Dendritic cells in the treatment of cancer

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A rapidly accumulating body of evidence in preclinical studies has demonstrated the critical importance of antigen presentation to effector elements (T cells and B cells) in the control of the immune response. The professional antigen-presenting cell is the dendritic cell.

Autologous dendritic cells obtained from monocytes by culturing can be loaded with tumor-associated or specific peptides or other antigens. These antigen-loaded dendritic cells, when reinjected into experimental animals, resulted in the generation of activated T cells that selectively destroyed malignant cells in vivo, resulting in cures. Human dendritic cells may enable the development of a powerful means of inducing an immune response against cancer. Dendritic cells derived from CD34+ hematopoietic progenitor cells may be more effective than dendritic cells from monocytes. We are now able to generate large numbers of dendritic cells in vivo and ex vivo, thus enabling the design and implementation of clinical trials in the treatment of cancer using these cells.

As the biology of dendritic cells continues to unfold, it is clear that specific dendritic cell subtypes are more effective than others in the generation of cytotoxic T cells against a neoplastic cell. Other dendritic cell subtypes are responsible, in part, for the induction of immune tolerance. Work at the Baylor Institute for Immunology Research has resulted in a new treatment for melanoma using dendritic cell vaccinations. Similar treatment strategies are planned for breast cancer, prostate cancer, and hematologic malignancies.

The human immune system, comprising antibodies and effector cells, provides a powerful means of destroying invading infectious agents and cancer cells. To selectively destroy neoplastic disease in humans using the immune system has been the goal of clinical scientists for decades. Such an effort takes advantage of antigenic differences that neoplastic cells possess as compared with normal tissue and then targets these differences with a specific cytotoxic agent using monoclonal antibodies or activated T lymphocytes (T cells) or natural killer cells. In many instances, monoclonal antibodies specific to cancer cell antigens can be manufactured and biochemically coupled with a cellular toxin (e.g., ricin or a radioactive isotope) (1). Successful treatment results in selective cancer cell death. Depending on the cancer cell antigen, certain monoclonal antibodies result in a T-cell attack on target cells. Antibody therapy for cancer has shown great promise but has significant limitations. These include the nonspecific toxicity (e.g., capillary leaking syndrome) associated with many immunotoxins, the poor penetration of the tumor by monoclonal antibodies, and the complexity of the synthesis of immunotoxins(2). The manufacture of monoclonal antibodies to specific cancer antigens demands discovery and characterization of these antigens. This has proved difficult.
Cellular therapy of cancer requires generation of effective numbers of T cells or natural killer cells (effector cells) against tumor-specific antigens. Several strategies have been explored in the clinic: 1) administration of cytokines that nonselectively expand T cells or natural killer cells in vivo, resulting in the cloning of cells that destroy cancer cells; 2) transfection of a cytokine gene into cancer cells, resulting in the development of tumor immunogenicity in the host; and 3) vaccination of the patient using tumor-specific or associated peptides or proteins (3-5). These approaches to cellular therapy for cancer have been effective but, like antibody therapy, are associated with significant limitations. Some of these limitations are toxicity to the host associated with in vivo cytokine administration; poor gene expression in the tumor cell, resulting in an ineffective immune response; and lack of an immune response after vaccination with tumor-specific peptides or proteins.

The fundamental problem in inducing an immune response to a tumor in vivo may be that the demands in initiating effective T-cell immunity are too high, or there may be an overpowering suppression of T-cell immunity by the tumor itself. Recently, dendritic cells (DC) have been recognized as the initiators and the modulators of the immune response. Dendritic cells are effective educators of B and T lymphocytes. Unlike B cells that can activate by antigen complexing with their cell surface receptors, T cells need antigen to be processed and presented to them by antigen-presenting cells (6). The DC is the professional antigen-presenting cell and possesses a unique ability to activate a powerful immune response in vivo (7). Therefore, while great strides have been made in understanding the role of T cells, natural killer cells, or antibodies in mediating antitumor immunity, clearly, these elements represent the end stage of an immune response. It is likely that the effect of T cells, B cells, and natural killer cells against a cancer cell is determined initially by DC.

Dendritic cells are found in all tissues and in the blood in extremely small numbers (less than 0.1% of circulating leukocytes). However, they are identifiable by immunophenotyping using sensitive multicolor flow cytometry and functionally with in vitro culture systems. Dendritic cells are heterogenous, and distinct subtypes can be identified by multicolor flow cytometry. They are recognized in tissues (so-called interstitial DC) and in the liver, kidney, heart, pancreas, gut, dermis and epidermis (Langerhans? cells), thymus, T cell?rich areas of lymph nodes (interdigitating DC), and blood. Dendritic cells can vigorously internalize solutes by micropinocytosis, thus permitting the delivery of soluble antigens into major histocompatibility class (MHC), class II?rich vesicles.

