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Determining intra-tumoral heterogeneity and immune escape mechanisms in melanoma using spatial transcriptomics

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Melanoma, like other cancers, originates from a single clone. As the cancer progresses, the tumor thickens and immune evasion ensues. However, few studies have investigated the mechanisms involved in these processes using spatial transcriptomics. We aimed to elucidate genetic and transcriptional heterogeneity in relation to melanoma thickness and to explore the molecular mechanisms related to immune escape. Five punch-biopsied fresh tissue samples and saliva were obtained from a single patient and used for paired whole exome sequencing. The subsequent excision specimen was prepared for formalin-fixed paraffin-embedded block and profiled using spatial transcriptomics. DNA-level mutation accumulation was commensurate with the thickness of the melanoma. Spatial transcriptome analysis indicated that immune evasion involves changes in antigen presentation as well as defects in β2-microglobulin and human leukocyte antigen class I processing. Levels of these molecules, which are critical for T cell recognition of tumor antigens, tended to significantly decrease as the melanoma depth increased. We also found that the expression of caspases and interferon alpha inducible protein-encoding genes inversely correlated with tumor thickness. The study was based on sampling a lesion from a single patient. Spatial transcriptomics can increase our mechanistic understanding of tumor immune escape.

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Comparison of S100A8 and PRAME as biomarkers for diagnosing melanoma

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Early diagnosis of melanoma is crucial to improved patient prognosis but can be difficult to achieve from histopathology alone. PRAME is used increasingly in dermatology as an ancillary tool to help differentiate between benign vs. malignant melanocytic tumors. S100A8 is another biomarker found to be expressed in melanoma-associated epidermal keratinocytes, but its diagnostic utility has not been compared to other biomarkers, including PRAME. In this retrospective case-control study, we compared S100A8 and PRAME immunohistochemistry (IHC) in melanocytic nevi and melanoma (n=209). An S100A8 and PRAME IHC score were assigned to each tumor sample, indicating the proportion of tumor-associated epidermis stained or the proportion of tumor cells stained, respectively. S100A8 IHC scores were previously reported (Kiuru et al., 2021). We analyzed diagnostic accuracy in detecting melanoma and melanoma *in situ* by using receiver operating characteristic curves, which showed an area under the curve (AUC) of 0.8326 for S100A8 and 0.8741 for PRAME. These AUCs were both significantly greater than chance, or AUC=0.5 ($p<0.001$), but not significantly different from each other ($p=0.22$). For S100A8, when a positive test was defined as a score of 4 or 5 (>50% of tumor-associated epidermis stained), the sensitivity was 42.42%, and specificity was 98.18%. For PRAME, when a positive test was defined as a score of 3 (>50% of tumor stained), the sensitivity was 79.80%, and the specificity was 87.27%. When a positive test was defined as >50% of tumor stained for both S100A8 and PRAME, sensitivity was 39.39%, and specificity was 99.09%. Thus, both biomarkers are useful for accurately detecting malignant melanocytic tumors. When combined with PRAME, S100A8 increases specificity, demonstrating the utility of S100A8 when interpreted alongside other histopathological features and ancillary tests.

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Comparison of soluble proteins from skin sections of acne and TCA induced postinflammatory hyperpigmentation and erythema

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Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis occurring after cutaneous inflammation or injury that can arise in all skin types, but more frequently affects skin-of-color. The differences in the ethology of PIH and Postinflammatory erythema (PIE) in skin of color were evaluated from soluble protein extracts collected from skin section samples, using Somascan protein kit1.3 k (n=5). The skin samples were collected from selected gluteal TCA-induced lesions and truncal acne pustules, of either PIH or PIE, at day 28 post initial evaluation. Differences between proteins (FDR<0.05) from PIH and PIE were analyzed with STRING version 11.5 and analysis points toward involvement of JAK/STAT signaling pathway and enhanced IL17 signaling in PIH compared to PIE lesions (OSM, CSF3, IL10RA, IL12RB2, IL10RB, IL3, CSF2, IL17D, IL17F, IFNA2, IFNA10, CRLF2, IL5RA, TYK2, IL12RB1, PRLR, GHR). The involvement of JAK/STAT signaling pathway has been described for some chronic cutaneous inflammatory conditions and acne. A higher occurrence of dermal remodeling proteases and inhibitors were found in PIE (MMP1, MMP2, MMP7, TIMP2) indicating a dermal remodeling phase at the time of excision. Concurrently, elevated levels of IL-1β, and TGF-β (critical for triggering and continuing differentiation programs of naïve $CD4^+$ T cells to IL-17 secreting Th17 cells) in PIH samples suggests continuing promotion of macrophage infiltration and sustained inflammation. In addition to MMP13 and MMP16, the protein Keap1 was found to be increased in the PIH samples. Keap1, a repressor of master cellular defense against oxidative and electrophilic stresses, has been reported to be involved in the imbalance of proteolysis that can lead towards premature aging and in a senescent phenotype of endothelial cells. The sustained inflammation with excess of Keap1 protein might contribute to an altered proteostasis and ethology of PIH.

