Chapter

Introductory Chapter: Overview of the Cellular and Molecular Basis of Inflammatory Process

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1. Introduction

Tissue or cell injuries and assorted infections are targets to major studies on inflammation. These conditions play a central role for the understanding of the inflammatory mechanism as a pathophysiological process. In addition, tissue-resident macrophages can create an adaptive response against stressed or unwell environments, which may lead to various pro-inflammatory pathways. Together, these conditions may be associated with a broad spectrum of acute and chronic inflammation in some of contemporary human disorders [1].

In general, inflammation is a natural response to avoid the progress from fester to deadly in any kind of injury. Its very well-balanced network of anti- and pro-factors should be constantly checked by the immune system to make sure the healing process does not miss your goal and becomes unreliable to the point of creating an incorrigible damage [1, 2].

Regardless of its etiology, patients suffering from inflammatory episodes or disorders have higher risk of facing other clinical complications. Acute and chronic inflammations have their particular dynamics and prognostics but, even if it is unclear in several aspects, it has been pertinent in addressing any analysis on inflammation under a translational approach.

In face of that, the following review is a summary report on essential aspects related to inflammation as a biological event, considering the potentially wide range of questions and action lines, from its molecular basis to some potential clinical outcomes.

2. Causes and early stages of inflammation

Different agents can promote inflammatory events, such as (a) necrosis, due to the decrease in blood flow and lack of nutrients and oxygen in the target tissue, which results in tissue death; (b) chemical or physical traumas, like radiation, burn, frostbite, corrosion by oxidizing, alkalis, or acid; (c) displaced or delayed immunological response due to genetic conditions or unstable metabolism; and (d) infections or coexistent microbiome unbalanced status, mainly from very common performers as bacteria, through endotoxins release, and virus, which encroach cells for its proliferation until the host wrecking [2–6].

Basic signs of inflammation are (1) edema or swelling caused by gradual deposit of fluid outside of blood vessels; (2) pain, caused by mechanical action of edema and/or direct response to prostaglandin, serotonin, and bradykinin

reactions; (3) redness, as a consequence of vasodilation at damage site; and (4) fever caused by pro-inflammatory mediators that contribute to the rise of local and/or systemic temperature [1, 2].

Vasoconstriction, the constriction of blood vessels, which increases blood pressure, is one of the first and brief reactions to inflammatory process. In the beginning of inflammatory process, it is followed by a counterreaction, the vasodilation. During vasodilation the blood flow increases into the target area, and it can take from few minutes to long-time periods to be released. These contractile events on the vessel affect the blood flow and, for consequence, the blood vessel wall permeability. When the vessel wall becomes more permeable, the transit of fluids also is raised, beyond usual salt- and water-based liquids [7].

A protein-rich fluid, the exudate, increases its transposition through the wall, which affects the distribution of anti-inflammatory elements, as coagulation factors and antibodies, in the sense to refrain the spreading of infectious agents.

3. Cellular setup and molecular mediators

The inflammatory environment with fluid leaking out the blood vessels creates the conditions for white cell adhesion to the blood vessel wall since the blood flow starts to slowdown. This is the initial step of a serial process moving out the white cells from the vessel lumen to the interstitium of the damaged tissue.

Two major aspects related to the body's reaction to inflammation are the speed and the amount of white cells taken to the target tissue. Phagocytes are the predominant form of leukocytes designated to clean up the site of injury, eating bacteria and strange elements, removing the cellular remains produced during the injury progress [2].

Neutrophils are a class of white cells involved in acute inflammation. This particular type of phagocyte holds granules of enzymes capable of destroying toxic substances, such as reactive oxygen species, proteins, and cells, making these cells the major components in the injury processing. For local and weak damages, the amount of circulating neutrophils is enough for inflammatory response. However, for wide damages, sources of neutrophils from the bone marrow are constantly requested for acting on the injured site as the early agents. Even if in its immature form, neutrophils can reach the local spot quickly after the inflammatory process starts [2].

Monocytes are the second group of blood cells requested for acting on the inflamed area, usually several hours after the beginning of this process. These white blood cells when matured are called macrophages, and they are responsible for the ultimate step of engulfing and disposing the invasive cells and foreign elements. Macrophages are also the predominant agents in the chronic inflammation healing [1–2].

The cells required to act at the site of inflammation actually move from blood vessels to injured tissue. Both neutrophils and macrophages use chemical recognition properties, called chemotaxis, to guide themselves through the pathway. While the lesion itself has an important role in the inflammation healing initiation, chemotaxis is responsible for determining how far fast and effective will be its processing. It is a complex network working from the chemical signals given out by the injured tissue. Structural compounds, such as endothelial cells, operate together with blood plasma elements, platelets, and mast cells, creating a chemical communications to address the differentiated white blood cells to the right site, according to each role and time frame [8, 9].

