Health Innovation Reports 2026,2(1):32-39
DOI: 10.64048/hir.v2n1.007

Narrative Review

# Molecular Mechanisms of Inflammation and Their Role in the Development of Chronic Diseases: A Narrative Review

**Jihad Haji Saleh** [1*]

Received: 3 September 2025 Revised: 29 September 2025 Accepted: 1 November 2025 Published: 15 January 2026


## Abstract

Inflammation is a fundamental and protective biological response, yet when it becomes chronic and unresolved it emerges as a central driver in the pathogenesis of many of the most burdensome human diseases. The molecular machinery governing the inflammatory response, when persistently activated, contributes to progressive tissue injury and organ dysfunction. This narrative review comprehensively examines the molecular mechanisms of inflammation and clarifies how these mechanisms participate in the development of chronic diseases. The cellular sensing of danger through pattern recognition receptors, the activation of the nuclear factor-κB (NF-κB) signalling pathway, the assembly of the NLRP3 inflammasome, and the resulting production of pro-inflammatory cytokines and lipid mediators are described in an integrated manner. The distinction between self-limiting acute inflammation and persistent low-grade chronic inflammation is emphasized, since the failure of resolution is now recognized as a key pathological event. The review further details how these molecular processes converge on the pathogenesis of atherosclerosis and cardiovascular disease, type 2 diabetes and metabolic dysfunction, cancer, neurodegenerative disorders, and autoimmune conditions. The role of specialized pro-resolving mediators and the therapeutic opportunities arising from targeting inflammatory pathways are also considered. By synthesizing current mechanistic understanding with its clinical consequences, this review provides both a conceptual framework and a practical reference for researchers and clinicians. In sum, the work positions chronic inflammation as a unifying mechanism across diverse diseases and underscores the value of resolution-based and pathway-specific strategies for prevention and treatment.

**Keywords** Inflammation · Chronic Inflammation · Molecular Mechanisms · NF-κB · NLRP3 Inflammasome · Cytokines · Resolution of Inflammation · Atherosclerosis · Type 2 Diabetes · Cancer · Neuroinflammation · Innate Immunity · Chronic Disease

✉ Jihad Haji Saleh
Jihad.7ajy@gmail.com
[1] Department of Biology, Harran University, Şanlıurfa, Turkey

* Corresponding author: Jihad Haji Saleh, Department of Biology, Harran University, Şanlıurfa, Turkey, Jihad.7ajy@gmail.com

## 1. Introduction

Inflammation is one of the most fundamental protective responses of the body, serving to eliminate harmful stimuli such as pathogens, damaged cells, and irritants, and to initiate tissue repair (Medzhitov, 2008). It is an evolutionarily conserved process that, under normal circumstances, is tightly regulated and self-limiting. The classical signs of redness, heat, swelling, pain, and loss of function reflect the underlying vascular and cellular events that characterize the acute inflammatory response. The success of this response depends on its precise initiation, amplification, and, crucially, its timely resolution.

Although acute inflammation is generally beneficial, it is now widely recognized that inflammation which fails to resolve becomes a major contributor to disease (Medzhitov, 2010; Nathan and Ding, 2010). When the inflammatory response persists, it transitions into a chronic, low-grade state that can silently damage tissues over months or years. This concept of chronic inflammation as a common basis for diverse pathologies has reshaped the understanding of many non-communicable diseases (Furman et al., 2019). The persistence of inflammatory signalling, rather than its initiation, is the feature most strongly linked to chronic disease.

At the molecular level, the inflammatory response is orchestrated by a network of sensors, signalling pathways, and effector molecules (Takeuchi and Akira, 2010). Pattern recognition receptors detect danger signals and activate intracellular cascades, of which the nuclear factor-κB (NF-κB) pathway is among the most central (Liu et al., 2017). These cascades culminate in the production of cytokines, chemokines, and other mediators that coordinate the recruitment and activation of immune cells. Dysregulation at any of these molecular nodes can convert a protective response into a pathological one.

The link between these molecular mechanisms and chronic disease has become a major focus of biomedical research (Furman et al., 2019). Conditions as diverse as atherosclerosis, type 2 diabetes, cancer, and neurodegenerative disease share inflammatory pathways in their pathogenesis. Understanding how the same core mechanisms contribute to such varied diseases offers the prospect of common therapeutic strategies. This shared molecular basis is increasingly viewed as an opportunity for prevention and treatment.

