LMS researchers identify unexpected nucleolar mechanism for gene regulation in early embryo development

Researchers from the MRC London Institute of Medical Sciences (LMS) Chromatin and Development group have revealed an intriguing mechanism for gene regulation at the two-cell stage of embryo development.

Previous research has shown that a transposon or 'jumping gene' called MERVL is highly expressed in two-cell stage embryos and must be rapidly switched off for embryos to successfully grow beyond the two-cell stage. The expression of MERVL is known to be regulated by an upstream factor called Dux, but little is known about how Dux is regulated.

This is what the LMS Chromatin and Development research group sought to explore, and they made a surprising discovery. They found an organelle called the nucleolus is central to Dux repression.

"This surprised us as the nucleolus is more commonly associated with the production of ribosomal RNA, not gene regulation," said Dr Michelle Percharde, Head of the LMS Chromatin and Development research group.

"The way we were able to show that the nucleolus was key was by a combination of experiments, including directly disrupting nucleolar function, which we found rapidly re-activated Dux expression. We also found more repressive chromatin around the nucleolus after the two-cell stage, which we think is important for Dux repression".

The nucleolus is the largest organelle within the nucleus, which is where ribosomal RNA (rRNA) is made. It exists in the form of nucleolar precursor bodies at early stages following fertilization. Dr Percharde found that in cells resembling the two-cell embryo, the nucleolus was markedly more immature, compared to the blastocyst stage that follows. It lacked functionality, with a lower rRNA output, less repressive chromatin, and had a different shape.

In order to check whether the changes in nucleolus were linked to Dux *(*and therefore MERVL expression) the team manipulated the nucleolus of embryonic stem cells to inhibit their rRNA production. This led to the cells reverting back to a two-cell-like state thus confirming that maturation of the nucleolus was linked to repressing MERVL expression.

“We really weren’t expecting to find anything when we started looking at the nucleolus”, said Dr Percharde “but we’re glad we did take a look because it has opened it up as a really exciting area to study, not only for its role in early development, but potentially in disease and aging too.

“We enjoyed bringing together two areas of biology that we wouldn’t normally have thought of as being linked. It will now be important to see whether the gene regulation roles of the nucleolus are also disrupted in disease, as this might open up new therapeutic strategies.”

This paper was published in Genes and Development on 10 March 2022. You can read more about Dr Percharde’s work at the LMS here.