Proper cell–cell interactions are required for the cells of early embryos to develop normally

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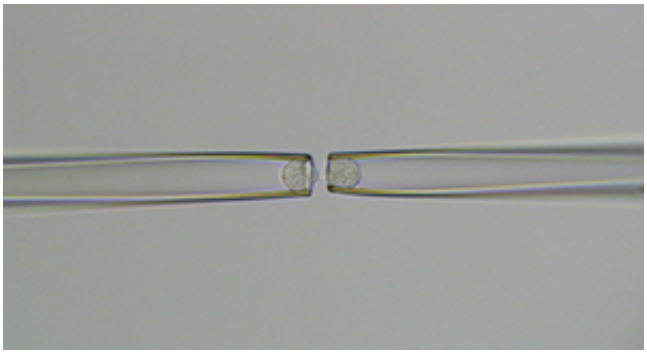

Pulling pipettes apart to gently separate early embryonic cells. Credit: 2013 C. Lorthongpanich et al.

Some 50 years have passed since scientists first proposed the so-called 'inside–outside model' of development, which holds that the inner cells of the early embryo eventually form all the definitive structures of the fetus, whereas the outer cells give rise to the placenta. Yet, the determinants of this developmental duality have remained elusive: are lineage decisions predetermined in the egg or is cell–cell contact needed to determine cell fate?

By physically separating cells in young mouse embryos, a team led by Barbara Knowles and Davor Solter from the A*STAR Institute of Medical Biology has definitively shown that extensive cell–cell interactions are required for proper lineage commitment.

After five rounds of cell division, a fertilized egg reaches the 32-cell stage. Chanchao Lorthongpanich, a postdoctoral fellow in the Knowles–Solter laboratory, mechanically separated cells at this and prior stages and then cultured the cells individually (see image). With her colleagues, she then measured the gene expression profiles of the separated cells. They showed that the pattern was out of sync with normal development, owing to the lack of proper cell–cell contact and the associated positional information that it confers.

Each of the cells, known as blastomeres, failed to display gene markers characteristic of either the inner cell mass—the part of the embryo that gives rise to the fetus proper—or the nourishing trophectoderm, the precursor to the placenta. However, the researchers observed a tendency toward 'trophectoderm-like' expression consistent with cells receiving an 'outside' signal. Furthermore, when the researchers reassembled the cells, they could not organize themselves into the multiple tissue layers needed for proper development.

"In the absence of structure and the clues provided by it, haphazard and incoherent gene expression is coupled with loss of lineage determination," says Solter, who is now working to determine the exact cues by which cell–cell interactions lead to proper development. This process is reversible for a short time, but the subsequent loss of proper signals results in permanent damage to the blastomeres, according to Solter.

In addition to providing insights into the basic biology of mammalian development, the results could have important implications for human reproductive medicine. Currently, embryo screening techniques to test for genetic diseases require destroying one or two cells from the embryo at the eight-cell stage. Since the fate of blastomeres is determined by positional cues, rather than any predetermined fate, such diagnostic testing is unlikely to result in fetal malformation, Solter notes.

More information: Lorthongpanich, C. et al. Developmental fate and lineage commitment of singled mouse blastomeres. *Development* 139, 3722–3731 (2012). dev.biologists.org/content/139/20/3722.abstract

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