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Role of chaperones and FcγR in immunogenic death

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Abstract

Cell death under physiologic conditions does not lead to the induction of immunity. However recognition of stressed or opsonized cells can trigger immune responses. Recent studies have begun to illustrate the critical role of molecular chaperones such as inducible heat shock proteins in mediating immunogenicity of stressed cells. Immunity to opsonized cells depends in part on the engagement and the balance of activating and inhibitory FcγRs on antigen presenting dendritic cells. Understanding both these pathways of immunogenic cell death may yield novel approaches to regulate immunity.

Two forms of immunogenic cell death

Billions of cells die each day and are replaced by newly differentiated progeny. Corpses of such dying cells are rapidly removed by phagocytes; do not elicit immunity and may induce tolerance. However under some settings, recognition of dying cells leads to inflammatory responses and immunity[1]•. Two aspects of such “immunogenic death” are the focus of this review. A common response to cellular stress is the transcriptional activation of molecular chaperones that belong to the class of inducible heat shock proteins (HSPs). Another setting wherein dying cells might induce immunity is when they are opsonized by antibodies due to antibody mediated recognition of determinants on dying cells. Such opsonized cells can be recognized by FcγR mediated pathways on antigen presenting cells (APCs). Below, we will discuss recent insights into how both of these pathways play an important role in regulating immunogenicity of dying cells and can be dysregulated in autoimmunity.

Heat shock proteins (HSPs) and immunogenic cell death

HSPs are referred to as stress proteins or molecular chaperones, although most HSPs are constitutively expressed. Known best for their roles in regulating intracellular protein homeostasis, HSPs were immunologically implicated because of the observations that tumor-derived HSPs, although having no tumor-specific mutations, can immunize for tumor-specific T cell immunity[2]•. Efforts to explain the phenomenon have led to two

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hypotheses[2]: HSPs chaperone peptides for presentation to MHC molecules, and HSPs activate professional APCs. Studies have shown that most of HSPs are indeed able to chaperone peptides and HSP-peptide complexes are critical for cross-priming of peptide-specific $CD8^+$ T cells[3]••. The interaction between HSPs and APCs is thought to depend on receptors on APCs. Several candidate receptors have been suggested, including CD91, SR-A (scavenger receptor A), TLR2/4, CD40 and Lox1[4]. However the nature of specific HSP receptors remains to be completely resolved.

gp96 is a prototype HSP, whose immunological properties have received the most attention. In addition to the biochemical evidence, roles of gp96 in immune response are also supported genetically. Tumor cells engineered to express gp96 on cell surfaces [5] or secrete gp96[6] are able to activate dendritic cells (DCs) and prime $CD8^+$ T cells. Transgenic mice with ubiquitous expression of membrane-bound gp96 suffered from lupus-like autoimmune diseases spontaneously, which was dependent on MyD88[7]. This line of research suggests that extracellular gp96 might be able to engage innate receptors to cause inflammation. An important recent insight into the biology of gp96 is its ability to serve as a master chaperone for toll like receptors, and regulate their function[8••,9]. Surface translocation of HSPs might therefore result in the alteration of cellular responsiveness to environmental stimuli. For example, surface translocation of gp96 leads to hyperresponsiveness to endotoxin, due to the TLR4 chaperoning function of gp96 [8,10]. Pro-inflammatory properties of extracellular HSPs have also been observed with HSP60, HSP70, GRP170, HSP90 and calreticulin [11]. Collectively, the intrinsic immunological properties of extracellular HSPs indicate that exposure of HSPs, as a result of cell death or stress, is likely to have immunological consequences.

Regulation of HSP export

The presence of HSP receptors on the surface of DCs strongly suggests that HSPs, being exclusively intracellular molecules under normal conditions, may gain access to the extracellular milieu to elicit their proinflammatory properties. gp96 possesses an endoplasmic reticulum (ER) retention signal lys-asp-glu-leu (KDEL) at the carboxyl terminus [12] and resides mostly in the lumen of the ER. Cell surface expression of gp96 in several studies has been shown to depend on the active ER to Golgi transport. The cell biological basis for the plasticity of the cellular transport of gp96 remains unknown. It was recently shown that gp96 associates tightly with p43, a versatile protein known for its ability to associate with multiprotein complexes (such as tRNA synthetase) [13]. The interaction between gp96 and p43 leads to retention of gp96 inside cells, as overexpression of p43 significantly reduced the cell surface gp96. Cell surface gp96 is also significantly increased in many cell types in $p43^{-/-}$ mice. Therefore, one of the functions of p43 may be to “hold” gp96 intracellularly to prevent unnecessary DC activation and detrimental immune responses, due to gp96-DC interactions. The mechanism of the export of other HSPs is less clear. There is a membrane-bound variant of HSP90 whose regulation is yet to be worked out [14]. A recent study implicated sphingolipid Gb3 in membrane localization of HSP70 in tumor cells[15]. Understanding the pathways or molecules that regulate the cellular localization of HSPs may have major implications for immune activation.

