TUMOURIGENESIS

A new pathway for CYLD

DOI:
10.1038/nrm1977

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In humans, the loss of both *CYLD* alleles causes the development of benign and disfiguring skin tumours called cylindromas. Using skin cells from *Cyld*$^{-/-}$ mice, Reinhard Fässler and colleagues show that the deubiquitinase CYLD, in addition to its known effects on the nuclear factor (NF)-κB pathway, can control the nuclear translocation of the NF-κB co-activator BCL3.

The authors showed that the *Cyld*$^{-/-}$ mice they generated are more prone to DMBA (7,12-dimethylbenz(a)anthracene) and TPA (12-*O*-tetradecanoylphorbol-13-acetate)-induced skin tumours than wild-type mice. BrdU incorporation and Ki67 expression indicated increased proliferation in *Cyld*$^{-/-}$ tumours compared with wild-type tumours, but no difference in the rate of apoptosis was observed. In addition, *Cyld*$^{-/-}$ tumours showed increased expression of cyclin D1 (encoded by *Ccnd1*), and increased cyclin D1 expression was also observed in isolated primary *Cyld*$^{-/-}$ keratinocytes treated with TPA or UVB light.

Is there a link between CYLD loss and cyclin D1 expression? Using reporter assays, the authors showed that TPA or UVB activates the *Ccnd1* promoter in *Cyld*$^{-/-}$ keratinocytes in an NF-κB-dependent manner, indicating that CYLD is a negative regulator of this pathway. CYLD has been implicated in the inhibition of tumour-necrosis factor-α (TNFα)-induced activation of the NF-κB p65–p50 heterodimer, in part through the stabilization of the NF-κB inhibitor IκBα. However, TPA treatment failed to increase p65–p50-dependent transcription, indicating that TPA triggers NF-κB activity in an IκBα-independent manner in keratinocytes.

So, which NF-κB-family member(s) regulates cyclin D1 expression? Transfection of *Cyld*$^{-/-}$ and wild-type keratinocytes with the *Ccnd1* promoter reporter construct and various NF-κB-family members showed that p50 or p52, as well as the co-activator BCL3, activated the promoter in the absence of CYLD. Co-immunoprecipitation analyses showed that CYLD associates with BCL3 in keratinocytes in response to TPA, and TPA or UVB treatment increased nuclear translocation of BCL3 in *Cyld*$^{-/-}$ keratinocytes, DMBA/TPA-induced *Cyld*$^{-/-}$ tumours and human cylindromas. Furthermore, chromatin immunoprecipitation showed that in *Cyld*$^{-/-}$ keratinocytes, TPA treatment recruits BCL3 and p50 or p52, but not p65, to the *Ccnd1* promoter.

Is the deubiquitylating activity of CYLD required to prevent BCL3 nuclear accumulation? TPA treatment significantly increased polyubiquitylation of BCL3 in *Cyld*$^{-/-}$ keratinocytes, and CYLD removed Lys63-linked polyubiquitin chains from BCL3 *in vivo* — ubiquitin chains at this site usually serve as docking sites for other proteins. Catalytically inactive CYLD was unable to prevent BCL3 nuclear accumulation and activation of the *Ccnd1* promoter. These data indicate that deubiquitylation by CYLD is necessary to prevent BCL3 nuclear accumulation.

Previous data have shown reduced CYLD expression in human kidney, liver and cervical tumours, and the authors found reduced or absent CYLD expression in human basal-cell and squamous-cell carcinomas. Therefore, the mechanism of CYLD-mediated suppression of NF-κB signalling proposed by Fässler and colleagues might be important in several tumour types.

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ORIGINAL RESEARCH PAPER Massoumi, R. *et al.* Cyld inhibits tumor cell proliferation by blocking Bcl-3-dependent NF-κB signaling. *Cell* **125**, 665–677 (2006)