**042**

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

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More than four million Americans each year are affected by basal cell carcinoma (BCC). BCCs are not life threatening, this malignancy if untreated can destroy the tissues, causing disfigurement and pain. Basal cell carcinoma (BCC) is the most 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 promote tumor immunity T cells. We previously described that melanoma expressing the TGFβ-activating integrins αvβ6 and αvβ8 when compared to melanocytic nevi. Taken together, these data indicate that CD8+ T cell competition for active TGFβ occurs in the context of persistent tumor antigen and suggest that increased expression of TGFβ-activating integrins in melanoma may prevent the accumulation of antigen specific CD8+ TILs, representing a novel mechanism of tumor immune-evasion.

**043**

**Loss of DLX3 tumor suppressive function is associated with poor prognosis in human SCCs**

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Development and progression of cutaneous squamous cell carcinoma (cSCCs) is known to be regulated by traditional oncogenic and tumor suppressive proteins; however, new evidence indicates that oncogenes or tumor suppressors can act as cancer mediators through regulation of proliferation, migration and survival. We carried out a human clinicopathologic analysis of DLX3 expression in 121 cSCCs and 6 benign skin tumors. Correlation analysis showed that tumors of increased pathologic stage had diminished levels of DLX3 expression. Kaplan-Meier analysis of overall survival OS revealed a statistically significant difference between patients with high DLX3 expression and low DLX3 expression. We then used a two-stage dimethylcyanoazene (DMBA)/12-O-tetradecanoylphorbol 13-acetate (TPA) mouse skin carcinogen treatment regimen to observe DLX3 knockdown mice Dlk1-KO and wild type mice expressing the resident memory markers, CD69 and CD103. Moreover, rendering CD8+ T cells DLX3-deficient skin. Whole transcriptome analysis (RNA-seq) of tumor and skin tissue from our mouse model uncovered a molecular dependence on the proliferation regulators responsible for tumor promotion, supporting a tumor suppressive function for DLX3 in skin.

**044**

**Nonmelanoma skin cancer in children and young adults with iatrogenic risk factors**

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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 described more affected male patients with at least one identifiable factor, either a predisposing genetic condition or iatrogenic exposure (prolonged immunosuppression, radiation therapy, chemotherapy, and/or voriconazole use). Different factors were associated with the development of BCC versus SCC. We hypothesize that the mechanism of tumorigenesis is distinct in these patients due to differing immunologic microenvironments of these cancers. Our study aims to characterize and compare the immunogenicity of BCC and SCC in order to better understand the underlying mechanisms of cancer development. We identified obtained and banked tissue samples of SCC and BCC from pediatric patients from Boston Children’s Hospital and Massachusetts General Hospital. In this cohort, SCC and BCC did not co-occur in the same patient, with SCC found in all patients with prolonged immunosuppression and SCC, more common in patients who have undergone radiation therapy and chemotherapy. We characterized these samples using immunohistochemical staining for antibodies identifying T cells and antigen presenting cells. Our preliminary findings clearly show that SCC is infiltrated by CD8+ T cells, which can explain the dependency of SCC development on immunosuppression. Our data suggest that even in patients with low UV burden and chronic immunosuppression, resident T cells may be present and active, serving as a target for cancer directed therapy. In contrast, BCC has minimal T cell infiltrate and therefore can develop in the absence of bystander Trm. Whether or not competition for active TGFβ signaling or tumor infiltration by cytokines (TIL) in an iatrogenic setting is a potential mechanism is yet to be determined.

**045**

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

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Immunotherapies for Merkel cell carcinoma (MCC) have shown limited success. MCC is a rare but aggressive skin cancer that arises from Merkel cells, a type of skin cell that recognize and respond to touch. Despite the development of checkpoint inhibitors, the response rate to these therapies is low. MCCs have high glucose consumption, but the mechanism behind this metabolic activity is not well understood. In this study, we aimed to investigate the correlation between glucose utilization and MCC malignancy. We analyzed tumor samples from MCC patients and matched normal skin samples using mass spectrometry to identify differentially expressed genes. We found that the glucose-6-phosphate dehydrogenase (G6PD) gene was highly upregulated in MCCs compared to normal skin. Expression of G6PD correlated with increased tumor size and decreased overall survival. We then performed a human clinicopathologic analysis of MCCs and identified a short list of genes that are activated in both MCCs and SCCs, which can be induced by these signals in vitro. This short list provided guidance for functional studies that identify key genes involved in the process. Overall, these data show that native or iatrogenic risk factors can affect T cells in the microenvironment of skin cancer and that these factors are associated with poor prognosis. The identification of these genes could potentially be used to improve immunotherapy response in MCC.

**046**

**Knockdown of IGF2BP1 reduces the tumorigenicity of basal cell carcinoma cells in mice**

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We previously reported that knockdown of IGF2BP1 in UW-BCC1 cells significantly reduced tumor growth in mice compared to controls. We also observed that knockdown of IGF2BP1 in UW-BCC1 cells significantly reduced tumor growth in mice compared to controls (P < 0.0001). In addition, a reduction in the expression of Wnt and Hh signaling was observed in the tumors. Interestingly, a gender disparity in the development of tumors using UW-BCC1 cells was observed. IGF2BP1 appears to contribute to BCC development and might represent a novel target in the treatment of basal cell carcinoma.

**047**

**Parallels between wound healing and cancer: An avenue to cancer therapy**

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Adult stem cells (SCs) located in barrier tissues such as the skin must endure repeated bouts of wound repair, which is achieved through a process called epidermal wound repair. This process is similar to the process of tumor promotion, where cancer cells can activate the Wnt signaling pathway to promote tumor development. During epidermal wound repair, hair follicle stem cells (HFSCs) enter the highly inflammatory wound, where they are exposed to similar signals in the microenvironment. Comparisons of transcriptome data revealed a common gene signature and immune-evasion. Cancer, then, can be thought of as a wound that never heals, especially given that patients suffering from chronic wounds have increased risk of developing malignancy. Recent work has confirmed that wounded and tumorigenic SCs indeed display common gene signatures, leading us to hypothesize that common signaling pathways may be activated in the wound and tumor environment and that these mechanisms promote SC survival in the face of inflammation. To test this, we studied HFSCs, which are responsible for epidermal wound repair as well as give rise to skin SCC upon acquiring mutations that elevate RAS/MAPK signaling. Using a sophisticated genetic reporter system, we found that both normal HFSCs during wounding and iSCs initiating oncogenic Hras-G12V-driven SCC respond to similar signals in the microenvironment. Comparisons of gene expression profiles revealed a short list of genes that are activated in both wounded HFSCs and SCC-iSCs, which can be induced by these signals in vitro. This short list provided guidance for functional studies that identify key genes involved in the process. Overall, these data show that native or iatrogenic risk factors can affect T cells in the microenvironment of skin cancer and that these factors are associated with poor prognosis. The identification of these genes could potentially be used to improve immunotherapy response in MCC.