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REVIEW

Common principles of early mammalian embryo self-organisation

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ABSTRACT

Pre-implantation mammalian development unites extreme plasticity with a robust outcome: the formation of a blastocyst, an organised multi-layered structure ready for implantation. The process of blastocyst formation is one of the best-known examples of self-organisation. The first three cell lineages in mammalian development specify and arrange themselves during the morphogenic process based on cell-cell interactions. Despite decades of research, the unifying principles driving early mammalian development are still not fully defined. Here, we discuss the role of physical forces, and molecular and cellular mechanisms, in driving self-organisation and lineage formation that are shared between eutherian mammals.

KEY WORDS: Blastocyst, Pre-implantation development, Self-organisation, Epiblast, Primitive endoderm

Introduction

One of the most fundamental questions in biology is: how can one cell, a fertilised zygote, give rise to all of the different cell types found in the adult body? The sequential formation of different types of cells that arrange themselves into tissues and organs has been studied extensively in various model organisms. The mammalian embryo offers a unique perspective for tackling this question, as its early development is not 'pre-programmed' by the arranged deposition of maternal determinants (neither proteins nor mRNA, as in other organisms), nor does it fully depend on the position-related information linked to the sperm entry point or any specific landmarks related to the oocyte (Plusa and Hadjantonakis, 2018; Wennekamp et al., 2013). Instead, a combination of cell-cell and cell-environment interactions, geometrical constraints, changing physical forces and adaptive gene regulatory networks drive the formation of the first mammalian embryonic lineages and their robust organisation into a three-dimensional structure in preparation for implantation. Such a system relies on self-organisation; therefore, when the naïve architecture of the embryo is changed, for example by the death of some of its cells or external manipulation, the embryo can adapt and continue developing (reviewed by Klimczewska et al., 2018).

Although there is some variation, pre-implantation development of all eutherian mammals follows similar morphological stages (discussed below) and results in the formation of a fluid-filled blastocyst made of three distinct lineages. The outer layer of the blastocyst, the trophectoderm (TE), is the first to be specified from cells that occupy an 'outside position' in the embryo before blastocyst formation. The fully-specified TE forms an epithelium, and during implantation it facilitates contact between maternal and embryonic tissues, later giving rise to the embryonic part of the placenta (Aplin and Ruane, 2017; Hemberger et al., 2020). Concomitantly with the formation of the outer layer surrounding the embryo, the cells positioned inside give rise to the inner cell mass (ICM), a group of inner cells pushed to one side of the embryo by the growing blastocyst cavity (Johnson and McConnell, 2004; Johnson and Ziomek, 1981a). The ICM further differentiates into the epiblast (Epi), the founding lineage of the foetus, and the primitive endoderm (PrE, also known as the hypoblast), a supportive lineage that separates the Epi from the blastocyst cavity and contributes to the endoderm of the yolk sac (Dickson, 1966; Gardner and Rossant, 1979). Specification of these three lineages, as well as preparation for implantation, are the main objectives of mammalian pre-implantation development.

Despite considerable progress in our understanding of the genetic networks that direct the specification of the first three lineages in development, we still know very little about how these networks integrate and respond to the physical forces affecting cells in early embryos. The questions surrounding how the cell microenvironment modulates and transmits these forces have only recently begun to be answered.

Mounting evidence for differences in pre-implantation development among mammalian species has been recently presented and demands re-evaluation of information we have gleaned so far from the mouse model, as well as posing questions about conserved and fundamental features of pre-implantation mammalian development. In this Review, we explore the diversity of embryos from different mammalian species, looking for the common denominator of early eutherian development. The development of monotremes and marsupials is beyond the scope of this Review and is reviewed elsewhere (Frankenberg et al., 2016).

Morphological changes during pre-implantation development

Cleavages

Similarities in early embryo architecture among different groups of eutherian mammals suggest common mechanisms driving pre-implantation development. After fertilisation, the mammalian embryo undergoes sequential morphological changes before it reaches the blastocyst stage (Fig. 1). The zygote divides into two, then four, then eight identical-looking cells called blastomeres. These early divisions are not fully synchronous; for example, 3-cell embryos may transiently exist during the 2- to 4-cell-stage transition. However, synchronicity might be important for proper embryo development, as a high synchronicity of divisions has been correlated with a higher probability of successful implantation of human embryos resulting from *in vitro* fertilisation (IVF) treatment (Cetinkaya et al., 2015; Wong et al., 2010; reviewed by Milewski and Ajduk, 2017). There is no growth phase during the cell cycle for these divisions. Therefore, each subsequent division produces

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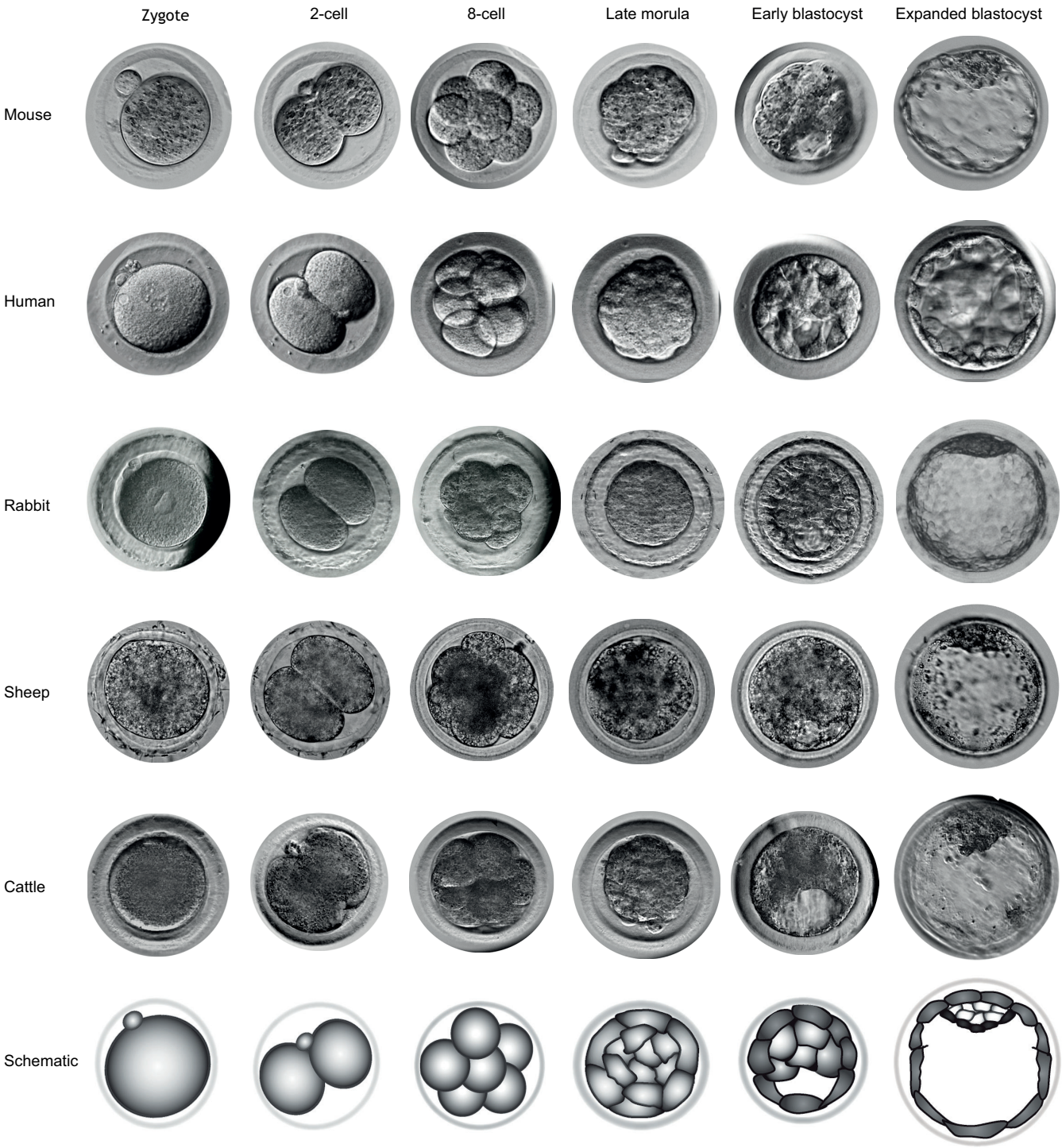

