The way genes are switched on in one-cell embryos may resemble the trigger for cancer

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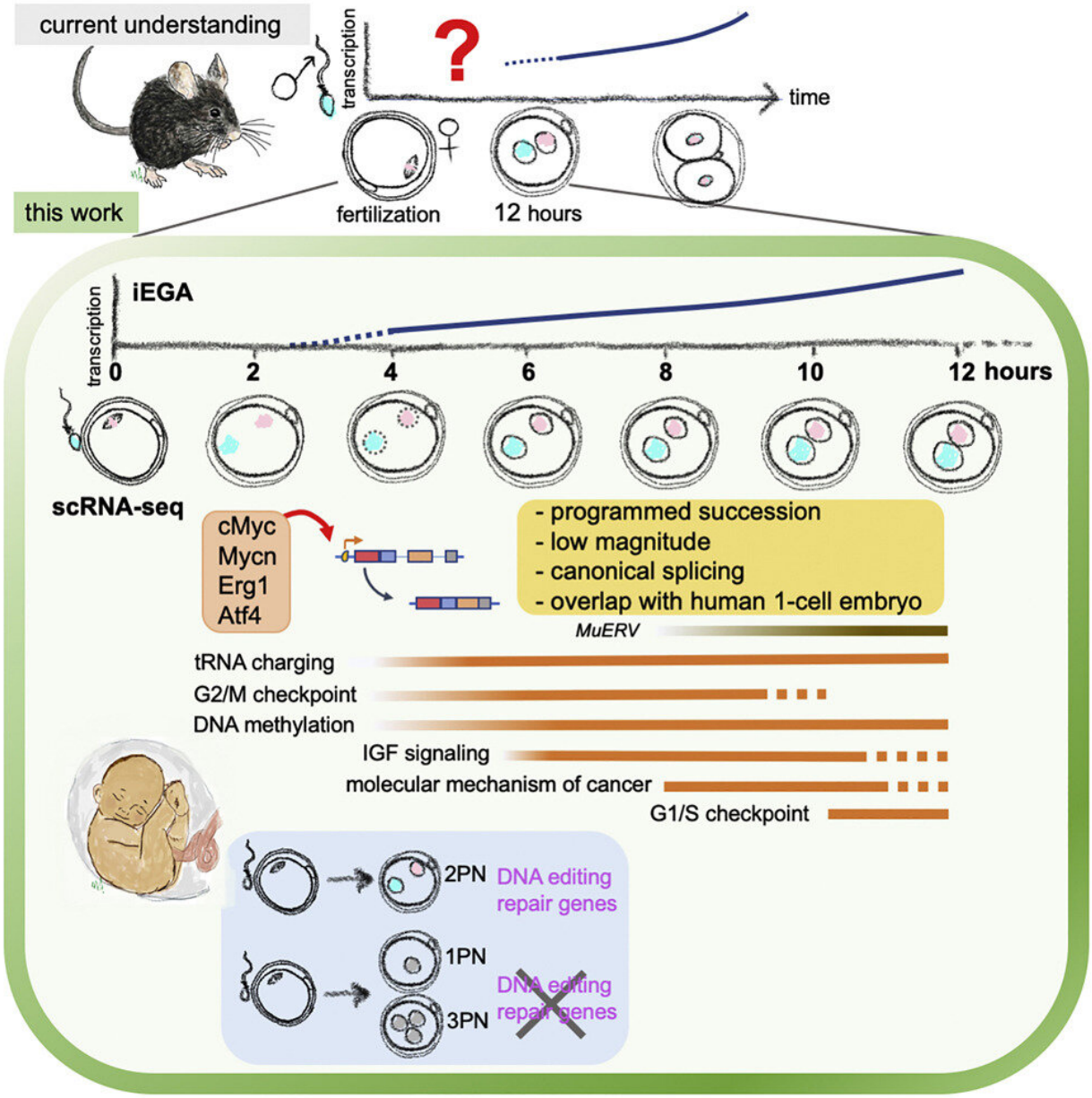

Graphical Abstract. Credit: *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.112023

When an embryo is formed, its genes—donated by a fertilizing sperm and egg—are silent. Somehow, at an early stage of development, embryo genes must be switched on. Without this vital 'genes on' switch in the embryo, none of us would be here, yet surprisingly little is known about what the switch looks like, or the identity of the 'molecular finger' that pushes the switch.

Thanks to research published today in *Cell Reports*, however, embryologists have now described the switch and can reveal the identity of the finger that pushes it. The study was a collaborative effort between biologists at the University of Bath, the University of Cambridge and colleagues in Germany and the US.

The team made their discovery in mice by combining a state-of-the-art method to inject sperm into eggs with the latest techniques in messenger RNA (mRNA) sequencing.

mRNA is the genetic 'middleman' that reads information from genes and delivers it to regions in the cell where proteins (the building blocks of life) are made. mRNA is produced in eggs before fertilization but also in embryos when the genome has been switched on: the researchers were able to differentiate between the two types and to characterize the embryo 'on' switch.

Their approach identified gene activity at precise times after fertilization in new embryos. It was found that in mouse embryos, the activity kicks off within four hours of sperm injection and follows a program: the genes aren't switched on willy-nilly, but in a pre-set order.

The team identified the sequence of gene activation in this pre-set order in one-cell embryos for the first time in any species—and showed that the functions of the active genes fit with features of early embryo development.

Scientists have previously worked out in many cases which 'molecular fingers' switch on which genes, and because of this, the authors of the new study were able to predict which fingers were responsible at the start of embryonic development: the fingerprints of some were on the embryo genes, allowing the culprit fingers to be identified.

In an extraordinary turn, this detective work showed that many of the trigger suspects are also associated with cancer.

"Many factors responsible for the dawn of gene activity in embryos have long been known to be major oncogenes," said Professor Tony Perry who led the research from the Department of Life Sciences at Bath. "Quite possibly, carcinogenesis recapitulates embryogenesis."

The team followed up on its detective work by showing that the suspected factors ('molecular fingers') are indeed present in one-cell embryos, which inherit them from eggs. When they prevented the factors from working by applying inhibitors that block their activity after fertilization, the embryos stopped developing almost immediately.

The researchers went further for one molecular finger—a cancer-associated factor called c-Myc. If c-Myc were actually responsible for switching on genes at the start of development, the group reasoned that inhibiting it should prevent the switch. That is exactly what they found: without c-Myc activity, many of the genes were not switched on, indicating that c-Myc is indeed a molecular finger that switches on embryo genes.

The group suggests c-Myc and other factors are dormant in eggs until they are themselves activated by fertilization. This work on mice overlaps with findings published recently by the researchers showing gene activity in human embryos also starts at the one-cell stage.

"Many genes switched on from the get-go in mouse and human one-cell embryos are counterparts," said Dr. Maki Asami, also from Bath and lead author of the work. "The involvement of the same oncogenic transcription factors is predicted in both species."

It therefore appears that this study's findings not only illuminate the mechanisms that regulate the start of mammalian development but also promise to set the scene for game-changing insights into processes that trigger cancer, which in the majority of cases are elusive and remain unknown.

"Our work could open a new clinical chapter for the early detection of cancer," said Professor Perry.

He added that he hoped to follow the leads provided by the team's detective work so that parallels between embryos and cancer could in the future be exploited to close gaps in our understanding of both.

More information: Maki Asami et al, A program of successive gene expression in mouse one-cell embryos, *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.112023

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