Journal of Nanomedicine & Biotherapeutic Discovery

Krysko, J Nanomed Biotherapeut Discov 2012, 2:4
DOI: 10.4172/2155-983X.1000e118

Editorial Open Access

Immunogenic Cell Death and Emission of Damps: Calreticulin and ATP

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Abbreviations: ATP: Adenosine Triphosphate; CRT: Calreticulin; DAMP: Damage-Associated Molecular Pattern; MYD88; Myeloid Differentiation Primary Response Gene 88; NLR: The Nucleotide-Binding Oligomerization Domain (NOD)-Like Receptor; PRR: Pattern-Recognition Receptor; RLR: RIG-I-Like Receptor; TLR: Toll-Like Receptor

The 'danger theory' was first proposed by Polly Matzinger in 1994. This theory states that the immune system can distinguish self from non-self and dangerous from innocuous signals [1]. This theory has become widely accepted in recent years, especially with the formulation of immunogenic cell death (ICD) concept [2]. Immunogenic characteristics of ICD are mediated mainly by molecules called 'Damage-Associated Molecular Patterns' (DAMPs). These are intracellular molecules normally hidden within live cells, but they acquire immunostimulatory properties upon exposure/release/secretion by damaged/dying cells.

It was recently reported that only certain agents (*e.g.* anthracyclines, γ-irradiation and hypericin based photodynamic therapy) induce active emission of DAMPs by dying apoptotic cells, and this property determines the efficacy of anti-cancer therapy in the experimental tumor prophylactic vaccination model [3-5]. These studies have shown that surface exposure of calreticulin (CRT), a soluble protein normally located in the lumen of the endoplasmic reticulum, on tumor cells undergoing ICD in response to certain chemotherapeutics (*e.g.* anthracyclines) facilities their engulfment by dendritic cells (DCs). This leads to tumor-antigen presentation and tumor-specific cytotoxic-T lymphocyte (CTL) responses [3]. It is important to stress that the molecular signaling pathways involved in CRT exposure are strongly dependent on the ICD inducer [4,5]. Another DAMP shown to be actively secreted from cells undergoing ICD is ATP [5,6]. Secretion of ATP, which occurs very early during apoptosis, is also tightly regulated by molecular program(s) [5].

Upon their exposure or release by dying cells, DAMPs interact with membrane-bound or vesicular pattern-recognition receptors (PRRs), including Toll-like receptors (TLRs), purinergic receptors, NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs) [7,8]. For example, it has been shown that extracellular ATP released from cells undergoing ICD activates purinergic P2X7 receptors on DCs. This activates the NALP3–ASC–inflammasome and drives the secretion of IL-1β, which is required for the polarization of interferon-γ (IFN-γ)-producing CD8+ T cells and for the immune response to tumor cells [9]. We also recently demonstrated that the TLR-2/TLR-9-MyD88 signaling pathways have a central role in initiating the acute inflammatory response to cells undergoing ICD [10].

Substantial progress has been made over the past few years in identifying the DAMPs exposed/released/secreted during ICD and the molecular mechanisms of their emission and recognition by the innate and adaptive immune systems. Indeed, nanoparticles and their applications in biomedicine and medicine has become an extensive area of research [11]. It is important to analyze whether nanopartciles act as DAMPs, whether they can be designed with unique immunomodulatory properties (dependent on size, shape, surface charge and solubility), and if they can instigate different immunological responses. These immunomodulatory properties might be specific for a precise physical type of engineered nanoparticle, and further studies are required to identify and analyze nanoparticle-associated molecular patterns (NAMPs) [12]. Since nanoparticles are also designed to target tumors *in vivo* and are intended for use as therapeutic drug carriers [11], it will be important to analyze whether drugs delivered in nanoparticles will have increased (or changed) immunogenic potential in terms of induction of ICD and emission of DAMPs.

Acknowledgments

I thank Dr A Bredan for editing the manuscript. This work was supported by project grants from the Fund for Scientific Research Flanders (FWO-Vlaanderen, G.0728.10 and 3G067512 to DVK). DVK is a senior postdoctoral fellow paid by fellowship from FWO-Vlaanderen.

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Received July 03, 2012; **Accepted** July 04, 2012; **Published** July 06, 2012

Citation: Krysko DV (2012) Immunogenic Cell Death and Emission of Damps: Calreticulin and ATP. J Nanomed Biotherapeut Discov 2:e118. doi:10.4172/2155-983X.1000e118

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