the immune and metabolic systems can lead to chronic, low-grade systemic inflammation, resulting in metabolic disorders (20).

Regulation and Therapeutic Interventions

The body has mechanisms to regulate the activity of pro-inflammatory cytokines. For instance, M2 macrophages express anti-inflammatory molecules that inhibit pro-inflammatory mediators (21). Therapeutic interventions can target these cytokines to reduce inflammation. Histone deacetylate inhibitors (HDACi) can suppress pro-inflammatory cytokine production (22), and vitamin D has been shown to reduce the secretion of specific inflammatory cytokines (23).

In conclusion, immune cells such as macrophages, T cells, cytokines, and chemokines play a central role in the inflammatory process. Understanding these components and their interactions is crucial for developing treatments for inflammatory diseases.

CHAPTER 4

THE ROLE OF BLOOD VESSELS IN INFLAMMATION

Inflammation is a complex biological response of the body's vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective response involving immune cells, blood vessels, and molecular mediators. Inflammation aims to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged by the original insult and the inflammatory process, and initiate tissue repair.

Vascular Changes During Inflammation

Blood vessels play a crucial role in the inflammatory process. During inflammation, a series of vascular changes occur that facilitate the body's defense mechanisms:

1. **Vasodilation and Increased Blood Flow**: Initially, small blood vessels constrict to prevent blood loss, but soon after, arterioles and venules dilate, leading to increased blood flow to the affected area. This results in the classic signs of redness and heat as more blood reaches the injured tissue (1).

2. **Increased Vascular Permeability**: In response to inflammatory mediators like histamine, bradykinin, and prostaglandins, the walls of the blood vessels become more permeable. This allows protein-rich fluid (exudate) to leak into the tissues, causing swelling and pain (2,3).

3. **Emigration of White Blood Cells**: As the blood flow slows due to fluid leakage, white blood cells move to the edges of the blood vessels and adhere to the vessel wall. They then migrate from the blood vessels into the tissue to engage pathogens and clear debris (4,5).

