Pancreatic Cancer Is Not Noble

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For the last century, immunity was based on specificity, first, serological responses, and then over the last three decades, T cell immunity. We now recognize that innate immunity represents the solid core of immunity on which adaptive responses have been draped. This has most recently been acknowledged with the 2011 Nobel Prize in Physiology or Medicine being awarded to Bruce Beutler, Jules Hoffman and Ralph Steinman. As many of our readers know, our friend Dr. Ralph Steinman was afflicted by pancreatic cancer, working tirelessly for almost 5 years with immune therapies to alter his disease trajectory. Sadly, he never knew of the prize awarded to him, dying a scant few days before it was announced. We dedicate this issue of the *Journal of Innate Immunity* to his memory.

Pathogen-Associated and Damage-Associated Molecular Pattern Molecules

As posed in the last three decades, we would like to address the molecular pathways by which pathogen-associated molecular pattern molecules are recognized. In the setting of tissue injury including ischemia/reperfusion [1, 2], arthritis [3], tissue damage [4] and cancer [5–9], damage-associated molecular pattern molecules (DAMPs) are released. We now recognize that as a biological response to starvation and metabolic stress, when ATP levels are

low [10, 11], epithelial and stromal cells turn to autophagy [12–14]. Without a proper interaction with adjacent stroma, substrate provision to the tissues cannot be maintained. When this programmed survival pathway fails, epithelial cells die a necrotic death and release DAMPs. These include HMGB1 [1–9, 11–14], as reported by Nace et al. [15] and Berthelot et al. [16] in this issue of the *Journal of Innate Immunity*. Stromal cells respond by providing substrate to the metabolically stressed epithelial cells. We hypothesize that DAMPs perpetuate this shift in bioenergetics, promoting further autophagy [12–14]. The receptors that play a role, including RAGE (receptor for advanced glycation end products) [2, 14], as reported by Dessing et al. [17] in this issue, appear to be important for the response to low levels of HMGB1 but not to higher levels, where Toll-like receptor 2 and Toll-like receptor 4 (TLRs) play predominant roles. Other receptors include the NOD1/NALP-like receptors (NLRs) as put forward by Mason et al. [18], the RIG-I receptors (RLRs) and the AIM2-like DNA receptors (ALRs). Other proteins apart from HMGB1 play a role as DAMPs. In addition to heat shock factors (reviewed in part by Gally et al. [19] in this issue) and the S100 molecules (also reviewed in this issue, by Srikrishna [20]), extracellular proteins such as hyaluronan, heparin sulfate and fibronectin (Sofat et al. [21], in this issue) also play a role in alerting the innate immune response. Much clearly remains to be done to resolve the important role of these molecules in disease.

Invitation to Heidelberg and the Fifth International DAMPs and Alarmins Symposium, 11–15 July, 2012

This will be the 5th International DAMPs and Alarmins Symposium (iD&As-V). It is to be held in Heidelberg on the 11–15 July, 2012, in conjunction with the

German Cancer Research Institute. The first symposium was in 2004 (Stockholm), followed by meetings in 2006 (Milano), 2008 (Pittsburgh) and 2010 (Helsinki). We would like to invite our readers to this meeting for a modern explication of DAMPs and their role in innate immunity.

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