Exposure of HSPs during cell death

Initial studies focused on the differences in HSP content between cells undergoing apoptotic or necrotic cell death, and subsequent activation of phagocytic DCs [2]. However the distinction between apoptosis and necrosis as immunogenic or nonimmunogenic forms of cell death respectively, may be too simplistic. Recent studies have shown that apoptotic death of tumor cells by certain agents (such as anthracyclines, proteasome inhibitors, or viral infection) can be immunogenic[16-19], while necrotic cell death may impair tumor

immunity in vivo[20]. Moreover destroying the anthracycline induced apoptotic bodies by freeze thaw abolished their immunogenicity[18]. Recently, Obeid et al. identified the exposure of calreticulin (CRT) as a critical marker of immunogenicity of tumor apoptosis induced by anthracyclines and γ-irradiation [18••,21]. In these experiments, the immunogenicity of CRT appears to be linked to its capacity as an "eat me" signal, rather than as a chaperone for tumor derived peptides. The mechanism behind CRT exposure is not known but may involve phosphorylation of eukaryotic initiation factor 2α (eIF2α), as a result of unfolded protein response[18]. Another example of immunogenicity of HSP exposure came from *in vitro* studies of human myeloma. Bortezomib (a proteasome inhibitor) induces the exposure of HSP90 on the surface of dying human myeloma tumor cells [19]••. Recognition of such tumor cells by human monocyte derived DCs leads to efficient generation of anti-tumor T cells. Collectively, we propose that immunity and tolerance from cell death are dictated mechanistically not by necrosis and apoptosis, but rather by whether HSPs are exposed or not (Figure 1). Further studies are needed to better understand the mechanism of HSP exposure on dying cells and which additional signals are needed to mediate immunity to dying cells by phagocytic DCs[22]. In addition to activation of APCs, extracellular HSPs have also been implicated in activation of NK cells[23].

HSPs as carriers for damage-associate molecular patterns: a hypothesis

It remains unclear if extracellular HSPs possess unique structural moieties for recognition by innate receptors. The presence of HSPs predates the emergence of immune system in evolution. As stress proteins whose functions are primarily in accelerating protein folding and preventing protein misfolding, HSPs in the unicellular organisms can be considered as a primitive form of defense. As discussed earlier, in the steady state, HSPs in multicellular organisms are primarily confined intracellularly. In the situation of stress, they are induced and exposed to external milieu. Thus if there is a molecular definition of cell stress or danger, HSPs may fulfill such a role due to their inducibility by stress, their ability to interact with and to alarm immune cells, and their ubiquity to signal stress of all cells and all tissues. Just like microbes whose presence can be sensed by the pattern recognition receptors (PRR) on host cells, it has been argued that the pattern of stress or damage can be found in the extracellular HSPs. Since HSPs prefer to interact with hydrophobic stretches of proteins and have been found to be in complex with misfolded proteins, we argue that HSPs are the carriers of damage-associated molecular patterns (DAMP) [24] ••. We suggest that the fundamental stimuli in the immunogenic cell death are not HSPs or DAMPs, but the HSP-DAMP complex (Figure 1). We term the receptors for such a complex as DAMPRR, or DAMP recognition receptor. This hypothesis can potentially explain many conflicting data in the field and current opposing views of HSPs in innate immunity. For example, tissue-derived HSPs (containing stress peptides) are clearly immunostimulatory [2], whereas recombinant HSPs are generally not [25]. It is notable that HSPs may in addition, provide additional signals such as "eat me" signals that promote immunogenicity[18]. Overall, the "context" in which HSPs are released or prepared may have profound impact on the immunogenicity of HSPs. HSPs from stressed cells are more immunogenic than these isolated from un-stressed cells, which may explain why inducible HSPs are more immunogenic than HSPs expressed constitutively [26,27]. Improved understanding of interactions between HSPs and DAMPs may provide novel insights into autoimmunity and improving vaccines.

