CHROMOSOME BIOLOGY

Keeping oocytes young

The frequency of egg aneuploidies and trisomic pregnancies increases dramatically with maternal age, often leading to miscarriage. But the causes of increased chromosome missegregation (which arises primarily from meiosis I) in ageing oocytes are not understood. Aneuploid pregnancies have been associated with exposure to toxins and oxidative damage, as well as with the weakening of sister chromatid cohesion. Tachibana and colleagues now report that the suppression of ovulation protects against chromosomal abnormalities in ageing mouse eggs, which can be partly explained by increasing REC8–cohesin retention on chromosomes and thus reducing ageing-associated loss of chromosome cohesion.

As ovulation involves the rupture of epithelial tissue and the production of reactive oxygen species (ROS), the authors postulated that ovulations and repeated cycles of damaging ROS determine the physiological age of mammalian resting oocytes.

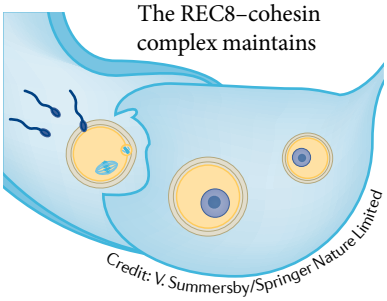
> “suppression of ovulation protects against chromosomal abnormalities in ageing mouse eggs, which can be partly explained by increasing REC8–cohesin retention on chromosomes”

Oocytes from mouse females that went through successive pregnancies and therefore fewer ovulation cycles were compared to oocytes from virgin females. Live-cell imaging of chromosome dynamics revealed that repeated pregnancies substantially reduced the formation of chromosome bridges (which lead to segregation errors) in aged oocytes at meiosis I. Consistently, chromosomal abnormalities in meiosis II were also reduced.

A reduction in chromosomal abnormalities associated with reduced ovulation was confirmed in pre-pubertal mice models in which ovulation is suppressed without a pregnancy-like hormonal state.

The REC8–cohesin complex maintains the cohesion of bivalents, and its abundance decreases with age. Whereas REC8 was almost undetectable on chromosomes in oocytes from aged virgin females, it was more abundant on chromosomes in oocytes from aged mated females, suggesting that reduced ovulation protects against REC8 loss. Moreover, single-nucleus Hi-C analysis revealed that long-lived oocytes had larger chromatin loops formed by loop extrusion, indicative of a deterioration of 3D chromatin organization that might result from the loss of REC8.

Thus, preventing ovulation reduces the risk of egg aneuploidy in ageing female mice by reducing cohesion loss and possibly changes in chromatin organization. It will be interesting to study whether ovulation is linked with other factors that reduce egg aneuploidy, such as calorie restriction.



Credit: V. Summersby/Springer Nature Limited

Kim Baumann

ORIGINAL ARTICLE Chatzidaki, E. E. et al. Ovulation suppression protects against chromosomal abnormalities in mouse eggs at advanced maternal age. *Curr. Biol.* https://doi.org/10.1016/j.cub.2021.06.076 (2021)

RNA INTERFERENCE

Dicing viral RNA in stem cells

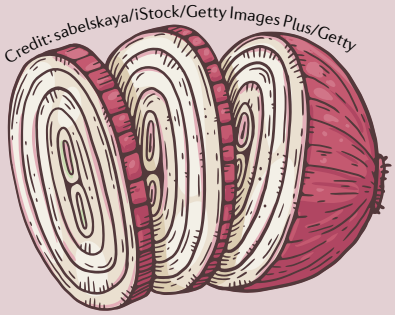
The innate immunity response to viral infection in mammalian cells relies on the expression of interferon-stimulated genes; notably, this response is limited in stem cells. Invertebrates and plants also lack antiviral interferon responses, instead relying on RNAi to combat RNA viruses. Poirier et al. now show that an isoform of the RNAi protein Dicer limits virus infection in mammalian stem cells.

Mammals encode one canonical Dicer, which is an RNase that processes precursor-microRNAs but has low capacity for processing double-stranded RNA (dsRNA) into siRNAs, as this activity is suppressed by its own helicase domain. The authors identified an alternatively spliced, in-frame transcript encoding a Dicer lacking part of its helicase domain, and found it is expressed in various mouse and human cells types. They named this isoform antiviral Dicer (aviD), as recombinant aviD produced about twice as much siRNA in vitro compared with recombinant Dicer.

> “an isoform of … Dicer limits virus infection in mammalian stem cells”

To test the relevance of aviD to viral infection, human embryonic kidney (HEK) cells lacking the *DICER* gene but complemented with either aviD or Dicer were infected with Sindbis virus or with Zika virus (ZIKV). Lower virus titres were observed in cells expressing aviD than in cells expressing Dicer or a catalytically deficient aviD. Furthermore, *DICER*-null HEK cells engineered to express the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry receptor ACE2, and expressing aviD, were three times less infected by SARS-CoV-2 than their Dicer-expressing counterparts.

In mice, aviD mRNA was expressed predominantly in various LGR5$^+$ or SOX2$^+$ stem cells, and in brain organoids, SOX2$^+$ neural stem cells expressed more aviD transcripts than differentiated cells. Upon ZIKV infection, wild-type brain organoids grew quicker and produced lower virus titres than



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Dicer$^{+/+}$aviD$^{-/-}$ organoids, despite their low level of endogenous aviD expression. In Dicer$^{+/+}$aviD$^{-/-}$ organoids, SOX2$^+$ stem cells displayed increased infection with ZIKV and accumulated more viral dsRNA and less viral siRNAs than in aviD-expressing organoids. Absence of aviD also promoted SARS-CoV-2 infection of ACE2$^+$ embryonic stem cell-derived brain organoids.

In summary, an aviD-mediated RNAi response helps protect mammalian stem cells against RNA virus infection.

Eytan Zlotorynski

ORIGINAL ARTICLE Poirier, E. Z. et al. An isoform of Dicer protects mammalian stem cells against multiple RNA viruses. *Science* **373**, 231–236 (2021)