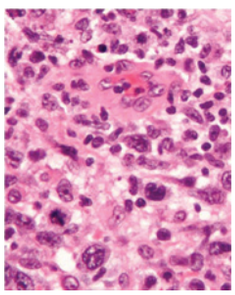
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
AACR American Association for Cancer Research

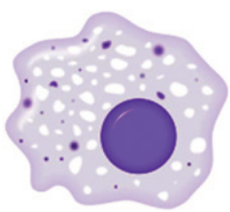
Convergence on the STAT3 Pathway in Lymphoma



Crescenzo and colleagues sequenced 155 ALK-negative anaplastic large cell lymphomas (ALCL), identifying oncogenic *JAK1* or *STAT3* mutations leading to constitutive activation of STAT3, also activated by tyrosine kinase fusions involving transcription factors *NFKB2* or *NCOR2* and tyrosine kinases *ROS1* or *TYK2*. These findings underscore that mutated STAT3 proteins are potent transcriptional activators and that STAT3-mediated transformation requires modulation of numerous genes and can occur in the absence of *JAK1*/*STAT3* mutations. The clinical outcome for patients with ALK-negative ALCL is dismal, but these findings, if validated in larger cohorts, provide the opportunity to selectively target the JAK/STAT3 pathway. The central role of STAT3 in human cancer also provides an opportunity for emphasis on drug development against this key pathway. (*Image by Nephron courtesy of Wikimedia Commons.*)

Crescenzo R, Abate F, Lasorsa E, Tabbo' F, Gaudiano M, Chiesa N, et al. Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. Cancer Cell 2015;27:516–32.

Targeting Myeloid Cells as a New Antiangiogenic Strategy



Rivera and colleagues observed in mouse models of pancreatic neuroendocrine and mammary tumors that VEGF inhibitors did not act by directly blocking endothelial cell proliferation and sprouting. Rather, these agents indirectly turned myeloid cells into immune-stimulating and angiostatic cells that induced CXCL chemokines. CXCL14/4 in turn reduced vessel density and induced immune stimulation and T-cell infiltration. Due in part to hypoxia, tumors respond to that angiostatic process, activating PI3K in myeloid cells, converting them into highly immune suppressive and now proangiogenic cells that were refractory to anti-VEGF therapy. Importantly, combination therapy with a PI3Kγδ inhibitor, isoforms restricted to myeloid cells, sustained the antiangiogenic treatment and prolonged survival. These data reveal a novel mechanism of antiangiogenic therapy evasion that may be reversed with PI3Kγδ inhibitors. (*Image courtesy of Wikimedia Commons.*)

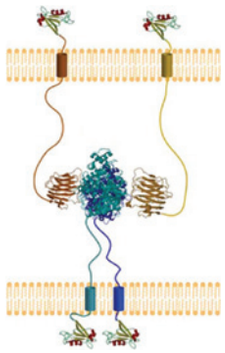
Rivera LB, Meyronet D, Hervieu V, Frederick MJ, Bergsland E, Bergers G. Intratumoral myeloid cells regulate responsiveness and resistance to antiangiogenic therapy. Cell Rep 2015;11:577–91.

Coordinating EMT: It's All about Vimentin, ERK, and Phospho-Slug

Virtakoivu and colleagues demonstrate that endothelial–mesenchymal transition (EMT)-linked proteins vimentin, Slug (SNAI2), and ERK exhibit similar localization in triple-negative breast cancer samples, and that loss of expression of any of these proteins inhibited migration and invasion of cancer cells. Vimentin and ERK interacted directly and functionally *in vitro* and *in vivo*. This interaction promoted a positive feedback loop that supported ERK activity, vimentin transcription, and recruitment of Slug to activated ERK. Mass spectrometry and site-directed mutagenesis demonstrated Slug-serine-87 as the dominant ERK phosphorylation site, with Slug phosphorylation by ERK required for EMT induction and vimentin and Axl receptor tyrosine kinase expression. However, this posttranslational modification had no impact on Slug's known role in repressing E-cadherin expression, another important driver of EMT. Instead, this novel Slug phosphorylation imparted another level of control to transcriptional roles for Slug and appeared to be pivotal in coordinating key EMT hallmarks. (*Image by Guillaume Brocker courtesy of Wikimedia Commons.*)

Virtakoivu R, Mai A, Mattila E, De Franceschi N, Imanishi SY, Corthals G, et al. Vimentin-ERK signaling uncouples Slug gene regulatory function. Cancer Res 2015;75:2349–62.

