Academic International Journal of Medical Science
ISSN: 2984-7583
Aca. Intl. J. Med. Sci. 2023; 1(2) 34-43
Journal homepage: www.aipublishers.org/aijms

Document heading

The Impact of Inflammation on Pathological Processes

Riadh Hnewa[1], Duha Maithem Hassan[2]

[1] Department of Pathology, College of Medicine, University of Warith Al Anbiyaa, Karbala, Iraq.
[2] Health and Medical Technical College. University of Al Zahraa for women- Iraq.
E-mail: riadh.ab@uowa.edu.iq

ArticleInfo.
Article history:
Received 05 June 2023
Revised 01 July 2023
Accepted 25 July 2023
Keywords:
Acute Inflammation, pathological processes, Chronic Inflammation
How to cite:
Riadh Hnewa, and Duha Maithem Hassan. The impact of inflammation on pathological processes. Aca. Intl. J. Med. Sci. 2023; 1(2) 34-43

Abstract:

The term "inflammation" initially referred to a variety of well-known symptoms and signs, including erythema (redness), oedema, warmth, pain, and function loss (immobility and stiffness). Today, inflammation is understood to be a complicated, changing response to tissue damage brought on by noxious substances, certain environmental factors, trauma, infection or overuse. Some of these responses may be deleterious, as in many chronic disease states, while some could help with infection control and healing of wounds. Inflammation is a "second-line" defence against pathogenic microorganisms. The responses that inflammation causes are the basic processes of pathology. The suffix "-itis" denotes illnesses characterized by pathological inflammation. Cell-mediated and humoral immune system reactions largely produce inflammation. This study examines the association between inflammation and two major worldwide causes of death and morbidity: cardiovascular disease (CVD) and cancer.

Introduction:

Acute Inflammation

Acute inflammation is characterized by a sudden onset, typically resolving within a few days, marked by classic signs like redness, swelling, pain and heat, due to higher blood flow via vasodilation. Neutrophils are the primary immune cells at the site of injury, playing a vital role in the initial response to injury or infection. Cryotherapy is often an effective treatment for musculoskeletal injuries, reducing pain and hastening recovery.[1]

Chronic Inflammation

Chronic inflammation, as opposed to acute inflammation, develops gradually over time and can last for years. Unlike acute inflammation, the classic indications of redness, swelling, and strong pain are generally less evident or absent in chronic inflammation, making identification difficult. Chronic inflammation is distinguished by the predominance of immune cells such as monocytes, macrophages, and lymphocytes, which indicate the body's reaction to continuing irritants or dangers. It is frequently

associated to long-term exposure to dangerous substances such as cigarette smoke and toxic chemicals, which perpetuates the inflammatory response and contributes to a variety of health problems. It is critical for healthcare providers to grasp the differences between acute and chronic inflammation in order to effectively identify and manage inflammatory disorders.[2]

Inflammatory Response Mechanisms

The coordinated activation of signals that control the amount of inflammatory mediators in tissue cells and draw inflammatory cells is called the inflammatory response. This process is critical in the genesis of many chronic diseases, including cancer, arthritis, diabetes, gastrointestinal problems, and cardiovascular disease. Regardless of the particular causes and locations of inflammation throughout the body, they all follow a general process that may be summarized in four important steps: [3]

1. Pattern Recognition Receptor Activation

PRRs ("Pattern-recognition receptors"), which are found on both non-immune and immune cells, identify harmful stimuli and initiate the process. PRRs recognize microbiological structures (PAMPs) and signals from tissue or cell damage (DAMPs), and they include C-type lectin receptors (CLRs), Toll-like receptors (TLRs), NOD-like receptors (NLRs), and retinoic acid-inducible gene (RIG)-I-like receptors (RLRs). DAMPs, or host macromolecules, can trigger and sustain non-infectious inflammation in the absence of pathogens by recruiting innate inflammatory cells. [4]

