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From cell regulation to patient survival: 2nd Cancer immunotherapy and immunomonitoring (CITIM) meeting, Budapest, 2–5 May 2011

Viktor Umansky,

Skin Cancer Unit (G300), German Cancer Research Center, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany, V.Umansky@dkfz-heidelberg.de

Anatoli Malyguine,

Laboratory of Cell Mediated Immunity, SAIC-Frederick, Inc., NCI-Frederick, Frederick, MD, USA

Beatrix Kotlan,

Department of Molecular Immunology and Toxicology, Center of Surgical and Molecular Tumorpathology, National Institute of Oncology, Budapest, Hungary

Natalia Aptsiauri, and

Laboratory of Clinical Analysis and Immunology, University Hospital Virgen de las Nieves, Granada, Spain

Michael R. Shurin

Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Abstract

The 2nd International Conference “Cancer Immunotherapy and Immunomonitoring (CITIM)” took place in Budapest, Hungary, and was organized by the International (Chair—Michael Shurin) and Local (Chair—Beatrix Kotlan) Organizing Committees. The main aim was to bring the world’s best tumor immunologists to Budapest to discuss the mechanisms of immune regulation in the tumor microenvironment, the efficacy of anticancer immunotherapeutic modalities, the results of clinical trials and the methods of patients’ immunomonitoring. This report provides a short overview of novel concepts, strategies and clinical achievements in this quickly developing field of oncology since the first CITIM meeting held in Kiev, Ukraine, in 2009. Almost 200 participants from more than 30 countries of Europe, Asia, Africa, North and South America as well as from Australia were attracted by the scientific program that consisted of presentations from 58 international experts. Good memories remain from the lively discussions of ten plenary sessions, four Keynote lectures, two special plenary presentations, best abstract award session and 75 posters.

Immunity and the malignant process

The conference was opened by the Keynote Lecture of D. Gabrilovich (Tampa, FL, USA) who discussed the role of myeloid-derived suppressor cells (MDSC) as a major contributor to tumor escape. MDSC accumulate in tumor-bearing hosts and can strongly suppress T-

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Correspondence to: Viktor Umansky.

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cell-mediated immune responses by production of nitric oxide, reactive oxygen species and TGF- β , as well as by up-regulation of arginase-1 and cyclooxygenase-2 activities. A “two-signal” model of regulation of MDSC accumulation was proposed, in which cytokines and growth factors (like GM-CSF, IL-6 and VEGF) acting via the signal transducer and activator of transcription (STAT) 3 and STAT5 are responsible for MDSC expansion and pro-inflammatory molecules (like IFN- γ or IL-1 β) utilizing STAT1 and NF- κ B drive MDSC activation. R. Apte (Beer-Sheva, Israel) described the mechanisms of IL-1 β involvement in the tumor progression, which is mainly induced through recruitment, retention and pro-invasive function of MDSC and the immunotherapeutic implications of IL-1 β neutralization. It seems that IL-1 β in the microenvironment keeps MDSC in their immature state, while its neutralization induces their maturation to M1 macrophages. Whereas IL-1 β promotes tumor-mediated angiogenesis and immuno-suppression, IL-1 α is less inflammatory and induces effective anti-tumor immunity. The treatment for tumor-bearing hosts with the IL-1Ra could reduce tumor angiogenesis and invasiveness, supporting a possible therapeutic application of IL-1 β blockers in anti-tumor therapy. Important issues of inhibition of tumor-specific effector T-cell (Teff) activity by tumor-specific regulatory T cells (Treg) in cancer patients were analyzed by P. Beckhove (Heidelberg, Germany). During cancer progression, these Treg from the bone marrow become activated and migrate into the tumor, where they can suppress anti-tumor activities of infiltrating tumor-specific Teff. A selective blocking of the tumor infiltration by Treg combined with the selective increase in Teff at the tumor site may provide an important therapeutic option for cancer treatment. S. Neelapu (Houston, TX, USA) focused on the immunosuppressive mechanisms in lymphoma patients. The Treg cell population and the interaction between programmed death-1 (PD-1) receptor and PD1-ligand have been identified as important negative regulatory pathways that inhibit T-cell function in non-Hodgkin lymphoma. At the end of the session, F. Marincola (Bethesda, MD, USA) presented an interesting concept of transcriptional signatures of tumor rejection that include a switch from chronic to acute inflammation and could be used as a predictive of responsiveness to biological therapy. It was emphasized that tumor rejection mechanisms overlapped largely those associated with other aspects of immune-mediated tissue-specific destruction during allograft rejection, graft-versus-host disease, acute clearance of pathogens and autoimmunity. Understanding the mechanisms that may switch chronic inflammatory processes into a tumor destroying acute reaction could guide the development of novel therapies.

