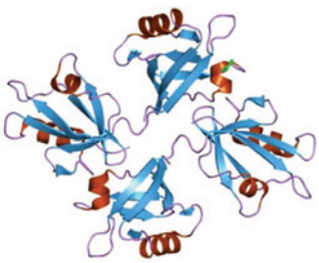
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
American Association for Cancer Research

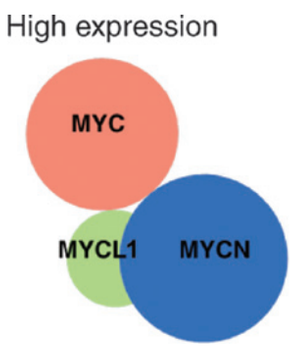
Novel Role of MDA-9/Syntenin in Glioma



Invasion in glioblastoma multiforme is a key mediator of pathogenesis, contributing to poor outcome. Genomic database analysis demonstrated that elevated expression of *mda-9/syntenin* was correlated with decreased survival. Using gain-of-function and loss-of-function approaches *in vitro*, Kegelman and colleagues showed that MDA-9/Syntenin altered invasion, migration, anchorage-independent growth, and angiogenesis. MDA-9/Syntenin led to activation of c-Src (SRC), p38 MAPK (MAPK14), and NF-κB (RELA), followed by increased expression of MMP2 and IL-8. *In vivo*, silencing of MDA-9/Syntenin expression caused decreased tumor size, and tumors displayed a less invasive phenotype. These studies confirm MDA-9/Syntenin as a novel mediator of invasion that may provide a target to treating invasion in glioblastoma. (*Image courtesy of Wikimedia Commons and European Bioinformatics Institute.*)

Kegelman TP, Das SK, Hu B, Bacolod MD, Fuller CE, Menezes ME, et al. MDA-9/syntenin is a key regulator of glioma pathogenesis. Neuro Oncol 2014;16:50–61.

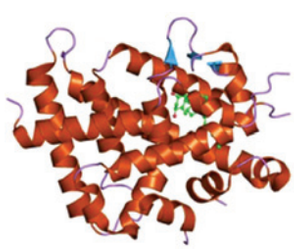
Epigenetic Modulation of MYC Oncogenes



Medulloblastomas harboring amplification of MYC oncogenes (MYC, MYCN, and MYCL1) are highly lethal childhood tumors. Bandopadhayay and colleagues demonstrate efficacy of the BET bromodomain inhibitor JQ1 in cell lines and xenografts with MYC amplification. JQ1 downregulated MYC and MYC activation pathways and decreased viability, G_1 arrest, and apoptosis preferentially in cell lines driven by MYC, and in cells derived from a murine model of MYCN-driven medulloblastomas. Additionally, JQ1 prolonged survival of MYC-amplified medulloblastoma xenograft models. shRNA suppression of the epigenetic reader bromodomain 4 (BRD4), a JQ1 target, resulted in both decreased cell proliferation and reduced MYC mRNA and protein levels. These data provide a compelling rationale for BET bromodomain inhibition in MYC-driven medulloblastoma. (*Image from cited article courtesy of publisher.*)

Bandopadhayay P, Bergthold G, Nguyen B, Schubert S, Gholamin S, Tang Y, et al. BET bromodomain Inhibition of MYC-amplified medulloblastoma. Clin Cancer Res 2014;20:912–25.

A Novel Ontogeny-Based Breast Cancer Classification

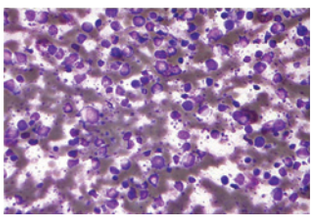


Santagata and colleagues developed a novel reclassification of breast cancers based on cell of origin. Testing 37 validated biomarkers against more than 15,000 normal breast epithelial cells, they identified 11 differentiation states for normal luminal cells. This information was used to classify primary breast tumors into four subtypes centered on the expression of estrogen, androgen, or vitamin D receptors (HR0-HR3). Reclassifying a cohort of 3,157 human breast tumors, they showed their classification was distinct from the current classification based on expression of the estrogen, progesterone, and HER2 (ERBB2) receptors. HR3 patients showed the highest, and HR1 and HR0 exhibited the lowest survival rates. This system could help organize emerging breast cancer genomics data. (*Image courtesy of Wikimedia Commons.*)

Santagata S, Thakkar A, Ergonul A, Wang B, Woo T, Hu R, et al. Taxonomy of breast cancer based on normal cell phenotype predicts outcome. J Clin Invest 2014;124:859–70.