TLRs, a critical PRR family, collaborate with MyD88, or myeloid differentiation factor 88 to initiate intracellular signaling cascades. As a result of this, transcriptional regulators such as IRF3 stands for interferon regulatory factor, NF-B, and activator protein 1 (AP-1) enter the nucleus. Notably, several receptors, such as TLR4, respond to both DAMPs and PAMPs, emphasizing the similarities between viral and noninfectious inflammatory responses. These insights into the mechanisms behind inflammation, which are critical for understanding and treating inflammatory disorders in a range of diseases, underscore the complexities of inflammation and its role in chronic health issues. [5]

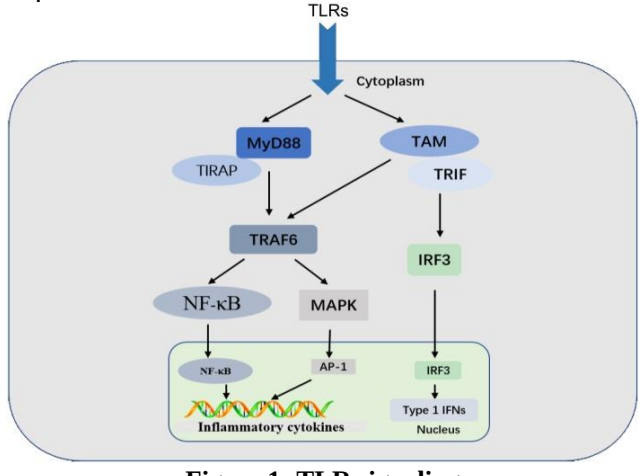

Figure 1: TLR signaling

TRIF- and MyD88-dependent pathways are shown. TLR signaling induces "intracellular signaling cascades" that nuclear translocate AP-1, NF-B, or IRF3, modulating inflammation.[6]

2. Activation of Inflammatory Pathways

The activation of inflammatory pathways is critical in the intricate realm of the inflammatory response and impacts the development of many chronic diseases. These pathways, which determine how the body reacts to various inflammatory stimuli, include widespread inflammatory regulatory processes and mediators. Intracellular signaling pathways are activated by these triggers, which eventually result

in the inflammatory mediator's production. Among the primary inflammatory triggers are a range of substances, containing microbial metabolites and cytokines as interleukin-1 (IL-1), IL-6 (interleukin-6), and TNF (tumor necrosis factor). These mediators bind to a variety of receptors, including TLRs (toll-like receptors), the interleukin-1 receptor (IL-1R), the interleukin-6 receptor (IL-6R), and the TNF receptor (TNFR). [7]

- **NF-κB Pathway**

The nuclear factor kappa-B (NF-B) transcription factor regulates inflammation, immunological responses, cell survival, and apoptosis. The NF-B family—P50, p52, RelA (p65), RelB, and c-Rel—responds to pathogen-generated chemicals, cell-produced inflammatory cytokines, and enzymes. Cytoplasmic inhibitory I-B proteins block NF-B under healthy circumstances. [8]

A combination containing regulatory IKK, IKK kinase subunits, and IKK activates NF-B. This complex phosphorylates I-B, allowing the proteasome to break it down and let NF-B into the nucleus. NF-B stimulates nucleus gene transcription, which affects pro-inflammatory cytokines and inflammatory cell recruitment. The NF-B pathway's role in inflammatory response and its effects on chronic inflammation-related disorders need a basic understanding of the route. [9]

