Epigenetic control of meiosis by a novel histone methyltransferase, Meisetz

○Yasuhisa Matsui (IDAC, Tohoku Univ.)
Katsuhiko Hayashi (Univ of Cambridge)

In sexual reproduction, meiosis reduces the ploidy of the genome and generates genomic diversity by shuffling information between homologous chromosomes. To accomplish meiosis, transcription of a number of meiotic genes must be properly orchestrated according to progression through meiosis. Transcriptional control of gene expression depends critically on DNA accessibility, which is epigenetically regulated by histone modification. The methylation of H3K4 is a well-characterized mark of transcriptionally active genes, indicating that the action of histone methyltransferase (HMTase) on H3K4 marks genes for transcriptional activation according to tissue- and temporal-specific patterns. Although HMTases that catalyze H3K4 methylation have been identified in mammals, it remains unclear how the epigenetic modification is regulated during meiosis.

To understand transcriptional controls for initiation and progression of meiosis, we identified genes whose expression was increased during entry into meiosis by subtracting cDNAs of mitotic primordial germ cells (PGCs) at embryonic day (E) 11.5 from those of meiotic female PGCs at E13.5. Of the genes identified, we focused on a novel histone methyl transferase, named *Meisetz*, (mei osis-induced factor containing PR/SET domain and zinc-finger). *Meisetz* transcripts were detectable only in germ cells entering meiotic prophase in female fetal gonads and in postnatal testis. Meisetz has catalytic activity specific for trimethylation, but neither mono- nor di-methylation, of lysine 4 of histone H3 (H3K4), and transactivation activity that depends on its methylation activity. Mice disrupted in *Meisetz* (*Meisetz*$^{-/-}$) exhibited sterility in both sexes due to severe impairment of double-strand break repair, pairing of homologous chromosomes and sex body formation. In *Meisetz*$^{-/-}$ testis, H3K4 trimethylation was attenuated, and meiotic gene transcription altered. These findings indicate that meiosis-specific epigenetic events in mammals are critical for proper meiotic progression.