Cancer Research
Breaking Insights
Highlights from Recent Cancer Literature
AACR American Association for Cancer Research

Tracking Melanoma Development in Zebrafish

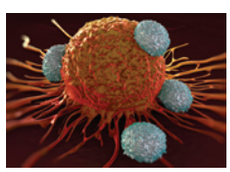
Despite significant improvements in the management of melanoma treatment, resistant disease remains a major clinical problem. MITF-low is a transcriptional subtype of melanoma with poor survival. Using a new inducible zebrafish model that mimics the human MITF-low subtype, Travnickova and colleagues showed that a MITF-low state is causal for melanoma development and that MITF is a lineage-dependent oncogene. They then tracked cells during melanoma regression and identified a small population of cells at the regression site that were resistant to complete MITF loss. These MITF-independent cells share similar molecular expression signatures with human therapy-resistant disease.

Expert Commentary: The identification of a MITF-independent cell state in residual disease that preexists in primary melanoma may explain the poor outcomes in patients with MITF-low melanomas and could represent an important new target. *(Image from cited article courtesy of the publisher.)*

Travnickova J, Wojciechowska S, Khamseh A, Gautier P, Brown DV, Lefevre T, et al. Zebrafish MITF-low melanoma subtype models reveal transcriptional subclusters and MITF-independent residual disease. Cancer Res 2019;79:5769–84.

An EZ Way for Cancer to Escape Immunity

Although immune escape in cancer can occur through mutations in the antigen-processing pathway (APP) that reduce expression of MHCI, epigenetic mechanisms that reduce APP are lacking. Burr and colleagues identified members of the polycomb repressive complex 2 (*EED*, *SUZ12*, *EZH2*, *MTF2*) as key negative regulators of MHCI antigen presentation in cancer cells, particularly neuroblastomas and small cell lung cancers (SCLC). Inhibition of EZH2 either pharmacologically or by expression of the histone H3 K27M mutation increased expression of MHCI genes *HLA-A*, *-B*, *-C*, and also of APP genes NLRC5, PSMB8/9, and TAP1/2 that promote expression of MHCI at the cell surface. Importantly, blocking PRC2 function enhanced the sensitivity of cancer cells to interferon-induced upregulation of MHCI. In a transplantable model of murine SCLC with little/no MHCI expression, genetic deletion of EZH2 was sufficient to make cancers susceptible to immune-mediated rejection.

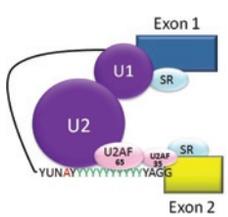


Expert Commentary: Blocking the activity of EZH2 can enhance cancer immunity by promoting MHCI expression on cancer cells.

Burr ML, Sparbier CE, Chan KL, Chan YC, Kersbergen A, Lam EYN. An evolutionarily conserved function of polycomb silences the MHC class I antigen presentation pathway and enables immune evasion in cancer. Cancer Cell 2019;385–401.

Aberrant Splicing Drives a Subset of Aggressive Cancers

A handful of noncoding genomic alterations have been identified as cancer drivers. In two companion papers, Suzuki and colleagues (1) and Shuai and colleagues (2) analyzed 141 medulloblastoma and 2,583 whole-genome sequenced tumors (37 types) and identified highly recurrent mutations of the U1 small nuclear RNA. These mutations were specific to two distinct subtypes of adolescent and adult Sonic hedgehog-driven tumors, and in a subset of chronic lymphoblastic leukemia and hepatocellular carcinoma. In all three entities, the presence of U1 mutations was an independent predictor of tumor aggressiveness and poor outcome. Aberrant splicing was observed in tumor suppressor genes including PTCH1, GLI2, CCND2, and PAX5 in medulloblatoma, and in CD44 in leukemia.



Expert Commentary: This highly recurrent small nuclear RNA is mutated and drives a variety of cancers. The identification of tumor specific splice isoforms represents a potentially new and exciting therapeutic avenue. *(Image courtesy of Wikimedia Commons.)*

1. *Suzuki H, Kumar SA, Shuai S, Diaz-Navarro A, Gutierrez-Fernandez A, De Antonellis P, et al. Recurrent non-coding U1-snRNA mutations drive cryptic splicing in Shh medulloblastoma. Nature; Published online October 9, 2019; doi: 10.1038/s41586-019-1650-0.*

2. *Shuai S, Suzuki H, Diaz-Navarro A, Nadeu F, Kumar SA, Gutierrez-Fernandez A, et al. The U1 spliceosomal RNA is recurrently mutated in multiple cancers. Nature; Published online October 9, 2019; doi: 10.1038/s41586-019-1651-z.*