FcR-mediated recognition of dying cells

FcγR as a balance of activating and inhibitory receptors

Recognition of cells opsonized with antibodies is mediated in part by Fcγ receptors (FcγRs). The FcγR system represents a balance of activating and inhibitory receptors that determines

the outcome of immune complex-mediated inflammation and immunity. In human cells, the major activating receptors are FcγRI, IIa and III, while the sole inhibitory receptor is FcγRIIB. Activating receptors are characterized by an immune tyrosine activating motif (ITAM) in their cytoplasmic domain. Signaling via the activating receptors generally leads to the recruitment of signaling adaptor molecules (e.g. syk) to these receptors and downstream activation of PI3 kinase and other pathways[28] •. The net result is generally cellular activation, although it is now apparent that in some instances, some ITAM containing receptors can also mediate inhibitory signals[29]. Inhibitory Fcγ receptors contain an immune tyrosine inhibitory motif (ITIM) and inhibit signaling through the activating receptors by recruitment of phosphatases including inositol phosphatase SHIP and the tyrosine phosphatase SHP-1[28]. Most FcγR bearing cells express both activating and inhibitory receptors. Therefore, the relative engagement of activating versus inhibitory FcγRs represents a balance that determines the net cellular effects of these signals.

Role of FcγR balance in adaptive immunity

Dendritic cells (DCs) play a critical role in the induction of immunity and tolerance. Recognition, uptake and presentation of dying cells by DCs plays a critical role in immunologic consequences of cell death[30]. Uptake of opsonized cells and immune complexes depends on both Fc receptors and complement system. Several aspects of the interaction between dying cells and DCs or macrophages is altered by FcR mediated uptake. Opsonized cells taken up via FcγRs undergo reduced processing in the phagosomes, a process termed as phagosome maturation[31]. Altered degradation of antigens in DCs may facilitate both the induction of antibody responses[32] as well as T cell immunity[33]. Antigen uptake in the form of immune complexes or opsonized cells is associated with enhanced antigen presentation by DCs and the generation of antigen specific T cells[34-37]. This pathway may also be important for immunity to opsonized pathogens[38]. FcγR mediated internalization enhances not only MHC II restricted antigen presentation, but also presentation on MHC I molecules (termed cross presentation), thereby activating both CD4 and CD8+ T cell responses[35].

DCs express both activating and inhibitory Fcγ receptors, and the balance of these receptors may have a major effect on DC function[39-41••] (Figure 2). Selective blockade of the inhibitory Fcγ receptor, FcγRIIB leads to maturation of human DCs and presentation of antigens derived from phagocytosed tumor cells and immune complexes[40,42,43]. The balance of activating versus inhibitory FcγRs may also be altered by cytokines, thereby regulating FcγR mediated cross presentation[44]. In mice genetically lacking inhibitory FcγRIIB, targeting immune complexes to DCs can lead to enhanced generation of antigen specific CD8+ T cell immunity in vitro and in vivo[45,46]. Likewise, genetic deletion of FcγRIIB leads to spontaneous autoimmunity in genetically prone mice[47]. The importance of FcγRs on DCs has been further supported by recent studies showing that targeting antigen to activating FcγRs on DCs helps break tolerance in mice, while the ligation of inhibitory FcγR promotes tolerance[48,49] ••. The ability of IC to enhance antigen presentation depends on the recruitment of syk to the activating FcRs, as well as activation of PI3 kinase pathway[50,51]. FcγRs mediated activation leads to a distinct form of DC activation, including the induction of a type I interferon response program and proinflammatory cytokines[39,52]. Polymorphisms that impact the balance of activating versus inhibitory FcγRs may therefore have implications for both autoimmunity and resistance to pathogens[53]. In addition to FcγRs, the complement proteins also interact with immune complexes and opsonized cells. A recent study described a novel role for complement factor C1q in augmenting presentation of antigens from immune complexes[54]. In addition to ICs, targeting of pathogens to activating FcγRs via C-reactive protein also leads to enhanced immunity[55].

Summary

Herein, we have discussed two distinct pathways (HSPs and FcγR) that regulate the immunogenicity of dying cells. Dysregulation of these pathways, for example, by exposure of HSPs on dying cells and altered balance of activating versus inhibitory FcγRs may have implications for the development of autoimmunity. These pathways may also be useful targets for enhancing immunity to tumors and pathogens in the clinic. Targeting HSPs may in principle be accomplished both by injection of purified HSPs, as well as with drugs (such as bortezomib, anthracyclines) that induce these genes[18,19]. Similarly, FcγR signaling may impact the efficacy of anti-tumor antibodies in cancer and provide novel approaches to improve their efficacy by antibody engineering[56].

