Dendritic cells: at the clinical crossroads

Commentary

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Dendritic cells (DCs) are highly potent antigen-presenting cells of bone marrow origin that can stimulate both primary and secondary T- and B-cell responses (1). First described by Steinman, DCs display a characteristic veiled appearance with multiple extending cellular processes. These cells possess the necessary components for potent antigen-presenting functions, including the production of a variety of important immunostimulatory cytokines and the expression of critical cell-surface molecules. Depending on their level of maturity, DCs express prominent levels of MHC class I and class II molecules, as well as costimulatory molecules such as CD40, CD80, and CD86. Animal studies show them to be responsible primarily for sensitizing naive T cells in their first exposure to antigen. Because of this unique property in inducing immunity, DCs have been termed "nature's adjuvant" (1).

Antigen distribution in the host environment often favors uptake and presentation by DCs rather than macrophages or B cells, and subsequent migration of primed DCs to lymphoid organs enhances targeted presentation of antigens to the immune system. More recently, it has also been shown that murine monocytes residing in subcutaneous tissue can become lymph-borne DCs that localize in draining lymph nodes (2). Once in the lymph nodes, these DCs can present both MHC class I– and class II–restricted antigens and can therefore stimulate both resident $CD8^+$ and $CD4^+$ T cells. Whether the migration to the lymph nodes is strictly required for DCs to be competent to stimulate these responses remains less certain. In this regard, Banchereau's group has reported that in human breast carcinomas, immature DCs can reside within the tumor mass itself, whereas the mature ones are located in peritumoral areas (3). As possible evidence of an ongoing immune response in situ, some peritumoral areas of the specimens showed T cells clustered around the mature DCs, which resembled clusters often reported for secondary lymphoid organs.

The maturation state of DCs appears to be important for their optimal use in immunization strategies, with more mature DCs demonstrating higher production of some key cytokines (e.g., IL-12), increased antigen presentation in vitro and in vivo, and, at least in mice, increased localization to draining lymph nodes and more potent induction of broad T-cell immunity and antitumor activity (1, 4). CD40L, LPS, monocyte-conditioned medium, and TNFα have all been used to promote DC maturation. Human DCs can arise from bone marrow–derived and cord blood–derived $CD34^+$ hematopoietic cell progenitors and also from PBMCs and $CD14^+$ blood monocytes. Highly enriched rodent or human DCs can now be produced in great numbers by culturing progenitor cells in the presence of cytokines, notably GM-CSF and IL-4, with or without TNFα.

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Virally infected human DCs can elicit potent proliferative and cytolytic T-cell reactivity in vitro (5). In animal models, immunization with antigen-presenting DCs can result in strong protective immunity to viruses (e.g., lymphocytic choriomeningitis virus, LCMV) and to tumors (4, 6, 7). With respect to the latter, tumor antigen–pulsed DCs can successfully treat established mouse tumors in vivo. Tumor-associated and model antigens, in the form of whole cell lysates, apoptotic cell bodies, peptides, proteins, RNA, and DNA have been used and may initiate tumor-specific $CD4^+$ and $CD8^+$ T-cell responses (7, 8).

DCs have now reached a watershed — their efficacy in immunization approaches for the protection from and the treatment of human disease is finally being tested. The establishment of human DC cultures from the peripheral blood of patients has facilitated their use as immunotherapeutic agents, most notably in the treatment of infectious diseases and against a variety of human tumors. Initial clinical trials involving DC-based immunization of patients with tumors of hematologic and solid origin are promising: subjects show increased antitumor T-cell reactivity and experience partial or complete clinical responses (9–14). However, meaningful comparisons of the immunologic and clinical outcomes of these trials have been complicated by variability regarding the source of the DCs, their level of maturity, the nature of the antigen used to pretreat them, as well as the dosing regimen and route of administration used. An additional complication centers on the fact that these immunizations have been conducted in advanced cancer patients with various tumor types, at different stages of disease, and with different histories of previous therapy.

The study of Dhodapkar et al. reported in this issue of the *JCI* represents an important step toward optimizing some of these variables (15). These same investigators reported earlier in the *JCI* that, remarkably, a single subcutaneous injection of fewer than 3×10^6 mature DCs could rapidly expand

CD4$^+$ and CD8$^+$ T-cell immunity specific to several distinct antigens, including keyhole limpet hemocyanin (KLH), influenza matrix peptide (MP), and tetanus toxoid (TT) (16). Significantly, these immunizations were conducted in normal, healthy volunteers with control immunizations of antigen alone (without DCs) and DCs alone (without antigen) to determine their separate contribution, if any, to the response. The immunologic monitoring comprised state-of-the-art assays of high sensitivity and specificity. In the current report, Dhodapkar et al. follow up on a cohort of these previously immunized volunteers to examine the durability and kinetics of the immunologic responses to KLH, TT, and MP, as well as the impact of providing a booster injection of MP-primed, mature DCs. The CD8$^+$ T-cell immune response to the MP peptide after the booster immunization was more rapid and of greater magnitude than the first immunization. These responding T cells could also recognize lower doses of the peptide. Moreover, the booster injection of the antigen-primed DCs was efficacious in the absence of any provision of additional epitopes to elicit help to the responding CD8$^+$ T cells.