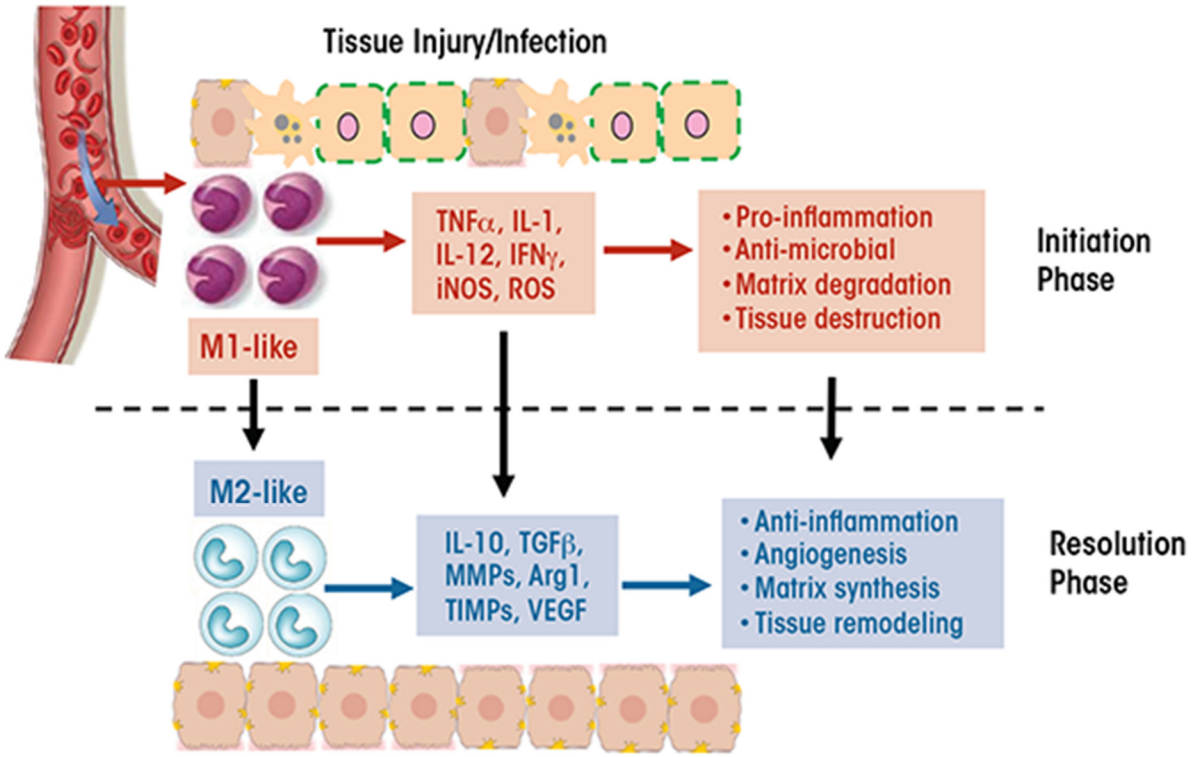


Fig. 4-1 Macrophages recruited to the site of an injury or infection during the initiation phase of the inflammatory reaction have an M1 phenotype. They produce pro-inflammatory and stress mediators and cytokines, such as tumor necrosis factor α (TNFα), interleukin (IL)-1 and -12, interferon γ (IFNγ), an enzyme generating nitric oxide (iNOS), and reactive oxygen species (ROS). These macrophages have proinflammatory and antimicrobial effects, leading to matrix degradation and tissue destruction. During the resolution phase of the injury, these M1 macrophages are converted into an M2 phenotype with a different cytokine and chemokine repertoire, including IL-10, transforming growth factor β (TGF-β), matrix metalloproteinases (MMPs), arginase 1 (Arg1), tissue inhibitors of metalloproteinases (TIMPs), and vascular epithelial growth factor (VEGF). These M2 macrophages are anti-

inflammatory and promote blood-vessel formation (angiogenesis), matrix synthesis, and tissue remodeling. Cynthia Ju, Ph.D., and Pranoti Mandrekar, Ph.D. http://www.arcr.niaaa.nih.gov/arcr/arcr372/article09.htm (Creative Commons – free usage)

Consequences of Vascular Inflammation

Inflammation of the blood vessels, or vasculitis, can have several consequences:

1. **Thickening of Blood Vessel Walls**: Inflammation can cause the walls of blood vessels to thicken, narrowing the passageway and potentially restricting blood flow, which can damage organs and tissues (6).
2. **Organ-Specific Impact**: Vasculitis may affect one or more organs, and its severity can vary. Some types of vasculitis can be severe, leading to significant organ damage (7).
3. **Formation of Blood Clots**: Inflammation can lead to the formation of blood clots within the vessels, further obstructing blood flow and exacerbating tissue damage (8).
4. **Vision Loss**: In cases like untreated giant cell arteritis, a type of vasculitis, inflammation can lead to vision loss or even blindness (9).
5. **Chronic Inflammation**: If the inflammatory response persists, it can become chronic, leading to ongoing tissue damage and requiring different treatment strategies than acute inflammation (10).

Treatment and Management

Inflammation, particularly vasculitis, is often treated with medications that control inflammation and prevent flare-ups. The goal is to reduce symptoms and prevent further damage to the blood vessels and organs (11).

Understanding the Four Cardinal Signs of Inflammation

The four cardinal signs of inflammation are redness, heat, swelling, and pain. These are directly related to the changes occurring in the blood vessels during the inflammatory response:

- **Redness** is due to the dilation of small blood vessels within the damaged tissue (12).
- **Heat** results from the increased blood flow through the area (13).
- **Swelling**, or edema, is primarily caused by fluid accumulation outside the blood vessels (14).
- **Pain** can result from the distortion of tissues caused by edema and is also induced by chemical mediators of inflammation (15).

In summary, blood vessels are integral to the inflammatory response. They facilitate the delivery of immune cells and mediators to the site of injury and contribute to the symptoms and potential complications of inflammation. Understanding these processes is crucial for developing effective treatments for inflammatory diseases.

