Tumor Immunology: New Perspectives

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Introduction

This second meeting, organized by the Cancer Immunology Working Group of AACR, concentrated mainly on three areas of importance; these included (a) ways to increase the success rate of vaccination by improving the peptides themselves, improving tumor recognition by using costimulatory molecules or the use of antibodies; (b) how the tumor microenvironment influences T-cell activity and how it can be manipulated to favor survival and action of activated T cells; and (c) a better understanding of myeloid-derived suppressor cells, which represent an ever-growing and diverse group of cells with activities leading to the inhibition of immune responses. It has been accepted that many of these improved therapies may only benefit relatively few patients and recent but rapidly developing research is currently focusing on methods that would allow clinicians to stratify patients receiving immunotherapy into responders and nonresponders, thereby predicting those who are likely to benefit from a specific vaccine therapy; this approach may benefit future clinical trials. [Cancer Res 2009;69(18):7157–9]

How to Improve the Success Rate of Current Vaccinations?

Advances made in understanding the nature of the antitumor response and mechanisms whereby a more effective T-cell response could be generated were addressed by several speakers. The immune response to naturally occurring tumor antigens, such as Melan-A/MART-1, can be enhanced by sequential immunization with native and modified peptide-based vaccines, wherein the enhanced T-cell receptor (TCR) affinity/avidity largely compensates for the poor short-term response induced by the native peptide. Immunization using peptide-based vaccination strategies, together with CpG-ODN plus Montanide, was shown to significantly increase tetramer-positive T cells, coincidental with a reduction in the diversity in T-cell clones (Dr. Pedro Romero, Ludwig Institute for Cancer Research, Lausanne, Switzerland). By further extending the COOH and NH2 terminals of the Melan-A/MART-1 HLA-restricted peptide specific CD4-positive T-cells could be induced, and, upon vaccination, a reduction in the normally large proportion of Foxp3+-Tregs was shown in melanoma patients concomitant with an increase in the frequency of Melan-A/Mart-1–specific CD8-positive effector T cells. Other vaccination strategies combined the use of immunogenic peptides with granulocyte macrophage colony-stimulating factor and adjuvant, administered together with treatments that decreased Treg activity. In prostate cancer, it was observed that peptide vaccination against hTert resulted in both CD8-positive and CD4-positive T cell infiltration into the tumor (Dr. Robert H. Vanderheide, Abramson Cancer Center, Philadelphia, PA). Administration of immunosuppressive antibodies, such as Daclizumab [a therapeutic nondepleting humanized monoclonal IgG1 antibody that binds to the a subunit of the interleukin 2 (II-2) receptor, thereby blocking II-2 binding], might help maintain the reduction in Tregs, which would in turn improve antitumor activity. In pancreatic cancer, which has a particularly poor prognosis and where only 20% to 30% of patients have resectable cancers, a newly identified T-cell target, mesothelin, showed efficacy in a trial in which HLA-A2– and HLA-A1–positive patients were shown to develop mesothelin-specific T cells after vaccination, the presence of which correlated with patient survival (Dr. Elisabeth M. Jaffee, Johns Hopkins University, Baltimore, MD).

In attempting to understand how antitumor T-cell activity can be promoted, it is necessary to consider how TCR/MHC/peptide interactions occur and whether improving the intrinsic ability of peptides to bind to MHC antigen and/or TCR integrity can be optimized to enhance T-cell killing of tumor cells. Dr. Philippa Marrack (keynote speaker, Howard Hughes Medical Institute, Denver, CO) described the molecular features of the TCR and the importance of V regions of the CDRI, CDR2, and CDRS of the a and b chains of the TCR for binding MHC/peptide complexes. It can be further shown that, by selecting peptide sequences that mimic the binding capability of the wild-type peptide, antitumor T-cell activity and immunity can be induced; however, it remains to determine why some amino acids are better than others at inducing CD8–positive T cells capable of producing high levels of IFN-g when both the affinity and avidity appear the same. From work undertaken at Ludwig Institute in Brussels (Dr. Pierre van der Bruggen, Ludwig Institute for Cancer Research, Brussels, Belgium), it was shown that, after activation, CD8-positive T cells lose their effector function and MHC binding capacity due to the delocalization of CD8 and the TCR on their surface. This separation of TCR and CD8 molecules could be one major mechanism resulting in T-cell anergy in tumors. Indeed, it has been found that for human infiltrating lymphocytes, shown to be anergic, their TCR was distanced from CD8 molecules; ex vivo incubation with galectin disaccharide ligands was able to restore both the colocalization of TCR with CD8 molecules and restore their function. Interestingly, many tumors seem to express or even secrete galectin-3, which is thought to be responsible for the dissociation of the TCR and CD8 molecules. The concept of combining vaccination with LacNac treatment, which competes with galectin-3 for the same binding, may promote a more effective antitumor immune response in a larger proportion of patients than vaccination alone.

