KIDNEY CANCER

OCT2 demethylation cracks open oxaliplatin resistance

The prognosis of renal cell carcinoma (RCC) is extremely poor owing to its resistance to various treatments, including the platinum-based chemotherapeutic agent oxaliplatin. Now Su Zeng, Lushan Yu and colleagues report that the global demethylating agent decitabine sensitizes RCC cells to the cytotoxic effects of oxaliplatin *in vitro* and in xenograft models.

The researchers previously showed that organic cation transporter 2 (OCT2) — the main transporter involved in the cellular uptake of oxaliplatin — is transcriptionally repressed in RCC cells. In their new study, they uncovered the mechanisms of this repression and designed a new therapeutic intervention to restore oxaliplatin sensitivity.

Zeng, Yu and colleagues identified increased methylation of CpG islands in the *OCT2* promoter, which correlated with transcriptional repression of *OCT2*, in RCC tissue compared to adjacent nontumour tissue. In particular, the fourth CpG site, located in the E-box consensus sequence, was exclusively hypermethylated in RCC tissues with strong (>70%) repression of *OCT2* transcription. They report that global inhibition of DNA methylation using decitabine

restored *OCT2* expression in RCC cell lines. This effect was mediated by MYC, which selectively occupies the unmethylated E-box and functions as a transcription factor. MYC directly interacts with and recruits MLL1, which catalyzes trimethylation of lysine 4 on histone H3 (H3K4me3), a marker of the active chromatin state that is enriched in normal kidneys. H3K4me3 expression was reduced by 80% in RCC tissues with strong repression of *OCT2*.

Next, the researchers investigated the therapeutic potential of decitabine. Pretreatment with this agent markedly increased the sensitivity of cultured RCC cell lines to oxaliplatin, but not to cisplatin or carboplatin, other platinum-based chemotherapy drugs that are not *OCT2* substrates.

In xenografted RCC tumours, decitabine treatment resulted in a 40% decrease in *OCT2* promoter methylation and induced *OCT2* expression. Combination treatment with decitabine and oxaliplatin led to oxaliplatin accumulation in the tumours, delayed tumour growth, and >50% tumour shrinkage with prolonged administration. In mice, no nephrotoxicity or altered *OCT2*

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expression in normal renal tissue was observed with the combination therapy.

“We now plan to perform a clinical trial in patients with RCC based on our sequential combination therapeutic strategy (decitabine followed by oxaliplatin) and test its effectiveness in patients with cancer,” says Zeng.

Andrea Aguilar

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