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YTHDC1: a new epigenetic factor in the pathophysiology in B cell lymphoma

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YTHDC1, is a nuclear RNA binding protein which recognises and binds the N6-methyladenosine (m6A) mark on RNA. Through the latter interaction, YTHDC1 mediates methyl-RNA-dependent silencing of lineage-specific genes and repeat elements. By exome sequencing in a case of treatment refractory mantle cell lymphoma (MCL), we have identified a novel, clonal loss-of-function YTHDC1 gene somatic mutation. Additional screening in a large DLBCL exome data set, identified a further 16 somatic mutations targeting the YTHDC1 gene, as well as deregulated YTHDC1 expression. Interestingly, the latter was associated to inferior prognosis in diffuse large B cell lymphoma (DLBCL) of the activated B cell (ABC) subtype. By immunohistochemistry, we confirmed misregulated YTHDC1 expression in a subset of MCL and DLBCL cases. Functional analyses of selected YTHDC1 mutants. We find that expression of mutant YTHDC1 leads to mislocalisation/expression of wild type (WT) YTHDC1, suggestive of a dominant interference mechanism. Subsequent CRISPR-Cas9 YTHDC1 deletion in Jeko-1 MCL cells, revealed YTHDC1 to be a critical survival gene. RNA-seq/gene set enrichment analyses in surviving heterozygous YTHDC1 knock-out MCL cells revealed engaged of multiple signaling pathways of relevance to lymphoma biology. In keeping with the functional relevance of these findings, exploratory xenotransplant assays (tail vein injection) with YTHDC1 heterozygous K/O and control Jeko-1 MCL cells revealed marked lymphoma cell grafting in lymph nodes compared to controls, suggestive of a tumour-promoting function for reduced YTHDC1 expression in this model. Taken together, these

results point to a potential role for altered YTHDC1 function - by mutation or gene dosage - as a novel disease driver in MCL and DLBCL, and suggests that YTHDC1 may have biomarker value for precision medicine approaches in these B cell lymphoma.