


INSIGHTS

Immune cells—A curse and a blessing!

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Innate immune cells are crucial in the development and regulation of cardiovascular disease. In this issue, two groups, Davis et al. (2021. *J. Exp. Med.* <https://doi.org/10.1084/jem.20201839>) and Li et al. (2021. *J. Exp. Med.* <https://doi.org/10.1084/jem.20210008>) describe the impact of the innate immune system on the development of cardiovascular disease.

Inflammation resolution and tissue regeneration are fundamental for human system catabasis. The harmony between inflammation and homeostasis presents us with great challenges on a daily basis; as most recently experienced by the world, COVID-19 clearly demonstrated this challenge to us.

New ways of looking at inflammation are taking over the science of inflammation. As Rudolf Virchow postulated, inflammation is a pathological phenomenon, and Elie Metchnikoff considered inflammation to be an important aspect of homeostasis. These statements by the two great pioneers of the theory of inflammation lay an extremely important foundation for the way we look at and consider the pathophysiology of individual diseases.

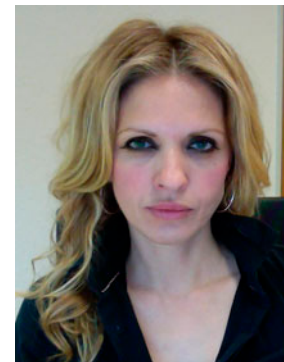
Inflammation is based on cellular dynamics that categorically recruit leukocytes to the site of the disease process. Over the past 30 yr, this aspect has been described as a key component in the pathophysiology of many diseases. A major impact of this process has been characterized especially in infectious diseases, cardiovascular diseases, and tumor immunology.

The inflammatory response can be classified into four phases, namely (i) initiation of inflammation, (ii) transition, (iii) resolution, and (iv) return to homeostasis. An inflammatory stimulus triggers the release of chemical mediators such as chemokines, cytokines, and lipid mediators in the context of infection via pathogen-associated molecular patterns and in the context of sterile

infection damage-associated molecular patterns. This stimulus activates the recruitment of polymorphonuclear leukocytes (PMNs) in the affected tissue in the early stages of inflammation (de Oliveira et al., 2016; Meizlish et al., 2021).

The main problem with inflammation is not the frequency of its onset in early stage, but rather the frequency of its failure to resolve following this (Nathan and Ding, 2010). Checkpoints exist to balance homeostasis with so-called “physiological” inflammation before it progresses into pathological inflammation, which can transition into chronic inflammation with organ dysfunction. One of these checkpoints is placed in the field of resolution of inflammation. It had long been hypothesized that removal of the inflammatory stimulus prevents the production of chemoattractants that promote further leukocyte recruitment. Based on this statement, researchers hypothesized that simply diluting the chemoattractants in the tissue would prevent continued recruitment of inflammatory cells. Resolution of inflammation was seen as a passive event.

Charles N. Serhan has been a pioneer in the field of inflammation resolution. He demonstrated in his studies of acute self-limiting responses using a systems-based approach that resolution of tissue inflammation is an active process, in which cell-cell interactions lead to the generation of endogenous active specialized pro-resolving mediators (i.e., lipoxins, resolvins, protectins, and maresins). These mediators



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limit further neutrophil recruitment to the tissue and enhance the efferocytosis of neutrophils by macrophages, promoting a return to homeostasis (Serhan, 2014; Serhan and Levy, 2018). At the cellular level, multifaceted immune cell dynamics proceed. PMNs exit the postcapillary venules and subsequently start efferocytosing microbes and cellular debris. At this point, neutrophils take on a pro-resolving function by first neutralizing the invaders before they get eliminated. A balance between PMN recruitment and pro-resolving actions is essential for a sufficient resolution process. However, if an imbalance occurs, resulting, for example, in an excessive infiltration of PMNs into the tissue, this mismatch may then lead to frustrated efferocytosis or an increase in cell death/necrosis (de Oliveira et al., 2016).

As a result, inflammation in the tissues would worsen, which may lead to a chronic

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process and limitation of injury repair, resulting in loss of organ function. PMN-induced inflammation is a cornerstone of many diseases. Therefore, it is of tremendous importance to explore and understand mechanisms of PMN recruitment and further immune subsets to finely control these inflammatory events.

The highly interesting work of Li et al. (2021) addresses exactly these components in a model of myocardial ischemia-reperfusion injury. In this study, the authors demonstrated that myeloid-derived netrin-1 has a central role in attenuating myocardial ischemia-reperfusion injury.

