Conference Scene

Immune effector mechanisms in tumor immunity

The 19th Annual Cancer Research Institute Cancer Immunotherapy Symposium
3–5 October 2011, New York City, NY, USA

The 19th Annual Cancer Research Institute Cancer Immunotherapy Symposium was organized by the Cancer Research Institute in order to bring together researchers in basic, translational and clinical research, and industry representatives in order to exchange data, tools and opinions to further cancer immunotherapy. Our increasing understanding of immune mechanisms that mediate either the regression or progression of cancer is being translated into therapies that have begun to show true clinical benefit for cancer patients. The conference built on these early successes and aimed to push further into the uncharted territories of successful cancer immunotherapy.

The 19th Annual Cancer Research Institute Cancer Immunotherapy Symposium took place in New York City (NY, USA) on 3–5 October 2011. This article provides a short overview of the reported progress in understanding the mechanisms by which the immune system can recognize and destroy cancer cells, and of new insights into the remaining obstacles to immune-mediated tumor eradication. Over 400 participants from academia and industry participated in the scientific program that included platform presentations from 25 international experts and over 150 poster presentations. The conference experience was enhanced by the smooth organization, the conference center's central Times Square location and the lively discussions with colleagues and friends long-known and newly made.

The meeting opened with congratulations to James Allison, who took over as director of the Cancer Research Institute (CRI)'s Scientific Council from Lloyd Old, the CRI's founding scientific and medical director since 1971. Next came the bittersweet news that Ralph Steinman (Rockefeller University, NY, USA) had received the Nobel Prize in Medicine for his discovery of the dendritic cell, 3 days after he had passed away from pancreatic cancer. Steinman had received the CRI's highest honor, the William B Coley Award for Distinguished Research in Basic and Tumor Immunology, in 1998 for the same discovery. The meeting participants' shared appreciation for his monumental contribution towards cancer immunotherapy was palpable throughout the conference.

Antibodies: mechanisms of antitumor activity

Jeffrey Ravetch (Rockefeller University) kicked off the first session with a provocative presentation on the importance of antibody Fc domains for the antitumor activity of agonistic antibodies to TNF receptor family members such as CD40, Fas and DR4/5. Antibody isotypes that engage the inhibitory FcγRIIB receptor confer the strongest antitumor activity, probably via effects on myeloid cells, an idea supported by recent clinical results with agonistic anti-CD40 antibodies in pancreatic cancer. Ronald Levy (Stanford University, Stanford, CA, USA) similarly showed that agonistic anti-41BB antibodies can activate killer cells to enhance ADCC after lymphoma therapy with rituximab or intratumoral CpG. In addition, Ana Carrizosa Anderson (Brigham and Women's Hospital, MA, USA) presented preclinical results extending the recent success of anti-CTLA-4-checkpoint blockade with additional antibody blockade of the inhibitory receptors, PD-1 and Tim-3. Overall, antibodies that directly modulate the immune system are quickly becoming a major category of immunotherapeutic intervention with great clinical promise.

Myeloid-derived cells in the antitumor immune response

Irving Weissman (Stanford University) described the efficacy of anti-CD47 antibodies as a therapeutic for hematopoietic and solid tumors. Blocking the 'don't eat me' signal, CD47, showed good efficacy

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in a variety of human solid tumor xenografts in immunodeficient mice, and synergized with rituximab in last year's clinical trial in non-Hodgkin's lymphoma, possibly allowing the removal of currently used chemotherapeutics from the treatment regimen. Steven Albelda (University of Pennsylvania, PA, USA) presented evidence that the well-established paradigm of M1 (tumoricidal) and M2 (tumor-promoting) tumor-associated macrophages may be paralleled by a similar N1–N2 dichotomy among tumor-associated neutrophils. The TGFBR–SMAD axis may enforce the tumor-promoting tumor-associated neutrophil phenotype in a TGFBR1-dependent and blockable fashion.

Alberto Mantovani (University of Milan, Milan, Italy) described a novel role for IL-4-induced c-Myc as a driver of M2 macrophage polarization via activation of STAT6 and expression of downstream genes such as *VEGF*, *MMP9*, *HIF-1 α* and *TGF- β* . Another driver of intratumoral inflammation is pentraxin 3, induced in macrophages and dendritic cells by IL-10 and downregulated by IFN- γ . It is such a potent regulator of leukocyte recruitment (via P-selectin) that it could serve as a marker of tumor-associated inflammation.

Vincenzo Bronte (Verona University, Verona, Italy) presented surprising new data on abrogation of T-cell trafficking into tumors due to nitration of the CCL2 chemokine by peroxynitrite produced by myeloid-derived suppressor cells. Interestingly, nitrated CCL2 retained the ability to attract myeloid cells into the tumor, thus selectively inhibiting trafficking of T cells, but not suppressive myeloid cells, into tumors. Peroxynitrite production can be blocked by nitroaspirin treatment, elucidating yet another immunosuppressive mechanism preventing tumor destruction and its therapeutic reversal. Jeffrey Pollard (Albert Einstein College of Medicine, NY, USA) also highlighted CCL2 as a critical chemokine mediating monocyte recruitment into tumors, and CCL2 inhibition inhibited metastasis, pointing to CCL2 as a chemokine of continuing interest to the field. Yet another chemokine, CCL28, was presented by George Coukos (University of Pennsylvania) to be upregulated in ovarian cancer via HIF-1 α , and to recruit CCR10⁺

Tregs into the tumors. Interestingly, these Tregs then expressed VEGF-A, promoting angiogenesis in these hypoxic tumors, thus mechanistically linking immune suppression and angiogenesis.