The use of antibodies to improve antigen/drug uptake has been highlighted in several communications and includes (a) the use of Food and Drug Administration (FDA)–approved liposomes coated

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with antibodies and incorporating drugs; (b) the use of immune complexes antibody antigen interaction to increase the delivery of antigen via the Fc receptor and enhance both CD4 and CD8 T-cell responses; and (c) the use of antibody-coated tumor cells to promote engulfment by dendritic cells (DC) and stimulate immunity (Dr. James D. Marks, University of California, San Francisco, CA and Dr Raphael Clynes, Columbia University, New York, NY).

Interestingly, human DCs coexpress activating (CD32a) and inhibitory (CD32b) isoforms of IgG Fcγ receptor II (CD32). The balance between these two receptors seems to determine the activation threshold and enables immune complexes to mediate opposing effects on DC maturation and function. Blocking the specific inhibitory receptor on DCs at the time of vaccination is an interesting concept (Dr. Kavita M. Bhodapkar, Rockefeller University, New York, NY).

It is well recognized that many tumor antigens express an altered glycosylation pattern upon cell transformation, and as depicted with MUC-1, this also results in an alteration in cellular topography, with a change in expression pattern from apical to nonapical antigen expression. In malignant cells, glycosylation occurs at three sites in each of the tandem repeat sequences (11 × 20 amino acid repeats) of the molecule, resulting in MUC-1 developing a highly tumor-specific expression pattern. For mucinous tumors, such as breast and ovarian, MUC-1 has been extensively studied and investigated as a vaccine candidate, and, interestingly, it was also shown that hypoglycosylation of MUC-1 can be brought about in normal cells during inflammation and infections (bacterial and viral), especially during childhood, which may result in the induction of T-cell reactive clones that would potentially provide immunity against tumors expressing such antigens in later life (Dr. Olivera J. Finn, University of Pittsburgh, Pittsburgh, PA). In fact, a large study in ovarian cancer showed that women who experienced infections early in life had a decreased risk of developing cancer. Lack of MUC-1 antibodies was associated with ovarian cancer and possibly breast cancer, suggesting that childhood infections could be protective against the development of ovarian cancer later in life; this may also prove to be the case for many other cancers expressing "abnormal self" antigens. Lactation allows glands to express abnormal hypoglycosylated MUC-1 antigen, and as previously noted by Sir Peter Medawar, women who gave birth early on in their lives had a reduced risk of developing cancer. Whether or not a preventative vaccine could be developed, which incorporates MUC-1 and other antigens such as CEA, PSA, and PSMA, is interesting to consider for the future.

The Tumor Microenvironment, Its Role in Tumor Progression, and How It Can Be Manipulated to Promote Tumor Rejection

In considering the tumor microenvironment, there was general agreement that, although antigen-specific CTLs can be generated and detected in the circulation of vaccinated patients, these do not act against the actual tumor, implying that many other mechanisms/cells such as regulatory cells, inhibitory ligands such as PD-L1, and soluble factors such as transforming growth factor-β (TGF-β) and indoleamine 2,3-dioxygenase operate within the tumor microenvironment (Dr. Thomas F. Gajewski, University of Chicago, Chicago, IL). Moreover, the type of DCs present at the tumor site will dictate the activation/tolerization status of T lymphocytes. The presence of plasmacytoid DCs in the murine Tramp model of prostate cancer was indeed shown to induce suppression, whereby T-cell responses are prevented from mediating cytotoxic activity toward tumor cells; in contrast, the trafficking of CD4-positive cells into tumors alters the microenvironment and promotes immunity mediated by CD8-positive effector cells (Dr. Andy A. Hurwitz, National Cancer Institute, Frederick, MD).

