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## **GATA6 phosphorylation by Erk1/2 propels exit from pluripotency and commitment to primitive endoderm**

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### **Abstract**

The transcription factor GATA6 and the Fgf/Ras/MAPK signaling pathway are essential for the development of the primitive endoderm (PrE), one of the two lineages derived from the pluripotent inner cell mass (ICM) of mammalian blastocysts. A mutant mouse line in which *Gata6*-coding exons are replaced with H2BGFP (histone H2B Green Fluorescence Protein fusion protein) was developed to monitor *Gata6* promoter activity. In the *Gata6*-H2BGFP heterozygous blastocysts, the ICM cells that initially had uniform GFP fluorescence signal at E3.5 diverged into two populations by the 64-cell stage, either as the GFP-high PrE or the GFP-low epiblasts (Epi). However in the GATA6-null blastocysts, the originally moderate GFP expression subsided in all ICM cells, indicating that the GATA6 protein is required to maintain its own promoter activity during PrE lineage commitment. In embryonic stem cells, expressed GATA6 was shown to bind and activate the *Gata6* promoter in PrE differentiation. Mutations of a conserved serine residue (S264) for Erk1/2 phosphorylation in GATA6 protein drastically impacted its ability to activate its own promoter. We conclude that phosphorylation of GATA6 by Erk1/2 compels exit from pluripotent state, and the phosphorylation propels a GATA6 positive feedback regulatory circuit to compel PrE differentiation. Our findings resolve the longstanding question on the dual requirements of GATA6 and Ras/MAPK pathway for PrE commitment of the pluripotent ICM.

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