KDM2A maintains H3K36me2/3 deposition and recruits HCFC1 and E2F1 to orchestrate male meiotic entry and progression

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In mammals, the switch from mitosis to meiosis ensures the successive formation of gametes. However, the mechanisms regulating meiotic initiation remain unclear, especially in the context of complicated histone modification. Herein, we show that KDM2A acts as a lysine demethylase targeting H3K36me3 in male germ cells and plays an essential role in modulating meiotic entry and progression. Conditional deletion of *Kdm2a* in mouse pre-meiotic germ cells results in complete male sterility, with spermatogenesis ultimately arrested at the zygotene stage of meiosis. Mechanistically, KDM2A maintains a close functional relationship with *Stra8* and *Meiosin* in promoting the meiotic gene expression and binds a wide range of meiosis-related genes. Interestingly, KDM2A deficiency disrupts the deposition of H3K36me2/3 in c-KIT$^+$ germ cells, characterized by a reduction of H3K36me2 but a drastic increase of H3K36me3. Furthermore, KDM2A could recruit the transcription factor E2F1 and its co-factor HCFC1 to the promoters of key genes required for meiosis entry and progression, such as *Stra8, Meiosin, Spo11, and Sycp1*. Thus, our study unveils an essential role for KDM2A-mediated H3K36me2/3 deposition in controlling the programmed gene expression necessary for mitosis to meiosis transition.

Keywords: KDM2A, Histone modification, Meiosis, Male germ cells, Fertility