The blood plasma is an important source of inflammatory mediators. Some complex proteins are connected through its elaborate cascade pathways, such as the complement, coagulation factors, the fibrinolytic system, and the kinins.

Activated complement proteins, for example, are able to increase vascular permeability, make mast cells release histamine, and work for neutrophils as chemotactic elements.

On the other hand, the vascular permeability is directly influenced by a serial process among the coagulation, fibrinolytic, and kinin systems. Coagulation, in a cascade of activations, contributes to fluid exudate formation, polymerizing fibrinogen to fibrin, which is part of the exudate. Fibrin, in its turn, is quickly broken by the plasmin produced from fibrinolytic system, resulting in chemical compounds that interfere with the permeability of blood vessels. Overlapping these events, the kinin system also generates mediators responsible to increase vascular permeability. Moreover, an essential kinin named bradykinin is in charge of two of the main uncomfortable effects of inflammation, itching and pain.

Prostaglandins are considered major inflammatory mediators. This type of fatty acids plays an essential role on the platelet cluster formation, also interfering on clotting process. Some prostaglandins can promote vascular permeability too. This group of molecules is targeted for many anti-inflammatory drugs, since they are related to fever and pain caused by inflammation [10, 11].

Another group of inflammatory mediators, including histamine, cytokines, and lysosomal compounds, has a significant role on the capacity to exchange the permeability of vessels, even with its distinct characteristics. Histamines, for example, are the first line of agents released to increases vascular permeability, since they are easily accessed from mast cells and basophils. The activation of histamine H1 receptors promptly changes some pro-inflammatory pathways. Moreover, the histamine regulates the synthesis of cytokine in some inflammation process, such as allergies. In turn, cytokines released by different cells exhibit features that affect vessel dilatation and the ability to chemically transport white blood cells through the blood vessel into the interstitium of injured parenchyma [7].

Closing this overview, it is important to highlight that the time of inflammation processing is the key to distinguish an acute response, which usually takes a couple of days, from a chronic inflammation, which trends to request long time for healing and its outcomes may persist. From autoimmune diseases to long-term inflammatory sequels, many different targets may be addressed in classic inflammatory pathway, alternative networks, and its upshots. From microbiome interactions, richly reported in recent studies [3–6], to chronic side effects of traditional or innovative treatments, many therapeutics targets have being studied to develop new inflammation mediators that could be helpful, either in scientific or clinical decisions.

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References

[1] Medzhitov R. Inflammation 2010: New adventures of an old flame. Cell. 2010;**140**(6):771-776. DOI: 10.1016/j.cell.2010.03.006

[2] Nathan C, Ding A. Nonresolving inflammation. Cell. 2010;**140**(6):871-882. DOI: 10.1016/j.cell.2010.02.029

[3] Lau WL, Vaziri ND. The leaky gut and altered microbiome in chronic kidney disease. Journal of Renal Nutrition. 2017;**27**(6):458-461. DOI: 10.1053/j.jrn.2017.02.010

[4] Lau WL, Savoj J, Nakata MB, Vaziri ND. Altered microbiome in chronic kidney disease: Systemic effects of gut-derived uremic toxins. Clinical Science (London). 2018;**132**(5):509-522. DOI: 10.1042/CS20171107

[5] Lau WL, Vaziri ND. Gut microbial short-chain fatty acids and the risk of diabetes. Nature Reviews. Nephrology. 2019;**15**(7):389-390. DOI: 10.1038_s41581-019-0142-7

[6] Jazani N, Savoj J, Lustgarten M, Lau WL, Vaziri ND. Impact of gut dysbiosis on neurohormonal pathways in chronic kidney disease. Diseases. 2019;**7**(1):pii:E21. DOI: 10.3390/diseases7010021

[7] Marone G, Granata F, Spadaro G, Genovese A, Triggiani M. The histamine-cytokine network in allergic inflammation. Journal of Allergy and Clinical Immunology. 2003;**12**(4):S83-S88. DOI: 10.1016/S0091-6749(03)01881-5

[8] Strassheim D, Gerasimovskaya E, Irwin D, Dempsey E, Stenmark K, Karoor V. RhoGTPase in vascular disease. Cell. 2019;**8**(6):551. DOI: 10.3390/cells8060551

[9] Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ. C-reactive protein and the risk of incident colorectal cancer. JAMA. 2004;**291**(5):585-590. DOI: 10.1001/jama.291.5.585

[10] Rodríguez-Hernández, Heriberto et al. Obesity and inflammation: Epidemiology, risk factors, and markers of inflammation. International Journal of Endocrinology. 2013:**2013**:678159. DOI: 10.1155/2013/678159

[11] Serhan CN, Chiang N, Dalli J, Levy BD. Lipid mediators in the resolution of inflammation. Cold Spring Harbor Perspectives in Biology. 2015;**7**(2):a016311. DOI: 10.1101/cshperspect.a016311