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Editorial

The Importance of Inflammation in Medicine

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Inflammation is a constant companion in mostly all pathologies known. Traditionally, there were some diseases considered inflammatory such as inflammatory arthropaties or respiratory diseases. Today however, we know that almost all pathologies involve inflammation -dysregulation of inflammatory mechanisms- at some stage. Although inflammation is a beneficial process designed to eradicate threats to the organism, a dysregulation of the magnitude or duration of inflammation contributes to multiple pathologies [1]. Thus, chronic inflammation is considered to be the cause of most chronic diseases and presents a major threat to the health and longevity of individuals, being the major contributor to several diseases including cancer, diabetes, rheumatoid arthritis, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), allergic asthma, inflammatory bowel disease (IBD), chronic kidney disease (CKD), and neurodegenerative diseases such as Alzheimer [2-4]. The prevalence of these diseases has increased rapidly over the past decades [5], which challenges the question of why diseases of such different etiology are associated with chronic inflammation.

Among the risk factors associated with chronic inflammation obesity, smoking and diet play an important role through the induction of inflammatory cytokines and mediators. Age is another element that influences the inflammatory estate because of the increase in inflammatory mediators possibly due to mitochondrial dysfunction or free radical accumulation over time. Physical and emotional stress is associated with inflammatory cytokine release and sleep disorders, which is considered an independent risk factor for chronic inflammation. Testosterone and estrogen can suppress the production and secretion of several pro-inflammatory markers, and low levels of these hormones increases the likelihood of inflammation [6].

The inflammatory process -characterized by a sequence of events comprising an induction phase, which leads to the peak of inflammation and is gradually followed by a resolution phase-, is a defense mechanism necessary in order to solve injuries, but it occurs at a cost to normal tissue function. Thus, acute inflammation aims to protect and eliminate the injury. Chronic inflammation on the other hand, represents the failure of acute inflammatory mechanisms to repair tissue injury with the recruitment of the adaptive immune system.

The activation of inflammatory control mechanisms leads to chronic inflammation, further altering the normal tissue functions. Dysregulation of the inflammatory processes can cause the disruption of homeostasis and can promote other pathologies, including atopic and cardiovascular diseases, obesity, type-II diabetes, metabolic diseases and other diseases of homeostasis due to the interference with maintenance programs incompatible with inflammation [7]. Failure to resolve inflammation leads to diseases like rheumatoid arthritis, Crohn's disease, and asthma, as well as the cellular and molecular components that contribute to resolution of joint, gut, lung inflammation, cardiovascular disease, cancer, and osteoporosis [8-11].

In some extreme circumstances -such as anaphylaxis and septic shock-, the protective role of inflammation becomes detrimental when the response becomes excessive in magnitude or duration, and then, the dysregulated inflammatory reaction can cause inflammatory tissue damage and sepsis [12,13]. Nevertheless, although excessive inflammation can be pathogenic, dysregulation alone cannot explain the widespread association of inflammation and diseases.

While inflammatory tissue damage caused by an excessive response is the most negative outcome, alteration in the normal function of tissues is another price to pay with the pathological inflammation regardless of the magnitude and duration of the response.

Some cases of alterations in tissues induced by inflammation that provides an adaptive benefit in response to infection include increased endothelial adhesiveness and permeability in response to the inflammatory cytokines tumor necrosis factor α (TNFα) and interleukin-1β (IL-1β) [14] can impair hemostasis [15]; or synthesis and secretion by hepatocytes of acute phase proteins (APPs) in response to IL-6, to promote host defense from infection [16] leads to a reduction in synthesis of albumin and other serum proteins [16-19].

Inflammatory responses can be broken down into four common components of the inflammatory pathway: inflammatory inducers -such as exogenous pathogens and toxins, or endogenous ATP and urate crystals [20]-; sensors -like macrophages and mast cells that detect inducers and respond producing inflammatory agents-; mediators -different according to the varied combination of inducers-; and target tissues [21].

Both the induction and resolution phase of inflammation depend on lipid and proteins. Prostaglandin E2 (PGE2) and TNFα are mediators involved in the initiation, while a network of other mediators control the resolution.

Three key processes have been identified, which are intrinsic to resolution of inflammation: resolution, removal of neutrophils, and changes in macrophage function.

Resolution of inflammation depends on stopping the recruitment of neutrophils -the most abundant leukocyte population- at the inflammatory site, switching the production of pro-inflammatory agents such

as PGE2 and Leukotriene B4 (LTB4) to pro-resolving lipid mediators such as PGD2, PGJ2, lipoxin A4 (LXA4), resolvin E1 (RvE1), protectin D1, and maresin-1 [22].

Removal of the neutrophils, which can undergo apoptosis induced by death ligands produced by macrophages [23,24] -such as TRAIL or FasL- or produced by regulatory T cells -like transforming growth factor beta (TGFβ)- during the resolution phase of inflammation [25], and taken in by macrophages through efferocytosis.

Macrophages -key players in the innate immune response- contribute to cytokine production and pathogen clearance. In order to resolve the inflammation, these cells change their role and acquire anti-inflammatory and pro-resolving functions [26], clearing apoptotic cells, releasing pro-resolving lipids [27], expressing anti-inflammatory receptors such as TGFβ receptor 2 (TGF-R2) and formyl peptide receptor 2 (FPR2), and increasing the production of immune regulatory intracellular messengers such as cAMP [28].

Cells involved in the activation phase of inflammation -such as inflammatory M1-like macrophages-, must provide energy rapidly to fuel inflammation; M2-like macrophages, on the other hand, are involved in immune regulation and resolution of inflammation.

Although the resolution of inflammation is a universal protective response, mechanisms tissue and disease-specific have been identified that funnel the resolution of inflammation in arthritis, colitis, and asthma [11]. These pathways represent a promising therapeutic value to reverse chronicity in distinctive inflammatory diseases without holding back the overall inflammatory response. Additionally, the identification and characterization of new players that boost this response might foster the development of novel therapies for non-resolving inflammatory diseases.

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