Epidermal ablation reduces keratinocytoc cancer occurrence by reducing skin mutation burden caused by chronic ultraviolet radiation

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Ultra-Violet (UV) radiation from sunlight is the main carcinogen driving keratinocyte cancers of the skin. The accumulation of UV-induced mutations on sun-exposed areas leads to field carcinisation. Knowing the regenerative property of the skin, we investigated if epidermal ablation removes mutations on the epidermis and allows mutated cells from the deeper part of the epidermis to replicate in the UV-ablated superficial layer of skin. Healthy epidermal skin cancers were subjected to epidermal ablation on their forearms with three different depths of laser (600nm, 400nm and fractional laser). Deep targeted DNA sequencing of 152 cancer-related genes was performed and revealed the mutation burden on ablated and non-ablated epidermis. There were 12.9 mutations per megabase (Muts/Mb) found in non-ablated control epidermis compared to 2.55 Muts/Mb in 600nm, 4.45 Muts/Mb in 400nm and 3.58 Muts/Mb in fractional laser ablated and regenerated epidermis (n=7). To evaluate the efficacy of epidermal ablation on skin carcinogenesis, we developed a UV-induced keratinocytoc cell carcinoma (BCC) murine model (K1C4Cre::Pchlox/+). These mice were subjected to 10 weeks of UVB radiation. Half of the dorsal epidermis was ablated, after an additional 10 weeks of UVB radiation was administered. Wholemount staining of a BCC biomarker, Keratin-17 (K17), revealed a significant reduction in the number of K17 patches in the ablated area (0.35 patches/mm² ± 0.04 compared to 0.07 patches/mm² ± 0.03) suggesting epidermal ablation can be used to reduce BCC occurrence. Deep targeted sequencing of the epidermis from the ablated and non-ablated area has revealed that there was 15-fold fewer mutations in the ablated area (18.65 mutations/Mb to 1.19 mutations/Mb). Overall, our findings propose a potential treatment to prevent accumulation of mutations in the skin. This study may also pave the way to a larger clinical trial of epidermal ablation as an adjuvant therapy for high-risk keratinocyte cancer patients.

A developmental cellular hierarchy in melanoma uncouples growth and metastatic phenotypes

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Although melanoma is notorious for its high degree of heterogeneity and plasticity, the origin and magnitude of state diversity remains poorly understood. Equally, it is not known whether melanoma growth is supported by a subfraction of Melanoma Stem-like Cells (MCSs) and if so, whether MCSs and Metastasis-Initiating Cells (MICs) represent overlapping, interchangeable, or distinct cell populations. By combining single-cell gene expression profiling, multicolour lineage tracing and quantitative modelling, we developed a spatially and temporally resolved map of the diverse and heterogeneous melanoma cell hierarchy. By combining this map with a primary tumour growth and metastatic dissemination in a clinically-relevant mouse model of melanoma. We show that melanoma growth and metastatic dissemination are fuelled, respectively, by two transcriptionally and spatially distinct melanoma subpopulations. Our findings implicate a hierarchical model of tumour growth that is supported by a population of cancer stem-like cells, which reside in a perivascular niche and exhibit a transcriptional signature of pre-migratory neural crest cells established transiently during embryonic development. Metastatic dissemination is, instead, driven by a “mesenchymal-like” subpopulation, which preferentially accumulates at the invading front of primary lesions. We identified the transcription factor Prrx1 as a driver of the mesenchymal-like melanoma phenotype, and demonstrated that this population fuels metastatic invasion of lymph nodes and distant organs through a MET-MEK-like continuum. These results will pave the way for the development of strategies that detect and, ultimately, intercept melanoma before its dissemination to vital organs.

C-FOS drives reversible basal to squamous cell carcinoma transition

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While squamous transdifferentiation within subpopulations of adenoacarcinomas represents an important drug resistance problem, its underlying mechanism remain poorly understood. Here, using surface markers of resistant skin basal cell carcinomas (BCC-RM) and patient single cell and bulk transcriptomic data, we uncover the dynamic epigenetic roadmap of basal to squamous cell carcinoma transition (BST). Experimentally induced BST identifies API family members in regulating tumor plasticity, and we show that C-FOS plays a central role in BST by regulating the accessibility of distinct API regulatory elements. Remarkably, despite prominent changes in cell morphology and BST marker expression, we show using inducible in vitro and in vivo model systems that c-FOS-mediated BST remains a reversible process. Preventing the activation of the EGFR pathway after c-FOS induction reverts BST in both mouse models and human tumors. Thus, by identifying the molecular basis of BST, our work reveals a therapeutic opportunity targeting plasticity as a mechanism of tumor resilience.

C-H2, a potential therapeutic target in Merkel cell carcinoma

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Merkel cell carcinoma (MCC) is an aggressive skin cancer. In 2008, the integration of the Merkel cell Polyomavirus (MCPyV) and the expression of the two viral oncogenes were identified as main MCC oncogenic triggers. Recently the expression of EZH2 (Enhancer of Zeste 2) was shown to be required for MCPyV-driven tumor formation. Here, we focused on the role of EZH2 in MCC carcinogenesis, single cell RNA sequencing was applied on a premalignant and an aggressive sample of MCC from the same patient. We uncovered several immune cell subsets depleted in cMCC compared to AK, particularly B and plasma cells, and a specific cluster of macrophages and T cells enriched in the tumor. To conclude, our data suggest that metabolic and immune features of cMCC could be used as pertinent biomarkers for stratification of cMCC.