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Abstract

The mammalian maintenance methyltransferase DNMT1 [DNA (cytosine-5-)methyltransferase 1] mediates the inheritance of the DNA methylation pattern during replication (Gruenbaum et al. 1982)(Li et al. 1992). Previous studies have shown that depletion of DNMT1 causes a severe growth defect and apoptosis in differentiated cells (Chen et al. 2007)(Jackson-Grusby et al. 2001). However, the detailed mechanisms behind this phenomenon remain poorly understood. Here we show that conditional ablation of Dnmt1 in murine embryonic fibroblasts (MEFs) resulted in an aberrant DNA replication program showing an accumulation of late-S phase replication and causing severely defective growth. Furthermore, we found that the catalytic activity and replication focus targeting sequence of DNMT1 are required for a proper DNA replication program. Taken together, our findings suggest that the maintenance of DNA methylation by DNMT1 plays a critical role in proper regulation of DNA replication in mammalian cells.