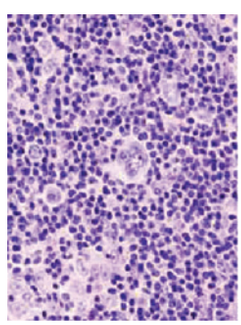
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
AACR American Association for Cancer Research

How Much and When to TWIST?

TWIST1, the basic helix-loop-helix transcription factor, is overexpressed in squamous cell carcinoma (SCC), counteracts MYC-induced apoptosis, facilitates invadopodia-dependent metastasis, and maintains stemness. Elegant work by Beck and colleagues demonstrates that TWIST1 was upregulated in 15% of premalignant papilloma cells, in 50% of SCC cells, and in DMBA/TPA and *KRAS*-driven skin cancer models. Interestingly, the transition from papilloma to SCC was abolished by genetic ablation of a single *Twist1* allele, whereas homozygous deletion was necessary to inhibit papilloma formation. Mechanistically, TWIST1 suppressed p53-induced apoptosis and cell-cycle arrest during hyperplasia, and increasing TWIST1 levels promoted epithelial-to-mesenchymal transition (EMT) and invasion in SCC. Unexpectedly, cancer stem cell properties induced by TWIST1 at tumor onset were uncoupled from TWIST1's role in EMT during invasion. This study highlights how the multifaceted role of TWIST1 is precisely regulated throughout cancer progression. *(Image courtesy of Wikimedia Commons.)*

Beck B, Lapouge G, Rorive S, Drogat B, Desaedelaere K, Delafaille S, et al. Different levels of Twist1 regulate skin Tumor initiation, stemness, and progression. Cell Stem Cell 2015;16:67–79.

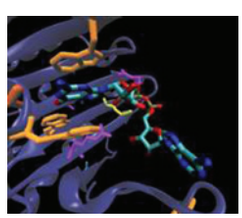
Genetic Sensitivity to PD-1 Blockade in Hodgkin Lymphoma



The PD-1 (PDCD1) pathway limits T-cell mediated immune responses, and PD-1 blocking antibodies are being used to enhance immunity in human cancers. Ansell and colleagues hypothesized that this approach would be effective against Hodgkin lymphomas, in which there is an underlying genetic basis for PD-1 ligand (CD274) overexpression and an ineffective immune-cell infiltrate. Twenty-six patients with relapsed/refractory Hodgkin lymphoma were treated with nivolumab-mediated PD-1 blockade, with an overall response rate of 87% and progression-free survival of 86% at 24 weeks. All patients with available tumor tissue had evidence of gain and overexpression of the PD-1 ligand and activation of JAK-STAT signaling. In concordance with previous studies, tumor-infiltrating cells expressed low levels of PD-1, with PDL-1 expression on tumor cells as a more reliable predictor of response. *(Image courtesy of Wikimedia Commons.)*

Ansell, SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372:311–9.

Reduced Cancer Growth and Metastasis by Inhibiting EIF4E



The oncogene translation initiation factor EIF4E is overexpressed in primary breast cancers and metastases. Pettersson and colleagues demonstrate that pharmacologic inhibition of EIF4E using ribavirin suppresses breast tumor growth and metastasis. Ribavirin, an antiviral drug, inhibits EIF4E by competing with the 7-methylguanosine mRNA cap. Administration of ribavirin suppressed growth of mammary tumors in several models. In an invasive model, ribavirin could also inhibit lung metastases. Inhibition of EIF4E either by siRNA or ribavirin reduced tumor growth and metastases by decreasing MMP3 and MMP9 activity. EMT was also suppressed upon inhibition of EIF4E. The authors present a preclinical rationale for exploring the clinical utility of ribavirin, which is being tested in leukemia patients, to treat solid tumors such as metastatic breast cancer. *(Image from cited article courtesy of publisher.)*

Pettersson F, Del Rincon SV, Emond A, Huor B, Ngan E, Ng J, et al. Genetic and pharmacologic inhibition of EIF4E reduces breast cancer cell migration, invasion and metastasis. Cancer Res 2015; Published OnlineFirst January 21, 2015; doi:10.1158/0008-5472.CAN-14-1996.