Regulatory and effector mechanisms in the tumor environment

Of special interest was the Keynote Presentation by I. Witz (Tel Aviv, Israel) who analyzed the interaction of tumor cells with the metastatic microenvironment that regulates site-specific metastasis to particular organs. Recently developed mouse xenograft models for melanoma and neuroblastoma metastasis allowed a molecular signature of site-specific metastasis to be established and the identification of cancer genes controlled by the metastatic microenvironment. These genes could serve as specific biomarkers and targets for efficient anti-tumor therapy. A. Cesano (San Francisco, CA, USA) reported on insights into autoimmune and malignant disease via signal cell network profiling that represents an approach for analyzing and interpreting post-translational protein modifications (like phosphorylation or acetylation) at the single cell level. Endogenous proteins were measured in viable cells before and after exposure to drugs or cytokines. Multivariate analysis should permit development of predictive models that can be validated in independent studies. A pivotal significance of IL-1 β secreted by tumor and surrounding host cells for tumor progression and angiogenesis was stressed in the presentation by E. Voronov (Beer-Sheva, Israel). Matrigel plugs supplemented with recombinant IL-1 β or VEGF or B16 melanoma cells were used to study interactions between angiogenesis and inflammation. Neutralization of IL-1 β at the tumor site was demonstrated to inhibit tumor angiogenesis. The critical issue

of immune suppression in the tumor microenvironment and the role of myeloid cells was discussed by S. Ostrand-Rosenberg (Baltimore, MD, USA). Two major myeloid cell populations facilitating tumor progression are MDSC and alternatively activated (M2) macrophages. It was stressed that chronic inflammation contributed to tumor progression by blocking tumor immunity via MDSC stimulation. Since MDSC not only respond to pro-inflammatory mediators but also produce these factors, inflammation could provide an autocrine feedback loop sustaining MDSC levels in tumor-bearing hosts. L. Vannucci (Prague, Czech Republic) proposed to use gnotobiologic animals to evaluate the role of chronic inflammation in the bowel mucosa in the onset and progression of cancer. Experimental data showed that germ-free animals developed fewer tumors than animals with intestinal bacteria, suggesting a tumor-inducing capacity of pro-inflammatory products and a different threshold of tolerance in germ-free conditions. The complexity of stromal structures associated with intestinal lymphatic follicles was found to develop consensually with the activated lymphatic tissue. Cancer-associated fibroblasts (CAFs) as cells in the tumor microenvironment supporting tumor progression were analyzed by O. Aprelikova (Bethesda, MD, USA). A striking alteration of gene expression patterns in CAFs was found to be mediated by alterations in microRNA (miR) expression. The discovery of the tumor-promoting role of decreased miR-148a expression in CAFs from endometrial cancer may provide a useful therapeutic target.

New insights in cancer immunotherapy

Short special plenary presentations that covered the latest insights in cancer immunotherapy were opened by G. Shurin (Pittsburgh, PA, USA) who reported on the immunosuppressive and protumorigenic function of tumor-associated regulatory dendritic cells (DC). These cells express low levels of CD11c and CD11b, do not express Gr1 and plasmacytoid DC markers and suppress proliferation of mitogen-activated syngeneic T cells. Prevention of their accumulation in tumor-bearing hosts leads to the enhancement of the anti-tumor efficiency of DC vaccines, indicating another important approach for neutralization of tumor-associated immunosuppression induced by myeloid regulatory cells. B. Kotlan (Budapest, Hungary) characterized antibodies against glycosphingolipid structures on the surface of melanoma cells showing selective binding capacities and strong anti-proliferative and pro-apoptotic potential with a promising therapeutic application. An important issue of the immune escape of metastatic melanoma cells with β 2-microglobulin gene alterations was discussed by N. Aptsiauri (Granada, Spain). The structural defect in this gene may represent a serious barrier for T-cell-mediated immunotherapy and should be taken into account when treatment protocols are designed. Therapeutic effects of cyclophosphamide in low doses in the transgenic mouse melanoma model were analyzed by A. Sevko (Heidelberg, Germany). Despite the reduction in Treg numbers, this therapy showed no anti-tumor efficiency due to the dramatic expansion of MDSC with a strong immunosuppressive activity. Finally, M. Haeryfar (London, Canada) pointed out a potential application of rapamycin to treat recipients of allografts harboring tumor antigens since it improves the cross-primed CD8 T-cell responses to tumor antigens while weakening T-cell-mediated alloreactivity.

