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Review

Nutrition as a modulator of inflammatory responses

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ABSTRACT

Inflammation is a critical biological response to tissue damage or infection, aimed at restoring homeostasis and initiating healing processes. Historically, inflammation was described by ancient scholars, with Celsus highlighting redness, swelling, heat, and pain, and Galen associating it with loss of function. In contemporary terms, inflammation is defined as a biological reaction to harmful stimuli, which can resolve or lead to chronic conditions if uncontrolled. Acute inflammation is vital for pathogen defense and tissue repair, but chronic inflammation is linked to cardiovascular disorders, diabetes, and autoimmune conditions. The immune system plays a key role in inflammation, with innate immunity providing a rapid response to infections, while acquired immunity offers a more specific, delayed reaction. Inflammation is regulated by mediators such as cytokines, chemokines, and prostaglandins, which facilitate immune cell migration and activation. Omega-3 polyunsaturated fatty acids have been shown to reduce inflammation by interfering with pro-inflammatory eicosanoid production and modulating gene expression. Diet plays an essential role in modulating inflammation, with anti-inflammatory diets like the Mediterranean diet showing beneficial effects in managing inflammatory markers. Conversely, Western diets rich in processed foods tend to exacerbate inflammation. Combining pharmacological approaches with anti-inflammatory dietary changes may offer a more sustainable strategy for preventing and treating inflammation-related diseases. This review aims to explore the mechanisms, impacts, and management strategies of inflammation, emphasizing its role in health and chronic disease.

Keywords: Diet, immunity, inflammation, nutrition.

In the Ancient Roman period, inflammation was described by Celsus as redness, swelling, heat changes in the body, and pain, while Galen referred to it as a loss of function. In the current literature, inflammation is defined as the "reaction" or the accompanying changes that occur when living tissue is damaged, provided that the damage is not severe enough to immediately destroy its vitality and structure.[1] Inflammation is a biological response necessary to maintain tissue homeostasis and initiate the healing process in response to harmful stimuli. It acts by eliminating harmful stimuli and initiating the repair process. Therefore, inflammation is a vital defense mechanism. In general, acute inflammatory responses ensure the effective minimization of infections through molecular and cellular interactions. This minimization process contributes to the resolution of acute inflammation and the restoration of tissue homeostasis. However, uncontrolled acute inflammation can progress to chronic inflammation, leading to various diseases. In response to tissue damage, the body generates chemical signaling pathways aimed at tissue repair.[2] If inflammation persists, meaning it is not controlled, there is always the potential for it to spread to healthy tissues.[3] The final stage of inflammation is referred to as the resolution of inflammation. Inflammation that does not reach the resolution phase can lead to organ failure and, ultimately, death. Virtually every tissue has the ability to carry out an infectious process, and this process is pre-programmed and stereotypical. Inflammatory reactions can occur as either acute or chronic and are generally localized, though they can also manifest systemically.[4]

IMMUNE SYSTEM

The immune system is an effective defense mechanism designed to combat invading

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pathogens and uncontrolled tumor growth. Its primary goal is to eliminate threats; however, distinguishing between harmful invading pathogens and harmless commensal bacteria, or between tumors and normal tissues, can be challenging due to subtle differences. The immune system prevents potential damage by avoiding the presence of self-reactive lymphocytes.[5]

Innate and acquired immunity

The mechanisms of innate immunity, such as antimicrobial peptides, phagocytic cells, and alternative complement pathways, are rapidly activated immediately after infection. These mechanisms quickly work to control the proliferation of the infecting pathogen. Therefore, the primary function of innate immunity is to keep the infection under control until lymphocytes begin to respond. However, innate immunity cannot always completely eliminate infectious organisms, and there are some pathogens it may fail to recognize.[6]

Acquired immunity is organized around two types of specialized cells: T cells and B cells. Since each lymphocyte displays a structurally distinct receptor, the population of lymphocytes has a vast and diverse array of antigen receptors. The size and diversity of this repertoire increase the likelihood that a lymphocyte will encounter an antigen that can bind to its receptor. This triggers the activation and proliferation of the cell. This process is known as clonal selection and explains many of the key characteristics of the acquired immune system.[7]

Additionally, the cells of the innate immune system play a critical role in controlling infections during the four to seven-day delay before acquired immune responses are effectively initiated. Since acquired immune responses take time to activate, the innate immune response is crucial for managing infections during this period.[6]