This narrative review aims to provide an integrated account of the molecular mechanisms of inflammation and their role in the development of chronic diseases. It begins with an overview of the inflammatory response and the distinction between acute and chronic inflammation, proceeds to the key molecular pathways, and then examines how these mechanisms drive specific chronic diseases. The review closes by considering the resolution of inflammation and the therapeutic implications that follow from this mechanistic understanding.

## 2. The inflammatory response: an overview

The inflammatory response can be broadly divided into acute and chronic phases, which differ in their duration, cellular participants, and outcomes (Medzhitov, 2008). Acute inflammation develops rapidly following infection or injury and is characterized by vasodilation, increased vascular permeability, and the recruitment of neutrophils to the affected site. These events are driven by mediators released by resident immune cells and damaged tissue, and they serve to contain and eliminate the inciting stimulus. In most cases, acute inflammation is self-limiting and is followed by a coordinated phase of resolution that restores tissue homeostasis.

Resolution is now understood to be an active, tightly regulated process rather than a passive fading of the response (Medzhitov, 2010; Serhan, 2014). Specialized pro-resolving mediators promote the clearance of apoptotic cells and debris, the cessation of neutrophil recruitment, and the return of the tissue to its normal state. When resolution proceeds successfully, the inflammatory response leaves no lasting damage. The failure of these resolution programmes is a critical event that allows inflammation to persist.

When the inciting stimulus is not eliminated, or when resolution fails, inflammation becomes chronic (Nathan and Ding, 2010). Chronic inflammation is characterized by the persistent presence of macrophages, lymphocytes, and plasma cells, and by simultaneous tissue destruction and attempted repair. Unlike acute inflammation, the chronic form is often of low intensity but long duration, and it may be clinically silent for extended periods. This sustained, smouldering response is the form most closely associated with chronic disease (Furman et al., 2019).

The contrast between these two outcomes is fundamental to understanding the role of inflammation in disease. A controlled, resolving response protects the host, whereas a persistent, non-resolving response damages it. Figure 1 summarizes the two contrasting trajectories of the inflammatory response. The molecular events that determine which path is taken are the subject of the following sections.

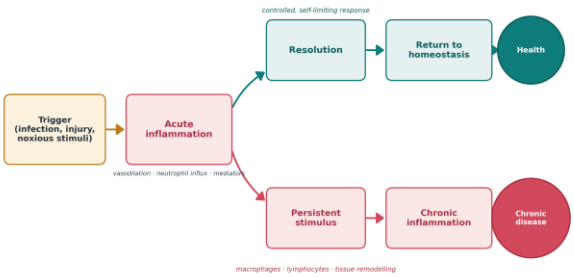


**Figure 1**. Two contrasting trajectories of the inflammatory response: resolution and a return to homeostasis, or persistence and progression to chronic disease.

## 3. Molecular mechanisms of inflammation

The inflammatory response is governed by a sophisticated molecular network that senses danger, transmits signals, and generates effector molecules (Takeuchi and Akira, 2010). This section describes the principal components of that network, beginning with the receptors that detect inflammatory stimuli and proceeding through the major intracellular signalling pathways to the mediators that execute the response.

### *3.1. Pattern recognition receptors and the initiation of inflammation*

The inflammatory response begins with the recognition of danger by pattern recognition receptors (PRRs), which detect conserved molecular structures associated with pathogens or tissue damage (Takeuchi and Akira, 2010; Kawai and Akira, 2010). Pathogen-associated molecular patterns (PAMPs), such as bacterial lipopolysaccharide, and damage-associated molecular patterns (DAMPs), released from injured cells, are sensed by families of receptors that include the Toll-like receptors (TLRs) and the NOD-like receptors. Toll-like receptors, located on the cell surface and within endosomes, are among the most extensively characterized of these sensors (Kawai and Akira, 2010). Upon ligand binding, PRRs initiate intracellular signalling cascades that activate transcription factors and drive the expression of inflammatory genes. The engagement of these receptors thus represents the critical first step that couples the detection of a threat to the mounting of an inflammatory response.

