REST controls nerve cell growth via TSC2 and β-catenin
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The transcription factor REST orchestrates differentiation of nerve cells and sustains neuroblastomas and medulloblastomas growth, via mechanisms that largely remain to be defined. Working with pheochromocytoma PC12 clones expressing either low or high levels of REST, and respectively showing or lacking neurosecretory properties, we found that high-REST expressing cells are enlarged in size, and have a growth advantage. High-REST PC12 cells exhibit hyperactivation of mTORC1 and inhibition of mTORC2, which is likely due to low TSC2 levels. In spite of mTORC1-dependent constitutive signalling, however, Rapamycin fails to significantly prevent cell proliferation, which is rather favoured by β-catenin accumulation. In these cells high REST levels cause nuclear accumulation of transcriptionally active β-catenin. Overexpression of β-catenin in turn increases REST levels, and decreases TSC2 expression, favouring cell growth. Likewise, TSC2 knockdown, favours β-catenin accumulation, and expression of its target genes, among which REST. Together these data imply the existence of a feed-forward signalling loop linking REST, TSC2, and β-catenin and provide the first mechanistic explanation for the role of REST in normal and tumoral nerve cell growth.