Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Systems Biology

(De)constructing the blastocyst: Lessons in self-organization from the mouse

Berenika Plusa[1,2] and Anna-Katerina Hadjantonakis[3]

Abstract

Mammalian pre-implantation development - from the zygote to the blastocyst - offers a simple, tractable model for investigating how cell fate specification is coordinated across a population, and how it is integrated with morphogenetic events, at single-cell resolution. Mouse zygotes cultured *ex utero* in the absence of extrinsic factors readily develop to the blastocyst stage, mimicking events taking place *in utero*. This remarkable feature of the earliest stages of mammalian development represents a paradigm of an evolutionarily-conserved program of self-organization. At the centre of this self-organizing ability lies an extraordinarily labile developmental program, which can sense and respond to perturbations. To date, the blastocyst is also the only embryonic stage and of any species, from which stem cells representing each of its constituent lineages can be captured and propagated *in vitro*. Gaining insights into the mechanistic underpinnings of blastocyst development underscores our understanding of the inherent flexibility and robustness in the intrinsic developmental program *in vivo*, and underscores methods to recapitulate it *in vitro*.

Addresses

[1] Faculty of Biology, Medicine and Health, The University of Manchester, Oxford Road, Manchester M13 9PT, UK

[2] Department of Experimental Embryology, Institute of Genetics and Animal Breeding, Polish Academy of Sciences, Postępu 36a, 05-552 Jastrzębiec, Poland

[3] Developmental Biology Program, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

Corresponding author: Hadjantonakis, Anna-Katerina (hadj@mskcc.org)

Current Opinion in Systems Biology 2018, ■:1–8

This review comes from a themed issue on **Development and differentiation**

Edited by **Robert Zinzen** and **Stas Shvartsman**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.coisb.2018.08.002

The mammalian blastocyst – a *bona fide* self-organizing system

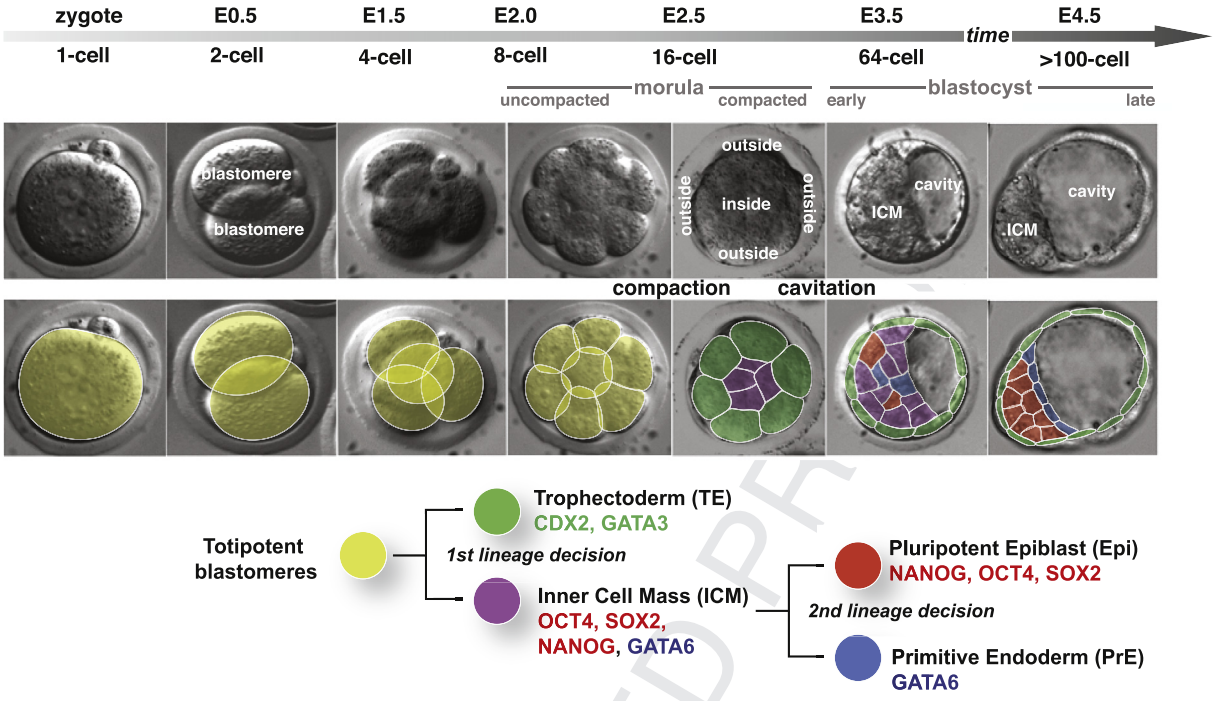
Self-organising systems constitute an important aspect of many diverse fields, with multiple artificial systems exploiting the principle of self-organisation inspired by living systems. In biology the pre-implantation mammalian embryo can be considered a *bona fide* of self-organising system, in which the first three cell lineages arise and organise themselves into a structure referred to as the blastocyst (Figure 1).