### *3.2. The NF-κB signalling pathway*

Among the signalling pathways activated downstream of PRRs, the nuclear factor-κB (NF-κB) pathway is the principal regulator of inflammatory gene expression (Liu et al., 2017; Lawrence, 2009). In the resting state, NF-κB dimers, commonly composed of the p50 and p65 subunits, are held inactive in the cytoplasm by inhibitory IκB proteins. Stimulation of receptors such as TLR4, the tumour necrosis factor receptor (TNFR), and the interleukin-1 receptor (IL-1R) leads, through adaptor proteins such as MyD88 and TRAF6, to activation of the IκB kinase (IKK) complex. The IKK complex phosphorylates IκBα, marking it for proteasomal degradation and thereby releasing NF-κB to translocate into the nucleus. Once in the nucleus, NF-κB drives the transcription of numerous pro-inflammatory genes, including those encoding TNF-α, IL-1β, IL-6, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) (Liu et al., 2017). The canonical NF-κB signalling cascade is illustrated in Figure 2. Because this pathway sits at the heart of inflammatory signalling, its deregulation is implicated in a wide range of chronic inflammatory diseases.

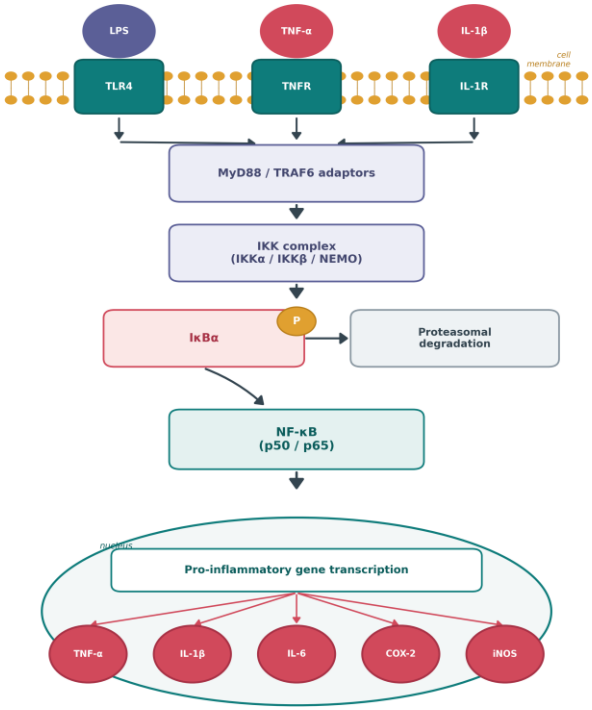


**Figure 2**. The canonical NF-κB signalling pathway, from receptor activation at the membrane to pro-inflammatory gene transcription in the nucleus.

### *3.3. The NLRP3 inflammasome*

A second pivotal molecular mechanism is the inflammasome, a multiprotein complex that controls the maturation of certain pro-inflammatory cytokines (Broz and Dixit, 2016). The best-characterized of these is the NLRP3 inflammasome, which is assembled in response to a broad range of microbial and endogenous danger signals (Swanson et al., 2019). Its activation typically requires two signals: a priming signal, often delivered through TLR-NF-κB signalling, that increases the expression of NLRP3 and the precursors pro-IL-1β and pro-IL-18; and an activation signal, provided by stimuli such as extracellular ATP, potassium efflux, reactive oxygen species, or particulate matter, that triggers assembly of the complex. The assembled inflammasome, comprising NLRP3, the adaptor ASC, and pro-caspase-1, activates caspase-1, which in turn cleaves pro-IL-1β and pro-IL-18 into their mature, secreted forms and cleaves gasdermin D to induce the inflammatory cell death known as pyroptosis (Swanson et al., 2019). The assembly and outputs of the NLRP3 inflammasome are depicted in Figure 3. Dysregulated inflammasome activity has been linked to metabolic, cardiovascular, and neurodegenerative diseases.

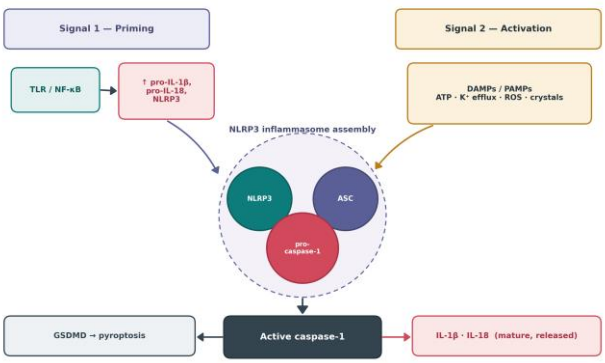


**Figure 3**. Assembly and activation of the NLRP3 inflammasome, leading to caspase-1-dependent maturation of IL-1β and IL-18 and to pyroptotic cell death.

