An epigenetic target for synthetic lethality

Genome-wide sequencing studies have revealed that the gene *ARID1A*, which encodes a component of a chromatin remodelling complex, is among the most frequently mutated genes in human cancers. Now, reporting in *Nature Medicine*, Zhang and colleagues show that inactivation or absence of *ARID1A* acts in a synthetic lethal manner with the inhibition of the methyltransferase *EZH2* — opening up new therapeutic possibilities for cancers with *ARID1A* mutations.

The highest mutation rate for *ARID1A* had been reported in ovarian clear cell carcinomas (OCCCs), with approximately half of the samples being found to carry frame-shift or nonsense mutations that lead to the functional loss of *ARID1A*.

“ Intraperitoneal injection of GSK126 caused marked tumour regression in two different orthotopic xenograft models ”

As *ARID1A* is involved in the epigenetic regulation of genes (it is a member of the SWI–SNF nucleosome remodelling complex), the authors tested whether its deficiency might render cells vulnerable to the inhibition of a second epigenetic regulator. To test this, 3D cultures of OCCC cell lines with wild-type *ARID1A* were established, and *ARID1A* was knocked down by short interfering RNA (siRNA). Then, 15 commercially available small molecule inhibitors of epigenetic regulators were tested for their ability to kill *ARID1A*-deficient cells but not their *ARID1A* wild-type counterparts.

The compound with the highest selectivity for *ARID1A*-deficient cells was GSK126, a highly specific inhibitor of *EZH2*, which is a histone methyltransferase that is part of the polycomb repressive complex 2. *EZH2* catalyses lysine 27 trimethylation on histone H3 (H3K27Me₃), thereby silencing gene expression.

Interestingly, the polycomb complex and the SWI–SNF complex are known to have antagonistic effects on the expression of a number of genes. To elucidate the underpinnings of the synthetic lethal relationship between *ARID1A* and *EZH2*, the authors searched for genes that are differentially regulated by the two proteins. They found a significant overlap of genes that are upregulated by either *ARID1A* restoration or by *EZH2* inhibition. The most interesting of these genes was *PIK3IP1* (phosphoinositide 3-kinase interacting protein 1), encoding a negative

regulator of the phosphoinositide 3-kinase (PI3K)–AKT pathway, which is a well-known oncogenic signalling axis.

ARID1A and *EZH2* were found to associate with the promoter of *PIK3IP1*. Based on further biochemical experiments, the authors propose that *ARID1A*, which activates *PIK3IP1* expression, usually dominates over *EZH2*, which suppresses *PIK3IP1* expression. When *ARID1A* is absent, *EZH2* silences *PIK3IP1*. Subsequent inhibition of *EZH2*, in turn, reinstates the expression of *PIK3IP1* — and thereby the inhibition of the PI3K–AKT pathway.

To test whether this relationship can be exploited *in vivo*, *ARID1A*-mutated OCCC cells were used to establish tumours in mice. Intraperitoneal injection of GSK126 caused marked tumour regression in two different orthotopic xenograft models, and reduced metastases in a model of disseminated OCCC. Immunohistochemical staining showed lower levels of activity of the PI3K–AKT pathway in tumours of GSK126-treated mice than in vehicle-treated tumours.

These results point to a novel synthetic lethal strategy based on inhibition of *EZH2* in *ARID1A*-mutated cancers. Given the frequency of *ARID1A* mutations, this approach may potentially have wide-ranging applications.

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