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KIDNEY CANCER

Open gates for oxaliplatin

Epigenetic modifications block the expression of the main transporter of oxaliplatin into renal cell carcinoma (RCC) cells, but combination treatment with decitabine can sensitize tumour cells to oxaliplatin therapy in RCC models, according to new research published in *Science Translational Medicine*.

Clinical trials of oxaliplatin in patients with RCC showed little efficacy of this platinum-based chemotherapeutic agent. Oxaliplatin activity depends on uptake of the drug into cells, plausibly mediated by the organic cation transporter 2 (OCT2). However, in contrast to normal kidney tissue, OCT2 expression seems to be downregulated in RCC samples. Now, researchers from Zhejiang University in China have investigated the molecular basis of oxaliplatin resistance of RCC and developed a treatment regimen to improve RCC response to this drug.

First, the team demonstrated that OCT2 expression in RCC tissues was repressed at both the mRNA and protein level, which was epigenetically mediated by hypermethylation of CpG islands in the *OCT2* promoter. Mechanistically, they found that hypermethylation at an E-box site inhibited transactivation of OCT2 expression by the proto-oncogene c-Myc. Furthermore, the absence of c-Myc at the *OCT2* promoter prevented recruitment of histone-lysine *N*-methyltransferase 2A, which would usually catalyse H3K4me3 at the *OCT2* promoter and activate *OCT2* transcription.

Next, the researchers tested whether treatment of RCC cell lines with decitabine, which blocks DNA methyltransferases resulting in global inhibition of DNA methylation, would increase responses to oxaliplatin: drug uptake and DNA adduct formation were increased by 66–93% and 88–153%, respectively. Of note, expression of the cellular transporter MATE-2, which exports oxaliplatin out of cells and is also repressed in RCC, was not induced.

Finally, testing the drug combination in two RCC xenograft models, involving treatment with decitabine 1 week before repeated oxaliplatin administration, showed that E-box methylation was decreased, and OCT2 expression, drug uptake and DNA adduct formation were increased compared with oxaliplatin-only treatment. In addition, in one mouse model under prolonged combination treatment, xenograft tumour growth was delayed and tumours shrunk by >50%.

Examining possible adverse effects of the combination treatment, the team found no signs of increased risk of neuropathy, nephrotoxicity or hepatotoxicity in mice receiving decitabine.

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ORIGINAL ARTICLE Liu, Y. *et al.* Epigenetic activation of the drug transporter OCT2 sensitizes renal cell carcinoma to oxaliplatin. *Sci. Transl. Med.* **8**, 348ra97 (2016)