Fig. 1. Consecutive stages of preimplantation development of mouse, human, rabbit, sheep and cattle embryos. Bright-field images of *in vivo* (mouse and rabbit) and *in vitro* (human, cattle and sheep) derived embryos. Note that the length of time between morphological events depicted here may vary between species. Schematic representation of lineage formation: epiblast, white; trophectoderm, grey; primitive endoderm, black. Pictures not to scale.

smaller and smaller cells, which leads to changes in the surface area-to-volume ratio (Aiken et al., 2004). These types of divisions are called cleavages and they appear to persist through most of the pre-implantation period (reviewed by Rossant and Tam, 2009). During early cleavages, the embryonic genome remains transcriptionally inactive, and progression of early development depends on maternally stored proteins and mRNA. The timing of embryonic genome activation differs among mammalian species: major embryonic genome activation occurs as early as the 2-cell stage in rodents (Latham et al., 1992), between the 4- and 8-cell stages in humans (Braude et al., 1988; Dobson et al., 2004) and at the 8- to 16-cell stages in sheep (Crosby et al., 1988) and cattle (Meirelles et al., 2004). These temporal differences correlate with the timing of other developmental events such as lineage specification, which generally occurs much earlier in rodents than in other mammals (reviewed by Piliszek and Madeja, 2018).

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Compaction and polarisation

After several rounds of division, mammalian embryos undergo the first major morphological change: compaction (Fig. 1; Fig. 2) (Ducibella and Anderson, 1975). During compaction, loosely attached blastomeres transform into a compact, ball-like structure, in which individual cells cannot be easily distinguished; the embryo at this stage is referred to as a morula (Ducibella et al., 1975; Ducibella and Anderson, 1975). The timing of compaction differs among mammals, varying between the 8-cell stage in mouse and up to the 32-cell stage in rabbit and cattle (Table 1) (Soom et al., 1997; Ziomek et al., 1990), whereas pig embryos initiate partial compaction at the 8-cell stage, with full compaction occurring only shortly before cavitation (Reima et al., 1993). Despite this relatively high variability in the timing of compaction among different mammalian species, the initiation of this event is tightly controlled, as premature compaction may lead to impaired developmental progress towards the blastocyst stage (Iwata et al., 2014). In mice, the timing of compaction can be modulated by treatment with conventional protein kinase C (PKC) activators or inhibitors (Bloom, 1989; Winkel et al., 1990). However, it is currently not clear which PKC subfamily is involved in this process or what influences the timing of PKC activity during the pre-implantation period (reviewed by Saini and Yamanaka, 2018).

The initial model of compaction proposed that the whole process is driven by the Ca^{2+}-dependent and cell-cell contact-positioned adhesion molecule E-cadherin (also known as uvomorulin, encoded by *Cdh1*) (Sefton et al., 1996, 1992; Vestweber et al., 1987). This hypothesis has been supported by the observation that culturing mouse embryos in calcium-free medium or in the presence of neutralising antibodies against E-cadherin in the medium prevents compaction, whereas placing already compacted embryos in such culture conditions results in complete de-compaction of the morula (Ducibella and Anderson, 1979, 1975; Shirayoshi et al., 1983). Similar observations have been made in human (De Paepe et al.,