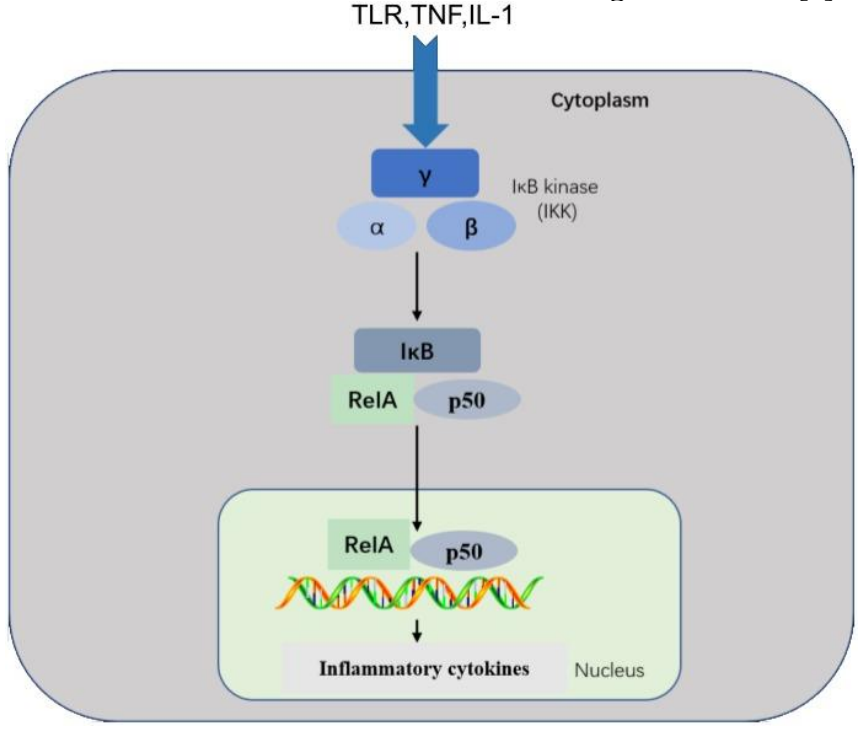

Figure 1 **NF-κB pathway**

TLRs and inflammatory cytokines like TNF and IL-1 activate this pathway, activating RelA/p50 complexes that regulate cytokine production. NF-B signaling requires IKK subunits. which controls pathway activation via IB phosphorylation.[10]

- MAPK pathway

Mitogen-activated protein kinases (MAPKs) are key serine/threonine protein kinases that regulate cell responses to heat shock, osmotic stress, mitogens, and inflammatory cytokines including IL-1, TNF-, and IL-6. They control cell survival, differentiation, and apoptosis. c-Jun N-terminal kinases and ERK1/2, p38 MAP Kinase are mammals' MAPKs. Three components make up each MAPK pathway: a MAPK, a MAPKKK, and a MAPKK. MAPKKKs trigger MAPKKs, which activate MAPKs. [11]

Inflammatory and stress-related signals activate JNK and p38, whereas mitogens and differentiation cues stimulate ERKs. Certain MAPKKs, such as MKK2 and MKK1 for MKK7, MKK4 and ERK1/2 and MKK7 for JNK, and MKK6 and MKK3 for p38, enhance these activations. MAPKs such as ERK1/2 and JNK, when activated, phosphorylate the p38 transcription factors in the nucleus or cytoplasm to initiate the inflammatory responses. This mechanism is critical for regulating how cells respond to a wide range of pathological stimuli and physiological. [12]

