DC vaccine generated by ALA-PDT-induced immunogenic apoptotic cells for skin squamous cell carcinoma

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ABSTRACT
Dendritic cell (DC) vaccines were generated by apoptotic squamous cell carcinoma (SCC) cells induced by 5-aminolevulinic acid (ALA)-mediated photodynamic therapy (PDT). ALA-PDT-DC vaccine inhibited the growth of SCC in mice, indicating that immunogenic apoptotic cells can activate an effective antitumor adaptive immunity and lead to a DC vaccine-based cancer immunotherapy.

We studied the effect of ALA-PDT on host immune system. ALA-PDT induced apoptosis, inhibited SCC growth, and reduced tumor volume. The numbers of DCs, CD4+ and CD8+ T cells distributed in the tumor tissues increased gradually after ALA-PDT. In addition, there was a marked increase in TNF-α expression after treatment.

We further investigated the effect of ALA-PDT-induced apoptotic tumor cells on potentiating maturation of DCs. We studied the effect of ALA-PDT on host immune system. ALA-PDT induced apoptosis, inhibited SCC growth, and reduced tumor volume. The numbers of DCs, CD4+ and CD8+ T cells distributed in the tumor tissues increased gradually after ALA-PDT. In addition, there was a marked increase in TNF-α expression after treatment.

We also developed a DC vaccine using ALA-PDT-treated apoptotic tumor cells and used the DC vaccine against SCC tumors in mice. The observed protection against tumor growth by the DC vaccine at the challenge site showed successful priming of the adaptive immune system. In contrast, although freeze-

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Auto-commentary
Failure of the host immune system for cancer immunosurveillance is recognized as one of the key factors for both cancer occurrence and metastasis. Ideal anticancer therapies are expected to not only kill tumor cells directly, but also induce systemic antitumor immunity. The majority of current anticancer regimens mediate killing of the target cells by activating apoptosis. In a ‘classical’ sense, apoptosis is often considered to be an immunologically ‘silent’ or even an immunosuppressive cell death process. However, recent studies indicated that some cancer therapies, such as chemotherapy, radiotherapy, and hypericin-mediated PDT, could lead to apoptosis in an immunogenic fashion and these dying tumor cells often release or expose damage-associated molecule patterns (DAMPs) as ‘immunogenic signals’, inducing an effective antitumor immune response.

To induce effective antitumor immune responses, killed cells must be distinguished from normal cell death processes, and recognized as the ‘altered selves’ by the immune cells that provide innate immunity. DCs are the major link between the innate and adaptive immune systems, considered as the most professional antigen-presenting cells (APCs), since they are crucial in the uptake, transport, processing, and presentation of antigens to T cells, leading to induction of tumor-specific immune responses. It was recently reported that DC-based vaccines obtained through stimulation of DCs by ex vivo prepared tumor antigens enhanced therapeutic antitumor immune responses.

Topical ALA-mediated PDT, ALA-PDT, is a novel therapeutic modality widely used to treat actinic keratosis, Bowen’s Disease, superficial skin SCC, and other cancers and precancerous skin diseases with the advantages of minimal invasiveness, great aesthetic outcomes, low morbidity, minimal functional disturbance, and high-level tolerance.

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thawed SCC cells were able to activate DCs to express IFN\(\gamma\) and IL-12, which are critical to the development of a cellular immune response, they failed to generate an effective DC vaccine to resist tumor challenge.\(^{10}\) This may be due to the fact that F/T-DCs simulated production of IL-10, which suppresses immune responses.

Our findings indicated a strong antitumor immunity induced by the ALA-PDT-DC vaccine, stimulated by immunogenic apoptotic cancer cells. Its mechanism, using ALA-PDT-treated apoptotic cells as sources of tumor antigens, is shown in Fig. 1. ALA-PDT-induced immunogenic tumor cells stimulated the maturations of DCs, including morphology maturation (enlargement of dendrites and increase of lysosomes), phenotypic maturation (upregulation of surface expression of MHC-II, DC80, and CD86), and functional maturation (enhanced capability to secrete IFN\(\gamma\) and IL-12, and to induce T cell proliferation and activation). The mature DCs worked as tumor vaccines to prevent tumor growth.

Our study may lead to an improved treatment modality against metastatic cancers.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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