

Immunogenic Cell Death

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Contributor: Michal Kielbik

Immunogenic cell death (ICD) is a type of death, which has the hallmarks of necroptosis and apoptosis, and is best characterized in malignant diseases.

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1. Introduction

Cell death is an important process that plays a great role in the development and maintaining of the homeostasis of every living organism. There are many different types of eukaryotic cell death, classified depending on morphological changes inside the cell (i.e., shrinkage of the cytoplasm, chromatin condensation, nuclear fragmentation, degradation of intracellular organelles, rupture of cell membrane); enzymological criteria (i.e., participation or not of nucleases or proteases); functional aspects (i.e., programmed, accidental, physiological, pathological); immunological character (immunogenic or non-immunogenic) . Liu et al. [1][2][3] performed literature research and counted that there are over 34 different cell death modes, among which best-known and most studied are apoptosis, necrosis, autophagy, necroptosis, anoikis and pyroptosis. The traditional process of apoptosis is a non-immunogenic one, even termed as tolerogenic cell death, that actively inhibits immune reaction [4][5]. In contrast, necrosis is uncontrolled, immunologically harmful process in which increased secretion of pro-inflammatory cytokines as well as recruitment of different immune cells leading to the development of immune responses in the tissue are observed [1][6][7][8]. Necroptosis (programed necrosis) is a regulated cell death type that mimics features of both apoptosis and necrosis and is also known to induce immune-related processes [9][10]. Apoptosis, on the other hand, under certain conditions, may occur in the way that the immune system is alerted, triggering immunity against the dying cell, which releases its cellular content into the microenvironment, that in turn leads to the recruitment and activation of immune cells. Such a form of apoptosis, which may also occur in the context of necroptosis, is called immunogenic cell death (ICD) [11]. ICD is characterized by the emission of particular molecules that induce the immune response. This kind of cell death is especially important and best characterized in malignant diseases. One of the best-known/most important molecules implicated in ICD is chaperone called calreticulin [12][13].

Calreticulin (also termed as CRT or CALR) is an endoplasmic reticulum (ER)-associated chaperone with numerous biological activities. Its functions strongly depend on cellular localization. In ER it is a main regulator of Ca^{2+} homeostasis and is also responsible for loading of cellular antigens into major histocompatibility complex (MHC) class I molecules. In cytoplasm, calreticulin is considered to be integrin activator and mediator of integrin-dependent cell adhesion [14][15][16]. Very important biological role of CRT is connected with cell death. In stressed or dying cells this chaperone is expressed on the surface of cell membrane or even release into extracellular milieu [17]. Plasma membrane CRT (also called ecto-CRT) serves as a co-stimulatory and pre-mortem ("eat-me") signals to variety of immune cells but mainly to antigen presenting cells (APCs). Moreover, ecto-CRT is one of the main hallmarks of ICD in malignant diseases. Calreticulin present on outer membrane of tumor cells not only stimulates their phagocytosis by APCs, but also activates the adaptive immune response, thus it is believed to be crucial for surveillance against tumors [18][19][20]. The role of CRT in ICD in malignant diseases have been recently widely studied on both in vitro (cell lines) and in vivo (animals, patient's tumor specimens) models. However, up to this date, available data is still scarce and highly controversial. As it has been shown in published research, ecto-CRT may be either positive or negative marker of patients/tumor cells survival, depending on type of tumor [21][22].

One of the most dangerous malignant diseases is ovarian cancer. The mortality of patients suffering from this kind of tumor is still very high in both the United States and Europe. The 5-year-survival of women with advanced ovarian cancer is very low and does not exceed 25%. There are a number of reasons for such a poor outcome. Among the most important are: late diagnosis of the disease (an overwhelming number of patients are diagnosed in the advanced stage of disease), high resistance of cancer cells to chemotherapeutics, unique metastatic properties and poor immunogenicity of

ovarian cancer cells [23][24][25]. It is considered that better identification and evaluation of immune-modulating therapeutic approaches can be one of the pathways to overcome poor prognosis of ovarian cancer patients. In this context ICD might be a promising way [24].

