Recruitment of Pontin/Reptin by E2f1 amplifies E2f transcriptional response during cancer progression.

Changes in gene expression during tumorigenesis are often considered the consequence of de novo mutations occurring in the tumour. An alternative possibility is that the transcriptional response of oncogenic transcription factors evolves during tumorigenesis. Here we show that aberrant E2f activity, following inactivation of the Rb gene family in a mouse model of liver cancer, initially activates a robust gene expression programme associated with the cell cycle. Slowly accumulating E2f1 progressively recruits a Pontin/Reptin complex to open the chromatin conformation at E2f target genes and amplifies the E2f transcriptional response. This mechanism enhances the E2f-mediated transactivation of cell cycle genes and initiates the activation of low binding affinity E2f target genes that regulate non-cell-cycle functions, such as the Warburg effect. These data indicate that both the physiological and the oncogenic activities of E2f result in distinct transcriptional responses, which could be exploited to target E2f oncogenic activity for therapy.