

## Editorial

# The immune response against dying tumor cells: avoid disaster, achieve cure

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Metazoans are engaged in a constant combat against infectious microorganisms as well as in a perpetual strive for cohesion of the multicellular ensemble. Paradoxically, one of the most primitive antimicrobial responses consists of the sacrifice via programmed cell death (PCD) of infected cells; a response that is found in all metazoan phyla including plants (which do not possess any mobile cells and hence lack an immune system). In mammals, microbial invasion does not only trigger PCD of infected cells but also elicits an immune reaction, which is hierarchically organized in the first-line response by innate immune effectors (that is infiltrating phagocytes and killer cells) and later recruitment of cognate immune effectors (that is T- and B lymphocytes). Innate immune effectors recognize pathogens, pathogen-infected cells, as well as pathogen-induced cell stress and cell death to eliminate the pathogen (and the infected cell) and to generate a protective immunological memory.

One major challenge for the regulation of the immune system (and its comprehension by immunologists) is to distinguish 'normal' PCD as it occurs in development and tissue homeostasis from pathogen-induced PCD. Homeostatic PCD should not cause inflammation and should not trigger a cognate immune response (because this would cause autoimmune disease), while pathogen-induced PCD must activate an immune response (first innate and then cognate) to avoid illness and organismal death. As a result, during evolution animals have accumulated a perplexing variety of receptors, which are expressed on the surface or within the cytoplasm of innate immune effectors. These receptors recognize the so-called pathogen-associated molecular patterns (PAMPs). As a simple equation, cell death without PAMPs fails to induce an immune response, while cell death that is accompanied by the activation of PAMP receptors, which detect microbial products, does alert the immune system.

Nonetheless, the above equation is complicated by the fact that the immune system has an additional, frequently neglected function; it has to eliminate mutated, potentially tumorigenic cells, a process that is called 'immunosurveillance'.

Two major barriers usually avoid the malignant transformation of cells in the human body. First, activation of oncogenes ('oncogenic stress') often stimulates a DNA damage response that finally culminates in PCD (either through direct apoptosis or after senescence) and hence elimination of the mutated cells. Second, the immune system recognizes transformed cells, based on the tumor-specific expression of abnormal (mutated or ectopic) molecules, as well as on the abnormal behavior of (pre-)neoplastic cells that respond to oncogenic stress. This implies that, in addition to PAMPs, the so-called 'danger-associated molecular patterns' (DAMPs) can trigger the immune response. Efficient recognition of cell death associated with DAMPs is hence important for immunosurveillance.

Recently, it has been discovered that chemotherapy-induced cell death can also, at least in some cases, elicit an immune response against dying tumor cells.<sup>1–3</sup> This immune response is actually required for an optimal therapeutic effect of anticancer chemotherapy. At least in some malignancies, patients that bear major immune defects (including in receptors recognizing specific DAMPs) have a particularly negative prognosis.

Thus, immune response elicited by tumor cells that spontaneously undergo apoptosis can abort incipient tumors during immunosurveillance. In addition, immune responses can be triggered by treatment-induced tumor cell deaths, thereby contributing to the therapeutic efficacy of chemotherapy or radiotherapy.

The present series of reviews attempt to decipher the intricate interplay between tumor cell death (as it occurs spontaneously in response to chemotherapy or in response to immune effectors), the first-line response of phagocytic cells (in particular, macrophages and dendritic cells) to dying tumor cells, as well as the second-line response of lymphocytes that are instructed to mount a productive or abortive immune response. In this combinatorial game, PCD may affect the tumor cell, the phagocytic cells as well as the tumor-specific T lymphocyte, in a lethal waltz that ultimately determines the fate of the tumor-bearing host. This is the topic of this

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compendium of reviews in which the following specific questions will be addressed:

- What are the DAMPs that tumor cells expose or secrete in response to oncogenic or chemotherapeutic stress and death?<sup>1</sup>
- Which is the spatiotemporal code of DAMP exhibition/secretion that renders tumor cell death immunogenic?<sup>1–3</sup>
- What are the chemotherapeutic agents that provoke immunogenic cancer cell death and through which mechanisms do they operate?<sup>1,2</sup>
- How do macrophages and dendritic cells recognize and engulf cells that succumb to apoptosis or necrosis?<sup>4</sup>
- What are the specific requirements of tumor cell death and DAMPs to allow dendritic cells to present tumor antigens to T-cells and to elicit an anti-tumor immune response?<sup>5</sup>
- What are the specific characteristics of killer dendritic cells, a fascinating population of cells that may actively kill tumor cells, phagocytose them, and finally present tumor antigens to T-cells?<sup>6,7</sup>
- What is the impact of T-cell death on the regulation of the system? Do cancers induce T-cell death to avoid immunosurveillance? Through which strategies can T-cell

death be suppressed to improve the anti-tumor immune response?<sup>8</sup>

- Do tumor-derived products such as exosomes subvert the anti-tumor immune response? Is it possible to improve anti-cancer therapies by neutralizing the tumor-dependent immunosuppression?<sup>9</sup>

We are confident that the interested reader will find (partial) answers to these important questions in the accompanying special issue of *Cell Death & Differentiation*. More importantly, we anticipate that the full comprehension of this topic – and its translation into human medicine – will eventually improve the clinical management of cancer.

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