

Meiotic machinations

DNA replication is a central event in each mitotic cell cycle, and the factors involved in this process are coming into finer focus. For example, it was recently established that the conserved mini-chromosome maintenance (MCM) proteins help to initiate replication by assembling a pre-replicative complex that mediates origin firing during S phase¹.

DNA replication is also a critical prelude to chromosome segregation during meiosis, but less is known of its molecular players. The naïve assumption would be that analogous events of mitotic and premeiotic DNA replication are coordinated by the same molecules. On page 263, however, Susan Forsburg and Jeffrey Hodson² trounce this assumption. Upon screening mutants with defective mitotic DNA replication, they discovered that a group of initiation genes essential to replication in vegetative cells (including *mcm2*⁺ and *mcm4*⁺) are dispensable during meiosis. In contrast, elongation factors, such as DNA



polymerases and DNA ligase, are required for premeiotic S phase—just as they are for mitotic DNA replication. These surprising results indicate that mitotic initiation factors have no role in premeiotic DNA replication, or, alternatively, are rendered redundant by one or more overlapping meiosis-specific pathways.

It would seem that meiosis has evolved from mitosis and, in so doing, imposes

new constraints on mitotic processes. For example, double-strand break-repair proteins that repair damage during mitosis have been co-opted by meiosis-specific proteins, so that the choice recombination partner—that is, homologous chromosome rather than sister chromatid—serves the specialized needs of haploid gamete formation³. Whether the observations of Forsburg and Hodson are due to a similar imposition of meiosis-specific constraints upon the mitotic replication machinery remains to be determined. In any case, the lesson is clear: when it comes to extrapolating from mitotic events to their meiotic counterparts, check your assumptions at the door. —Scott Keeney

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2. Forsburg, S.L. & Hodson, J.A. *Nature Genet.* **25**, 263–268 (2000).
3. Zickler, D. & Kleckner, N. *Annu. Rev. Genet.* **33**, 603–754 (1999).

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The labyrinthine placenta

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Fetal nutrition depends on the placenta, and specifically, the branching of a layer of placental trophoblast cells that sits between the maternal blood and fetal blood vessels. The discovery that expression of the transcription factor *Gcm1* in trophoblast stem cells regulates branching of this specialized epithelium offers new insights into a process whose pivotal features have been generally obscure.

The formation of a proper placenta is key to mammalian fetal development: without the placenta, fetuses die even in the absence of obvious defects¹. On page 311 of this issue, Lynn Anson-Cartwright and colleagues² report that the branching that generates the labyrinthine structure at the centre of the placenta is regulated by *Gcm1*, which encodes the transcription factor glial cells missing-1. Anson-Cartwright *et al.* and Jorg Schreiber *et al.*³ (who have recently reported a similar study in *Molecular Cellular Biology*) found that mice lacking *Gcm1* fail to form the labyrinthine layer and succumb to placental insufficiency.

The placenta starts to form at a time when the metabolic requirements of the growing mouse embryo approach the capacity of the yolk sac. It is formed from the fusion of two tissues: the allantois, which

derives from extra-embryonic mesoderm and eventually develops into the umbilical cord, and the extra-embryonic chorion (Fig. 1a), which derives from the polar trophoderm overlying the inner cell mass of the blastula. Fetal blood vessels grow out of the allantoic mesoderm, invade the chorionic plate and instruct the trophoblast stem cells that reside within the chorionic plate to differentiate (Fig. 1b,c). At this point, the trophoblast cells fuse, forming syncytiotrophoblasts, and the three layers (allantoic mesoderm, interstitial syncytiotrophoblasts and chorion) come together to form the haemotrichorial labyrinth. Integration of fetal and maternal blood vessels within the labyrinth is critically dependent on the differentiation of the trophoblast stem cells to syncytiotrophoblasts. As the labyrinth forms, the chorion gives rise to trophoblast

stem cells of the ectoplacental cone. Trophoblast giant cells differentiate from these stem cells and migrate outwards, embedding themselves in the uterine wall to anchor the forming placenta.

Despite superficial differences, the labyrinth in the mouse and the floating chorionic villi in human are homologous structures, both characterized by extensive branching. And the similarities seem unlikely to stop there. The development of both mouse and human placentae (Fig. 2) may be partly regulated by the *Gcm* and basic helix-loop-helix (bHLH) gene families. In the mouse, two bHLH family members, *Hand1* and *Mash2*, have antagonistic actions in determining trophoblast cell fate. Whereas *Mash2* maintains trophoblast stem cells, *Hand1* promotes the differentiation of tro-