Embryonic stem cells go against aging

The dream of regenerative medicine is now becoming true by the usage of versatile stem cells that are capable of differentiating into all types of cells in the body. This capability is called ‘pluripotency’ and there are two kinds of pluripotent stem cells: embryonic stem (ES) cells derived from embryos, and induced pluripotent stem (iPS) cells artificially induced from somatic cells. Both can be differentiated into a desired cell type while remaining undifferentiated and replicate indefinitely under certain condition.

Why they are able to replicate indefinitely was a long lasting question. Generally, when cells divide, the edge of the genomic DNA called ‘telomere’ becomes short. When the telomeres become too short, the cells stop dividing, which is considered as ‘aging’ of the cells. It is known that germ cells, stem cells and cancer cells express an enzyme called telomerase to elongate the telomeres and overcome aging. In addition, it was recently found that ES cells express a molecule called Zscan4 that elongates the telomeres. Despite this important role, the expression pattern of Zscan4 has been a mystery – it is expressed transiently only in 5% of a given population at a given time.

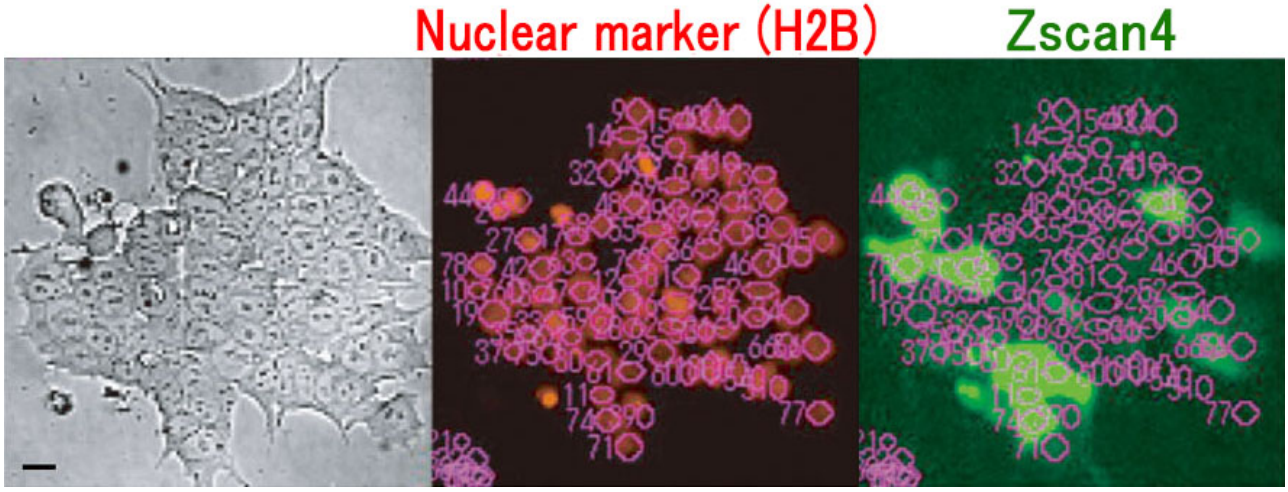

Fig. 1. Cell tracking under the microscope. Using nuclear marker H2B (middle, red) as a reference marking individual cells, expression level of Zscan4 (right, green) was measured. Pink circles and numbers are the marks of cell tracking. (modified from Nakai-Futatsugi and Niwa, Stem Cell Reports, 2016 doi: 10.1016/j.stemcr.2016.02.010)

To elucidate when, under what circumstances, this important molecule is expressed, we made an ES cell that turns green when Zscan4 is expressed (Fig. 1). We tracked each of this ES cell under the microscope for 120 hours. First thing we noticed was the time for each cell to divide, which is thought to be around 12 hours in ES cells, was much diverse than expected (Fig. 2A, green numbers). Then we found when Zscan4 was expressed the cell cycle lengths tended to become

long (Fig. 2B). Considering the role of Zscan4 in telomere elongation, we thought the extended cell cycle length accompanied by Zscan4 expression might be the time taken for telomere repair. In fact, ES cells with longer cell cycles did have shorter telomeres that may be waiting for repair. If Zscan4 is expressed to repair the shortened telomeres, and if the time for repair after Zscan4 expression made the cell cycles longer, would the next cell cycle after Zscan4 expression return short? The answer was yes. After transient expression of Zscan4, the next cell cycle tended to become short (Fig. 2C).