Tumor microenvironment and cancer immunotherapy

The next session started with a presentation by A. Hurwitz (Frederick, MD, USA) who characterized several molecules such as indoleamine-pyrrole 2,3-dioxygenase (IDO), arginase and TGF- β produced by tumor-associated plasmacytoid DC, which were shown to impair the anti-tumor T-cell reactivity in the prostate cancer transgenic mouse model. Moreover, levels of the forkhead box protein (FOXO3a) were elevated in these DC. Silencing of FOXO3a significantly enhanced CD8 T-cell effector functions after co-culture and could be applied as a novel strategy of cancer immunotherapy. A broad overview of

immunosuppressive factors in human tumor microenvironment with a special focus on the role of adenosine and prostaglandin E2 (PGE2) was presented by T. Whiteside (Pittsburgh, PA, USA). Large amounts of adenosine produced by conversion of exogenous ATP via ectonucleotidases CD39 and CD73 as well as PGE2 produced through COX-2 were shown to significantly contribute to the immunosuppression mediated by human Treg. The pharmacologic blockade of both pathways by metabolic inhibitors relieved suppression, restored anti-tumor immune responses and may be used for the immunotherapy of cancer patients. Tumor-mediated dysfunction in adaptive and innate immunity in cancer patients was also discussed by L. Rivoltini (Milan, Italy). In advanced human melanoma, a consistent accumulation of immunosuppressive myeloid cells was demonstrated. These cells, considered to be a human counterpart of mouse MDSC, were shown to inhibit T-cell immunity via TGF- β release. Importantly, these immunosuppressive cells could be generated in vitro upon co-culture of normal monocytes with tumor-derived exosomes expressing IL-13, suggesting a possible mechanism of the MDSC accumulation in melanoma patients. The important issue of strong links between chronic inflammation and tumor progression was addressed by M. Baniyash (Jerusalem, Israel). Chronic inflammation can not only predispose a host to cancer but can also be induced by developing tumors. The immunosuppressive environment (represented by MDSC and soluble inflammatory factors) generated under both conditions induces T- and NK-cell dysfunction associated with TCR ζ chain down-regulation. Therefore, neutralization of immunosuppression detected in tumor-bearing hosts should be applied prior adoptive cellular immunotherapy to enhance the efficiency of the latter. E. Rajnavölgyi (Budapest, Hungary) analyzed the characteristics of different DC subsets as adjuvants for anti-tumor vaccines pointing out that proper targeting of DC could be effective. Furthermore, a selected DC subset should be properly stimulated to induce protective anti-tumor immune responses.

