Aberrations in the SWI/SNF–MYC Network Drive Small Cell Lung Cancer

- *MAX* is recurrently inactivated in SCLC and regulated by the SWI/SNF protein BRG1.
- BRG1 depletion is selectively toxic in *MAX*-deficient cells, indicative of synthetic lethality.
- MAX and BRG1 upregulate expression of neuroendocrine differentiation and glycolytic genes.

Small cell lung cancer (SCLC) frequently exhibits amplification of *MYC* genes and is often characterized by features of neuroendocrine differentiation. Similar to other neural-related tumors such as pheochromocytoma, Romero and colleagues found that MYC-associated factor X (*MAX*) was recurrently inactivated via homozygous intragenic deletions in SCLC cell lines and 6% of SCLC tumors examined, supporting a tumor-suppressive role for MAX in this subtype of lung cancer. *MAX* alterations were mutually exclusive with homozygous inactivation of the gene encoding the MAX dimerization protein MGA, as well as with *MYC* amplification and mutations in *BRG1* (also known as *SMARCA4*), which encodes an ATPase component of the SWI/SNF chromatin remodeling complex with tumor suppressor activity. Consistent with a functional connection between these proteins, BRG1 directly bound the *MAX* promoter and stimulated its expression in response to glucocorticoids. Furthermore, BRG1 depletion selectively inhibited the growth of *MAX*-deficient SCLC cells, indicative of synthetic lethality between these two proteins. Intriguingly, reconstitution of MAX expression in SCLC cells triggered the upregulation of genes implicated in neural differentiation and glycolytic metabolism, including several MYC target genes, and induction of this MAX transcriptional program was dependent on BRG1 expression. Although additional work is necessary to define the mechanisms connecting BRG1 and MAX in the regulation of SCLC growth and transcription, these findings support the idea that disruption of SWI/SNF–MYC function suppresses differentiation and promotes lung tumorigenesis and suggest potential therapeutic strategies for SCLC. ■

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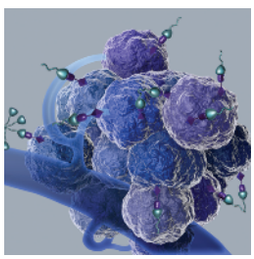
The Sialyltransferase ST6GALNAC2 Suppresses Breast Cancer Metastasis

- An *in vivo* RNAi screen identified ST6GALNAC2 as an inhibitor of breast cancer metastasis.
- ST6GALNAC2 loss enhances tumor cell retention in the lung via galectin-3 binding to *O*-glycans.
- Low ST6GALNAC2 levels are associated with sensitivity to galectin-3 inhibition in ER- tumors.



Galectin-3 is a soluble lectin protein that binds unmodified core 1 *O*-glycans on the cell surface and has been implicated in tumor cell–endothelial cell interactions and metastasis. Tumor cells frequently exhibit alterations in cell-surface glycoprotein modifications, such as increased sialylation, but the functional impact of these changes on metastatic potential are poorly understood. Using an *in vivo* RNA interference (RNAi) metastasis screen, Murugaesu and colleagues identified ST6GALNAC2 (α-N-acetylgalactosaminide α-2, 6-sialyltransferase 2), a sialyltransferase that catalyzes sialic acid attachment to N-acetylgalactosamine on *O*-glycans, as a suppressor of breast cancer metastasis. ST6GALNAC2 depletion enhanced secondary site colonization by breast cancer cells and increased metastatic burden in mice. This effect was mediated by changes in the sialylation profile of cell-surface *O*-glycans, in particular increased unmodified core 1 *O*-glycan, which augmented galectin-3 binding and promoted tumor cell aggregation, adhesion to endothelial cells, and retention in the lung vasculature *in vivo*. Importantly, this increase in metastatic potential was reversed by galectin-3 depletion or pharmacologic inhibition only in cells expressing low levels of ST6GALNAC2, suggesting that ST6GALNAC2 expression determines sensitivity to galectin-3 blockade. Furthermore, high *ST6GALNAC2* expression in human estrogen receptor-negative (ER^-) tumors was correlated with prolonged survival, whereas galectin-3 expression was not associated with clinical outcome. These results indicate that ST6GALNAC2 activity suppresses the prometastatic function of galectin-3 and suggest that *ST6GALNAC2* expression may identify patients with ER^- breast cancer who may benefit from galectin-3 inhibition. ■

See article, p. 304.