2. Immunogenic Cell Death—ER Stress Connection

ICD has been defined as an unique class of regulated cell death that is able to elicit complete antigen-specific adaptive immune response through the emission of particular molecules that belong to a class of the damage-associated molecular patterns (DAMPs) family [12][26]. ICD is a stressor-dependent cell death, since it is induced as an effect of ER stress combined with the generation of reactive oxygen species (ROS). In response to stress conditions, when there is accumulation of misfolded proteins, ER initiates the activation of a complex signaling pathways network, called the unfolded protein response (UPR). There are three different ER membrane-associated sensors that initiate UPR signaling pathway: protein kinase R-like endoplasmic reticulum kinase (PERK), activating transcription factor-6 (ATF6) and inositol-requiring transmembrane kinase/endoribonuclease 1 (IRE1) [27][28]. PERK is one of the major signaling pathways responsible for attenuation of mRNA translation under ER stress, preventing the influx of newly synthesized proteins into ER compartments. This type I transmembrane protein, when activated, triggers the phosphorylation of α -subunit of eukaryotic initiation factor 2 (eIF2 α), leading to the inhibition of polypeptide chain synthesis. Generally, the activity of PERK pathway may result in cell cycle arrest, and under prolonged or severe stress conditions activation of this kinase enhances the apoptosis-signaling pathway [27][29]. ATF6, a type II transmembrane protein located on the ER surface, is a basic leucine zipper transcription factor which, after exposure to stressful conditions, translocates to the Golgi complex. Over there it is cleaved by site-1 and site-2 proteases and generated fragment then translocates to the nucleus where it can up-regulate the expression of genes encoding proteins involved in the UPR, including ER chaperones and transcription factor X-box-binding protein 1 (XBP1). IRE1, a type I transmembrane protein, after oligomerization and autophosphorylation, activates XBP1, which further induces the expression of UPR stress genes [27][28][30]. During prolonged stress exposure, IRE1 was also considered to be a key initiator of ER stress-induced cell death, as it interacts with tumor necrosis factor receptor associated factor 2 (TRAF2). This leads to the activation of apoptotic-signaling kinase-1 (ASK1), which induces downstream kinases: Jun-N-terminal kinase (JNK) and p38 mitogen activated protein kinase (MAPK), and in consequence promote apoptosis [29][31].

ICD has been well characterized in the context of tumor therapy, as its induction is one of the mechanisms, by which conventional chemotherapeutics can kill tumor cells. However, there is a range of specific stimuli that can initiate ICD. Among them are: (a) obligatory intracellular pathogens, including numerous bacterial and viral species; (b) conventional chemotherapeutics, such as anthracyclines, some DNA-damaging agents, proteasomal inhibitors, poly-A-ribose polymerase inhibitors or mitotic poisons; (c) anti-cancer agents that target different types of cell components or processes inducing cell death pathways; (d) various oncolytic potential molecules, i.e., viruses; (e) some chemicals; (f) physical stressors, such as ionizing radiation, hypericin-based photodynamic therapy, high hydrostatic pressure, nanopulse stimulation or severe cytotoxic heat shock [19][32][33].

Generally, based on their different mechanisms of action involved in ER stress, ICD inducers are divided either into type I or type II. Type I inducers initiate ER stress indirectly, as a downstream effect, while type II inducers can directly launch the ER stress response, provoking cell death [26][34]. Among the type I inducers are the best-known anti-cancer drugs, such as anthracyclines (doxorubicin, mitoxantrone), taxanes (paclitaxel, docetaxel), gemcitabine, cyclophosphamide, fluorouracil (5FU), and alkylating agent melphalan. Platinum derivatives such as cisplatin and carboplatin are believed to be controversial and their effectiveness to resolve ICD depends on the type of tumor cells, concentration used and treatment duration. In contrast, oxaliplatin, a third-generation platinum analogue, seems to be indisputable type I ICD inducer. On the other hand, physical methods, such as photodynamic therapy, high hydrostatic pressure or molecules as oncolytic viruses are the example of type II inducers [30][35][36][37]. Both types of inducers, by the combined action of ER stress and ROS generation which activates danger signaling pathways, are able to trigger the timely release or membrane exposure of a series of DAMPs. These endogenous danger molecules interact with a range of scavenger receptors (i.e., LDL receptor-related protein, LRP1/CD91), purinergic receptors (i.e., P₂RX₇/P₂RY₂) and pattern recognition receptors (PRR, i.e., Toll-like receptor 4—TLR4) on the innate immune cells, such as monocytes, neutrophils, macrophages or dendritic cells (DCs) [38].

Since the introduction of the danger model in 1994 [39], numerous DAMPs have been identified, and still the new ones are characterized. DAMPs are molecules that can be released, both, from extracellular matrix and intracellular compartments (ER, nucleus, cytosol, plasma membrane, mitochondria) as the response of dying cell [40]. The overall role of ICD-associated DAMPs involves: facilitating the recruitment of APCs or their precursors to the site of ICD; guiding the interaction between dying cell and APCs; triggering the phagocytosis of dead cells or their leftovers; promoting the

maturation of APCs and their ability for effective antigen cross-presentation or enabling the recruitment of T-cells [49]. Among DAMPs most frequently associated with ICD are CRT, adenosine-5'-triphosphate (ATP), non-histone chromatin-binding protein—high-mobility group box 1 (HMGB1), type I and II interferons (IFN), annexin A1 and heat shock proteins (HSPs) 70 and 90. The majority of these molecules have non-immunogenic functions inside cell, but when exposed on cell surface or released extracellularly they become immunogenic [22][35][36].

