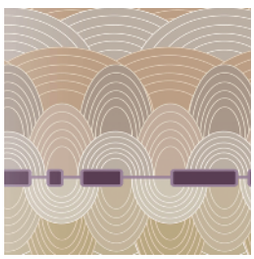
Alternative Splicing Occurs in Uveal Melanomas with *SF3B1* Mutations

- Uveal melanoma has a low mutation burden and lacks an ultraviolet radiation DNA damage signature.
- *SF3B1* mutations occur in ~15% of uveal melanomas and are associated with good prognosis.
- Specific alternative splicing events recur in uveal melanomas with *SF3B1* mutations.

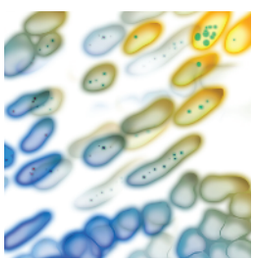


Uveal melanoma, the most common eye cancer in adults, arises from melanocytes in the iris, ciliary body, or choroid of the uvea. Some recurring mutations and chromosomal abnormalities have been identified in uveal melanomas that guide classification into low-risk and high-risk subtypes, but a comprehensive understanding of uveal melanoma genetics is needed. Furney and colleagues performed single-nucleotide polymorphism array analysis, whole-genome sequencing, and RNA sequencing on 12 primary uveal melanomas and found that uveal melanomas have markedly lower numbers of chromosomal abnormalities and somatic single-nucleotide variants than cutaneous, acral, and mucosal melanomas. Interestingly, unlike other melanoma subtypes, uveal melanomas lacked a mutational signature consistent with ultraviolet radiation–induced DNA damage, suggesting that these melanomas have a distinct etiology. Three tumors had mutations in splicing factor 3b, subunit 1 (*SF3B1*), as did 15 tumors in an extension set of 105 additional primary uveal melanomas, giving an overall frequency of 15%. Given that *SF3B1* encodes a subunit of the spliceosome, a ribonucleoprotein complex that mediates intron excision from precursor mRNA, the authors compared transcript splicing patterns in *SF3B1*-mutant and –wild-type uveal melanomas and found that *SF3B1* mutations were associated with specific alternative splicing events affecting a subset of genes. *SF3B1* mutations were also associated with improved progression-free and overall survival, suggesting that these mutations may not only provide insight into the underlying biology of uveal melanoma but also guide patient stratification. ■

See article, p. 1122.

A Telomere Biomarker Is Prognostic in Prostate Cancer

- Telomere length was prospectively assessed in single cells in men with prostate cancer.
- More variable length among tumor cells and shorter stromal-cell telomeres predict poor outcome.
- This biomarker may identify patients who will benefit from additional surveillance and treatment.

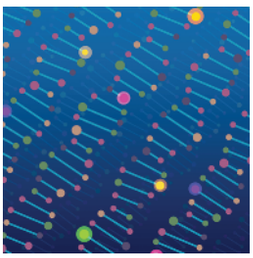


Telomere shortening frequently occurs in prostate cancer cells and contributes to malignant transformation and genomic instability, suggesting that increased telomere loss may be associated with more aggressive disease and poor clinical outcome. To test this hypothesis, Heaphy and colleagues performed a prospective analysis of 596 men with clinically localized prostate cancer from the Health Professionals Follow-up Study and determined telomere length and variability in telomere length in individual cancer cells and cancer-associated stromal cells using telomere-specific FISH. Greater variability in telomere length among prostate cancer cells and decreased median tumor length in cancer-associated stromal cells were individually associated with poor prostate cancer outcome. Furthermore, the combination of more variable telomere length among cancer cells and shorter telomeres in stromal cells, defined as the telomere biomarker, was strongly predictive of increased risk of lethal, metastatic disease and prostate cancer death independent of established prognostic indicators and in men with intermediate-risk disease. In addition, the telomere biomarker improved the capability of currently used prognostic indicators to predict poor outcome. In contrast, men with the combination of less variable cancer-cell telomere length and longer stromal-cell telomeres were less likely to experience tumor progression or die from prostate cancer. These findings support the potential utility of this telomere measurement as a specific biomarker of prostate cancer outcome and suggest that it may enable stratification of patients who will benefit from additional surveillance and treatment. ■

See article, p. 1130.

