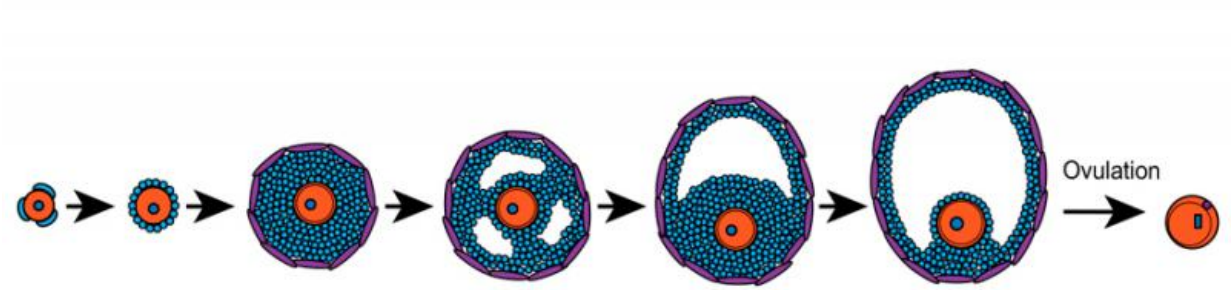
Packaging and unpacking of the genome

November 6 2015



DNA represents a dynamic form of information, balancing efficient storage and access requirements. Packaging approximately 1.8m of DNA into something as small as a cell nucleus is no mean feat, but unpacking it again to access the required sections and genes? That requires organisation.

In a nutshell, this is achieved through DNA condensed and packaged as chromatin, a complex of DNA and proteins called histones, which is constantly modified as the DNA is accessed. The histone proteins need constant replacement to maintain the correct chromatin structure required for all DNA related processes in the cell.

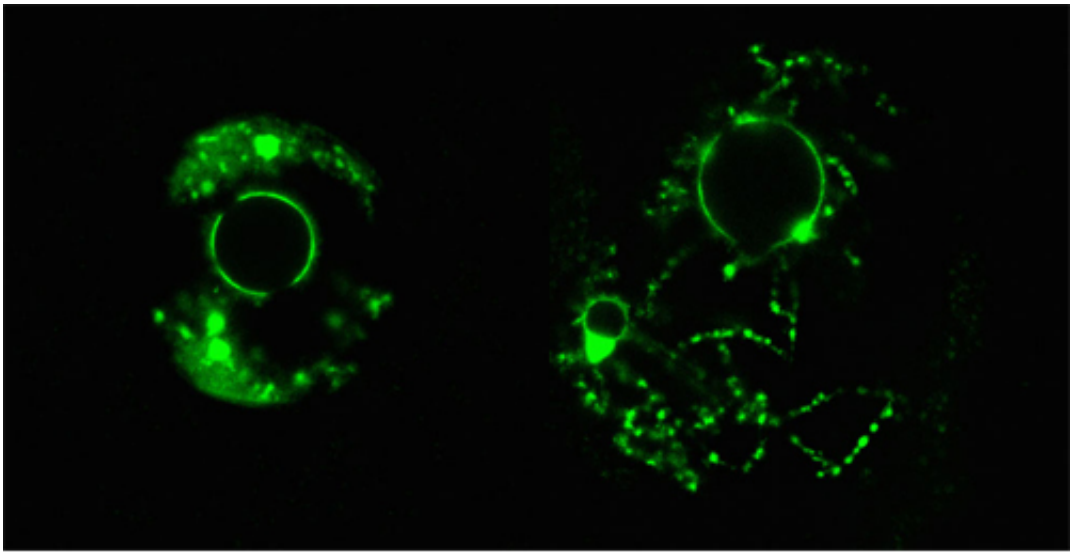
To understand more about the importance of histone replacement, researchers at the Babraham Institute and MRC Clinical Sciences Centre used developing mouse egg cells, oocytes. Developing oocytes provide a system where the mechanics of how DNA is packaged into cells can be explored in the absence of DNA replication, as egg cells do not divide. However, their genomes are highly active as the development of the egg involves widespread turning on and off of genes and DNA modification before the mature egg cell is ready for fertilisation. The work, published in the latest issue of *Molecular Cell*, relied on the Institute's expertise in single cell analysis, allowing accurate mapping of the epigenetic landscape in precious cells.

The researchers deleted a histone chaperone protein - one of a group of proteins that are responsible for replacing histones in the chromatin structure - and analysed the effects on egg cell development, DNA integrity and accumulation of DNA methylation.

"Oocytes lacking the Hira histone chaperone showed severe developmental defects which often led to cell death." said Dr Gavin Kelsey, research group leader in the Institute's Epigenetics programme and author on the paper. "The whole system is disrupted, eggs accumulate DNA damage and the altered chromatin means that genes cannot be efficiently silenced or activated. But we also uncovered an intricate relationship between the different epigenetic systems operating in the oocyte, where failure to ensure normal histone levels severely compromised deposition of methylation on the underlying DNA."

The research addresses the importance of histone turnover in maintaining genomic fidelity and adds to our understanding about the mechanisms in place to protect the integrity of the genome as it is remodelled and reshaped. Studying this in the context of the developing oocytes provides new insights into our dynamic genome, unclouded by the complications of DNA replication, and also reveals how important

maintaining chromatin dynamics is to the integrity of our gametes.



Hira deletion leads to increased DNA accessibility as shown by comparing the chromatin distribution in the two oocyes above. The cell on the left shows normal condensed chromatin (concentrated areas of green staining) whereas a cell that lacks Hira (right) shows dispersed chromatin. Credit: Buhe Nashun at the MRC Clinical Sciences Centre.

More information: Buhe Nashun et al. Continuous Histone Replacement by Hira Is Essential for Normal Transcriptional Regulation and De Novo DNA Methylation during Mouse Oogenesis, *Molecular Cell* (2015). DOI: 10.1016/j.molcel.2015.10.010

Provided by Babraham Institute