Primordial Germ Cells Stay Mobile with ROR2
BOR-Papers in Press published 4 January 2012
DOI: 10.1095/biolreprod.112.098889

The cells that give rise to gametes must migrate from the periphery of the early embryo through the hindgut to their eventual location in the developing gonads. Researchers are beginning to flesh out the molecular events behind this migration in mice, and have identified a receptor expressed by primordial germ cells (PGCs) that guides this migration.

The researchers initiated a genetic screen for mutants with germ cell defects and landed on Ror2 (receptor tyrosine kinase-like orphan receptor 2). ROR2 is known to act as a ligand for WNT5A, which has previously been implicated in PGC migration.

The researchers found that Ror2 and Wnt5a mutant mice both displayed similar germ cell migration defects, hinting that PGCs might migrate by following a trail of WNT5A. But WNT5A did not seem to act as a chemoattractant to beckon PGC migration. Instead, ROR2 activity was sensitive to another factor: secreted KIT ligand (also known as stem cell factor), which attracts PGCs to the primordial gonad. In cell culture experiments, application of secreted KIT ligand resulted in polarized expression of ROR2 in PGCs, elongation of the PGCs, and reorientation of the cells along the ligand gradient. In vivo, migrating PGCs are similarly elongated. Both of these in vitro and in vivo responses were blunted in Ror2 mutants.

The researchers propose a model for PGC migration in which KIT ligand interacts with KIT receptors on PGCs to signal polarization and migration. WNT5A in turn acts through ROR2 to amplify the polarization signal.

Curiously, regions of high WNT5A expression occur along the PGC migration route. Perhaps, the researchers say, WNT5A/ROR2 amplifies KIT signaling at these target regions, thereby helping to guide PGCs to the developing gonad.


MicroRNA from Dad Cleave the Zygote
BOR-Papers in Press published 11 January 2012
DOI: 10.1095/biolreprod.112.099085

A microRNA expressed in the testis and carried by sperm helps propel the first division of the mammalian zygote, according to a new report.

Previous studies in mice have shown that sperm contribute regulatory molecules to the oocyte. For instance, sperm proteins initiate calcium signaling that activates oocytes, and sperm RNAs are implicated in epigenetic inheritance.

Wei-Min Liu, Ronald Pang, and colleagues were interested in whether paternally supplied miRNAs could regulate early embryonic development. They identified six candidate miRNAs that were not found in oocytes, but were found in sperm and one-cell embryos. They focused their studies on one such miRNA, Mir34c, which was expressed highly in developing sperm.

To assess the role of Mir34c, the researchers injected an inhibitor of Mir34c into mouse zygotes. As a result, DNA synthesis was inhibited and the first cleavage division suppressed.

The signaling by Mir34c seems to operate, at least in part, by suppressing Bcl2, a gene known to quell cell cycle progression. The 3'UTR of Bcl2 contained sequences suggesting that it was a target of Mir34c, and the expression of a reporter gene linked up to the 3'UTR of Bcl2 increased in the zygote after injection of the Mir34c inhibitor. Moreover, injection of a BCL2 protein mimicked the effect of Mir34c inhibition in zygotes.

Oocyte activation was essential for Mir34c action in zygotes, a finding consistent with other studies of miRNA activity in oocytes. These studies demonstrate that the male gamete contributes more than just its chromosomes to the formation of the embryo. The role of the other sperm-supplied miRNAs identified in this study will be an interesting area for future study.


Methylation Makes It Male
BOR-Papers in Press published 18 January 2012
DOI: 10.1095/biolreprod.112.099333

Warm temperatures appear to quell a gene that determines whether fish develop as males or females, according to a new report on European sea bass. The findings provide insight into how shifts in temperature can affect the sex of a developing animal, a phenomenon widespread among fish and reptiles.

Most fish species have a chromosomal system of sex determination, but it’s not fixed; temperature can often throw it off. For instance, during the first 30 days of life of a European sea bass, when the gonads are developing, a four-degree Celsius increase in water temperature shifts the sex ratio from 50 percent males to around 80 percent males. In some other species of fish and most reptiles, genetics has even less influence and temperature mainly determines sex ratios.

Temperature-dependent sex determination has previously been shown to involve the gene cyp19a, which encodes P450aromatase, an enzyme that converts androgens to estrogens. For instance, cyp19a expression is elevated at feminizing temperatures in reptiles with temperature-dependent sex determination. CYP19A is also a highly-conserved enzyme, and the gene is regulated by methylation in other contexts, such as in human breast tissue. Laia Navarro-Martín et al. asked whether methylation of the gene might contribute to sex determination in the European sea bass.

The researchers compared juvenile males in this species to females and found that males’ DNA methylation levels are twice as high as females’ on the cyp19a promoter. Exposure to high temperature increased the females’ methylation levels of the cyp19a promoter. Moreover, methylation affected expression of cyp19a in vitro. Steroidogenic factor-1 (Nr5a1, a.k.a., SF-1) and the forkhead transcription factor Foxl2 are known to upregulate cyp19a, but methylation of the promoter suppressed their effects.