Calreticulin will be thoroughly described in the next chapter of this manuscript. ATP, under physiological conditions, is involved in various cellular metabolic processes and intracellular responses, but during apoptosis its releasement from dying cell occurs in autophagy-dependent manner. The presence of ATP in extracellular space acts as “find me” signal, being a chemoattractant for DCs precursors. ATP binds to the P₂RX₇ receptor on DCs, providing the inflammasome-mediated secretion of interleukin 1 β (IL-1 β), an important cytokine that plays crucial role in immune response development [41]. Another DAMP triggered by ICD is HMGB1, normally found in the nucleus (but with cytoplasmic localization due to shuttling), that serves various nuclear and cytosolic functions. HMGB1 is released from dying or stressed cells and when present in the extracellular space, can signal tissue injury. Through binding to a range of receptors, including TLR2, TLR4 and the receptor for advanced glycosylation end products (RAGE), this molecule can initiate the inflammatory response. However, it should be stressed that TLR4 seems to be the exclusive HMGB1 receptor and it is relevant in the context of considering cell death as immunogenic. HMGB1-TLR4 triggers the synthesis of pro-inflammatory cytokines, such as type I IFN. Furthermore, this signal is crucial for activating DCs and facilitating antigen presentation to T cells [7][32][42]. Next markers principally associated with ICD are HSP70 and HSP90. These chaperones, present in the cytoplasmic compartment, are involved in protein folding and can be upregulated to express protective response to stress conditions, such as heat shock. Moreover, both HSPs may be exposed on the cell membrane and act as “eat me” particles, attracting phagocytes and natural killer (NK) cells [30]. Moreover, HSP70 and HSP90 play important role in the cross-presentation of tumor-derived antigenic peptides on MHC class I molecules, providing the cytotoxic T lymphocytes (CTLs, CD8⁺) response [7].

The development of anti-tumor immune response, initiated by ICD, involves a few important steps: (1) induction of ICD by the exposure of tumor cell to specific ICD inducers; (2) changes inside the tumor cell, leading to ER stress; (3) chronic release and membrane exposure of DAMPs, especially CRT, HMGB1, HSP70, HSP90 and ATP; (4) recognition of DAMPs by particular PRR on APCs, mainly on DCs; (5) activation and maturation of DCs; (6) promotion of dying tumor cell engulfment by mature DCs; (7) processing of tumor-derived antigen specific cargoes inside DCs; (8) triggering T-cell immune response by tumor antigen presentation along with MHC I and costimulatory molecules, especially to CTLs; (9) killing of tumor cells. Each step can be amplified by the action of specific DAMPs [22][35][43]. Moreover, during and after the induction of ICD in malignant cells, numerous cytokines and chemokines are identified, for example pro-inflammatory cytokines such as IL-6, IL-1 β or tumor necrosis factor α (TNF- α), which can increase the MHC class I expression on APCs, promote T cell differentiation and NK cell activation. Furthermore, activated DCs, release IL-12 that enhances the functionality of NK cells. On the other hand, tumor cells treated with ICD inducers also secrete immunomodulatory cytokines as IL-8 or IL-6 [30] (Figure 1).

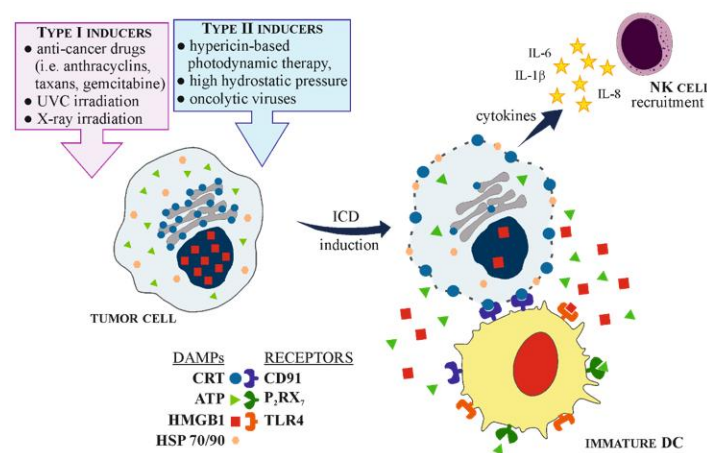


Figure 1. Schematic presentation of immunogenic cell death (ICD) mechanism. (a) ICD is induced after the exposure of tumor cell to type I or type II ICD inducers. Dying tumor cell releases and exposes on its plasma membrane different damage associated molecular patterns (DAPMs) molecules that are recognized by specific pattern recognition receptors (PRRs) on immature dendritic cells (DCs), leading to their maturation and activation. Additionally, tumor cells secrete cytokines that recruit natural killer (NK) cells. (b) Mature DC engulfs dying tumor cell, processes tumor antigens and

presents it along with major histocompatibility complex (MHC) class I and costimulatory molecules (CD83/86) to CD8⁺ T-cells. Moreover, mature DCs secrete a range of cytokines that promote T-cells differentiation into CD8⁺ phenotype, as well as activate NK cells. Finally, activated NK cells and CD8⁺ T-cells are able to kill tumor cells.

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