Osteosarcoma

Major finding: Altered enhancer activity allows for dynamic gene expression to promote osteosarcoma metastasis.

Approach: Epigenomic profiling reveals differential enhancer activity in primary versus metastatic tumors.

Impact: The discovery of metastasis-linked enhancers suggests potential targets for antimetastatic therapies.

ENHANCER-DRIVEN GENE EXPRESSION CHANGES FACILITATE METASTASIS

Osteosarcoma is a bone malignancy that frequently metastasizes to the lung. In order to colonize the metastatic site, tumor cells shift their transcriptional output to adapt to the local microenvironment, but it is not clear what genetic or epigenetic mechanisms drive this shift. To determine the contribution of enhancer elements to the metastatic phenotype, Morrow and colleagues performed epigenomic profiling of primary and metastatic osteosarcomas and metastatic and nonmetastatic osteosarcoma cell lines. Loci with differential enhancer activity in primary versus metastatic tumors and cells were termed metastatic variant enhancer loci (Met-VEL). On average, 9.3% of enhancers were gained in metastatic samples and 16.4% of enhancers were lost. Twenty-two percent of Met-VELs were distributed in dense clusters across the genome, often in close proximity to individual genes, suggesting a nonrandom acquisition due to selective pressure during metastasis, and Met-VELs were associated with increased gene expression. In an *ex vivo* mouse model of osteosarcoma lung metastasis, the difference in Met-VEL associated gene expression was even greater between parental and metastatic cells than in *in vitro* cultures, indicating a dynamic modulation of gene expression as tumor cells engage the lung microenvironment. Further, expression of Met-VEL–associated genes was required for metastatic colonization, including genes with gained Met-VEL clusters (*F3*, *FBXO42*, *FLNA*, and *FOXO3*) and genes that encode AP1 complex transcription factors that bind to Met-VELs (*FOS* and *FOSL1*). Thus, disrupting Met-VEL–associated gene expression with BET inhibitors or AP1 transcription factor depletion reduced metastasis. F3 was highly expressed in lung metastases from patients with osteosarcoma, and in an *in vivo* metastasis model, metastatic osteosarcoma cells expressed higher levels of F3 than nonmetastatic cells. F3 depletion inhibited metastasis in a spontaneous metastasis model but did not suppress primary tumor growth. These findings indicate that altered enhancer activity at Met-VELs can drive metastasis, suggesting potential targets for antimetastatic therapies. ■

Morrow JJ, Bayles I, Funnell APW, Miller TE, Saiakhova A, Lizardo MM, et al. Positively selected enhancer elements endow osteosarcoma cells with metastatic competence. Nat Med 2018;24:176–85.

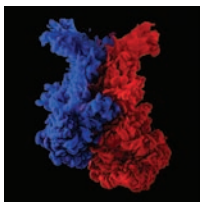
Lung Cancer

Major finding: Wild-type KRAS increases survival and resistance to MEK inhibitors in KRAS-mutant lung cancer cells.

Concept: Blocking KRAS dimerization suppresses downstream signaling and the growth of KRAS-mutant tumors.

Impact: Targeting KRAS dimerization may be a potential therapeutic strategy in patients with KRAS-mutant tumors.

DIMERIZATION IS CRITICAL FOR THE FUNCTIONS OF WILD-TYPE AND MUTANT KRAS



Activating *KRAS* mutations occur frequently in patients with lung adenocarcinoma, and there are currently no effective targeted therapies available to treat patients with KRAS-driven tumors, as targeting downstream MAPK signaling with MEK or ERK inhibitors has not provided a clinical benefit in these patients. KRAS can function as a dimer, suggesting the potential for targeting dimer formation. However, it is not clear if dimerization is required for the oncogenic activity of mutant KRAS or what effect the remaining wild-type *KRAS* allele has. Ambrogio and colleagues found that loss of wild-type *Kras* accelerated cell proliferation in KRAS-mutant ($KRAS^{G12C}$, $KRAS^{G12D}$, or $KRAS^{G12V}$) mouse embryonic fibroblasts. *In vivo*, in a mouse model in which mutant $Kras^{G12V}$ is expressed in lung epithelial cells and the wild-type *Kras* allele can be conditionally deleted ($Kras^{lox/LSLG12V}$), mice that retained the wild-type *Kras* allele exhibited extended survival. Further, expression of the wild-type KRAS protein reduced sensitivity to MEK inhibitors in KRAS mutant cells. A charge-reversal $KRAS^{D154Q}$ mutant blocked KRAS dimerization and was sufficient to block the growth-inhibitory effect of wild-type KRAS on mutant KRAS and restore sensitivity to MEK inhibitors, indicating that wild-type KRAS dimerizes with mutant KRAS to produce its growth-inhibitory effects. *In vivo*, $KRAS^{D154Q/G12C}$ tumors with impaired KRAS dimerization grew more slowly than $KRAS^{G12C}$ tumors, suggesting that blocking mutant-KRAS dimerization suppresses its oncogenic activity. Indeed, in $KRAS^{D154Q/G12C}$ tumors MEK and ERK phosphorylation were reduced, and ERK target genes were downregulated. Taken together, these findings reveal that wild-type KRAS dimerizes with mutant KRAS to impair its oncogenic effects and promote resistance to MEK inhibitors and that mutant KRAS dimerization drives tumorigenesis. These findings suggest the potential for therapeutic targeting of KRAS dimerization in KRAS-mutant tumors. ■

Ambrogio C, Köhler J, Zhou ZW, Wang H, Paranal R, Li J, et al. KRAS dimerization impacts MEK inhibitor sensitivity and oncogenic activity of mutant KRAS. Cell 2018;172:857–68.e15.