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DC-derived exosomes (Dex) are nanometer-sized membrane vesicles that are secreted by the sentinel antigen-presenting cells of the immune system: DCs. Like DCs, the molecular composition of Dex includes surface expression of functional MHC-peptide complexes, costimulatory molecules, and other components that interact with immune cells. Dex have the potential to facilitate immune cell–dependent tumor rejection and have distinct advantages over cell-based immunotherapies involving DCs. Accordingly, Dex-based phase I and II clinical trials have been conducted in advanced malignancies, showing the feasibility and safety of the approach, as well as the propensity of these nanovesicles to mediate T and NK cell–based immune responses in patients. This Review will evaluate the interactions of Dex with immune cells, their clinical progress, and the future of Dex immunotherapy for cancer.

Introduction

As the sentinel antigen-presenting cells (APCs) of the immune system, DCs play a central role in initiating antigen-specific immunity and tolerance (1). In cancer, DCs act as the initial link between oncogenesis and the host immune system, the first step of a cancer/immunity cycle that aims to eliminate cancer cells through the activation of T cells (2). Tumor-proximal DCs can capture neoantigens created and released during oncogenesis, which the DCs subsequently process and present to cognate T cells to generate antitumor T cell responses. However, such T cell responses can only be generated if certain additional conditions are met in the local environment (2). These conditions consist of locally present immunogenic signals, such as proinflammatory cytokines, danger-associated molecular patterns (DAMPs), or pathogen-associated molecular patterns (PAMPs). Such signals trigger DCs to present captured tumor-associated antigens (TAAs) via MHC class I (MHC-I) and MHC-II molecules to T cells in cooperation with costimulatory molecules such as CD80 and CD86, resulting in the priming and activation of TAA-specific effector T cells.

Therapies harnessing these properties of DCs to generate immune responses against tumors have great potential, though clinical progress of this application remains in its infancy. One notable exception is the success of the immunotherapy sipuleucel-T for early-stage, hormone-refractory prostate cancer. Sipuleucel-T is composed of autologous peripheral blood mononuclear cells (PBMCs) including APCs (such as DCs and their precursors) that have been stimulated ex vivo with a fusion protein consisting of the cytokine granulocyte macrophage colony-stimulating factor (GM-CSF), which drives DC differentiation and activation, combined with a prostate antigen (3). Nonetheless, DC-based immunotherapy is challenging to practice in clinical settings. Implementing such therapies across large populations is costly, requires dedicated expertise, and requires monitoring of well-defined quality control parameters. Furthermore, it is difficult to store DCs over long periods of time while maintaining their efficacy (4).

The use of DC-derived exosomes (Dex) has been heralded as a solution to many of the technical challenges associated with DC-based immunotherapy (see Table 1) because they maintain the essential immunostimulatory faculties of DCs (e.g., sharing the ability to present antigens to T cells), while the stable nature of exosomal membranes allows their frozen storage for at least 6 months (5). As biologics, Dex are also more amenable to a strictly regulated and monitored manufacturing process (e.g., their composition and MHC-I and MHC-II content can be easily defined), and they lack the risks associated with viable cellular or viral therapies such as the risk of in vivo replication (6). Finally, treatment with cell-free Dex may be more resistant to immunomodulatory events that occur in tumors than other anticancer vaccines; such events can downregulate costimulatory molecules on DCs and impede stimulation of T cell responses (7).

As discussed in detail in other sections of this review series, DCs are one of the many cell types able to secrete membrane vesicles, such as exosomes, into the extracellular environment. This manner of signaling can modulate recipient cells, such as immune cells or cancer cells, to a level beyond classical ligand/receptor signaling pathways and can create complex cellular modifications that may play a substantial role in how tumor development or immune responses proceed. Moreover, detection of circulating, cancer cell–derived exosomes can serve as a noninvasive diagnostic and screening tool to detect early stages of cancer, facilitating

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