A Prostate Cancer Model Reveals a Switch from AKT- to MYC-Driven Metastasis

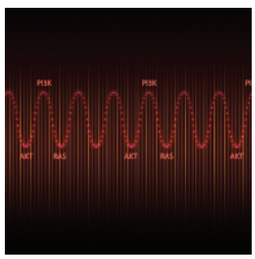
- The RapidCap GEM model delivers transgenes to the prostate via surgically injected virus.
- *Pten/Trp53*-deficient RapidCap mice develop metastases with high penetrance.
- Metastasis is driven by MYC upregulation, not AKT activation, and responds to a bromodomain inhibitor.

Although many candidate prostate cancer genes have been uncovered by genomic profiling, few have been validated because of the effort involved in generating genetically engineered mouse (GEM) models and the inability of these models to faithfully recapitulate the hallmarks of human prostate cancer, including focal disease initiation, highly penetrant metastasis, and castration resistance. To address this problem, Cho and colleagues developed a mouse model of metastatic prostate cancer, called RapidCap, based on surgical injection of the anterior prostate gland with a transgene-bearing lentivirus whose stable genomic integration is tracked by expression of a luciferase marker. Prostate-specific deletion of *Pten* and *Trp53* in prostate epithelial cells using this strategy induced focal proliferation and AKT activation. Furthermore, *Pten;Trp53*-deficient RapidCap mice also displayed high rates of metastasis, with over 50% of animals developing disseminated disease in distant tissues including the lymph nodes, spleen, liver, and lung. Androgen ablation via castration triggered disease regression followed by aggressive tumor relapse, indicating the development of castration-resistant prostate cancer. Surprisingly, the metastatic tumors displayed low levels of AKT activation despite *Pten* deficiency, and instead were characterized by MYC overexpression, which was both necessary and sufficient to drive the growth and maintenance of metastases as demonstrated by their response to the bromodomain inhibitor JQ1, which suppresses MYC. These data validate the RapidCap GEM system as a means to explore mechanisms and vulnerabilities of human prostate cancer metastasis and identify MYC as a potential target for therapeutic intervention. ■

See article, p. 318.

PI3K Inhibitors Suppress Both AKT and RAS–ERK Signaling

- AKT inhibition blocks AKT–mTOR signaling and activates ERK, but PI3K inhibitors block both.
- PI3K acts upstream of RAS, as PI3K inhibitors lead to rapid inhibition of wild-type RAS activity.
- Transient inhibition of ERK is required for induction of apoptosis by PI3K inhibitors.

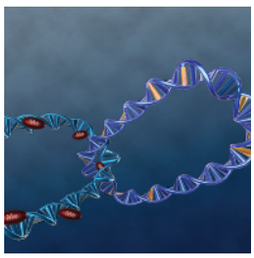


Hyperactive PI3K–AKT–mTOR signaling is a common feature of human cancers, but inhibitors of this pathway have shown limited clinical efficacy. Will and colleagues compared the biologic consequences of selective inhibition of PI3K or AKT in cancer cells with upregulated PI3K activity and found that only PI3K inhibitors rapidly induced a significant amount of apoptotic cell death. Mechanistically, PI3K inhibition led to a rapid but transient decrease in RAF, MEK, and ERK phosphorylation, whereas AKT inhibition relieved feedback inhibition of ERK signaling. However, PI3K inhibition had no effect on ERK phosphorylation in cells harboring *RAS* mutations, raising the possibility that PI3K inhibitors might specifically block activation of wild-type RAS. Indeed, PI3K inhibition, but not AKT inhibition, significantly reduced levels of GTP-bound RAS, suggesting a model in which PI3K regulates wild-type RAS independently of AKT. Transient inhibition of ERK was required for induction of apoptosis, and combined MEK and AKT inhibition caused significantly more cell death than AKT inhibition alone. Consistent with these findings, PI3K inhibition had greater antitumor activity *in vivo* than AKT inhibition, but the combination of MEK and AKT inhibitors induced tumor regression almost as effectively as PI3K inhibition. Interestingly, pulsatile PI3K inhibitor treatment was more effective than continuous PI3K inhibition, suggesting that periodic PI3K inhibition may adequately block PI3K signaling while minimizing toxicity and feedback reactivation of other signaling pathways. ■

See article, p. 334.

