ONCOGENE REPRESSION

CDYL and REST — a silent team

RE1-silencing transcription factor (**REST**) is a repressor that, along with a number of co-repressors, can modify histones and shut down transcription. It is also a tumour suppressor gene, but the mechanism of how it prevents tumorigenesis has been unclear. Yang Shi and colleagues

now show that chromodomain Y-like protein (**CDYL**) is required to mediate REST-induced suppression of the neurotrophic tyrosine kinase receptor type 3 (**NTRK3**, also known as **TRKC**).

Yang Shi and colleagues were investigating the function of the enigmatic CDYL. Affinity purification of a Flag–HA-tagged CDYL from HeLa cell nuclear extracts and glycerol gradient sedimentation showed that REST is a component of a complex that includes CDYL, a number of methyltransferases and the histone methylase **G9a**. REST is known to recruit **G9a** and further investigations showed that CDYL acts as a bridging protein that enables REST to enlist **G9a** both *in vitro* and *in vivo*. The authors also found that RNA interference knockdown of **CDYL** in TLM-HMEC cells resulted in the loss of CDYL and **G9a** from RE1 sites in both **TRKC** and **NPTXR** and reduced methylation of histone H3 lysine 9 (H3K9) at these sites. The retention of REST and histone H3 at these sites in the absence of CDYL indicates that CDYL is a REST co-repressor that enables recruitment of **G9a** and subsequent H3K9 methylation.

What are the biological consequences of these interactions? RNA interference knockdown of any of **CDYL**, **REST** or **G9a** resulted in

transformation of TLM-HMEC cells with the concomitant loss of REST-mediated repression of **TRKC**. Importantly, knockdown of other REST co-repressors had no effect on **TRKC** expression, indicating that the CDYL–**G9a**–REST complex might specifically function to repress **TRKC** and prevent cellular transformation.

Interestingly, the authors also found that CDYL might restrict the transformation of cervical cells expressing oncoproteins from high-risk strains of human papilloma virus (HPV). The **CDYL** locus resides at 6p25, a region associated with loss of heterozygosity and poor prognosis in cervical carcinomas. Two different short hairpin RNAs that targeted **CDYL** in squamous epithelial cells transfected with HPV16 E6 and E7 increased the efficiency of colony formation compared with cells transfected with E6 and E7 alone.

These findings provide insight into how repressors such as CDYL and REST facilitate tumour suppression through the regulation of specific histone-modifying complexes.

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ORIGINAL RESEARCH PAPER Mulligan, P. et al. CDYL bridges REST and histone methyltransferases for gene repression and suppression of cellular transformation. *Mol. Cell* **32**, 718–726 (2008)