CHAPTER 5

MOLECULAR MEDIATORS IN INFLAMMATION

Molecular Mediators

1. Cytokines

Cytokines are small, protein-based cell-signaling molecules crucial to immune responses. They aid in cell-to-cell communication, stimulate cell movement toward sites of inflammation, infection, and trauma, and regulate cell survival, proliferation, differentiation, and functional activity (1). Cytokines are essential in controlling the growth and activity of immune system cells and blood cells, and their levels can increase significantly in response to infection or inflammation (2).

Types of Cytokines

- **Interleukins (ILs)**: These cytokines act as chemical signals between white blood cells (WBCs) (3). Key pro-inflammatory interleukins include IL-1, IL-6, and IL-1β, which are involved in various inflammatory processes (4).
- **Interferons (IFNs)**: These chemicals help the body resist viral infections and cancers (5).
- **Tumor Necrosis Factors (TNFs)**: TNF-α is a key pro-inflammatory cytokine that triggers the expression of vascular endothelial cells, enhances leukocyte adhesion molecules, and stimulates immune cell infiltration (6).
- **Chemokines**: These cytokines have chemotactic activities and are classified into four main subfamilies: CXC, CC, CX3C, and XC chemokines (7).

2. Toll-like Receptors (TLRs)

TLRs are a family of pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) found in microbial pathogens (8). Ligand binding activates TLRs, triggering a signaling cascade involving intracellular signaling adaptors such as MyD88, IRAKs, and TRAF6. This cascade activates the MAP kinase, NF-κB, and IRF signaling pathways (9). These pathways mediate inflammation by producing inflammatory cytokines, type I IFN, chemokines, and antimicrobial peptides (10).

3. Specialized Pro-resolving Mediators (SPMs)

SPMs are enzymatically derived from essential fatty acids and serve as a novel class of immunoresolvents that limit acute responses and orchestrate the clearance of tissue pathogens, dying cells, and debris from sites of inflammation (11). SPMs include lipoxins, E-series and D-series resolvins, protectins, and maresins (12). They play important regulatory roles in host responses to various microorganisms and promote the resolution of non-infectious inflammation and tissue injury (13). Defects in SPM pathways can contribute to chronic inflammatory diseases (14).

