CO maturation inefficiency sets up the baseline for elevated aneuploidy in human female meiosis

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Under the support of the National Natural Science Foundation of China, the research group led by Prof. Zhang Liangran (**张亮然**) from Shandong University, collaborated mainly with the research group led by Prof. Nancy Kleckner from Harvard University, has demonstrated that human female meiosis has a specific crossover maturation inefficiency, which sets up the baseline for elevated aneuploidy. This work has been published in *Cell* (2017, 168: 977—989).

Aneuploidy is the leading cause of infertility, abortion and congenital birth defects. A dramatically high frequency of aneuploidy pregnancies occurs in human. Surprisingly, ~90% of aberrancies derive from errors in human female meiosis. The frequency of aneuploidy increases with increasing maternal age, which can reach >50% at late reproductive age in females. However, even in young women the aneuploidy frequency is still very high (~10%), thus indicating intrinsic defects in female meiosis.

Inter-homolog DNA crossovers (COs) are crucial for successful meiosis. Aberrant COs lead to errors in chromosome segregation, thus aneuploidy. Comparisons of CO patterns between human male and female meiosis showed longer chromosome axes and thus more COs in females. Paradoxically, females have a higher frequency of chromosomes absence of COs and a lower density of COs, which imply that some COs may be "missing" in female meiosis. Further analyses have revealed that very similar recombination processes occur in males and females, but ~25% designated recombination sites fail to mature to actual COs in females, which we call "CO maturation inefficiency". Moreover, this inefficiency also leads to "irregular" distribution of COs, which promotes chromosome mis-segregation. In conclusion, CO maturation inefficiency sets up the baseline for aneuploidy frequency. When maternal age-dependent and -independent factors come into play, they would synergistically promote a higher level of chromosome mis-segregation and thus a higher level of aneuploidy.

These findings have discovered the specific CO maturation inefficiency in human female meiosis and demonstrated its critical roles in promoting elevated human aneuploidy. However, further studies are needed to understand the evolutionary significance and what molecule(s) cause this inefficiency.

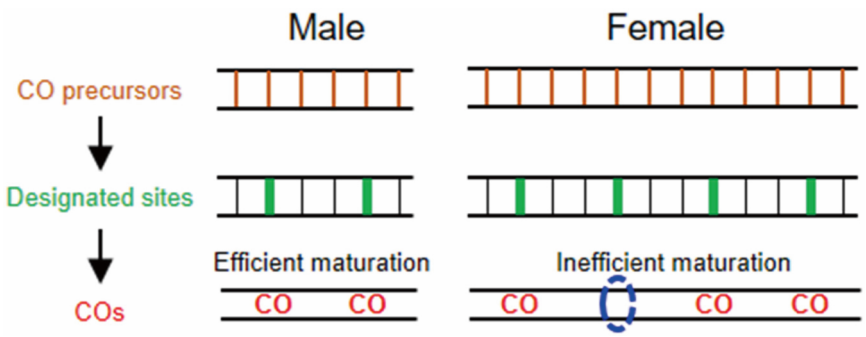

Figure Human females have a specific crossover maturation inefficiency in meiosis.