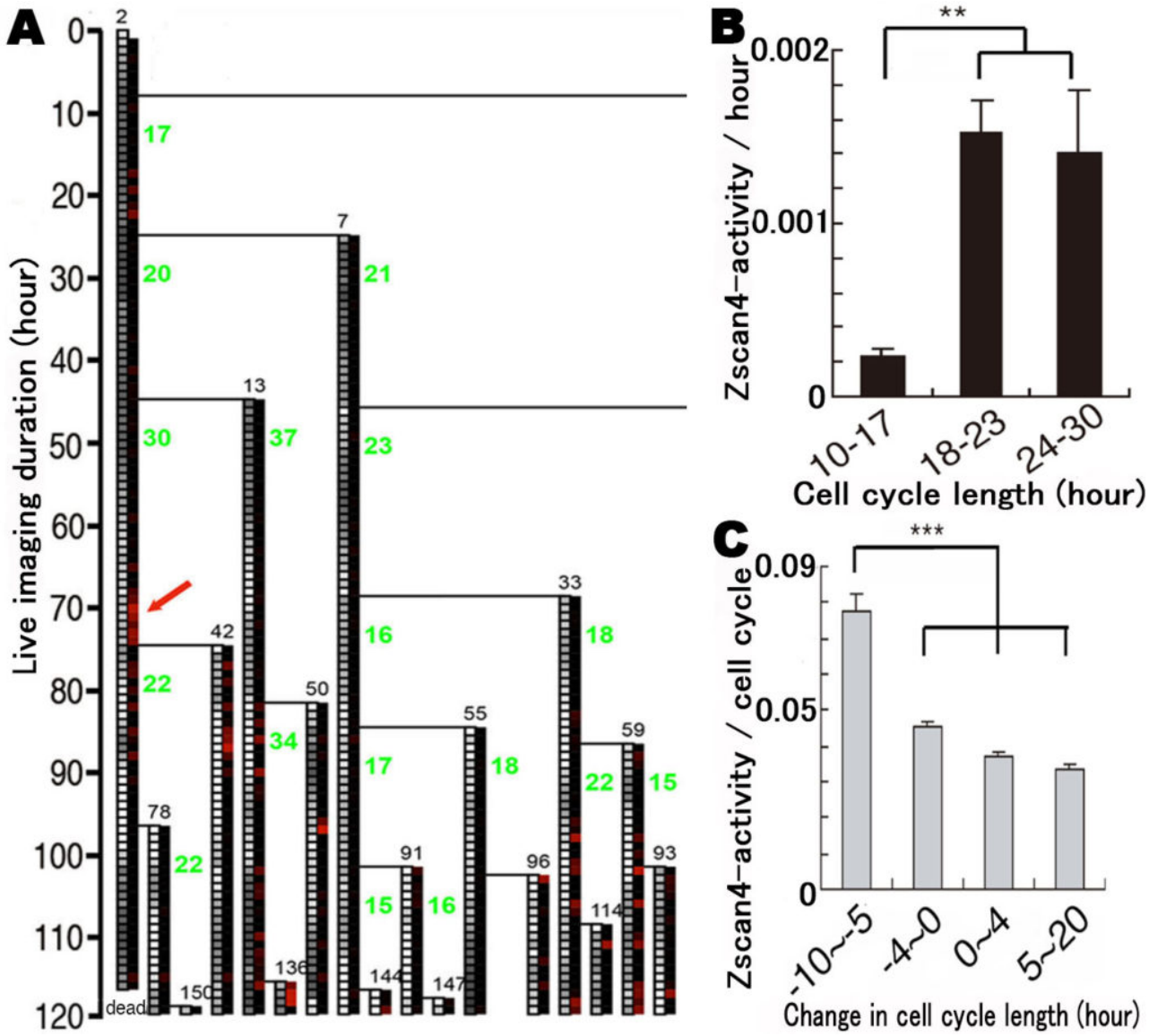

Fig. 2. A) Results of cell tracking was converted to lineage trees that show the fate of each cell. Cells were sequentially numbered in the order they emerged (small black numbers). Numbers in green indicate cell cycle length (hours). Zscan4 expression level is indicated by red intensity scale. Cells expressed Zscan4 transiently (red arrow). B) The expression level of Zscan4 was analyzed against the cell cycle length. When the expression level of Zscan4 was high, the cell cycle lengths

tended to be long. C) The expression level of Zscan4 was analyzed against how much the cell cycle length changed at the next cell cycle. When the expression level of Zscan4 was high, the next round of cell cycle tended to be shorter. (modified from Nakai-Futatsugi and Niwa, Stem Cell Reports, 2016 doi: 10.1016/j.stemcr.2016.02.010)

During mammalian development, Zscan4 is expressed at a very specific period before birth – at the two cell stage, which comes right after the most first cell division. Because of its expression at a very early stage, Zcsan4 is sometimes considered as a hallmark of higher potential of differentiation. However, when we looked at the expression of Zscan4 together with a pluripotency marker gene *Rex1*, there was no correlation.

Our results uncovered the mystery when and why Zscan4 is expressed – it is expressed presumably sensing shortened telomeres for the repair, irrespective of pluripotency. We hope the results of this study, revealing the underlying mechanisms for ES/iPS cell maintenance, will contribute to the progress of regenerative medicine.

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