Developmental Biology 395 (2014) 73–83

Contents lists available at ScienceDirect

Developmental Biology

journal homepage: www.elsevier.com/locate/developmentalbiology

Cell fate regulation during preimplantation development: A view of adhesion-linked molecular interactions

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ARTICLE INFO

Article history:
Received 27 June 2014
Received in revised form
20 August 2014
Accepted 21 August 2014
Available online 29 August 2014

Keywords:
Early embryogenesis
Junctions
Cell–cell interactions
Cell polarity
Compaction
Lineage specification

ABSTRACT

In the developmental process of the early mammalian embryo, it is crucial to understand how the identical cells in the early embryo later develop different fates. Along with existing models, many recently discovered molecular, cellular and developmental factors play roles in cell position, cell polarity and transcriptional networks in cell fate regulation during preimplantation. A structuring process known as compaction provides the "start signal" for cells to differentiate and orchestrates the developmental cascade. The proper intercellular junctional complexes assembled between blastomeres act as a conducting mechanism governing cellular diversification. Here, we provide an overview of the diversification process during preimplantation development as it relates to intercellular junctional complexes. We also evaluate transcriptional differences between embryonic lineages according to cell- cell adhesion and the contributions of adhesion to lineage commitment. These series of processes indicate that proper cell fate specification in the early mammalian embryo depends on junctional interactions and communication, which play essential roles during early morphogenesis.

Introduction

Mammalian development starts with the relatively long voyage of the embryo along the oviduct toward the uterus. The duration of this step varies according to the species, but it has a single purpose: forming a blastocyst to implant in the uterus. However, the majority of human embryos cannot complete this journey and fail to reach the blastocyst stage and/or implant (Ellish et al., 1996). Thus, this dynamic period is the most vulnerable process in mammalian development. During this period, the embryo undergoes a sequence of cellular, molecular and epigenetic changes, leading to the lineage segregation of blastomeres inside the developing blastocyst (Albert and Peters, 2009; Fujimori, 2010). Following these changes, specialization occurs, and three distinct lineages can be distinguished within the blastocyst: the pluripotent epiblast (EPI) and two extraembryonic lineages—the trophoblast (TE) and primitive endoderm (PE).

Expansion and differentiation of embryonic cell lineages occur as a series of events. These events work in perfect sequence during the developmental process. During the initial rounds of cleavage divisions, blastomeres morphologically have the same identity (Duranthon et al., 2008). Morphological differentiation is first observed during compaction, when blastomeres become adhesive and polarized. First, the junctional complexes are gradually formed at exclusively apicolateral and lateral sites; second, polarization is established within the outer cells (Eckert and Fleming, 2008; Johnson et al., 1986; Johnson and Ziomek, 1981). Both compaction and polarization processes in the 8-cell-stage mouse embryo generate cellular asymmetry leading to cellular diversification. As a result of cellular asymmetries, two differentiative cell divisions take place at the fourth (8–16-cell transition) and fifth (16–32-cell transition) cleavages and generate the outer (polarized) and inner (non-polarized) progenitors of the TE and inner cell mass (ICM), which later form the PE and EPI lineages (Can, 2014). Although human embryos go through these stages later in development compared with mouse embryos, as evidenced by embryonic genome activation (EGA) or blastocyst formation, both ultimately form the same lineages, which will contribute to the same layers (Fig. 1). To reveal the cellular origins of blastocyst lineages, it is important to understand the morphological changes controlled by compaction and polarization events that lead to blastocyst formation. Here, we briefly review how the intercellular junctional complexes contribute to this cellular diversification at the 8–16-cell stage onwards in the mouse, which is the most well-studied animal model of early embryo development, and in humans.

Preimplantation development: from fertilization to implantation

The developmental period between fertilization and implantation is defined as preimplantation, and it lasts approximately

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http://dx.doi.org/10.1016/j.ydbio.2014.08.028
0012-1606/

