The dendritic cell tool for oral cancer treatment

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Abstract

The link between oncology and immunology has a long history, and its development is forced by the necessity to develop innovative and highly efficient modalities for the immunological destruction of malignant cells. The success of cancer immunotherapy depends on two major factors: adequate tumor-specific antigens and a vehicle capable of inducing a tumor-specific immune response by effective delivery of these antigens. Dendritic cells (DCs) are the most powerful antigen-presenting cells, because of their unique characteristics, and these cells are actively used in cancer immunotherapy. DCs form a critical interface between innate and adaptive immunity. They integrate signals derived from tissue infection or damage and present processed antigen from these sites to naive T-cells in secondary lymphoid organs while also providing multiple soluble and surface-bound signals that help to guide T-cell differentiation. They are sentinel of immune system, as they are deployed through the body and monitor their surroundings for antigens and danger signals derived from pathogens or tissue damage. These cells (DCs) with their potent antigen-presenting ability are considered as critical factor in antitumor immunity. In recent years, the existence of immunosuppressive regulatory DCs in tumor microenvironment is well described. Monocytic myeloid-derived suppressor cells can contribute to the pool of tumor-associated DCs by differentiating to inflammatory DCs, which appear to have specific phenotype and are critical components of antitumor response. There is currently much interest in modulating DC function to improve cancer immunotherapy. Many strategies have been developed to target DCs in cancer, such as the administration of antigens with immunomodulators that mobilize and activate endogenous DCs and the generation of DC-based vaccines. Here, we highlight the role of DCs along with other DC subsets in the regulation of immune responses in cancer treatment.

Keywords: Adaptive immunity, dendritic cell, immunomodulators, immunotherapy, innate immunity

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INTRODUCTION

Dendritic cells (DCs) are professional antigen-presenting cells (APCs) located in the skin, mucosa and lymphoid tissues. Their main function is to process antigens and present them to T-cells to promote immunity to foreign antigens and tolerance to self-antigens. They also secrete cytokines to regulate immune response.[1]

Paul Enrich for the first time postulated that immune system has the ability to suppress majority of carcinoma.[2] However, the immune system can also promote tumor progression through chronic inflammation, selection of poorly oncogenic variants and suppression of antitumor immunity. Together, the dual host-protective and tumor-promoting actions of immunity are referred as cancer immune editing. According to this hypothesis, there

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are three phases in an immune response against tumors: the elimination, the equilibrium and the escape phase. During the elimination phase, cells belonging to the innate and adaptive immune system can recognize and kill the tumor cell. When the tumor cell cannot be eradicated, the tumor and immune system achieve balance. During this equilibrium phase, the immune system controls the tumor cells but cannot eliminate the tumor. In the escape phase, the tumor cell can evade the immune control and develop further toward a tumor with clinical manifestation.[3]

DCs are referred as "natures adjuvant" and recognized as the most potent APC, capable of activating both naive and memory immune response.[4]

During the development of an adaptive immune response, the phenotype and function of DCs play an extremely important role in initiating tolerance, memory and polarized T-helper 1 (Th1), Th2 and Th17 differentiation, for example, T-cells, natural killer (NK) cells, neutrophils and epithelial cells. For instance, experimentally, only one mature DC (mDC) is required to stimulate 100–3000 T-cells.[5]

DENDRITIC CELL ONTOGENY AND CHARACTERISTICS

DCs are rare, heterogeneous bone marrow (BM)-derived professional APCs that are disseminated ubiquitously in blood, lymphoid and peripheral tissues, particularly at the gates of antigen entry. They originate from hematopoietic stem cells throughout specialized progenitor subsets and are essential in innate and adaptive immune capacity and in managing the balance between immunity and tolerance. Under normal conditions, DCs are present throughout the body at low numbers representing 1%–2% of white blood cells.[6]

In the steady state, DCs reside in immature or semi-mature states in the periphery where they regularly take up and process self-Ags and maintain self-tolerance.[7]

DCs can exist in three states: immature, semi-mature and mDCs. The difference between immature and mDCs is distinctly based on variations occurring on a phenotypic level and functional level. Immature DCs manifested characteristics of primitive cells and defined by the expression of classical DC surface markers CD11c, CD11b and major histocompatibility complex Class II (MHC-II). Phenotypic maturation is accomplished when DCs upregulate surface maturation markers such as CD80, CD83 and CD86.[8]

DC precursors migrate from the BM through the bloodstream to almost every nonlymphoid tissue, where they reside in an immature state (iDC), continuously sampling their environment by endocytosis, macropinocytosis and phagocytosis. They can extend their processes through the tight junctions of epithelia to increase capture of antigens even when there is no overt infection/inflammation. During pathogen invasion, resident iDCs detect intruders through pattern recognition receptor (e.g., toll-like receptors), capture antigens and quickly leave the tissue. They crawl through the cells, cross the endothelium of lymphatic vessels and migrate to the draining lymph nodes (LNs) in response to a number of chemokines such as CCL19 and CCL21.[9]

