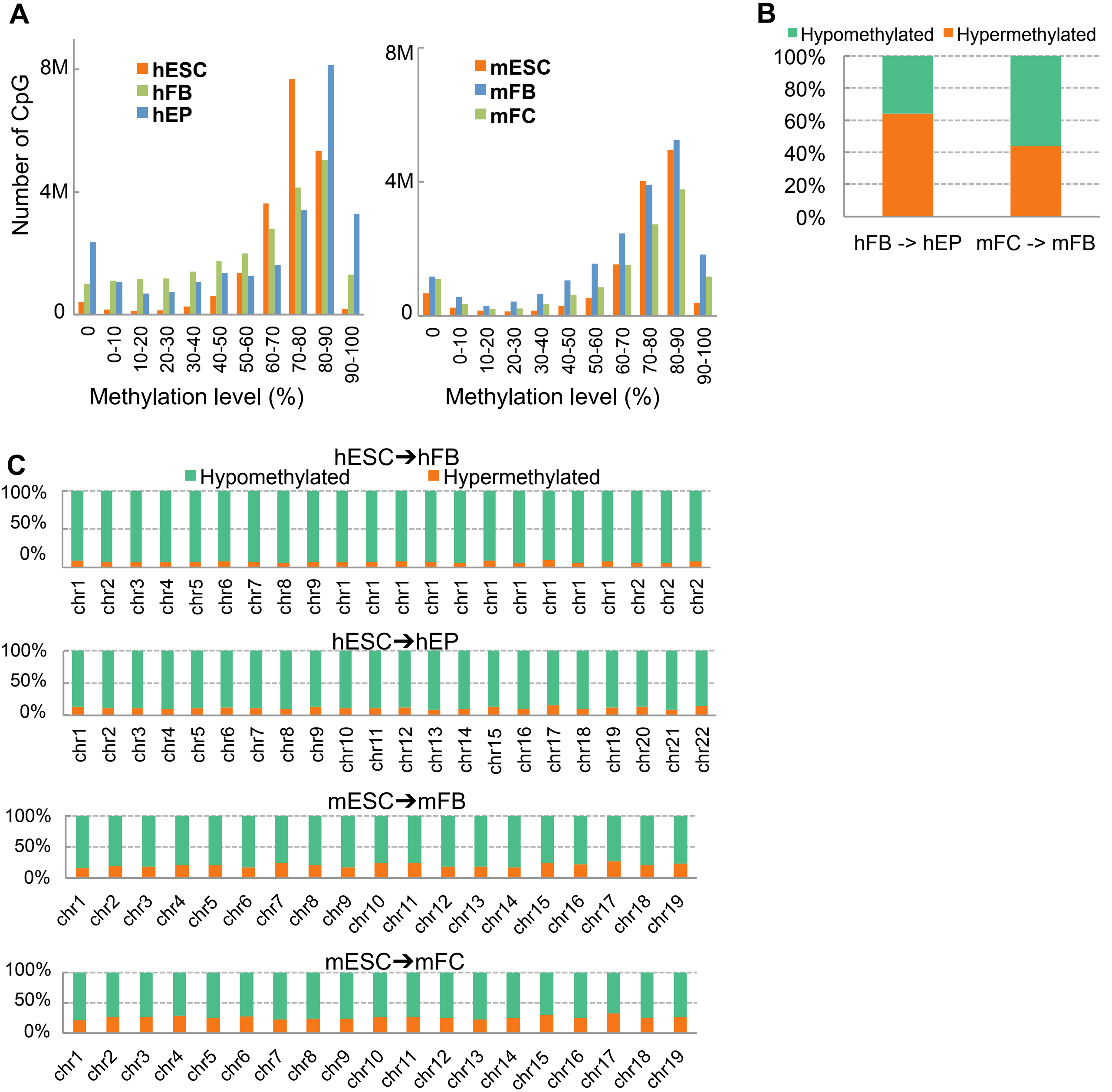

Figure S1. Global DNA methylation levels decrease during cellular differentiation in both human and mouse. (**A**) Distributions of CpG methylation levels in hESC, hFB, hEP, mESC, mFB, and mFC. M, million. (**B**) The percentage of diff-mCpGs that are hypomethylated or hypermethylated between somatic cells. (**C**) The percentage of diff-mCpGs that are hypomethylated or hypermethylated on each autosome during cellular differentiation.

