Two proteins maintain embryonic stem cell pluripotency through different means

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Two 'finger-like' proteins employ different mechanisms to help safeguard the ability of embryonic stem cells to differentiate into a variety of cell types, according to an A*STAR-led study. This finding could help researchers develop new ways to regenerate lost or damaged tissue.

PRDMs are a family of 17 proteins with finger-like structures that contain zinc, which are involved in regulating gene expression and modifying the structure of chromatin, the material that forms chromosomes.

Ernesto Guccione, of A*STAR's Institute of Molecular and Cell Biology, and colleagues throughout Singapore investigated the roles of two PRDMs, PRDM14 and PRDM15, in mouse embryonic stem cell (ESC) development.

They found that both proteins were critical for ESC self-renewal—the process that maintains their "naïve state," allowing ESCs to perpetuate the stem cell pool and mature into any cell type—but that they did this through different mechanisms.

PRDM14 helps keep stem cells naïve by turning off a group of genes, called DNMTs, which code for a family of enzymes that add methyl groups to DNA. PRDM15, however, was not involved in DNA methylation.

The team found that PRDM15 conserved the naïve state of ESCs by turning on genes involved in regulating two signaling pathways that communicate how the cell should function.

"I found it interesting, from an evolutionary standpoint, that different members of the same family, which bind to completely distinct targets, have evolved to regulate similar pathways, in a non-redundant fashion, to prevent embryonic stem cell differentiation," says Guccione.

Previous studies had determined 'downstream' details of what happens within embryonic stem cells when three different signaling pathways are switched on and off, but much remained unknown about the 'upstream' factors, including those discussed in this study, that affect these pathways. Understanding these signaling pathways is important for determining optimal culturing conditions for mouse ESCs, understanding the cues that regulate normal embryonic development in living organisms, and finding ways to reprogram the body's cells to regenerate other tissue types.

Guccione and his colleagues are now collaborating with geneticists to investigate whether mutations in PRDM15 lead to developmental defects in humans. "We think our findings could be incorporated into the routine screening strategies for families showing developmental defects," he says.

More information: Slim Mzoughi et al. PRDM15 safeguards naive pluripotency by transcriptionally regulating WNT and MAPK–ERK signaling, *Nature Genetics* (2017). DOI: 10.1038/ng.3922

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