Setdb1 regulates proper differentiation of adult intestinal stem cells via restraining permissive chromatin structure and transcriptional variability

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ABSTRACT

The histone methylase SETDB1 plays a pivotal role in embryonic stem cell maintenance and developmental lineage specification, but its function in adult stem cells remains elusive. Here we show that conditional inactivation of *Setdb1* in *Lgr5*$^{+}$ intestinal stem cells alters the transcription programs of progeny cell types and results in increased cell-to-cell transcriptional variability. Loss of *Setdb1* blocked differentiation towards absorptive enterocyte lineage, while the generation of secretory cell types were only marginally affected due to the activation of alternative developmental trajectories. *Setdb1* inactivation did not alter H3K9 methylation at large heterochromatin domains but led to the decrease of localized modifications at islands of gene-rich areas around transposase-accessible chromatin regions, which doubled in number, became broader and more heterogeneous in size. The results demonstrate that *Setdb1* regulates intestinal stem cell properties and epithelial lineage specification via limiting chromatin accessibility at open genomic areas and controlling cell-to-cell transcriptional variability.