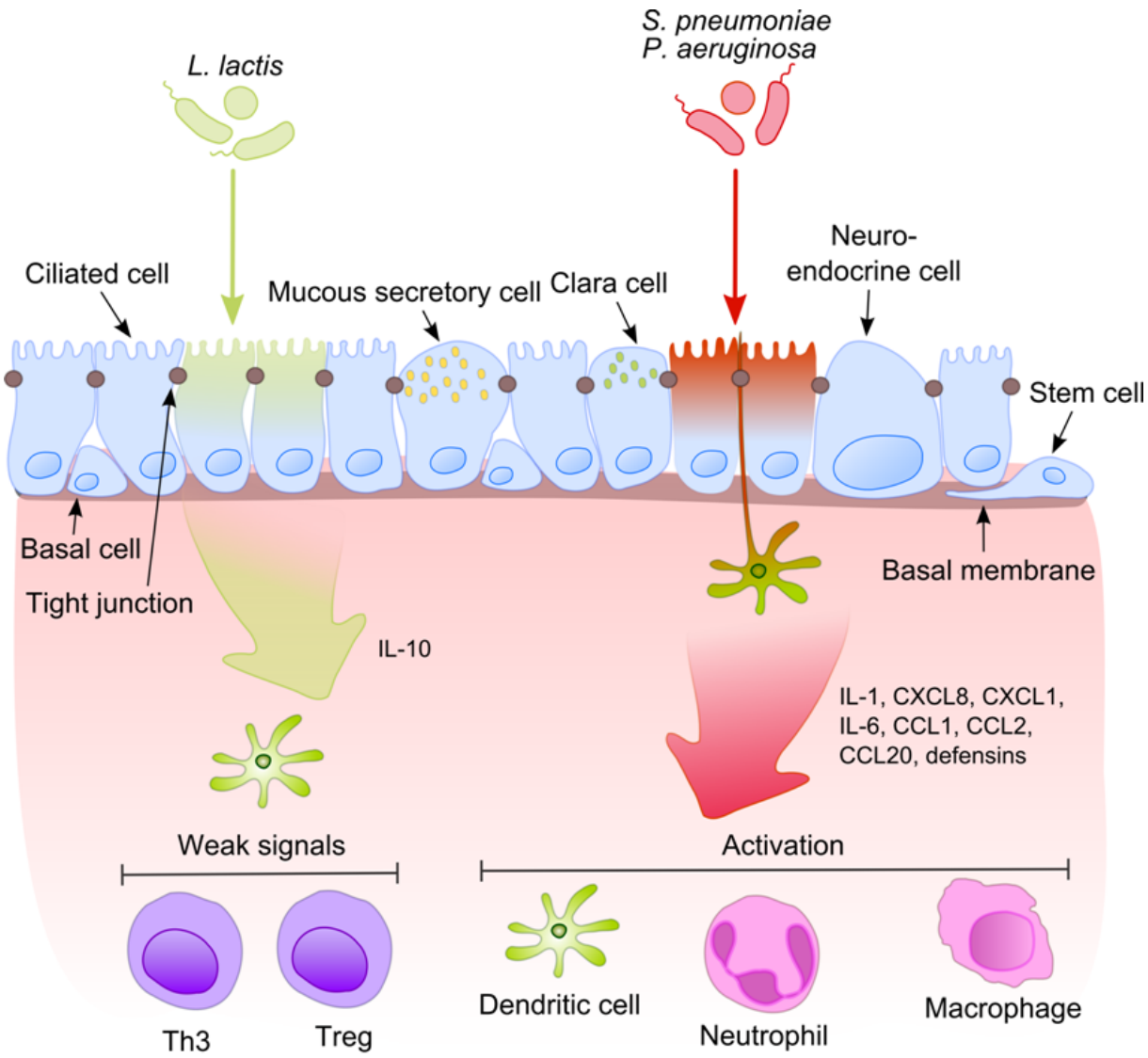


Fig. 5-1 Mechanisms underlaying the inflammation in COPD. The airway epithelium has a complex structure consisting of at least seven diverse cell types that interact with each other through tight junctions. Moreover, epithelial cells can deliver the signals into the underlying tissues, participating in innate and adaptive immune defense mechanisms. The key transmitters of the signals are dendritic cells. Once pathogenic bacterium (e.g., S. pneumoniae, P. aeruginosa) has activated pattern recognition receptors on/in epithelial cells, the proinflammatory signaling pathways are activated. This results mainly in IL-1, IL-6, and IL-8 production. These cytokines induce the chemotaxis to the site of infection in its target cells (e.g., neutrophils, dendritic cells, and macrophages). On the other hand, representatives of standard microbiota cause only weak signaling, preventing inflammation. The mechanism of distinguishing between harmless and harmful bacteria on the molecular and physiological levels is not entirely understood. БИОлогиня (Creative Commons – free usage)

4. Inflammatory Mediators in Cancer

Chronic inflammation is closely associated with the development and progression of cancer. Inflammatory mediators play a crucial role in this process. Their biochemical properties can be divided into seven groups: vasoactive amines, vasoactive peptides, cytokines, chemokines, fragments of complement components, lipid mediators, and proteolytic enzymes (15). Chronic, dysregulated inflammation has been linked to an increased risk of malignancies and the malignant progression of cancer (16).

Molecular mediators such as cytokines, TLRs, and SPMs are pivotal in the inflammatory response. Understanding these mediators and their pathways is crucial for developing targeted therapies for inflammatory diseases and conditions associated with chronic inflammation, such as cancer. Further research into these mediators holds promise for improving the management and treatment of inflammation-related diseases.

