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Inflammation: Complexity and significance of cellular and molecular responses

Serdar Özdemir✉

University of Health Science, Umraniye Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Inflammation is a multifaceted cellular and molecular response triggered by injury, infection, or various pathological conditions. Serving as a protective defense mechanism, the inflammatory response involves clinical signs like redness, swelling, pain, and increased body temperature. Immune cells, notably neutrophils and macrophages, play key roles in orchestrating this response. The delicate balance between proinflammatory and anti-inflammatory mediators, including cytokines and chemokines, regulates the inflammatory cascade. While acute inflammation is crucial for tissue repair, chronic inflammation may indicate an imbalance, contributing to conditions like autoimmune diseases. Understanding these mechanisms is vital for developing therapeutic strategies and managing chronic diseases.

KEYWORDS: Inflammation; C-reactive protein; Platelets; SCUBE1; Adrenomedullin; Calprotectin; Pentraxin-3; Immune response; Acute phase response; Vascular function

1. Inflammation and inflammatory cascade

Inflammation is a complex cellular and molecular response that the body initiates in reaction to injury, irritation, infection, or various pathological conditions. As a body's protective defense mechanism, the inflammatory response manifests through observable clinical signs such as redness, swelling, pain, and increased body temperature[1]. The inflammatory cascade typically begins with the interaction of immune cells, predominantly neutrophils, and macrophages, aiming to clear damaged tissues and combat pathogens. These cells play pivotal roles in initiating and orchestrating the intricate dance of the immune response[2]. The balance between proinflammatory and anti-inflammatory mediators intricately regulates the inflammatory response. Cytokines, chemokines, and prostaglandins, among other molecular signaling pathways, contribute significantly to this intricate orchestration[3]. While acute inflammation is a necessary and beneficial response for tissue repair and pathogen elimination, chronic inflammation may indicate a disruption in the body's equilibrium, leading to sustained attacks on its tissues. This chronic state is implicated in various health issues, particularly autoimmune diseases and chronic conditions like metabolic syndrome[4]. The interplay of immune cells, molecular mediators, and signaling pathways orchestrates a symphony that, when dysregulated, can contribute to a spectrum of health challenges[5]. Understanding the mechanisms of inflammation holds the key to developing novel therapeutic strategies and advancing research aimed at preventing or managing chronic diseases.

2. C–reactive protein

C-reactive protein (CRP) is a plasma protein known as an indicator of inflammatory processes and tissue damage. It is produced by the liver and its levels rapidly increase in response to inflammatory processes such as inflammation and tissue damage. When inflammation begins, or when the body's cells are damaged

✉To whom correspondence may be addressed. E-mail: dr.serdar55@hotmail.com

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or infected, the immune system releases signaling molecules such as cytokines in response to these events. These signals trigger the production of CRP in the liver. Elevated CRP levels are considered a defense mechanism of the body against potentially harmful conditions[6,7]. However, chronically high CRP levels may indicate that the body is in a constant inflammatory state, which could contribute to the development of chronic diseases. The roles of CRP are supporting the activation of immune cells and assisting the immune system in directing the defense cells, such as white blood cells, to areas of damage or infection[8], which help to control inflammatory processes. CRP levels can be used as an important marker to assess the presence of inflammation and monitor the progress of diseases[9,10].

3. Albumin

Albumin is a crucial plasma protein that plays a vital role in maintaining various physiological functions within the body. It is primarily produced by the liver and serves as a carrier for essential substances, including hormones, fatty acids, and various drugs. Beyond its role in regulating osmotic pressure and maintaining blood volume, albumin also contributes to the body's defense against inflammation[11].

In the context of inflammation, albumin undergoes notable changes in concentration and function. During inflammatory processes, the liver produces acute-phase proteins, including CRP, which can compete with albumin for binding to specific ligands. This competition often leads to decreased albumin levels, a condition known as hypoalbuminemia[12]. Hypoalbuminemia in inflammation is multifaceted. Firstly, it can be a consequence of increased vascular permeability during inflammation, allowing albumin to leak into tissues. Secondly, the liver's priority shifts towards producing acute-phase proteins, affecting albumin synthesis. Additionally, systemic inflammation can alter the metabolism of albumin, leading to its accelerated degradation[13]. The reduction in albumin levels during inflammation has clinical implications. As a widely recognized marker of nutritional status and liver function, hypoalbuminemia is often used as an indicator of the severity of inflammatory conditions. Monitoring albumin concentrations alongside inflammatory markers like CRP provides a comprehensive understanding of the inflammatory response and aids clinicians in assessing the overall health and prognosis of patients undergoing inflammatory processes[14].

