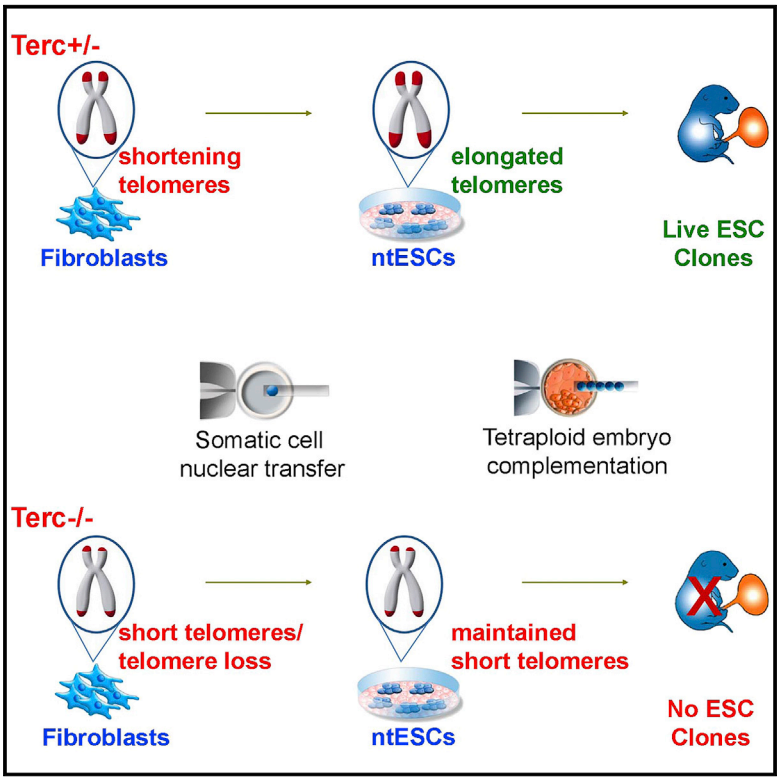
Report

Cell Reports

Telomere Elongation and Naive Pluripotent Stem Cells Achieved from Telomerase Haplo-Insufficient Cells by Somatic Cell Nuclear Transfer

Graphical Abstract



Highlights

Mouse ntESCs can be efficiently derived from telomerase-defective cells by SCNT

Terc$^{+/-}$ ntESCs support full-term development by tetraploid complementation assay

Telomeres of *Terc*$^{+/-}$ mouse cells are effectively elongated in the derived ntESCs

Telomere lengths are important for naive pluripotency of mouse ntESCs

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In Brief

Sung et al. demonstrate in a mouse model that telomeres of telomerase haplo-insufficient cells can be elongated by somatic cell nuclear transfer. Moreover, ntESCs derived from *Terc*$^{+/-}$ cells exhibit pluripotency evidenced by generation of *Terc*$^{+/-}$ntESC clone pups by tetraploid embryo complementation, the most stringent test of naive pluripotency.

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Report

Telomere Elongation and Naive Pluripotent Stem Cells Achieved from Telomerase Haplo-Insufficient Cells by Somatic Cell Nuclear Transfer

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SUMMARY

Haplo-insufficiency of telomerase genes in humans leads to telomere syndromes such as dyskeratosis congenital and idiopathic pulmonary fibrosis. Generation of pluripotent stem cells from telomerase haplo-insufficient donor cells would provide unique opportunities toward the realization of patient-specific stem cell therapies. Recently, pluripotent human embryonic stem cells (ntESCs) have been efficiently achieved by somatic cell nuclear transfer (SCNT). We tested the hypothesis that SCNT could effectively elongate shortening telomeres of telomerase haplo-insufficient cells in the ntESCs with relevant mouse models. Indeed, telomeres of telomerase haplo-insufficient (*Terc*$^{+/-}$) mouse cells are elongated in ntESCs. Moreover, ntESCs derived from *Terc*$^{+/-}$ cells exhibit naive pluripotency as evidenced by generation of *Terc*$^{+/-}$ ntESC clone pups by tetraploid embryo complementation, the most stringent test of naive pluripotency. These data suggest that SCNT could offer a powerful tool to reprogram telomeres and to discover the factors for robust restoration of telomeres and pluripotency of telomerase haplo-insufficient somatic cells.

INTRODUCTION

Mammalian telomere lengths are primarily regulated by telomerase, consisting of a reverse transcriptase protein (TERT), a RNA subunit (TERC), and stabilizing proteins including dyskerin, in a temporally and spatially dependent manner (Günes and Rudolph, 2013). Telomerase activity is high during early embryo development, but becomes undetectable in most adult cells in humans. Mutations of genes that encode telomerase components, *TERT*, *TERC*, or *DKC1*, cause premature aging and age-related diseases, including aplastic anemia, dyskeratosis congenital, and idiopathic pulmonary fibrosis, collectively referred to as "telomere syndromes" to reflect the short and dysfunctional telomeres commonly found in these patients' cells (Armanios and Blackburn, 2012). Heterozygous mutations of TERT and TERC represent major mutations in genetically defined telomere syndromes. Mutations of telomerase components are also associated with decreased fertility in both animals and humans (Herrera et al., 1999; Yan et al., 2014).

Stem cell failure in highly proliferative tissues, such as hematopoietic stem cells, due to progressive telomere loss caused by insufficient telomerase activity is considered as an important therapeutic target for telomere syndromes (Armanios and Blackburn, 2012). Indeed, allogeneic stem cell transplantation can reverse the aplastic anemia phenotype (Armanios and Blackburn, 2012; Young et al., 2006). However, it has been a challenge to establish patient-specific induced pluripotent stem (iPS) cells with proper restoration of telomere defects using donor cells from patients with telomere syndrome (Batista et al., 2011; Winkler et al., 2013).

Efficient generation of human pluripotent embryonic stem cells (ntESCs) with somatic cell nuclear transfer (SCNT) using oocyte factors represents a major advancement toward the realization of patient-specific cell therapies (Chung et al., 2014; Tachibana et al., 2013; Yamada et al., 2014). Mouse ntESCs are transcriptionally and functionally indistinguishable from ESCs generated from fertilized embryos (Brambrink et al., 2006;