'Rejuvenation factor' Zscan4 is expressed in response to telomere shortening

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Scientists from the RIKEN Center for Developmental Biology (CDB) in Kobe, Japan, have discovered that Zscan4, a protein believed to be involved in the development of pluripotency in stem cells, is actually a repair mechanism triggered by the shortening of telomeres that takes place during cell division.

Zscan4, a protein that binds to DNA, has posed a mystery during the past decade, as it is expressed in mouse embryos at a very specific point of time—the two-cell stage—but is also expressed in embryonic stem cells, but only transiently, so that it is on in about 5 percent of a given population at a given time.

The group led by Hitoshi Niwa, head the Laboratory for Pluripotent Stem Cell Studies at CDB, wondered why the protein was expressed in these specific situations. To solve the mystery, they grew a population of mouse embryonic stem cells in culture and took snapshots of the cells at 60-minute intervals for an extended period, seeking clues for what might cause the transient expression of Zscan4.

Their initial working hypothesis was that Zscan4 is involved in the maintenance of pluripotency, so they looked its correlation with expression of the Rex1 gene, which is known as a marker of pluripotency. "Unexpectedly," says Yoko Nakai-Futatsugi, the first author of the study published in *Stem Cell Reports*, "we found that there was no correlation between the two."

"Instead," she continues, "We were surprised to find that the stem cells have different cell cycle lengths, and that intriguingly, the expression of Zscan4 is linked to the length of the cell cycle. It tends to be expressed in cells with longer cell cycles."

From this finding and considering the 2010 research showing that Zscan4 is involved in telomere elongations, the researchers speculated that the longer cell cycles we see may be caused by the process, triggered by Zscan4, of the cells performing work to lengthen their telomeres. They also found that once cells had expressed Zscan4, in the next generation they had shorter cell cycles, adding weight to the hypothesis that the cells slow their cycle in order to allow the recovery of telomeres, and then speed it up again when the repair is completed. They also found that the cells with longer cell cycles did in fact have shorter telomere. In a final test, they engineered stem cells that had a deficiency in Zscan4 expression and, in accordance with the hypothesis, those cells failed to recover from the longer cell cycles and had a higher chance of undergoing cell death.

The authors say they were surprised, but also very happy at this finding, as they feel it could help to ensure the safety of iPS cells, which are currently moving into clinical use. The work has helped them gain a new understanding of the function of Zscan4 and how pluripotent cells work to maintain their ability to replicate in the face of telomere shortening."

An interesting remaining question, they explain, is the relationship between Zscan4 and telomerase, an enzyme also involved in telomere repair. They speculate that they are responding to different causes of telomere shortening, and plan to continue work to elucidate this. They are also interested in the question of why Zscan4 is expressed in vivo at the single point of the two-cell stage. It might be, they feel, that it is helping the cells recover from the process of meiosis that the cells undergo before reproduction.

More information: *Stem Cell Reports*, dx.doi.org/10.1016/j.stemcr.2016.02.010

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