Track 2(iv) 2(v)

29 November 2011 (Tuesday)

2(iv): Cell Therapy: Clinical Trails

2(v): Inflammatory Diseases and Cancer

Session Chair

Dr. Mahin Khatami
National Cancer Institute, USA

Session Introduction

Title: Understanding therapy resistance in multiple myeloma

Dr. Apollina Goel, University of Iowa, USA

Title: Inflammation, aging and cancer: 'Targeted' therapy- seeing 'Elephant' in the light

Dr. Mahin Khatami, National Cancer Institute, USA

Title: Tumor associated mesenchymal stem cells promote tumor development through CCR2-dependent recruitment of macrophages

Dr. Guangwen Ren, Child Health Institute of New Jersey, USA

Title: Evaluation of cyclin dependent kinase like 1 expression in breast cancer and regulation in cancer cell growth

Dr. Feng Yan, Jiangsu Cancer Hospital, China

Title: Immunotransplant for mantle cell lymphoma: Phase I/II study preliminary results

Dr. Joshua D Brody, Stanford University, USA

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Understanding therapy resistance in mutiple myeloma

Apollina Goel

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Multiple myeloma (MM) is hematologic malignancy characterized by the accumulation of malignant plasma cells in the bone marrow. The disease initially responds to alkylating agents, corticosteroids, and thalidomide but eventually becomes refractory. MM is extremely susceptible to radiation treatment and targeted radiotherapy with bone-seeking radiopharmaceuticals now offer a new paradigm to target this systemic malignancy. Samarium-153-ethylene diamine tetramethylene phosphonate (153-Sm-EDTMP) demonstrates good therapeutic ratio for palliation of pain in cancer patients with osseous metastases. We have shown that the proteasome inhibitor bortezomib (BTZ) can sensitize myeloma cells to conventional radiotherapy by both intrinsic and extrinsic apoptotic pathways. BTZ acts as a radiation modifier in MM predominantly by attenuating endogenous and radiation-induced NF-κB activity. In a mouse myeloma model, we demonstrated that the combination of BTZ with 153-Sm-EDTMP resulted in increased survival time without a corresponding increase in the myelosuppressive effects of 153-Sm-EDTMP. We have recently proposed a novel combination of dexamethasone (Dex) plus radiation for treatment of MM in which the combination of 153-Sm-EDTMP radiotherapy and Dex selectively enhanced killing of myeloma cells. Our ongoing studies provide evidence that increases in glutathione metabolism and manganese superoxide dismutase expression play a role in IL-6-induced resistance to Dex and radiation in myeloma cells. An increased understanding of the role of endogenous and therapy-induced oxidative stress, which results from an imbalance in the production of reactive oxygen species and cellular antioxidant defenses, may offer a biochemical rationale for designing novel ways to induce oxidative stress-mediated killing of myeloma cells by radiotherapy and/or chemotherapy.

Biography

Dr. Goel completed her PhD from Punjab University in India and postdoctoral studies from University of Nebraska Medical Center and Mayo Clinic. She is currently an Assistant professor in the Department of Radiation Oncology at the University of Iowa. She has published more than 25 papers in reputed journals. Dr. Goel's research interest is on B-cell malignancies (B-cell lymphoma and multiple myeloma). Their lab is studying mechanistic pathways that can result in selective radiosensitization of tumor cells..

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Inflammation, aging and cancer: 'Targeted' Therapy- Seeing 'Elephant' in the light

Mahin Khatami

National Cancer Institute, National Institutes of Health, USA

Despite heavy public investment for over four decades on cancer war, progress in understanding the complex biology of cancer is still fragmentary. Consequently, few, if any funded projects have proven worthy of seriously translating research into effective cancer diagnosis, prevention or therapy while incidence of cancer is projected to rise globally in the next decade, particularly for the growing older population.

Cancer cell is a defective cellular component whose growth is routinely monitored and arrested normal self terminating acute inflammatory processes of immune system, known as immune surveillance (killing of cancer cells). Cancer becomes a threat to body when dynamics of immune system alter, particularly during aging. Unresolved inflammation was recently defined as loss of balance between 2 biologically opposing arms of acute inflammation, 'Yin' (apoptosis, growth arresting or 'tumoricidal') and 'Yang' (wound healing, growth promoting or 'tumorigenic') responses. Under a variety of inflammatory conditions, unresolved inflammation could create an 'immunological chaos' or 'immune tsunami' in affected tissues by exaggerated co-expression and co-existence of apoptotic and wound healing factors leading to diverse manifestations of acute inflammatory diseases such as sepsis, meningitis or autoimmune and neurodegenerative diseases as well as many cancers.