Breaking Advances

Hippo Signaling and miRNA Biogenesis

Why are miRNAs globally downregulated in cancer? Cell-density–dependent fluctuations in miRNA levels have also been observed, leading Mori and colleagues to test whether the Hippo pathway, given its role in cell-density–dependent signaling, regulates miRNA biogenesis. During inactivation of the tumor-suppressive Hippo pathway in low cell density conditions and in cancer, YAP1 localized to the nucleus, sequestering the RNA helicase DDX17, a known regulator of miRNA biogenesis, globally decreasing mature miRNAs. Hippo pathway activation during high cell density resulted in cytosolic sequestration of YAP1, disrupting YAP1-DDX17 interactions and allowing DDX17 to complex with DROSHA and DGCR8 and to process primary miRNAs into mature miRNAs. Skin and liver tumor models induced by YAP1 exhibited globally decreased miRNA levels *in vivo*, forming tumors preserved even in the absence of YAP1 transcriptional activity, suggesting that downregulation of miRNAs is causal in tumor formation. *(Image courtesy of Wikimedia Commons.)*

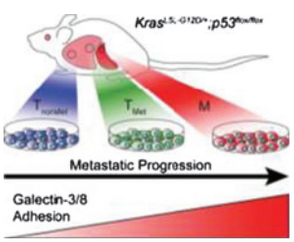
Mori M, Triboulet R, Mohseni M, Schlegelmilch K, Shrestha K, Camargo FD, et al. Hippo signaling regulates microprocessor and links cell-density-dependent miRNA biogenesis to cancer. Cell 2014;156:893–906.

SHH Signaling Prevents a Sustained TMZ Response in GBM

Biswas and colleagues collected primary tissues from glioblastoma (GBM) patients treated with the alkylating agent temozolomide (TMZ) and characterized response to TMZ in neurospheres. Responder neurospheres underwent cellular senescence while nonresponder neurospheres underwent apoptosis followed by selection of proliferating subclones. The authors compared the variant allele frequencies between these subsets of TMZ sensitive and insensitive GBM neurospheres using deep whole exon sequencing. Ingenuity Pathways Analyses suggested Sonic Hedgehog (SHH) as the one signaling pathway attenuating the sustained response to TMZ. The authors validated these findings using additional GBM neurospheres, as well as meta-analyses of GBM primary tissue expression data. Using the FDA-approved SHH inhibitor vismodegib, they show that attenuation of SHH signaling drives TMZ sensitivity. These results suggest that SHH inhibitors, such as vismodegib, might increase the efficacy of TMZ in patients with GBM. *(Image by E. Comikaze courtesy of Wikimedia Commons.)*

Biswas NK, Chandra V, Sarkar-Roy N, Das T, Bhattacharya RN, Tripathy LN, et al. Variant allele frequency enrichment analysis in vitro *reveals sonic hedgehog pathway to impede sustained temozolomide response in GBM. Scientific Reports 5. Published 21 January 2015.*

Altered Carbohydrates Sweeten the Metastatic Niche



In patients with advanced cancers, levels of soluble carbohydrate binding galectin-3 (LGALS3) proteins are often elevated. Reticker-Flynn and Bhatia identify critical interactions between galectin-3 (on myeloid cells) and carbohydrates on cancer cells that may drive metastasis. Using murine lung adenocarcinoma cell lines, they identified soluble factors released from the primary tumor mass, including IL6, that mobilized $Cd11b^{+}$, galectin-3^{+} leukocytes in the liver of tumor-bearing mice prior to metastasis. Galectin-3 contains carbohydrate recognition domains that have specific affinities for the oncofetal core 1 *O*-linked disaccharide termed the T-antigen, expressed in many carcinomas. Mechanistic studies have demonstrated that alterations in glycosyltransferase activity might contribute functionally to the increased abundance of the T-antigen in lung cancer. These data suggest that a dynamic cross-talk between tumor cells and myeloid cells, mediated in part through carbohydrate binding, promotes tumor metastasis. *(Image from cited article courtesy of publisher.)*

Reticker-Flynn NE, Bhatia SN. Aberrant glycosylation promotes lung cancer metastasis through adhesion to galectins in the metastatic niche. Cancer Discov 2015;5:168–81.

Note: Breaking Advances 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.