How Does the Absence of Both p53 and FasL Affect Development and Reproduction?

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Apoptosis is critically important for normal development and reproduction in both males and females. It has a major role in remodeling tissues during embryogenesis, folliculogenesis, spermatogenesis, regression of the corpora lutea and endometrium, and remodeling of the breast/mammary gland and prostate. Apoptosis is thought to be conserved among many tissues and species, and to be a process that is regulated by several proteins, including p53 and members of the Fas system (1). While it is known that such proteins regulate apoptosis in a variety of tissues and species, the specific roles of each protein in mammalian development and reproduction are unclear. More information about roles of p53 and the Fas system will be valuable for understanding normal development and reproduction as well as the origin and progression of developmental and reproductive abnormalities.

Powerful tools in elucidating the roles of p53 and the Fas system in development and reproduction have emerged in the form of transgenic mice deficient in p53, Fas, or Fas ligand (FasL). Use of these models has revealed that mice deficient in p53 or FasL have some developmental and reproductive defects, including an increased incidence of neural tube defects and abnormal spermatogenesis with p53 deficiency (2–3) and increased testis weights and spermatid head counts with FasL deficiency (4). Further, using transgenic animals deficient in p53, Embree-Ku and Boekelheide revealed for the first time that p53 deficiency reduces fertility in mice (5). Despite the importance of these findings, they are limited by the fact that each animal model has been generated to be deficient in either p53 or FasL. Apoptosis is regulated by several pathways, many of which are thought to be redundant. Thus, it is possible that a single gene deletion does not result in a severe phenotype because redundant pathways can compensate for the loss of one factor.

The report by Embree-Ku and Boekelheide of a novel mouse model with a deletion of both p53 and FasL has been selected for a Best Paper Award in the Experimental Biology Category for 2002 (5). Using this model, Embree-Ku and Boekelheide tested the hypothesis that the Fas system modifies the developmental and reproductive phenotypes observed in the p53 deficient mouse model. Collectively, their data show that the FasL system does not modify one of the developmental abnormalities observed in p53 deficient mice. Specifically, the increased incidence of neural tube defects normally observed in p53 deficient mice was not affected by the presence or absence of FasL. Their data also show that the FasL system does not modify several male reproductive outcomes in p53 deficient mice. Fertility rates, the mean time to copulation, testis weights, seminiferous tubule diameters, sperm head counts, and spermatogenesis were not altered in mice deficient in both p53 and FasL compared to wild-type mice or mice with a single deficiency in either p53 or FasL. Interestingly, there was evidence that the Fas system modifies the phenotype observed in female mice deficient in p53. For example, no pups were born alive to mice deficient in both p53 and FasL, whereas live pups were born to wild-type mice and mice deficient in either p53 or FasL. Further, two mice deficient in both FasL and p53 became pregnant and both died from dystocia, suggesting that the Fas system and p53 play complementary roles during parturition.

Taken together, these data are particularly exciting because they are the first to suggest that p53 and the FasL system may have complementary roles during some reproductive processes (i.e., parturition), but not during general development. In addition, these data are the first to demonstrate that absence of both p53 and FasL has sexually dimorphic effects on the reproductive system (i.e., the female reproductive system, but not the male reproductive system was affected by the double deficiency in p53 and FasL). This seminal study lays the foundation for an improved understanding of the potentially redundant roles of factors that regulate apoptosis in development and reproduction. Finally, as outstanding science often does, the work by Embree-Ku and Boekelheide raises several important questions about the mechanisms by which deficiency in both p53 and FasL interferes with parturition. Hopefully, future studies will begin to address this issue.

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