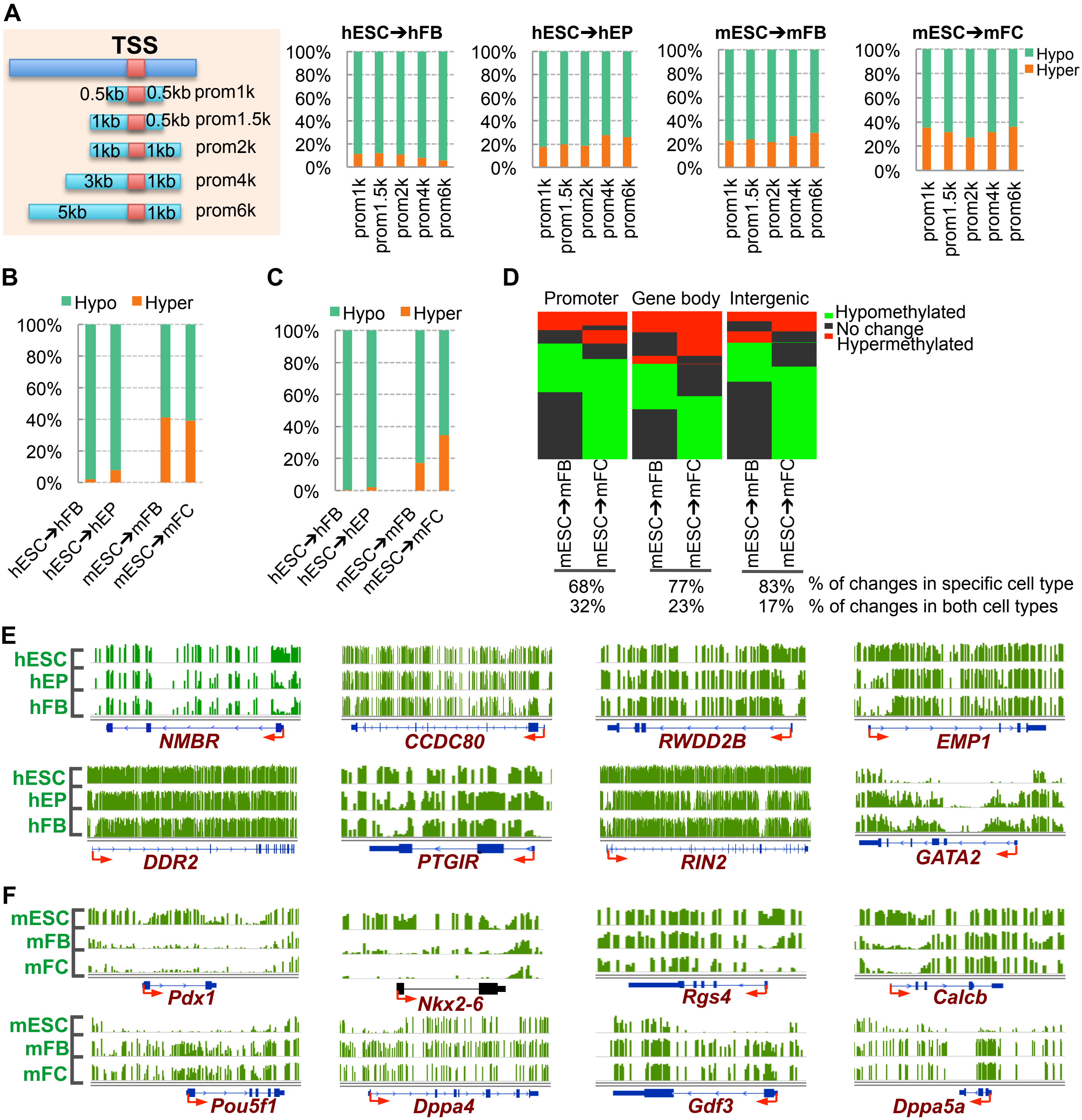

Figure S2. The decrease in DNA methylation levels during cellular differentiation is locus- and cell type-specific. (**A**) Different promoter definitions used in this study and the percentage of differentially methylated promoter regions that are hypomethylated or hypermethylated during cellular differentiation. Red rectangle indicates the transcription start site (TSS). (**B**) The percentage of differentially methylated gene body regions that are hypomethylated or hypermethylated during cellular differentiation. (**C**) The percentage of differentially methylated intergenic regions that are hypomethylated or hypermethylated during cellular differentiation. (**D**) Heat maps of differentially methylated genomic regions between mESC and the two mouse somatic cell types after clustering analysis. (**E,F**) Browser representation of methylation profiles of the genes with changes in methylation levels at their promoter regions during cellular differentiation. Each green vertical bar represents a CpG, and the height of the bar represents its methylation level (from 0 to 100%). Red arrow indicates the transcriptional orientation of each gene.