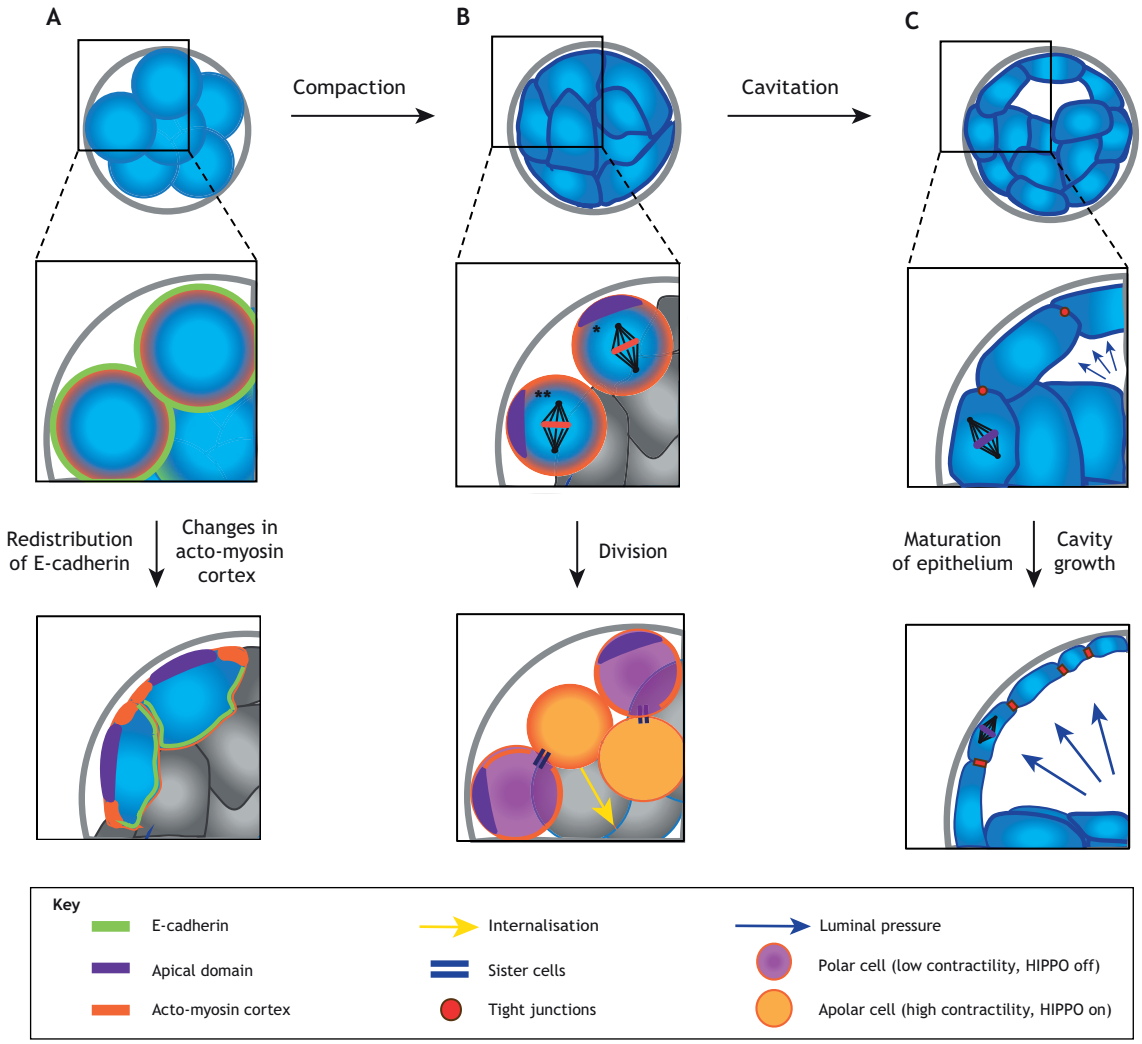

Fig. 2. Physical forces in pre-implantation development in mouse embryo. (A) The compaction process is driven by spatial rearrangement of E-cadherin, which in turn induces reorganisation of the acto-myosin cytoskeleton and increase of the cell-cell contact area. An ezrin-rich apical domain forms on the outside-facing surface. (B) During subsequent divisions, inside cells form either by asymmetric divisions, when the spindle is positioned perpendicular to the position of the apical domain (*), or due to internalisation of the apolar cells (**) because of the differences in contractility. Higher cortical tension in apolar cells leads to their internalisation (yellow arrow). Hippo pathway activity is restricted in polar cells due to the inheritance of the apical domain. In apolar cells the Hippo pathway is active. (C) A positive feedback loop between physical forces and tight junction maturation controls blastocyst cavity expansion. The increase in luminal pressure (blue arrows) leads to increased stiffness of the TE layer and stimulates tight junction maturation. This in turn strengthens TE integrity and allows for further cavity growth.

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Table 1. Examples of developmental timing in different species of eutherian mammals

Species	Compaction	Cavitation	Implantation
Mouse (*Mus musculus*)	8-cell stage (Ducibella et al., 1975)	3 dpc (Ducibella et al., 1975)	4.5 dpc (Finn and McLaren, 1967)
Human (*Homo sapiens*)	8- to 16-cell stage (Edwards et al., 1981; Steptoe et al., 1971)	5 dpc (Hertig et al., 1954; Hertig et al., 1956)	7-10 dpc (Hertig et al., 1956)
Cattle (*Bos taurus*)	32-cell stage (Van Soom et al., 1997a,b)	7-8 dpc (Van Soom et al., 1997a,b)	19-21 dpc (Wathes & Wooding, 1980)
Rabbit (*Oryctolagus cuniculus*)	32-cell stage (Ziomek et al., 1990)	3 dpc (Gamow and Daniel, 1970)	6-7 dpc (Enders and Schlafke, 1971; Nishimura, 2001)
Pig (*Sus scrofa*)	32-cell stage (Reima et al., 1993)	6-7 dpc (Reima et al., 1993)	18 dpc (Dantzer, 1985)

2013; Zakharova et al., 2014), pig (Matsunari et al., 2020) and hamster (Suzuki et al., 1999) embryos. Moreover, although zygotic *Cdh1*$^{-/-}$ mutant embryos are able to undergo compaction due to the presence of maternally deposited protein and maternal stores of *Cdh1* mRNA (Larue et al., 1994), maternal-zygotic (MZ) *Cdh1*$^{-/-}$ mutants fail to compact (Stephenson et al., 2010; Vries et al., 2004).

Recent studies in mice have revealed that E-cadherin drives compaction by reorganising the acto-myosin cytoskeleton (Anani et al., 2014; Maître, 2017; Maître et al., 2015) (Fig. 2A). E-cadherin accumulation at cell-cell interfaces induces the redistribution of acto-myosin-dependent contractility away from the cell-cell contact and leads to an increase in contractility on contact-free surfaces. This process allows for the extension of cell-cell contacts, with a concomitant contraction of the contact-free surfaces, leading to the transformation of the loosely-attached blastomeres into the compact morula (Maître et al., 2016, 2015). Therefore, according to this model, compaction does not depend on the adhesion forces generated by the interlinked E-cadherin/β-catenin complex, but rather it is induced by a twofold increase in the tension at the cell-medium interface due to the intense remodelling of the cytoskeleton (Maître et al., 2016). Indeed, extensive remodelling of the actin cytoskeleton during compaction has also been reported in pigs (Albertini et al., 1987; Reima et al., 1993). The increase in cell-cell contact during compaction facilitates the formation of adherens and then tight junctions, and is accompanied by the *de novo* establishment of apico-basal polarity in early blastomeres (reviewed by Johnson and McConnell, 2004; Mihajlović and Bruce, 2017; Saini and Yamanaka, 2018).

The first sign of polarisation is the formation of the non-adhesive apical, ezrin-rich, microvilli domain that spans the contact-free, outside environment facing the surface of the blastomeres in mouse (Louvet et al., 1996; Louvet-Vallée et al., 2001; Reeve and Ziomek, 1981), human (Nikas et al., 1996) and rabbit (Ziomek et al., 1990). Ezrin is an ERM (ezrin/radixin/moesin) family protein that links the actin cytoskeleton and plasma membrane proteins (Gautreau et al., 1999), and is known to localise to microvilli in epithelial cells as well as early blastomeres (Bretscher, 1983; Dard et al., 2004; Hanzel et al., 1991; Louvet-Vallée et al., 2001). In mouse, known polarity proteins such as atypical protein kinase C (aPKC) (Eckert et al., 2004) and the partitioning defective (PAR) proteins PAR3 (Plusa et al., 2005; Vinot et al., 2005) and PARD6B (Alarcon, 2010) also localise to the apical domain (the outward-facing blastomere surface), whereas PAR1 and scribble are positioned basolaterally, i.e. in the cell-cell contact-facing area (Kono et al., 2014; Mihajlović and Bruce, 2016; reviewed by Yamanaka et al., 2006).

Although compaction and polarisation are initiated at similar developmental stages, often involve overlapping sets of proteins (Dard et al., 2009a; Fleming et al., 1986; Johnson and Maro, 1984; Pratt et al., 1982), and can occur in the complete absence of mRNA and protein synthesis (Kidder and McLachlin, 1985; Levy et al., 1986), they do not rely on each other and can occur independently (Dard et al., 2009a; Hirate et al., 2013; Pratt et al., 1982; Stephenson et al., 2010). After the initial compaction and polarisation, during each subsequent cell division blastomeres de-compact and subsequently re-compact after all cell divisions are completed until the formation of the blastocyst in cattle (Betteridge and Fléchon, 1988; Ducibella et al., 1977), pig (Reima et al., 1993) and mouse (Skrzecz and Karasiewicz, 1987; Watanabe et al., 2014). Compaction and polarisation are the first steps in blastomere differentiation, and they initiate the cascade that leads to lineage specification in the mammalian embryo. These processes also pave the way for the next morphological event in development, the formation of the blastocyst (reviewed by Chazaud and Yamanaka, 2016).

Cavitation: formation of the blastocyst

Polarised blastomeres can divide in a way that leads to both blastomeres inheriting the ezrin-rich apical domain and maintaining an outside position (symmetric division; Fig. 2B). Alternatively, if the division plane is more parallel to the outside-facing surface, asymmetric division can result in only one of the cells inheriting the apical domain (remaining polarised and maintaining contact with the outside environment), whereas the other, apolar, blastomere will be positioned inside the embryo (Johnson et al., 1988; Johnson and Ziomek, 1981a,b). Polarised blastomeres envelop the non-polar cells, gradually forming a fluid-tight seal and gaining an epithelial character, as reported in mouse (Anani et al., 2014; Ducibella et al., 1975; Johnson and Ziomek, 1983), human (Gualtieri et al., 1992; Nikas et al., 1996), pig (Reima et al., 1993) and cattle (Barcroft et al., 2003; Manejwala et al., 1989; Manejwala and Schultz, 1989; Van Soom et al., 1997a,b).

