Gene-silencing complexes join forces to inactivate X chromosomes

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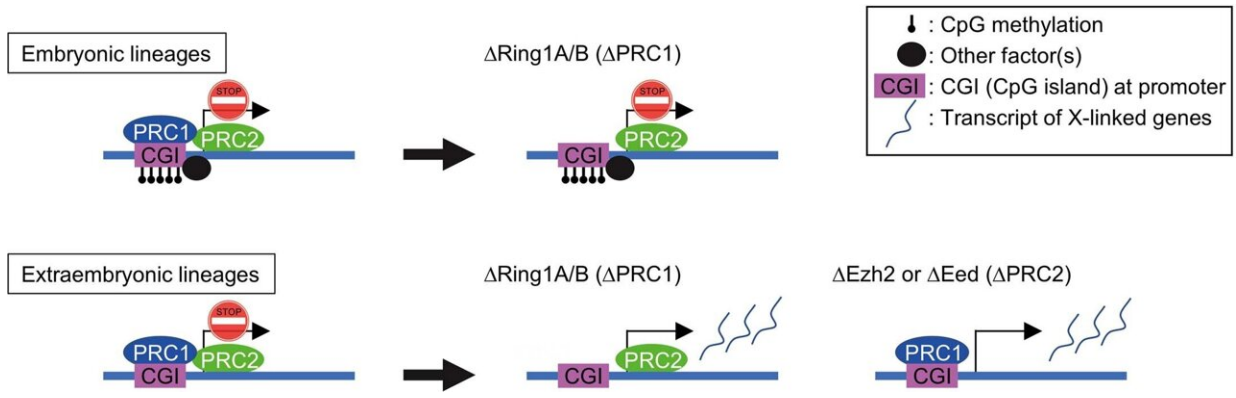

A model for the role of Polycomb complexes in the maintenance of XCI. (Left) X-linked genes in embryonic and extraembryonic lineages on the Xi are silenced by XCI. CGIs on the Xi are heavily methylated in embryonic lineages, but maintained as hypo-methylated in extraembryonic lineages. (Middle) Ring1A/B knockout resulted in a depletion of all PRC1 subcomplexes on the Xi, but PRC2 is still retained on the Xi, at least in extraembryonic lineages. In this situation, PRC2 accumulation on the Xi is retained at E7.5 but lost at E8.5 in embryonic lineages (here E7.5 is shown). (Right) Ezh2 or Eed knockout resulted in a depletion of PRC2 on the Xi, but PRC1 is still retained on the Xi, in extraembryonic lineages. (Middle and Right) In these situations, many of X-linked genes undergo robust reactivation from the Xi only in extraembryonic lineages. In embryonic lineages, however, X-linked genes are still silenced in the absence of PRC1 or PRC2. DNA methylation of CGIs and/or some other factor(s) might compensate a lack of PRC1 or PRC2 to secure a tight silencing of X-linked genes on the Xi in embryonic lineages. Credit: *Nature Cell Biology* (2023). DOI: 10.1038/s41556-022-01047-y

RIKEN researchers have shed new light on the roles two protein complexes play in the enigmatic process of turning off one X chromosome in female mammals. This finding could help researchers discover how certain cancers occur in women.

Males have one X chromosome and one Y chromosome, whereas females have a pair of X chromosomes. This redundancy of having two X chromosomes generally provides female mammals with extra robustness against genetic disorders and cancers compared with males.

During development, females employ a mechanism for turning off one of the X chromosomes, known as X-chromosome inactivation. When this process goes awry, women can develop major health problems such as breast cancer. A deeper understanding of proper X-chromosome inactivation could help to prevent or treat these types of tumor-fueling events in humans.

Now, by using mouse embryos, a team led by Haruhiko Koseki of the RIKEN Center for Integrative Medical Sciences (IMS) has shown how two protein clusters—known as polycomb repressive complex 1 (PRC1) and PRC2—serve independent and crucial roles in helping to keep one X chromosome in the developing embryo in a dormant state. The findings are published in the journal *Nature Cell Biology*.

Notably, the researchers found that only embryonic-support tissues rely on PRC1 and PRC2 to maintain gene silencing on the inactive X chromosome. In contrast, embryonic tissues themselves can keep the same chromosome in an idle position without using these epigenetic regulators, and thus must rely on some other molecular machinery to get the same job done.

"This study points out differential features of two major tissue lineages in developing embryos," says Osamu Masui, also of IMS.

The researchers pinpointed the functions of PRC1 and PRC2 by studying mice genetically engineered to lack one or the other protein complex. These experiments showed how each PRC changes the winding of DNA in different ways to each silence a unique set of genes on the inactive X chromosome.

Both complexes are needed for proper X-chromosome inactivation in extra-embryonic tissues that will form organs such as placenta. Yet both are also dispensable in the embryo tissue itself.

"This study clearly demonstrates that both PRC1 and PRC2 independently accumulate on the inactive X chromosome and differentially maintain X-linked gene silencing," says Masui. "This finding could contribute to our understanding of how female-specific tumors form."

The team is now trying to uncover the molecular mechanisms that allow embryonic tissues to tightly maintain X-chromosome inactivation. "These studies should help us further establish the fundamentals of gene regulation in the genome," says Masui.

More information: Osamu Masui et al, Polycomb repressive complexes 1 and 2 are each essential for maintenance of X inactivation in extra-embryonic lineages, *Nature Cell Biology* (2023). DOI: 10.1038/s41556-022-01047-y

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