L-7 The desirable death .... of the cancer cell

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The supreme goal of anticancer therapy is the induction of tumor cell death. Physiological cell death, which occurs as a continuous byproduct of cellular turnover, is non-immunogenic or even tolerogenic, thereby avoiding autoimmunity. However, cancer cell death elicited by radiotherapy and some chemotherapeutic agents such as anthracyclines and oxaliplatin can be immunogenic. Immunogenic death involves changes in the composition of the cell surface, as well as the release of soluble immunogenic signals that occur in a defined temporal sequence. This 'key' then operates on a series of receptors expressed by dendritic cells (DC, the 'lock') to allow for the presentation of tumor antigens to T cells and for the initiation of a productive immune response. Immunogenic cell death is characterized by the early cell surface exposure of calreticulin, which determines the uptake of tumor antigens by DC. The late release of the protein high mobility group box 1 (HMGB1), which acts on toll-like receptor 4 (TLR4), is required for the presentation of antigens from dying tumor cells. In addition, the release of ATP from dying cells causes the P2RX7 purinergic receptor-dependent activation of the NLRP3 inflammasome in dendritic cells, thereby allowing them to release interleukin-1ß and to polarize tumor antigen-specific CD8 T cells towards a Tc1 cytokine pattern. We postulate that the immune system determines the long-term success of anti-cancer therapies, and that this immune response is dictated by immunogenic tumor cell death. Hence we formulate two predictions: First, therapeutic failure can result from failure to undergo immunogenic cell death (rather than cell death as such). Thus, agents that fail to induce immunogenic cell death cannot yield a long-term success in cancer therapy. Moreover, tumors that are intrinsically unable to undergo immunogenic cell death are incurable. Importantly, it appears that mitochondrial events determine whether cancer cells die or not in response to chemotherapy, while an endoplasmic reticulum stress response determines whether this cell death is perceived as immunogenic. Second, therapeutic failure may result from subtle immune defects that compromise the immune system's capacity to perceive immunogenic cell death signals and/or to generate anti-cancer immune effectors. Indeed, we have found that loss-of-function alleles (that affect TLR4 or P2X7 receptors in the Caucasian population) can reduce the efficacy of conventional anti-cancer therapies, in anthracylin-treated breast carcinoma and oxaliplatin-treated colon cancer. In light of these postulates, the desirable death of a tumor cell is an immunogenic one.