EDITORIAL

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Get the balance right

The study of '*inflammare*', or inflammation, which describes the basic process whereby tissues respond to traumatic, infectious, ischemic, toxic or autoimmune injury, dates back over 3,000 years. The Roman Celsus, around 30 BC to 38 AD, is credited with first documenting the four cardinal signs of inflammation: *rubor et tumor cum calore et delore* (redness and swelling with heat and pain). Other notable figures in the history of inflammation research include Galan, who defined inflammation as a beneficial response to injury; Virchow, who described the fifth cardinal sign of inflammation, *function laesa* (loss of function); and Metchnikoff, who discovered that extravasated neutrophils can be cleared from peripheral tissues by being ingested by 'big eaters', or macrophages.

Inflammation encompasses many facets. The initial stages of inflammation involve changes in local blood flow combined with the accumulation of various inflammatory cells (neutrophils, monocytes, dendritic cells, mast cells and lymphocytes) at the site of tissue trauma. Foreign pathogens, cell debris caused by the inflammatory response, and the inflammatory cells themselves are then removed and tissue repair is stimulated. In normal circumstances, tissue function is restored. However, if this delicate balance between inflammation and resolution becomes dysregulated, inflammation can lead to disease pathology. Chronic diseases such as arthritis, inflammatory bowel disease and asthma are associated with such a breakdown in the inflammatory response. Given that inflammation not only is beneficial but also can be damaging if prolonged, it is not surprising that the entire process is tightly regulated.

It was traditionally believed that resolution of the inflammatory response occurs passively. Subsequent findings, however, have indicated that in fact this process is active. Many mechanisms are put in place to turn off leukocyte trafficking to the inflamed site, to reverse vasodilation and vascular permeability and to bring about the elimination of inflammatory cells. In this issue of *Nature Immunology*, we present a special Focus on Dampening Inflammation. A series of review articles examines the physiological mechanisms by which inflammation is regulated and also highlights possible pharmacological targets to block the inflammatory response. Our web focus (http://www.nature.com/ni/focus/inflammation/index.html) also features an annotated collection of classic papers that have helped move the field of inflammation research forward and a selection of notable papers published by Nature Publishing Group in this burgeoning area. Also included are brief summaries of research recently published on inflammatory resolution. All of the content will be freely available to registered users in the month of December.

As noted, the inflammatory response is highly coordinated and begins by the recruitment of inflammatory cells to the site of tissue trauma. Luster, Alon and von Andrian review the main participants and mechanisms of cell accumulation during the initial effector phase of inflammation. Inflammatory mediators such as chemokines, cytokines and lipid mediators are integral to this process. Chemokines, for example, provide essential guidance for interstitial leukocyte migration in the inflamed tissue. Also critical for leukocyte recruitment are adhesion molecules. Members of the selectin family, such as P-selectin, are inducibly expressed in endothelial cells and are important determinants for the trafficking of neutrophils, monocytes, natural killer cells, eosinophils and lymphocytes to the inflammatory site. Members of the integrin family such as VLA-1 mediate leukocyte migration across the basement membrane underlying blood vessels and the extracellular matrix, as well as leukocyte crossing or retention on inflamed stromal and epithelial cells. As discussed by Luster, Alon and von Andrian, blocking leukocyte trafficking by targeting inflammatory mediators or adhesion interactions pharmacologically represents likely points of control for dampening inflammation.

A few hours after the influx of leukocytes to the site of inflammation, the active process of resolution begins. As discussed by Serhan and Savill, this process involves lipid mediators that initially function as proinflammatory molecules only to become anti-inflammatory mediators in a carefully coordinated sequence of events. Granulocyte entry to the inflammatory sites promote the switch from proinflammatory arachidonic acid–derived prostaglandins and leukotrienes to lipoxins. The latter retard entry of new neutrophils to the inflammatory site as well as reduce vascular permeability and trigger macrophages to ingest and clear apoptotic neutrophils. Other lipid mediators produced during this phase include resolvins and protectins, which initiate neutrophil apoptosis. The macrophages that 'mop-up' the apoptotic neutrophils stimulate the release of anti-inflammatory and reparative cytokines such as transforming growth factor-β. The program ends with the departure of the macrophages via the draining lymphatics.

Han and Ulevitch consider resolution of inflammation in the context of intracellular signaling pathways. Specifically, they discuss how signals emanating from the pattern-recognition receptor families TLR and Nod, which recognize infectious agents and the products released by injured or dying cells, are dampened. Not unexpectedly, there are multiple points along these signaling pathways that reduce or dampen the function of these key receptors. These include TLR homologs such as RP105 and ST2, many intracellular proteins such as Myd88s, which function as TLR antagonists by interfering with signaling molecules in the signaling pathway, and negative regulators of TLR signaling that include PI(3)K, Tollip, SOCS1 and A20. Post-transcriptional control is also thought to be an important mechanism for regulating gene expression of inflammatory mediators.

We have clearly come a long way in the last few years in understanding how the inflammatory response is regulated. This progress has led to the development of new targets for pharmacological agents, which have already shown some promise in the clinic. For example, Odulimomab, which interferes with cell trafficking by inhibiting α_L-integrin, is used for the treatment of graft-versus-host disease. However, a complete block of the inflammatory response would not be desirable because it would leave the body immunocompromised and unable to defend against infection. As described by Henson in a Perspective on Dampening Inflammation, herein lies the paradox of the inflammatory response: it is both essential and potentially detrimental.