Antitumor lymphocytes

Khashayarsha Khazaie (Northwestern University, IL, USA) cautioned us not to regard all FoxP3⁺ Tregs as equal, demonstrating how increasing levels of the ROR γ t transcription factor block their anti-inflammatory properties. ROR γ t^{hi}, IL-10^{low} and IL-17^{hi} cells are present alongside 'classic' ROR γ t^{low}, IL-10^{hi} and IL-17^{low} suppressive Tregs in human colon cancer samples, and promote polyposis in a mouse model. Willem Overwijk (MD Anderson Cancer Center, TX, USA), showed that tumor-specific CD8⁺ T-cell localization can be powerfully controlled by cancer vaccine formulations, with persistent, antigen-rich vaccine depots sequestering and eventually deleting the bulk of vaccine-primed T cells, while short-lived depots release primed T cells to localize to tumors and destroy them. Carl June (University of Pennsylvania) summarized his work on lymphoma treatment with T cells that were genetically modified to express CD19 lymphoma antigen-specific chimeric antigen receptors with a 4-1BB-containing signaling endodomain, which induced strong T-cell expansion and persistence *in vivo*, as well as dramatic clinical responses.

Metabolism & cancer immunity

Nicholas Haining (Dana-Farber Cancer Institute, MA, USA) presented molecular signatures of HIV-specific T cells from HIV progressors and nonprogressors, leading to a new role for the transcription factor BATF in suppressing immunity. Yongwon Choi (University of Pennsylvania) showed surprising results on TRAF6-dependent generation of CD8 T-cell memory via stimulation of fatty acid oxidation. Tak Mak (University of Toronto, Toronto, Canada) gave a sweeping overview of the connections between hypoxia, oncogenes and metabolic dysregulation in cancer cells, arguing that the PI3K pathway, active in a majority of cancers, is intimately involved in mediating the Warburg effect that allows cancer cells to produce most of their energy through glycolysis. Frequent

mutations in cancer cells of genes encoding ‘innocuous’ metabolic enzymes such as isocitrate dehydrogenase indicate a more integral role for metabolism in cancer cell survival than previously appreciated.

Advances in clinical immunotherapy

Sacha Gnjjatic (Memorial Sloan-Kettering Cancer Center, NY, USA) showed that poly-inosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose (poly-ICLC), a nucleic acid derivative, can function as a potent vaccine adjuvant for NY-ESO-1 polypeptide vaccines in ovarian cancer patients. Poly-ICLC increased the rate of successful immunization, as well as the speed and level of specific antibody induction, while skewing the T-cell response to a more type-1 cytokine profile. Charles Drake (Johns Hopkins University, MD, USA) reported preliminary clinical results on checkpoint blockade of the exhaustion-related molecule, PD-1, as well as preclinical results on combination blockade of PD-1 and LAG-3. However, he cautioned that PD-1 induction does not occur in some immune responses including *Listeria* infection, and that PD-1 expression on T cells does not always correlate with T-cell exhaustion, thus pointing to the need for a more personalized approach to therapeutic coinhibitory blockade. Stephen Hodi (Dana-Farber Cancer Institute) showed that the combination of CTLA-4 checkpoint blockade (ipilimumab) and anti-VEGF-A antibody therapy (bevacizumab), yielded at least comparable clinical activity compared with ipilimumab alone, and more activated tumor endothelium and T-cell infiltration as well as increased systemic levels of central memory T cells.

Future perspective

This conference strengthened the recent sentiments in the immunotherapeutic community that we are finally getting

a better handle on the specific immune responses that promote and inhibit cancer initiation and progression, as well as on the molecules that either promote or inhibit these immune responses. At this meeting alone, specific targetable molecules that were highlighted included CD40, Fas, DR4/5, PD-1–PD-1L, Tim-3, LAG-3, CD47, 4-1BB, CTLA-4, OX40, TGF- β , CCL2, CCL28, CCR2, CCR10, NKG2D, ROR γ t, TLR3/7/9, TRAF6, PI3K, STAT6, HIF-1 α , VEGF-A, EGFR, MMP-9, IL-2, IL-10, Her2/3, CD19, CD20, NY-ESO-1, EpCAM, gp100 and GD2, the large majority of which we currently know how to target with blocking or agonistic antibodies, vaccines or other agents. It appears that, as a cancer immunology community, we are now facing at least three major challenges:

- To identify the best candidate agents for combination therapy;
- To develop and produce currently unavailable clinical-grade agents;
- Raising patient, public, business and political awareness of the importance of, and develop incentives for, making existing agents that are currently kept intentionally unavailable for use in combination therapy available for the benefit of all patients.

We are looking forward to progress in all these areas at next year’s CRI conference.

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