TUMORIGENESIS

RB, lost in progression

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The retinoblastoma (RB) tumour suppressor is well known for its role in suppressing the transcription of genes required for S phase entry by repressing the activity of the E2F transcription factors. Inactivation of the RB pathway by mutations in different proteins upstream of RB is a common event in tumour development. However, mutations in *RB1* are fairly rare and even more so in tumour progression. In a new study by Karen Knudsen and colleagues, RB has a leading role in the progression of prostate cancer.

The authors were interested in investigating the possible role of RB in preventing cancer progression. Given that prostate cancer undergoes different stages of progression from carcinoma *in situ* to metastatic castrate-resistant prostate cancer (CRPC), the authors analysed a set of human prostate cancer samples and observed that, whereas there was no alteration in the abundance of *RB1* mRNA in primary tumours, there was a substantial reduction in the CRPC samples. A gene expression pattern associated with the loss of *RB1* was observed in most of the CRPC samples. To further investigate the effects of *RB1* loss in CRPC, xenografts derived from human prostate cancer cells in which *RB1* had been silenced were grown in mice. RB loss dramatically increased tumour growth, but only after castration of the mice. In these circumstances, high levels of prostate-specific antigen — an androgen receptor (AR) target that is not expressed in mice — were detected in serum. Moreover, RB depletion resulted in increased *AR* mRNA and protein levels in both cultured cell lines and xenografts.

But how is loss of RB altering AR function? As a chromatin immunoprecipitation assay showed, loss of RB increased the recruitment of AR to the promoters of its target genes resulting in their increased expression even in the absence of hormonal agonists of AR. As RB represses the transcriptional activity of E2F1, the authors speculated about the possibility of AR being directly regulated by E2F1. Indeed, E2F1 was found to bind the *AR* promoter, and this occupancy was enriched in the absence of RB. Further experiments confirmed the regulation of *AR* by E2F1 at the G1/S transition of the cell cycle.

Does the E2F1-mediated deregulation of AR that is triggered by RB loss truly affect prostate cancer progression? The analysis of 39 human CRPC soft tissue metastases showed that loss of RB significantly correlated with increased *AR* and *E2F1* mRNAs.

These findings identify *AR* as a gene under the control of E2F1, which in turn is stringently regulated by RB. This opens up the possibility that other nuclear receptors might be regulated by RB and E2F1 in other types of cancer. These data also imply that a new role for RB in controlling the late stages of cancer such as castration-resistant tumour growth could now be considered in cancer therapy.

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