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Cutaneous cylindroma: it’s all about MYB#

Gabriele Corda 1,2,* and Arturo Sala 1,2,*

1. College of Health and Life Sciences, Brunel University, London, UK
2. Institute of Environment, Health and Societies, Brunel University, London, UK
*Correspondence to: A Sala, Institute of Environment, Health and Societies, College of Health and Life Sciences, Heinz Wolff Building, Brunel University, London UB8 3PH, UK. E-mail: arturo.sala@brunel.ac.uk

Abstract

Cutaneous cylindroma is a rare benign tumour that occasionally turns into malignant cylindrocarcinoma. The cancer can be sporadic or emerge in the context of Brooke–Spiegler syndrome (BSS), an inheritable condition characterized by mutation of the gene CYLD, encoding a tumour suppressor protein that controls the activity of the transcription factor NF-kB. Sporadic cylindromas present histological features shared with adenoid cystic carcinoma (ACC), a head and neck cancer originating from salivary or other exocrine glands. Like ACCs, sporadic cylindromas express, although at lower frequency, the aberrant fusion transcript MYB–NFIB. In a paper recently published in the Journal of Pathology, the research teams led by Neil Rajan and Goran Stenman demonstrate that CYLD-defective cylindromas in BSS patients are negative for the MYB–NFIB fusion. Only the wild-type MYB oncoprotein is activated in the majority of these tumours. RNA interference studies in cells derived from BSS patients indicate that ablating MYB expression results in a striking reduction of cylindroma cell proliferation, suggesting that MYB plays a pivotal role in the biology of this cancer. The take-home message of the study is that activation of MYB, in its wild-type form or fusion derivatives, is a common feature of spontaneous and hereditary cylindromas, constituting a potentially actionable therapeutic target.

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In a study recently published in the *Journal of Pathology*, Rajan *et al* [11] investigated the role of *MYB* in CYLD-defective cylindromas and spynyadomas. The same group previously observed a relatively high incidence of *MYB–NFIB* fusion transcripts in sporadic cylindromas [3]. Surprisingly, when the researchers analysed a cohort of samples deriving from CYLD-defective familial tumours, they did not detect *MYB–NFIB* fusion transcripts or rearrangements of the *MYB* locus. However, immunohistochemical analysis revealed strong nuclear expression of MYB in the majority of BSS tumours. Importantly, they verified that the expression of the oncoprotein is significantly higher in cancer than in normal skin. To verify the functional significance of MYB activation in cylindromas, the research team implemented RNA interference to promote survival or proliferation of different cell types, supporting the hypothesis that it may act as a tumour suppressor. Prior to the study by Rajan *et al* [11], there was no evidence of a link between MYB and CYLD pathways in cancer cells. The authors of the study suggest that a possible explanation for the activation of *MYB* in CYLD mutant cells may rest in the loss of control of NF-kB activity. Indeed, CYLD inactivation causes increased NF-kB signalling and it was previously reported that the *MYB* promoter contains NF-kB binding sites, transactivated by NF-kB [13,14]. Perplexingly, however, Rajan *et al* [11] did not observe perturbation of *MYB* expression after drugging NF-kB in cylindroma cells, suggesting that another circuitry linking CYLD and MYB must be operating in cutaneous tumours. It is tempting to speculate that CYLD could alter chromatin dynamics in the *MYB* locus, since recent studies have revealed that CYLD negatively controls the activity of histone deacetylases HDAC6 and HDAC7 in mammalian cells [15,16]. Intriguingly, the pan-HDAC inhibitor Givinostat has been shown to strongly down-regulate MYB expression in leukaemic cells, indicating that histone acetylation changes might be crucially linked to MYB activation in cancer. This hypothesis is corroborated by a study demonstrating epigenetic activation of the *MYB* locus in *MYB–NFIB*-negative, but translocation-positive, ACCs [10]. Taken together, these studies strongly indicate that the pathogenic cause of cylindromas and ACCs is the activation of *MYB*.

Of course, there are still important questions awaiting an answer: is MYB necessary and sufficient for the transformation of cutaneous and glandular cells? What are the critical MYB target genes? To start answering the latter question, Rajan *et al* [11] conducted gene expression analyses on previously published microarray datasets. Among others, they detected two MYB target genes...
involved in the control of apoptosis, BCL2 and BIRC3, which were significantly up-regulated in cylindromas compared to normal skin. Satisfyingly, ablation of MYB reduced the expression of BCL2 and BIRC3 in cylindroma cells, suggesting that MYB also precipitates cutaneous tumourigenesis through inhibition of apoptosis. Whether or not MYB is the key driver of cylindroma, or other head and neck cancers, will only be established by developing appropriate transgenic models or by implementing DNA-editing strategies that reproduce the genomic rearrangements leading to MYB activation.

These findings of Rajan et al. [11] give hope to patients affected by malignant cylindroma. Small-molecule inhibitors of MYB are being developed, some of which show promise in preclinical experiments. For example, the multi-kinase inhibitor Rigosertib induces selective killing of diffuse large B cell lymphoma by suppressing TRAF6 and MYB [17]. Interestingly, TRAF6 is an adaptor protein involved in tumour development and was previously shown to be a CYLD target protein [18]. It will be important to assess whether Rigosertib kills or reduces the proliferation of cylindroma cells in preclinical experiments.

**Author contributions**

Both authors were involved in preparing the manuscript.

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