DNA discovery reveals a critical 'accordion effect' for switching off genes

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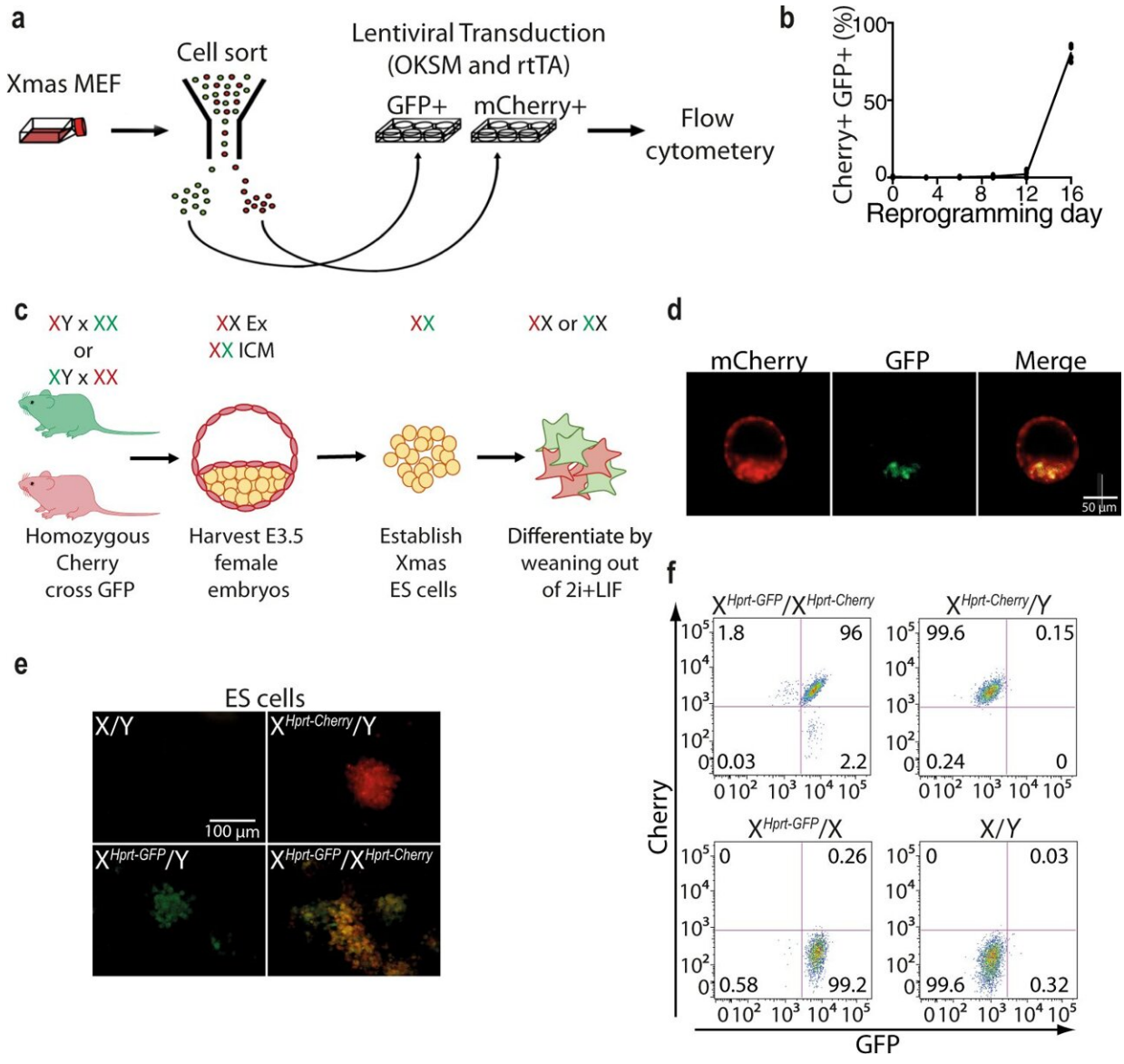

Xmas reporters allow detection of X chromosome expression in mESCs and

iPSCs. a Schematic showing the strategy for reprogramming and analysis of Xmas MEFs. b Flow cytometry data from primary female Xmas MEFs during the reprogramming process (n = 4 independent replicates). c Schematic of the breeding strategy to produce Xmas mESCs, their XCI status in vivo and during culture and differentiation in vitro. Extraembryonic (Ex), Inner Cell Mass (ICM). d Live fluorescent image of $X^{Hprt\text{-}GFP}/X^{Hprt\text{-}mCherry}$ Xmas female blastocysts. e Live fluorescent image of cultured mESCs from the indicated genotypes carrying different combinations of the fluorescent reporter alleles. Images shown are from a single experiment. f Flow cytometry of cultured mESCs from the indicated genotypes carrying different combinations of the fluorescent reporter alleles. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-29333-1

WEHI researchers have revealed how an "accordion effect" is critical to switching off genes, in a study that transforms the fundamentals of what we know about gene silencing.

The finding expands our understanding of how we switch genes on and off to make the different cell types in our bodies, as we develop in the womb.

It also offers a new way to potentially harness gene silencing in the future, to treat or reverse the progression of a broad range of diseases including cancer, congenital and infectious diseases.

Gene silencing is regulated by how tightly DNA is packed into a cell. The findings from a team led by Dr. Andrew Keniry and Professor Marnie Blewitt reveal a new accordion-like trigger that is crucial to the process.

The research is published in *Nature Communications*.

All in the DNA

The DNA that makes up our genetic material is wrapped tightly around proteins, like thread wraps around a spool. When it is loosely packaged the genes can be switched on; when it is tightly compacted, genes are switched off.

In the new study, the researchers found that to switch a gene off, the DNA packaging must initially loosen up, before then being tightly compressed.

Professor Marnie Blewitt said discovering the accordion-style trigger took the team by surprise, changing their fundamental understanding to date of this critical process.

"We were amazed to learn that the DNA first needs to relax, to trigger this process," she said. "Similar to how an accordion needs to open up before it is compressed to elicit a musical note, we found our DNA needs to be opened up first, before it can be compressed and the gene is silenced."

Silencing power

Dr. Andrew Keniry said gene silencing had amazing therapeutic potential.

"If we could learn exactly how to switch genes off, we may one day be able to switch off detrimental genes in a variety of diseases," Dr. Keniry said.

"If you could switch off the oncogenes that drive cancer, for example, you potentially could have a new treatment.

"To be able to realize this dream, we first need to know how the process happens so it can be mimicked with medicines, and our discovery is one more vital piece of this puzzle."

The fundamental mechanistic study was focused on efficiently searching for new factors involved in the gene silencing process.

To enable this, the team created a system they called "Xmas," based on red and green tags that are normally switched off during development. The system reported gene activity from each X chromosome through the expression of a red and green fluorescent protein, to reveal if the gene silencing process was occurring normally.

The study uncovered a new molecular mechanism of gene silencing, with the researchers pinpointing the protein complex required for this process, known as the BAF complex.

The next steps for the research will investigate why the accordion effect is required for gene silencing and the relevance of the process for genes on other chromosomes, such as the autosomes.

More information: Andrew Keniry et al, BAF complex-mediated chromatin relaxation is required for establishment of X chromosome inactivation, *Nature Communications* (2022). DOI: 10.1038/s41467-022-29333-1

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