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TUMOUR SUPPRESSORS

A microdependency of importance?

> “even partial inhibition of these miRNAs might have therapeutic value”

Retinoblastoma is characterized by the loss of the tumour suppressor gene *RB1* and is frequently accompanied by impaired p53 function. Therapeutic strategies to counteract loss of function of tumour suppressors are challenging to devise, but a new study pinpoints a promising tumour-specific reliance on particular microRNAs (miRNAs).

Chris Marine and colleagues used a mouse model of retinoblastoma in which the Cre recombinase, driven by the retinal-specific *Chx10* promoter, excises one or more chosen tumour suppressor genes that are flanked by *loxP* sites. An accompanying green fluorescent protein (*GFP*) gene provided a marker of cells in which Cre is active.

Having previously shown that complete loss of the miRNA-processing enzyme DICER1 inhibits the development of retinoblastoma caused by the loss of *Rb1*, the authors initially investigated the viability of cells that are affected by *Dicer1* loss combined with tumour suppressor loss. In mice with retinal loss of only *Dicer1*, many GFP^+ cells were present in adult retinas, which had normal histology. The mice with additional loss of *Rb1* had retinas with fewer GFP^+ cells, but still had fairly normal histology. This shows that combined deletion of *Rb1* and *Dicer1* causes a mild cell viability defect, but can still be tolerated in normal retinal cells.

p53 is known to mediate an antiproliferative response to *Dicer1* loss; so, the authors tested whether the additional deletion of *Trp53* (which encodes p53) would restore viability. Surprisingly, the opposite effect was seen: no GFP^+ retinal cells were found, suggesting that deletion of all three genes was incompatible with cell viability. In support of this, GFP^+ cells that transiently emerged during embryogenesis were found to undergo apoptosis.

Overall, the authors propose that cells with defects of both RB and p53 signalling, but not of either pathway alone, are reliant on DICER1, such that *Dicer1* loss could be a powerful mechanism to selectively kill advanced retinoblastoma tumour cells. Indeed, whereas mice with combined retinal deficiency of *Trp53* and *Rb1* developed advanced retinoblastoma disease with high penetrance, no retinoblastoma occurred in mice with additional loss of *Dicer1*.

However, *Dicer1* is an essential gene and is also a haploinsufficient tumour suppressor. This means that targeting DICER1 as a therapeutic strategy is problematic because complete systemic inhibition is likely to be toxic, whereas partial inhibition might be tumorigenic. The authors reasoned that the dependency on DICER1 in retinoblastomas deficient for p53 and RB1 might be mediated by a particular subset of crucial miRNAs. They analysed mouse and human retinoblastoma samples for upregulated miRNAs and identified the miR-17~92 miRNA cluster. Importantly, retinoblastoma formation in mice deficient for both *Trp53* and *Rb1* was suppressed by either biallelic or monoallelic deletion of the *mir-17~92* cluster, indicating that even partial inhibition of these miRNAs might have therapeutic value. Furthermore, the growth of human retinoblastoma cells *in vitro* was suppressed by combinatorial targeting of miRNAs of this cluster, and the strength of the effect correlated with the completeness of p53 deficiency.

This study has uncovered an intriguing dependency, and it will be important to assess the efficacy of miR-17~92 inhibition for treating established retinoblastomas *in vivo*. The recent demonstrations of miR-17~92 acting as an oncogene in various tumour types highlights that this miRNA cluster might be a valuable therapeutic target in cancer.

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ORIGINAL RESEARCH PAPER Nittner, D. *et al.* Synthetic lethality between Rb, p53 and Dicer or miR-17–92 in retinal progenitors suppresses retinoblastoma formation. *Nature Cell Biol.* 5 Aug 2012 (doi:10.1038/ncb2556)

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