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Abbreviations

HSP	heat shock proteins
APC	Antigen presenting cells
MHC	Major histocompatibility complex
TLR	Toll like receptors
ER	Endoplasmic reticulum
CRT	calreticulin
DAMP	damage associated molecular pattern
DAMPRR	DAMP recognition receptor
ITAM	Immune tyrosine activation motif
DC	Dendritic cell
FcγR	Fcγ receptor

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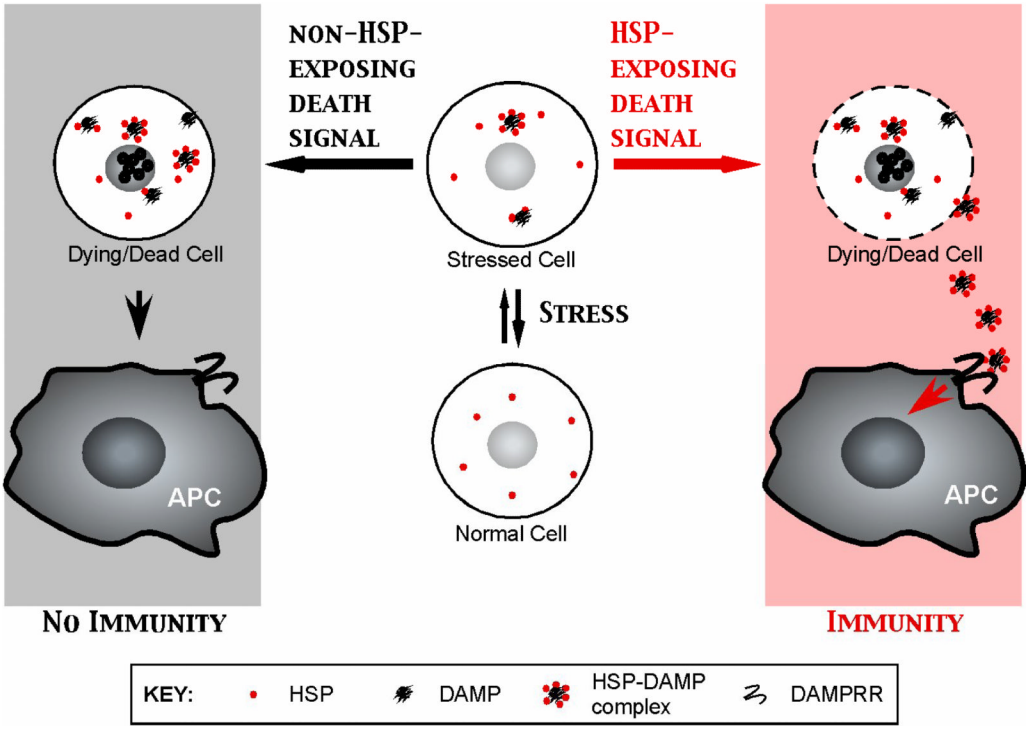

Figure 1. Exposure of HSPs dictates the immunological fate of dying cells

Intracellular HSPs patrol cells for misfolded proteins that contain DAMPs and are responsible for their refolding. After encountering HSP-exposing death signals, HSP-DAMP complexes engage DAMP recognition receptors (DAMPRR) on APCs to elicit immune response. Cells dying under conditions of no HSP exposure are rapidly cleared by APCs to achieve tissue homeostasis and do not lead to immunity, unless dying cells are presented in other proinflammatory contexts such as opsonization or viral infection (not depicted).

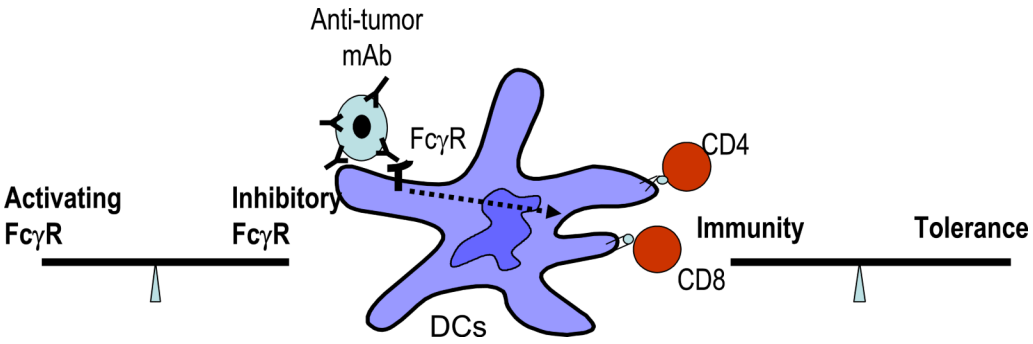

Figure 2. Balance of activating versus inhibitory FcγRs regulates immunity versus tolerance

Uptake of opsonized dying cells is mediated in part by FcγRs expressed on DCs. The balance of activating versus inhibitory FcγRs determines the activation status of DCs and resultant T cell activation. Alteration of this balance may lead to inadvertent immune activation.