THE COMPONENTS OF THE IMMUNE SYSTEM AND INFLAMMATION

Inflammatory inducers can be foreign or self-antigens that trigger the immune response. Sensors such as Toll-like receptors are expressed in immune cells like macrophages and dendritic cells. These sensors detect the presence of inflammatory inducers and initiate the production of inflammatory mediators. Inflammatory mediators include cytokines; tumor necrosis factor-alpha, interleukin (IL)-1, IL-6, chemokines; CCI2, CXCL8, and prostaglandins. These mediators are released by tissue immune cells in response to the detection of inflammatory inducers. They affect target tissues, including blood vessels, causing vasodilation, increased permeability, and the migration of immune cells to the site of inflammation. Through the release of inflammatory mediators, circulating leukocytes are attracted to the inflammation site via chemotaxis. Resident macrophages and dendritic cells in tissues play roles such as phagocytosis, cytokine secretion, and antigen presentation to lymphocytes. Activated leukocytes secrete additional cytokines and inflammatory mediators, thereby contributing to the amplification of the inflammatory response. The type of inflammatory response varies depending on the nature of the inflammatory trigger. While bacterial pathogens are detected by innate immune receptors, viral infections lead to interferon-mediated inflammation, and allergens primarily affect mucosal epithelium, smooth muscles, and vascular structures.[8]

Process of acute and chronic inflammation

The four main components of the inflammatory response inducers, sensors, inflammatory mediators, and target tissues work together in a coordinated manner to initiate and execute the inflammatory process. Acute inflammatory response is a critical defense mechanism against injury and infection, while chronic inflammation can lead to various diseases such as atherosclerosis, diabetes, non-alcoholic fatty liver disease, and autoimmune disorders.[9] When the body is exposed to acute inflammation, it responds by increasing blood flow and capillary permeability in the affected area, allowing neutrophils to migrate from the capillary wall into the tissue.[10]

Chronic inflammation arises from persistent or unresolved stimuli. The underlying causes include chronic infections, environmental factors, physical inactivity, microbiome dysbiosis, diet, psychological stress, and toxins. Neutrophils, the most common type of leukocyte in humans, are involved in both chronic and acute inflammation. While they serve as the first responders in acute inflammation, they are also involved in

the resolution process and are recruited to the tissue site. Neutrophils contribute to the process by releasing serine proteases, forming neutrophil extracellular traps, and activating other immune cells, thereby directing the inflammatory response.[9]

As an infection becomes chronic, the composition of white blood cells changes, and macrophages and lymphocytes begin to replace neutrophils. Macrophages release cytokines and growth factors that contribute to the progression of tissue damage and secondary repair, including fibrosis and granuloma formation. Macrophages, which can produce pro-inflammatory cytokines, also have the function of processing antigens and presenting them to T cells.[11] These cytokines induce endothelial cells to release selectins and integrins, which stimulate the chemotaxis and diapedesis of circulating leukocytes, allowing them to migrate to areas of tissue damage or pathogen infection. In addition to the accumulation of leukocytes, tissue macrophages, and dendritic cells play roles in antigen clearance through phagocytosis, cytokine secretion, and acting as antigen-presenting cells to lymphocytes. When circulating leukocytes enter the local infection site, they are activated by various cytokines and chemokines secreted by macrophages and dendritic cells. Upon activation, leukocytes secrete cytokines and other inflammatory mediators. Neutrophils migrate primarily to the infection site through granules rich in lysozyme, matrix metalloproteinases, and myeloperoxidase. Subsequently, they play a key role in phagocytosing free pathogens or killing infected cells. Lymphocytes involved in the immune response contribute to various cell types, including T cells and B cells, which are responsible for producing antibodies and aiding in the fight against infections.[12]

PHARMACOLOGICAL AND DIETARY APPROACHES TO INFLAMMATION

Disease-related malnutrition (DRM) is common in both acute and chronic diseases, with a prevalence of 30% in hospitalized patient populations. Three key factors contribute to the development of DRM: first, inflammation plays a significant role in the development of malnutrition. Inflammation in the body accelerates metabolism and leads to a faster depletion of the body's energy.[13] The positive effects of polyunsaturated fatty acids (PUFAs) on human health, particularly in relation to cardiovascular diseases, are being discussed. When consumed in adequate amounts, long-chain omega-3 PUFAs have been shown to reduce the production of inflammatory substances such as eicosanoids, cytokines, reactive oxygen species, and adhesion molecules. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 PUFAs found in fatty fish and fish oil. The EPA and DHA exert their effects both directly and indirectly. They directly replace arachidonic acid (AA) as a substrate for the production of eicosanoids, thereby inhibiting the synthesis of pro-inflammatory compounds derived from AA. Additionally, EPA and DHA can indirectly modulate the expression of genes involved in inflammation by influencing the activation of transcription factors.[14]

