Editorial

Monocyte-Derived Dendritic Cells: A Promising Armament for Immunotherapy in Human Malignancies

Commentary on Tokunaga N et al., p. 1312

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Recent insights into immune system function have fostered a better appreciation of the role of specialized antigen-presenting cells (i.e., dendritic cells). Initially described by Steinman and Cohn (1) in 1973 as an adherent cell type among mouse splenocytes with a distinctive stellate morphology, dendritic cells soon became known for their role as the sentinels of the immune system (2). In their immature state, dendritic cells reside in peripheral tissues, where they survey for incoming pathogens. An encounter with pathogens leads to dendritic cell activation and migration to secondary lymphoid organs, where they trigger a specific T-cell response. Dendritic cells are cells that not only can stimulate quiescent naive CD4+ and CD8+ T and B cells and initiate primary immune responses but also can induce a strong secondary immune response at relatively low numbers and with low amounts of antigen. Furthermore, dendritic cells are involved in polarization of T-cell response via secreted cytokines and in induction of tolerance through deletion of self-reactive thymocytes and anergy of mature T cells (3). Given their central role in controlling immunity, dendritic cells are logical delivering vehicles for many clinical disease states that involve T cells, such as transplantation, allergy, autoimmune disease, resistance to infection and to tumors, immunodeficiency, and vaccination.

In vivo, dendritic cells are continuously produced from hematopoietic stem cells in the bone marrow and are widely distributed as immature cells, such as epidermal Langerhan’s cells, splenic marginal zone dendritic cells, and interstitial dendritic cells, in both lymphoid and nonlymphoid tissues (2). However, circulating dendritic cells are rare (they account for <1% of human peripheral blood mononuclear cells) and are difficult to maintain in culture. Most experimental and clinical studies currently rely on the in vitro development of dendritic cell–like cells from CD34+ progenitor cells or nonproliferating cells (i.e., dendritic cells). Initially described by Steinman and Cohn (1) in 1973 as an adherent cell type among mouse splenocytes with a distinctive stellate morphology, dendritic cells soon became known for their role as the sentinels of the immune system (2). In their immature state, dendritic cells reside in peripheral tissues, where they survey for incoming pathogens. An encounter with pathogens leads to dendritic cell activation and migration to secondary lymphoid organs, where they trigger a specific T-cell response. Dendritic cells are cells that not only can stimulate quiescent naive CD4+ and CD8+ T and B cells and initiate primary immune responses but also can induce a strong secondary immune response at relatively low numbers and with low amounts of antigen. Furthermore, dendritic cells are involved in polarization of T-cell response via secreted cytokines and in induction of tolerance through deletion of self-reactive thymocytes and anergy of mature T cells (3). Given their central role in controlling immunity, dendritic cells are logical delivering vehicles for many clinical disease states that involve T cells, such as transplantation, allergy, autoimmune disease, resistance to infection and to tumors, immunodeficiency, and vaccination.

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Due to their ready availability, monocyte-derived dendritic cells have been widely used as stimulators for in vitro or ex vivo generation of tumor-specific CTLs. To activate CD8+ T cells, presentation of tumor antigens on MHC class I molecules is needed. Dendritic cells are proving to be quite specialized in their capacity to form MHC class I-peptide complexes, via a mechanism of “cross-presentation” of proteins derived from immune complexes or inactivated microbes, or antigens originally synthesized in other cells (6). Several dendritic cell receptors lead to MHC class I-peptide complex formation via the exogenous pathway, including FcγR, the integrin αβ, and the phosphatidylserine receptor, and various receptors for heat shock proteins (6). The ability of dendritic cells to cross-present antigen is on MHC class I molecules to CD8+ T cells has prompted many preclinical studies pulsing dendritic cells with soluble tumor antigens or lysates or loading dendritic cells with necrotic or apoptotic tumor bodies to generate tumor-specific CTLs in various tumor settings, including solid tumors (7) and hematologic malignancies (8, 9).

In this issue of Clinical Cancer Research, Dr. Tokunaga and coworkers provide another good example of using the ability of dendritic cells to cross-present soluble tumor antigen to CD8+ T cells. In their study, monocyte-derived dendritic cells from HLA-A2-positive or HLA-A24-positive healthy individuals were used and pulsed with purified, full-length, wild-type p53 protein. The antigen-pulsed monocyte-derived dendritic cells were then used as stimulator cells in culture with autologous T cells to generate p53-specific CTLs. The resulting CTLs were able to kill p53-overexpressing tumor cells, and the cytotoxicity was MHC class I restricted. Thus, it is evident that the exogenously pulsed p53 protein was successfully presented, in the form of antigenic peptides in the context of MHC class I molecules, to CD8+ T cells. It should be noted that, although many investigators exploit dendritic cells for their ability to cross-presentation tumor antigens to CD8+ T cells, dendritic cells simultaneously present exogenous proteins and cellular antigens on both MHC class I and II molecules (2). By doing so, dendritic cells are also able to activate specific CD4+ helper T cells, which not only are important for antibody production and amplification and sustaining of CD8+ CTL response but also may by themselves exert antitumor activity, especially the type 1 helper T cells (2).

Monocyte-derived dendritic cells are also the favorite choice of cells for dendritic cell–based immunotherapy in human
patients. Among different clinical studies in cancer patients reported to date, most have used monocyte-derived dendritic cells as the vaccines (10, 11). Based on preliminary data, dendritic cell vaccines may prime and boost antigen-specific T-cell responses in patients, and dendritic cell–based immunotherapy has been proven to be feasible, nontoxic, and effective in some patients, especially if the dendritic cells have been appropriately matured and activated (10, 11). Nevertheless, as the full potential of these cells has not yet been entirely exploited, many strategies could improve the immunogenicity of these vaccines.

REFERENCES
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