Improving cancer immunotherapy: new targets, vaccines and models

Presentations in this plenary session were focused on immune regulation in the tumor environment to increase the efficiency of cancer immunotherapy. F. Garrido (Granada, Spain) discussed two types of alterations in HLA class I expression on tumor cells. If these changes are reversible by cytokines (so-called soft lesions), tumor-specific T-cell responses will be enhanced and tumor lesions will regress. In the presence of structural defects ("hard" lesion), immune escape mechanisms will dominate and tumors will progress. These results emphasize a key role of the unaltered HLA class I expression for effective T-cell-mediated cancer immunotherapy. An interesting approach of identifying common targets for anti-tumor and anti-inflammatory therapy was reported by Z. Szekanecz (Debrecen, Hungary). For example, some inhibitors of angiogenesis currently used for cancer treatment have been applied in clinical trials for rheumatoid arthritis. Moreover, antibodies against cytokines like TNF- α or IL-6 used to treat arthritis, lupus or scleroderma may be considered to neutralize chronic inflammation and immunosuppression in the tumor microenvironment. A. Jewett (Los Angeles, CA, USA) presented another strategy of cancer immunotherapy using NK cells that were shown to preferentially target human oral squamous carcinoma stem cells as well as human mesenchymal stem cells and induced pluripotent stem cells. However, this efficient lysis could be substantially prevented by monocytes, suggesting that the efficiency of repeated allogeneic NK cell transplantation for specific elimination of cancer stem cells will be increased if combined with the inhibition of monocyte function. Mechanisms of cancer cell lysis by NK cells were summarized by A. Porgador (Beer-Sheva, Israel). Natural cytotoxicity receptors (NKp30, NKp46 and NKp44) were reported to interact with their multiple ligands on cancer cells. Although most of these ligands are membrane-associated, some of them represent nuclear proteins. Recently, he has identified a nuclear factor that functions as an inhibitory ligand for one of the natural cytotoxicity receptors. A comprehensive analysis of current targeted therapies of metastatic melanoma was presented

by P. Ascierto (Naples, Italy). One approach utilizes the blocking of several pathways involved in tumor growth, survival and angiogenesis. Another strategy is aimed in enhancing anti-tumor immune responses by targeting tolerance inducing molecules on T cells, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and PD-1. In addition, agonistic mAbs against CD137 (4-1BB) on antigen-primed T cells were found to increase anti-tumor immunity. As a new class of cancer therapeutics, immunostimulatory mAbs require a substantial change in the definition of therapy response criteria.

Immunotherapeutic approaches to pediatric malignancies

The plenary session was devoted to new immunotherapeutic approaches to pediatric malignancies. The Keynote Presentation by M. Brenner (Houston, TX, USA) was focused on adoptive immunotherapy of patients with solid tumors or hematologic malignancies using genetically modified virus-specific cytotoxic T cells. Significant response rates were obtained in patients with EBV+ lymphoma and nasopharyngeal carcinoma. These cytotoxic T cells can be further modified with chimeric antigen receptors (CAR) to provide them with dual specificities. Such CAR expressing T cells are currently applied in clinical trials in patients with neuroblastoma, lung cancer and glioblastoma. The tumor immunotherapeutic strategy with CAR-modified T cells was further discussed by G. Dotti (Houston, TX, USA) and L. Cooper (Houston, TX, USA). Several problems of broad clinical application of these cells could be solved by using the *Sleeping Beauty* transposon and transposase system to reduce the production cost; by applying molecular sensor for oxygen enabling the genetically modified T cells to express CAR only under hypoxia conditions at the tumor site; or by co-expressing membrane-bound cytokines along with antigen-specific CAR to provide a survival signal thorough the common γ chain. Preliminary results from numerous clinical trials in patients with solid tumors and hematological malignancies indicate that the costimulation through CAR molecules is essential for the in vivo survival and expansion of CAR-modified T cells. Future improvements in this cancer immunotherapy will depend on the optimization of T-cell migration into the tumor site and on the choosing of a suitable T-cell subset to be redirected with CARs. The next two presentations by L. Metelitsa (Houston, TX, USA) and J. Anderson (London, UK) were focused on the importance of NKT cells and $\gamma\delta$ T cells, respectively, in modern tumor immunotherapy. Human NKT cells are CD1d-restricted. CD1d expression has been found in leukemia and lymphoma cells as well as in tumor-associated macrophages (TAM). NKT were found to suppress the growth of neuroblastoma indirectly by targeting CD1d+TAM in a CD1d-dependent manner. Thus, direct lysis of CD1d+ tumor cells and tumor-supportive TAM by NKT provides a basis for developing efficient cancer immunotherapies. Human $\gamma\delta$ T cells representing 1–5% of circulating T cells and binding phenyl pyrophosphates in an MHC unrestricted manner were shown to be associated with infection and cancer. Upon activation with pyrophosphate, these cells are able to take up antigens and to present them to CD4 or CD8 T cells. In addition to this antigen-presenting function, they could exert a potent killing capacity against tumor cells.