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Depletion of senescent cells improves targeted therapy outcome in melanoma

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Cellular senescence is a non-proliferative but viable state that can be induced by oncogene expression and anti-cancer therapeutics, such as BRAF inhibition, and has long been considered a beneficial tumor suppressive mechanism. However, senescent cells express a well-characterized senescence-associated secretory phenotype (SASP), which may contribute to an immunosuppressive microenvironment and an increased malignant phenotype, leading to tumor recurrence and metastasis. To investigate the role of senescent cells in tumor growth, we treated B1610 (B16) melanoma cells *in vitro* with the senolytic drug ABT737 or vehicle control and injected $5x10^4$ viable cells into syngeneic mice. We found that senolytic pre-treated B16 cells grew into significantly smaller tumors compared to controls. Tumors from senolytic-treated cells had significantly fewer senescence-associated β-galactosidase and p16 expressing cells, which correlated with decreased SASP expression, and reduced tumor infiltration of myeloid-derived suppressor cells. We next treated BRAF mutant human melanoma cells *in vitro* with the BRAF inhibitor PLX4720, and found a significant increase in the number of senescent cells and expression of SASP members such as IL-1β, IL-6, and IL-8, a phenomenon known as therapy-induced senescence. Further, there was a significant increase in apoptotic cells when treated with a combination of PLX4720 and ABT737, suggesting that this combination may be more effective for tumor eradication than BRAF inhibition alone. We then asked whether eliminating senescent cells with senolytic drugs enhanced tumor control by BRAF inhibition anti-cancer therapy. We treated YUMM1.7 subcutaneous tumors with PLX4720 and the senolytic drug ABT263 and showed a durable repression of tumor regrowth compared to controls. Our findings suggest that therapy-induced senescence is a potential mechanism for acquired resistance and evasion of anti-tumor immune responses, which can be overcome by depleting senescent cells with senolytic drugs.

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Reprogramming the tumor microenvironment by a second-generation recombinant modified vaccinia virus Ankara

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Immune checkpoint blockade (ICB) therapy has brought hope to many cancer patients, but the response rate is low in many cancer types, and acquired resistance to ICB can develop over time. Oncolytic viruses are promising therapeutic agents for advanced cancers. Modified vaccinia virus Ankara (MVA) is an attenuated, replication-deficient poxvirus safe for human use, making it a favorable platform for cancer immunotherapy. Our first-generation recombinant MVA has shown promising antitumor efficacy in multiple murine tumor models due to the deletion of the E5R gene (encoding an inhibitor of the DNA sensor cGAS) from the MVA genome and the insertion of two membrane-anchored transgenes — Flt3L and OX40L, which leads to the activation of the host innate and adaptive antitumor immunity. Here in this study, we engineered our second-generation recombinant MVA (MQ833) with the deletion of two more viral immune evasion genes — E3L and WR199, and the insertion of IL12 anchored to the extracellular matrix to mitigate toxicity. Intratumoral (IT) delivery of MQ833 resulted in an 80-100% cure in the mouse B16-F10 melanoma model, which is dependent on nucleic acid-sensing and IFN signaling pathways. Single-cell RNA sequencing analysis revealed that IT MQ833 injection reprogrammed the tumor microenvironment into an immune-stimulating state, by activating $CD8^+$ and $CD4^+$ T cells, depleting regulatory T cells, recruiting and activating neutrophils, and polarizing M1 macrophages. Interestingly, MQ833 treatment cured 70% of B2m knock-out melanomas likely due to combined effects of IL-12 and type I and II IFN. Loss of MHC-I is the most common mechanism of tumor resistance to ICB. Hence, our results support the use of MQ833 for ICB-resistant tumors.

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Identification and functional implication of variants associated with skin pigmentation in Chinese population

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Skin pigmentation is a major feature of skin, and a marker associated with beauty, health and aging. Among the past genome-wide association studies on skin pigmentation, a relatively small proportion have focused on Chinese population. Large-scaled studies based on measured skin pigmentation phenotypes are particularly rare in Chinese and other East Asian populations. In the Jidong cohort study (N = 3,544), we measured the skin pigmentation on low-exposed area with colorimeter and performed genome-wide scans on skin color and melanin index. We identified associated loci on 9p22.2, 10q26.11, 12q21.33, 15q12.6 and 15q13.1, and validated in independent cohorts. Functional annotation and luciferase report assays revealed evidence for the top SNP on 12q21.33 functioning as an enhancer, and regulating pigmentation-related gene TMTC3, although in previous studies, this top SNP has been mapped to the nearby gene *KITLG*, another well-known pigmentation-related gene. From publicly available database, we found further evidence suggesting regulation pathway on how TMTC3 altering skin pigmentation. This study provided additional insight into the genetics underlying skin pigmentation.