Given their small size (<120 microns), semi-transparency, and limited cell number (<200 cells in the mouse), pre-implantation mammalian embryos provide excellent specimens for single-cell analyses and systems biology approaches [1]. The pre-implantation embryo is currently one of the few multicellular systems where the complete cohort of cells can be sampled over time, at the single-cell level (for example using imaging or transcriptomics techniques), and in reasonable numbers of specimens. Cell fate decisions are taken within a relatively short time (24–36 h) when the cell cycle duration is about 14 h, and there is significant transcriptional heterogeneity between cells [2,3]. Despite this noise and short window of time, the system is remarkably robust.

Recent studies in other mammals have revealed a comparable sequence of morphological events and lineage-specific localisation of homologous markers, suggesting the general mechanisms driving blastocyst formation are evolutionarily conserved [4–6]. Therefore, although our current understanding predominantly derives from studies in the mouse, the general principles that control the pre-implantation period can likely be extrapolated (with some caution) to other mammalian systems, with the expectation that there will be species-specific adaptations. (See Figures 2 and 3).

Pre-implantation embryo development occurs in a robust reproducible manner, seemingly without a need for extrinsic inputs (i.e. growth factors, chemical inhibitors or serum). Indeed, the early mammalian embryo exhibits a unique ability to compensate for manipulations of its native architecture; accommodating changes in the relative position of cells, as well as the loss or introduction of supernumerary cells [7–11]. Even when the architecture of an embryo is completely destroyed with all cells being disaggregated, they can efficiently re-aggregate, appearing to recognize their new context, and accordingly adjust their developmental program, at least when such manipulations are performed at or before the 8–16 cell stage [12–16]. Even after this initial period of elevated cellular plasticity, a subset of the cells within the inner cell mass (ICM, a group of cells that occupy an internal position and representing the future

Figure 1



Schematic of mouse preimplantation development – from the zygote to the blastocyst. Three lineages arise from two sequential binary fate decisions, and two sequential morphological events – compaction and cavitation.

embryonic region, Figure 1) remain plastic and can adopt more than one fate [11,17,18]. Finally, by the time the embryo implants into the maternal uterus, all three blastocyst lineages are fully committed and correctly positioned, and consequently plasticity is lost [11,19]. This inherent ability to compensate for various perturbations makes investigations of early mammalian development challenging, and can, at least in part, explain why our understanding of how the lineages of the blastocyst robustly arrise is still somewhat rudimentary.

Basic principles of pre-implantation mammalian embryo development

Blastocyst development is devoted to the specification and correct positioning of three cell lineages: the pluripotent epiblast (EPI), the precursor of somatic cells and germ cells, and two extra-embryonic lineages: the trophectoderm (TE), which gives rise to the foetal portion of the placenta, and the primitive endoderm (PrE), the precursor of the yolk sac endoderm (Figure 1, [3]). These three cell lineages are generally considered to arise through two sequential binary cell fate decisions (TE-vs.-ICM followed by EPI-vs.-PrE). EPI and PrE are specified within the ICM, whereas TE cells envelope the ICM and the fluid-filled blastocyst cavity.

When the fertilised zygote divides it gives rise to two comparably sized and shaped cells (referred to as blastomeres), that are totipotent; able to contribute to all the lineages of the blastocyst, both embryonic (EPI-derived) and extra-embryonic (TE and PrE-derived). After 3 rounds of cell division, the embryo reaches the 8-cell stage and the first morphologically-recognizable event - compaction - takes place in the mouse [20–22]. Compaction occurs when blastomeres increase their cell–cell contact areas and acquire apico-basal polarity. The initial polarization and specification of an outside-facing apically-localized actin-rich domain initiates a cascade of events leading to the first differentiation event taking place in mammalian embryos (Figure 1); the formation of outside cells characterized their inheritance of an apical domain and apolar inside cells [23,24].

The polarized apical domain of outside cells acts as an off-switch for the Hippo signalling pathway and leads to the nuclear accumulation of the Yes-associated protein (YAP) which complexes with the transcription factor TEAD4 to drive expression of a TE-specific program [25]. The subsequent maturation of the TE epithelium results in the acquisition of features of a water-tight layer and formation of a fluid-filled blastocoel through active ion transport [26–28]. These events of mark the second morphologically-recognizable event occurring in mammalian development - cavitation - and herald the formation of the blastocyst.