New aspects of immune regulation

New aspects of immune regulations were discussed in additional special plenary presentations. E. Klein (Stockholm, Sweden) reported modifications of the expression of EBV-encoded proteins in B cells by cytokines. In a Hodgkin-derived cell line that was infected with EBV in vitro and expressed only EBNA-1, exposure to IL-4 or IL-13 induced expression of the latent membrane protein (LMP-1), thus resulting in the EBV expression pattern that is the characteristic of EBV-positive Reed/Sternberg cells in vivo. This was shown to involve the STAT6. Since Hodgkin/Reed/Sternberg cells are known to secrete IL-13, to have constitutively activated STAT6 and to be closely surrounded by IL-4-

producing CD4 T cells, these mechanisms may operate in the expression of LMP-1. L. Radvanyi (Houston, TX, USA) focused on inducible T-cell costimulator (ICOS)-positive Treg cells that showed a high immunosuppressive capacity and were found to be accumulated in metastatic melanoma patients. Although treatment of these patients with high-dose IL-2 substantially increased the numbers of ICOS⁺ Treg, the responders to IL-2 therapy exhibited a much lower augmentation of this highly suppressive Treg subpopulation than non-responders. Differential effects of triggering endothelin-1 (ET-1) receptors on murine DC were reported by G. Guruli (Richmond, VA, USA). Whereas the blockade of ET_A receptors might impair immune responses and prolong graft survival, the neutralization of ET_B receptors seems to increase the immunostimulatory functions of DC that might be used for cancer immunotherapy. A. Ben-Baruch (Tel Aviv, Israel) presented an inflammatory network of cytokines (TNF- α and IL-1 β) and chemokines (CCL2 and CCL5) in breast cancer that contributes to the tumor-promoting activities of cancer-associated fibroblasts. In addition, both cytokines could potentially induce epithelial-to-mesenchymal transition in tumor cells that lead to the progressed and recurred disease, indicating a necessity of the targeting of multiple inflammatory cytokines and chemokines for the effective treatment for breast cancer.

Cancer immunotherapy: lessons and perspectives

The next session was opened by E. Yefenof (Jerusalem, Israel) who reported on the molecular rationale of steroid-based therapy of lymphoma and leukemia. Since the resistance of acute T lymphoblastic leukemia to glucocorticoid-induced apoptosis is mediated by transcription factor Notch1 leading the Akt activation, inhibition of the PI3 K-Akt survival pathway could shift leukemia cells to an apoptosis-prone phenotype. Promising therapeutic effects were also achieved by the broad-acting protein kinase inhibitor staurosporine that induced the expression of the pro-apoptotic Nur77 orphan receptor that overcomes an apoptotic blocking by Bcl-2. A novel subpopulation of human CD8 T cells specific for heme oxygenase-1 (HO-1) and exerting regulatory functions was described by P. thor Straten (Herlev, Denmark). HO-1 is expressed at high levels in malignant cells and exerts anti-inflammatory functions. Remarkably, HLA-restricted HO-1-specific CD8 T cells detectable in cancer patients could suppress IFN- γ release, proliferation and cytotoxicity of tumor-reactive T cells much more strongly than regulatory CD4 T cells. The inhibitory activity of HO-1-specific T cells seems to be mediated at least partly by soluble factors. The possibility of restructuring the tumor microenvironment by CD40-based interventions was analyzed by J. Weiss (Frederick, MD, USA). He found that the combination of anti-CD40 mAbs and IL-2 in metastatic renal cell carcinoma induced clinical responses which the immunosuppressive tumor milieu was converted to a predominantly anti-tumor Th1 environment. This modulation induced a heavy infiltration of established tumors by NK and CD8 T cells producing high amounts of IFN- γ , whereas the amount of MDSC and Treg, as well as the expression of arginase and Th2 cytokines, was decreased. J. Timar (Budapest, Hungary) focused on gene signatures in human melanoma that are responsible for its resistance to IFN treatment. The majority of genes involved in IFN-resistance formed a differential metastatic gene signature of human melanoma, indicating that this resistance can be genetically linked to the enhanced metastatic potential. N. Haran-Ghera (Rehovot, Israel) presented data on treatment for mouse multiple myeloma with moderately low doses of cyclophosphamide that drastically reduced tumor load and prolonged the survival, inducing transition from an acute to a chronic disease phase. Treg depletion in treated mice was associated with an increase in the number of IFN- γ -producing NKT cells capable of controlling tumor growth in vivo.