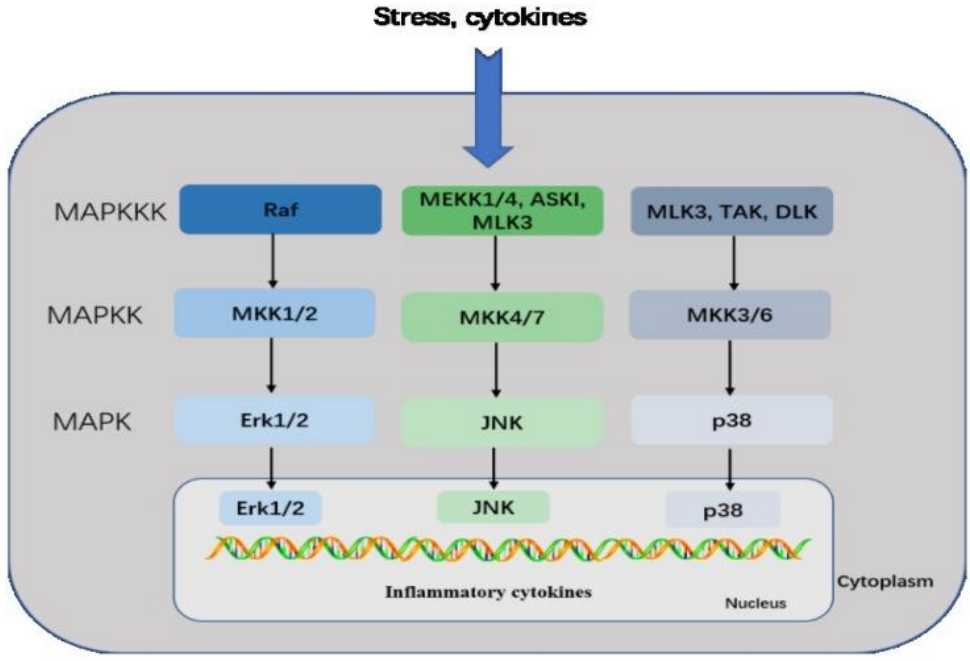

Figure 2 **MAPK pathway**

This pathway is responsible for mediating intracellular signaling that is started by external stimuli such as stress and cytokines. activate MAPKKs and MAPKKKs phosphorylate, who activate MAPKs and phosphorylate in turn. Erk1/2, JNK, and p38 are all members of the mammalian MAPK family. Erk1/2 is triggered by MKK1/2, which is activated by Raf in the Erk1/2 pathway. JNK is triggered in the JNK pathway via MKK4/7, which is activated by MEKK1/4, MLK3, and ASK1. MKK3/6, which is triggered by MLK3, TAK, and DLK, activates p38 in the p38 pathway. MAPKs that are activated phosphorylate a variety of proteins, containing transcription factors, resulting in the control of inflammatory responses.[13]

- JAK-STAT pathway

The JAK-STAT system controls several cytokines, growth factors, interferons, and related substances including leptin and growth hormone. External stimuli can accurately alter gene expression using this method. When triggered by ligands, receptor-associated JAKs cooperatively phosphorylate, forming cytoplasmic STAT-binding sites. Phosphorylated active STATs dimerize and enter the nucleus. **[**14]

STAT tyrosine phosphorylation is necessary for dimerization and DNA binding, allowing extracellular signals to directly affect transcription. For instance, IL-6 family members interacting with plasma membrane receptors activate JAK-STAT proteins, which translocate to target gene promoters and regulate inflammatory gene transcription. [15]

Note that NF-B, MAPK, and JAK-STAT dysregulation is connected to inflammation, autoimmune illness, metabolic disease, and cancer. These transcription factors control inflammatory

genes such IL-1, TNF-, IL-6, CSF, interferons, TGF, and chemokines through a signaling cascade. Understanding the complex JAK-STAT pathway is essential to understanding the molecular causes of many illnesses and how certain inflammatory genes are regulated. [16]

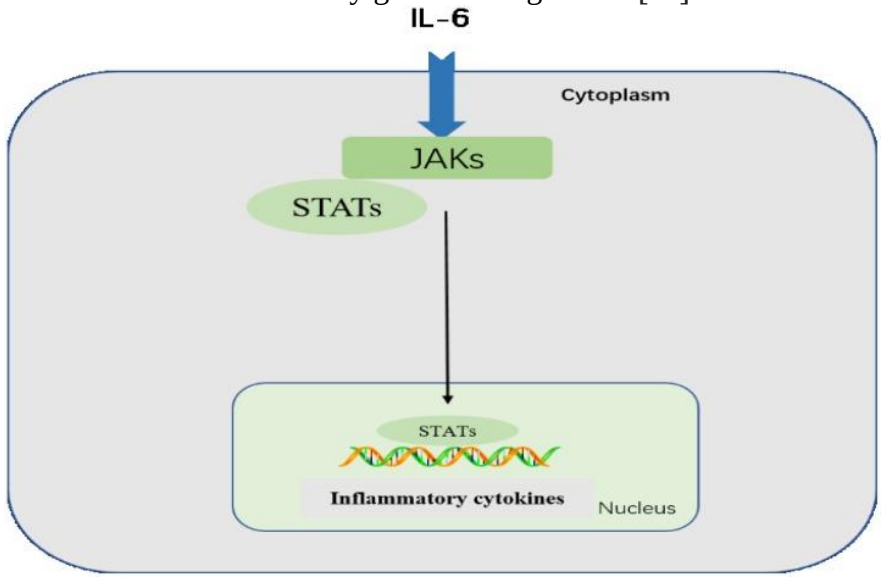

Figure 3 JAK-STAT pathway

Following IL-6 binding, a receptor transduces the signal to activate JAKs, which subsequently activate STATs. STATs are dephosphorylated in the nucleus, causing downstream cytokines to be activated.

