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Mini-review

Anthracyclines potentiate anti-tumor immunity: A new opportunity for chemoimmunotherapy

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ABSTRACT

Anthracyclines are a class of drugs, including doxorubicin, epirubicin and idarubicin, used in cancer chemotherapy which are derived from *Streptomyces* bacterium *Streptomyces peucetius* var. *caesius*. Traditionally, substantial pieces of evidence have demonstrated that anthracyclines could harness the host immune system to prevent cancer progression. But nowadays, researches also implied that anthracyclines could sensitize tumor cells to immune cell driven cytotoxicity, like dendritic cells and CD8+ T cell. The ability of anthracyclines in tumor immune cycle, including trigger direct tumor cell death, enhance immune effector cell activation and eliminate immunosuppressive myeloid-derived suppressor cells (MDSCs), explained its capacity to relieve tumor induced immunosuppression and restore anticancer immune responses. And current pre-clinical and clinical trials implied that combination therapies using anthracyclines with immunotherapy have further enhanced the clinical benefit. Here, we discuss how the increased understanding of the immune-driven effects of anthracyclines prompts the design of relevant cancer chemoimmunotherapy strategies.

Introduction

Anthracyclines (ANT) are a class of drugs, including doxorubicin (DOX), epirubicin (EPI) and idarubicin (IDA), which were initially described in 1963 as antibiotics, derived from *Streptomyces* bacterium *Streptomyces peucetius* var. *caesius*. ANT exhibit stronger efficacy in anticancer therapy for many years and now have a vital role in the treatment of leukemia, lymphoma, uterine, ovarian, and breast malignancies [1–3]. The major anti-tumor mechanisms was inhibition of DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand, thus preventing the replication of rapidly growing cancer cells [4]. Beyond the cytotoxic properties, current studies have reported that ANT have the capacity to boost the host's immune system to improve the efficacy of chemotherapy, and in some instances even to evoke protective immune cell responses, thus facilitating tumor eradication [5,6]. Accordingly, after exposure to ANT contained neoadjuvant chemotherapy, breast cancer residual specimen appeared highly infiltrated by cytotoxic T cells, with a concomitant reduction of B lymphocytes and Th2 cells [7,8]. And higher proportions of infiltrating cytotoxic T cells predict the pathological responses to neoadjuvant anthracycline-based chemotherapy and overall survival in locally advanced breast cancer [9,10]. Current preclinical and clinical trials implied that combination therapies using anthracyclines with immunotherapy have further enhanced the clinical benefit. Here, we discuss the immune response evoked by anthracyclines and analyze the influence on cancer immunotherapy.

Cancer immunomodulation by anthracyclines

Anthracyclines (ANT), like most chemotherapy agents, are endowed with intrinsic immunosuppressive properties owing to the fact that they preferentially kill rapidly proliferating cells [11]. The understanding of cancer microenvironment has a crucial role in the response of cancer cells to therapy, and with the continuously increasing interest in chemotherapy, several off-target and cancer cell-exogenous immune mechanisms have been discovered that contribute to the efficacy of ANT [12] (Fig. 1).

Anthracyclines enhance tumor immunosurveillance

ANT triggered the translocation process of intracellular calprotectin (CRT) to the cell surface, serving as an 'eat me' signal for adjacent immune cells, and induced cancer cells' immunogenic death [13,14]. ANT also stimulate the rapid production of type I interferons (IFNs) by malignant cells after activation of the endosomal pattern recognition receptor Toll-like receptor 3 (TLR3)

