ANTICANCER DRUGS

# Think globally, act globally


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Although microRNAs (miRNAs) are increasingly appreciated to have an important role in malignancies, miRNA-based cancer therapeutics are still at an early stage in development, partly owing to the delivery challenges associated with oligonucleotide agents. Furthermore, the majority of strategies aim to target a single miRNA molecule. Writing in Proc. Natl Acad. Sci. USA, Esteller and colleagues now describe the activity of a small molecule, enoxacin, that acts more broadly by targeting the miRNA biogenesis pathway.

The authors initially found that enoxacin upregulated the expression of 24 mature miRNAs in colorectal cancer cells. Next, by treating cultured cancer cells from seven common malignancies, they uncovered its antiproliferative effects.

So, is there a common mechanism linking enoxacin to both mature miRNA production and growth inhibition? TAR RNA-binding protein 2 (TARBP2) is an attractive candidate target; it is a component of the miRNA processing machinery that is required for the assembly of mature miRNAs into multiprotein effectors called RNA-induced silencing complexes (RISCs), which act by repressing translation. Using both surface plasmon resonance and isothermal titration calorimetry, the authors found that enoxacin can bind to TARBP2. Additionally, a colorectal cancer cell line containing an inactivating mutation in the TARBP2 gene was found to be resistant to enoxacin's growth-suppressive effect — a phenotype that was restored following reconstitution with wild-type *TARBP2*.

Next, animal tumour models were evaluated in the hope of uncovering TARBP2-regulated, cancer-specific growth inhibitory phenotypes for enoxacin in vivo. The authors implanted human primary colorectal tumours harbouring either wild-type or mutant TARBP2 in the ceacum of nude mice. Compared to control-treated mice, drug-treated mice displayed both strong tumour growth inhibition and enhanced miRNA production. Conversely, both effects were substantially reduced in TARBP2-deficient mice. Furthermore, enoxacin treatment shifted the miRNA expression signature to one that is known to occur in the normal colon — a result that was once again not observed in TARBP2-impaired mice. The results from these orthotopically implanted mice were reproduced in colorectal cancer cell xenografted nude mice, which together suggest that enoxacin-enhanced, TARBP2-regulated miRNA processing inhibits tumour growth.

The authors also tested whether enoxacin can affect cancer dissemination. Specifically, HCT-116 cancer cells were injected into the spleen and tail vein of mice, in order to promote distal seeding in the chief organs that are affected by dissemination of this cancer — the lungs and liver, respectively. Indeed, treatment with enoxacin markedly decreased the number of metastases in these two tissues.

So, as many human tumours may be characterized by impaired miRNA production and global miRNA downregulation, restoring the normal cell microRNAome with small molecules such as enoxacin might be a promising broad anticancer strategy.

*Kira Anthony, Editor, NCI-Nature Pathway Interaction Database*

**ORIGINAL RESEARCH PAPER** Melo, S. A. *et al.* Small molecule enoxacin is a cancer-specific growth inhibitor that acts by enhancing TAR RNA-binding protein 2-mediated microRNA processing. *Proc. Natl Acad. Sci. USA* **108**, 4394–4399 (2011)

**FURTHER READING** Garzon, R. *et al.* Targeting microRNAs in cancer: rationale, strategies and challenges. *Nature Rev. Drug Discov.* **9**, 775–789 (2010)