Breaking Insights

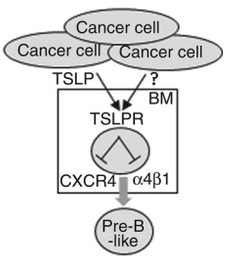
Synthetic Lethality to CDK4/6 Inhibition

The VHL tumor suppressor is a defining alteration in clear cell renal cell carcinoma (RCC) and leads to accumulation of HIF2α. Nicholson and colleagues performed cross-species genetic and chemical synthetic lethality screens to identify evolutionary conserved synthetic lethal interactions in cells null for *VHL*. They demonstrated that genetic or pharmacologic inhibition of CDK4 and CDK6 was preferentially efficacious against *VHL* null cells of *Drosophila* or human origin. This effect was due to on-target CDK4/6 inhibition but did not depend on HIF2α. Palbociclib was effective in $VHL^{-/-}$ RCC and synergized with HIF2α inhibitors, both *in vitro* and *in vivo*.

Expert Commentary: This study provides the preclinical rationale for testing CDK4/6 inhibitors in the clinic for RCC.

Nicholson HE, Tariq Z, Housden BE, Jennings RB, Stransky LA, Perrimon N, et al. HIF-independent synthetic lethality between CDK4/6 inhibition and VHL loss across species. Sci Signal 2019;12:eaay0482. doi: 10.1126/scisignal.aay0482.

The Pre-B Cell–TSLP Axis in Cancer

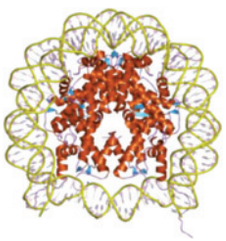


How B cells influence cancer remains poorly understood, although their infiltration in tumors can be associated with poor outcome. Immature B cells travel from marrow to spleen during adult lymphopoiesis. Some murine and human cancers can induce accumulation of B-cell precursors in circulation. Using mouse and human bone marrow aspirates and mouse models challenged with highly metastatic 4T1 breast cancer cells, Ragonnaud and colleagues demonstrated that this was caused by secretion of thymic stromal lymphopoietin (TSLP) by cancer cells. TSLP triggered premature exodus of early B-cell precursors from bone marrow, and their subsequent survival and expansion in the circulation. The circulating B-cell precursors were used by 4T1 cancer cells to generate $CD25^{+}$ Bregs, which then downregulated antitumor immune responses and promoted lung metastasis.

Expert Commentary: Loss of TSLP expression in cancer cells alone or TSLPR deficiency in B cells blocks both accumulation of pre-B-like cells in the circulation and cancer metastasis, suggesting the pre-B cell-TSLP axis as a therapeutic target. *(Image from cited article courtesy of the publisher.)*

Ragonnaud E, Moritoh K, Bodogai M, Gusev F, Garaud S, Chen C, et al. Tumor-derived thymic stromal lymphopoietin expands bone marrow B-cell precursors in circulation to support metastasis. Cancer Res 2019;79:5826–38.

Incorporation of Histone H3 Variants Mediates Metastases



Histone variants and their respective chaperones drive epigenetic reprograming. Gomes and colleagues hypothesized that histone variants regulate metastasis. Consistent with this hypothesis, induction of endothelial-to-mesenchymal transition in breast epithelial cells resulted in large increases in H3.3-embedded chromatin and simultaneous decreases in canonical H3.1/H3.2 chromatin. A similar H3 switch was observed comparing a nonmetastatic breast cancer cell line with a highly metastatic clonal variant. Metastatic activators reduced levels of the histone chaperone chromatin assembly factor 1 (CAF-1) in breast and non-small-cell lung carcinoma cells, decreasing canonical histones in chromatin. This decreased level of chromatin integrity resulted in "gap filling" mediated by H3.3 and its associated chaperone HIRA, remodeling chromatin to express genes important for metastases. CAF-1 suppression was sufficient to trigger this process, inducing chemotherapeutic resistance, expression of stemness biomarkers, and increased metastases *in vivo* via a HIRA-dependent mechanism.

Expert Commentary: CAF-1 regulation is a pivotal signaling node that regulates metastases in breast and lung cancers. *(Image courtesy of Wikimedia Commons.)*

Gomes AP, Ilter D, Low V, Rosenzweig A, Shen ZJ, Schild T, et al. Dynamic incorporation of histone H3 variants into chromatin is essential for acquisition of aggressive traits and metastatic colonization. Cancer Cell 2019;36:402–417.e.13. doi: 10.1016/j.ccell.2019.08.006.

Note: Breaking Insights are written by *Cancer Research* editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.