Breaking Advances
Highlights from Recent Cancer Literature

Synthetic Lethal Approaches to Targeting Myc

Many oncogenes, such as Ras and Myc, are difficult to target pharmacologically. Kessler and colleagues used a genome-wide RNA interference (RNAi) screen to search for Myc-synthetic lethal (MySL) short hairpin RNAs (shRNA) in human mammary epithelial cells (HMEC) that express an inducible c-Myc-estrogen receptor fusion transgene (Myc-ER HMEC). The authors identified many candidate genes with previously unknown functions in Myc biology, most significantly the SUMO-activating enzyme (SAE1/2), a critical component of the SUMOylation pathway. They also did several experiments to demonstrate the physiologic significance of Myc-SAE2 synthetic lethal interaction. For example, they showed that SUMOylation activity of SAE2 is required for HMECs to support Myc oncogenic signaling. Additionally, they identified the mechanism by which Myc-SAE2 synthetic lethal interactions occur by showing that deregulation of mitotic spindle fibers underlies the cell death observed in Myc-overexpressing cells in the presence of SAE2 shRNA. Specifically, inactivation of SAE2 SUMOylation activity induced a switch from activation to repression of Myc transcriptional activity, impinging on specific genes referred to as SUMOylation-dependent-Myc-switchers (SMS genes). The authors revealed a subset of these SMS genes as mitotic spindle regulators. Loss of function of these genes was similarly synthetically lethal in the presence of Myc hyperactivation. This observation strongly suggests that the involvement of Myc in mitotic spindle homeostasis is important for its oncogenic program to maintain cellular transformation. A xenograft model was used to show that SAE2 is also essential for tumors induced by Myc-overexpressing cells. Kessler and colleagues compiled a human breast cancer dataset to establish that patients with tumors harboring high levels of Myc and low levels of SAE2 expression had better metastasis-free survival than did patients with tumors harboring high levels of SAE expression. Therefore, targeting SUMOylation represents a new therapeutic intervention for Myc-induced tumorigenesis. *(Image courtesy of Arcimboldo/Eckhard Pecher through Wikimedia Commons.)*

Kessler JD, Kahle KT, Sun T, Meerbrey KL, Schlabach MR, Schmitt EM, et al. A SUMOylation-dependent transcriptional subprogram is required for Myc-driven tumorigenesis. Science 2011 Dec 8. [Epub ahead of print].

Notch Signaling, Cancer Stem Cells, and Translation Control

The cellular origins of cancer stem cells (CSC) and the molecular and cellular mechanisms important to maintain their tumorigenic phenotype are still poorly understood. Song and Lu report on their use of a simple but very powerful model, type II neural stem cells known as neuroblasts, to study CSCs. They show that *Drosophila* larval brain CSCs can arise from the dedifferentiation of transit-amplifying progenitor cells back to a stem cell–like state. This process is dependent on the hyperactivation of Notch signaling, important for maintaining cell growth in neuroblasts. The authors further show that Notch-dependent cell growth is associated with increases in nucleolar size. They used an RNA interference (RNAi) approach to demonstrate that decreased eIF4E activity can effectively impair CSCs but not normal stem cells. They also uncovered a feedback loop between eIF4E and dMyc that was important to maintain cell growth, nucleolar size, and ectopic stem cell formation in the larval *Drosophila* brain. Specifically, Myc transcription activity increased eIF4E mRNA levels and, intriguingly, eIF4E may regulate Myc transcription activity potentially by directly binding to it. Low eIF4E activity suppressed the high cellular growth rate of ectopic neuroblasts and brain tumor formation. Finally, the authors show that the CSC-like phenotype in *Drosophila* ovaries also relies on eIF4E-dMyc activity. This article provides new information on how Notch signaling is important to sustain the CSC state and tumor formation, highlighting the significance of targeting the translational initiation factor eIF4E in stem cell maintenance and cancer.

Song Y, Lu B. Regulation of cell growth by Notch signaling and its differential requirement in normal vs. tumor-forming stem cells in Drosophila. Genes Dev 2011;25:2644–58.

The Ubiquitin-Mediated Proteolysis Pathway in Renal Cell Carcinoma: VHL and Beyond

Renal cell cancer is the most aggressive of the urologic malignancies, and clear cell–renal cell carcinoma (ccRCC) is the most common of these tumors. Mutations in *VHL*, a component of the ubiquitin-mediated proteolysis pathway (UMPP), are common in ccRCC. To identify additional alterations, the authors screened 10 ccRCC tumors using whole-exome sequencing followed by targeted sequencing in additional samples. As a result of this analysis, they found somatic mutations in 23 genes, 12 of which were not previously known to occur in this cancer. As expected, mutations in *VHL* were common. However, by performing pathway analysis of mutated genes, they found additional genes associated with the UMPP in these tumor samples. HIF1α and HIF2α are 2 hypoxia regulatory factors that have been intensively investigated in renal cancers. Both HIF isoforms are the VHL targets that are degraded through UMPP. Accordingly, the authors examined the relationship between HIF expression and somatic mutations in UMPP genes. They found a positive correlation between mutations in UMPP gene tumors and overexpression of HIF1α and HIF2α. They also looked at the proportion of ccRCC tumor samples that show lesions in the pathway. Overall, 5 of the 10 tumors that were deep sequenced showed somatic alterations

in UMPP genes. Targeted sequencing of all 135 genes in the UMPP in additional tumors showed a similar proportion of tumors with these alterations. Out of 98 ccRCCs, 49 (50%) showed nonsilent somatic mutations in genes encoding components of the UMPP, including *VHL* (altered in 27%), *BAP1* (altered in 8%), *CUL7* (altered in 3%), *BTRC* (altered in 2%), and other genes. This pathway analysis suggests that alternations of the UMPP, not just of *VHL*, potentially have important roles in ccRCC tumorigenesis. Overall, by showing alterations in both *VHL* and other components of the UMPP, the authors show the importance of this pathway in the molecular pathogenesis of a large proportion of ccRCC tumors.