The 'accidental' discoveries that we established over 20 years ago, on experimental models of acute and chronic inflammatory diseases are suggestive of the first evidence for a direct association between inflammation and tumorigenesis. Analyses of these ground-breaking findings led to a first report on time-course kinetics of inflammation-induced identifiable phases of inflammation induced immune dysfunction and tumorigenesis and angiogenesis. Further extension, confirmations and validations of these studies are required to systematically identify developmental stages of inflammation-induced changes in immune responses that lead to carcinogenesis. Inflammation is likely a common denominator in the genesis and progression of chronic diseases and cancer. Understanding dynamics of unresolved inflammation that would lead to cancer growth may prove to be most rational cost-effective strategies for diagnosis, prevention and therapy of age-associated chronic diseases and cancer and for ideal 'Targeted' therapies.

Biography

Dr. Mahin Khatami immigrated to USA in 1969 after training in Chemistry (BS) and Science Education (MS) in Iran. She received her MA in Biochemistry from SUNY at Buffalo (1977) and Ph.D. in Molecular Biology from the University Of Pennsylvania (UPA, 1980). Her Postdoctoral framings were in physiology, protein chemistry and immunology at UVA, Fox Chase Cancer Center & UPenn. She became A Faculty of Medicine at Dept. Ophthalmology-UPA until 1992; and in collaboration with a team of scientists, under direction and support of John H Rockey, MD, Ph.D., she quickly earned her supervisory responsibilities on two major projects; cell/molecular biology of diabetic retinopathy/maculopathy and experimental models of acute and chronic inflammatory diseases. As a junior Faculty, she was perhaps a most productive scientist in the country as she published 39 scientific articles and over 60 abstracts in conference proceedings in the first decade of her academic career. Since 1998, at NCI/NIH, extension of her earlier discoveries on immunobiology of inflammatory diseases became closely relevant to her duties as Program Director-HAS for developing concepts for molecular diagnosis ,prevention and therapy of cancer for large clinical Trials (Prostate-Long-Colorectal- Ovarian) and designs of cohort clinical studies. Dr. Khatami has lectured internationally; served as scientific judge; consultant to pharmaceutical companies; research advisor; member of professional societies; editorial member ships & reviewer activities; symposia organizer; president of graduate women In Science, Washington Chapter. Before retiring in 2009, her position title was Assistant Director for Technology Program Development, Office of Technology and Industrial Relations and Program Director-IMAT, Office of Director, NCI/NIH. She is currently Book Editor on Inflammatory Diseases.

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Tumor associated mesenchymal stem cells promote tumor development through CCR2-dependent recruitment of macrophages

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Mesenchymal stem cells (MSCs) tend to infiltrate into tumors and form a major component of the tumor microenvironment. Yet, the mechanisms through which these tumor-resident MSCs may affect tumor growth are largely unknown. We found that MSCs isolated from spontaneous mouse lymphomas (L-MSCs) could strikingly enhance lymphoma growth, whereas bone marrow MSCs (BM-MSCs) did not. Surprisingly, tumor promotion by L-MSCs was not related to immunosuppression by these cells, while they recruited abundant CD11b+Gr-1+ myeloid suppressor cells and F4/80+ macrophages to the tumor. Depletion of macrophages but not myeloid suppressor cells completely abolished the tumor-promoting effect by L-MSCs. Furthermore, L-MSCs expressed high levels of CCR2 ligands-CCL2, CCL-7 and CCL-12, and macrophage accumulation and tumor-promotion by L-MSCs were absent in CCR2-/- mice. Interestingly, inflammatory cytokine-treated BM-MSCs acted similarly with L-MSCs, indicating the importance of the inflammatory cytokines in remodeling the tumor stroma. Finally, these findings were found nonspecific to lymphomas, but also applicable to other tumor types, such as mouse melanoma. Therefore, our findings demonstrate that tumor-associated MSCs contribute to tumor development through CCR2-dependent recruitment of macrophages to the tumor, a novel mechanism through which tumor-resident MSCs function in the tumor microenvironment. This study also bears important information for current MSC-based therapies.

Biography

Guangwen Ren completed his Ph.D from UMDNJ-Rutgers University and postdoctoral studies from Robert Wood Johnson Medical School. He is currently a research teaching specialist of Child Health Institute of New Jersey. His studies are focusing on the immunoregulation of mesenchymal stem cells, which have been published in Cell Stem Cell, Journal of Experimental Medicine, Stem Cells, Journal of Immunology and Cell Research, with him as the leading author. He served as peer-reviewers for over 25 scientific journals and editorial board members of World Journal of Stem Cells, Journal of Medical Science and The Open Autoimmunity Journal.

