The H3K4me3/2 histone demethylase RBR-2 controls axon guidance by repressing the actin-remodeling gene wsp-1

The dynamic regulation of histone modifications is important for modulating transcriptional programs during development. Aberrant H3K4 methylation is associated with neurological disorders, but how the levels and the recognition of this modification affect specific neuronal processes is unclear. Here, we show that RBR-2, the sole homolog of the KDM5 family of H3K4me3/2 demethylases in Caenorhabditis elegans, ensures correct axon guidance by controlling the expression of the actin regulator wsp-1. Loss of rbr-2 results in increased levels of H3K4me3 at the transcriptional start site of wsp-1, with concomitant higher wsp-1 expression responsible for defective axon guidance. In agreement, overexpression of WSP-1 mimics rbr-2 loss, and its depletion restores normal axon guidance in rbr-2 mutants. NURF-1, an H3K4me3-binding protein and member of the chromatin-remodeling complex NURF, is required for promoting aberrant wsp-1 transcription in rbr-2 mutants and its ablation restores wild-type expression of wsp-1 and axon guidance. Thus, our results establish a precise role for epigenetic regulation in neuronal development by demonstrating a functional link between RBR-2 activity, H3K4me3 levels, the NURF complex and the expression of WSP-1.