042 Competition for active TGFβ augments accumulation of antigen-specific CD8+ T cells in murine melanoma

Il Ngayan*, S Dho*, D Srinivas* and DH Kaplan* 1 Department of Immunology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States, 2 Department of Dermatology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States, 3 BIKEN Innovative Vaccine Research Research Institute and RIKEN Institute of Viral Diseases, Machida, Gunma, Japan and 4 National Cancer Institute, Bethesda, Maryland, United States

Melanoma is the least common skin cancer but is responsible for the majority of skin-cancer related mortality. Successful anti-tumor immunity is mediated in part by tumor antigen specific CD8+ T-cells. Our group has shown that competition for limiting amounts of active TGFβ allows antigens to selectively recruit memory T cells. In this study, we investigated the expense of bystander Tm. Whether or not competition for active TGFβ affects T cells in the context of chronic antigen is unknown. Using a model which renders CD8+ T-cells independent of TGFβ (Bcl2Cre/ER; TgRBA), we explored the effects of constitutive TGFβ signaling in CD8+ tumor infiltrating lymphocytes (TIL) in an intraepithelial papilloma (TIL) mouse skin cancer model. We found that while the total number of CD8+ TILs was unaffected, the percentage of CD8+ T-cells expressing TgRBA was increased in the tumor but not spleen or lymph nodes thereby demonstrating a tumor selective enrichment of these cells. Enrichment was most evident in CD8+ T-cells expressing the resident memory markers, CD69 and CD103. Moreover, rendering CD8+ T-cells independent of TGFβ resulted in more rapid growth of implanted B16 tumors. A survey of human skin cancers revealed that melanomas express significantly higher levels of active TGFβ, the activator of these antigens. We therefore propose that competition for active TGFβ may be a potential target for therapeutic intervention.

043 Loss of DLX1 tumor suppressor function is associated with poor prognosis in human SCC

M Nakamura1, K Nagase2, M Yoshimitu1, T Magara1, Y Nosii1, H Kato1, T Kobayashi3, Y Takeda4, Y Uehara5, H Wada6, T Goya7, Y Umemori8, D Ogita1 and A Morita1 1 Nagoya Shintu Daigaku, Nagoya, Aichi, Japan, 2 Saga Daigaku, Saga, Saga, Japan, 3 Kanazawa Daigaku, Kanazawa, Ishikawa, Japan, 4 Saitama Ika Daigaku Kokusai Iyo Center, Hieda, Saitama, Japan, 5 Gunma Daigaku, Maebashi, Gunma, Japan, 6 Yokohama Shiritsu Daigaku, Yokohama, Kanagawa, Japan, 7 Osaka Shintu Daigaku, Osaka, Osaka, Japan, 8 Nagasaki Sekijyu Byoin, Nagasaki, Nagata, Japan and 9 Saitama Ika Daigaku, Iruma-gun, Saitama, Japan

Immune checkpoint therapy (ICT), such as PD-L1 or PD-1 blockade therapy, for Merkel cell carcinoma (MCC), has recently shown successful results. Approximately 50% of patients, however, remain without durable benefit due to these early treatment failures. Further treatment strategies are, therefore, still required. We collected 90 specimens from 71 patients and 53 additional blood serum samples from 21 patients with MCC at 10 facilities. RNA sequencing was performed to evaluate patients’ immune activity and classified tumors into 2 types: the “immune active type” and the “cell division type”. Expression of the glucose-6-phosphate dehydrogenase (G6PD) gene was highly significantly upregulated in the “cell division type”. Among 395 genes, G6PD expression correlated with the presence of lymph node or distant metastases during the disease course and significantly negatively correlated with PD-L1 expression and PD-L1 expression. A blood serum test could measure G6PD activity. The detection values significantly increased in the non-responder to ICIs and decreased in the responder to ICIs. G6PD expression was an immunohistochemically and serum-detectable prognostic marker that was negatively correlated with immune activation and PD-L1 levels and could be used to predict the immunotherapy response.

045 Glucose-6-phosphate dehydrogenase is a promising predictor of immunotherapy response for Merkel cell carcinoma

046 Knockdown of IFG2BP1 reduces the tumorigenicity of basal cell carcinoma cells in mice

AC Garza-Mayers1, M Azin1, J Huang2 and S Demehri1 1 Dermatology, Massachusetts General Hospital, Boston, Massachusetts, United States and 2 Boston Children’s Hospital, Boston, Massachusetts, United States

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are rare in pediatric patients and not well characterized. A multicenter retrospective case-control study by colleagues recently demonstrated most affected patients have at least one identifiable risk factor, either a predisposing genetic condition or iatrogenic exposure (prolonged immunosuppression, radiation therapy, chemotherapy, and/or vonozonzeau) use. Different factors were associated with the development of BCC versus SCC. We previously demonstrated that G6PD expression was an immunohistochemically and serum-detectable prognostic marker that was negatively correlated with immune activation and PD-L1 levels and could be used to predict the immunotherapy response.

047 Parallels between wound healing and cancer: An avenue to cancer therapeutics

F Nouibeh1, C Harris2, M Hajahmed2 and C Yedou2 1 Biology, Jackson State University, Jackson, Mississippi, United States and 2 Biology, Florida Agricultural and Mechanical University, Tallahassee, Florida, United States

More than 120,000 Americans each year are affected by basal cell carcinoma (BCC). Anyone with a history of sun exposure can develop BCC. However, people who are at highest risk are the ones in the fair skinned populations. Immunocompromised patients have also been reported to have a 10 fold higher risk of developing BCC than the general population and BCCs appear to show a more aggressive behavior in these patients. Although most of BCCs are not life threatening, this malignancy if untreated can destroy the tissues, causing ulceration and disfigurement. BCC therefore causes considerable morbidity and places a huge burden on healthcare systems worldwide. The challenge therefore is to prevent the cancers in the Medicare population in the United States. Constitutive activation of Hh signaling pathway drives the development of BCC through activation of GlI1 which is the transcription factor mediating the Hh pathway. GlI1 is regulated by the Wnt signaling through activation of its target, IGF2BP1. Moreover, the regulation of GlI1 by the Hh upstream signal appears to be dependent on IGF2BP1. We hypothesize that the constitutive overexpression of Hh in the microenvironment of cancer cells plays an important role in the development of BCC. We used the CRISPR/Cas9 approach to knock down IGF2BP1 in UW-BCC1 cells and test our hypothesis. Two million UW-BCC1 cells with conditional knockdown of IGF2BP1 were injected subcutaneously in the flank of immunocompromised mice. We found that knockdown of IGF2BP1 in UW-BCC1 cells significantly reduced tumor growth in mice compared to controls (P < 0.001). In addition, a reduction in the expression of Wnt and Hh target genes was observed in the tumors. Interestingly, a gender disparity in the development of tumors using UW-BCC1 cells was observed. IGF2BP1 appears to facilitate BCC development and might represents a novel target in the treatment of basal cell carcinoma.