piRNAs trigger the turnover of MIWI in late spermatogenesis

The genome integrity of germ cells is of fundamental importance for maintaining individuals and species. The predominant biological factor that causes genome mutations is mobile genetic elements (such as transposon and retrotransposon). Recently, a new class of 26—32 nt long small RNAs termed as PIWI-interacting RNAs (piRNAs) was identified in animal germline, revealing a distinct small RNA pathway that controls the activity of mobile genetic elements in germ cells. In contrast to the recent advance in our understanding of the biogenesis and function of PIWI/piRNA machinery, little is known about the regulation of the turnover of this important machinery. Funded by NSFC, MOST and CAS, researchers led by Prof. Liu Mofang and Prof. Wang Enduo from Shanghai Institute of Biochemistry and Cell Biology, CAS, studied the regulation of PIWI/piRNA metabolism in mice. Their study shows that piRNAs trigger the degradation of its binding protein MIWI and themselves at a specific developmental stage and such event is essential for sperm formation. This work has recently been published in *Developmental Cell* (**2013**, 24(1): 13—25).

They found that MIWI is a substrate of Anaphase-Promoting Complex/Cyclosome (APC/C), and most interestingly, piRNA loading onto MIWI is a prerequisite for its ubiquitination by APC/C. They further show that APC/C-mediated ubiquitination and subsequent proteasomal degradation of MIWI *in vivo* occur only in late spermatids (LS) (Figure **A**). MIWI destruction in turn leads to the elimination of piRNAs in LS (Figure **B**), suggesting a feed-forward mechanism for coordinated removal of the MIWI/piRNA machinery during late spermiogenesis (Figure **C**). Importantly, inhibition of MIWI degradation in late spermatids prevents the formation of mature sperms, indicating that proper temporal regulation of the MIWI/piRNA machinery is essential for normal spermiogenesis. In short, this new study uncovers an unexpected mechanism for the developmental regulation of MIWI/piRNA metablolism and suggests the biological importance of such regulation for male germ cell development in mammals, shedding new lights on piRNA pathway in spermatogenesis.

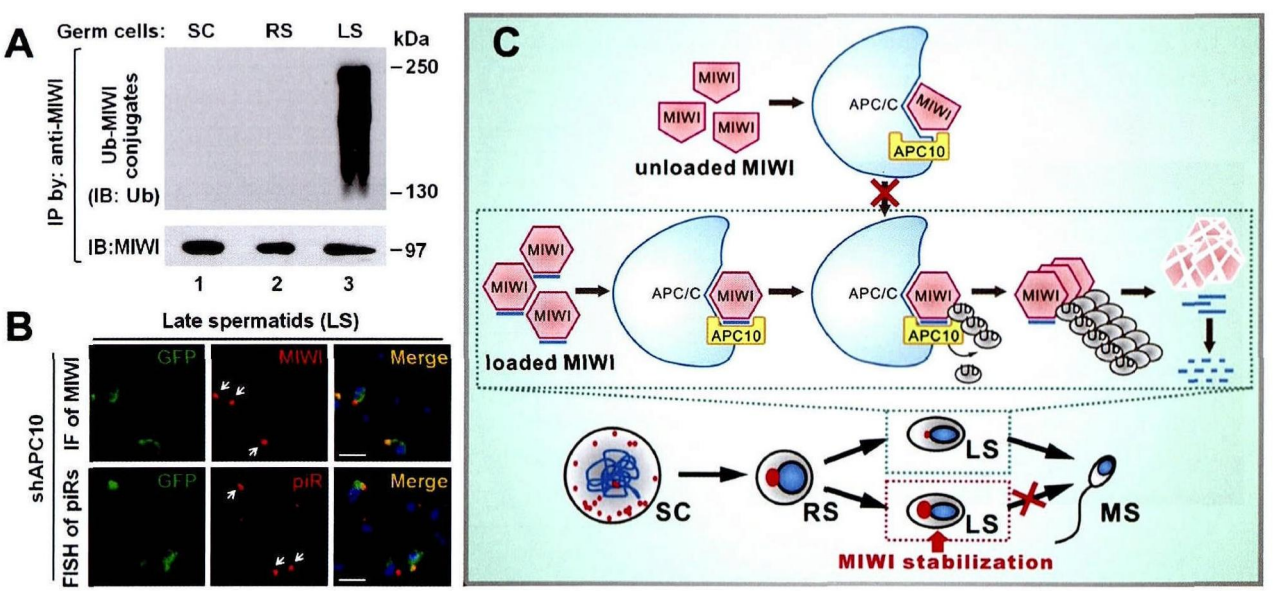

Figure **A** Detection of MIWI ubiquitination in spermatocytes (SC, lane 1), round spermatids (RS, lane 2), and late spermatids (LS, lane 3). **B** Immunostaining of LS from testes transduced by shAPC10:GFP with anti-MIWI (top), FISH assay of piRNAs in LS from testes transduced by shAPC10:GFP (bottom). **C** Model for coordinated elimination of MIWI and piRNAs in late stages of spermatogenesis. MIWI protein in SC, RS, and LS is shown in red.