During their migration from the peripheral tissues, DCs undergo phenotypical and functional maturation. Most remarkably, they stop capturing antigens while upregulating the expression of co-stimulatory molecules such as CD80 and CD86 and the chemokine receptor CCR7 and secrete pro-inflammatory cytokines such as tumor necrosis factor alpha and interleukin 12. After reaching the subcapsular sinus of the LN, DCs move to T-cell zones. Here, the interdigitating DCs are actively involved in the presentation of antigens to T-cells.[10]

TYPES OF DENDRITIC CELLS

1. Conventional DCs (cDCs): in the steady state, cDCs present typical DC characteristics (e.g., cytoplasmic dendrites) and function (e.g., Ag uptake, processing and exhibition). cDCs can be divided into migratory DCs, such as skin epidermal Langerhans cells, dermal DCs, which present Ag in LNs following its uptake in peripheral tissue and resident DCs, which take up and process Ag within a lymphoid organ, such as splenic or thymic DCs[11]
2. Plasmacytoid DCs: pDCs are a subset of precursor DCs which possess an immature phenotype in the steady state and plasma cell morphology (e.g., lack dendrites). On activation, pDCs strictly match cDCs in form and function[12]
3. Monocyte-derived DCs (moDC) or inflammatory DCs are similar to cDCs in form and function and related to *in vitro* granulocyte macrophage colony-stimulating factor (GM-CSF)-generated DCs.[13]

DENDRITIC CELL VACCINATION

Antitumor vaccines have been broadly used for immunotherapy of different cancers.[14]

The ability of DC to initiate and direct immune responses is exploited in cancer immunotherapy, especially in DC vaccination. With DC vaccination, mDCs loaded with

tumor antigen *ex vivo* are injected into cancer patients to induce tumor-specific effector T-cell that aims to recognize and eliminate cancer cells and induce immunological memory to control tumor growth.[15]

Cell-based therapies are particularly desirable as they pose low risk of toxicity and hold the potential of activating other immune modulators such as NK cells in addition to T-cells in anticancer mechanisms. Preclinical studies in 1990s first introduced the concept of using autologous BM-derived DCs as a viable vaccination option.[16]

SIPULEUCEL-T

The first DC vaccines were tested in humans in 1998. In 2010, the first DC vaccine was the Food and Drug Administration approved for the treatment of patients with advanced prostate cancer. This vaccine showed a survival advantage of 4.3 months. This vaccine was extremely safe, with low rates of adverse events.

Sipuleucel-T is a vaccine comprising of an enriched preparation of white cells containing a significant fraction of APCs, including DCs. These are pulsed with prostatic acid phosphatase fused with GM-CSF (PA2024) *ex vivo* and then reintroduced in the patient intravenously to induce immunity.

The novelty of sipuleucel-T comes from its success as the first approved immune therapy for a solid tumor, the first to show improvement in OS (although not in time to progression) and the first "personalized" therapy for cancer. While understanding, the mechanism of action was not felt initially to be a concern as long as a survival benefit was seen, nevertheless, data by Sheikh *et al.* showed that T-cell-activating cytokines were detected following the 2nd and 3rd infusions of the immune product and that antigen-specific T-cells could be detected as early as following the initial treatment; T-cell proliferation and interferon-gamma production supported these findings.[17]

MONOCYTE-DENDRITIC CELL

Numerous phase I/II clinical trials with moDC vaccines have been performed in cancer patients. Side effects were minimal and included Grade 1–2 flu-like symptoms, fever and local injection site reactions. Grade 3–4 toxicity is very uncommon after DC vaccination but can occur with more potent moDC formulations. Thus, DC vaccination can be concluded to be safe when used as monotherapy.

Tumor-associated antigens can also be directed toward DCs *in vivo* to induce immune responses. The use of antigens coupled to monoclonal antibodies or to nanoparticles specific for DC receptors can be a way of directing antigen delivery specifically to DCs. Using the artificial tumor antigen ovalbumin, a group recently showed that it was possible to specifically deliver the ovalbumin antigen when bound to cell-based therapies are particularly desirable as they pose low risk of toxicity and hold a nanoparticle specific for the complement C3 receptor that is expressed by APCs.[18]

CONCLUSIONS

In conclusion, there is a pronounced hope to study these strategies and use tumor antigen-bearing DCs as a vaccine in oral cancer. Human clinical investigations are continuing in numerous research institutions to use DCs to initiate immunity to antigens against breast cancer, lung cancer, melanoma, prostate, oral and renal cell cancers. DCs are being examined as adjuvants for vaccines or as a principal therapy to aggravate immunity against cancer.

DCs burdened with tumor lysates, tumor antigen-derived peptides, MHC Class I-modified peptides or whole protein have all been shown to yield anticancer immune responses and actions, including in some cases the ability to begin broad relapse of existing tumor. Understanding the role of the immune system in controlling and supporting tumor initiation, formation, growth and progression has crucial implications for cancer therapy and will, therefore, guide the future development of cancer immunotherapy and its combination with conventional therapies to achieve optimal antitumor effects in patients with different types of cancer.

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Conflicts of interest
There are no conflicts of interest.

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