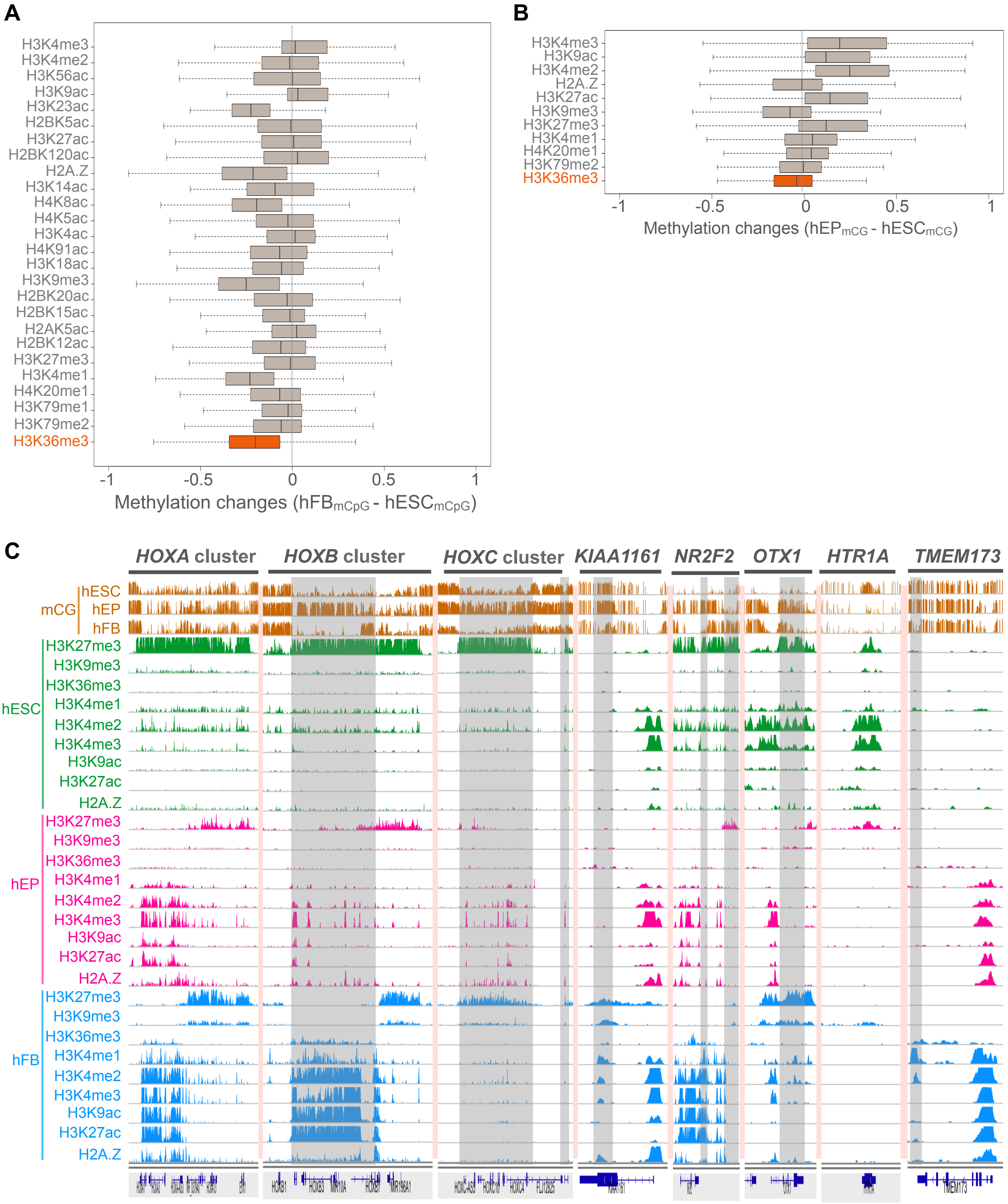

Figure S3. A switch from DNA methylation to histone modifications during cellular differentiation in human. (**A**) DNA methylation changes in the highly dynamic lose regions that lose histone modifications during the differentiation of hESC to hFB. (**B**) DNA methylation changes in the highly dynamic lose regions during the differentiation of hESC to hEP. (**C**) Browser representation of regions that switch from DNA methylation to histone modifications during cellular differentiation in human. The track scale for all histone modifications is from 0 to 50 normalized reads.

