Microrna-96 Improves the Fighting Power of Chemotherapy

August 20, 2012

EM Scherer

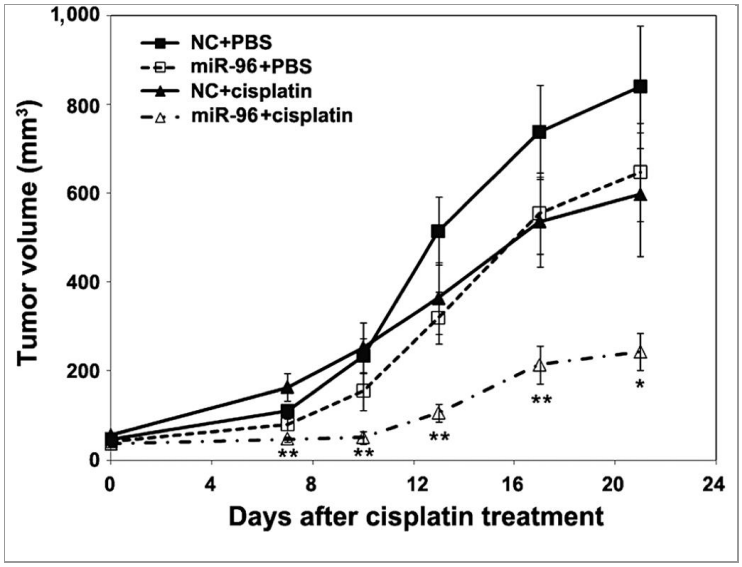
Small molecule drugs that chemically crosslink double-stranded DNA are commonly used to treat cancers that harbor defective DNA repair pathways. For example, interstrand crosslink (ICL)-inducing agents like cisplatin provide effective treatments for breast and ovarian cancers that lack homologous recombination DNA repair factors BRCA1 and BRCA2. However, multiple pathways can repair DNA lesions resulting from ICL, which may explain why cancer cells develop chemoresistance to certain ICL-inducing agents. Therefore, Drs. Toshiyasu Taniguchi and Christopher Kemp of the Human Biology and Public Health Sciences divisions are leading efforts to identify novel cancer therapeutics that inhibit diverse ICL repair pathways. In their most recent work, former postdoctoral fellow Dr. Yemin Wang and graduate students Jen-Wei Huang and Philamer Calses of the Taniguchi Lab discovered a cellular microRNA that downregulates two key factors involved in separate, but integrated, ICL repair pathways. Not only does this finding shed light on how these different pathways are regulated, but it also provides a novel strategy for targeting chemoresistant cancers.

To find novel therapeutics that downregulate ICL repair pathways, the authors screened small molecules for candidates that reduced RAD51 accumulation in the nuclei of cancer cells following ICL induction, as accumulation of RAD51 indicates that homologous recombination has been activated. In this study, the small molecules being screened were microRNAs, cellular RNA molecules that regulate diverse processes with high specificity, and microRNA (miR)-96 was identified as a lead candidate.

Using three different algorithms, Wang and colleagues found that RAD51 and REV1 are predicted cellular targets of miR-96, where REV1 is a central component of translesion DNA synthesis that is required for cisplatin resistance in certain cancers. Indeed, miR-96 downregulated RAD51 and REV1 expression in a luciferase reporter assay and improved cancer cell line sensitivity to DNA-damaging agents (*e.g.*, cisplatin and PARP inhibitors). The authors then showed that tumor cells pre-treated with a lentiviral vector to induce miR-96 overexpression prior to engraftment in an animal tumor model exhibited a more significant reduction of tumor growth following cisplatin treatment compared

to cancer cells that were treated with cisplatin alone. This suggests that miR-96 holds promise as a cancer therapeutic and presents a powerful approach to improve ICL-based cancer treatment.

Wang Y, Huang JW, Calses P, Kemp CJ, Taniguchi T. 2012. MiR-96 downregulates REV1 and RAD51 to promote cellular sensitivity to cisplatin and PARP inhibition. *Cancer Research*, Epub ahead of print, doi: 10.1158/0008-5472.CAN-12-0103.



Modified from paper

Cancer cells overexpressing microRNA (miR)-96 exhibit significantly reduced tumor growth following engraftment and cisplatin treatment in an in vivo tumor model compared to cells expressing a negative control miR (NC + cisplatin), or established tumors that express miR-96 but did not receive cisplatin treatment (mir-96 + PBS). MiR-96 is small RNA molecule that targets two factors in separate, but related, DNA repair pathways that are required for cellular resistance to DNA-damaging chemotherapy agents. PBS, or phosphate buffered saline, is a vehicle control for cisplatin. *, $p < 0.05$, **, $p < 0.01$.