Maturation of the outside cells towards a fully functional TE epithelium requires the activity of Na^+/K^+ ATPases and aquaporins, which are important for the active transport of ions into the intracellular space and for the passive transport of water along the osmotic gradient (Barcroft et al., 2003; Manejwala et al., 1989; Manejwala and Schultz, 1989); reviewed by Marikawa and Alarcon, 2012). The maturation of gap and tight junctions ensures that fluid stays in the area surrounded by the mature epithelium, as reported in mouse (Eckert and Fleming, 2008; Moriwaki et al., 2007), human (Bloor et al., 2004; Gualtieri et al., 1992) and cattle (Barcroft et al., 1998; Moriwaki et al., 2007). In addition, recently it has been proposed that expansion of actin rings, called 'actin ring zippering', plays an important role in the formation of a water tight seal (Zenker et al., 2018). These processes culminate in the formation and expansion of the fluid-filled cavity, and the formation of the blastocyst, in a process known as cavitation (Fig. 1; Fig. 2C) (Smith and McLaren, 1977; reviewed by Johnson and McConnell, 2004). Mutation in zonula occludens (ZO-1; also known as TJP1), a tight junction protein, prevents cavity formation in the mouse (Wang et al., 2008). The expanding cavity forms adjacent to the ICM and the resulting asymmetry defines the first axis in mammalian

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development: the embryonic-abembryonic axis (reviewed by Rossant and Tam, 2009).

Specification of ICM lineages

In the next phase of pre-implantation development, the ICM cells differentiate into Epi and PrE progenitors, which are first distributed in a seemingly random 'salt-and-pepper' pattern within the ICM, but then gradually segregate into two distinct layers (Chazaud et al., 2006; Plusa et al., 2008; Saiz et al., 2016). The PrE forms a second epithelium that separates the blastocyst cavity from the most inner-positioned Epi in mouse (Dickson, 1966; Gardner and Rossant, 1979) and human (Blakeley et al., 2015). The correct specification and positioning of all three lineages is crucial for successful implantation and further development *in utero*, whereas the number of cells at the time of blastocyst formation and the timing of implantation vary substantially among different mammalian species (Table 1; reviewed by Madeja et al., 2019).

Molecular control of lineage specification in the mammalian embryo

As we have discussed, mammalian embryos pass through similar developmental stages and all form a blastocyst composed of the Epi, TE and PrE. Therefore, one could assume that the basic molecular mechanisms of early lineage specification are shared among different mammalian groups. However, several studies have revealed differences in the expression patterns of some lineage markers, as well as differences in the responses to modulation of various signalling pathways among different groups of mammals (Fig. 3). Despite these differences, mammals appear to share several general principles that govern lineage formation in pre-implantation development, on which we focus in this Review.

In all the studied mammalian embryos, lineage specification is preceded by a period of high molecular heterogeneity between cells, when transcription factors that drive the specification of different lineages display overlapping, and often highly variable, expression at both the mRNA and protein levels (Fig. 3; reviewed by Martinez-Arias et al., 2013). Indeed, this is the case in mouse (Dietrich and Hiiragi, 2007; Guo et al., 2010; Plusa et al., 2008), human (Blakeley et al., 2015; Niakan and Eggan, 2013; Petropoulos et al., 2016), non-human primates (Boroviak et al., 2015), pig (Ramos-Ibeas et al., 2019) and rabbit embryos (Piliszek et al., 2017b). Subsequent refinement of these expression patterns leads to the segregation of the TE and ICM transcriptional profiles, which is followed by the establishment of separate PrE and Epi lineages (Chazaud et al., 2006; Guo et al., 2010; Plusa et al., 2008; Saiz et al., 2016). The timing of the lineage separation events differs among mammals and, although in most mammals the specification of the TE versus the ICM appears to precede PrE versus Epi formation, in humans it has been reported that all lineages are specified simultaneously rather than consecutively (Petropoulos et al., 2016).

Trophectoderm versus inner cell mass specification

Interestingly, compaction and cavitation appear not to be prerequisites for the initiation of TE- and ICM-specific transcriptional programmes (Box 1). Recent studies have shown that the Hippo signalling pathway is responsible for interpreting polarisation signals in the mouse morula and for initiating the TE-specific programme in the outside cells (Anani et al., 2014; Hirate et al., 2012; Nishioka et al., 2009, 2008; Yagi et al., 2007). In the polarised (outside) cells, the junction-associated angiomotin proteins AMOT and AMOTL2 are sequestered from the cell junction to the apical domain, resulting in inactivation of the Hippo

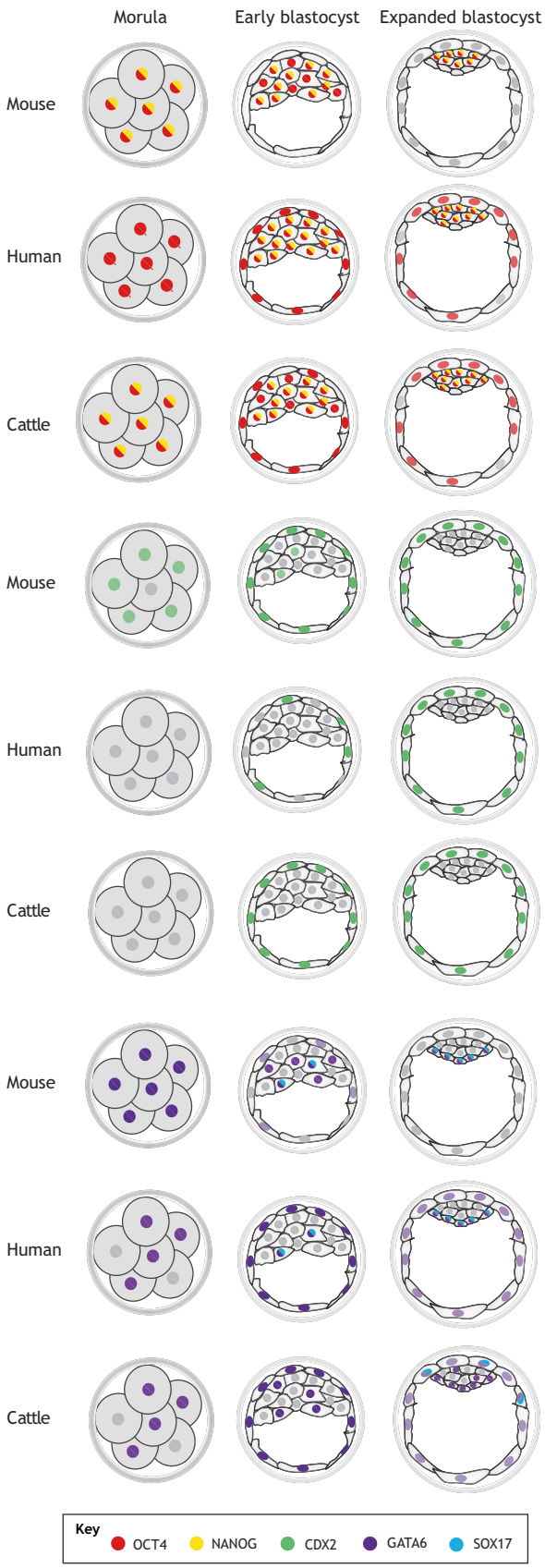

Fig. 3. Schematic showing lineage-specific transcription factor localization in mouse, human and cattle embryos at morula, early blastocyst and expanded blastocyst stage. CDX2 (green); OCT4 (red); NANOG (yellow); GATA6 (purple); SOX17 (blue).