DNA Methylation Patterns and Genetic Aberrations Coevolve in CLL

- CLL tumors maintain allele-specific methylation, which is highly variable between patients.
- A subset of CLL exhibits increased methylation heterogeneity associated with poor prognosis.
- High methylation heterogeneity in CLL is indicative of coevolution of genetic alterations.

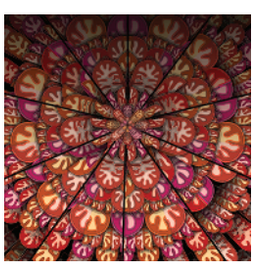


Epigenetic changes often contribute to cancer development, but the potential relationship between DNA methylation patterns, tumor heterogeneity, and genetic evolution remains unclear. Chronic lymphocytic leukemia (CLL) is an ideal system for investigating this relationship, as it tends to be epigenetically stable and pure tumor cell populations are easily obtained. Oakes and colleagues used methylation arrays and next-generation sequencing to analyze the genome-wide epigenetic and genetic diversity in primary CLL samples. Intriguingly, allele-specific methylation (ASM) was observed in all CLL samples at much higher rates than in other cancers and normal B cells. ASM could be attributed to monoallelic loss of methylation in founder clones that persisted through later generations, and ASM at specific CpG locations was highly variable between CLL samples. Despite the highly stable nature of most CLL cases, a subset of samples displayed elevated intratumor methylation heterogeneity, which was inversely correlated with ASM and was associated with poor prognostic indicators, shorter time to treatment, and reduced durable response to therapy. Furthermore, increased methylation heterogeneity was strongly associated with genetic heterogeneity, with many common cancer driver mutations evolving codependently with epigenetic diversity. Taken together, these results indicate that elevated methylation heterogeneity is associated with aggressive disease and increased genetic evolution in CLL. Therefore, monitoring methylation heterogeneity as well as evolving genetic changes during the course of CLL may be beneficial in patient treatment. ■

See article, p. 348.

The Selective BCL-2 Antagonist ABT-199 Has Activity in AML

- AML cell lines and primary patient samples are sensitive to the selective BCL-2 antagonist ABT-199.
- ABT-199 sensitivity correlates directly with BCL-2 expression and inversely with BCL-XL expression.
- Mitochondrial BH3 profiling may be a predictive biomarker of *in vivo* ABT-199 response in AML.



Acute myelogenous leukemia (AML) cells are dependent on the anti-apoptotic protein BCL-2 for survival, and inhibition of BCL-2 family members with small-molecule BH3 mimetics has shown promise in clinical trials for treatment of some lymphoid and solid tumors. Pan and colleagues found that ABT-199, a BH3 mimetic specific for BCL-2 but not BCL-XL, induced rapid apoptosis of multiple AML cell lines at nanomolar concentrations and inhibited leukemia progression in an *in vivo* murine AML xenograft model. AML cytotoxicity inversely correlated with BCL-XL expression and directly correlated with BCL-2 expression and mitochondrial membrane depolarization, indicating on-target BCL-2 inhibition at the mitochondria. Importantly, ABT-199 induced apoptosis in a large percentage of both chemosensitive and chemorefractory primary patient AML myeloblasts and AML stem/progenitor cells *in vitro*. As with AML cell lines, ABT-199 cytotoxicity of primary patient samples tightly correlated with BCL-2 expression and mitochondrial-mediated apoptosis, and was largely independent of genetic mutation status. Of note, the authors found that BH3 profiling, a functional assay of mitochondrial apoptotic function in response to selective BH3-mimetic peptides, predicted responsiveness of AML primary cells to ABT-199 both *in vitro* and in an *in vivo* patient-derived xenograft model. Together, these findings support further clinical investigation of the small-molecule BCL-2 antagonist ABT-199 for the treatment of refractory AML and identify BH3 profiling as a potential predictive biomarker of therapeutic response to ABT-199. ■

See article, p. 362.

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