Tumorigenesis

Major finding: *Eif4e* haploinsufficiency is compatible with development but impairs oncogenic transformation.

Mechanism: eIF4E controls an oncogenic translation program that includes mRNAs important for ROS regulation.

Impact: Targeting eIF4E-dependent oncogenic translation may increase sensitivity to ROS induction.

CANCER CELLS REQUIRE eIF4E TO TRANSLATE PRO-ONCOGENIC mRNAs

The major cap binding protein eukaryotic initiation factor 4E (eIF4E) is thought to represent the limiting factor for mRNA translation efficiency. However, the dose of eIF4E required for normal development and for global and specific mRNA translation remains unknown. Truitt, Conn, and colleagues addressed this question by generating mice heterozygous for *Eif4e* (*Eif4e*$^{+/-}$), which developed normally and showed no defect in global protein synthesis. However, when challenged with an oncogenic insult, *Eif4e*$^{+/-}$ mouse embryonic fibroblasts (MEF) were resistant to cellular transformation compared with their wild-type counterparts. Unbiased translational profiling identified genes translationally induced by oncogenic transformation in an eIF4E-dependent manner, including a subset of genes involved in reactive oxygen species (ROS) regulation and the response to oxidative stress. The 5′ untranslated region of many of these mRNAs contained a 15-nucleotide *cis*-acting motif, termed the cytosine-enriched regulator of translation domain, which was enriched in eIF4E targets induced upon oncogenic transformation and required for eIF4E-selective translation of target mRNAs. Transformed *Eif4e*$^{+/-}$ cells exhibited increased intracellular ROS levels associated with enhanced induction of apoptosis, supporting the requirement of eIF4E to promote the growth and survival of cancer cells by controlling ROS levels. Depletion of specific eIF4E target mRNAs in wild-type cells reduced transformation efficiency, whereas treatment of *Eif4e*$^{+/-}$ cells with ROS scavengers rescued their tumorigenic potential. Consistent with these findings, *Eif4e* haploinsufficiency increased oxidative stress, reduced tumor burden, and sensitized tumors to pharmacologic ROS induction in a KRAS-driven lung cancer model. Together, these data support the hypothesis that cancer cells require physiologic levels of eIF4E to selectively translate mRNAs necessary to control escalating ROS levels. Furthermore, this phenomenon reveals a potential therapeutic window in which the eIF4E-dependent translational program might be targeted to manipulate ROS levels in cancer cells. ■

Truitt ML, Conn CS, Shi Z, Pang X, Tokuyasu T, Coady AM, et al. Differential requirements for eIF4E dose in normal development and cancer. Cell 2015;162:59–71.

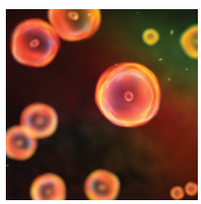
Leukemia

Major finding: Negative feedback regulation of ERK is required for oncogenic transformation in pre-B ALL.

Concept: ERK negative regulators are selectively induced in B-cell lineage leukemia and predict poor outcome.

Impact: Targeted inhibition of DUSP6 induces apoptosis in ALL cells and may overcome TKI resistance.

ERK NEGATIVE CONTROL PERMITS ONCOGENE ACTIVATION IN PRE-B ALL



Pre-B acute lymphoblastic leukemia (ALL) is frequently characterized by RAS pathway mutations and oncogenic tyrosine kinases such as BCR–ABL1 that result in ERK hyperactivation. Treatment with tyrosine kinase inhibitors (TKI) induces remission in patients with Philadelphia chromosome–positive (Ph$^+$) ALL, but tumors frequently relapse due to lesions that drive oncogenic ERK signaling. Shojaee and colleagues demonstrated that, although the majority of pre-B cells died upon acute activation of oncogenes, the small fraction of cells that survived and underwent oncogenic transformation expressed high levels of negative regulators of ERK signaling, including dual specificity phosphatase 6 (DUSP6), ETS variant 5 (ETV5), and Sprouty 2 (SPRY2), which function as tumor suppressors in other tumor types. These negative regulators of ERK were selectively expressed at high levels and associated with poor clinical outcome in human pre-B ALL, but not acute myeloid leukemia. Genetic deletion of *Dusp6*, *Etv5*, or *Spry2* in pre-B cells prevented oncogenic RAS- and BCR–ABL1-induced malignant transformation *in vitro* and suppressed the initiation of leukemia *in vivo*. Loss of ERK negative regulators resulted in hyperactivation of ERK signaling, accumulation of reactive oxygen species, increased p53 protein expression, and the induction of senescence and acute toxicity, indicating that pre-B ALL cells are dependent on robust negative feedback regulation to calibrate ERK signaling. Consistent with these findings, pharmacologic inhibition of DUSP6 in patient-derived Ph$^+$ ALL cells using a small molecule, BCI, resulted in ERK hyperactivation, global loss of tyrosine phosphorylation, and p53-driven cell death. Furthermore, BCI synergized with imatinib and overcame imatinib resistance to induce toxicity in relapsed pre-B ALL cells and patient-derived Ph$^+$ ALL xenografts. These results support the hypothesis that pre-B cells are only permissive to oncogenic signaling in the presence of strong negative feedback control, and suggest that targeting negative regulators of ERK may be effective in pre-B cell ALL. ■

Shojaee S, Caeser R, Buchner M, Park E, Swaminathan S, Hurtz C, et al. ERK negative feedback control enables pre-B cell transformation and represents a therapeutic target in acute lymphoblastic leukemia. Cancer Cell 2015;28:114–28.

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