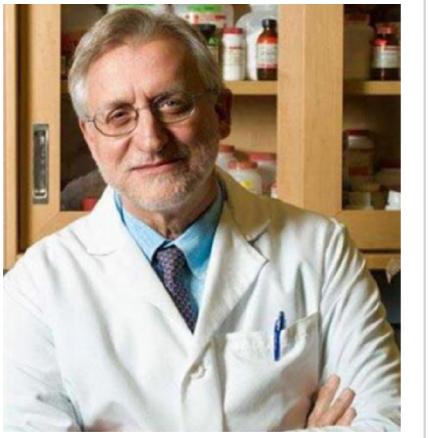
Editorial

Danger Signals and Inflammation



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This special themed update includes 6 articles by experts in the field covering the role of different classes of molecules and processes involved in alerting an organism of the presence of real or perceived, external or internal, dangers that threaten its survival. These reviews address the role of purinergic signaling and immune responses in sepsis, the alarmin properties of DNA and DNA-associated nuclear proteins, the key role of damage-associated molecular patterns in inflammation and tissue repair, the potential therapeutic aspects of alarmin cytokine interleukin (IL)-33 or its inhibitors in various diseases, the role of alarmins in antitumor immunity, and nanotube formation, a rapid form of alarm signaling.[1–6] Better understanding of these danger signals, also known as alarmins, and their possible containment in case of false or sustained alarm would help prevent or treat a number of diseases.

Selye[7] was the first to write about the stress response to explain how a mammal responds to danger to survive (the fight or flight response). Although he tried to identify a responsible hypothalamic factor, he missed corticotropin-releasing hormone (CRH),[8] which is considered a master alarmin that mediates the effect of stress on the body, especially the skin.[9] It is interesting that CRH also promotes inflammation,[10] an evolutionary defense response[11] that preceded the development of the immune system. Inflammation is now known to depend on a unique, ancient,[12] multitasking cell[13]—the mast cell[14]—which has existed throughout the phylogenetic tree.[15,16] The body has the ability to secrete hormonal, immune, and neural substances[14] resembling the behavior of unicellular organisms dating back some 500 million years.[17,18] In fact, Selye[19] wrote in his comprehensive book *The Mast Cells* that "the so-called metachromatic corpuscles found in certain protozoa may be related to mast cells" and "the metachromatic volutin granules of yeast resemble mast cell granules."

CRH can promote the development of skin mast cell progenitors[20] and stimulate skin mast cells.[21] Human mast cells express the high affinity CRH receptor-1 (CRHR-1), activation of which leads to selective release of vascular endothelial growth factor without degranulation.[22] Intradermal administration of CRH activates skin mast cells and increases vascular permeability through activation of CRHR-1 in humans.[23] In fact, stress increases the expression of CRHR-1 in bone marrow mast cells.[24] Moreover, CRH can be secreted from mast cells[25] and can stimulate the hypothalamic-pituitary axis, triggering the fight or flight reaction.[26,27] Different life forms and tissues developed a variety of molecules to sound the alarm and keep them out of danger (**Table**). The horseshoe crab, which resembles species that existed more than 500 million years ago, survived by using defenses that involved a close interplay between the coagulation and innate immune systems.[28] It is, therefore, interesting that among the most potent triggers of mast cells is bradykinin, which is generated by the action of kallikrein on kininogen derived from Hageman factor XII of the clotting cascade,[29,30] and mast cells are the richest source of the anticoagulant heparin.[31]

Table. Danger signals.

AMPs	Histamine	Nucleolin
Annexins	HMCB1	PAMPs
ATP	HDGF	PRRs
Cathelicidins	HSPs	SPMs
CLRs	IFNs	S100s
CRH	IL-1	Thymosins
DAMPs	IL-33	TLRs
Defensins	mtDNA	Uric acid
EDN	NAMPs	Urocortin
Galectins		

AMPs = antimicrobial peptides; CLRs = C-type lectin receptors; CRH = corticotropin-releasing hormone; DAMPs = damage-associated molecular patterns; EDN = eosinophil-derived neurotoxin; HDGF = hepatoma-derived growth factor; HMGB1 = high mobility group box 1; HSPs = heat shock proteins; IFNs = interferons; mtDNA = mitochondrial DNA; NAMPs = nanoparticle-associated molecular patterns; PAMPs = pathogen-associated molecular patterns; PRRs = pattern recognition receptors; SPMs = specialized pro-resolving mediators; TLRs = toll-like receptors;

Pattern recognition receptors,[32,33] which include damage-associated molecular patterns, nanoparticle-associated molecular patterns, and pathogen-associated molecular patterns,[34] C-type lectin receptors[35] are major danger signals (Table) acting through activation of toll-like receptors. It is interesting that toll-like receptors are also expressed by mast cells,[36] activation of which allows them to augment allergic stimulation[37] and regulate responses to pathogens.[38–40]

Among the recent molecules to have emerged as a key danger signal is IL-33, which has been linked to autoimmune and inflammatory diseases,[41–43] possibly acting through mast cells.[44,45] IL-33 augments also mast cell stimulation by the neuropeptide substance P.[46] In fact, stimulated mast cells secrete the substance P-related peptide hemokinin-1, which acts in an autocrine manner to augment their stimulation by allergic triggers.[47]

Unfortunately, danger signals often go overboard, leading to a heightened or sustained alarm state that becomes deleterious to the organism. Such is the case of the autoinflammatory diseases characterized by high serum IL-1[48] and generalized sepsis associated with cytokine storms.[49] It is therefore important to explore ways that may protect the organism from overzealous alarmins with molecules such as specialized proresolving mediators,[50] high mobility group box 1,[51] and microRNAs.[52]

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