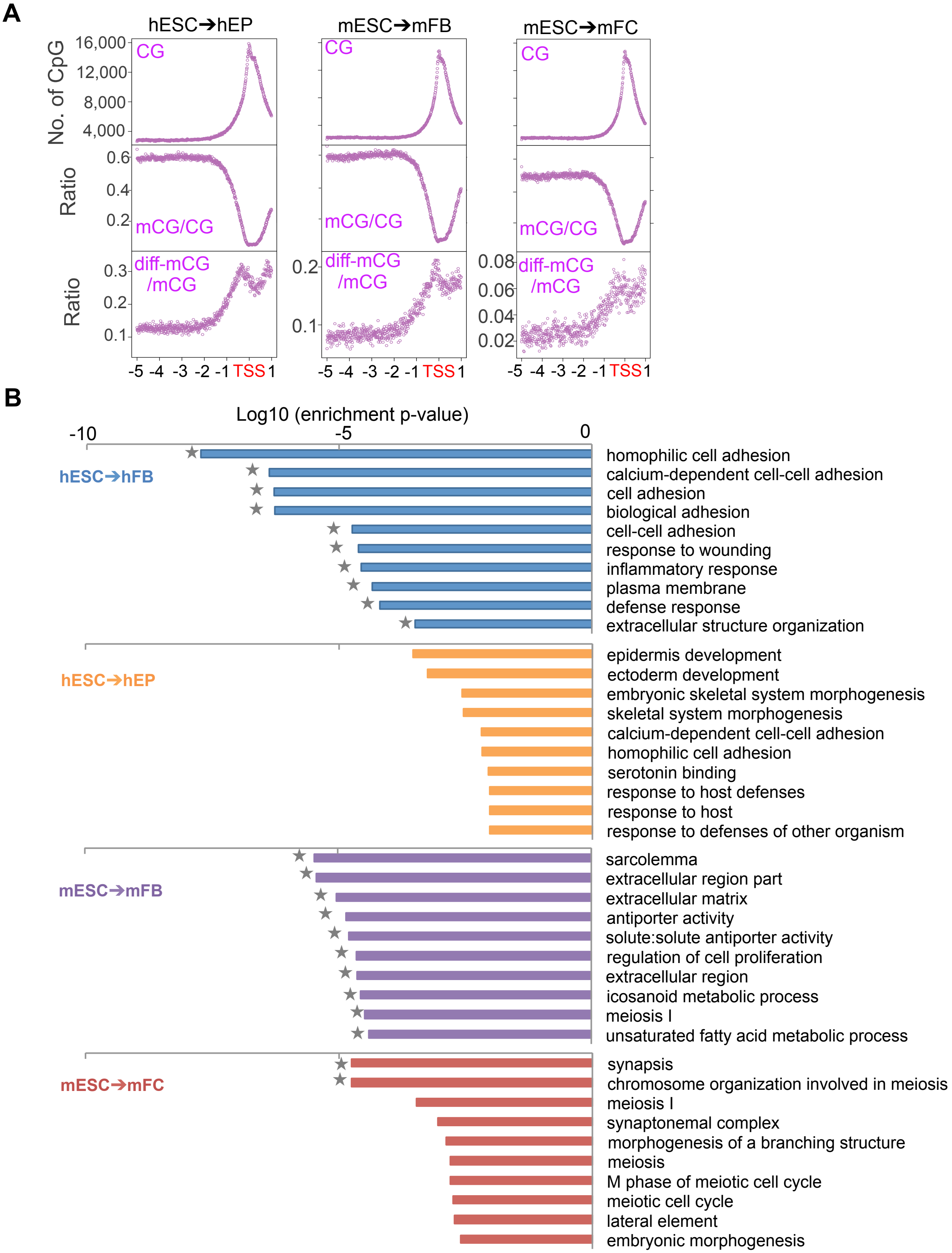

Figure S4. Epigenomic reconfiguration at promoter regions. (**A**) Scatter plots of the number of genomic CpGs, the ratio of mCpG, and the ratio of diff-mCpG in 10 bp bins within the regions of 5 kb upstream and 1 kb downstream of known transcription start site (TSS). (**B**) Top 10 enriched GO terms of genes with hypomethylated promoters. ★ indicates GO terms with Benjamini-corrected p-values < 0.05.

