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News & views

Developmental biology

Universal assembly instructions for placentas

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Our understanding of how mammalian embryos develop is based largely on mice. A study now reveals striking similarities and intriguing differences between mouse, cow and human embryos.

The placenta is a defining feature of being a mammal, and its formation is one of the first steps in mammalian development. The embryo begins to make its placenta without direct guidance from its mother – rather, it follows a set of molecularly encoded, do-it-yourself assembly instructions. Whether these instructions are universal or unique to each species of mammal is a long-standing mystery. Writing in *Nature*, Gerri *et al.*[1] report a remarkable similarity in how mouse, cow and human embryos make their placentas.

Historically, the mouse embryo has served as the model for elucidating the molecular mechanisms that guide cell-fate outcomes (decisions) during mammalian development. Now-classic studies established that the ball-shaped mouse embryo develops an external 'rind' of cells fated to become placenta about three days after fertilization. These cells, called the trophectoderm, encircle a group of inner cells that are considered pluripotent – they possess the capacity to produce all cell types of the body (reviewed in ref. 2).

In mouse embryos, this first cellular differentiation involves the polarization of trophectoderm cells along one axis, known as the apical–basal axis. Cell-polarity proteins accumulate on the apical side of trophectoderm cells, repressing signalling through the HIPPO pathway[3,4]. By contrast, HIPPO signalling is active in the pluripotent cells, because they are unpolarized. In the pluripotent cells, HIPPO signalling prevents the transcription factor YAP1 from moving to the nucleus[5]. In trophectoderm cells, nuclear YAP1 promotes the expression of the trophectoderm genes *Cdx2* and *Gata3*, and represses the pluripotency gene *Sox2* (refs 5–7). These discoveries in mouse embryos were an essential step towards understanding how embryos of other species create distinct cell types.

Early mouse, cow and human embryos are structurally quite similar, raising the possibility that molecular mechanisms guiding the first cell-fate decision in development are evolutionarily conserved across mammalian species. But, curiously, the CDX2 protein, which is thought to be a master regulator of trophectoderm in mouse, does not seem to be present in cow or human embryos at the time of trophectoderm formation[8,9], suggesting that other genes must regulate the first cell-fate decision in these species. However, the mechanism(s) for species other than mouse have not yet been described.

This is where Gerri and colleagues add a new page to the mammalian embryo instruction book. First, the authors analysed gene expression in human and cow embryos, and demonstrated that YAP1 localization and *GATA3* gene expression are conserved between species as the trophectoderm emerges. Next, they disrupted cell polarization in each species by inhibiting atypical protein kinase C (aPKC), a key polarization protein. This prevented nuclear localization of YAP1, and disrupted *GATA3* expression. These observations point to a conserved gene-regulatory module that governs the first cell-fate decision in mouse, cow and human embryos (Fig. 1a).

The observations also raise exciting possibilities for future study. For example, it is still unknown whether aPKC influences *GATA3* through YAP1 in cow and human embryos as it does in mice. Although disruption of aPKC interfered with YAP1 nuclear localization and *GATA3* expression in cow and human embryos, the requirement for YAP1 in *GATA3* regulation was not tested in cow or human embryos. This leaves open the possibility that an aPKC-regulated transcription factor other than YAP1 could regulate *GATA3* in cow and human trophectoderm. To distinguish between these possibilities, YAP1 should be hyperactivated or inhibited in cow and human embryos, as has been done previously in mice.

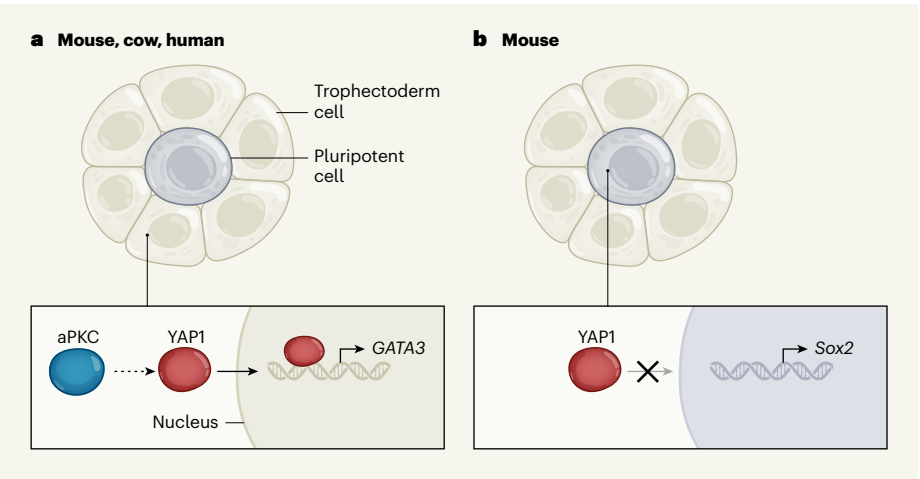

Figure 1 | Shared pathways during early mammalian development. In the very early stages of the development of mouse, cow and human embryos, the outer cells of the embryo become trophectoderm (a cell type destined to give rise to the placenta), whereas the inner cells become pluripotent (capable of producing all cell types of the body). **a**, Gerri *et al.*[1] demonstrate that, in the trophectoderm cells of all three species, the presence of a protein called atypical protein kinase C (aPKC) leads (through inhibition of the HIPPO signalling pathway, not shown) to the movement of YAP1 protein into the nucleus. Here, YAP1 promotes transcription of the gene *GATA3* – a key trophectoderm-promoting factor. **b**, In mice, YAP1 does not move to the nucleus in pluripotent cells – *GATA3* is not expressed, whereas the pluripotency gene *Sox2* is. The mechanisms that govern the establishment of pluripotency in cow and human embryos remain unclear.

These analyses will bring us closer to understanding the conserved programs underlying mammalian early development.

In spite of the striking conservation in how cell polarity and HIPPO signalling regulate *GATA3* expression in mouse, cow and human embryos, Gerri and colleagues also report a notable difference. In mice, YAP1 inhibits expression of the pluripotency gene *Sox2* in the trophectoderm, so restricting *Sox2* expression to the embryo's core[7] (Fig. 1b). By contrast, in cow and human embryos, the *SOX2* gene is initially expressed in both trophectoderm and pluripotent cells. Thus, YAP1 does not affect the initial patterning of *SOX2* gene expression in cows or humans, as it does in mice[8,10]. Gerri *et al*. find that *SOX2* expression does eventually become restricted to pluripotent cells in cow and human embryos, but it is not yet known whether this later process depends on YAP1. If so, the role of the signalling pathway would be conserved between species, although its timing would not.

The fact that *SOX2* is initially broadly expressed in cow and human embryos raises intriguing follow-up questions. For instance, does it indicate that pluripotency is defined at a later developmental stage in cow and human embryos than in mice? Or could there be alternative genes defining pluripotency at the earlier stages in cow and human? Future studies to address these possibilities will have broad-ranging implications.

Discoveries in mouse and human embryos contribute directly to our understanding of stem-cell biology. Cultured stem cells were first derived from both pluripotent and trophectoderm cells of the mouse embryo, paving the way for the establishment of stem-cell lines from human embryos[2,11]. Human stem cells have since been used in visionary efforts to study development and disease[12]. The knowledge gleaned from embryos thus guides our understanding of how to optimize protocols to manipulate the identity and function of stem cells, as well as bringing us closer to understanding the universal assembly instructions for mammalian embryogenesis.

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