Mediators and Biomarkers of Inflammation

Recent advances have substantially increased our understanding of inflammation's complicated function in numerous disease processes, owing primarily to the discovery of cellular and molecular inflammatory mediators and the creation of sensitive biomarkers. These biomarkers are critical for detecting and assessing the existence and intensity of inflammation, as well as offering insight into the underlying processes.[17]

ROS and RNOS, DNA adducts suggesting genetic damage, cytokines such as IL-6 and TNF-alpha, chemokines, acute-phase proteins such as CRP, and prostaglandins are all important inflammatory indicators. Transcription factors such as NF-kappaB, inflammation-related growth factors, and various immune cell types add to the complexity of the inflammatory landscape, with particular mediators and cell types differing depending on the nature, timing, and genetic variances of the damage. CRP, which exists in native and monomeric forms, is a commonly utilized inflammatory biomarker in clinical practice. Its conventional and high-sensitivity tests give critical insights into the type and amount of inflammation, allowing for more accurate diagnosis and treatment of inflammatory disorders.[18]

Inflammation and Cardiovascular Disease

Hs-CRP as a Cardiovascular Disease Risk Marker

High-sensitivity C-reactive protein (hs-CRP) is a useful marker for assessing the risk of cardiovascular disease (CVD), providing new information in addition to established risk factors such as LDL-cholesterol and metabolic syndrome. Inflammation has a varied function in cardiovascular health, with diseases such as periodontal disease and arthritis contributing to inflammation-driven arterial endothelial damage. Individuals with metabolic syndrome and central obesity, in particular, have higher hs-CRP levels, underscoring its importance as a risk indicator. Nonetheless, the precise function of CRP

in the formation of atherosclerosis within CVD and the feasibility of targeting hs-CRP reduction as a key CVD preventive method are ongoing topics of research.[19]

CANTOS Trial and hs-CRP Reduction

The CANTOS study, which concluded in 2018, gave important insights into the potential advantages of lowering hs-CRP levels, particularly in individuals with a history of myocardial infarction (heart attack). The study found that canakinumab, a monoclonal antibody targeting interleukin-1-beta that was not affected by plasma lipoprotein levels, resulted in a 25% decrease in major cardiovascular disease (CVD) events. Notably, this decrease was especially significant in patients whose therapy successfully reduced hs-CRP levels below 2 mg/ml. It's worth noting that the majority of CANTOS study participants were already on statin medication, making these findings especially relevant for people who had pre-existing CVD risk factors.[20]

Statin Effects and the Role of NSAIDs

Statin medications, which are commonly used to lower LDL cholesterol, also have an effect on hs-CRP levels. More study into cardiovascular disease prevention is needed since their effectiveness in avoiding initial major vascular events is consistent across all CRP levels.[21]

Nonsteroidal anti-inflammatory drugs (NSAIDs) have a range of effects, and each NSAID affects CRP levels differently. Lumiracoxib, for example, increases CRP in rheumatoid arthritis due to specific COX enzyme inhibition, but naproxen reduces it. Celecoxib is an outlier in the US market for COX-2 selective inhibitors (coxibs), which can raise CRP but are typically associated with an increased risk of major cardiovascular events.[22]

The interaction of statins, NSAIDs, and hs-CRP is a current therapeutically relevant research topic. There are also links between aging, cancer, and inflammation. Chronic inflammation increases the risk of getting cancer since it is associated with higher ROS and RNOS.