4. Neutrophil–to–lymphocyte ratio

The neutrophil-to-lymphocyte ratio (NLR) serves as a hematological marker providing insights into the status of the immune system. Calculated by comparing the counts of white blood cells, particularly neutrophils, and lymphocytes, NLR is interpreted as an indicator of an inflammatory response or a stress condition when elevated[15]. Neutrophils are rapid responders to infections, actively combating bacteria as key white blood cells. On the other hand, lymphocytes are responsible for specific immune responses. Therefore, an increased NLR suggests a rise in neutrophil count and/or a decrease in lymphocyte count, typically signifying an ongoing inflammatory response[16]. The clinical utility of NLR has been explored, particularly as an indicator in monitoring inflammatory diseases, infections, or malignancies. However, relying solely on NLR as a diagnostic tool is generally considered inadequate, and its interpretation is recommended in conjunction with the clinical context, patient history, and other laboratory findings[17]. An elevated NLR may signify the body's response to an infection or an inflammatory condition, prompting further investigation and clinical evaluation. Nevertheless, a comprehensive assessment and integration with other diagnostic tools remain crucial before making any definitive diagnostic or therapeutic decisions[18].

In summary, NLR, as a hematological parameter, has potential applications in early diagnosis, monitoring treatment responses, and assessing prognosis in various medical conditions. However, its effectiveness is maximized when used as part of a broader clinical evaluation strategy, emphasizing the need for a multidisciplinary approach in medical decision-making.

5. Platelets

Platelets play a crucial role not only in conditions of thrombocytopenia but also in the regulation of inflammatory responses. Platelets contribute to the initiation and sustenance of inflammation by actively releasing various cytokines and regulating the inflammatory process[19]. One of the key roles of platelets in the inflammatory response is their ability to detect various cytokines through receptors on their surface and transmit signals. This process involves platelets migrating to inflamed tissues, interacting with other immune cells, and regulating cytokine release[20]. Additionally, the inflammatory response of platelets includes the release of microRNAs and other genetic materials on the surface of platelets, contributing to the regulation of inflammation[21]. In this context, the inflammatory role of platelets is crucial not only for vascular homeostasis but also for the effectiveness of the immune system. Their capacity to regulate inflammatory processes contributes to a balanced functioning of the body's defense mechanisms.

6. Signal peptide–CUB–EGF domain–containing protein 1

Signal peptide-CUB-EGF domain-containing protein 1 (SCUBE1) stands out as a protein that plays a role in various pathological

conditions associated with inflammation. Elevated expression levels of this protein have been observed, particularly in diseases related to inflammation. The involvement of SCUBE1 in inflammatory processes may occur through mechanisms such as the regulation of immune responses, cellular signal transduction, and modulation of vascular functions[22]. The role of SCUBE1 in inflammatory responses typically occurs through cellular signal transduction. This protein interacts with specific receptors on the cell surface, initiating or modulating intracellular signaling pathways. These signaling pathways can influence the expression of genes associated with inflammation, thereby affecting inflammatory processes[23]. Furthermore, the effects of SCUBE1 on vascular functions may involve changes in the structure and function of blood vessels in diseases associated with inflammation. This could be related to its ability to regulate the effects of inflammation on the vascular system[24].

In conclusion, the involvement of SCUBE1 in inflammatory processes occurs through its ability to modulate cellular signal transduction and vascular functions. Through these mechanisms, SCUBE1 may play a significant role in regulating inflammatory responses.

7. Adrenomedullin

Adrenomedullin is a versatile peptide hormone known for its vasodilation, anti-inflammatory, and neuroprotective effects. During inflammation, the release of adrenomedullin increases, regulating various cellular and molecular responses. Adrenomedullin is highly expressed in inflammatory cells, particularly macrophages, and endothelial cells. This peptide intervenes in inflammatory processes by regulating the release of cytokines and controlling vascular permeability[25]. Additionally, it contributes to maintaining cellular homeostasis by modulating various pathways associated with oxidative stress and tissue damage linked to inflammation[26]. Therefore, adrenomedullin is believed to play a protective and regulatory role during inflammation.

