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Ovulation suppression prevents the increase in egg aneuploidy with maternal age

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Abstract

The frequency of egg aneuploidy and trisomic pregnancies increases with maternal age. Since multiple causes contribute to egg aneuploidy, it is likely challenging to prevent the "maternal age effect" using a single approach. To test our hypothesis that ovulations contribute to oocyte ageing and chromosome missegregation, we used genetics, hormonal contraception and successive pregnancies to reduce ovulations. We observed that ovulation reduction is sufficient to prevent egg aneuploidy and age associated errors during meiosis I division of the oocyte, in aged mice. By interrupting ovulations with successive pregnancies, we discovered that eggs from aged mated females display lower aneuploidy and reduced precociously separated sister centromeres compared to those from aged virgin females. When putting mice on hormonal contraception we find a near 2 fold reduction in aneuploidy incidence. To reduce ovulations further, we generated Gpr54 knockout mice, which remain in a pre-pubescent state. Remarkably, aneuploidy is reduced 3-fold in eggs from Gpr54-/- versus Gpr54+/+ aged females. These data suggest protection is due to reduced ovulations. We further observed that ovulations contribute to loss of Rec8-cohesin, which is essential for sister chromatid cohesion in meiosis. Single-nucleus Hi-C revealed a deterioration of 3D chromatin organization that depends on ovulation frequency and Rec8, which restricts loops extrusion. We conclude that ovulation suppression leads to retention of Rec8, which maintains chromatin structure and promotes chromosome segregation and production of euploid eggs. Our work implies that hormonal contraception can reduce the risk of Down's syndrome pregnancies at advanced maternal age.

Biography:

Emmanouella Chatzidaki has completed his PhD at the age of 26 years from the Univeristy of Cambridge, UK and postdoctoral studies from Karolinska Isntitute, Sweden and the Institute of Molecular Biotechnology, Austria. She is a senior PostDoc at the Institute of Molecular Biotechnology, Austria. She has published several papers in reputed journals with over 3,000 citations.

Speaker Publications:

1. "Variation in germline mtDNA heteroplasmy is determined prenatally but modified during subsequent transmission"; Nature Genetics volume 44, pages1282–1285(2012).
2. "Aging: Is caloric restriction anti-aging?"; Archives of Hellenic Medicine 27(4):599-606.
3. "Kisspeptin Signaling Is Required for Peripheral But Not Central Stimulation of Gonadotropin-Releasing Hormone Neurons by NMDA"; Journal of Neuroscience 2010, 30 (25) 8581-8590.
4. "Bovine spongiform encephalopathy and Creutzfeldt-Jacob's disease 15 years later, where do we stand?"; Archives of Hellenic Medicine/2010/27(3):471-474
5. "Two conserved modules of Schizosaccharomyces pombe Mediator regulate distinct cellular pathways"; Nucleic Acids Research/2008/ 36(8):2489-504.

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