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Testicular teratomas: Germ cells cycling in the wrong direction

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Teratomas, from the Greek work *tera* meaning monster, are germ cell tumors which contain well-differentiated cells from all 3 germ layers, such as hair, bone, teeth and neurons.[1] How germ cells fail to follow their normal developmental program, and instead begin to differentiate into somatic tissues is a fascinating problem that has yet to be solved.

Gametogenesis begins early in embryogenesis when the primordial germ cells are specified as distinct from somatic cells.[2] After specification, the primordial germ cells divide mitotically and migrate to the gonad. Once in the gonad, they initiate sex-specific differentiation, eventually leading to the production of either sperm or eggs. In the mouse, sex-specific differences are already detected in the embryonic gonad. In the ovary, germ cells initiate meiosis, then enter meiotic arrest until ovulation. In the testis, germ cells do not initiate meiosis and instead enter G1/G0 mitotic arrest until after birth. As they arrest, germ cells of both sexes also downregulate a set of pluripotency genes, which were necessary for the initial specification and maintenance of primordial germ cell fate (Fig. 1).

It has long been thought that if male embryonic germ cells fail to arrest on schedule they will give rise to testicular teratomas in the adult.[1] Studies carried out several years ago provided considerable support for this idea by correlating prolonged germ cell proliferation in the embryo with teratoma incidence in the adult.[3,4] Moreover, these proliferating germ cells were found to ectopically express a number of genes, including the Cyclin D1 encoding gene *Ccnd1*.[3,4] Although Cyclin D1 is a known human oncogene,[5] the possibility that Cyclin D1 plays a similar role in teratoma initiation in mice has remained untested–until now.

In this volume of *Cell Cycle*, Jason Heaney and colleagues, including Denise Lanza and Emily Dawson as joint first authors, report that they have unequivocal evidence that aberrant expression of Cyclin D1 is required for teratoma formation.[6] To build their case, Lanza et al., first establish that the Cyclin D1 protein is the only aberrantly expressed D-type Cyclin in germ cells that fail to enter cell cycle arrest on schedule. This was done by comparing expression in fetal germ cells from inbred strains of mice with different frequencies of teratoma incidence: a high risk strain (80% of males affected), a low risk strain (8% of male affected) and a completely resistant (*i.e.* wild type) strain. Next, the authors use a classic genetic suppression assay to establish that ectopic Cyclin D1 expression is what drives the tumor phenotype. They show that removal of the *Ccnd1* gene in the high risk strain results in a dramatic reduction in teratoma incidence in the adult. Moreover, in the embryo these germ cells resemble normal male germ cells in that they exit mitosis on schedule, and no longer express the pluripotency marker, Nanog. With these results, Lanza et al., establish that aberrant Cyclin D1 expression plays a large and important role in misdirecting germ cell development.

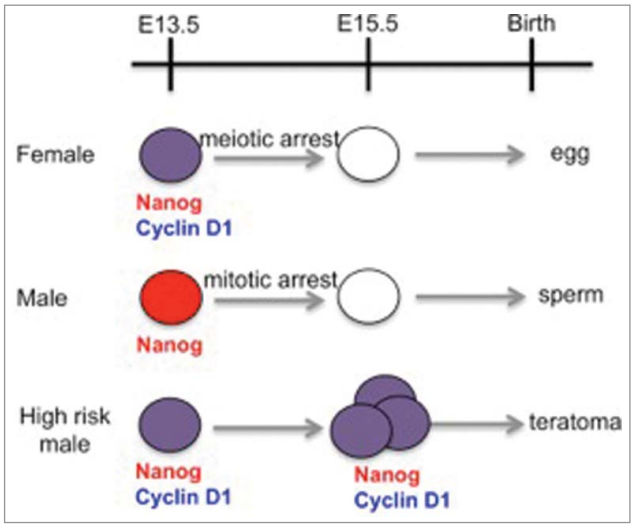

Figure 1. Timeline of germ cell development in the mouse embryo: A comparison of female, male and male germ cells from a high teratoma risk strain. Germ cells from the high risk strain fail to enter cell cycle arrest on schedule, and inappropriately express Nanog (red) and Cyclin D1 (blue). Age is given in days post conception.

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Intriguing questions remain. How does ectopic Cyclin D1 protein derail germ cell development? Might forcing Cyclin D1 expression in a resistant strain of mice be all that is necessary to misdirect a germ cell into a terminally differentiated somatic cell type? Can the steps in the germ cell to somatic cell conversion pathway be identified? What is the underlying cause of ectopic Cyclin D1 expression in the high risk strain of mice? Cyclin D is normally not expressed in embryonic male germ cells, but it is detected in the adult germline where it is associated with spermatogonial differentiation[7]–Are the germ cells in this strain attempting to differentiate prematurely? On the other hand, in female embryos Cyclin D1 is expressed in germ cells, where it is limited to the cells about to enter meiosis[4]–Perhaps the underlying defect in the high risk strain is a failure to maintain male identity? The answers to these and other questions will provide insights into the biology of these curious tumors, an essential first step toward developing new therapies.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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