

RESEARCH WATCH

Epigenetics

Major finding: EZH2 promotes epigenetic silencing of *SLFN11* to drive acquired resistance to chemotherapy.

Approach: Paired chemosensitive and chemoresistant patient-derived xenografts model acquired resistance.

Impact: EZH2 inhibitors may augment standard cytotoxic therapy and prevent resistance in patients with SCLC.

EZH2 INHIBITION MAY PREVENT CHEMORESISTANCE IN SCLC

Patients with small cell lung cancer (SCLC) are initially responsive to chemotherapy, but chemoresistance develops rapidly. The molecular mechanisms underlying the development of resistance are not well understood, prompting Gardner and colleagues to model acquired resistance using ten paired chemosensitive and chemoresistant SCLC patient-derived xenografts (PDX). Whole-exome sequencing of the paired PDXs showed that key genetic alterations were maintained through the acquisition of chemoresistance, suggesting that epigenetic mechanisms may be responsible for acquired chemoresistance. Gene expression profiles were largely similar between chemosensitive and chemoresistant tumors. However, a minority of genes exhibited altered expression, including *SLFN11*, which contributes to DNA-damage repair deficiencies and was significantly downregulated in 4 of 10 PDX models. *SLFN11* expression was reduced in SCLC cell lines and tumor samples from previously treated patients, indicating that *SLFN11* may be silenced by chemotherapy. The histone methyltransferase EZH2 is highly expressed in SCLC, and inhibition of EZH2 with EPZ011989 (EPZ) increased *SLFN11* expression and restored sensitivity to topoisomerase inhibitors in cell lines and *ex vivo* cultures from the chemoresistant PDXs. Further,

overexpression of *SLFN11* was sufficient to sensitize cells to topotecan, implicating *SLFN11* as a critical factor in SCLC sensitivity to DNA-damaging agents. Chemotherapy caused a global increase in H3K27me3 and a decrease in H3K27ac in chemoresistant cells. EZH2 and H3K27me3 were highly concentrated at the transcription start site of *SLFN11*, and the acquisition of chemoresistance was accompanied by H3K27me3 spreading to the gene body and a near-complete loss of H3K27ac. EPZ treatment removed H3K27me3 throughout the *SLFN11* gene body, promoting its reexpression. EPZ was well tolerated in mice and slowed tumor growth in PDX models that acquired resistance by *SLFN11* silencing. Further, in combination with chemotherapy, EPZ induced tumor regression and prevented chemoresistance. The finding that EZH2 promotes chemoresistance through *SLFN11* silencing suggests that EZH2 inhibition may prevent chemoresistance in patients with SCLC and enhance the efficacy of chemotherapy. ■

Gardner EE, Lok BH, Schneeberger VE, Desmeules P, Miles LA, Arnold PK, et al. Chemosensitive relapse in small cell lung cancer proceeds through an EZH2-*SLFN11* axis. *Cancer Cell* 2017;31:286–99.

Tumor Heterogeneity

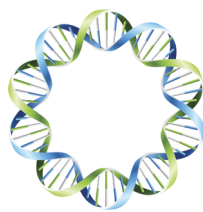
Major finding: Circular extrachromosomal DNA (ecDNA) amplifications promote tumor heterogeneity and evolution.

Concept: ecDNA is detected in nearly half of human cancers but rarely in normal cells.

Impact: Tumor heterogeneity introduced by ecDNA amplifications may allow tumor cells to adapt to maximize survival.

EXTRACHROMOSOMAL DNA AMPLIFICATIONS INCREASE ONCOGENE COPY NUMBER

Genomic amplifications in cancer can occur in chromosomes or in circular extrachromosomal DNA (ecDNA). However, ecDNA has not been well quantified in cancer, in part due to a lack of methods for analysis, and the oncogenes targeted by ecDNA amplification have not been determined. Turner, Deshpande, Beyter, and colleagues developed ECdetect, an image analysis software package, to quantify ecDNA in DAPI-stained metaphases. Integration of whole-genome sequencing data from 117 cancer cell lines and tumors, with bioinformatic and cytogenetic analysis of 2,049 metaphase cells from 72 cancer cell samples and 233 metaphase cells from normal tissues, revealed that ecDNA was abundant in cancer cells, found in nearly half of tumor samples from 17 different cancer types, but rarely detected in normal cells. The ecDNA level varied among tumor types and between cells within a tumor culture. Amplified oncogenes detected by whole-genome sequencing were found either exclusively in the ecDNA or in both the ecDNA and chromosomal DNA, and ecDNA amplification increased



expression of the corresponding mRNA transcript. ecDNA is prone to unequal segregation to daughter cells, suggesting that it may induce a rapid genetic heterogeneity. Indeed, mathematical modeling indicated that ecDNA oncogene amplifications resulted in higher copy number than chromosomal oncogene amplifications, which was predicted to result in increased intratumor heterogeneity. Further, experimental data confirmed that ecDNA was associated with higher heterogeneity, validating the predictions of the model. The finding that ecDNA amplifications can promote expression of key driver oncogenes suggests that ecDNA may contribute to tumor progression and drug resistance. Further, these results define a role for ecDNA in accelerating intratumor heterogeneity, which may accelerate tumor cell evolution. ■

Turner KM, Deshpande V, Beyter D, Koga T, Rusert J, Lee C, et al. Extrachromosomal oncogene amplification drives tumour evolution and genetic heterogeneity. *Nature* 2017;543:122–5.

CANCER DISCOVERY

EZH2 Inhibition May Prevent Chemoresistance in SCLC

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