Breaking Advances

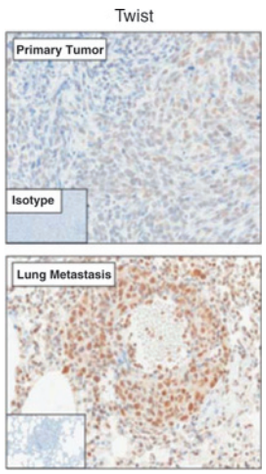
T-cell Surveillance in B-cell Lymphoma



Afshar-Serle and colleagues demonstrate that T cells can block lymphoma. Whereas loss of the tumor suppressor *BLIMP1* (*PRDM1*) or deregulated expression of the oncogene *BCL6* are common in diffuse large B-cell lymphomas (DLBCL), targeted mutations of either gene in mice rarely causes lymphoma. In mice with *Blimp1* deficiency or *Bcl6* overexpression in the B lineage, impairment of T-cell control resulted in DLBCL-like disease, which could be eradicated by polyclonal CD8 T cells in a T-cell receptor, CD28, and Fas ligand–dependent manner. Thus, transformation of mature B cells requires mutations that impair intrinsic differentiation processes and also permit escape from T cell–mediated tumor surveillance. (*Image courtesy of Wikimedia Commons.*)

Afshar-Sterle S, Zotos D, Bernard NJ, Scherger AK, Rödling L, Alsop AE, et al. Fas ligand–mediated immune surveillance by T cells is essential for the control of spontaneous B cell lymphomas. Nat Med 2014 Feb 2. Epub ahead of print.

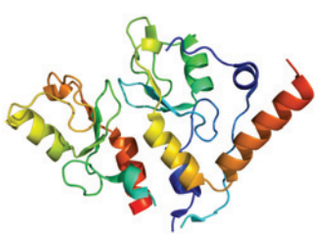
Blocking Transcription via Vaccine-Mediated Immunotherapy



Epithelial–mesenchymal transition (EMT) driven by transcription factors including TWIST, enhances tumor progression, metastases, and drug resistance. The 4T1 mammary tumor model has been used to examine the role of TWIST in experimental cancer metastases, in which silencing decreases metastasis. While transcription factors are undruggable, T-cell–mediated immunotherapy offers an approach to targeting. The authors generated recombinant yeast expressing TWIST, which induced both $CD8^+$ and $CD4^+$ TWIST-specific T-cell responses *in vivo*. Mice treated with this recombinant yeast vaccine had decreased tumor sizes and an even greater decrease in lung metastases. This study shows the potential of vaccine-induced T-cell–mediated therapy of transcription factors involved in metastasis. (*Image from cited article courtesy of publisher.*)

Ardiani A, Gameiro SR, Palena C, Hamilton D, Kwilas A, King TH, et al. Vaccine-mediated immunotherapy directed against a transcription factor driving the metastatic process. Cancer Res; Published OnlineFirst February 11, 2014; doi:10.1158/0008-5472.CAN-13-2045.

Specific Targeting of Colorectal Cancer–Initiating Cells



Can drugs that specifically target self-renewal, a characteristic theorized to be exclusive to cancer-initiating cells (CIC), curtail colorectal cancer? Kreso and colleagues targeted BMI1, a component of the polycomb repressive complex 1, using PTC-209. PTC-209 affected survival and proliferation of CICs differentially from non-CICs. As the authors acknowledge, it is difficult to distinguish between the effects on self-renewal and proliferation/survival. Thus, PTC-209 may not only affect self-renewal. While the mechanism by which PTC-209 inhibits tumor growth remains to be elucidated, this drug may provide a lead to test other drugs that target self-renewal as opposed to conventional proliferation regulators when these do not have overlapping functions. (*Image courtesy of Wikimedia Commons.*)

Kreso A, Galen P, van Pedley NM, Lima-Fernandes E, Frelin C, Davis T, Cao L, et al. Self-renewal as a therapeutic target in human colorectal cancer. Nat Med 2014;20:29–36.

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.

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Cancer Res 2014;74:1623-1624.