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Evaluation of cyclin dependent kinase like 1 expression in breast cancer and regulation in cancer cell growth

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Background: Cyclin dependent kinase like 1 (CDKL1) is a member of cell division control protein 2 (CDC2), plays an important impact on the progress. This study aimed to evaluate the related serine/threonine protein kinases family, and it is likely to occur in malignant tumors expression of CDKL1 in breast cancer and regulation in cancer cell growth.

Methods: We investigated both the CDKL1 mRNA level in fresh biopsy tissues from 62 breast cancer patients and 20 benign tissues by real-time PCR, and CDKL1 protein in 20 paraffin-embedded tissues from primary breast cancer patients by immunohistochemistry. The roles of CDKL1 in cell growth were analyzed with CDKL1 shRNA inhibitor-transfected cells.

Results: CDKL1 was overexpressed in patients with breast cancer. CDKL1 provided a positive detection efficiency of 89%, which was significant higher than that of 44% by estrogen receptor and 27% by progesterone receptor ($P<0.001$). CDKL1 shRNA inhibitor-transfected cells exhibited obvious accumulation at G2/M phase and reduced cell growth when treated with the chemotherapeutic drugs.

Conclusion: Both the CDKL1 level and its behavior in shRNA interference suggested that CDKL1 could be potentially developed as a tumor assistant marker for diagnosis and as a potential therapeutic target for breast cancer.

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Immunotransplant for mantle cell lymphoma: Phase I/II study preliminary results

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Mantle cell lymphoma (MCL) has a poor long-term prognosis. Though autologous transplant prolongs survival, novel and mechanistically distinct therapies are needed to target residual, myeloablation-resistant tumor cells that result in relapse.

Trials of CpG-based vaccines for *low-grade* lymphoma have shown induction of anti-tumor T cells and clinical responses. In a pre-clinical model, we developed the *immunotransplant* maneuver combining: 1) CpG-based vaccination, 2) harvest of vaccine-primed T cells, 3) myeloablation with stem cell rescue, and 4) T cell re-infusion. Immunotransplant amplifies the proportion of anti-tumor T cells by an order of magnitude and cures even bulky, systemic lymphoma burden

Methods: We initiated a phase I/II study of immunotransplant for newly diagnosed MCL patients to test the hypothesis that immunotransplant will amplify anti-tumor T cells as in the pre-clinical model. Anti-tumor T cells are assessed by co-culturing autologous tumor with peripheral blood T cells and measuring their production of: IFNg, TNF, IL2, CD137, perforin and granzyme by multiplex surface and intracellular flow cytometry. A secondary endpoint is measurement of molecular residual disease (MRD) using both standard allele-specific oligonucleotide (ASO) qPCR as well as high-throughput sequencing (HTS) of the entire IgH repertoire. The study is powered to detect a 50% improvement in sustained molecular remission rate compared to recent trials of standard transplant . Using the same HTS technology, we have also initiated studies of the entire TCRβ repertoire as an alternate approach of tracking the amplification of vaccine-induced T-cells.

Results: Accrual has been rapid with 25 patients enrolled in 22 months and 13 patients completing the complete protocol so far. Flow-cytometric immune response testing has demonstrated that immunotransplant amplifies the proportion of tumor-reactive T cells in 83% of patients thus far. Notably, we have observed some patients with primarily CD8 T cell responses, some with CD4 T cell responses, and some with a combination of the two. In some cases, tumor-reactive T cells have been tested for reactivity to autologous, non-malignant B cells and have demonstrated a significant proportion that are tumor-specific. TCRβ repertoire sequencing has also demonstrated instances of significant clonal amplification after immunotransplantation, some exceeding three orders of magnitude. In extreme cases, these have yielded dominant clones comprising as much as 50% of a patient's entire peripheral blood T cell repertoire post-transplant. HTS of the IgH repertoire has been an effective measurement of MRD bypassing the assay individualization of ASO qPCR and has been shown to be more sensitive than conventional flow cytometry.

Conclusions: Pre-clinically, amplification of anti-tumor T cells correlates with cure of even myeloablation-resistant disease. The reiteration of anti-tumor T cell amplification in our preliminary patient data raises the possibility that immunotransplant may improve clinical outcomes. Ongoing MRD testing should suggest whether certain patterns of T cell response –measured functionally per flow cytometry or clonally per HTS- correlate with clinical benefit and whether the cohort has a better-than-expected molecular remission rate.