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## CUL4B: Trash talking at chromatin

Erin M. Green and Or Gozani

Department of Biology, Stanford University, Stanford, CA, USA

### Summary

In this issue, Nakagawa and Xiong (2011) reveal a mechanism targeting WDR5 for proteolysis dependent on the X-linked mental retardation gene, *CUL4B*. This provides a link between the stability of a chromatin factor and gene expression implicated in neurological pathogenesis.

X-linked mental retardation (XLMR) is a constellation of disorders affecting intellectual and learning ability for which the genetic determinants have been mapped to the X-chromosome. XLMR is genetically heterogeneous; up to 11% of the genes on the X-chromosome (~90 genes total) have been implicated to date (Gecz *et al.*, 2009), making determination of causal relationships between genotype and phenotype challenging. In this issue, Nakagawa and Xiong (2011) dissect the molecular function of the gene *CUL4B*, a cullin family member, of which several mutations have been identified in families with XLMR.

Cullins partner with small RING finger proteins to form E3 ubiquitin ligases, or cullin-RING ligases (CRLs), which are recruited to their ubiquitylation substrates via adaptor proteins. Nakagawa and Xiong (2011) show that nuclear localized CRL4B functions as an E3 ubiquitin ligase targeting WDR5, a core member of the SET1/MLL family of histone methyltransferase complexes (Yokoyama *et al.*, 2004), which are largely responsible for generation of the transcription activation-associated histone H3 lysine 4 trimethylation (H3K4me3) mark. The levels of H3K4me3 and the expression of a subset of neuronal genes were found to increase in the absence of the CUL4B-mediated degradation of WDR5, although levels of a non-neuronal control, *ARF*, did not change. Furthermore, in a rat neuroendocrine cell line, knock-down of *CUL4B* limited neurite extension, and XLMR-patient derived point mutations in *CUL4B* were unable to rescue this defect in neuronal differentiation. While the molecular defect induced by these point mutations is not yet understood, the half-life of overexpressed mutant CUL4B proteins was decreased relative to wildtype.

Nakagawa and Xiong have therefore uncovered a mechanism in which proteasome-mediated degradation of a general chromatin factor may lead to the specific suppression of an aberrant gene expression program. If the primary target of CUL4B is WDR5, the question remains how does stabilization of WDR5, a common and core component of multiple histone modifying complexes, result in its recruitment and subsequent regulation of a specific set of neuronal genes? It is plausible that this cohort of promoters is inherently sensitive to WDR5 levels, and highlights the possibility that deregulation of other general chromatin modifiers may have unanticipated, highly specific outcomes. An alternate possibility is that CRL4B ubiquitylates additional nuclear substrates, and it may be that combinatorial control of the

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degradation of multiple proteins, including WDR5, results in targeted gene expression changes, and ultimately, the development of the disease state. Global analysis of CUL4B- and WDR5-dependent genomic expression patterns in neuronal cell lines and investigation of additional CUL4B targets will provide further insight into the specificity of this regulatory mechanism. Extending these studies to XLMR disease models will also be critical to address how gene expression results obtained in cell culture translate to the pathogenic state.

The link between CUL4B and H3K4 methylation adds to a growing list of epigenetic regulators implicated in XLMR. The histone H3K4 tri- and di-demethylase *SMCX* (*KDM5C/JARID1C*) is frequently mutated in XLMR (Gécz *et al.*, 2009). Disease-associated point mutations compromise the demethylase activity of SMCX and interfere with dendritic morphogenesis (Iwase *et al.*, 2007). SMCX regulates gene expression in concert with other histone modifiers and neuron restrictive silencing factor NRSF/REST (Tahiliana *et al.*, 2007), a repressor of terminal neuronal differentiation genes in non-neuronal cell types. Loss of functional SMCX results in elevated levels of H3K4me3 and increased expression of NRSF-regulated genes, such as *SYN1*, which encodes for the synaptogenesis factor synapsin I (Tahiliana *et al.*, 2007). Intriguingly, Nakagawa and Xiong (2011) also observed upregulation of *SYN1* following knock-down of *CUL4B*, and *SYN1* itself has been implicated in an X-linked syndrome associated with epilepsy and learning disabilities (Garcia *et al.*, 2004), suggesting its function is required for normal neuronal development (Figure 1). Another histone demethylase mutated in XLMR is PHF8 (Gécz *et al.*, 2009). PHF8 recognizes H3K4me3 at chromatin (Kleine-Kohlbrecher *et al.*, 2010), interacts with WDR5 in cells (Feng *et al.*, 2010) and acts to upregulate gene expression of target genes, including *SMCX* (Kleine-Kohlbrecher *et al.*, 2010). Further investigation will elucidate the complex regulatory relationship between these XLMR-related histone modifiers and reveal how genes commonly regulated by these epigenetic programs contribute to the pathogenesis of XLMR.

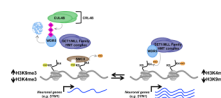
Proteasome-mediated degradation of chromatin modifying enzymes allows for rapid and precise control of gene expression programs in response to dynamic changes in environmental and cellular conditions. In an interesting parallel to WDR5, SMCX and its yeast orthologue, Jhd2, have been shown to be polyubiquitinated by the hNOT4/Not4 E3 ubiquitin ligase, and degraded in a proteasome-dependent manner, which acts to regulate H3K4me3 levels in the case of Jhd2 (Mersman *et al.*, 2009). Although further studies are required, it may be that the control of protein levels of WDR5 and SMCX via the ubiquitin-proteasome system is essential to maintaining the proper balance of H3K4me3 in cells. This balance is critical to the control of gene expression, and is antagonized by levels of H3K9me3, which acts as a repressive mark. Controlled proteolysis of histone modifiers as a rapid and effective method for achieving an appropriate balance in histone marks may be critical to prevent pathogenesis, and moderate disruption in this balance may lead to altered gene expression programs that promote disease. Therefore, there will most certainly be other disease mechanisms that originate from abnormal half-lives of chromatin proteins, either targeted for proteolysis by nuclear CUL4B or other nuclear E3 ubiquitin ligases, and it will be insightful to see these revealed as more molecular details emerge.

The convergence of multiple XLMR-related mutations on these epigenetic programs and their complex and inter-dependent regulation clearly indicate that unrestrained gene expression via aberrant histone methylation is likely to be a driving force behind neurological pathologies (Figure 1). XLMR patient mutations in both *CUL4B* and *SMCX* lead to the upregulation of H3K4me3, generating permissive chromatin environments at neuronal-specific genes, such as *SYN1*, that might ultimately manifest in a disease phenotype. It is therefore imperative to molecularly dissect how the CUL4B-mediated

degradation of WDR5 integrates with other chromatin-based mechanisms in the development of XLMR, and also to understand its specific contribution and that of other chromatin modifiers to disorders that affect learning and intellectual ability.

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**Figure 1.**

Maintaining appropriate levels of H3K4me3 and H3K9me3 is a key regulatory mechanism in the control of gene expression. An increase in gene expression is observed when H3K4me3 levels increase, such as when the protein levels of the SET1/MLL family histone methyltransferase (HMT) complex member WDR5 are stabilized and not subject to CUL4B-mediated degradation or when the histone demethylase SMCX is not functional. The increase in H3K4me3 levels is antagonized by increases in H3K9me3, which acts to depress gene expression.