A High-Throughput Assay Classifies *BRCA1* Sequence Variants

- Complementation assays showed the functionality of *BRCA1* variants of unknown significance (VUS).
- *BRCA1* VUSs that did not rescue *Brca1*-null cell growth or DNA repair defects were deemed pathogenic.
- All unambiguously predicted pathogenic *BRCA1* mutations reside in the RING or BRCT domains.

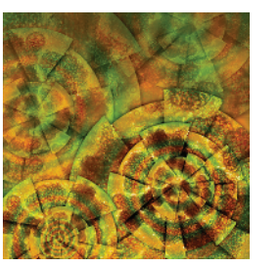


Germline loss-of-function *BRCA1* and *BRCA2* mutations underlie most cases of hereditary breast and ovarian cancer, but the clinical relevance of many sequence variants identified during patient screening is uncertain. Over 1,200 *BRCA1* variants of unknown significance (VUS) exist, and it has not been possible to assay the consequences of these mutations on a large scale in the context of the full-length BRCA1 protein. Bouwman and colleagues developed a high-throughput functional complementation assay to determine the pathogenicity of 74 unclassified *BRCA1* VUSs. The ability of *BRCA1* VUSs to rescue the proliferation defect of murine embryonic stem cells lacking endogenous *Brca1* was evaluated to determine whether functional BRCA1 protein was produced. These results were validated and, in some cases, clarified by assaying the ability of *BRCA1* VUSs to rescue the cisplatin sensitivity inherent to DNA repair-defective *Brca1*-null cells. The ability of *BRCA1* VUSs to rescue growth defects and cisplatin sensitivity correlated with the homologous recombination activity of mutant proteins, confirming these classifications. Testing for sensitivity to PARP1 inhibition revealed functional defects in VUSs with intermediate phenotypes, pointing to the importance of performing multiple complementation assays. Notably, all variants unambiguously predicted to be pathogenic were located in the RING and BRCT domains. This approach has the potential to rapidly characterize many *BRCA1* VUSs and could be used in the clinical setting to identify germline mutations associated with increased cancer risk. ■

See article, p. 1142.

PDK1–PLK1 Signaling Is a Therapeutic Target in MYC-Dependent Tumors

- PDK1-driven phosphorylation of PLK1 promotes MYC phosphorylation and accumulation.
- PDK1–PLK1 signaling is required for transformation and CSC self-renewal in MYC-dependent tumors.
- PLK1 blockade synergizes with PI3K–mTOR inhibition to suppress colorectal tumor growth.



PDK1 (3-phosphoinositide dependent protein kinase-1) regulates cell growth and survival via phosphorylation of kinases including AKT and is often constitutively activated in human tumors with phosphoinositide 3-kinase (PI3K) deregulation. Recent studies have shown that accumulation of MYC protein in colorectal cancer cells is mediated by PDK1 and confers resistance to mTOR inhibition. However, the mechanisms by which PDK1 activates MYC signaling and whether PDK1 promotes tumorigenesis independent of the PI3K–AKT pathway remain unclear. Tan and colleagues found that PDK1-driven MYC accumulation induced oncogenic transformation in the absence of AKT activation, and that PDK1 was preferentially required for the survival of MYC-dependent breast cancer cell lines. This effect was dependent on PDK1-mediated phosphorylation of polo-like kinase 1 (PLK1), a mitotic kinase often overexpressed in cancer, and subsequent phosphorylation of MYC by PLK1 in human cancer cells, whereas PLK1 inhibition triggered apoptosis and suppressed the growth of PDK1- and MYC-driven xenograft tumors. Activation of PDK1–PLK1–MYC signaling resulted in increased sphere formation *in vitro* and enhanced tumor-initiating potential *in vivo*, suggesting that this pathway promotes cancer stem cell (CSC) self-renewal. Indeed, PDK1 activated a CSC-like transcriptional program including expression of known MYC targets that were enriched in high-grade tumor samples and associated with poor outcome. Importantly, combined treatment with PLK1 and PI3K–mTOR inhibitors prevented compensatory MYC accumulation and synergistically suppressed tumor growth, suggesting that PLK1 blockade may overcome mTOR inhibitor resistance in colorectal cancer. ■

See article, p. 1156.

