SL 101 Study of mouse spermatogenesis using transgenic technique: translational gene regulation during spermatid differentiation

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Transgenic technology which was first introduced about a decade ago to the study of male germ cell development has opened a new chapter for its molecular studies. Along with the development of this technology, translational gene regulation during spermatogenesis is one of subjects which have been extensively studied in the area of male germ cell development.

Spermatogenesis is a complicated process that includes mitosis, meiosis and very intensive haploid cell differentiation, spermiogenesis. In mice, where transcription ceases about midway through spermiogenesis, many specific proteins required for the assembly of spermatozoa are not synthesized until days after transcription ceases. Synthesis of these proteins, therefore, depends on messages, which have been already produced and stored either during meiosis or in early spermiogenesis.

Protamine 1 (*Prm-1*) which is a small highly basic protein and involved in nuclear condensation by replacing histones on DNA, is one of specific genes known to be under translational control during mouse spermatogenesis. Although the gene is first transcribed in round spermatids, its mRNA is not translated until up to a week later in elongating spermatids. Studies done in transgenic mice have shown that the translational regulation of *Prm-1* is mediated by its 3′ untranslated region (UTR), and this regulation is essential for normal spermatid differentiation. Additional transgenic studies have demonstrated that two different regions of the *Prm-1* 3′ UTR, the 5′-most 37 nts and the 3′-most 62 nts, are sufficient for the translational repression in vivo. These two regions were shown to be binding sites for a 48/50 kDa protein and *Prm-1* RNA binding protein (Prbp), respectively.

The gene for Prbp was cloned from screening mouse germ cell cDNA expression libraries with the *Prm*-1 3′ UTR RNA. Prbp has been characterized to have properties expected of a translational regulator of *Prm-1* mRNA. In an effort to define its role in the translational regulation of *Prm-1*, Prbp knockout mice were generated by gene targeting in embryonic stem cells. Analysis of the knockouts showed that male mutants were sterile and severely oligospermic due to abnormal spermiogenesis. A reporter transgenic mRNA carrying protamine 1 translational control elements was not properly translated in the Prbp mutants, suggesting that Prbp is required for proper translational activation of the *Prm-1* mRNA.