# HIPPO pathway members restrict SOX2 to the inner cell mass where it promotes ICM fates in the mouse blastocyst.

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**Public Summary:**
Pluripotent epiblast (EPI) cells, present in the inner cell mass (ICM) of the mouse blastocyst, are progenitors of both embryonic stem (ES) cells and the fetus. Discovering how pluripotency genes regulate cell fate decisions in the blastocyst provides a valuable way to understand how pluripotency is normally established. EPI cells are specified by two consecutive cell fate decisions. The first decision segregates ICM from trophectoderm (TE), an extraembryonic cell type. The second decision subdivides ICM into EPI and primitive endoderm (PE), another extraembryonic cell type. Here, we investigate the roles and regulation of the pluripotency gene Sox2 during blastocyst formation. First, we investigate the regulation of Sox2 patterning and show that SOX2 is restricted to ICM progenitors prior to blastocyst formation by members of the HIPPO pathway, independent of CDX2, the TE transcription factor that restricts Oct4 and Nanog to the ICM. Second, we investigate the requirement for Sox2 in cell fate specification during blastocyst formation. We show that neither maternal (M) nor zygotic (Z) Sox2 is required for blastocyst formation, nor for initial expression of the pluripotency genes Oct4 or Nanog in the ICM. Rather, Z Sox2 initially promotes development of the primitive endoderm (PE) non cell-autonomously via FGF4, and then later maintains expression of pluripotency genes in the ICM. The significance of these observations is that 1) ICM and TE genes are spatially patterned in parallel prior to blastocyst formation and 2) both the roles and regulation of Sox2 in the blastocyst are unique compared to other pluripotency factors such as Oct4 or Nanog.

**Scientific Abstract:**
Pluripotent epiblast (EPI) cells, present in the inner cell mass (ICM) of the mouse blastocyst, are progenitors of both embryonic stem (ES) cells and the fetus. Discovering how pluripotency genes regulate cell fate decisions in the blastocyst provides a valuable way to understand how pluripotency is normally established. EPI cells are specified by two consecutive cell fate decisions. The first decision segregates ICM from trophectoderm (TE), an extraembryonic cell type. The second decision subdivides ICM into EPI and primitive endoderm (PE), another extraembryonic cell type. Here, we investigate the roles and regulation of the pluripotency gene Sox2 during blastocyst formation. First, we investigate the regulation of Sox2 patterning and show that SOX2 is restricted to ICM progenitors prior to blastocyst formation by members of the HIPPO pathway, independent of CDX2, the TE transcription factor that restricts Oct4 and Nanog to the ICM. Second, we investigate the requirement for Sox2 in cell fate specification during blastocyst formation. We show that neither maternal (M) nor zygotic (Z) Sox2 is required for blastocyst formation, nor for initial expression of the pluripotency genes Oct4 or Nanog in the ICM. Rather, Z Sox2 initially promotes development of the primitive endoderm (PE) non cell-autonomously via FGF4, and then later maintains expression of pluripotency genes in the ICM. The significance of these observations is that 1) ICM and TE genes are spatially patterned in parallel prior to blastocyst formation and 2) both the roles and regulation of Sox2 in the blastocyst are unique compared to other pluripotency factors such as Oct4 or Nanog.