Altered eIF2α Signaling Turns on Advantageous Autophagy

Wengrod and colleagues reveal that cross-talk between mTOR and GCN2 (EIF2AK4) signaling is conserved from yeast to mammals and is defective in melanoma. Rapamycin inhibits mTOR, activating the PP6C phosphatase. PP6C (PPP6C), in turn, dephosphorylates and activates GCN2, an eIF2α kinase that senses amino acid deficiency through binding to uncharged tRNA. GCN2 activation allows for efficient induction of autophagy during amino acid deprivation that could not be achieved simply by inhibiting mTOR. Interestingly, 10% of melanomas have PP6C mutations. The authors show that the mutant PP6C allele was rapidly degraded, stabilizing or delaying degradation of the wild-type PP6C allele, leading to constitutive activation of GCN2 and eIF2α-dependent induction of autophagy. These changes rendered melanoma cells insensitive to mTOR inhibitors, allowing cells to survive mTOR pathway blockade and/or to survive in nonpropitious microenvironments. (Image courtesy of Wikimedia Commons.)


Adoption of the ALK Orphan Receptor Tyrosine Kinase

Anaplastic lymphoma kinase (ALK), important in neural development and implicated in such cancers as neuroblastoma, is no longer an orphan receptor tyrosine kinase. Murray and colleagues demonstrate heparin as a high-affinity ligand that induced ALK receptor dimerization, autophosphorylation, and activation of downstream signaling in the neuroblastoma cell line NB1. Heparin is a highly sulfated glycosaminoglycan, consisting of a chain of repeating disaccharide units. Interestingly, oligosaccharide chain length and sulfation status were critical determinants for autophosphorylation of ALK, with increased molecular weight of ALK–heparin complexes suggesting receptor oligomerization. Thus, ALK may be activated by heparin-induced ALK oligomerization. The authors hypothesize that, as is the case with FGFRs and RPTPs (receptor protein tyrosine phosphatase sigma), sulfated glycosaminoglycan-linked proteoglycans serve as coligands or ligands for ALK receptor activation. (Image courtesy of Wikimedia Commons.)


The E2F1–CIP2A–MYC Circuit Drives Imatinib Resistance in CML

Lucas and colleagues identify CIP2A (KIAA1524), the cancerous inhibitor of PP2A, as a marker to select patients with chronic myelogenous leukemia (CML) who might benefit from treatment with second-generation tyrosine kinase inhibitors (2GTKI). In patients with high CIP2A levels, 2GTKI but not imatinib prevented progression to blast crisis. Levels of E2F1 were elevated in CIP2A-high patients. Both E2F1 and CIP2A were suppressed following 1 month of 2GTKI, but not by imatinib treatment. Importantly, differences in TKI effects were not mediated by suppression of BCR–ABL but were dependent on inhibition of the E2F1–CIP2A–MYC circuit, in which each oncoprotein promoted the other's circuit. The authors propose that patients with high CIP2A levels could be offered either dasatinib or nilotinib upfront. In addition, CIP2A represents an attractive therapeutic target because high levels were only found in malignant cells. (Image by Difu Wu courtesy of Wikimedia Commons.)

Lucas CM, Harris RJ, Holcroft AK, Scott LJ, Carmell N, McDonald E, et al. Second generation tyrosine kinase inhibitors prevent disease progression in high-risk (high CIP2A) chronic myeloid leukaemia patients. Leukemia 2015 Mar 13 [Epub ahead of print].
Targeted Inhibition Paradoxically Promotes Drug Resistance

Obenauf and colleagues modeled therapeutic targeting of heterogeneous tumor cell populations in vivo in BRAF-driven melanoma models and demonstrate that cells resistant to BRAF inhibitors benefited from targeting of surrounding drug-sensitive cells. Interestingly, their data suggest that tumors regressing on therapy attract resistant circulating tumor cells that ultimately contribute to disease progression. Importantly, the authors show that signals derived from drug-sensitive cells in response to targeted therapy were secreted in the microenvironment and drove the outgrowth of resistant cells. BRAF, ALK, and EGFR mutant cells paradoxically secreted factors that supported survival of drug-sensitive cells and accelerated growth of drug-resistant minority clones. AKT signaling was a mediator of this tumor secretome-induced disease progression, providing a compelling rationale for combination therapy targeting the MAPK and AKT/PI3K/mTOR pathways.


SMO Mutations and Drug Resistance in BCC

While the Smoothened inhibitor vismodegib shows efficacy in metastatic basal cell carcinoma (BCC), ~20% of patients develop resistance. The authors of two recent articles found resistance mutations primarily in SMO itself. These were either constitutively activating or low basal activity mutations that maintained Hedgehog responsiveness. Interestingly, SMO mutations with low basal activity displayed differing degrees of vismodegib resistance, suggesting sensitivity to vismodegib at high doses. Surprisingly, many of the resistant SMO mutants were cross-resistant to structurally distinct Smoothened antagonists, suggesting little clinical benefit to treatment with multiple Smoothened antagonists. Vismodegib resistance also arose from mutational-pathway activation unlinked to Smoothened. These findings show that targeting the Hedgehog pathway downstream of SMO, at the level of the GLI transcription factors, could attenuate signaling of vismodegib-resistant SMO mutants.


Role of Oncogenic HRAS in Muscle-Invasive Bladder Cancer

Muscle-invasive urothelial carcinoma of the bladder is aggressive, with frequent progression to metastasis. In a mutant HRAS (HRAS\textsuperscript{C3}) transgenic mouse model, activation of the RTK/RAS pathway in urothelial cells caused hyperplasia. He and colleagues suggest that equilibrium between promitogenic factors and compensatory tumor barriers in the p19-MDM2-p53-p21 axis and a prolonged G\textsubscript{2} arrest might underlie the persistent hyperplastic state. Interestingly, conditional inactivation of p53 in urothelial cells of HRAS\textsuperscript{C3} transgenic mice resulted in high-grade muscle-invasive urothelial carcinoma. Genes that drove epithelial–mesenchymal transition and genes associated with multiple progenitor/stem cell markers were upregulated. Thus, RTK/RAS pathway activation along with p53 deficiency might serve as a biomarker for progression and for therapeutic response of urothelial carcinomas. Additionally, inhibition of components of the RTK/RAS pathway would be a useful therapeutic strategy in this type of cancer.

He F, Melamed J, Tang MS, Huang C, Wu XR. Oncogenic HRAS activates epithelial-mesenchymal transition and confers stemness to p53-deficient urothelial cells to drive muscle invasion of basal subtype carcinomas. Cancer Res; Published OnlineFirst March 20, 2015; doi:10.1158/0008-5472.CAN-14-3067.

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.
Highlights from Recent Cancer Literature

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