Signaling

Major finding: Long-term ERK inhibition induces *KRAS*-mutant PDAC cell senescence mediated by MYC degradation.

Clinical relevance: *De novo* resistance to ERK inhibition was associated with elevated PI3K–AKT–mTOR signaling.

Impact: ERK inhibitors may be more effective than RAF or MEK inhibitors in treating *KRAS*-mutant tumors.

PROLONGED ERK INHIBITION REDUCES *KRAS*-MUTANT TUMOR GROWTH

Most pancreatic ductal adenocarcinomas (PDAC) harbor activating *KRAS* mutations, which lead to the activation of RAF–MEK–ERK signaling. However, resistance to RAF or MEK inhibitors can occur through ERK reactivation in *KRAS*-mutant cells, suggesting that ERK may be a better target in *KRAS*-mutant tumors. Hayes and colleagues showed that approximately half of PDAC cell lines were sensitive to the ERK inhibitor SCH772984, including cell lines that were resistant to MEK inhibition. Short-term SCH772984 treatment reduced phosphorylation of ERK (pERK) and RSK (an ERK target), and reduced tumor cell growth through induction of apoptosis and inhibition of cell-cycle progression. SCH772984 also induced pAKT in PDAC cells sensitive to SCH772984, resulting in increased pAKT. Combining AKT inhibition (with the PI3K inhibitor AZD8186) with ERK inhibition resulted in further growth inhibition in SCH772984-sensitive cells, suggesting that combined ERK and PI3K inhibition may be effective in treating PDAC. Unexpectedly, outgrowth of resistant cells did not occur after long-term treatment of sensitive cells with SCH772984. ERK inhibition promoted a senescence-like phenotype associated with p16 upregulation and decreased RB phosphorylation that was dependent on degradation of MYC. In a PDAC orthotopic mouse model, SCH772984 treatment decreased pERK expression, reduced MYC levels, and suppressed tumor growth. *De novo* resistance to ERK inhibition was associated with elevated PI3K–AKT–mTOR signaling, but combined inhibition of PI3K did not overcome resistance, indicating more complex mechanisms driving *de novo* resistance. Combined treatment with SCH772984 and the CDK inhibitor dinaciclib improved tumor suppression, and the combined inhibition of ERK and PI3K also slowed tumor growth. Together, these data suggest that ERK inhibitors may be effective in treating patients with PDAC and potentially other *KRAS*-mutant cancers, and elucidate a mechanism by which short- and long-term ERK inhibition has differential effects. ■

Hayes TK, Neel NF, Hu C, Gautam P, Chenard M, Long B, et al. Long-term ERK inhibition in KRAS-mutant pancreatic cancer is associated with MYC degradation and senescence-like growth suppression. Cancer Cell 2016;29:75–89.

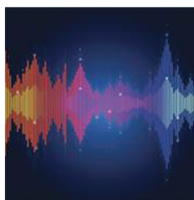
Epigenetics

Major finding: Super-enhancer copy-number gain increases expression of cancer-related genes.

Concept: Amplification of the identified super-enhancers leads to upregulation of *MYC*, *KLF5*, *USP12*, and *PARD6B*.

Impact: Lineage-specific super-enhancer amplification may promote tumorigenesis in multiple cancer types.

FOCAL AMPLIFICATION OF SUPER-ENHANCERS UPREGULATES ONCOGENIC DRIVERS



Copy-number alterations are important drivers of cancer; however, the specific mechanisms by which amplifications and deletions in noncoding regions promote cancer are not understood. By analyzing The Cancer Genome Atlas copy-number data and corresponding acetylated histone H3 lysine 27 (H3K27ac) chromatin immunoprecipitation sequencing (ChIP-seq) data across 29 tumor types, Zhang, Choi, Francis, and colleagues identified 55 focally amplified noncoding regions, 6 of which were tissue-specific amplifications in super-enhancer regions. In head and neck squamous cell carcinoma, *KLF5* was upregulated by amplification of a cluster of 3 super-enhancers marked by H3K27ac. Esophageal carcinomas harbored amplification of a distinct *KLF5* super-enhancer, further supporting super-enhancer amplification as a mechanism to upregulate putative oncogenes including *KLF5*. Focal amplification of *USP12* and *PARD6B* super-enhancers occurred in colorectal carcinoma and liver hepatocellular carcinoma, respectively. In addition, two distinct noncoding focal amplifications located 3′ of the *MYC* gene and associated with increased *MYC* expression were found in lung adenocarcinoma (*MYC*-LASE) and uterine corpus endometrial carcinoma (*MYC*-ECSE), and were in different regions than the previously identified *MYC* super-enhancers in T-cell acute lymphoblastic leukemia and acute myeloid leukemia. H3K27ac and p300 ChIP-seq confirmed that the *MYC*-LASE and *MYC*-ECSE super-enhancers were active only in cell lines of the respective tumor type, and chromosome conformation capture demonstrated that both super-enhancers physically interacted with the *MYC* promoter only in cells in which the super-enhancers were active. The active enhancer region of *MYC*-LASE was mapped to a 148bp region with the strongest activity in reporter assays, which required binding by the transcription factors NFE2L2 and CEBPβ for optimal activation. CRISPR/Cas9–mediated repression or deletion of the *MYC*-LASE active enhancer region reduced *MYC* expression and anchorage-independent growth. These findings suggest that amplification of super-enhancers can upregulate oncogenes in a lineage-specific manner to promote tumorigenesis. ■

Zhang X, Choi PS, Francis JM, Imielinski M, Watanabe H, Cherniack AD, et al. Identification of focally amplified lineage-specific super-enhancers in human epithelial cancers. Nat Genet 2015 Dec 14 [Epub ahead of print].

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