LB1014

Sensory nerves impede anti-melanoma immune responses

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Peripheral neurons are now recognized as a critical component of the tumor microenvironment (TME). However, the effect of the afferent (sensory) neurons on tumor progression remains unclear. Utilizing methods of surgical and pharmacological sensory denervation of the skin, we discovered that afferent neurons support melama growth by preventing the activation of effective anti-tumor immune responses. Sensory ablation led to improved leukocyte recruitment and effector cell activation in the TME, with decreased presence of immunosuppressive regulatory immune cells. Afferent nerves further hindered maturation of intratumoral high endothelial venules (HEV) and significantly limited formation of tertiary lymphoid structures . Furthermore, skin denervation dramatically increased intratumoral T cell clonality and B cell repertoire. Depletion of CD8a T cells prevented denervation-dependent anti-tumor effects. In human melanomas, we observed that gene signatures of inflammation and innervation were inversely correlated, with the latter being a negative prognostic marker of overall survival. Our results indicate that melanoma-associated sensory neurons negatively regulate protective anti-tumor immune responses, thereby defining a new target for therapeutic intervention.

LB1015

Evaluating ChatGPT's Accuracy in Answering the American Academy of Dermatology's Clinical Guideline Questions for Cutaneous Melanoma (2019)

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The recent progress in large language models (LLM) like ChatGPT has led to the exploration of their potential to streamline clinical workflows, particularly by addressing questions related to dermatology clinical guidelines. ChatGPT's (4.0) responses to clinical questions and recommendations were assessed and compared to the American Academy of Dermatology's (AAD's) 2019 guidelines of care for primary cutaneous melanoma (CM). ChatGPT was prompted with 25 questions provided by the guidelines, ensuring any abbreviations were fully expanded. The LLM's responses were compared to the recommendations provided by the guidelines. A PubMed literature review on CM diagnosis and treatment from May 2017 to February 2024 identified 33 articles, which were used to validate ChatGPT's replies. ChatGPT's answers were consistent with the AAD guidelines for 23 questions. It offered accurate recommendations for one question regarding pathology where the AAD guidelines provided inconclusive responses. However, it inaccurately responded to 1 question regarding surgery. The study underscores ChatGPT's potential in dermatology as a tool for delivering quick, accurate responses aligned with current guidelines, enhancing clinical decision-making and patient care, especially where access to the latest resources is limited. However, the need for comprehensive research to validate ChatGPT's clinical application is evident, aiming for standardized usage practices. This would improve both the quality and consistency of patient care. Incorporating specific prompt engineering can refine ChatGPT's effectiveness, leading to better outcomes by tailoring responses more closely to the clinical context. This approach could significantly improve healthcare delivery and outcomes.

LB1016

Role and functional significance of KIFC1 in human melanoma

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KIFC1 (Kinesin family member C1), a minus end-directed motor protein, is known to play a critical role in clustering of centrosomes in cancer cells and is being investigated as a potential target for management of certain cancers. We are investigating the role and functional significance of KIFC1 in melanoma. Previously, using TCGA and GTEX RNA-seq datasets and *in vitro* data, we found that KIFC1 is elevated in melanoma and inhibition of KIFC1 using its small molecule inhibitor, AZ82 resulted in significant growth inhibition and reduced clonogenic survival in human melanoma cells. To further support our data, we have now conducted a quantitative immunohistochemical analysis of KIFC1 in human melanoma tissues using tissue microarray (TMA). We performed immunohistochemical staining of KIFC1 paired with Vectra scanning and InForm analysis to quantitate KIFC1 levels in a human melanoma TMA. Our data demonstrated that KIFC1 levels were significantly higher in malignant (mean OD = 0.159), metastatic (0.170), and uveal (0.293) melanoma tumors when compared to normal skin (0.108) (p-value < 0.05). Next, we determined the effect of small molecule inhibition of KIFC1 in a panel of melanoma cells as well as normal melanocytes. We found that AZ82 treatment resulted in a significant anti-proliferative response in human melanoma cell lines (A375, Hs294T, and G361), but not in normal melanocytes, at the same level. Further, KIFC1 inhibition also resulted in G1 phase cell cycle arrest at the expense of S phase in A375 and G361 cells. Additionally, treatment of melanoma cells at 5 μM for 24 hours resulted in ~50% apoptosis, which was accompanied with a significant decrease in the mRNA expression of PCNA and Survivin, markers for proliferation and survival, respectively. Overall, our data suggest that KIFC1 has a potential tumor promoter role in melanoma and may provide a new target against melanoma.