Acute and chronic inflammations are driven by the production of pro-inflammatory eicosanoids derived from AA. Anti-inflammatory drugs target molecular components downstream of AA. These drugs work by inhibiting enzymes responsible for converting AA into pro-inflammatory eicosanoids or by preventing the release of AA from phospholipids in cell membranes. These drugs act on specific molecular targets to reduce inflammation. On the other hand, anti-inflammatory nutrition aims to reduce AA levels.[15] A relationship has been observed between the AA/EPA ratio in an individual's blood and the level of latent inflammation in their organs. When the AA/EPA ratio is high, it indicates a higher concentration of AA relative to EPA, which leads to the production of higher levels of pro-inflammatory compounds. Chronic low-grade inflammation, which develops gradually, can damage various organs over time and contribute to the development of chronic diseases such as cardiovascular diseases, diabetes, and cancer.[16]

Nutritional components can either activate or inhibit the inflammatory process of the innate immune system. As advancements in molecular biology have begun to unravel the control mechanisms of the innate immune system, a more detailed understanding has been gained regarding the effects of commonly used pharmacological drugs and nutritional

factors on inflammation. Similarly, these advances have shown how nutrition can influence inflammation induced by the innate immune system. However, it is known that anti-inflammatory drugs work by inhibiting the formation of pro-inflammatory eicosanoids derived from AA. While no known drug directly reduces AA, it has been observed that only proper nutrition can achieve this.[15] The World Health Organization acknowledges that the inflammatory effects of diet play a significant role in the prevention of many non-communicable diseases, such as cardiovascular diseases, type 2 diabetes, and cancer.[17] While anti-inflammatory drugs provide therapeutic benefits in obesity and diabetes, long-term use may lead to side effects. Alternatively, an anti-inflammatory diet is seen as a more sustainable intervention that offers similar benefits in managing inflammation in the body.[18]

A commonly overlooked factor is that the total calorie content of a meal can also raise insulin levels and increase inflammation. Overeating has been shown to cause inflammation in the hypothalamus and disrupt the delicate signaling balance of satiety/hunger hormones, leading to an increase in appetite. This results in an incorrect balance of satiety and hunger signals in the body, further enhancing appetite. Therefore, it is important to control calorie intake to maintain insulin regulation.[19]

The relationship between inflammation and the mediterranean diet

The Mediterranean diet demonstrates its positive effects on inflammation markers similarly in individuals treated with risk-reducing agents, such as angiotensin-converting enzyme inhibitors and statins, known for their anti-inflammatory properties, as well as in those who do not use these medications. This suggests that the anti-inflammatory effect of the Mediterranean diet works complementarily with pharmacological treatments. It also indicates that healthy foods provide potential anti-atherosclerotic effects that extend beyond the early stages of disease. Additionally, the Mediterranean diet enriched with olive oil or nuts suppresses humoral inflammation pathways.[20] In contrast, Western-style diets, which contain high amounts of processed foods, have been shown to lead to an increase in inflammation markers. The dietary inflammatory index developed to assess the overall effect of diet on infection has shown a relationship between nutrition and infection in adults. As a result, macro and micronutrients such as complex carbohydrates, omega-3 fatty acids, fibers, vitamins E and C, and magnesium have the potential to reduce infection levels.[21]

In conclusion, inflammation is a fundamental biological response of the organism to tissue damage or pathogens, but when uncontrolled, it plays a central role in the pathogenesis of various chronic diseases. Acute inflammation supports tissue healing and the restoration of homeostasis, while chronic inflammation can provide a foundation for the development of atherosclerosis, diabetes, autoimmune diseases, and other metabolic disorders. In this process, the interactions between the innate and adaptive components of the immune system are crucial. Additionally, the modulatory effect of nutrition on inflammatory mechanisms is noteworthy. While nutrients such as omega-3 fatty acids are scientifically supported for their anti-inflammatory effects, diets characterized by high-calorie and processed foods, typical of Western diets, have been shown to trigger inflammation. Diet models with anti-inflammatory properties, such as the Mediterranean diet, provide a complementary strategy for managing inflammatory processes alongside pharmacological approaches. In this context, the implementation of dietary and lifestyle changes alongside pharmacological treatments may provide more effective and sustainable outcomes in the prevention and treatment of inflammation-related diseases.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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