www.elsevier.com/locate/developmentalbiology

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

Yue Meng, Robert Moore, Wensi Tao, Elizabeth R. Smith, Jeffrey D. Tse, Corrado Caslini, Xiang-Xi Xu

PII: S0012-1606(17)30834-5
DOI: https://doi.org/10.1016/j.ydbio.2018.02.007
Reference: YDBIO7690

To appear in: *Developmental Biology*

Received date: 27 November 2017
Revised date: 13 February 2018
Accepted date: 13 February 2018

Cite this article as: Yue Meng, Robert Moore, Wensi Tao, Elizabeth R. Smith, Jeffrey D. Tse, Corrado Caslini and Xiang-Xi Xu, GATA6 phosphorylation by Erk1/2 propels exit from pluripotency and commitment to primitive endoderm, *Developmental Biology,* https://doi.org/10.1016/j.ydbio.2018.02.007

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

Yue Meng[1,2], Robert Moore[1], Wensi Tao[1,2], Elizabeth R. Smith[1], Jeffrey D. Tse[1,2], Corrado Caslini[3], and Xiang-Xi Xu[1,2,+]

[1]Department of Cell Biology; , University of Miami Miller School of Medicine, Miami, FL 33136 USA

[2]Graduate Program in Molecular Cell and Developmental Biology, , University of Miami Miller School of Medicine, Miami, FL 33136 USA

[3]Department of Pathology, University of Miami Miller School of Medicine, Miami, FL 33136 USA

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 linage 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.