The Tumor Suppressor DEAR1 Inhibits TGFβ–SMAD3 Signaling

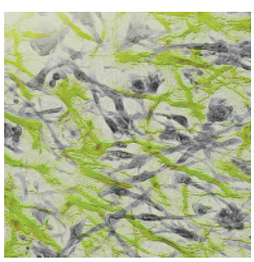
- *DEAR1* is mutated or deleted in human tumors and its loss induces tumor formation in mice.
- DEAR1 blocks TGFβ-induced EMT via induction of SMAD3 degradation and inhibition of SNAI1/2.
- Combined DEAR1 loss and increased SNAI2 is associated with poor prognosis in breast cancer.

Chromosome 1p35 is frequently deleted in human tumors, including pancreatic, colon, and breast cancers. Mutations in the ductal epithelium–associated RING chromosome 1 (*DEAR1*, also known as *TRIM62*) gene within this chromosomal region have recently been identified in breast cancer and are associated with loss of epithelial polarity, but the function of DEAR1 and its role in tumor development and progression are unclear. Chen and colleagues found that genetic deletion of *Dear1* in mice resulted in the formation of adenocarcinomas in multiple tissues, similar to the tumor spectrum observed in humans with *DEAR1* mutations, as well as lymphomas and sarcomas, implicating DEAR1 as a chromosome 1p35 tumor suppressor. Moreover, DEAR1 inhibited the transcriptional activity of TGFβ, a potent inducer of epithelial–mesenchymal transition (EMT). DEAR1 knockdown impaired acinar morphogenesis, enhanced cell migration and invasion, promoted anoikis resistance, and stimulated the expression of early EMT markers in response to TGFβ, indicating that DEAR1 inhibits TGFβ-driven EMT. DEAR1-driven negative regulation of TGFβ was mediated via repression of SMAD3-dependent signaling; DEAR1 directly interacted with SMAD3 and promoted its polyubiquitination and degradation, whereas loss of DEAR1 enhanced nuclear accumulation of active SMAD3 and specifically increased the expression of snail family zinc finger 1 (SNAI1) and SNAI2. Moreover, combined loss of DEAR1 and increased SNAI2 was significantly associated with decreased overall survival in a large cohort of patients with invasive breast cancer, suggesting that loss of this tumor suppressor is clinically relevant. ■

See article, p. 1172.

Collagen Modification by PLOD2 Promotes Sarcoma Metastasis

- Hypoxia-dependent activation of PLOD2 by HIF-1α drives metastasis in murine sarcoma models.
- PLOD2-mediated alteration of collagen networks facilitates sarcoma cell migration and metastasis.
- Pharmacologic inhibition of PLOD2 prevents collagen network formation and blocks metastasis.



Metastasis is the most common cause of sarcoma-associated death. The mechanisms that regulate sarcoma metastasis are not well understood, but primary sarcomas are known to generate extensive extracellular collagen networks that facilitate tumor cell migration to blood vessels. Increasing evidence suggests that extracellular matrix remodeling can be induced by intratumoral hypoxia and expression of hypoxia-inducible factor 1α (HIF-1α), both of which are associated with risk of metastasis in patients with sarcoma. Eisinger-Mathason and colleagues found that expression levels of HIF-1α and procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (PLOD2), a lysyl hydroxylase that is required for mature collagen formation, were higher in human metastatic undifferentiated pleomorphic sarcomas (UPS) than in nonmetastatic UPS and that PLOD2 expression was upregulated under hypoxic conditions in a HIF-1α–dependent manner. Interestingly, neither HIF-1α nor PLOD2 were required for primary tumor formation in murine UPS models, but both were required for sarcoma cell migration and pulmonary metastasis. Pharmacologic inhibition of PLOD2 expression with minoxidil suppressed sarcoma cell migration and metastasis, whereas ectopic expression of PLOD2 restored the metastatic potential of HIF-1α–deficient tumors, suggesting that HIF-1α–dependent PLOD2 procollagen lysyl hydroxylase activity facilitates the dissemination of sarcoma cells. Consistent with these findings, HIF-1α– and PLOD2-deficient tumors had significantly reduced collagen deposition as well as fewer associations between collagen fibers, tumor cells, and blood vessels. The identification of the HIF-1α–PLOD2 pathway as a determinant of sarcoma metastatic potential suggests that targeting PLOD2 may be a potential strategy to prevent sarcoma metastasis. ■

See article, p. 1190.

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