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Box 1. Compaction and cavitation appear not to be prerequisites for the initiation of TE- and ICM-specific transcriptional programmes

Maternal-zygotic E-cadherin mouse mutant embryos (MZ *Cdh1*$^{-/-}$) fail to compact and form a blastocyst, yet single blastomeres refine their expression pattern, with most of the blastomeres expressing CDX2 and some expressing OCT4. Outside blastomeres in such mutants cannot form an epithelium despite the existence of some residual cell adhesion, which could permit tight junction formation. Moreover, *Cdh1*$^{-/-}$ blastomeres express CDX2 regardless of their position within the embryo. Similarly, OCT4 expression in such cells is not position-dependent (Stephenson et al., 2010). Moreover, despite the lack of extensive cell-cell contact, blastomeres in MZ *Cdh1*$^{-/-}$ embryos can polarise and form an apical domain, which in turn leads to activation of CDX2 expression.

pathway (Hirate et al., 2013; Nishioka et al., 2008; Sasaki, 2017) and activation of TE-specific transcription factors, such as caudal type homeobox 2 (CDX2) and GATA binding protein 3 (GATA3) (Nishioka et al., 2009, 2008; Ralston et al., 2010; Yagi et al., 2007). In non-polarised (inside) cells, adherens junction-bound AMOT activates the Hippo pathway kinases LATS1/2, repressing the TE differentiation programme (Hirate et al., 2013) (Fig. 2B). The activated Hippo pathway also restricts SOX2 to the inside cells, independently of CDX2 activity (Frum et al., 2018), and blocks premature onset of pluripotency (Frum et al., 2019). Although the specific activity of the Hippo pathway in TE differentiation has only been shown in mouse embryos so far, it is likely to be a more general mechanism of TE differentiation, because the pathway activity is evolutionarily conserved. Indeed, modulation of Hippo signalling has been suggested as a key mechanism for the evolution of blastocyst formation in ancestral mammals (Frankenberg, 2018). The Hippo pathway components TEA domain transcription factor 4 (TEAD4) and yes associated protein (YAP) are found in the morula- and blastocyst-stage embryos of other mammals, such as pigs (Emura et al., 2019, 2016), cattle (Fujii et al., 2010; Ozawa et al., 2012; Sakurai et al., 2017) and horse (Iqbal et al., 2014). Furthermore, a recent study has shown that downregulation of *TEAD4* inhibits pig embryo development beyond the morula stage (Emura et al., 2019).

WNT signalling might also play a conserved role in the early development of non-murine mammals. Several studies have pointed to the role of WNT signalling in TE versus ICM differentiation. Specifically, WNT signalling activation leads to upregulation of several pluripotency-associated genes in cattle (Madeja et al., 2015), and concomitantly reduces the number of TE cells in both cattle (Denicol et al., 2014, 2013) and pig (Lim et al., 2013) embryos. Accordingly, WNT inhibition increases TE cell number in pig and cattle embryos. In human embryos, WNT activation promotes the expression of the TE-associated marker T-box gene eomesodermin (EOMES) (Krivega et al., 2015). Interestingly, the activation of Wnt/β-catenin signalling and inhibition of ERK signalling has a positive effect on blastocyst development *in vitro*, i.e. it increases survival, hatching and cell number in cattle (Harris et al., 2013) and pig (Kwon et al., 2019). In addition, Wnt/β-catenin signalling and inhibition of ERK signalling improves stem cell line derivation and maintenance of cattle trophoblast stem cells (Wang et al., 2019) and pluripotent mouse embryonic stem cells (Nichols et al., 2009).

Several transcription factors originally identified as lineage-specific in mouse are also present in other mammalian species (Table 2). For example, CDX2 is restricted to the TE after blastocyst formation in mouse (Blij et al., 2012; Strumpf et al., 2005), human (Niakan and Eggan, 2013) and cattle (Goissis and Cibelli, 2014b). Although its function is not necessary for the initial steps of TE specification, mouse *Cdx2* mutant blastocysts collapse soon after cavity formation because CDX2 is crucial for TE maintenance (Blij et al., 2012; Strumpf et al., 2005). TE-specific expression of *CDX2* has been confirmed in human, pig, cattle, rabbit, dog and sheep embryos (Table 2); however, in most of these species, there is no evidence of *CDX2* expression before cavitation. Conversely, in mouse (Dietrich and Hiiragi, 2007; Strumpf et al., 2005) and cattle morulae (Madeja et al., 2013), *Cdx2* expression is detected as early as the 8-cell stage. A recent analysis of a TE-specific enhancer in mouse embryos indicates a specific role for Notch signalling in early *Cdx2* expression, which is distinct from later Hippo-dependent activation (Menchero et al., 2019; Rayon et al., 2014). It is plausible that the Notch-dependent *Cdx2* expression that might occur in some species has been lost in others, for example where rapid TE specification is not necessary. Species-specific enhancer activity is strongly supported by studies in cattle where, in contrast to mouse, the *POU5F1* locus lacks a specific cis-acting regulatory region that is necessary to suppress TE-specific transcription (Berg et al., 2011).

Primitive endoderm versus epiblast specification

Of the mammals that have been studied so far, PrE versus Epi specification appears to depend on both stabilisation of the pluripotency network in Epi cells and activation of the endodermal programme downstream of GATA6 in the PrE (Table 2). A pluripotency network that consists of octamer-binding transcription factor 4 (OCT4; encoded by *Pou5f1*) (Frum et al., 2013; Nichols et al., 1998), SRY-related HMG box-containing transcription factor 2 (SOX2) (Avilion et al., 2003; Wicklow et al., 2014), and homeodomain-containing protein NANOG (Chambers et al., 2003; Mitsui et al., 2003) appears to be conserved among different mammals (Table 2; Fig. 3) (reviewed by Artus et al., 2020; Piliszek and Madeja, 2018). In the mouse, PrE versus Epi specification depends on FGF/ERK signalling; thus various methods of FGF or ERK pathway inhibition result in ICM cells adopting an Epi fate at the expense of PrE (Krawchuk et al., 2013; Nichols et al., 2009; Thamodaran and Bruce, 2016; Yamanaka et al., 2010). Conversely, overabundance of FGF2/4 results in biasing the specification of ICM cells towards PrE (Arman et al., 1998; Frankenberg et al., 2011; Kang et al., 2013; Krawchuk et al., 2013; Kuijk et al., 2012; Nichols et al., 2009; Roode et al., 2012; Yamanaka et al., 2010). FGF signalling has also been extensively studied in non-murine mammals, but its role is less clear. In human embryos, ERK signalling inhibition does not interfere with PrE-specific GATA6 or GATA4 expression in the ICM; therefore, unlike in the mouse embryo, it is not necessary for PrE specification (Kuijk et al., 2012; Roode et al., 2012). A similar treatment of cattle or pig embryos also does not eliminate GATA6 or GATA4-positive cells; however, it increases the proportion of NANOG-positive cells within the ICM, indicating that ERK signalling has a role in cattle and pig lineage specification (Kuijk et al., 2012; Rodríguez et al., 2012). In rabbit embryos, ERK signalling inhibition fully blocks formation of SOX17-positive PrE cells, but at the same time does not expand the Epi population within the ICM, suggesting that in some species pluripotency acquisition may require additional stimulus (Piliszek et al., 2017b). Increased levels of FGF in cattle embryos in *in vitro* culture expand the PrE compartment at the expense of the Epi, similar to what occurs in mouse (Kuijk et al., 2012). Similar results of FGF2/4 treatment have

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Table 2. Expression of lineage-specific markers in different mammalian species