Breaking Advances



Glioma Gets Help from Its Neighbors

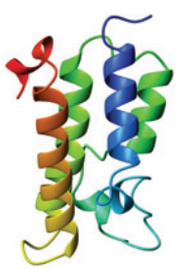
Venkatesh and colleagues investigate whether neuronal activity can also have a mitogenic effect on high-grade glioma. Thy1::ChR2 mice express the excitatory opsin channelrhodopsin-2 (ChR2) in deep cortical projection neurons. Stimulation with an optical fiber affords control of neuronal activity using *in vivo* optogenetics, with neuronal stimulation increasing proliferation of xenografted human glioblastoma cells. While the magnitude was relatively small, repeated rounds of neuronal stimulation resulted in significantly increased tumor cell burden. In optogenetically stimulated acute cortical slices, mass spectrometric analyses of conditioned media identified several candidate mitogens including neuroligin-3 (NLGN3). Pharmacologic inhibitors and shRNA-mediated knockdown demonstrated an essential role for the PI3K/mTOR pathway in the NLGN3-mediated effect. Levels of *NLGN3* in human glioblastoma correlated inversely with patient survival. These data suggest the mitogenic effect of NLGN3 may contribute to human disease. (*Image courtesy of Wikimedia Commons.*)

Venkatesh HS, Johung TB, Caretti V, Noll A, Tang Y, Nagaraja S, et al. Neuronal activity promotes glioma growth through neuroligin-3 secretion. Cell 2015;161:803–16.

tRNA Blocks Breast Cancer

Cells encountering stress are known to generate transfer RNA-derived RNA fragments (tRF) to help facilitate the stress response. Using next-generation small RNA sequencing, Goodarzi and colleagues identified specific tRFs upregulated in response to hypoxia in breast cancer cells and normal breast epithelium. The induction of these tRFs, however, was impaired in highly metastatic breast cancer cells, leading the authors to investigate these tRFs as potential tumor suppressors. Using an immunoprecipitation strategy with tRF^{Glu} as bait, they identified the RNA binding protein, YBX1, as a key target of hypoxia-induced tRFs. Targeting of YBX1 by these tRFs led to subsequent displacement of key oncogenic transcripts bound and stabilized by YBX1. Thus, progression of metastases in breast cancer is facilitated by negative regulation of hypoxia-related tRF induction. (*Image courtesy of Wikimedia Commons.*)

Goodarzi H, Liu X, Nguyen HC, Zhang S, Fish L, Tavazoie SF. Endogenous tRNA-derived fragments suppress breast cancer progression via YBX1 displacement. Cell 2015;161:790–802.



GLI2 Mediates Resistance to BET Bromodomain Inhibitors

BET inhibitors block binding of acetylated histones to bromodomain (BRD) proteins, uncoupling chromatin marks and transcriptional activation. The tumorigenic properties of pancreatic cells can be attenuated by the BET inhibitor JQ1, which blocks expression of target genes, including *MYC*. Kumar and colleagues show that pancreatic cancer cells can develop resistance to JQ1, resulting in cross-resistance to structurally distinct BET inhibitors as well as to BRD knockdown. JQ1-resistant cells express high levels of *GLI2*, induced by β-catenin–driven TCF sites on the *GLI2* promoter. GLI2 in turn occupies the *MYC* promoter, increasing its expression in a manner insensitive to BET inhibitors. Although attenuating *GLI2* expression did not block the growth of the JQ1-resistant cells, it resensitized cells to JQ1. This work demonstrates a mechanism of resistance to BET inhibitors, as well as suggesting a way to overcome such resistance. (*Image courtesy of Wikimedia Commons.*)

Kumar K, Raza SS, Knab LM, Chow CR, Kwok B, Bentrem DJ, et al. GLI2-dependent c-MYC upregulation mediates resistance of pancreatic cancer cells to the BET bromodomain inhibitor JQ1. Sci Rep 2015 Mar 25;5:9489.

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 2015;75:2403-2404.