DNA methyltransferase-3-dependent nonrandom template segregation in differentiating embryonic stem cells.

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Public Summary:
This work identifies a key mechanism that regulates differentiation of mouse and human embryonic stem cells.

Scientific Abstract:
Asymmetry of cell fate is one fundamental property of stem cells, in which one daughter cell self-renews, whereas the other differentiates. Evidence of nonrandom template segregation (NRTS) of chromosomes during asymmetric cell divisions in phylogenetically divergent organisms, such as plants, fungi, and mammals, has already been shown. However, before this current work, asymmetric inheritance of chromatids has never been demonstrated in differentiating embryonic stem cells (ESCs), and its molecular mechanism has remained unknown. Our results unambiguously demonstrate NRTS in asymmetrically dividing, differentiating human and mouse ESCs. Moreover, we show that NRTS is dependent on DNA methylation and on Dnmt3 (DNA methyltransferase-3), indicating a molecular mechanism that regulates this phenomenon. Furthermore, our data support the hypothesis that retention of chromatids with the "old" template DNA preserves the epigenetic memory of cell fate, whereas localization of "new" DNA strands and de novo DNA methyltransferase to the lineage-destined daughter cell facilitates epigenetic adaptation to a new cell fate.