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The histone H3K79 methyltransferase DOT1L regulates gene transcription and promotes neuroblastoma tumourigenesis

Myc oncoproteins exert tumorigenic effects by regulating the expression of target oncogenes. Histone H3 lysine 79 (H3K79) methylation at Myc-responsive elements of target gene promoters is a strict prerequisite for Myc-induced transcriptional activation. *DOT1L* is the only known histone methyltransferase that catalysis H3K79 methylation. Here, we showed that N-Myc up-regulated *DOT1L* mRNA and protein expression by binding to the *DOT1L* gene promoter. Knocking down *DOT1L* reduced mRNA and protein expression of the N-Myc target genes *ODC1* and *E2F2*. *DOT1L* and N-Myc formed a protein complex, and knocking down *DOT1L* reduced histone H3K79 methylation and N-Myc protein binding at the *ODC1* and *E2F2* gene promoters and reduced neuroblastoma cell proliferation. Ablating *DOT1L* expression with doxycycline significantly reduced *ODC1* and *E2F2* expression, reduced tumor progression and improved overall survival in mice xenografted with neuroblastoma cells stably expressing doxycycline-inducible *DOT1L* small hair-pin RNA. In addition, high levels of *DOT1L* gene expression in human neuroblastoma tissues correlated with high levels of *MYCN, ODC1* and *E2F2* gene expression, and independently correlated with poor patient survival. Taken together, our data identify *DOT1L* as a novel co-factor in N-Myc-mediated transcriptional activation of target genes and neuroblastoma oncogenesis, and as a target for novel therapeutic strategies against neuroblastoma.

Biography

Tao Liu originally trained as a Medical Practitioner specializing in Neurology. He studied PhD degree at UNSW Australia on the role of inflammatory mediators in chronic pain due to nerve injury. He then worked on the role of MIC-1, a new member of the transforming growth factor beta superfamily, in cancer cell proliferation, survival/apoptosis and metastasis at St Vincent's Centre for Applied Medical Research. He moved to Children's Cancer Institute as a Senior Research Officer in 2003. Since 2004, he has been focusing his research on the roles of histone deacetylases, histone demethylases, histone methyl transferases and long noncoding RNAs in modulating gene transcription and tumourigenesis, and the roles of histone deacetylase inhibitors and histone methyltransferase inhibitors as anticancer agents. He was promoted to Project Leader in 2009 and Group Leader in 2011. Over the past decade, he has authored a number of peer-reviewed publications in high impact scientific journals including *Lancet, Journal of the National Cancer Institute, Proceedings of the National Academy of Sciences USA, Nature Reviews Cancer, Nature Communications, Journal of Clinical Oncology, PLOS Genetics, Cell Death & Differentiation, and Cancer Research*.