Zebrafish and the evolution of sex determination mechanisms

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The genetic determinant for sex in vertebrates is known only in eutherian mammals and medaka fish, but mechanisms vary greatly. To better understand zebrafish sex determination, we investigated a mutation in the *fancl* gene that causes mutants to develop exclusively as fertile males. Fancl is a member of the Fanconi Anemia complex involved in DNA repair. The lack of mutant females is due to female-to-male sex reversal rather than female-specific lethality. In situ hybridization showed that wild-type gonads up-regulated fancl expression during meiosis. Gonads in *fancl* mutants failed to maintain the female expression profile, failed to down-regulate the male expression profile, and consequently, gonads masculinized and became testes due to an abnormal increase of germ cell apoptosis, which compromises oocyte survival beyond the stage of recombination during meiosis. Crosses showed that Tp53-mediated germ cell apoptosis is an important mechanism that tips the gonad fate towards the female or male pathway, and thus controls the definitive sex in zebrafish. This suggests a pivotal mechanism that can integrate both genetic and environmental factors affecting sex determination in zebrafish and points to a signal from post-recombinant oocytes that maintains the somatic expression of aromatase, the enzyme that converts testosterone to estrogen, and suppresses expression of anti-Mullerian hormone, an early marker for testis differentiation. Results are significant for biomedical research because mutations in Fanconi genes can cause increased apoptosis in hematopoietic stem cells that leads to anemia and leukemia in human patients, often accompanied by hypogonadism. Screening of small molecule libraries for compounds that can rescue the sex-reversal phenotype of zebrafish fancl mutants might identify compounds of therapeutic importance for Fanconi patients.

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