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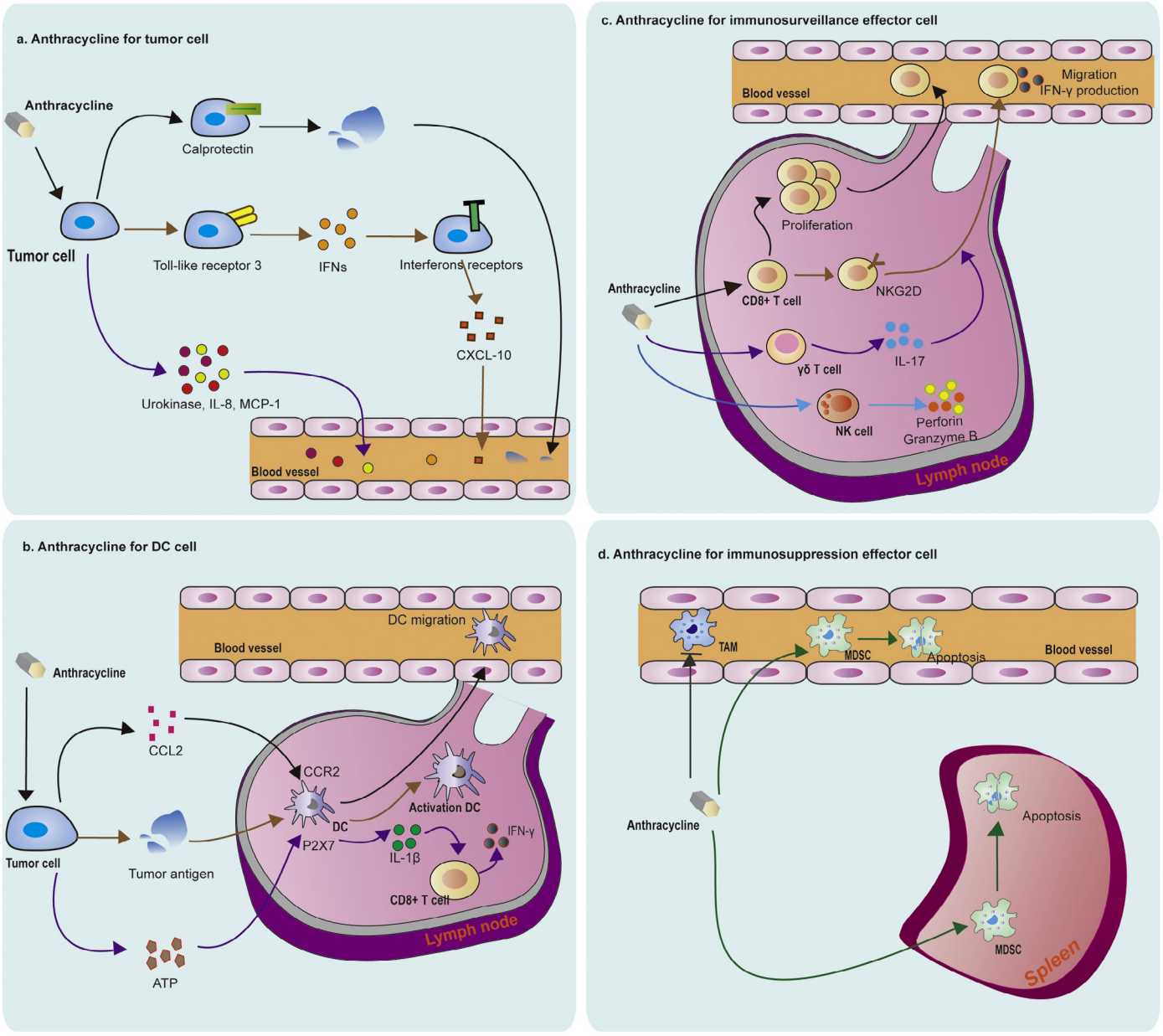

Fig. 1. Immunomodulation by anthracyclines in cancer microenvironment. (a) Anthracyclines directly kill cancer cells that release tumor antigens, or promote their product cytokines, to trigger immune response. (b) Aracyclines can recruit and activate APCs (dendritic cells). (c) For effect immune cells, aracyclines recruit and promote CD8+ T cells product INF-γ, IL-17 and granzyme B to inhibit tumor progression. (d) Aracyclines selectively eliminate Myeloid-derived suppressor cells (MDSCs) by ROS pathway triggering apoptosis.

[15]. By binding to IFN-α and IFN-β receptors (IFNARs) on neoplastic cells, type I IFNs trigger autocrine and paracrine circuitries that results in the release of chemokine (C–X–C motif) ligand 10 (CXCL10) [16]. ANT induced human small lung cancer cells producing urokinase, IL-8 and monocyte chemoattractant protein 1 (MCP-1) by activating gene expression. Those chemokines are the major chemoattractants for neutrophils and monocytes/macrophages; therefore, extensive induction of IL-8 and MCP-1 may provoke the interaction between inflammatory/immune cells and tumor cells under ANT stimulation and influence many aspects of tumor cell biology [17]. In turn, stimulation and presumably strengthen the antitumor effects of ANT, at least early during the course of chemotherapy.

What is more, ANT-based chemotherapy promotes the recruitment of (presumably blood-borne) myeloid cells, including cells with a dendritic cell-like phenotype that mediate antigen presentation into the tumor bed, but not into lymphoid organs, depending on the CCL2/CCR2 signaling axis [18,19]. ANT agents may indirectly activate dendritic cells (DCs) by inducing the release of 'danger' signals from dying tumor cells. Furthermore, ANT induced cancer cell death to release ATP, which acts on P2X7 purinergic receptors from dendritic cells (DCs) and triggers the NOD-like receptor family, pyrin domain containing-3 protein (NLRP3)-dependent caspase-1 activation complex ("inflammasome"), allowing for the secretion of interleukin-1β (IL-1β). Then IL-1β priming tumor antigen-specific CD8+ T cells produce interferon-γ (IFN-γ) to eradicate established tumors [15,20].

Beyond that, ANT could enhance the proliferation of CD8+ T cells in the tumor-draining lymph nodes and increased the expression of Natural killer group 2 member D receptor (NKG2D) in CD8+ T

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