### *3.4. MAPK and JAK-STAT signalling*

In addition to NF-κB and the inflammasome, the

mitogen-activated protein kinase (MAPK) and Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathways contribute substantially to the inflammatory response (Takeuchi and Akira, 2010). The MAPK cascades, which include the ERK, JNK, and p38 modules, are activated downstream of many inflammatory receptors and regulate the production and stability of inflammatory mediators. The JAK-STAT pathway transduces signals from numerous cytokines, including IL-6 and the interferons, and amplifies and sustains inflammatory gene expression. Together with NF-κB, these pathways form an interconnected signalling network whose combined output determines the magnitude and character of the response. Crosstalk between these pathways provides multiple points at which the response can be amplified or, conversely, therapeutically interrupted.

### *3.5. Inflammatory mediators*

The effector arm of the inflammatory response comprises a diverse array of mediators, including cytokines, chemokines, and lipid-derived molecules (Medzhitov, 2008). Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 coordinate the systemic and local features of inflammation, while chemokines direct the migration of immune cells to the site of injury. Lipid mediators derived from arachidonic acid, such as the prostaglandins and leukotrienes, contribute to vasodilation, pain, and leukocyte recruitment. The balance between these pro-inflammatory mediators and their anti-inflammatory and pro-resolving counterparts ultimately determines whether inflammation resolves or persists. The principal inflammatory mediators and their functions are summarized in Table 1.

**Table 1**. Major inflammatory mediators and their principal functions.

| Mediator | Class | Principal function |
|---|---|---|
| TNF-α | Cytokine | Promotes inflammation, endothelial activation, and cell death |
| IL-1β | Cytokine | Activates immune cells; drives fever and systemic inflammation |
| IL-6 | Cytokine | Induces the acute-phase response; sustains chronic inflammation |
| IL-18 | Cytokine | Promotes interferon-γ production and immune activation |
| Chemokines (e.g. CXCL8) | Chemokine | Direct the migration of leukocytes into inflamed tissue |
| Prostaglandins | Lipid mediator | Mediate vasodilation, pain, and fever |
| Leukotrienes | Lipid mediator | Promote leukocyte recruitment and vascular permeability |
| Reactive oxygen species | Reactive species | Antimicrobial activity; cause oxidative tissue damage |
| IL-10 | Cytokine | Anti-inflammatory; limits and helps resolve the response |
| Pro-resolving mediators | Lipid mediator | Actively promote resolution and tissue repair |

## 4. Inflammation in the development of chronic diseases

The molecular mechanisms described above do not act in isolation; when chronically engaged, they converge on the pathogenesis of a broad spectrum of diseases (Furman et al., 2019; Chen et al., 2018). This section examines how persistent inflammation contributes to several of the most important chronic conditions. The shared involvement of common pathways across these diseases is illustrated in Figure 4.

### *4.1. Cardiovascular disease and atherosclerosis*

Atherosclerosis, the principal cause of cardiovascular disease, is now firmly established as a chronic inflammatory disorder of the arterial wall (Libby, 2012). The retention and modification of lipoproteins within the vessel wall trigger the recruitment of monocytes, which differentiate into macrophages and ingest modified lipids to become foam cells. These cells, together with activated endothelial and smooth muscle cells, sustain a local inflammatory milieu rich in cytokines such as IL-1β and TNF-α. Inflammasome activation by cholesterol crystals further amplifies this response and contributes to plaque progression and instability (Libby, 2012). The clinical importance of this inflammatory mechanism is underscored by evidence that targeting IL-1β can reduce cardiovascular events.

### *4.2. Type 2 diabetes and metabolic disorders*

Chronic low-grade inflammation, often termed metaflammation, is a central feature of obesity and type 2 diabetes (Hotamisligil, 2006; Hotamisligil, 2017). In the setting of nutrient excess, expanding adipose tissue becomes infiltrated by macrophages that adopt a pro-inflammatory phenotype and secrete cytokines such as TNF-α and IL-6. These mediators interfere with insulin signalling and contribute to insulin resistance, a key step in the development of type 2 diabetes (Donath and Shoelson, 2011). The NLRP3 inflammasome, activated by metabolic danger signals, links nutrient surplus to IL-1β production and islet dysfunction. Thus, the same molecular pathways that mediate host defence also underlie metabolic disease when chronically engaged.