Elevated CRP levels have been linked to a number of cancer types, and obesity is another key risk factor that raises this risk. Furthermore, aging is an unchangeable risk factor, and "inflamm-aging" raises the risk of acquiring cancer as inflammatory biomarkers grow with age, a condition that may be exacerbated by changes in the gut microbiota as people age. It is critical to continue studying the complicated relationships between cancer, aging, and inflammation.[23]

Inflammation and Neoplastic Progression

Peyton Rous' seminal study established the concept that cancers arise from "subthreshold neoplastic states" caused by chemical or viral carcinogens and resulting in somatic changes. These early stages, now termed as "initiation," involve DNA modifications that are typically persistent and can linger in seemingly healthy tissue for an eternity. Many factors, such as chemical irritants, wound-related chemicals, partial organ resection, hormones, and prolonged irritation or inflammation, contribute to "promotion," which is the transition from a pre-existing neoplastic state to a full-blown neoplastic condition. Several promoters, according to their functional effects, either directly or indirectly boost cell division, attract inflammatory cells, enhance the formation of reactive oxygen species, resulting in oxidative DNA damage, and reduce the effectiveness of DNA repair processes.[24]

Normal cell death and repair processes are frequently altered in chronically inflamed tissues, resulting in unregulated DNA replication and cell proliferation. The inflammatory response is often self-limiting because anti-inflammatory cytokines are released in a strictly regulated way in response to pro-inflammatory signals. Chronic inflammation, on the other hand, can be caused by persistent inflammatory stimuli or the ineffectiveness of anti-inflammatory responses. The elements determining the chronic inflammatory response to tumors are currently being studied. This motivated researchers to investigate these characteristics.[25]

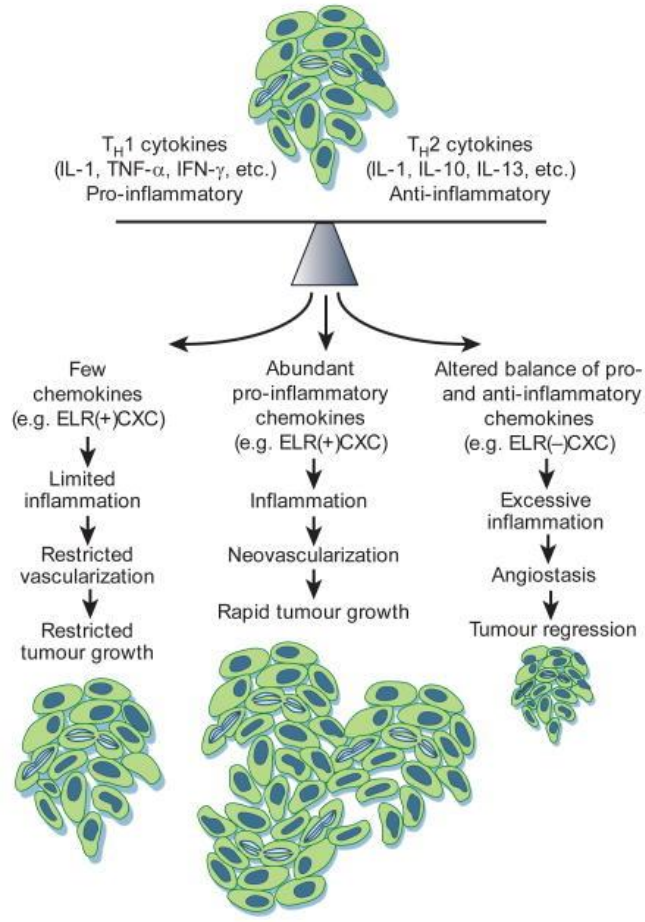

Figure 4 Cancer outcome depends on cytokine and chemokine ratios. Any tumor's cytokine balance controls the type and intensity of inflammatory infiltration. Little or no cytokines or an excess of anti-inflammatory cytokines inhibit inflammatory and vascular responses, limiting cancer development. In contrast, excessive pro-inflammatory cytokines can increase angiogenesis and neoplastic development. Cytotoxicity, angiostasis, and tumor regression can result from increased monocyte and neutrophil infiltration due to a changed pro-versus anti-inflammatory cytokine balance. Tumor cells and macrophages produce interleukin-10.