CHAPTER 6

INTERLEUKINS IN INFLAMMATION

Interleukins (ILs) are a group of cytokines that play a crucial role in the immune system by mediating communication between cells. They are involved in various physiological processes, including inflammation, immune response, and hematopoiesis. This chapter synthesizes key points from recent research to provide a comprehensive overview of the interleukins involved in inflammation.

Key Interleukins in Inflammation

General Role of Interleukins

Interleukins are signaling molecules produced by various cells, including leukocytes, T cells, B cells, dendritic cells, and macrophages. They are essential for cell-to-cell communication and modulate growth, differentiation, and activation during inflammatory and immune responses (1-6).

Pro-Inflammatory Interleukins

Pro-inflammatory interleukins are crucial for initiating and amplifying the immune response to infectious agents. They include IL-1, IL-6, and TNF-α, which are key players in the inflammatory process (7,8).

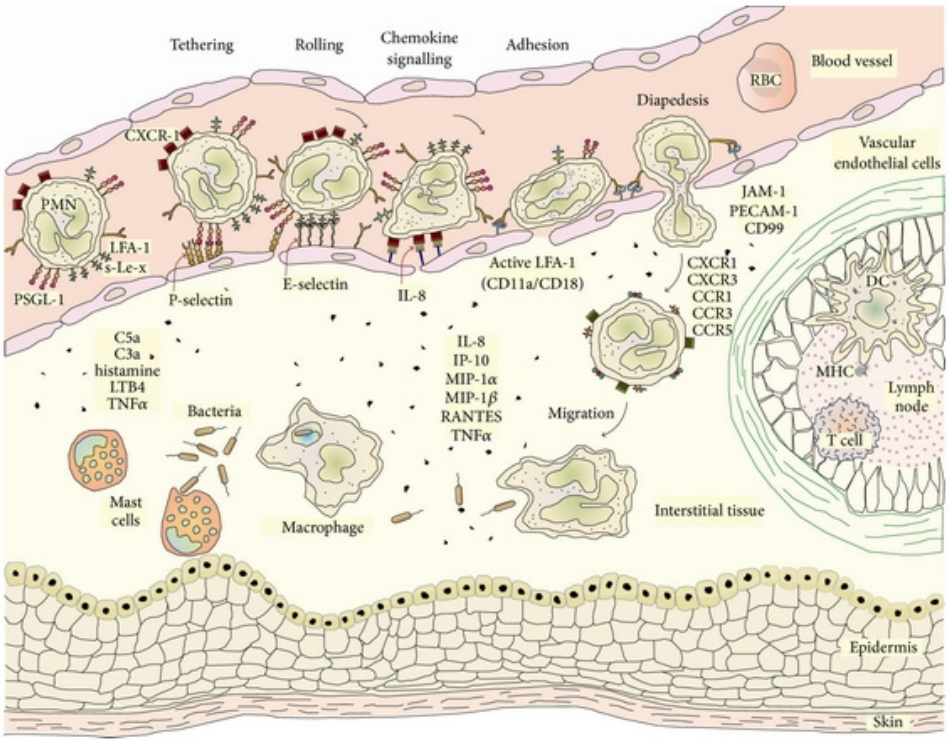


Fig. 6-1 Schematic representation of an immune response to a bacterial infection. Tethering: P-selectins bind to PSGL-1 and tether PMN. Rolling: P-selectins bring PMN near E-selectins, and slow rolling commences. Chemokine signaling: slow rolling allows IL-8 binding to CXCR1, then integrin activation results in more adhesive interactions with endothelial ligands. Adhesion: activated LFA-1 binds ICAM-1 or ICAM -2 for firm adhesion. Diapedesis: PMN begins diapedesis by exchanging tight junction molecules with endothelial cells. Migration: PMN follows a gradient of inflammatory chemokines to pathogens. Attack: Complement attacks the incoming pathogens, mast cells, and macrophage phagocytose pathogens; toll-like receptor molecules trigger inflammation; antigen-presenting dendritic cells express MHC molecules to activate T lymphocytes and to recruit neutrophils. PMN = polymorphonuclear neutrophil; CXCR/CCR = chemokine receptor; s-Le-x = sialyl-Lewis X; LFA = lymphocyte function-associated antigen; PSGL = P-selectin glycoprotein ligand; IL = interleukin; CD = cluster of differentiation; CD11a/CD18 = integrins; RBC = red blood cell; JAM = junctional adhesion molecule; PECAM = platelet endothelial cell adhesion molecule; DC = dendritic cell; MHC = major histocompatibility complex; T cell = T lymphocyte; IP-10 = interferon-gamma induced protein-10; MIP = macrophage inflammatory

