

P036 Different mechanisms of DNA damage checkpoint induction in response to telomere dysfunction in adult stem cells compared to fibroblasts
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Telomere dysfunction in telomerase knockout mice (*Terc*^{-/-}) leads to depletion of stem and progenitor cells in different organ compartments including hematopoietic system and intestinal epithelium. Chk2 is a downstream target of ATM leading to p53 activation in response to DNA double strand breaks. Here we crossed Chk2^{-/-} mice with *Terc*^{-/-} mice to analyze the *in vivo* role of Chk2 in response to telomere dysfunction. Our study shows that Chk2 deletion does not rescue stem cell function, organ maintenance, and lifespan of iG4*Terc*^{-/-} mice with dysfunctional telomeres. iG4*Terc*^{-/-} mice showed increased expression of activated (phosphorylated) Chk2, which was not detectable in *Terc*^{+/+} mice. Immunohistochemistry staining showed nuclear localization of phospho-Chk2 in senescent human fibroblasts. However, expression of phospho-Chk2 in iG4*Terc*^{-/-} mice was restricted to the cytoplasm of intestinal stem and progenitor cells and nuclear expression was only detected in terminal differentiated epithelial cells. In correlation with the cytoplasmic localization, Chk2 deletion did not rescue the induction of DNA damage signals and checkpoints in intestinal stem and progenitor cells of iG4*Terc*^{-/-} mice. Our study suggests that Chk2 is dispensable for checkpoint induction in adult stem and progenitor cells harboring telomere dysfunction. Together, this study provides first experimental evidence for differences in DNA damage checkpoint induction in response to telomere dysfunction in adult stem and progenitor cells compared to fibroblasts.