	Epiblast			PrE/Hypoblast		Trophectoderm	
Species	OCT4	NANOG	SOX2	GATA6	SOX17	CDX2	GATA3
Mouse (*Mus musculus*)	Frum et al., 2013; Nichols et al., 1998; Palmieri et al., 1994	Chambers et al., 2003; Mitsui et al., 2003	Avilion et al., 2003; Wicklow et al., 2014	Chazaud et al., 2006; Schrode et al., 2014	Artus et al., 2011; Niakan et al., 2010	Dietrich and Hiiragi, 2007; Strumpf et al., 2005	Home et al., 2009; Ralston et al., 2010
Human (*Homo sapiens*)	Chen et al., 2009; Niakan and Eggan, 2013	Cauffman et al., 2009; Hyslop et al., 2005	Cauffman et al., 2009	Deglincerti et al., 2016; Roode et al., 2012	Niakan and Eggan, 2013	Chen et al., 2009; Niakan and Eggan, 2013	Blakeley et al., 2015
Cattle (*Bos taurus*)	Berg et al., 2011; Kirchhof et al., 2000; van Eijk et al., 1999; Madeja et al., 2013	Khan et al., 2012; Kuijk et al., 2012, 2008; Madeja et al., 2013	Goissis and Cibelli, 2014a; Khan et al., 2012; Ozawa et al., 2012	Khan et al., 2012; Kuijk et al., 2012, 2008; Madeja et al., 2013	Canizo et al., 2019; Kohri et al., 2019; Negrón-Pérez et al., 2017	Berg et al., 2011; Goissis and Cibelli, 2014b; Kuijk et al., 2012; Madeja et al., 2013	Ozawa et al., 2012; Smith et al., 2010
Rabbit (*Oryctolagus cuniculus*)	Kobolak et al., 2009; Táncos et al., 2015	Piliszek et al., 2017b; Táncos et al., 2015	Piliszek et al., 2017b; Táncos et al., 2015	Bontovics et al., 2020; Piliszek et al., 2017b	Piliszek et al., 2017b	Piliszek et al., 2017a	Piliszek et al., 2017a
Pig (*Sus scrofa*)	Blomberg et al., 2008; Kirchhof et al., 2000; Kuijk et al., 2008	Cao et al., 2014; Hall et al., 2009; Liu et al., 2015; Wolf et al., 2011	Hall et al., 2009; Liu et al., 2015	Cao et al., 2014; Hall et al., 2009; Kuijk et al., 2008; Wolf et al., 2011	Ramos-Ibeas et al., 2019; Shen et al., 2019	Bou et al., 2017; Kuijk et al., 2008; Liu et al., 2015	Fujii et al., 2013; Ramos-Ibeas et al., 2019
Marmoset (*Callithrix jacchus*)	Boroviak et al., 2015	Boroviak et al., 2015	Boroviak et al., 2015	Boroviak et al., 2015	Boroviak et al., 2015	Boroviak et al., 2015	

been observed in sheep (Moradi et al., 2015), rabbit (Piliszek et al., 2017b) and pig (Rodríguez et al., 2012) embryos. Interestingly, inhibition of FGF receptor signalling by small molecule inhibitors has no effect on human, cattle, sheep or pig lineage specification, suggesting differences in receptor specificity or different pathway components. In addition, the WNT pathway might play a role in PrE versus Epi specification in non-human primates, as WNT inhibition is able to increase NANOG expression in the marmoset Epi (Boroviak et al., 2015).

The specification of Epi and PrE progenitors within the ICM is asynchronous, and initially the ICM is a mixture of committed PrE and Epi progenitors, and non-committed double-positive cells, as evidenced in mouse ($GATA6^+$/$NANOG^+$ cells; Grabarek et al., 2012; Saiz et al., 2020 preprint, 2016), non-human primates (SOX17+/NANOG+; Boroviak et al., 2015), pig (SOX17+/NANOG+; Ramos-Ibeas et al., 2019) and rabbit (SOX2+/SOX17+ cells; Piliszek et al., 2017b). A combined mathematical modelling and experimental data analysis approach in mouse revealed that specification of a subset of Epi progenitors precedes specification of PrE progenitors, as the induction of the PrE fate depends on FGF4 production by Epi cells (Bessonnard et al., 2014; Grabarek et al., 2012; Kang et al., 2013; Krawchuk et al., 2013; Ohnishi et al., 2014; Saiz et al., 2016).

The cell sorting process is initiated concomitantly with PrE and Epi progenitor specification and the formation of the salt-and-pepper pattern, as shown in mouse (Chazaud et al., 2006; Gerbe et al., 2008; Plusa et al., 2008; Saiz et al., 2013) and rabbit (Piliszek et al., 2017b). Originally, differences in cell adhesion were proposed to be responsible for the Epi and PrE cell sorting process (Chazaud et al., 2006; Rossant et al., 2003); however, recent studies have found no evidence for the involvement of E-cadherin-mediated cell adhesion in the cell sorting process in mouse embryos (Filimonow et al., 2019). Whether other adhesion molecules are involved remains to be determined. On the other hand, it has been demonstrated that cell sorting can be largely explained by a selective mechanism involving cell displacement during cell division and cavity expansion, aPKC-dependent immobilisation of the PrE progenitors once they reach the blastocyst cavity, and selective apoptosis of mispositioned cells (Meilhac et al., 2009; Morris et al., 2010; Plusa et al., 2008; Saiz et al., 2013; Xenopoulos et al., 2015). Interestingly, in mouse embryos, the Hippo pathway has been implicated in the selective elimination of unspecified cells with low levels of pluripotency factors via a cell competition mechanism (Hashimoto and Sasaki, 2019).

The mechanics of pre-implantation development: the mammalian embryo as a self-organising system

The cell microenvironment is constantly changing during development because of cell divisions and morphogenic events such as compaction, cavitation and lineage segregation. Existence of the extensive crosstalk between biochemical and mechanical inputs during pre-implantation development is now well established (Maître, 2017; Plusa and Hadjantonakis, 2016).

The specification of the outside and inside cells in mouse embryos is one of the best-studied examples of how a redistribution of physical forces can influence the lineage specification process. Originally, it was proposed that the differences in cell position within the embryo determined future cell fate. Outside cells contribute to the TE, whereas inside cells contribute to the ICM – the so-called ‘inside-outside’ model (Tarkowski and Wróblewska, 1967).

The most recent theory of TE versus ICM specification combines the elements of the inside-outside model and changes in mechanical force distribution with polarity and Hippo pathway activity. In this model, the formation of the low-contractility apical domain during compaction and polarisation in early embryos creates differences in force distribution that influence cell position during subsequent divisions (Fig. 2B) (Anani et al., 2014; Maître et al., 2016; Niwayama et al., 2019). As a result, the cells that inherit the apical domain are less contractile than their non-polar counterparts,

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envelop more contractile cells and differentiate into the TE (Anani et al., 2014; Maître et al., 2016). Highly contractile non-polar cells compete for the inside position and become internalised due to the angle of division via asymmetric divisions (Fig. 2B; Johnson and Ziomek, 1981a; Watanabe et al., 2014) or become internalised shortly after division, giving rise to ICM cells – as is most frequently the case (Anani et al., 2014; Korotkevich et al., 2017; Watanabe et al., 2014). In mice, the apical domain plays an important role in orienting cell division (Anani et al., 2014; Dard et al., 2009a,b) via the recruitment of one of the poles of the mitotic spindle (Korotkevich et al., 2017). The presence of the polarised apical domain inhibits Hippo pathway activity in the outside polar cells (Fig. 2B) and allows for the initiation of expression of TE-specific genes, such as *Cdx2* and *Gata3* (Hirate et al., 2013; Nishioka et al., 2009, 2008; Ralston et al., 2010; Rayon et al., 2014; Yagi et al., 2007). In contrast, inside blastomeres with an activated Hippo pathway retain *Pou5f1*, *Sox2* and *Gata6* expression and downregulate *Cdx2* (Frum et al., 2013; Schrode et al., 2014; Wicklow et al., 2014). Differences in contractility also facilitate cell sorting: if an apolar cell is positioned outside owing to an oblique division plane or is placed there by mechanical manipulation, it will 'sink' inside the embryo (Maître et al., 2016). Alternatively, in the rare case when such a cell inherits only a small portion of the apical domain, it can extend the polarity domain and contribute to TE (Anani et al., 2014). This elegant mechanism explains how morphogenic events during pre-implantation development are closely linked to changes in the forces and mechanical properties of the embryonic cells. Considering that all mammalian embryos appear to have the ability to reconstitute the whole embryo after disaggregation, and that different mammalian embryos can be reaggregated together, a model in which cells use the information provided by polarity and cell-cell contact to recognise their new position and adjust their developmental path accordingly is probably common to most, if not all, eutherian mammals.

