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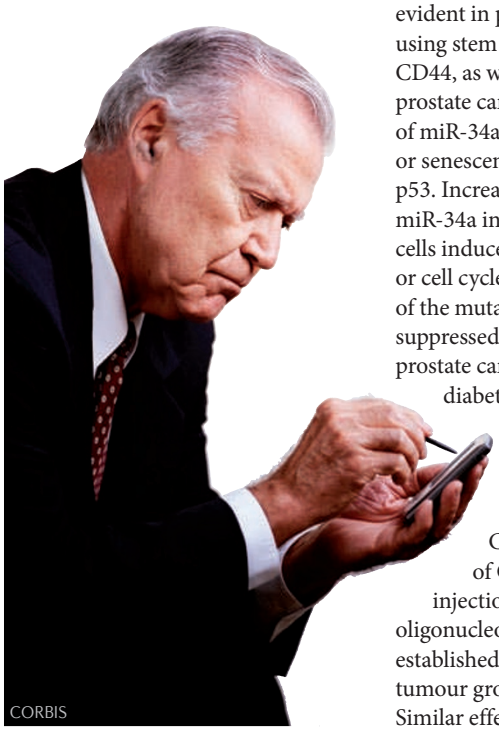
MICRORNA

Micromanaging CD44

CD44 is a receptor for hyaluronan and although heralded as a marker of cancer stem cells (CSCs) in many tumours, whether and how CD44 expression contributes to the biology of CSCs are questions that still require answers. By finding that CD44 is a target of the microRNA miR-34a, Dean Tang and colleagues identified one way of looking at the requirement of CD44 for CSC function in prostate cancer.



CORBIS

> “suppression of endogenous miR-34a using antagomirs increased the tumorigencity and metastasis of CD44$^-$ prostate cancer cells *in vivo*”

In cells purified from three prostate cancer xenografts that express high levels of CD44, an analysis of expression levels of miRNAs showed that miR-34a was consistently downregulated. This relationship was also evident in prostate CSCs selected using stem cell markers other than CD44, as well as in 18 human prostate cancer samples. Expression of miR-34a induces cell cycle arrest or senescence and is regulated by p53. Increasing the expression of miR-34a in human prostate cancer cells induced senescence, apoptosis or cell cycle arrest independently of the mutation status of p53 and suppressed the growth of various prostate cancer cells in non-obese diabetic–severe combined immunodeficient mice. Moreover, inhibition of tumour growth by miR-34a was also seen in CSCs selected on the basis of CD44 expression, and injection of synthetic miR-34a oligonucleotides into mice with established prostate cancers reduced tumour growth and metastasis. Similar effects were seen when CD44 expression levels were knocked down in prostate cancer xenografts and orthotopic tumours. Conversely, the suppression of endogenous miR-34a using antagomirs increased the tumorigencity and metastasis of CD44$^-$ prostate cancer cells *in vivo*.

miR-34a regulates a number of genes that are implicated in cancer development, such as *BCL2*, *MYC* and *MET*; so, to verify the importance of CD44 as a target of miR-34a, the authors identified the miR-34a binding sites in the 3′ untranslated region (UTR) of *CD44* and established that miR-34a regulates CD44 expression using luciferase assays. Overexpression of a mutant CD44 that lacked the 3′ UTR containing the miR-34a binding sites in a prostate cancer cell line expressing miR-34a inhibited miR-34a suppression of invasive growth *in vitro*. Therefore, CD44, a protein known to have many functions in cell biology, including the promotion of invasive growth, seems to be a key target for the miR-34a-mediated inhibition of prostate tumour progression. However, as CD44 has also been shown to be downregulated by pro-metastatic miR-373 and miR-520c, its regulation by miRNAs could be context dependent.

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ORIGINAL RESEARCH PAPER Liu, C. *et al.* The microRNA miR-34a inhibits prostate cancer stem cells and metastasis by directly repressing CD44. *Nature Med.* 16 Jan 2011 (doi:10.1038/nm2284)