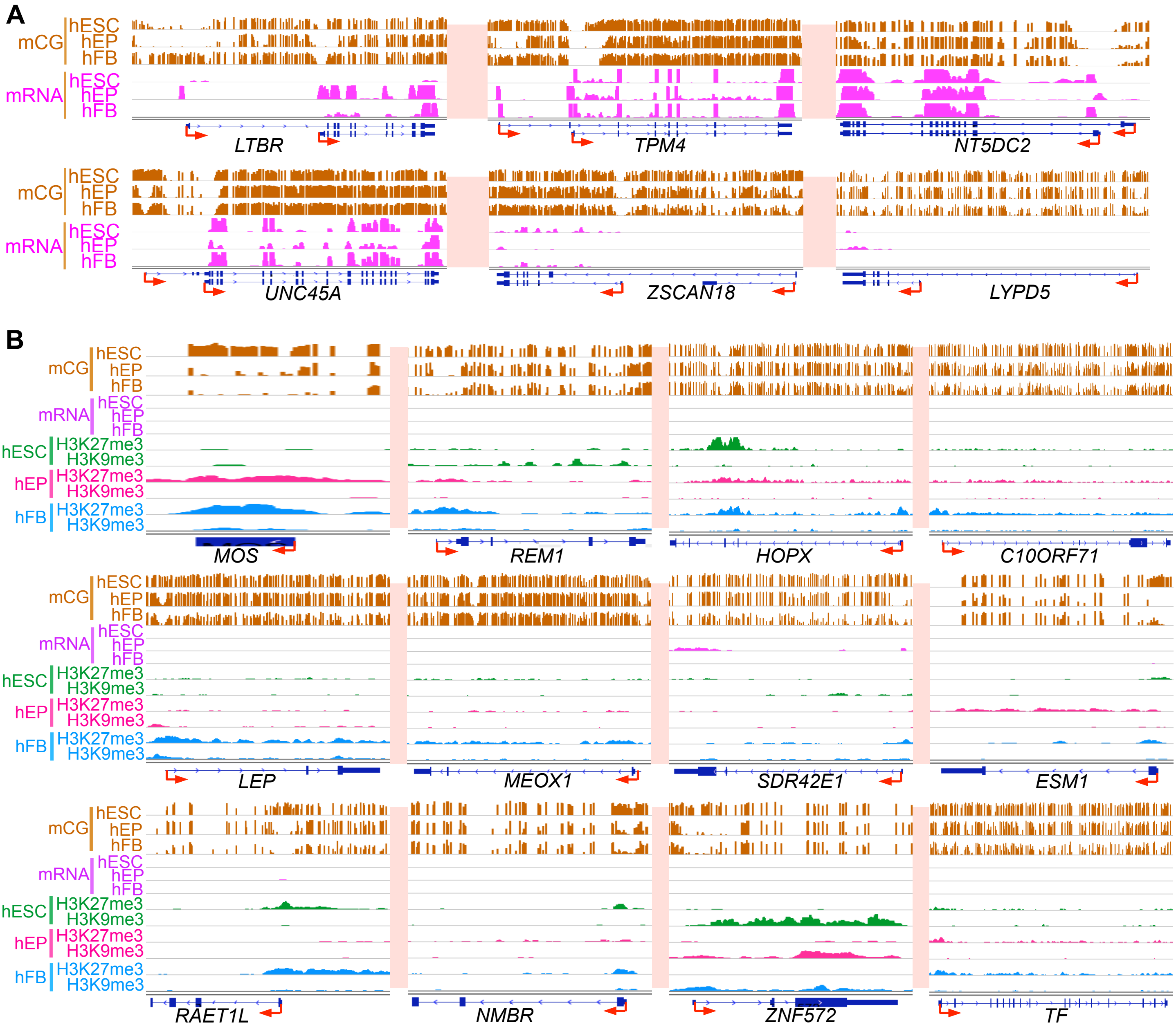

Figure S5. Epigenomic reconfiguration at promoter regions. (**A**) Browser representation of six genes with alternative promoter usage. Red arrow indicates the transcriptional orientation of each gene. The track scale for all mRNA-seq is from 0 to 45 normalized reads. (**B**) Browser representation of twelve genes with epigenomic reconfiguration at their promoter regions during cellular differentiation. The track scale for all mRNA-seq was from 0 to 45. The track scale for all histone modifications is from 0 to 50 normalized reads.