THERAPY

microRNA suppresses liver cancer

Hepatocellular carcinoma is a particularly lethal form of cancer, owing to typically late diagnosis and a lack of effective therapies. Now, writing in *Cell*, Kota and colleagues demonstrate that reinstating the expression of a single microRNA (miRNA) that is specifically down regulated in liver cancer cells suppresses tumour progression, unveiling a new potential anticancer strategy.

Abnormal expression of specific miRNAs has been implicated in the pathogenesis of various human cancers, and miRNA expression profiles have proved useful in tumour classification, prognosis and predicting response to therapy. As most miRNAs are downregulated in tumours, Kota and colleagues proposed that replacing an miRNA that is diminished in cancer cells, but highly expressed and therefore tolerated in normal cells, may provide a safe and effective treatment approach.

Neil Smith

To explore their theory, they first set out to identify miRNAs that fitted this profile. miR-26a was found to be the most dramatically downregulated miRNA in cancer cells from a mouse liver tumour model, as compared with normal liver cells. This finding was confirmed in human liver-derived hepatocellular carcinoma cells.

Next, the authors investigated whether miR-26a exhibited antiproliferative properties. Following retroviral-mediated enforced expression of miR-26a in HepG2 cells (to achieve a level similar to that observed in normal liver tissue), flow cytometry revealed that there were fewer cells in S phase and more cells in G1 than in controls. This indicated that miR-26a induced a G1 cell cycle arrest. Prediction using the Targetscan algorithm, followed by *in vitro* confirmation, demonstrated that miR-26a induced this G1 arrest through the repression of cyclin D2 and cyclin E2.

To evaluate the therapeutic potential of miR-26a, Kota and colleagues first developed an adeno-associated virus (AAV) vector system for *in vivo* delivery, which was targeted to the liver following systemic administration. A single tail vein injection of the miR-26a AAV vector into mice led to high miR-26a liver expression without any toxic effects when assessed 3 weeks later.

They then assessed the vector in the mouse model of liver cancer at 11 weeks of age — a time when animals typically have multiple small- to medium-sized tumours. After 3 weeks, 6 out of 8 control mice had developed fulminant disease, whereas 8 out of 10 treated mice were protected from disease progression and exhibited only small tumours or a complete absence of tumours. In addition, the lack of response in the other two treated mice seemed to be due to technical failures. Further studies revealed that miR-26a-mediated tumour suppression is associated with sustained inhibition of proliferation and specific induction of apoptosis.

Overall, this study identifies a new target for liver cancer treatment and provides proof-of-concept for the systemic delivery of tumour-suppressing miRNAs as an anticancer approach. The reported deregulation of miR-26a in various other tumours suggests that this strategy might have a broad application.

Sarah Crunkhorn
Associate Editor,
Nature Reviews Drug Discovery

ORIGINAL RESEARCH PAPER Kota, J. *et al.* Therapeutic microRNA delivery suppresses tumorigenesis in a murine liver cancer model. *Cell* **137**, 1005–1017 (2009)