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Cancer Immunity, Vol. 3 Suppl. 1, p. 23 (6 February 2003)

Dendritic cell-based vaccination against cancer

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Abstract

Among the many cancer therapeutics being presently developed, antigen-specific immunotherapy is considered a particularly promising approach. Active immunotherapy or vaccination to induce tumor-specific killer and helper T cells directly in the patient is potentially the most powerful and broadly applicable strategy, but has yet to be developed for humans. A novel approach is to take advantage of DCs as "nature's adjuvant" and to actively immunize cancer patients with a sample of their own DCs charged with tumor antigens (reviewed in [1](#), [2](#)). The use of DCs as adjuvants is supported by many animal experiments, and also by the trials reported so far for humans. DC vaccination is, however, still in an early stage, and most potentially important variables like type and maturational stage of DCs, type of antigen and loading method, cell dose, route and frequency of injections have still to be systematically addressed in future studies. Despite this need for establishing an optimized DC vaccine even in some of the initial exploratory clinical trials, vaccination with DCs loaded with tumor antigens in the form of peptides has induced a) tumor-specific killer and helper T cells ("proof of concept"), and b) occasional regression of metastases even in far-advanced cancer patients. This was reported for DCs directly isolated from blood ([3](#)) as well as for DCs generated *ex vivo* from either CD34+ ([4](#)) or CD14+ precursors ([5](#), [6](#)). Most of the studies including informative ones in volunteers ([7](#)) have been performed by using DCs generated from CD14+ monocytes (so-called Monocyte-derived DCs or Mo-DCs) which are now considered as a gold standard. These Mo-DCs can be reproducibly generated within a few days in large numbers (300-500 million mature DCs per apheresis) from precursors in blood without any need for pretreating the patients with cytokines like GM-CSF or Flt3-L ([8](#)). Importantly, it is possible to obtain populations of immature DCs by exposing monocytes to GM-CSF + IL-4, which can then be transformed into homogeneously mature DCs by various stimuli such as TLR ligands (e.g. microbial products such as LPS or poly I:C), inflammatory cytokines like TNF-alpha, monocyte-conditioned medium or its mimic (IL-1beta + TNF-alpha + IL-6 + PGE2), or CD40L. The use of *mature* DCs is likely critical to induce strong immunity as it has become clear that antigen delivered on immature or incompletely matured DCs can even induce tolerance ([9](#)). Interestingly, it has recently also become evident that in case of the Mo-DCs the choice of maturation stimulus is probably critical for success. Specifically, PGE2 has to be part of the maturation stimulus in order to obtain CCR7 expressing Mo-DCs that migrate in response to CCL19 and CCL21 that guide DCs into lymphoid organs ([10](#), [11](#)). It is of note that many trials employing Mo-DCs have not used such optimally matured DCs while we and some others have favored both the use of mature DCs and monocyte conditioned medium or its mimic as maturation stimulus. Using such DCs loaded with tumor peptides their migratory capacity *in vivo*, the induction of tumor-specific cytotoxic and helper T cells, and the presence of tumor-antigen specific T cells *in situ* in regressing metastases have been demonstrated. Recently, new approaches to charge DCs with antigens have become evident which promote the DC vaccination approach. The observation that DCs can take up naked RNA, express antigens encoded by the RNA and induce antigen-specific T cells *in vitro* as well as *in vivo* in patients has given an enormous additional momentum to the use of DCs as vectors for antigen delivery

and cancer vaccination (12). This is particularly relevant as the variable transfection with naked RNA can be substituted by a reproducible electroporation protocol (13). This now allows one to administer to DCs both defined antigens, including universal ones such as telomerase or survivin as well as the total antigenic repertoire of a given tumor (as total tumor or PCR amplified RNA). The use of dying tumor cells, notably antibody-coated ones, is an alternative (14). Other preclinical research has shown that the delivery of defined antigens as antigen-antibody complexes to DCs enhances crosspresentation and allows for the potent induction of both CD4+ and CD8+ T-cell responses (15, 16, 17). Several recent results suggest that DCs might even be useful to directly trigger NK (18) and to mobilize the additional power of the innate immune system to attack tumor cells. It appears, therefore, rational and timely to optimize the use of DCs as vectors for the delivery of antigens to vaccinate against cancer.

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