Global translation during early development depends on the essential transcription factor PRDM10

Tuesday, 11 Aug 2020

Authors

Brenda Y. Han[1], Michelle K.Y. Seah[1], Imogen R. Brooks[1], Delia H.P. Quek[1], Dominic R. Huxley[1], Chuan-Sheng Foo[2], Li Ting Lee[1], Heike Wollmann[1], Huili Guo[1,3], Daniel M. Messerschmidt[1]*, Ernesto Guccione[1,4]*

Affiliations

[1]Institute of Molecular and Cell Biology (IMCB), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore

[2]Institute for Infocomm Research (I2R), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore

[3] Department of Biological Sciences, National University of Singapore, Singapore

[4] Mount Sinai Center for Therapeutics Discovery, Departments of Pharmacological Sciences and Oncological Sciences, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States

(*) Corresponding authors

Published in ***Nature Communications*** on 17 July 2020.

ABSTRACT

Members of the PRDM family of zinc finger transcriptional regulators play diverse developmental roles. PRDM10 is a yet uncharacterized family member, and its function *in vivo* is unknown. Here we report an essential requirement for PRDM10 in pre-implantation embryos and embryonic stem cells (mESCs), where loss of PRDM10 results in severe cell growth inhibition. Genomic and biochemical analyses reveal that PRDM10 functions as a sequence-specific transcription factor. We identify *Eif3b*, which encodes a core component of the eukaryotic translation initiation factor 3 (eIF3) complex, as a key downstream target, and demonstrate that growth inhibition in PRDM10-deficient mESCs is in part mediated through EIF3B-dependent effects on global translation. Our work elucidates the molecular function of PRDM10 in maintaining global translation and establishes its essential role in early embryonic development and mESC homeostasis, providing new insights into the functional repertoire of PRDMs as well as the transcriptional mechanisms regulating translation.

FIGURE

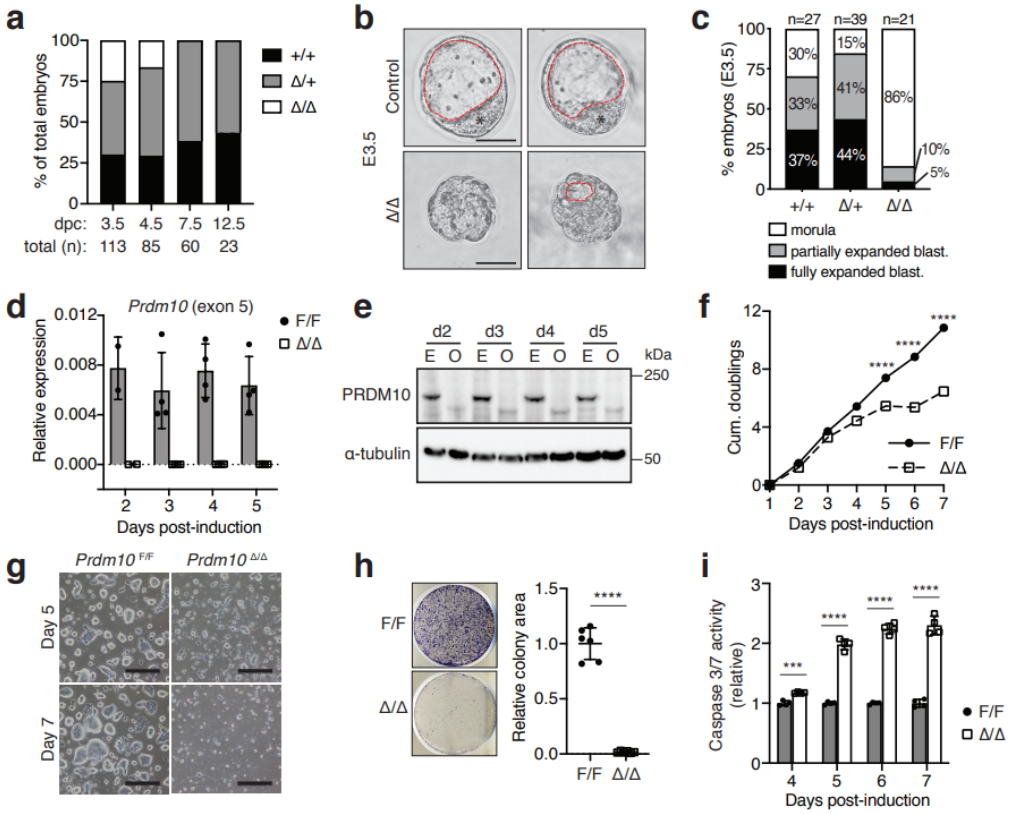

FIGURE LEGEND

(a) Embryo genotypes from heterozygous intercrosses. E3.5 embryos are recovered at the expected Mendelian distribution; no *Prdm10*$^{\Delta/\Delta}$ embryos are observed by E7.5. **(b)** Mutant (*Prdm10*$^{\Delta/\Delta}$) and control (*Prdm10*$^{+/+}$, *Prdm10*$^{\Delta/+}$) embryos isolated at E3.5. Asterisk: inner cell mass (ICM); red dashed line: blastocoel. Scale bar: 50 μm. **(c)** E3.5 embryos scored into 3 phenotypic categories: morula, partially expanded blastocyst, or fully expanded/cavitated blastocyst. *n* = 27 (*Prdm10*$^{+/+}$), *n* = 39 (*Prdm10*$^{\Delta/+}$), *n* = 21 (*Prdm10*$^{\Delta/\Delta}$). **(d)** *Prdm10* exon 5 expression in OHT-treated *Prdm10*$^{F/F}$; CreER^{T2} (Δ/Δ) mESCs compared to vehicle-treated (F/F) controls. Expression normalized to *Ubb*; *n* = 3 biological replicates. **(e)** PRDM10 protein levels in *Prdm10*$^{F/F}$; CreER^{T2} mESCs after exposure to EtOH (E) or OHT (O). **(f)** PRDM10-depleted mESCs exhibit an increasingly severe cell growth defect over time. *n* = 4 samples. Y-axis: cumulative population doublings. **(g)** *Prdm10*$^{F/F}$ and *Prdm10*$^{\Delta/\Delta}$ mESC colonies at Day 5 and 7. Cells were plated at equal densities 2 days prior to image acquisition. Scale bar: 500 μm. **(h)** Colony formation assay; *n* = 6. **(i)** Caspase 3/7 activity in *Prdm10*$^{\Delta/\Delta}$ mESCs relative to *Prdm10*$^{F/F}$ controls. Data are presented as mean ± s.d. Representative data shown from one out of three independent experiments (**f, g** and **i**). ***P < 0.001, ****P < 0.0001; two-tailed unpaired Student's *t*-test (**f**, **h** and **i**).