8. Calprotectin

Calprotectin is a protein known as a marker in inflammatory processes, particularly used in assessing inflammatory conditions such as intestinal inflammation. Calprotectin is a protein predominantly found in neutrophil granulocytes, which are essential cells of the immune system that respond to situations like infection or tissue damage as part of the inflammatory response[27]. Since calprotectin is released when neutrophils in the mucosa of the intestines are activated in inflammatory conditions of the intestines, such as inflammatory bowel disease, which are associated with increased activity of neutrophils in the intestinal mucosa, an elevation in calprotectin levels is observed[28]. As calprotectin is a marker that can be measured in stool samples, it offers a non-invasive way of evaluating intestinal inflammation. Elevated levels of calprotectin in the stool may indicate intestinal inflammation or other inflammatory conditions.

In conclusion, calprotectin actively participates in the inflammatory process, particularly in the context of intestinal inflammation. It serves as a valuable marker for assessing inflammatory bowel conditions and other related inflammatory states.

9. Pentraxin–3

Pentraxin-3 is a member of the pentraxin family, a group of proteins involved in the acute phase response to inflammation. Unlike classical pentraxins, such as CRP, pentraxin-3 is produced at the site of inflammation by various cell types, including immune cells and endothelial cells[29].

The roles of pentraxin-3 in inflammation include: (1) innate immunity: pentraxin-3 plays a crucial role in the innate immune system. It recognizes and binds to various microbial agents, including bacteria, fungi, and viruses. This recognition is part of the early immune response, helping to activate the immune system against potential threats. (2) Tissue repair: pentraxin-3 contributes to tissue repair and remodeling following inflammation or injury. It interacts with components of the extracellular matrix and promotes tissue healing processes. (3) Anti-inflammatory functions: while involved in the immune response, pentraxin-3 also exhibits anti-inflammatory properties by modulating the activity of immune cells. It can help to regulate the balance between pro-inflammatory and anti-inflammatory signals, contributing to the resolution of inflammation. (4) Vascular function: pentraxin-3 is implicated in maintaining vascular integrity. It plays a role in regulating the function of blood vessels, including endothelial cells, and has protective effects on the cardiovascular system[30,31].

In summary, pentraxin-3 is a versatile protein with key roles in innate immunity, tissue repair, anti-inflammatory processes, and vascular function. Its dynamic functions make it a valuable player in facilitating body's response to inflammation and maintaining tissue homeostasis.

10. Presepsin

Presepsin is a biomarker associated with inflammatory processes, specifically highlighted as an indicator of bacterial infections and systemic inflammation. This biomarker is a precursor protein, and it emerges as a fragment released from monocytes and macrophages during inflammatory responses caused by microorganisms[32]. Presepsin particularly stands out in cases of sepsis, a condition characterized by a severe inflammatory response in the presence of

a bacterial infection in the bloodstream. Measuring presepsin levels can be valuable in the diagnosis and monitoring of sepsis[33]. In this context, presepsin serves as an indicator of inflammatory processes in clinical applications. However, it is crucial to evaluate presepsin measurements in conjunction with other clinical and laboratory findings, considering specific disease conditions and clinical contexts.

11. Conclusion

The in-depth exploration of inflammation and its associated biological processes in this review sheds light on new treatment strategies and the management of chronic diseases. Inflammation is a complex cellular and molecular response initiated by the body to clear damaged tissues and combat pathogens. It manifests through observable clinical signs and serves as a crucial assessment tool for healthcare professionals.

Acute inflammation is a necessary defense mechanism for tissue repair and pathogen elimination, requiring precise regulation. However, prolonged chronic inflammation may indicate an imbalance in the body, leading to autoimmune diseases and chronic conditions. The regulation of molecules such as CRP, platelets, SCUBE1, adrenomedullin, calprotectin, presepsin, and pentraxin-3 plays a pivotal role in controlling inflammation. Monitoring the levels of these molecules serves as a valuable tool in evaluating inflammatory conditions. Understanding inflammation and the molecular factors involved not only inspires future treatment strategies but also guides effective management of chronic diseases.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

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