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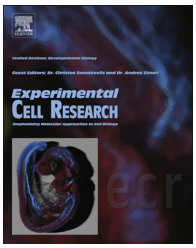

Review Article

# Lineage specification in the early mouse embryo

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ABSTRACT

Before the mammalian embryo is ready to implant in the uterine wall, the single cell zygote must divide and differentiate into three distinct tissues; trophectoderm (prospective placenta), primitive endoderm (prospective yolk sac), and pluripotent epiblast cells which will form the embryo proper. In this review I will discuss our current understanding of how positional information, cell polarization, signaling pathways, and transcription factor networks converge to drive and regulate the progressive segregation of the first three cell types in the mouse embryo.

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## Contents



## Introduction

The totipotent single cell zygote can generate all subsequent cell-types of the future embryo and the supportive extraembryonic tissue. The dividing cells of the developing embryo are progressively specialized into the first three distinct tissues that can be morphologically recognized prior to implantation at the late blastocyst stage. The outer layer of the late blastocyst consists of trophectoderm (TE) cells, which will form the future placenta and serve to connect the growing fetus with the mother's circulatory system. The inner cell mass (ICM) is divided into two distinct tissues, an outer layer of primitive endodermal (PE, also called hypoblast)

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cells facing the blastocoel, and inner epiblast (EPI) cells. The hypoblast cells are restricted to the yolk sac tissue, whereas the cells of the epiblast are pluripotent and can give rise to all tissues of the future embryo. From the aforementioned cell lingeages, three stem cell types have been isolated from the blastocyst: (1) trophectoderm stem (TS) cells form the TE, (2) extraembryonic endoderm stem (XEN) cells from the PE, and (3) embryonic stem (ES) cells from the EPI. These stem cells have served as in vitro cellular models and have been instrumental for the acquisition of knowledge pertaining to how these lineages are controlled through cell–cell signaling and transcriptional networks.

In this brief review, I will summarize our current understanding of how positional information, cell polarization, signaling pathways, and transcription factor networks all converge to drive and regulate the progressive segregation of the first three cell types in the mouse and how this field has developed. Special attention will be devoted to how members of the Hippo signaling pathway controls TE specification, while also describing the unexpected findings that transcription factors, traditionally associated with epiblast lineage and pluripotency, also serve a critical role in differentiating the extraembryonic PE lineage.

## Cellular position and polarity controlling TE–ICM segregation

Both the cellular position and polarization have been implicated in setting up the first lineage segregation of TS vs. ICM. During the first three cell divisions, the fertilized egg produces an embryo consisting of eight morphologically indistinguishable blastomeres. At this stage, where all blastomeres have exposure to the outer surface of the embryo, two tightly linked processes occur:

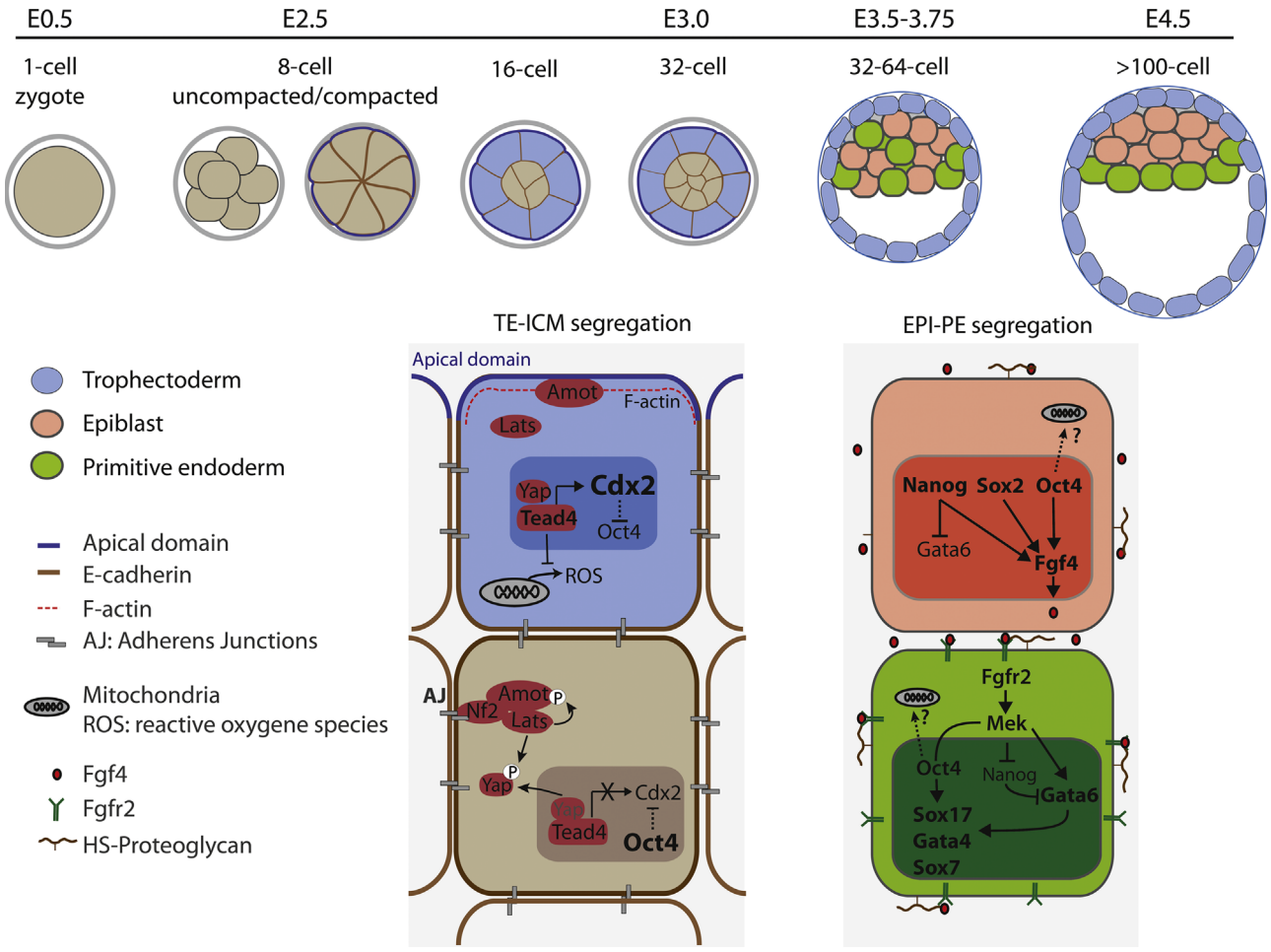


**Fig. 1 – Model summarizing lineage specification in the mouse embryo. Prior to lineage segregation, the 8-cell embryo undergoes compaction and polarization. Trophectoderm (TE) and inner cell mass (ICM) segregation is then initiated in the 16–32-cell stage embryo with formation of an outer and inner compartment. Polarized outer cells can then either undergo symmetric division giving rise to two polar outer TE progenitors or asymmetric division generating one polar outside and one apolar inner cell (ICM progenitor). In inner cells, the Hippo pathway is activated through the formation of a Nf2-Amot-Lats complex associated with adherens junctions, leading to nuclear exclusion of the transcriptional co-activator Yap through phosphorylation and reduction of TEAD4-driven Cdx2 expression. Epiblast and primitive endoderm (PE) segregation is controlled through combined Fgf4-Fgfr2-Mek signaling and lineage specific transcription factor networks. In addition to cell-autonomous functions of Nanog, Sox2, and Oct4 in the epiblast cells, they provide a non-cell autonomous function for PE lineage through transcriptional induction of Fgf4. In the PE progenitors, Fgfr2-Mek signaling alleviates Nanog repression of Gata6. Subsequent PE maturation involves sequential activation of Sox17, Gata4, and Sox7 and is found to be dependent on Oct4 in an autonomous manner.**

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