Which road will human DC-based vaccines now travel? Additional key comparisons remain to be done. The present studies point to the use of mature, rather than immature, DCs and the subcutaneous, rather than intravenous or intranodal, immunization, but their level of significance can be ascertained only by comparative, randomized studies. Moreover, if mature DCs are shown to be more beneficial in immunization, additional issues remain: how best to optimize DC maturation? Which source of antigens — apoptotic cell bodies, lysates, or peptides — should be delivered to DCs to optimize the response? Does it matter whether DCs are generated from CD34$^+$ progenitors or from monocytes? Data are eagerly anticipated from direct clinical comparisons that will address these questions.

1. Banchereau, J., and Steinman, R.M. 1998. Dendritic cells and the control of immunity. *Nature.* **392**:245–252.
2. Randolph, G.J., et al. 1999. Differentiation of phagocytic monocytes into lymph node dendritic cells in vivo. *Immunity.* **11**:753–761.
3. Bell, D., et al. 1999. In breast carcinoma tissue, immature dendritic cells reside within the tumor, whereas dendritic cells are located in peritumoral areas. *J. Exp. Med.* **190**:1417–1425.
4. Labeur, M.S., et al. 1999. Generation of tumor immunity by bone marrow-derived dendritic cells correlates with dendritic cell maturation stage. *J. Immunol.* **162**:168–175.
5. Bhardwaj, N., et al. 1994. Influenza virus-infected dendritic cells stimulate strong proliferative and cytolytic responses from human CD8$^+$ T cells. *J. Clin. Invest.* **94**:797–807.
6. Ludewig, B., et al. 1999. Protective antiviral cytotoxic T cell memory is most efficiently maintained by restimulation via dendritic cells. *J. Immunol.* **163**:1839–1844.
7. Fields, R.C., Shimizu, K., and Mulé, J.J. 1998. Murine dendritic cells pulsed with whole tumor lysates mediate potent antitumor immune responses in vitro and in vivo. *Proc. Natl. Acad. Sci. USA.* **95**:9482–9487.
8. Albert, M.L., and Bhardwaj, N. 1998. Resurrecting the dead: dendritic cells cross-present antigen derived from apoptotic cells on MHC I. *The Immunologist.* **6**:194–198.
9. Hsu, F.J., et al. 1996. Vaccination of patients with B cell lymphoma using autologous antigen-pulsed dendritic cells. *Nat. Med.* **2**:52–58.
10. Murphy, G., et al. 1996. Phase I clinical trial: T cell therapy for prostate cancer using autologous dendritic cells pulsed with HLA-A020-specific peptides from prostate-specific peptides from prostate-specific membrane antigen. *Prostate.* **29**:371–380.
11. Nestle, F.O., et al. 1998. Vaccination of melanoma patients with peptide- or tumor lysate-pulsed dendritic cells. *Nat. Med.* **4**:328–332.
12. Morse, M.A., et al. 1999. A phase I study of active immunotherapy with carcinoembryonic antigen peptide (CAP-1)-pulsed, autologous human cultured dendritic cells in patients with metastatic malignancies expressing carcinoembryonic antigen. *Clin. Cancer Res.* **5**:1331–1338.
13. Weber, J.S., et al. 1999. A phase I trial of gp100/tyrosinase peptide-pulsed dendritic cells for metastatic melanoma. *Proc. Am. Soc. Clin. Oncol.* **18**:432.
14. Thurner, B., et al. 1999. Vaccination with Mage-3A1 peptide-pulsed mature, monocyte-derived dendritic cells expands specific cytotoxic T cells and induces regression of some metastases in advanced stage IV melanoma. *J. Exp. Med.* **190**:1669–1678.
15. Dhodapkar, M.V., et al. 2000. Mature dendritic cells boost CD8$^+$ T-cell in humans without foreign helper epitopes. *J. Clin. Invest.* **105**:R9–R14.
16. Dhodapkar, M.V., et al. 1999. Rapid generation of broad T-cell immunity in humans after a single injection of mature dendritic cells. *J. Clin. Invest.* **104**:173–180.