LB1017

Cutaneous melanocytic mosaicism with associated melanoma

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Melanoma incidence has markedly risen in recent decades, yet our understanding of its genetic risk factors remains limited. A particularly understudied area is cutaneous melanocytic mosaicism (CMMo), which we define as the emergence of distinct pigmentation patterns that visibly differ from the surrounding unaffected skin, and its association with melanoma development. Prior case reports have employed varied terminology, often not recognizing CMMo, and thereby hindering further research of its role in melanoma pathogenesis. Our objective is to concretize the relationship between CMMo and melanoma. The present case series presents six Caucasian adults with CMMo associated with melanoma at the Cleveland Clinic between 2008 and 2023. Clinical data, histopathological samples, and genetic testing were collected. The cohort was predominantly male with a mean age at diagnosis of first melanoma within the mosaic area of 48 years. The most frequently observed mosaic pattern was segmental. Three patients presented with a single melanoma, while three patients had two or more melanomas within the affected area. Five patients underwent germline genetic testing through Invitae's Multi-Cancer and Melanoma panels, without identification of any pathogenic variants. When patients with CMMo develop melanoma, it predominantly arises within the mosaic area and at a younger age than expected, even when there are no identified pathogenic variants associated with melanoma and no family history of the disease. This pattern is consistent with findings from the literature review of previous case reports on CMMo associated melanomas. Identifying mosaic patients serves to alert healthcare providers to potential high-risk areas for melanoma development, enabling more effective patient education for self-skin checks. Further ongoing genetic studies on the mutations leading to CMMo, particularly when associated with melanoma, will help elucidate the underlying causative mechanisms for both CMMo and melanoma.

LB1018

Regulatory T cells inhibit CD8$^+$ T$_{RM}$-like cells during the early stages of tumor immune escape

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Tissue-resident memory T (T$_{RM}$) cells have emerged as key players and potential immunotherapeutic targets in antitumor immunity. However, the study of T$_{RM}$ cells within the TME has been hampered by a lack of adequate tumor models. Cell lines injected subcutaneously do not contain the same biological cues as tumors arising from the dermis and epidermis, while most other models lack a known tumor-specific antigen to track immune responses. We have addressed these two issues by modifying the Braf/PTEN model of melanoma to express OVA as a tumor antigen (abbreviated as BPO). In this novel model, we confirmed a robust endogenous tumor-antigen specific immune response against OVA as measured by IFN-γ ELISPOT, pentamer staining, and adoptive transfer of tumor-antigen specific OT-I T cells. Longitudinal analysis revealed that CD103$^+$ T$_{RM}$-like cells composed a majority of CD8$^+$ TILs in nascent tumors, but this population steadily declined over time. The CD103$^+$ T$_{RM}$-like subset was phenotypically unique. Unlike CD103$^-$ CD8$^+$ TILs, the CD103$^+$ fraction expressed low levels of the inhibitory receptors PD1 and Tim3, but uniquely expressed CD101. Intriguingly, CD103$^+$ regulatory T (Treg) cells were also found to be enriched in nascent tumors. With this data, we hypothesized that Treg-mediated suppression of CD8$^+$ T$_{RM}$-like cells is important for immune escape at the earliest stages of tumor development. Transient depletion of Treg cells in BPO/Foxp3DTR mice led to a decrease in tumor growth, augmentation of the OVA-specific antitumor immune response, a ~7-fold increase in CD8$^+$ TILs, and upregulation of PD-1 and Tim-3 on CD103$^+$ CD8$^+$ TILs. FTY720 was administered after Treg depletion to discern between systemic and local effects, which revealed that the increase in CD8$^+$ TILs was due to tumor infiltration, as opposed to local expansion of T cells, and activation of CD103$^+$ T$_{RM}$-like cells was due to Treg depletion within the tumor. Together, these data indicate that the earliest stages of tumor immune escape may be orchestrated by regulatory T cells.

LB1019

Successful treatment of in-transit metastatic melanoma with intralesional TVEC and topical imiquimod

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In-transit metastasis of malignant melanoma presents a clinical challenge, and while the individual use of talimogene laherperepvec (TVEC) and imiquimod has demonstrated successful treatment of in-transit disease, the combination use of TVEC and topical imiquimod and its synergistic effects have not been studied. This case series evaluated 5 patients with in-transit melanoma metastasis who were treated at Northwestern Memorial Hospital with intralesional TVEC and topical imiquimod 5% cream from November 2018 to May 2023. Patients received a median of 13 (range 8-20) TVEC injections over a median of 6 months (range 5-9), of which 4 of those months were with concurrent TVEC and imiquimod. Four of the 5 patients achieved complete response (CR) by the end of the treatment course. Intralesional TVEC and topical imiquimod can be a safe and effective treatment of in-transit metastasis of malignant melanoma, especially in patients with locally advanced disease, disease in sensitive locations, transplant histories, and other comorbidities that limit surgical candidacy.