Dendritic Cell Vaccines for Brain Tumors

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• Brain tumor • Immunotherapy • Dendritic cells
• Cancer vaccines

Dendritic cells (DC) have long been regarded as the most potent antigen-presenting cells within the immune system. Their ability to sample environmental antigens and stimulate T-cell activity in a major histocompatibility complex (MHC)–restricted manner has attracted much attention given the poor antigen-presenting ability and immunogenicity of tumor cells.[1,2] Although DCs constitute approximately 0.3% of all circulating blood leukocytes, they serve as the sentinels of the immune system and are found nearly ubiquitously throughout the body.[3] In their immature state, DCs are highly specialized antigen samplers capable of surveying their microenvironment through several mechanisms including engulfment, macropinocytosis, and receptor-mediated endocytosis.[3] On encountering an antigen the DC processes it through MHC pathways and directs it to the cell surface to form an MHC-peptide complex (**Fig. 1**). In line with traditional antigen presentation following uptake from the environment, many antigens are channeled through MHC-class II pathways with resultant MHC-peptide complexes being capable of stimulating CD4+ T cells. In addition, DC possesses the unique ability to "cross-present" acquired antigens. In this process, DC endosomes release captured antigenic material into the cytosol where it is broken down by proteasomes.[4] The degraded peptides are then transported to the endoplasmic reticulum by a transporter-associated protein and bound to MHC-class I molecules for presentation to CD8+ T cells.[5,6] These distinct mechanisms allow DCs to stimulate T cells in an MHC-class I and II manner, overcoming classical restrictions in antigen processing and presentation[7] and diversifying the resultant immune response.

DCs are capable of handling a vast range of antigenic mediums. The sources of antigen that have been used in DC immunotherapy include exogenous MHC-restricted peptides, acid-eluted tumor peptides, tumor RNA and cDNA, viral vectors, apoptotic tumor cells, tumor cell lysate, and whole tumor cells. Many of these methods have been used with varying degrees of success. A growing sentiment has emerged, however, which argues for the use of a diverse range of antigens that cover both MHC classes rather than constructing specific MHC-matched peptides. The reasoning for this is multifold. First, stimulating T cells with a broad range of antigens reduces the likelihood of an escape phenomenon in which tumor cells lacking the specific antigens of interest avoid immune detection and continue to grow unhindered. Second, it is now well established that the stimulation of both CD4+ and CD8+ T cells is crucial in the activation and maintenance of antitumor immunity.[7–10] By allowing DCs to present and cross-present antigens on MHC-class II and I molecules, respectively, one avoids having to laboriously engineer peptides for each MHC class.[9,11] Finally, the methods used to load the spectrum of antigens for a particular tumor obviate the need of characterizing each individual antigen used. Although the use of unfractionated tumor material containing unknown antigens has long raised the concern of inducing autoimmunity, particularly in the form of experimental allergic encephalomyelitis, no reports of this complication have been seen following DC vaccination in humans to date.[3]

DC vaccine is defined as DCs loaded with antigens (eg, those found on glioma), which are

