TUMORIGENESIS

Cone cells set the stage

Retinoblastoma is a childhood cancer of the retina initiated by the mutation of both copies of *RB1*. The protein encoded by *RB1,* the tumour suppressor RB, regulates a signal transduction pathway controlling cell cycle progression that is disrupted in most cancers. Despite this knowledge, the identity of the cell of origin of retinoblastoma in humans and the basis for its extreme sensitivity to *RB1* inactivation have been unclear.

By staining a panel of human retinoblastomas with markers of postmitotic cone precursors, David Cobrinik and colleagues identified these photoreceptors as the predominant cell type in human retinoblastoma. Although other cell types were present in the tumours, they almost always expressed RB and were therefore presumed to be non-neoplastic. Moreover, the rare cells that lacked both RB and cone markers probably came from the normal retina, based on their retention of two *RB1* alleles. The tumorigenic potential of RB-negative cone precursors was confirmed by the ability of serially engrafted cells to produce retinoblastomas in the subretinal space of nude mice.

What makes cone cells particularly susceptible to transformation through the loss of *RB1*? The authors proposed that a cell type-specific signalling network exists within the maturing cone precursors that sensitizes them to the oncogenic effects of *RB1* mutations and sets the stage for transformation. A common countermeasure to the loss of RB activity is the activation of the ARF pathway. ARF binds to and inactivates the p53 inhibitor MDM2, leading to p53-mediated apoptosis. High levels of MDM2 were detected in both cone precursors and retinoblastoma cells, suggesting that these cells are unable to activate ARF-mediated apoptotic responses. Accordingly, knockdown studies showed that MDM2 suppresses ARF-induced apoptosis in cultured retinoblastoma cells and is required for cell proliferation and survival. It was further determined that *MDM2* expression in retinoblastoma was regulated by the cone-specific transcription factor retinoid x receptor γ (RXRγ). Knockdown of RXRγ reduced *MDM2* expression and retinoblastoma cell growth and survival. The authors also found that cone precursors expressed NMYC and that another cone-specific transcription factor, TRβ2, was necessary for retinoblastoma cell survival and proliferation.

Therefore, retinoblastoma seems to originate in cone precursors that contain intrinsic signalling networks that suppress cell death and promote cell survival after the loss of *RB1*. These findings also indicate that drugs targeting components of the cone precursor network, such as MDM2, might be useful for the treatment of this disease.

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ORIGINAL RESEARCH PAPER Xu, X. L. *et al.* Retinoblastoma has properties of a cone precursor tumor and depends upon cone-specific MDM2 signaling. *Cell* **137**, 1018–1031 (2009)
FURTHER READING Burkhart, D. L & Sage, J. Cellular mechanisms of tumour suppression by the retinoblastoma gene. *Nature Rev. Cancer* **8**, 671–682 (2008)