Cancer immunotherapy: regulatory and effector cell interactions

A detailed analysis of the distribution of T-cell subsets in the peripheral blood of long-term melanoma survivors was presented by G. Pawelec (Tübingen, Germany). Identifying such “immune signatures” would be useful for predicting patient responsiveness to therapy and for manipulating the system to enhance anti-tumor immunity. Melanoma patients studied were involved in clinical trials of peptide, RNA or DNA vaccination, local IL-2 or systemic anti-CTLA-4 antibody treatment. In the retrospective setting, most exceptionally long-term survivors showed New York-ESO-1 (NY-ESO-1)-specific CD4 and CD8 T-cell responses predominantly associated with pro-inflammatory cytokine production; strikingly, this was independent of the nature of the therapy patients had received. C. Leclerc (Paris, France) focused on the comparative evaluation of the repertoire of tumor-infiltrating effector and regulatory CD4 T cells. Using TC1 and MO-5 mouse tumor models and immunoscope technology, the group demonstrated alterations in the length distribution of complementarity-determining region 3 (CDR3) on all Vb chain families in both Treg and Teff cells, suggesting a selective expansion of T-cell clones. The presentation by V. Umansky (Heidelberg, Germany) was based on the transgenic mouse model of spontaneous malignant melanoma that closely resembles the clinical situation and is of critical importance for the design of novel immunotherapies. Development of chronic inflammation and accumulation of MDSC with strong immunosuppressive capacity was found to be associated with the reduction in TCR ζ chain expression in T cells in skin tumors. Metabolic inhibition of MDSC activities by the inhibitor of phosphodiesterase-5 sildenafil or by ultra-low, non-cytotoxic doses of paclitaxel led to the prolonged mouse survival and partial normalization of T-cell functions.

Cancer immunotherapy: new approaches

In the next Keynote Presentation, W. Murphy (Sacramento, CA, USA) addressed the important question of bystander activation of memory T cells upon immunotherapy. Strong immunologic stimuli like IL-2, agonistic anti-CD40 mAbs or toll-like receptor triggering induce anti-tumor responses associated with the expansion of memory CD8 T cells. These cells fail to express activation markers CD25 and PD-1, can be induced to undergo bystander activation and expansion and behave in an antigen-nonspecific manner resulting in significant anti-tumor effects. Given the weakly immunogenic nature of human cancers and the tremendous ability of tumor cells to select for antigen-loss variants, the importance of such bystander memory T cells in successful anti-tumor responses may be considerable. M. Shurin (Pittsburgh, PA, USA) focused on the targeting immune regulatory cells for therapeutic purposes. Some chemotherapeutic drugs in ultra-low non-cytotoxic concentrations were shown to directly stimulate maturation and functional activation of conventional DC in vitro and in vivo. This new phenomenon was called chemomodulation. Importantly, such treatment also converted tumor-induced regulatory DC into immunostimulatory cells and supported the differentiation of MDSC into conventional immunostimulatory DC. Moreover, chemomodulation up-regulated the expression of components of the antigen-presenting machinery in tumor cells, thereby increasing their immunogenicity and recognition by specific T cells. Modulation of human DC and tumor cells with ultra-low concentrations of selected chemotherapeutic agents was also discussed by R. Kaneno (Botucatu, Brazil). It has been shown that this treatment, i.e., chemomodulation, increased costimulatory molecule expression on DC and enhanced generation of tumor-specific CTL, so improving the efficiency of DC-based vaccine. Novel insights into impairments in components of the MHC class I antigen processing machinery (APM) in tumor cells were presented by B. Seliger (Halle, Germany). These abnormalities could occur at the epigenetic, transcriptional or post-transcriptional levels. Some APM components like tapasin were shown to be deregulated due to the altered binding of

transcription factors. In addition, IFN- γ transcription signal transduction pathway seems to be important for the proper expression of MHC class I APM components.