The influence of mechanical forces in early development is not restricted to specification of the TE and ICM. For example, it has been reported that hydraulic fracturing of the cell-cell contacts and uneven cortical tension between TE and ICM cells assure that blastocyst cavity forms on the TE and ICM interface (Dumortier et al., 2019) whereas increasing luminal pressure during cavity growth contributes to maturation of TE tight junctions (Box 2; Fig. 2C).

Box 2. Mechanical forces participate in blastocyst maturation

It has been recently demonstrated that increased luminal pressure related to blastocyst cavity growth result in increased cortical tension and stiffness of the TE layer surrounding the cavity (Fig. 2C) (Chan et al., 2019). The cellular response to the increased cortical tension (mediated by vinculin mechano-sensing) leads to rapid maturation of tight junctions, and this in turn strengthens the integrity of the epithelium and allows for further cavity growth, creating a positive feedback loop. Moreover, TE cells under increased pressure flatten, which ensures that there are no asymmetric divisions or additional ICM cells formed after the blastocyst cavity reaches a certain size (Chan et al., 2019). During cavity growth, cell-cell adhesion cannot be sustained above a critical threshold during subsequent TE cell divisions. This phenomenon leads to a series of TE 'collapse and re-expansion' cycles that have been linked to mitotic rounding during TE cell division (Chan et al., 2019; Leonavicius et al., 2018; Niimura, 2003). In addition, Chan and colleagues suggested a tissue size control mechanism in which hydraulically-generated tissue-yield stress may set up a threshold size for the mature blastocyst. Importantly, the increase in hydrostatic pressure within the blastocyst cavity has been implicated in the blastocyst hatching from the zona pellucida – a process that needs to occur in order to allow contact between maternal and embryonic tissues during implantation (Leonavicius et al., 2018).

Potency and plasticity in mammalian development

Mammalian blastomeres retain high developmental potency for most of the pre-implantation period. Totipotency is commonly defined as the ability of the cell to give rise to the whole organism and, by definition, totipotency is a key feature of the mammalian zygote (Condic, 2014). It has been shown that even following one or two cleavage divisions of the zygote, the resulting individual cells can retain totipotency and can give rise to the whole organism. Isolated 2-cell stage mouse and rat blastomeres (1/2 blastomeres) are able to produce healthy offspring after transplantation to a foster mother (Tarkowski, 1959). In larger animals, the same is true for 1/4 blastomeres and even 1/8 blastomeres. In cattle, a live birth of genetically identical quadruplet calves has been reported after the transfer of separated 1/4 blastomeres originating from the same embryo (Johnson et al., 1995). In rabbit (Moore et al., 1968), sheep (Willadsen, 1981) and horse (Allen and Pashen, 1984), the transfer of embryos originating from single isolated 1/8 blastomeres can also result in live births. Similarly, individual human 1/4 blastomeres are able to form blastocysts *in vitro* (Van de Velde et al., 2008), and the birth of a child after transfer of an embryo with only one viable blastomere at the 4-cell stage has been reported. This confirms that in humans, at least one blastomere at the 4-cell stage can support development until birth, rendering it totipotent (Veiga et al., 1987). It is important to note that the prolonged totipotency period of larger mammalian species might be a result of larger embryo volume, longer pre-implantation period and higher cell number around time of lineage commitment but not greater plasticity per se. This concept is supported by the early observation that isolated 1/4 and 1/8 mouse blastomeres can form blastocyst-like structures *in vitro* (Tarkowski and Wróblewska, 1967) and, in some cases, can initiate implantation *in vivo*, but are not able to support development to term (Rossant, 1976). Moreover, single isolated 1/16 blastomeres (either outside or inside cells) can give rise to healthy mice when combined with tetraploid carrier blastomeres (that normally do not contribute to the embryonic lineages), suggesting that even 16-cell stage blastomeres might be totipotent (Tarkowski et al., 2010).

Totipotency can be also defined as the ability of a cell to contribute its progeny to all embryonic and extra-embryonic cell types. According to such a definition, mammalian blastomeres retain totipotency even after the process of cell lineage specification is initiated. It should be noted that the initiation of lineage differentiation does not necessarily equal or coincide with the final specification of cell fate. Shortly after blastocyst formation, mouse ICM cells retain the ability to re-form the TE layer, if the nascent TE is removed by immunosurgery, but this potential is quickly lost after cavitation (Gardner and Johnson, 1972; Posfai et al., 2017; Rossant, 1975a,b; Suwińska et al., 2008; reviewed by Klimczewska et al., 2018). This period of full ICM potency can be prolonged until the 64- to 128-cell stage in mouse when embryos are cultured in ERK inhibitors from the morula stage, suggesting that ERK activity is not only necessary for PrE formation, but it also plays a role in final TE and ICM specification (Wigger et al., 2017). A significantly extended period of ICM potency has been observed in non-murine mammals such as in cattle, where blastocysts regenerated from isolated ICMs and transferred to the recipient mother can result in live births (Kohri et al., 2019).

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The plasticity of isolated embryonic cells can be also effectively tested by transplantation into different embryonic environments, i.e. by chimera complementation assay (Tam and Rossant, 2003). In this assay, single TE or ICM cells are transplanted into an early embryo (for example at the 8-cell or 16-cell stage) and the contribution of the progeny of the transplanted cells into different lineages can be assessed. Studies on human (De Paepe et al., 2013) and cattle (Berg et al., 2011) embryos have shown that a single cell isolated from a morphologically well-distinguished TE is able to contribute to both the TE and ICM after transplantation into morulae indicating that, even at that stage, these cells are not fully committed and retain a certain degree of plasticity. The length of the high plasticity period may be partially related to the timing of implantation. Mouse embryos implant after reaching about 128 cells, ∼4.5 days post coitum (dpc), whereas human and cattle embryos implant much later (7 and 22 dpc, respectively) (Bazer et al., 2009). This difference may explain why mouse TE cells isolated at the late 32-cell or 64-cell stage are unable to contribute to the ICM lineage if introduced into a morula-stage embryo (Posfai et al., 2017), whereas in human and cattle embryos TE cells from later stages can still contribute to all lineages (Berg et al., 2011; De Paepe et al., 2013). Even though TE versus ICM fate is determined early in mouse development, single ICM cells exhibit prolonged plasticity: following experimental transplantation to 8-cell embryos, they are able to contribute to all three cell lineages in the blastocyst (Grabarek et al., 2012), and embryos reconstructed entirely from isolated inner/ICM cells from 32-cell- or even 64-cell-stage embryos are able, in some cases, to re-form a whole blastocyst (Posfai et al., 2017; Suwińska et al., 2008).