### *4.3. Cancer*

The relationship between inflammation and cancer has long been recognized and is now understood at the molecular level (Coussens and Werb, 2002; Grivennikov et al., 2010). Chronic inflammation can promote tumour initiation,

progression, and metastasis through several mechanisms, including the generation of reactive oxygen species that damage DNA, the production of cytokines that support cell proliferation and survival, and the creation of a microenvironment conducive to angiogenesis and immune evasion. NF-κB and STAT3 signalling are particularly important in linking inflammation to cancer, as they regulate genes that govern both inflammation and tumour cell survival (Grivennikov et al., 2010). Inflammatory conditions affecting various organs are associated with an increased risk of malignancy, illustrating the breadth of this connection (Chen et al., 2018).

### *4.4. Neurodegenerative diseases*

Inflammation within the central nervous system, termed neuroinflammation, is increasingly implicated in neurodegenerative diseases such as Alzheimer's disease (Heneka et al., 2015). Misfolded and aggregated proteins are recognized by pattern recognition receptors on microglia and astrocytes, triggering an innate immune response and the release of inflammatory mediators. Although initially protective, sustained activation of glial cells contributes to neuronal injury and disease progression. The NLRP3 inflammasome has been specifically implicated in the neuroinflammatory response to protein aggregates (Heneka et al., 2015). This mechanistic understanding has raised the possibility of targeting neuroinflammation as a therapeutic strategy.

### *4.5. Autoimmune and inflammatory disorders*

Many autoimmune and chronic inflammatory disorders, including rheumatoid arthritis and inflammatory bowel disease, are driven by dysregulated inflammatory signalling (Liu et al., 2017). In these conditions, the persistent activation of pathways such as NF-κB leads to the sustained production of pro-inflammatory cytokines that perpetuate tissue damage. The success of biologic therapies that neutralize TNF-α or block IL-6 signalling in these diseases provides direct evidence of the causal role of these mediators. These disorders illustrate how the failure to restrain inflammatory signalling translates into chronic, organ-specific pathology.


**Figure 4**. Chronic low-grade inflammation as a shared mechanism converging on the development of major chronic diseases.

**Table 2**. Representative chronic diseases and their underlying inflammatory mechanisms.

| Disease | Key mediators / pathways | Inflammatory contribution |
|---|---|---|
| Atherosclerosis / CVD | IL-1β, TNF-α, NLRP3 | Macrophage-driven plaque formation and instability |
| Type 2 diabetes | TNF-α, IL-6, NLRP3 (metaflammation) | Adipose inflammation and insulin resistance |
| Cancer | NF-κB, STAT3, reactive oxygen species | Tumour promotion, survival, and immune evasion |
| Alzheimer's disease | Microglial activation, NLRP3 | Neuroinflammation and progressive neuronal injury |
| Rheumatoid arthritis | TNF-α, IL-6, NF-κB | Sustained synovial inflammation and joint damage |
| Inflammatory bowel disease | TNF-α, NF-κB | Chronic mucosal inflammation and tissue damage |

## 5. Resolution of inflammation and therapeutic implications

The recognition that resolution is an active process has transformed the approach to treating inflammatory disease (Serhan, 2014). Specialized pro-resolving mediators, including lipoxins, resolvins, protectins, and maresins, actively terminate inflammation and promote the return to homeostasis. The failure of these resolution programmes, rather than excessive initiation alone, is increasingly viewed as central to chronic inflammation. Strategies that promote resolution, rather than simply suppress inflammation, therefore represent a promising therapeutic direction.

At the same time, the molecular pathways described in this review offer numerous targets for intervention (Tabas and Glass, 2013). Agents that inhibit specific cytokines, block inflammasome activation, or interrupt key signalling nodes have shown benefit across several chronic diseases. However, because inflammatory pathways are also essential for host defence and homeostasis, such interventions must be carefully balanced to avoid impairing protective immunity. The challenge for future therapy lies in selectively targeting pathological inflammation while preserving its beneficial functions.

## 6. Conclusion

The molecular mechanisms of inflammation lie at the intersection of host defence and disease. A response that evolved to protect the organism becomes, when chronically engaged and inadequately resolved, a powerful driver of pathology. This review has traced the molecular logic of inflammation from the recognition of danger by pattern recognition receptors, through the central NF-κB signalling pathway and the NLRP3 inflammasome, to the production of the cytokines and mediators that execute the response. It has further shown how these same mechanisms converge on the pathogenesis of atherosclerosis, type 2 diabetes, cancer, neurodegenerative disease, and autoimmune disorders, establishing chronic inflammation as a unifying thread across otherwise disparate conditions. The growing appreciation that resolution is an active and targetable process, together with the identification of specific molecular nodes amenable to therapeutic intervention, offers genuine hope for the prevention and treatment of these diseases. A continued, integrated understanding of inflammatory mechanisms and their clinical consequences will be essential to translate this knowledge into effective strategies that reduce the global burden of chronic disease.

