THE INFLAMMATORY RESPONSE

Inflammation plays a vital role in host defense against invasive pathogens, tissue damage and wound repair (11). Inflammation is part of the innate immune response which ultimate goal is to bring to the invaded or injured area phagocytes and plasma proteins that can isolate, destroy, or inactive the invaders, remove debris, and prepare for subsequent healing and repair (16).

An acute inflammatory response is, by definition, divided into an initiation phase and a resolution phase (17). During the initiation phase there is a sequence of events that typically occur when there is a disturbance of tissue homeostasis: Firstly, a defense by macrophages already in the injured area, immediately begin phagocytizing when invasion of foreign microbes. Almost at the same time, mast cells release histamine which leads to a localized vasodilation and to an enlarging of the capillary pores (16). These changes in local blood vessel perfusion and permeability permit the directional extravasation of circulating leucocytes that achieve tissue disinfection, and of a range of plasma proteins which play distinct roles in regulating the inflammatory process (1), such as walling off the inflamed area in order to prevent, or at least delay, the spread of bacterial invaders and their toxic products. The end result of the shift in fluid balance is localized edema which is accompanied by the cardinal signs of inflammation: heat, redness, swelling and pain (16).

Eventual losses of function are going to be controlled, for the most part, by local chemical autacoids (7). A majority of these chemical messengers are in the form of peptides (cytokines and chemokines), proteins, and lipid-derived mediators (prostaglandins and leukotrienes) that form chemical gradients that regulate leukocyte trafficking via chemotaxis and diapedesis from the blood stream into the injured tissue (17). Polymorphonuclear neutrophil (PMN) and the slower-moving monocytes (than latter mature into macrophages) are the responsible for the phagocytosis function.

Phagocytosis is the main function of the inflammatory response. The process involves the engulfment and intracellular degradation, by PMN and macrophages, of foreign particles, tissue debris and environmental toxins that appear in tissues as a result of barrier disruption (17). PMN usually succumb after phagocytizing a number of cells, whereas macrophages survive much longer, so at the end macrophages have to clear the area of dead leucocytes in addition to other tissue debris.

All together, the repertoire of edema, polymorphonuclear neutrophil (PMN) infiltration, and monocyte-macrophage accumulation ensues as a characteristic sequence of events during the initiation of the acute inflammatory response (2,6,8,18).

The second phase of the inflammatory process is the resolution. The resolution of inflammation involves the termination of PMN recruitment, counterregulation of proinflammatory mediators, stimulation of macrophage-mediated clearance, and tissue remodeling (17).

Up to here, it is clear enough, that an acute inflammatory response is beneficial and host-protective. The problem begins when there is not an appropriate termination of the process and both, activated PMN and macrophages, accumulate in the inflamed tissue. This uncontrolled and non-resolving clearance of phagocytes can lead to persistent chronic inflammation which can result in tissue damage, organ fibrosis and loss of function, so this is way resolution needs to be ensured (17).

The mediators and mechanisms implicated in the resolution of inflammation have remained largely ignored. However, at present, the identification of four families of distinct structures, namely lipoxins, resolvins, protectins and maresins, all of which are biosynthesized within the resolution phase of acute inflammation (17), have permitted to envision resolution not as a mere passive process of dilution of inflammation, but as a highly orchestrated and complex active process in which many endogenous anti-inflammatory and proresolving mediators counteract the effects of proinflammatory mediators (14,9).

By the way, the same lipid mediators that initially trigger the inflammatory response (i.e. PGs and LTB4) derived from the omega-6 polyunsaturated arachidonic acid also signal the termination of inflammation by stimulating the biosynthesis of proresolving lipid mediators (i.e. resolvins and protectins) derived from omega-3 polyunsaturated docosahexaenoic and eicosapentaenoic acids (DHA and EPA) (10,11,15).

Conventional treatment against inflammation is directed towards either blocking or antagonizing proinflammatory mediators in a quest to control unwanted excessive inflammation (3,4,12). SPM's are seen to act not only counteregulating inflammatory gene transcription, but also paving the way for monocyte migration and their differentiation to macrophages, which remove dead cells (efferocytosis) and then terminate the inflammatory response by promoting macrophage efflux into lymphatics (13). The modulation of these "stop signals" that promote the timely resolution of inflammation is emerging as a strategy to maintain inflammation self-limiting, and to prevent tissue injury and disease (5).

Therefore, these Specialized Proresolving Lipid Mediators (SPMs) play pivotal roles in the resolution of many common pathologies, that are associated with chronic inflammation and that affect a large part of the population. Some examples are arthritis, musculoskeletal injurie, periodontitis, asthma and even metabolic diseases such as diabetes, obesity and cardiovascular disease.

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