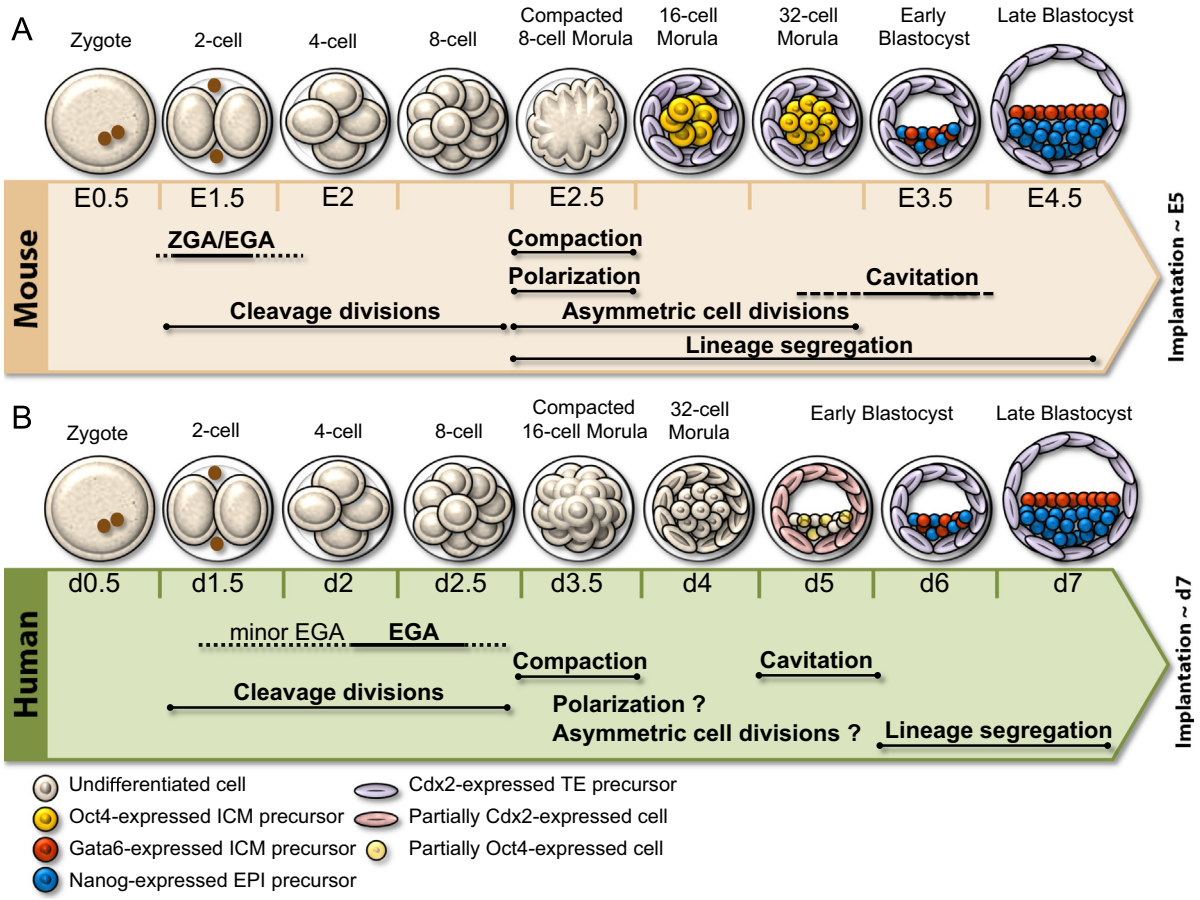

Fig. 1. Timing of preimplantation development events in mouse (A) and human embryos (B). (A) In the mouse, the zygote undergoes three rounds of cleavage to become an 8-cell embryo, and the compaction occurs at E2.5, mediated by E-cadherin activation. Lineage segregation concurrently begins at E2.5 with TE differentiation during compaction. Establishment of the intercellular complexes generates polarized blastomeres and results in asymmetric (differentiative) cell divisions (from E2.5 to E3.5) that produce daughter cells of different sizes that inherit different lineage-specific transcriptional regulators; these cells are considered precursors. After the formation of the cavitation at E3.5, randomly distributed PE and epiblast precursors within the ICM are sorted into their ultimate localization at E4.5, when all three embryonic lineages can be distinguished clearly. (B) Although the human preimplantation period progresses through the same sequence of events, the timing is quite different, with human embryos showing delayed development compared to mouse embryos. In humans, the zygote undergoes four rounds of cleavage, existing as a 16-cell embryo when the compaction occurs at day 3.5 (mediated by E-cadherin activation). Precursor cells first appear during cavitation at day 6, two days later than in mice. Lineage segregation is completed at approximately day 7, when all three embryonic lineages can be distinguished. Retardation of lineage segregation in human embryos occurs due to the prolonged coexpression of Cdx2 and Oct4 in the TE. Polarization and asymmetric cell division events in human preimplantation embryos have not yet been identified.

4.5 days in mice and approximately one week in humans (Fig. 1) (Niakan et al., 2012). Fertilization forms a diploid cell called a zygote, which will give rise to a new organism. The zygote is not an ordinary cell; rather, it has an enormous potential that can reflect all features of cellular components. Once fertilization is accomplished, the zygote undergoes successive cleavage divisions within the following days that occur at intervals of 12–24 h. The first cleavage division takes place approximately 16–20 h after fertilization in mice and 30 h after fertilization in humans. Although there are different opinions about the position of the first cleavage axis (Davies and Gardner, 2002; Plusa et al., 2002), the most commonly accepted model is that the first cleavage axis is associated with the position of the polar bodies; thus, it is assumed that polar bodies guide the first cleavage. One of the major events in preimplantation development is the zygotic or, more appropriately, embryonic genome activation (ZGA or EGA), which begins at the 2-cell stage in mice and approximately the 4- to 8-cell stage in humans; minor human EGA may also occur at the 2-cell stage (Fig. 1) (Taylor et al., 1997). This process constitutes *de novo* nuclear reprogramming and ensures the transcriptional competence of the early embryo. Activation of embryonic transcription is accompanied by the deadenylation of DNA and finally the degradation of maternally provided RNAs. Extensive reviews on EGA can be found elsewhere (Duranthon et al., 2008; Hamatani et al., 2004; Li et al., 2010; Zeng and Schultz, 2005).

Preimplantation development can be divided in two successive phases with respect to the transcriptional profile of the embryo: phase I represents the oocyte-to-embryo transition (until the late 2-cell stage in mouse embryos or the 4-8-cell stage in human embryos), and phase II represents the cellular differentiation from EGA until the blastocyst stage (Zernicka-Goetz et al., 2009). In the mouse embryo, initially, transcriptional profile of cells becomes dissimilar by the orientation and order of second cleavage division (Piotrowska-Nitsche and Zernicka-Goetz, 2005; Plachta et al., 2011; Torres-Padilla et al., 2007). Such differentiated profile allows them to gain a different developmental fate and potency (Tabansky et al., 2013; Torres-Padilla et al., 2007). On the other side, the first structural alteration of embryos within phase II is the compaction process, which occurs at the mid-8-cell stage in mouse (E2.5) and at the 16-cell stage in humans (day 3.5). Compaction is the triggering event of morphogenetic and cellular differentiation. The most important event occurring during compaction is the emergence of two different cell populations: the outer blastomeres residing outside the embryo are selected to form the trophectoderm (TE) layer, whereas blastomeres that are situated inside are selected to form the ICM. Upon completion of