protein; RANTES = regulated on activation, normal T cell expressed and secreted (CCL5 chemokine); TNF α = tumor necrosis factor alpha; C3a and C5a = complement components 3a and 5a; LTB4 = leukotriene B4.

Chris Tsopelas "Radiotracers Used for the Scintigraphic Detection of Infection and Inflammation", The Scientific World Journal doi:10.1155/2015/676719 (Creative Commons – free usage).

Interleukin-1 (IL-1)

IL-1 is a potent pro-inflammatory cytokine with two forms: IL-1α and IL-1β. Lymphocytes, macrophages, and monocytes primarily produce it in response to microbial molecules. IL-1β, in particular, is involved in initiating and amplifying the immune response (9-11). IL-1 family cytokines, including IL-1β, regulate cell survival, proliferation, and differentiation, thereby modulating immune responses to infectious agents (12).

Interleukin-6 (IL-6)

IL-6 is a pleiotropic cytokine that affects the immune system, other biological systems, and physiological events. It is produced by various cell types, including macrophages, monocytes, fibroblasts, and endothelial cells (13-15). IL-6 is essential for B-cell differentiation and the stimulation of acute phase proteins (15).

Tumor Necrosis Factor-alpha (TNF-α)

TNF-α is another critical pro-inflammatory cytokine that triggers the expression of vascular endothelial cells and enhances leukocyte adhesion molecules, stimulating immune cell infiltration (16). It is crucial in coordinating cell-mediated immune responses and modulating the immune system (17).

Other Notable Interleukins

Several other interleukins also play significant roles in inflammation and immune responses:

- **IL-2**: Promotes T-cell proliferation and differentiation and is used in immunotherapy for advanced kidney cancer and metastatic melanoma (18-20).
- **IL-17**: Produced by CD4 T cells, it enhances the activities of antigen-presenting cells and stimulates chemokine synthesis by endothelial cells (21-22).
- **IL-18**: Induces IFN synthesis and contributes to the immune response against viral infections by activating T cells and natural killer (NK) cells (23-24).
- **IL-10**: Inhibits the synthesis of IFN and IL-2, decreasing antigen presentation and downregulating pathogenic Th17 cell responses (25-26).

Conclusion

Interleukins are vital immune system components that play significant roles in inflammation and immune responses. Key pro-inflammatory interleukins such as IL-1, IL-6, and TNF-α are essential for initiating and amplifying the immune response to infectious agents. Understanding the functions and mechanisms of these interleukins can provide insights into their roles in various diseases and potential therapeutic approaches.

CHAPTER 7

INTERFERONS IN INFLAMMATION

Interferons (IFNs) are signaling proteins that play a crucial role in the immune response, particularly in inflammation. They are categorized into three main types: Type I (IFN-α and IFN-β), Type II (IFN-γ), and Type III (IFN-λ). Each type has distinct roles and mechanisms of action in regulating immune responses and inflammation.