The initial totipotency within the ICM must be lost eventually to allow the full specification of pluripotent Epi and extra-embryonic PrE cells (Boroviak et al., 2014). In the mouse embryo at the embryonic day (E)3.5 mid-blastocyst stage, during formation of the salt-and-pepper pattern, PrE and Epi precursors stained for respective lineage markers appear to be intermingled with some bipotent cells (Chazaud et al., 2006; Grabarek et al., 2012; Plusa et al., 2008; Saiz et al., 2016). The presence of bipotent cells that can still differentiate into the PrE or Epi lineage ensures the proper balance of cells in each lineage and explains why, even after both lineages start the segregation process, at least some of the ICM cells retain their ability to contribute to different lineages (Grabarek et al., 2012; Saiz et al., 2020 preprint, 2016).

Cell fate specification in a regulatory system

The ability of mammalian embryos to self-organise does not depend on any pre-patterning or any particular cues originating from the oocyte, as cleavage-stage embryos can be disassociated into single blastomeres and then re-assembled again without any detrimental effect on further development, as demonstrated in mouse (Tarkowski, 1961), rat (Mayer and Fritz, 1974), sheep (Tucker et al., 1974), rabbit (Gardner and Munro, 1974), cattle (Brem et al., 1984), pig (Matsunari et al., 2013) and non-human primates (Tachibana et al., 2012). Moreover, the re-assembled embryo can contain blastomeres from several different embryos and even different developmental stages (Stern and Wilson, 1972). This remarkable feature crosses species boundaries, as shown by the aggregation of cleavage-stage embryos of different species, creating inter-specific chimeras between goat and sheep (Fehilly et al., 1984; Jaszczak et al., 1991; Meinecke-Tillmann and Meinecke, 1984), between *Bos taurus* and *Bos indicus* (Summers et al., 1983; Williams et al., 1990), and between mouse and rat (Bożyk et al., 2017) (reviewed by Zyzynska-Galenska et al., 2017).

How cell fate specification and lineage allocation occurs so robustly during pre-implantation development, in spite of high plasticity, is still debated. Although early blastomeres until the early 8-cell stage look seemingly identical, a few studies have reported that certain cleavage patterns between the 2- and 4-cell stage can produce ‘lineage-biased’ blastomeres, with a higher propensity to contribute to the TE or ICM lineage (Piotrowska et al., 2001; Piotrowska-Nitsche et al., 2005; Tabansky et al., 2013). Such variability in cell fate predispositions has been linked to differences in epigenetic modifications between blastomeres at the 4-cell stage (Torres-Padilla et al., 2007) and this in turn has been related to differences in the distribution of chromatin modifiers among early blastomeres (Burton et al., 2013; Wu et al., 2016). Subtle differences in the expression of certain key elements of the transcriptional machinery have been suggested to alter the lineage contribution probability of early blastomeres (Goolam et al., 2016; Shahbazi and Zernicka-Goetz, 2018). Moreover, differences in the levels of various lineage priming factors (such as transcription factors and polarity proteins) or in the different intracellular dynamics of pluripotency transcription factors, such as OCT4, NANOG and SOX2 (Burton et al., 2013; Frankenberg et al., 2011; Plachta et al., 2011; Plusa et al., 2005; Torres-Padilla et al., 2007; White et al., 2016), can lead to bias in the contribution of the progeny to a particular lineage. The authors who favour this hypothesis argue that in mammalian embryos, early cells are not homogenous/equivalent and that the compartmentalisation of subtle intracellular reactions is followed by amplification of the differences in subsequent development, leading eventually to the specification of different cell fates (Shahbazi and Zernicka-Goetz, 2018; Shi et al., 2015; White et al., 2018, 2017). Therefore, the gradual amplification of the original differences (Shahbazi and Zernicka-Goetz, 2018) or ‘partition errors’ (Shi et al., 2015) is at the heart of this model. However, the ‘cell-bias’ alone does not explain how separated blastomeres can re-assemble the whole embryo in a relatively short period of time or how cells recognise their new position and adjust their developmental paths. Moreover, it has also been suggested that developmental biases may originate from extrinsic constraints, such as the zona pellucida that encompasses the whole embryo (Kurotaki et al., 2007; Motosugi et al., 2005), and not necessarily be a manifestation of the differences in the intrinsic properties of the embryos.

In contrast to the ‘cell bias’ model, others have proposed that lineage allocation is stochastic and is achieved via cell-cell interactions and the existence of both positive and negative feedback loops, which integrate information about cell position with expression patterns (Dietrich and Hiiragi, 2007; Kurotaki et al., 2007; Motosugi et al., 2005). Moreover, the intra-embryonic variability of transcription factors and signalling molecules related to cell fate determination is well documented in the literature with regard to the pre-implantation development of several groups of mammals, including mouse (Dietrich and Hiiragi, 2007; Guo et al., 2010; Plusa et al., 2008), human (Blakeley et al., 2015) and rabbit (Piliszek et al., 2017b). In addition, single cell transcriptomic analyses have shown that, although slight differences in transcript abundance may be detectable between blastomeres of the early embryo, in most cases there is no consistent correlation – positive or negative – between lineage-specific transcription factors before the lineage specification process is initiated [mouse (Guo et al., 2010; Ohnishi et al., 2014), human (Blakeley et al., 2015; Boroviak et al., 2018; Petropoulos et al., 2016; Stirparo et al., 2018), non-human primates (Boroviak et al., 2018) and pig (Ramos-Ibeas et al., 2019)].

These observations favour the opinion that the observable heterogeneity of lineage-specific factors in either the TE versus

ICM or the PrE versus Epi may be induced after the lineage specification process has begun, and is not inherited from previous events. In such a view, the initial variability in transcription levels is likely a representation of cell-unbound potential, not cell fate bias (Martinez-Arias et al., 2013; Dong and Liu, 2017).

Conclusions

Historically, most of our information about mammalian development originated from mouse studies, and for many years it was assumed that that knowledge could be easily applied to other mammalian species. Recently, however, an emerging body of evidence has pointed towards high variability in developmental control among different groups of mammals. Despite that variability, all eutherian mammals share several developmental features and all mammalian embryos seems to be able to assess and adjust to changes in embryo architecture, the feature closely linked to the way cells acquire and adjust their fate in unperturbed development.

All data collected thus far confirm that the observed variability in the intrinsic properties of early blastomeres is an important element of self-organisation in early mammals. Whatever their origin, these differences allow for the robust organisation of the early embryo, with an 'assess and adjust' mechanism that allows for the interpretation of the differences and correct positioning of the cells.

Many of the factors influencing cell behaviour and lineage contribution are interdependent, which leads to further complexity in the system. Moreover, cell micro-environment (outside or inside positions within the embryo, the shape and contractility of the neighbouring cells) have a relatively strong influence on cell fate at first; subsequently, the gradual establishment of the lineage-specific regulatory circuits increases the contribution of intrinsic factors to cell behaviour, whereas the contribution of extrinsic factors gradually weakens. Eventually, after cells become fully specified, the high levels of previous plasticity are lost. Studying different mammalian species is crucial to developing a deeper understanding of the processes governing pre-implantation development, including the acquisition and maintenance of pluripotency. This knowledge can then provide the foundation for further advances in pluripotent stem cell derivation, regenerative medicine, assisted reproduction techniques in humans and domestic animals, and conservation efforts for endangered species.

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Competing interests

The authors declare no competing or financial interests.

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