## Statements and Declarations

### *Ethics Approval*

Ethical approval was not required, as this review did not involve human participants, animal subjects, or the collection of primary data.

### *Funding*

This article did not receive any financial support.

### *Data Availability*

No data were used in the research described in this article.

### *CRediT Authorship Contribution Statement*

**Jihad Haji Saleh:** Conceptualization, Investigation, Writing – original draft, Writing – review and editing.

### *Declaration of Competing Interest*

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### *Acknowledgements*

The author thanks all the peer reviewers and editors for their opinions, suggestions, and support of this research.

## References

BROZ, P. & DIXIT, V. M. 2016. Inflammasomes: mechanism of assembly, regulation and signalling. *Nature Reviews Immunology,* 16, 407-420. https://doi.org/10.1038/nri.2016.58

CHEN, L., DENG, H., CUI, H., ET AL. 2018. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget,* 9, 7204-7218. https://doi.org/10.18632/oncotarget.23208

COUSSENS, L. M. & WERB, Z. 2002. Inflammation and cancer. *Nature,* 420, 860-867. https://doi.org/10.1038/nature01322

DONATH, M. Y. & SHOELSON, S. E. 2011. Type 2 diabetes as an inflammatory disease. *Nature Reviews Immunology,* 11, 98-107. https://doi.org/10.1038/nri2925

FURMAN, D., CAMPISI, J., VERDIN, E., ET AL. 2019. Chronic inflammation in the etiology of disease across the life span. *Nature Medicine,* 25, 1822-1832. https://doi.org/10.1038/s41591-019-0675-0

GRIVENNIKOV, S. I., GRETEN, F. R. & KARIN, M. 2010. Immunity, inflammation, and cancer. *Cell,* 140, 883-899. https://doi.org/10.1016/j.cell.2010.01.025

HENEKA, M. T., CARSON, M. J., EL KHOURY, J., ET AL. 2015. Neuroinflammation in Alzheimer's disease. *The Lancet Neurology,* 14, 388-405. https://doi.org/10.1016/S1474-4422(15)70016-5

HOTAMISLIGIL, G. S. 2006. Inflammation and metabolic disorders. *Nature,* 444, 860-867. https://doi.org/10.1038/nature05485

HOTAMISLIGIL, G. S. 2017. Inflammation, metaflammation and immunometabolic disorders. *Nature,* 542, 177-185. https://doi.org/10.1038/nature21363

KAWAI, T. & AKIRA, S. 2010. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nature Immunology,* 11, 373-384. https://doi.org/10.1038/ni.1863

LAWRENCE, T. 2009. The nuclear factor NF-κB pathway in inflammation. *Cold Spring Harbor Perspectives in Biology,* 1, a001651. https://doi.org/10.1101/cshperspect.a001651

LIBBY, P. 2012. Inflammation in atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology,* 32, 2045-2051. https://doi.org/10.1161/ATVBAHA.108.179705

LIU, T., ZHANG, L., JOO, D. & SUN, S. C. 2017. NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy,* 2, 17023. https://doi.org/10.1038/sigtrans.2017.23

MEDZHITOV, R. 2008. Origin and physiological roles of inflammation. *Nature,* 454, 428-435. https://doi.org/10.1038/nature07201

MEDZHITOV, R. 2010. Inflammation 2010: new adventures of an old flame. *Cell,* 140, 771-776. https://doi.org/10.1016/j.cell.2010.03.006

NATHAN, C. & DING, A. 2010. Nonresolving inflammation. *Cell,* 140, 871-882. https://doi.org/10.1016/j.cell.2010.02.029

SERHAN, C. N. 2014. Pro-resolving lipid mediators are leads for resolution physiology. *Nature,* 510, 92-101. https://doi.org/10.1038/nature13479

SWANSON, K. V., DENG, M. & TING, J. P. 2019. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nature Reviews Immunology,* 19, 477-489. https://doi.org/10.1038/s41577-019-0165-0

TABAS, I. & GLASS, C. K. 2013. Anti-inflammatory therapy in chronic disease: challenges and opportunities. *Science,* 339, 166-172. https://doi.org/10.1126/science.1230720

TAKEUCHI, O. & AKIRA, S. 2010. Pattern recognition receptors and inflammation. *Cell,* 140, 805-820. https://doi.org/10.1016/j.cell.2010.01.022