Novel cancer vaccines in clinical trials

Interesting data on the promotion of type-1 cytotoxic T-lymphocyte (CTL) responses for effective immunotherapy of human brain tumor were reported by H. Okada (Pittsburgh, PA, USA). Based on preclinical data from his laboratory, a phase I/II vaccination trial in patients with recurrent malignant glioma was implemented. This study included a combination of type-1 polarizing DC loaded with glioma-associated antigens and administration of polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose and revealed safety, immunogenicity and clinical efficiency of this treatment. Evaluation of clinical vaccination strategies was also made by G. Chatta (Pittsburgh, PA, USA). In patients with prostate cancer, several different trials are currently in progress with the aim of reversing cancer-related immunosuppression and generating DC resistant to immunosuppression and/or tumor-mediated apoptosis. DC-based cancer immunotherapy could be useful in inducing CTL, Th1 and NK cell anti-tumor responses. Another strategy of cancer treatment by targeting the cancer stem cells was proposed by T. Sayers (Frederick, MD, USA). Transfection of the mouse breast carcinoma cells 4T1.2 with green fluorescent protein (GFP) driven by the promoter for the embryonic transcription factor Nanog resulted in less than 1% of the cells expressing GFP. However, these cells had many of the hallmarks of cancer stem cells both in vitro and in vivo. This approach may allow detecting or isolating populations highly enriched for cancer stem cells. The responses of these cells and more differentiated cancer cells to standard chemotherapy and immunotherapy can therefore be compared. M. Ravindranath (Los Angeles, CA, USA) presented data on HLA class Ia and HLA-E Abs in melanoma patients in response to autologous vaccine. The HLA-E expression is augmented when the expression of MHC-Ia alleles is down-regulated in tumor cells. Anti-HLA-E Abs and several allo-HLA-Ia Abs were found in patients before immunization. Upon the treatment, amounts of Abs reacting to HLA-E, HLA-B and HLA-Cw were significantly increased. Importantly, HLA-E and HLA-Ia reactivities of the sera were inhibited by the peptide sequences shared by HLA-E and allo-HLA-B and -Cw alleles. Soluble HLA-E shed from tumor cells may elicit Abs reacting with HLA-E and HLA-Ia alleles that share peptide sequences.

Recent advances in immunomonitoring of clinical trials

The last session covered different aspects of biomarkers and immunological monitoring of clinical trials. ELISPOT and other immunoassays, including Fluorospot, intracellular cytokine staining and FACS-based immunophenotypic analysis, were comprehensively discussed in presentations by P. Lehmann (Shaker Heights, OH, USA) and A. Malyguine (Frederick, MD, USA). In addition to traditional IFN- γ , other ELISPOT assays have been developed to detect T cells producing granzyme B, IL-2, IL-4, IL-13, IL-17 and perforin. Possible reasons for discrepancy in T-cell monitoring data and clinical outcome could be epitope spreading as well as the avidity and effector class of T cells. L. Buonaguro (Naples, Italy) presented data of an ex vivo analysis of an idiotypic vaccine for HCV-related lymphoproliferative disorders such as B-cell non-Hodgkin's lymphoma. Protein vaccination with variable κ (VK)3-20 light chain idotype has been demonstrated to induce DC activation and maturation. U. Hoffmüller (Berlin, Germany) reported on the immunomonitoring-based quantitative PCR targeting epigenetic markers specific for particular immune cells. This allows the monitoring of patients in multicenter and retrospective studies, a comparison of results between different studies and a routine monitoring.

Concluding remarks

The 2nd International CITIM Conference was focused on cellular and molecular mechanisms of immune regulation in the tumor environment, on the efficacy and usefulness of anti-tumor immunotherapeutic strategies as well as on the immunomonitoring of cancer patients in clinical trials. A special emphasis was placed on topics presenting new ideas allowing an improvement of existing immunotherapeutic approaches including combined chemo-immunotherapy, immunomodulators, antibodies and therapeutic targets. Participants learned how to manipulate the immune system to generate tumor-specific immune response in cancer patients. The results of recent studies suggest that we are on the edge of a real breakthrough in cancer immunotherapy. The CITIM conference demonstrated that by supporting open communication between scientists and clinicians and sharing ideas and plans, we could accelerate the progress in this area and eventually save cancer patients' lives. Finally, targeting the microenvironment and suppressor cells and inhibitory molecules will be increasingly focused upon by researchers, and this will no doubt be reflected in the next CITIM meeting in spring of 2013. (www.CancerITIM.org).

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