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ABSTRACT

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Short talk: "DOT1l Protects Neural Stem Cells from ER Stress In Vitro"

Growing evidence suggests that the lysine methyltransferase DOT1L has important roles in proliferation, survival and differentiation of stem cells in development and in disease. We investigated in vitro the function of DOT1L on mammalian neural stem cells (NSCs) of the cerebral cortex, on mouse embryonic fibroblasts (MEFs) and on the human acute myeloid leukemia cell line MOLM-13. Pharmacological inhibition of DOT1L impaired proliferation and survival of NSCs and MOLM-13, but not of MEFs. Inhibition of DOT1L induced specifically transcription of genes involved in the chronic endoplasmic reticulum (ER) stress response and in metabolism in NSCs. Chromatin-immunoprecipitation (ChIP) analyses revealed that two genes encoding for central molecules involved in the ER stress response, Atf4 and Ddit3 (Chop), are marked with H3K79 dimethylation. Interference with DOT1L activity resulted in transcriptional activation of both genes accompanied by decreased levels of H3K79me2. Using the other two cell types we determined if the induction of ER stress genes was a global phenomenon or a cell type specific effect. Our analysis revealed that the effect was mainly restricted to the NSCs. Recently, we analysed ER stress genes in the dorsal and ventral telencephalon from a conditional Dot1l knock out mouse line. In this case we could not detect any changes in the transcription levels of ER stress genes. We hypothesize that the induction of ER genes upon inhibition of DOT1L is rather an acute effect, while the deletion of DOT1L causes other effects.

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