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FOCiS on Damage Associated Molecular Pattern Molecules*

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Introduction

Members of the Federation of Clinical Immunology Societies are invited to attend an exciting meeting on damage associated molecular pattern molecules [DAMPs] in acute and chronic inflammation including cancer. This day long interactive symposium is going to be held in San Diego June 7th, 2007 as part of the Annual FOCiS meeting. The Clinical Immunology Society (CIS) and the International Society of Biologic Therapy (ISBT), member societies in FOCiS, will be sponsoring this symposium examining the emergent role of these DAMPs in disease. Much attention has been paid to the so-called pathogen associated molecular pattern molecules or PAMPs, which recruit and activate inflammatory cells, largely through the Toll-like receptors [TLRs], the Nod1-like Receptors [NLRs], and the most recently identified RIG-I like receptors [RLRs]. This critical requirement for sensing and responding rapidly with these innate immune sensors is mirrored in the need to have systems sensing nonpathogenic stress.

Trauma, ischemia, and tissue damage are recognized at the cellular level by pattern recognition molecules with detection of intracellular proteins and nucleotides released by the dead cells. The ability of intracellular proteins, DNA, and RNA to promote leukocyte recruitment and activation as DAMPs in acute inflammation is limited by their rapid oxidation and opsonization in tissues. When Redox conditions are such that extracellular reducing conditions persist, or are hypoxic, persistent inflammation may result ^{1, 2}. Eosinophils ³⁻⁵, recruited to the site of tissue damage appear to provide a rich source of oxidants with immunoregulatory activities promoting remodeling activities. Conversely, antigen presenting cells appear to condition the local environment by providing reductants ², promoting T-cell responses. The immunologic defects observed in aging and chronic inflammatory states including cancer, in part could be related to continuous release of DAMPs and complex immunoregulatory circuits and pathways engaged ⁶.

“Danger signals” recruit and activate granulocytes, monocytes, and eosinophils

High mobility group box 1 (HMGB1) is a highly conserved, ubiquitous protein present in the nuclei and cytoplasm of nearly all cell types. It is released upon necrotic but not apoptotic death of normal cells and secreted by a variety of activated immune and nonimmune cells ⁷⁻¹⁸. Administration of HMGB1 to normal animals causes inflammatory responses, including fever, weight loss and anorexia, acute lung injury, epithelial barrier dysfunction, arthritis, and even death. Moreover, HMGB1 given intratracheally produces acute inflammatory injury within the lungs, with neutrophil accumulation, development of lung edema, and increased pulmonary

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production of IL-1 β , TNF- α , and macrophage-inflammatory protein-2. Collectively HMGB1, S100 proteins, purine metabolites RNA and DNA can serve as DAMPs^{19, 20}.

Efficacy of DAMP blockade

Significantly, anti-DAMP treatments with antibodies or specific antagonists, rescues mice from lethal endotoxemia or sepsis and ameliorates the severity of collagen-induced arthritis and endotoxin-induced lung injury²¹⁻²³. In addition activated macrophages, mature dendritic cells [DCs], and NK cells are able to secrete HMGB1. Thus, in addition to its role as a constituent of chromatin proteins, HMGB1 acts to promote leukocyte chemotaxis and activation, including the amplification of adaptive immune responses and DC maturation⁹⁻¹¹. Specifically, HMGB1 induces the migration and activation of human DCs and acts as an alarmin¹¹. These activities position HMGB1 as a unique “danger signal” identifying tissues with cell stress/necrosis serving to attract and activate myeloid cells within damaged tissues and serve as an important signaling molecule during the integration of host inflammatory responses and wound repair.

RAGE (receptor of advanced glycation endproduct), is a DAMP receptor

Besides TLR2 and TLR4¹², RAGE has been identified as a receptor for HMGB1. We [MTL] have shown that neutrophils and eosinophils both express RAGE^{24, 25}. RAGE is a member of the immunoglobulin superfamily of cell surface proteins that has been implicated as a progression factor in a number of pathologic conditions from chronic inflammation to cancer to Alzheimer's disease. In such conditions, RAGE acts to facilitate pathogenic processes. Its secreted isoform, soluble RAGE or sRAGE, has the ability to prevent RAGE signaling by acting as a decoy. sRAGE has been used successfully in animal models of a range of diseases to antagonize RAGE-mediated pathologic processes. sRAGE binds HMGB1 and neutralizes its effects in many models. sRAGE is mainly found in lung tissues, the hyperresponsiveness to DAMPs may be due to lower sRAGE concentration in the lung of asthma patients. If so, the application of sRAGE or other HMGB1 neutralizing factors may also reduce inflammation in the setting of asthma.

Endogenous ligands released from damaged cells, DAMPs, activate innate signaling pathways including the TLRs

Hepatic, warm ischemia and reperfusion (I/R) injury, generates local, noninfectious DAMPs. The resultant inflammation is TLR4-dependent and enhanced by increasing the number of DCs. TLR4 expression is also increased in hepatic DCs following HMGB1 stimulation *in vitro*. Interestingly, pretreatment with HMGB1 prior to ischemia reperfusion is associated with diminished liver damage and leukocyte recruitment following ischemia reperfusion which appears to be related to IRAK-M signaling²¹⁻²³.

S100A8 and A9 proteins expressed in phagocytes are also DAMPs

Another example of DAMPs, expressed in myeloid cells, are the phagocytic S100 proteins²⁰. They promote inflammatory responses, also recruiting cells to sites of tissue damage. S100A8, S100A9, and S100A12 are found at high concentrations during inflammation. Although S100A12, present in humans but not murine species, binds to RAGE and other members of the family with it and likely other receptors. In cancer²⁶⁻³², autoimmunity³³, and sepsis³⁴, such molecules appear to be important for promoting or limiting³⁵ information.

Conclusion

Analyzing the molecular basis of the specific effects exhibited by DAMPs in greater detail will elucidate important mechanisms of innate immunity, the transition to adaptive immunity, and generate novel biomarkers of inflammation. Anti-DAMPs including some of the purine metabolites such as adenosine, likewise, are emergent as important targets for study and blockade or enhancement. Ultimately these represent novel targets for innovative anti-inflammatory therapies important in autoimmunity, transplantation, chronic viral diseases, atherosclerosis, obesity, and cancer.

A schedule of speakers for the June 7th Minisymposium on DAMPs in San Diego follows the references. Information can be obtained on the web at <http://www.focisnet.org/index.php>

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