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REVIEW ARTICLE

Immunogenic effects of chemotherapy-induced tumor cell death

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Abstract Emerging evidence suggests that the clinical success of conventional chemotherapy is not solely attributed to tumor cell toxicity, but also results from the restoration of immunosurveillance, which has been largely neglected in the past preclinical and clinical research. Antitumor immune response can be primed by immunogenic cell death (ICD), a type of cell death characterized by cell-surface translocation of calreticulin (CRT), extracellular release of ATP and high mobility group box 1 (HMGB1), and stimulation of type I interferon (IFN) responses. Here we summarize recent studies showing conventional chemotherapeutics as ICD inducers, which are capable of modulating tumor infiltrating lymphocytes (TILs) and reactivating antitumor immunity within an immuno-suppressive microenvironment. Such immunological effects of conventional chemotherapy are likely critical for better prognosis of cancer patients. Furthermore, combination of ICD-inducing chemotherapeutics with immunotherapy is a promising approach for improving the clinical outcomes of cancer patients.

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Introduction

Cancer was previously thought to be a cell-autonomous disease. This cancer cell-centric perspective has been significantly modified recently by incorporation of the concept of immunosurveillance, largely due to the recent success of immunotherapy with immune checkpoint blockers (ICBs).[1–4] It is now clear that naïve tumor cells can be effectively eliminated by the immune system except for those that successfully dodge the immune attack and establish an immunosuppressive microenvironment.[1,2,5,6] During this process, tumor cells initiate pathological manifestations and eventually become malignant.[1,2] Such an evolutional process has been delineated by studies of immuno-competent syngeneic tumor models, in which the immune system protects the host from oncogenesis and shapes the immunogenicity of progressive tumors.[1] The highly dynamic immunosurveillance process comprises three phases: (1) removal of emerging tumor cells by the immune system (elimination); (2) failure of the elimination phase, leading to tumor dormancy (equilibrium) and the development of immunogenic stress that shapes genetically vulnerable tumors (editing); and (3) selection of tumor cell variants that cannot be recognized or eliminated by the immune system (escape).

Compromised immunosurveillance in the tumor microenvironment

Tumor development is not only driven by activation of oncogenes and inactivation of tumor suppressors, but also by alterations in the tumor microenvironment (TME), as indicated by altered density and composition of immune infiltrates in tumors.[7] The elimination and equilibrium phases of immunosurveillance are mediated by cytotoxic T lymphocytes (CTLs), type I helper (Th1) CD4+ T lymphocytes, and natural killer (NK) cells. The escape phase is characterized by diminishing of immune infiltrates and accumulation of cells that suppress anticancer immunity, such as regulatory T cells (Tregs) and immunosuppressive myeloid cells.[8] These alterations reflect the ability of tumors to generate immunosuppressive signals and foster immunosuppressive cells in the TME.

In anticancer immune response, CTLs utilize T cell receptor (TCR) and CD8 to recognize antigens presented by major histocompatibility complex (MHC) class I molecules on the plasma membrane of tumor cells, leading to release of perforin-1 (PRF1) and granzyme B to induce cytotoxicity.[9] CTLs also suppress tumor growth by releasing interferon γ (IFNγ), an immuno-stimulatory cytokine.[10] Th1 CD4+ T lymphocytes recognize antigens presented by MHC class II molecules on the plasma membrane of target cells through TCR and CD4, and release a variety of immunostimulatory cytokines such as IFNγ and interleukin-2 (IL-2).[11] Upon the activation of NK cells, cancer cells lose inhibitory signals and present ligands to NK cell-activating receptors including CD226 and KLRK1 (killer cell lectin-like receptor subfamily K, member 1).[12] CTLs and Th1 CD4+ T lymphocytes are actively involved in local immunosurveillance, while NK cells primarily defend against tumor metastasis.[12] Under the immunological stress from CTLs, target cells lose the expression of MHC class I molecules and become vulnerable to NK cells. An optimal TME is infiltrated by a mixture of CTLs, Th1 CD4+ T lymphocytes and NK cells.

An effective antitumor immune response is often triggered by a combination of lymphocytes and a subset of dendritic cells (DCs).[13,14] CD8α+CD134 + DCs first engulf fractions of cancer cells, process them, and then present tumor-associated antigens to CTLs, leading to cross-priming of CD8+ T cells and anticancer immunity.[15] In addition, DCs have a crucial immuno-modulatory effect on Th1 CD4+ T lymphocytes and NK cells.[16] Accumulating evidence suggests that reactivation of immunosurveillance is critical for better prognosis and improved patient survival, which can be achieved by using agents that induce immunogenic cell death in tumor cells.

Immunogenic cell death in cancer cells

Immunogenic cell death (ICD) is a type of tumor cell death which primes an anticancer immune response.[17] A variety of chemotherapeutic agents can induce ICD, as indicated by the alterations in TIL abundance and composition, which is a marker of favorable prognosis.[7] For example, in response to anthracyclines or oxaliplatin treatment, breast and colorectal cancer patients have increased numbers of TILs and higher ratio of CD8+ CTLs *vs.* FOXP3+ Tregs, leading to favorable therapeutic response.[18–22] ICD is defined by two criteria. First, tumor cells succumbing to ICD *in vitro* without any adjuvant can trigger antitumor immunity that protects mice against a subsequent challenge with live tumor cells of the same type.[17] Second, ICD induced *in vivo* can stimulate local antitumor immunity, which is characterized by attracting immune effector cells into the TME, leading to tumor suppression that at least partially relies on the immune system.[23,24] In response to ICD-inducing chemotherapeutics, tumor cells expose CRT on cell surface prior to death, and release damage-associated molecular pattern (DAMP) molecules such as ATP during apoptosis or HMGB1 upon secondary necrosis. These DAMPs stimulate the recruitment of DCs into the tumor bed, the uptake and processing of tumor antigens, and the optimal antigen presentation to T cells. Cross-priming of CD8+ CTLs is triggered by mature DCs and $\gamma\delta$ T cells in an IL-1β- and IL-17-dependent manner. Primed CTLs then elicit a direct cytotoxic response to kill remaining tumor cells through the generation of IFN-γ, perforin-1 and granzyme B (Fig. 1). Therefore, the hallmarks of ICD include calreticulin (CRT) plamsa-membrane translocation, extracellular ATP and/or HMGB1 release, and stimulation of type I interferon (IFN) responses.[25–28]

Cell-surface CRT as a key pro-phagocytic signal

ICD induced by chemotherapeutics often involves endoplasmic reticulum (ER) stress, which promotes translocation of CRT from ER lumen to the outer leaflet of plasma membrane.[29,30] This occurs prior to membrane exposure of phosphatidylserine (PS), a marker of apoptosis.[30] Upon treatment with the ICD-inducing chemotherapeutics such as anthracyclines or oxaliplatin, ER stress is initiated through

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