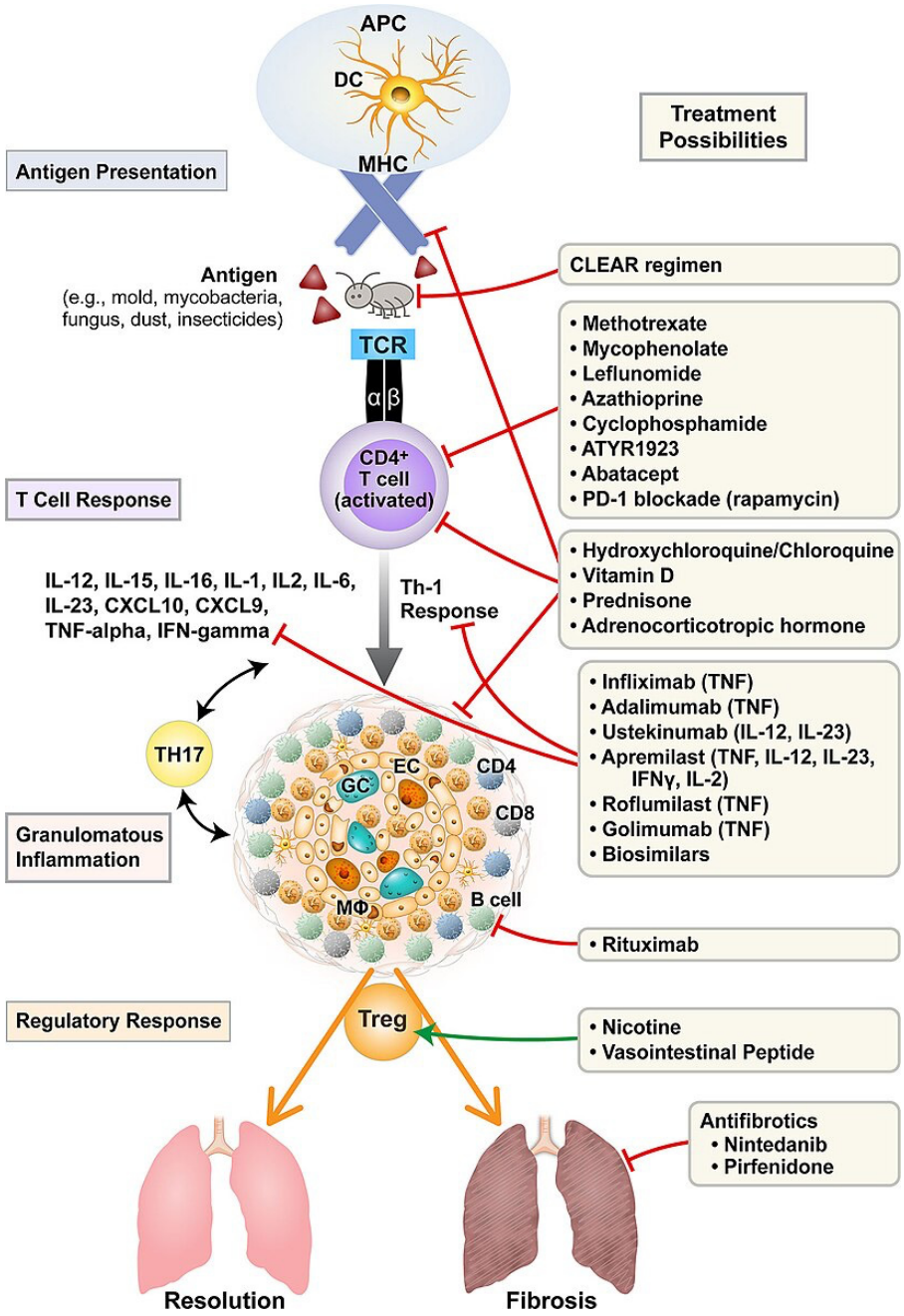


Fig. 7-1 Current and investigational treatments for sarcoidosis based on pathogenesis. Treatments for sarcoidosis target antigen presentation, T cell activation, cytokine/chemokine profiles, propagation of granulomatous inflammation, T-regulatory balance, and the fibrotic response. APC, antigen presenting cell; DC, dendritic cell; MHC, major histocompatibility complex; TCR, T cell receptor; GC, multinucleated giant cell; EC, epitheloid cell; Mφ, macrophage; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; PD-1, programmed cell death protein-1; CLEAR, Combined Levofloxacin; Ethambutol, Azithromycin and Rifampin. Alicia K. Gerke https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2020.545413/full (Creative Commons - free usage)