Asian Journal of Andrology (2011) 13, 363

www.nature.com/aja

COMMENTARY

A new Speedy/RINGO protein may help regulate male meiosis

Yukiko Yamazaki and W Steven Ward

Asian Journal of Andrology (2011) **13,** 363; doi:10.1038/aja.2011.30

Reproductive biology, although seen as a specialty study area, has many unique biology models that offer insight into the regulation of cellular processes that are shared by many different cell types. The most celebrated example of this was the discovery of the cyclins and their role in cell cycle regulation in *Xenopus* oocytes.[1–4] Meiosis is one such aspect of this field that presents an important window for the study of both cell cycle regulation and chromatin structure. Meiosis only occurs in the testis and ovaries, and only in the germ cells that eventually produce spermatogonia and oocytes.[5] In this issue, Cheng and colleagues[6] present data to suggest that a novel protein they originally identified in the rat testis, called LM23, is crucial for the regulation of meiosis in spermatogenesis. It is perhaps fitting that LM23 is a member of a family of proteins called Speedy/RINGO that regulate cyclins.[7]

The Speedy/RINGO family contains at least eight member from yeast to humans, and all share a central region called the Speedy/RINGO box.[7] These proteins participate in the cell cycle, DNA damage response and entry into meiosis, through direct binding to CDK1/2. Liu and colleagues originally identified *LM23* as a gene by differential display that was very highly expressed in rat testis in the cells that are undergoing meiosis, spermatocytes.[8] In this report, they demonstrated that LM23 has a Speedy/RINGO box that is 97% homologous to the mouse Speedy/RINGO A. At present, there are few models to study meiotic maturation of male germ cells in culture, and those that are available are technically difficult.[9] Oocytes, however, can be matured to complete meiosis in culture, and using this system two members of the Speedy/RINGO family have been shown to promote meiotic maturation, XRINGO in *Xenopus*[10] and porcine Speedy A2.[11] The proposal by Cheng *et al.*[6] that LM23 is involved in male meiosis therefore seems reasonable.

These authors supported this hypothesis with two key experiments. First, they prepared antibodies to LM23 and showed that it localized specifically to spermatocytes in the rat testis. They also performed a knockdown experiment using RNAi to the *LM23* gene and demonstrated that when LM23 is knocked down, spermatogenesis is arrested at the spermatogonial stage. Finally, the authors have provided microarray data to show that key proteins in the CDK pathway are affected. Altogether, the data strongly support a role for LM23 in male spermatogenesis.

This work may eventually lead to insights into the initiation of meiosis during spermatogenesis. Primordial germ cells (PGCs) are the embryonic precursors that give rise to either spermatogonia (male) or oogonia (female). The timing of meiosis is a key factor in sex differentiation of PGCs. After sex differentiation, female PGCs immediately enter meiosis, whereas male PGCs cease at G_0 cell cycle stage and finally enter meiosis after birth. By treatment with retinoic acid, however, male PGCs enter meiosis and exhibit female-specific methylation imprints.[9] The mechanisms of this redirection of the genetically programmed development of male PGCs are not yet understood. It will be interesting to determine whether the Speedy/RINGO proteins have an early role in directly spermatogonia into meiosis.

1 Wasserman WJ, Smith LD. The cyclic behavior of a cytoplasmic factor controlling nuclear membrane breakdown. *J Cell Biol* 1978; **78**: R15–22.
2 Reynhout JK, Smith LD. Studies on the appearance and nature of a maturation-inducing factor in the cytoplasm of amphibian oocytes exposed to progesterone. *Dev Biol* 1974; **38**: 394–400.
3 Maller J, Gautier J, Langan TA, Lohka MJ, Shenoy S *et al*. Maturation-promoting factor and the regulation of the cell cycle. *J Cell Sci Suppl* 1989; **12**: 53–63.
4 Moreno S, Hayles J, Nurse P. Regulation of $p34^{cdc2}$ protein kinase during mitosis. *Cell* 1989; **58**: 361–72.
5 Handel MA, Hunt PA. Sex-chromosome pairing and activity during mammalian meiosis. *Bioessays* 1992; **14**: 817–22.
6 Cheng YM, Liu ML, Jia MC. LM23 is a novel member of the Speedy/Ringo family at the crossroads of life and death of spermatogenic cell. *Asian J Androl*; 2011; **13**: 446–452.
7 Gastwirt RF, McAndrew CW, Donoghue DJ. Speedy/RINGO regulation of CDKs in cell cycle, checkpoint activation and apoptosis. *Cell Cycle* 2007; **6**: 1188–93.
8 Liu ML, Pei KY, Shi XQ, Liu DY, Jia MC. Identification and characterization of a novel spermatogenesis related gene *LM23* in rat testis. *Biochem Biophys Res Commun* 2007; **356**: 576–81.
9 Ohta K, Lin Y, Hogg N, Yamamoto M, Yamazaki Y. Direct effects of retinoic acid on entry of fetal male germ cells into meiosis in mice. *Biol Reprod* 2010; **83**: 1056–63.
10 Ferby I, Blazquez M, Palmer A, Eritja R, Nebreda AR. A novel $p34^{cdc2}$-binding and activating protein that is necessary and sufficient to trigger G_2/M progression in *Xenopus* oocytes. *Genes Dev* 1999; **13**: 2177–89.
11 Kume S, Endo T, Nishimura Y, Kano K, Naito K. Porcine SPDYA2 (RINGO A2) stimulates CDC2 activity and accelerates meiotic maturation of porcine oocytes. *Biol Reprod* 2007; **76**: 440–7.

Institute for Biogenesis Research, University of Hawaii at Manoa, Honolulu, HI 96822, USA
Correspondence: Dr WS Ward (wward@hawaii.edu)