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Mechanisms of programmed cell death

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The present volume of *Immunological Reviews* deals with the mechanisms of programmed cell death, obviously from an immunological perspective. What are the consequences of cell death on the organism and, in particular, on the immune recognition of stressed and dying cells? The long-distance effects of therapeutic manipulations resulting in the death of cancer cells are surprisingly vast, as this has been documented for the treatment with clinically approved or experimental chemotherapeutic agents. For example, cell death can cause neuropathic pain through mechanisms of neuroinflammation.¹ In addition, cell death induction can result in the production of Type I interferons by tumor cells that then mediate ambiguous adaptive responses ranging from an enhancement of cancer cell stemness and exhaustion of anticancer immune response within the tumor microenvironment to the stimulation of anticancer immune responses. Type I interferon can even trigger a systemic sickness response ranging from flu-like symptoms to a state of depression.² Such long-range effects of cell death are certainly also relevant to the pathophysiology of viral infections.

If induced in an appropriate fashion, one of the major positive effects of cancer cell stress and death is the induction of immune responses against tumor-associated antigen, thus sensitizing tumors to immunotherapy with immune checkpoint inhibitors.³⁻⁵ This has important therapeutic implications because chemotherapeutics that induce immunogenic cell death can be used as first-line treatments to sensitize major cancer types (exemplified by KRAS-mutated colorectal cancer, non-small cell lung cancer and triple-negative breast cancer) to subsequent immunotherapy with antibodies targeting

cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), or PD-1 ligand-1 (PD-L1), as this has been confirmed in several clinical trials.

Of note, there are multiple different subroutines of cell death, and several if not all of them can be immunogenic, as this has been documented for apoptosis (which involves mitochondrial membrane permeabilization and the activation of caspases 3 and 7)^{2,3} but also for necroptosis (with the implication of specific effector molecules including receptor-interacting kinase 3 (RIP3) and mixed lineage kinase domain-like pseudokinase (MLKL1)),⁶ pyroptosis (involving inflammasome/caspase-1-mediated activation of pore-forming gasdermins),⁷ a mixture of pyroptosis, apoptosis, and necroptosis dubbed PANoptosis,⁸ ferroptosis (involving lethal membrane damage by peroxidation),^{9,10} and cuproptosis (due to copper-induced aggregation of lipoylated dihydrolipoamide S-acetyltransferase).¹¹ In all cases, cell death can be preceded by immunogenic stress that favors the emission of danger-associated molecular patterns (DAMPs) appearing on the surface of the cells or secreted into the extracellular space. It is the sum of stress-associated DAMPs (that are surface-exposed or released before cells disintegrate) and that of death-associated DAMPs (that become accessible or are passively released when the plasma membrane and internal membrane of cells become permeable) that dictates the immunogenicity of cell death and hence the capacity of the immune system to detect dead cell antigens. Such antigens can be microbial (for instance in the context of infection by viruses or intracellular bacteria), tumor-associated, or autoantigens.

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Immunogenic cell death is not only induced by drugs but can also occur in the context of radiation therapy,¹² photodynamic, and photothermal therapy,¹³ as well upon infection by microbes including oncolytic viruses.¹⁴ Logically, attempts are underway to create novel galenic formulation including nanoparticle-based drug delivery systems to administer drugs that induce immunogenic cell death in tumors, yet do not mediate any systemic effects.^{13,15} Interestingly, cell death of cancer cells can be accompanied by the release of nanoscale extracellular vesicles dubbed exosomes that constitute potential biomarkers of ongoing cell death events and establish short- and long-distance communication with neighboring cells and distant tissues.¹⁶ As a possibility, such exosomes might be engineered for the nanodelivery of therapeutic agents.

When cells undergo immunogenic stress and death, they interact primarily with dendritic cells,¹⁷ in particular with Type-1 conventional dendritic cells (cDC1) that appear to be particularly competent in eliciting responses against dead cell antigens.¹⁸ Dendritic cells can be loaded with stressed and dying cancer cells and then be used as prophylactic or therapeutic vaccines.¹⁷ Moreover, dendritic cells can be manipulated pharmacologically to enhance their capacity to present tumor antigens to T cells.¹⁸ Such dendritic cells educate cytotoxic T lymphocytes to recognize and lyse malignant cells. Importantly, this process of T-cell-mediated cytotoxicity can elicit immunogenic cell death, hence amplifying the phenomenon and protracting the anticancer immune response.¹⁹ However, cell death affecting immune cells may play down such a desirable immunosurveillance. Specifically, it appears that dying neutrophil granulocytes produce so-called neutrophil extracellular traps (NETs) that shield cancer cells from cytotoxic immunity, hence impairing their clearance.²⁰ Moreover, dying neutrophils can stimulate unwarranted inflammatory and autoimmune responses.²¹

Altogether, this volume of *Immunological Reviews* illustrates to which extent different cell stress and death modalities affecting malignant cells, pathogen-infected cells, or immune cells can elicit innate and cognate immune responses with vast consequences for whole-body physiology. It appears that processes that for long have been studied exclusively by cell biologists have acquired a major immunological dimension that already yields tangible impact with respect to the clinical management of malignant diseases. Future will tell whether the knowledge generated in this field will also contribute to the prevention and treatment of infectious and autoimmune diseases.

CONFLICT OF INTEREST STATEMENT

The authors declare no relevant conflicts of interest.

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