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ZSCAN10 expression corrects the genomic instability of iPSC from aged donors by controlling redox status

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Induced pluripotent stem cells (iPSC) can be used to produce transplantable tissues. However, iPSC generated from aged donors (A-iPSC) exhibit higher genomic instability, defects in apoptosis, and a blunted DNA damage response compared to iPSC generated from younger donors (Y-iPSC). We defined the underlying mechanism as a homeostatic imbalance between reactive oxygen species (ROS) and glutathione (a ROS scavenging metabolite). Excessive glutathione activity can blunt the normal DNA damage response signalling pathway, allowing cells with genomic mutations to persist that otherwise would have been eliminated by apoptosis. We found that the pluripotent specific factor, ZSCAN10, was poorly expressed in A-iPSC, and ZSCAN10 expression allows the establishment of A-iPSC without the negative effects of aging. We found that A-iPSC have a higher level of glutathione due to excessive expression of glutathione synthetase (GSS), which causes an imbalance of ROS and glutathione. ZSCAN10 directly binds the GSS promoter to suppress GSS expression. We also found that ZSCAN10 not only controls GSS expression (to determine the total quantity of glutathione) but also glutathione peroxidase (GPX2), which suppresses the excessive catalytic activity of glutathione by controlling its transition from an oxidized inactive form to a reduced active form. We found that GPX2 is controlled by the exosome-mediated RNA degradation pathway and that ZSCAN10 expression induces RNA exosome complex expression. We found the third mechanism that ZSCAN10 controls activity of pluripotent stem cell-specific glucose transporter 3 (GLUT3) and facilitates a shift in carbon source metabolism that suppresses oxidative phosphorylation and limits ROS production, consequently providing a selective advantage for cells with elevated glutathione during reprogramming to maintain the ROS-glutathione balance. Correcting the genomic instability of A-iPSC may particularly benefit older patients who are more likely to suffer from degenerative diseases with safer transplantable tissues.

Biography

Kitai Kim has completed his PhD from the Univerity of Wisconsin at Madison, and Post-doctoral studies from Childrens Hospital Boston, Harvard Medical School. He is a faculty of the Memorial Sloan-Kettering Cancer Center, affiliated with Weill Medical College of Cornell University. He has reported major publications in stem cell field including histocompatible parthenogenetic ES cells, tissue-specific epigenetic memory of iPS cells, and biological significance of redox control by ZSCAN10.

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