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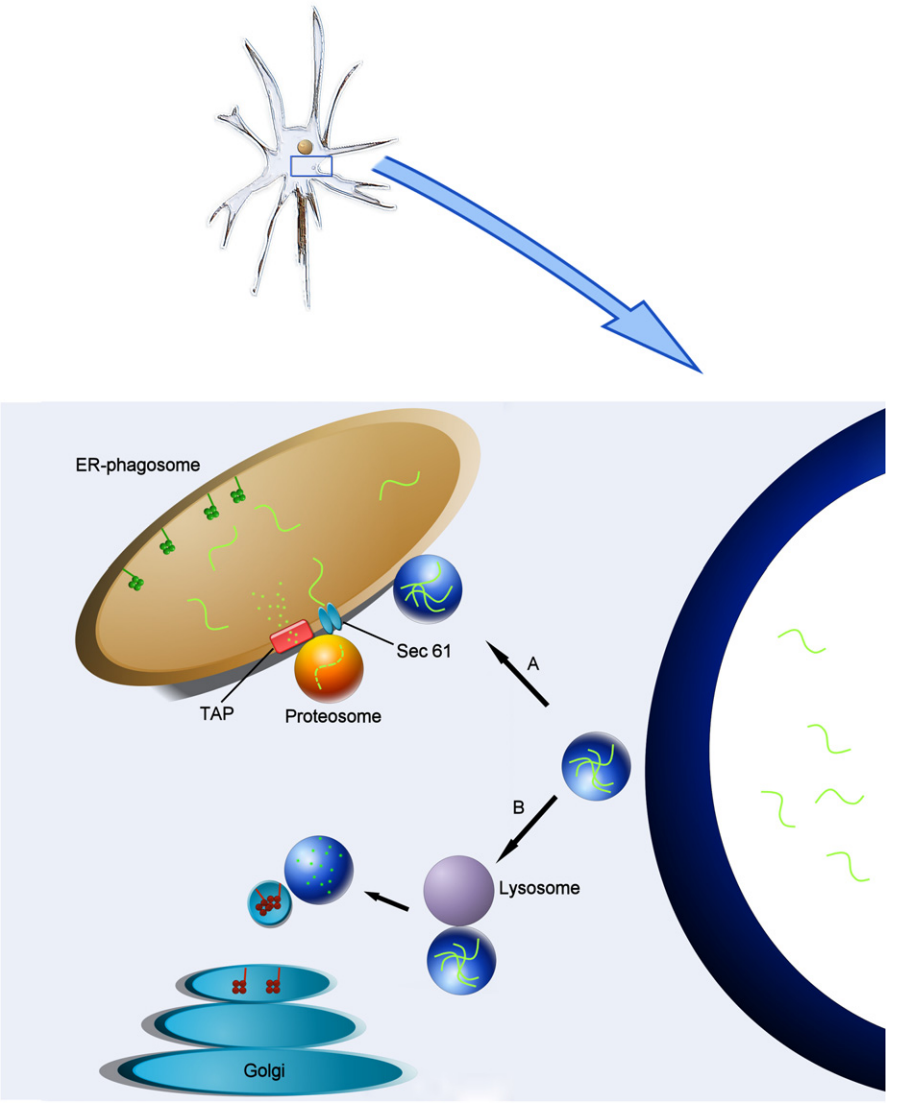

Fig. 1. Schematic of DC antigen processing and presentation by distinct MHC-I and MHC-II targeted pathways. Foreign antigens are sampled from the environment by dendritic cell phagocytosis or pinocytosis. Once vacuolized, antigen-containing vesicles are directed down one of two MHC pathways that result in cell surface presentation. (*A*) Antigen-containing vesicle encounters endoplasmic reticulum (ER)-phagosome. Antigen is retro-translocated into the cytoplasm by Sec 61 where proteosome complexes mediate peptide degradation. The resultant epitopes are translocated back into the ER-phagosome by the transporter-associated protein (TAP), where they are loaded onto MHC-I complexes and extruded for membrane integration and antigen presentation on the cell surface. (*B*) Antigen-containing vesicle encounters lysosome, which cleaves peptides using acid proteases. MHC-II complexes formed within the ER and subsequently processed and extruded from the Golgi apparatus are transported to peptide-containing endosomes for antigen loading.

administered to patients to induce an antigen-specific T-cell mediated antitumor response.[12] Although immature DC are not functionally ideal for the loading of antigens, they are unable to activate lymphocytes until an inflammatory signal or pathogen induces their maturation.[3,9,11] Some groups argue that ex vivo maturation of DCs through CD40L or interferon (IFN)-γ[13] is necessary before vaccine administration to ensure proper antigen presentation and T-cell activation.[14–17] Others maintain that maturation occurs naturally, and that no prior stimulus is required.[18] In the process of maturation, DCs lose their ability to uptake and process antigens. Moreover, they exchange their immature molecular signature for a mature (CD83+) phenotype, increasing