BIOACTIVE ACTIVIN AND ITS AFFECTS ON MURINE TESTIS DEVELOPMENT

***S. H. S. Mendis*[1], *S. Meachem*[3], *C. Brown*[4], *K. L. Loveland*[1,2]**

[1]Monash Institute of Reproduction and Development, Clayton, VIC, Australia; [2]The ARC Centre of Excellence in Biotechnology and Development, VIC, Australia; [3]Prince Henry's Institute of Medical Research, Clayton, VIC, Australia; [4]Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA

Activin is a member of the TGF β (Transforming Growth Factor β) superfamily of ligands which influence many aspects of male germ cell development. Formed by the linkage of two common β subunits, activin A (a βA:βA dimer) has been reported to *(1)* cause apoptosis of primodial germ cells, *(2)* inhibit the cellular transition of gonocytes into undifferentiated spermatogonia, and *(3)* enhance FSH-mediated stimulation of Sertoli cell proliferation in the newborn rat testis. Although closely related, activin βA and activin βB (a βB:βB dimer) differ in that activin βB is less bioactive. In this study we examined the role of activin during the first wave of spermatogenesis using knockout (*Inhba*$^{-/-}$) and transgenic (*Inhba*$^{BK/BK}$; two copies of the *βB* subunit gene coding sequence replace the *βA* coding sequence) mouse models with reduced levels of bioactive activin. Absolute gonocyte and Sertoli cell numbers were significantly elevated in the absence of activin A in newborn *Inhba*$^{-/-}$ testes compared to wild type, as determined by optical disector analysis. As the *Inhba*$^{-/-}$ mice die at birth, we next studied the BK/BK mice to examine postnatal effects of reduced activin bioactivity. Surprisingly, both body weight and testis weight were lower in the BK/BK compared to wild type mice at Day 7 and 14, but testis growth in proportion to body weight was significantly reduced between 7 and 14 days. At 2 weeks of age, the BK/BK animal displays a significant reduction in Sertoli cells and specific subpopulations of germ cells, the latter of which was evident only in heterozygote animals. Examination of these two models has identified that lower levels of bioactive activin affect Sertoli cells and germ cells at different stages of testicular development. Our ongoing studies involving RNA analyses of various candidate target genes will facilitate a greater understanding of the molecular basis for these observations.

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