Short telomeres impede germ cell specification by upregulating MAPK and TGFβ signaling

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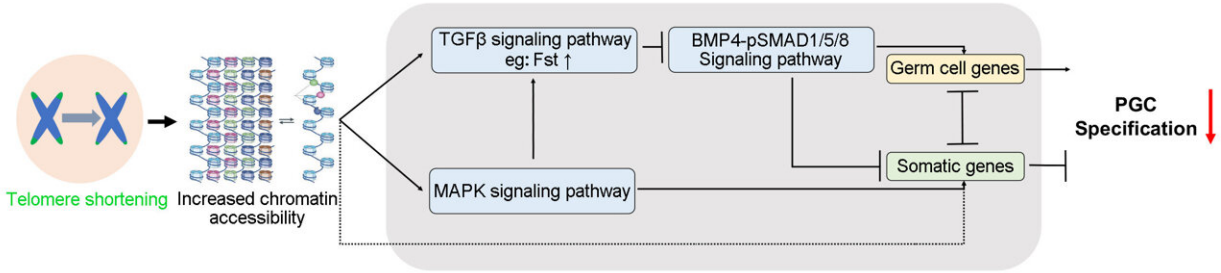

Short telomere promotes excessive chromatin accessibility locally, upregulating TGFβ and MAPK signaling. TGFβ signaling pathways such as Fst inhibit BMP4-pSMAD1/5/8 signaling pathway, induce somatic cell lineage and suppress germ cell specification. MAPK signaling also induces somatic cell lineage. Upregulation of somatic genes and downregulation of germ cell genes impair PGC specification both in vivo and in vitro. Credit: Science China Press

Functional telomeres protect chromosome ends and play essential roles in stem cell maintenance and differentiation. Over the past decade, telomeres have attracted increasing attention due to their role in fertility. Short telomeres negatively impact germ cell development and can contribute to age-associated infertility.

Moreover, telomere syndrome resulting from mutations of telomerase or

telomere-associated genes exhibits short telomeres and reduced fertility. However, it remains elusive whether and how telomere lengths affect germ cell specification.

In this work, the scientists in the Stem Cell and Developmental Biology lab at Nankai University (supervised by Prof. Lin Liu) report that the functional telomere is required for the coordinated germ cell and somatic cell fate decisions. They use telomerase gene Terc deficient mice as a model to show that short telomeres restrain germ cell specification of epiblast cells but promote differentiation towards somatic lineage.

Germ cell specification is a counteractive process to somatic differentiation during early embryonic development. Using ATAC-sequence and RNA-sequence analysis, they defined that short telomeres increase chromatin accessibility to elevate TGFβ and MAPK/ERK signaling for somatic cell differentiation.

Notably, elevated Fst expression in the TGFβ pathway represses the BMP4-pSmad signaling pathway, thus reducing germ cell formation. Importantly, re-elongation of telomeres by targeted knock-in of Terc restores normal chromatin accessibility to suppress TGFβ and MAPK signaling, thereby facilitating germ cell formation. Taken together, their data reveal that functional telomeres are required for germ cell specification by repressing TGFβ and MAPK signaling.

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