Discussion

The study presented here elucidates the multifaceted role of inflammation in the context of chronic diseases, providing valuable insights into the intricate mechanisms underlying inflammation and its implications for health. The key findings of this study underscore the fundamental processes involved in acute and chronic inflammation, the molecular pathways driving the inflammatory response, the interplay between inflammation, aging, and cancer, and the significance of inflammation in cardiovascular disease and neoplastic progression. These findings have significant implications for both clinical practice and ongoing research.[3]

First and foremost, the study clarifies the distinctions between acute and chronic inflammation, emphasizing the critical role of immune cell types involved and the temporal aspects of the inflammatory response. This distinction is vital for healthcare professionals to accurately diagnose and manage inflammatory conditions. Furthermore, the study provides a comprehensive overview of the inflammatory response mechanisms, highlighting the central role of pattern recognition receptors (PRRs) in identifying harmful stimuli and activating intracellular signaling pathways. This understanding is crucial for addressing inflammatory conditions across a spectrum of chronic diseases, such as cardiovascular conditions, bowel diseases, diabetes, arthritis, and cancer.[4,5]

The study delves into the specific molecular pathways orchestrating inflammation, focusing on the NF-κB, MAPK, and JAK-STAT pathways. These pathways serve as key regulators of inflammatory mediators and immune responses, influencing the development of various chronic diseases. In particular, the NF-κB pathway, with its transcriptional control over pro-inflammatory cytokines, is a central player in inflammation-related processes. This insight into the NF-κB pathway is invaluable for comprehending its role in shaping the body's response to inflammation and its implications for the pathogenesis of chronic diseases. [6,7]

The study further highlights the significance of high-sensitivity C-reactive protein (hs-CRP) as a cardiovascular disease risk marker, shedding light on its role in assessing cardiovascular health. The findings from the CANTOS trial, where hs-CRP reduction was associated with a substantial decrease in major cardiovascular disease events, underscore the potential benefits of targeting hs-CRP as a primary prevention strategy. This is particularly relevant for individuals with pre-existing cardiovascular risk factors.[9]

The interplay between statins, nonsteroidal anti-inflammatory drugs (NSAIDs), and hs-CRP is an emerging area of research with clinical significance. While statins and NSAIDs impact hs-CRP levels, the study reveals that their effectiveness in reducing initial major vascular events remains consistent across different CRP levels. Further investigations are needed to elucidate the intricate relationship between these interventions and hs-CRP in the context of cardiovascular disease prevention.

The study then explores the profound connection between inflammation, aging, and cancer. Chronic inflammation, characterized by increased production of reactive oxygen species (ROS) and reactive nitrogen oxygen species (RNOS), poses a heightened risk for cancer development. This risk is amplified by obesity, another significant modifiable risk factor, and age-related changes in gut microbiota that contribute to systemic chronic inflammation. The intricate relationship between inflammation, aging, and cancer warrants ongoing exploration, as it holds the potential to uncover new avenues for cancer prevention and management.[17]

Lastly, the study sheds light on the role of inflammation in neoplastic progression. The transition from initiation to promotion in cancer development involves various factors, including inflammation. The persistent inflammatory response to tumors remains a subject of ongoing investigation, highlighting the need to understand the factors contributing to its persistence and exploring potential interventions to modulate the inflammatory microenvironment of tumors.

In conclusion, this study significantly advances our understanding of the complex and multifaceted role of inflammation in the pathogenesis of chronic diseases. The findings have important implications for clinical practice, particularly in cardiovascular disease risk assessment and cancer management. Moreover, the study highlights the need for further research to explore the interplay between inflammation, aging, and cancer and to investigate the potential interventions targeting inflammation in various disease contexts.

Conclusion

In conclusion, this thorough study describes acute and chronic inflammation and their diagnostic significance. It examines complex inflammatory processes, emphasizing pattern recognition receptor activation and important pathways including NF-κB, MAPK, and JAK-STAT. It assesses cardiovascular disease risk using biomarkers like hs-CRP. The CANTOS experiment supports reducing hs-CRP in post-heart attack patients. Statins, NSAIDs, and hs-CRP interactions are being studied. The review examines inflammation's role in aging, cancer, and modifiable risk factors including obesity. These findings affect disease molecular pathways and healthcare professionals' inflammatory diagnosis, therapy, and prevention.

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