Neuronal guidance proteins have recently been suggested to have immunocompetent properties in peripheral acute or chronic disease, in addition to their role in controlling axonal growth. In the process of nervous system development, a balance of chemoattractive and chemorepulsive signals guide the axons precisely to their final location to flesh out the complex neuronal system.

Thus, a new approach emerged that showed that the nervous and immune systems share biological principles such as guidance mechanisms and the control of cellular migration. The study by Li et al. (2021) could show that circulating levels of netrin-1 were elevated in the blood of patients who had suffered a myocardial infarction. A hypothesis was put forward by the authors that PMNs could be an important source in this context. In murine experiments with antibody-based neutrophil depletion, they demonstrated that depletion of neutrophils before myocardial I/R revealed a significant reduction in blood netrin-1 concentrations compared with the control group. Treatment with netrin-1 protected from murine myocardial IR injury, and this effect was mediated by the myeloid-expressed adenosine 2B receptor. These results are of great importance because they show that this endogenous protein has protective properties in myocardial I/R damage. Pathophysiologically, this implies that netrin-1 supports the protective properties of an inflammatory response and, therefore, fewer adverse side effects can be expected after treatment with netrin-1.

The influence of netrin-1 in the onset of acute inflammation has been described in several studies previously. Netrin-1 reduces PMN recruitment into the lung during

pulmonary inflammation and also intestinal I/R injury, and thus has a protective effect on disease progression (Mirakaj and Rosenberger, 2017). In another study, Schlegel et al (2016) investigated the effect of netrin-1 in the phase of resolution in hepatic ischemia/reperfusion injury. In this work, the authors demonstrated the effect of netrin-1 on the specific cells such as monocytes and macrophages, which are, beside PMNs, central adjusters in the maintenance of tissue homeostasis and repair. In this context, netrin-1 is thought to have a dual function, an anti-inflammatory and pro-resolving one, and therefore belongs to the immunoresolvent.

At the cellular level, the main actions of these immunoresolvents are in restoring barrier integrity, terminating the recruitment of neutrophils, efferocytosis and phagocytosis of apoptotic cells, pathogens, and cell debris by specialized macrophages (Serhan, 2014).

The monocyte and macrophage lineages are central in inflammation resolution and tissue regeneration. Regardless of their origin, they are highly plastic and functionally diverse during the progress of pathological processes. An inflammatory stimulus induces metabolic and phenotypic changes that may allow differentiation and polarization into the classic proinflammatory M1, alternative anti-inflammatory M2, or intermediate M2 phenotype (Okabe and Medzhitov, 2016). These highly dynamic phenotype changes are evident, for example, in cardiovascular disease after myocardial infarction. Thus, cardiac macrophages exhibit dual roles. Upon injury, they respond by triggering the initial inflammatory response, and in the course of the process, they initiate tissue repair (Dick et al., 2019).

The highly interesting mechanistic study by Davis et al. (2021) investigated the role of macrophages within abdominal aortic aneurysm development. Pro-inflammatory macrophages differentiate and proliferate from hematopoietic progenitor cells and show an important influence on aortic expansion. In this process, epigenetic modifications regulate the expression of immune mediators in macrophages (Kuznetsova et al., 2020). Histone demethylase, chromatin modifying-enzyme Jumoni domain-containing protein D3 (JMJD3), influences macrophage polarization after LPS stimulation. Inhibition of JMJD3 results in a

reduction of cytokine production. The authors demonstrated that this mechanism is NF- κ B dependent and that JMJD3 expression in macrophages is regulated via IFN β and STAT1 pathway.

In addition to epigenetics, the field of immune cell metabolism has advanced significantly. For example, macrophage metabolism is shown to be extremely plastic and often reflects pathologies associated with specific disease states. Inflammation and homeostasis—two elements in the science of inflammation—are gaining significant attention in research and have a major impact in translational medicine. Nevertheless, many questions remain to be answered. Experimental approaches to define subpopulations of immune cells in tissues and their dynamics in health and disease play an important role.

Targeted personalized therapy based on temporal and spatial characteristics of the inflammatory process could be the bridge to specificity and personalized therapy.

The use of newer technologies such as the application of trans-omic approaches, technologies that enable high-rate analysis of cell phenotypes would greatly expand the understanding of the biological system. In addition, there should be an increased focus on therapeutic approaches using immunoresolvents to support agnostic and pro-resolution properties in inflammation or inflammation-associated diseases.

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