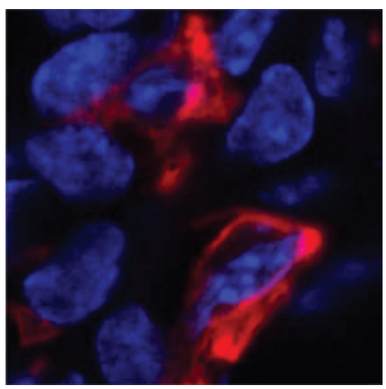
Guo G, Gui Y, Gao S, Tang A, Hu X, Huang Y, et al. Frequent mutations of genes encoding ubiquitin-mediated proteolysis pathway components in clear cell renal cell carcinoma. Nat Genet 2012;44: 17–9.

Personalized Medicine for Patients with Early-Stage Non–Small Cell Lung Cancer

Lung cancer accounts for more than 1 million deaths each year. Non–small cell lung cancer (NSCLC) accounts for 80% to 90% of these tumors. Thirty percent to 50% of early-stage patients relapse after resection and die of metastatic recurrence. Adjuvant chemotherapy improves the survival of patients with early-stage disease, with a small survival advantage at 5 years. Whereas adjuvant chemotherapy has become the standard treatment for all patients with resected stage II/III NSCLC, only a proportion of patients benefit from this therapy. Additionally, adjuvant chemotherapy causes significant morbidity, increasing the need for more precise definition of the patient subset in which this therapy is efficacious. To gain insights on predicting which patients might benefit the most from adjuvant chemotherapy, Chen and colleagues examined gene expression profiling data from the National Cancer Institute–funded Director's Challenge Consortium. The authors had previously defined a signature from breast cancer that was associated with prognosis. Given that this signature was rich in genes involved in cell proliferation, the authors reasoned that it might also be prognostic in NSCLC. They applied this signature to microarray data from 442 NSCLC patient samples and dichotomized the samples according to the median risk-malignancy score. Both univariate and multivariate analyses revealed significant differences in overall survival between patients with high risk scores and those with low risk scores. To establish the predictive value of this signature, they examined the effect of adjuvant chemotherapy after stratifying by risk score and found a benefit of adjuvant chemotherapy only in the patients with high risk scores. In contrast, patients with the low risk scores did not show a benefit from adjuvant chemotherapy. Previously, a number of signatures have been proposed for solid tumors, but few have been translated into routine clinical practice. Accordingly, the authors acknowledge that further testing is required, and that translation of this signature into a format amenable to routinely available formalin-fixed paraffin-embedded archival pathology samples would represent a major step toward clinical utility. If it is validated in additional samples, this signature could be used to personalize therapy in patients with early-stage NSCLC and select for patients most likely to benefit from adjuvant chemotherapy in this disease.

Chen DT, Hsu YL, Fulp WJ, Coppola D, Haura EB, Yeatman TJ, et al. Prognostic and predictive value of a malignancy-risk gene signature in early-stage non–small cell lung cancer. J Natl Cancer Inst 2011;103: 1859–70.

Cathepsin Proteases and Chemotherapy



It has recently been appreciated that macrophage infiltrations in some solid tumors not only correlate clinically with outcome but also correlate with response to various forms of cytotoxic therapy. Macrophages produce a multitude of factors, including growth factors, chemokines, reactive mediators, and various classes of proteolytic enzymes, that together provide a survival advantage to malignant epithelia as well as blunting antitumor activities of cytotoxic lymphocytes via paracrine interactions. Molecular mechanisms underlying the ways in which macrophages regulate responses to cytotoxic therapy in solid tumors have not been clearly described; however, in a recent report, Shree and colleagues provide insight into these mechanisms. These authors found that cathepsin protease-expressing macrophages—specifically cathepsin B and S—protect malignant mammary epithelial cells from paclitaxel-induced (as well as etoposide- and doxorubicin-induced) tumor cell death in *ex vivo* assays. *In vivo*, combining paclitaxel with cathepsin inhibition significantly enhanced chemotherapy efficacy against both primary and metastatic mammary tumors. These experimental results provide a compelling rationale for clinical evaluation of combinatorial strategies inhibiting macrophage recruitment into solid tumors, or altering macrophage response pathways and mediator expression/activity, in combination with "standard of care" chemotherapy, to overcome inherent resistance to cytotoxic drug regimens. *(Image courtesy of B. Rufell, University of California, San Francisco.)*

Shree T, Olson OC, Elie BT, Kester JC, Garfall AL, Simpson K, et al. Macrophages and cathepsin proteases blunt chemotherapeutic response in breast cancer. Genes Dev 2011;25:2465–79.

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.