Dendritic cells, in addition, are effective in presenting antigen by other methods, including ingestion of apoptotic bodies derived from tumor cells. Ex vivo incubation of DC with tumor lysates or transfection of genes encoding for tumor-associated antigen results in the generation of DC that activate T cells. Dendritic cells express high levels of antigen-presenting molecules (MHC class I and II and CD1) and so-called ?accessory? molecules, thus enabling initialization and amplification of a specific immune response to target antigens (7). Mature DC possess high expression of the CD28, CD80, and CD86 molecules, enabling efficient development of a cytotoxic T-cell response. CD40, in addition, is expressed in high density on DC, and its triggering results in up-regulation of accessory molecules and the production of cytokines including interleukin (IL)-12 (8). Interleukin-12 enhances the maturation of T cells toward the Th1 pathway and activates natural killer cells. The Th1 pathway mediates cellular toxicity against cancer cells or infectious pathogens.

The role of DC is to act as sentinels of invading infectious agents or tissue injury (like the
inflammation caused by cancer cell growth). When this occurs, DC, because of their motility and cell membrane biology, have the remarkable capability of capturing and processing antigens and migrating to secondary lymphoid organs to interact with T cells and facilitate T-cell activation against the target antigen. Dendritic cells are efficient; 1 DC can activate 100 to 3000 T cells.

Monocyte-derived DC vaccination experiments in animals prevented the growth of transplanted cancer cells and resulted in cures in animals with established tumors (9). Remarkably, immunization with DC that were pulsed with poorly immunogenetic tumors resulted in major responses (some cures), even with the use of whole tumor antigens (e.g., tumor lysates). Dendritic cells pulsed with whole tumor antigen may enable antigen presentation by both MHC class I and class II pathways, in contrast to the use of specific tumor peptides that solely rely on MHC class I presentation.

Recently it has become possible to harvest large numbers of human DC, enabling the design and implementation of vaccination. Recently it has become possible to harvest large therapy for cancer patients. Human blood monocytes cultured in vitro with IL-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF) result in large numbers of functional DC. These monocyte-derived DC have been loaded in vitro with melanoma antigens and, when vaccinated into patients with metastatic melanoma, resulted in significant measurable regressions of disease. Some patients experienced a complete remission (10). These antigen-loaded DC resulted in the generation of significant numbers of activated T cells that were toxic to melanoma cells in vitro. Further, monocyte-derived DC have been used in a similar fashion in the successful treatment of selected patients with non-Hodgkin’s lymphoma (11). In all of these preliminary clinical trials, antigen-loaded DC vaccinations were well tolerated and were associated with no significant side effects. Most patients in these trials developed in vitro antitumor cellular responses.

Evidence shows that antigen-loaded DC derived from the culture of CD34+ hematopoietic progenitor cells with cytokines may result in more efficient DC activation of T cells when compared with monocyte-derived DC (12). CD34+ cells can be collected from patients and cultured in vitro with Flt-3-ligand, GM-CSF, and tumor necrosis factor (TNF), resulting in significant numbers of DC (Palucka K, Banchereau J, Curiel T, Fay J, unpublished observations). Dendritic cells manufactured from CD34+ cells undergo several defined steps in cell maturation, resulting in the ability to culture DC subtypes. It is possible to study various DC subtypes when the starting cell in culture is the CD34+ progenitor cell. Such flexibility may enhance the design of effective trials using DC in the treatment of cancer patients. Investigators at Baylor University Medical Center are planning the first study of DC derived from CD34+ hematopoietic progenitor cells in the treatment of patients who have metastatic melanoma.

Most neoplastic diseases, including breast cancer, prostate cancer, and hematologic malignancies, may be treated effectively with DC-based vaccination therapy. The initial studies will involve patients with relatively advanced cancer in order to determine the safety and tolerability of tumor-specific DC vaccination therapy. Subsequently, however, when safety and tolerability have been proved, DC vaccinations may prove effective in the prevention of recurrent cancer after an initial remission has been accomplished with surgery, radiation, or chemotherapy.
There are reasons why DC vaccinations may prove ineffective in the treatment of cancer, and these hurdles must be addressed. Cancer cells, for example, often possess molecules that inactivate attacking T cells (e.g., Fas ligand) or prevent DC maturation (e.g., vascular endothelial growth factor or IL-10) (13, 14). In addition, patients whose T-cell repertoire has been depleted or suppressed by previous cytotoxic chemotherapy or radiation therapy may not have sufficient T cells for the generation of cytotoxic T cells against tumor cells (15). Alternatively, however, DC given to such patients may enhance the T-cell repertoire.

Clinical scientists at Baylor University Medical Center have been involved with studies using Flt-3-ligand, a cytokine that induces DC generation in vivo (16). Clinical trials at Baylor using Flt-3-ligand in the treatment of lymphoma are under way. In addition, studies are under way with normal volunteer subjects who receive Flt-3-ligand to determine the most effective way to generate DC for clinical use and, at the same time, to examine the effect of Flt-3-ligand on the immune response to commonly used peptide vaccinations.

In conclusion, studies of human DC and their use in the vaccination of patients against their own neoplastic disease are under way at Baylor University Medical Center. This new approach has great promise in the treatment of cancer.

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References