Appropriate T-cell activation by DCs may also occur as the result of inactivation of Treg function via the OX40 pathway. Thus, administration of monoclonal antibody to OX40 can lead to tumor rejection in murine models (Dr. Mario P. Colombo, Istituto Nazionale Tumori, Milan, Italy). OX40-L interactions are multifactorial, accounting for the expansion of the T-helper cell proliferation, down-regulation of Treg activity, and inhibition of degranulation of mast cells (MC). The antitumor role of MCs was established in MC-deficient mice, where it was shown that MC infiltration into tumors caused significant inhibition of their growth. These newly described mechanisms, together with strategies that block TGF-β (Dr. Zvi G. Fridlender, University of Pennsylvania, Philadelphia, PA) and anti-CTLA-4 therapy (Dr. Jeffrey Weber, H Lee Moffitt Cancer Center, Tampa, FL), are modalities that can be considered as strategies appropriate for altering the tumor microenvironment to the benefit of the host.

It is well known that down-regulation of MHC expression on tumor cells and defective TCRs expressed by CTLs account, in part, for the apparent low level of adaptive immunity operative within the tumor environment. The results presented at this conference described many new potential therapies that could overcome “immune suppression.” The number of CD3-positive T cells infiltrating the tumor microenvironment inversely correlates with vascular endothelial growth factor (VEGF) expression, and, in ovarian cancer, 55% of cases were shown to have CD3-positive infiltrating T cells, which was associated with long-term patient survival (Dr. Georges G. Coukos, University of Pennsylvania, Pennsylvania, PA). VEGF itself has immunosuppressive activity, and a decrease in its expression allows T-cell infiltration to occur, leading to tumor rejection. Two novel genes have been identified within the vasculature of ovarian cancer, namely endothelin receptor A, which induces blood vessel constriction, and endothelin receptor B (ETRB), which induces vasodilation. ETRB expression was found to be increased in vascular cells within tumors showing low T-cell infiltration, where the use of anti-ETRB blocking peptide (BQ-788) increases T-cell trafficking into tumors in a mouse model. Thus, ETRB regulates access of T cells into the tumor environment, and clinical trials will determine whether BQ-788 peptide shows clinical efficacy by improving patient survival. Furthermore, strategies that target both stroma and tumor cells at the same time could increase the success rate of vaccination (Dr. Hans Schreiber, University of Chicago, Chicago, IL); it was shown that stroma cells take up tumor-derived exosomes and become sensitive to antigen-specific cytotoxic T cells.

Myeloid-Derived Suppressor Cells, a Diverse Group of Cells That Require Further Study

Several speakers described the role of myeloid-derived suppressor cells (MDSC), which represent a heterogeneous group of immature myeloid cells that express GR-1 and CD11b and, upon entry into the tumor environment, undergo a functional change from antigen-specific to nonspecific suppression (Dr. Suzanne Ostrand-Rosenberg, University of Maryland Baltimore, Baltimore, MD). These cells...
may play a role in the induction of Th2 CD4-positive lymphocyte activity and show the ability to prolong allograft survival (Dr. Dimitri Gabrilovich, H Lee Moffitt Cancer Center, Tampa, FL; Dr. Vincenzo Bronte, Istituto Oncologico Veneto, Padova, Italy; Dr. Lisa M. Coussens, University of California, San Francisco, CA). Alternatively, MDSCs can promote CD4-positive/CD25-positive FoxP3+ Treg cells in the tumor-bearer host, and data presented showed that sunitinib malate, an FDA-approved inhibitor of tyrosine kinase activity, effectively reverses MDSC-mediated immune suppression (Dr. Shu-Hsia Chen, Mount Sinai School of Medicine, New York, NY). This treatment decreases both MDSCs and Treg cell numbers in advanced tumor-bearer animals, concomitant with the reduction of IL-10, TGF-β, and FoxP3 levels and an increase in IFN-γ. In preclinical models at least, sunitinib abrogates MDSC-mediated immune suppression, allowing CD8-positive and CD4-positive T lymphocytes to infiltrate tumors. STAT-3 when phosphorylated (p-STAT-3) is a key mediator of immune suppression in glioblastoma multiforme. Glioblastoma cancer stem cells (gCSC) have been shown to express CTLA-4 and B7-H1, which are known to induce apoptosis of T lymphocytes, a process that is mediated both through cell-cell contact and by soluble mediators. p-STAT-3 expression was found to be up-regulated in gCSCs, and, when inhibited with the STAT-3 inhibitor WP1066, this led to the blockade of this activation pathway and the induction of antitumor immunity (Dr. Jun Wei, University of Texas M.D. Anderson Cancer Center, Houston, TX).

In considering the results of clinical trials and the results presented at this conference, there is clearly a need to develop robust biomarkers to stratify patient response and to hasten the progress of new immunotherapy strategies into the clinic.

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No potential conflicts of interest were disclosed.

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