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DEVELOPMENTAL BIOLOGY

How to lose your inheritance

In developing embryos, molecular and physical differences divide the cells that will form eggs or sperm and those that will form the body. The mouse protein OTX2 directs this decision by blocking reproductive-cell fate.

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In an ultimate act of family planning, the instructive cues that travel between cells include proteins of the Wnt and BMP families. PGCs normally form at a predictable location in the epiblast (Fig. 1). However, in vivo grafting experiments in mouse embryos revealed that cells from elsewhere in the epiblast have the capacity to become PGCs if they are transplanted to that location. The search for the components that drive germine fate in epiblast cells in response to the ‘kingmaker’ BMP proteins identified the transcription-factor proteins BLIMP1, PRDM14 and AP2y (refs 4, 5). This trio of proteins not only drives the expression of genes required to make the germ line, but also blocks the expression of genes associated with a somatic–cell fate.

The process of PGC development can be recapitulated in vitro, starting from mouse embryonic stem (ES) cells that can be induced to form epiblast-like cells. If these epiblast-like cells are exposed to BMPs and certain other factors, then as many as 13.5% of the cells form PGCs. However, if such epiblast-like cells are engineered to express BLIMP1, PRDM14 and AP2y, more than 30% form PGCs without the requirement for BMPs. Yet knowing that a particular pathway can drive the formation of PGCs doesn’t answer the questions of whether the default pathway of cellular differentiation in embryonic development is to form germine or somatic cells, or whether all of the cells in the epiblast are equally capable of becoming germine cells. Both matters have implications for our understanding of the evolution of multicellularity, as well as for our ability to generate healthy eggs or sperm from stem cells for clinical applications.
Zhang and colleagues studied OTX2, a transcription factor known to be involved in the development of the nervous system. In vitro studies had revealed that OTX2 promotes the transition of mouse ES cells into epiblast-like cells. Zhang et al. scrutinized the expression of OTX2 in mouse stem cells that were differentiating into germline cells in vitro. They found that, in epiblast-like cells progressing towards PGC formation, OTX2 levels decline 12–24 hours before BLIMP1, PRDM14 and AP2γ are upregulated. The authors’ in vivo analysis in mice produced similar results (Fig. 1). Considered together, these patterns of expression make sense: the level of OTX2 is low in PGCs and ES cells, both of which exist in a state of pluripotency termed naive pluripotency, which is defined as the ability to give rise to all types of cell in the body. By contrast, the level of OTX2 is high in the epiblast and in ES-cell-derived epiblast-like cells, which are considered to be more restricted in the number of cell lineages they can form.

The timing of the OTX2 decline before the transition from epiblast-cell to PGC fate raises the question of whether OTX2 might prevent cells from transitioning into PGCs. To investigate this, Zhang et al. studied the formation of PGCs in the absence of OTX2. Compared with the situation for wild-type cells, elevated numbers of PGCs were found if embryos lacked the Otx2 gene, or if epiblast-like cells grown in vitro were Otx2-deficient. Conversely, if epiblast-like cells were engineered to express higher than usual levels of OTX2, the formation of PGCs was prevented.

Moreover, the authors found that the acquisition of PGC fate in the absence of Otx2 could be accomplished in vitro without the usual requirements of BLIMP1 and signalling molecules called cytokines. This was unexpected because in vivo and in vitro experiments4,5 have indicated that PGC production requires BLIMP1. How is the requirement for BLIMP1 in germline-cell formation bypassed? Given that OTX2 promotes a form of pluripotency in the epiblast that is more restricted than that of naive pluripotency, perhaps the primary function of BLIMP1 is to create a naive state of pluripotency for newly forming PGCs.

The authors’ results are consistent with a model in which BMPs, possibly acting through Wnts, cause the level of OTX2 to decline. This reduction in OTX2 is one of the earliest known steps that determine whether an epiblast cell will acquire a germ-cell or somatic-cell fate. In an intriguing parallel to the system in fruit flies melanogaster, the transcription factor N-myc. The known roles of Myc-family genes in metabolism and in a process known as cell competition13 suggest that even minor variations in OTX2 levels in the epiblast might reflect a biologically meaningful variation in the fitness of cells that will go on to form the somatic-cell lineages or the germ line. In other words, if it turns out that the levels of Myc correlate with the health of an epiblast cell and its ability to outcompete its neighbouring cells, and if Myc controls the level of OTX2 in mice, then OTX2 might have a role in the fitness of epiblasts, and perhaps in that of PGCs.

OTX2 could provide an avenue for investigating the cell-fate decision between forming germline and somatic cells, and might offer ways of improving PGC differentiation in vitro approaches. If this mechanism of OTX2-mediated regulation of PGC fate in mice is evolutionarily conserved, then perhaps similar progress might be made in such studies of human cells. 

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This article was published online on 3 October 2018.