

**P038** TRP53 protects against accumulation of damaged cells and organ dysfunction in telomere dysfunctional mice  
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It is known that the deletion of components of the DNA-damage signaling pathway can rescue the maintenance and the function of stem cells in aging telomere dysfunctional mice. The p53 protein is activated by ATM/ATR in response to DNA damage leading to induction of apoptosis or p21-dependent cell cycle arrest. Depletion of intestinal stem cells and atrophy of the intestinal epithelium represent major phenotypes in aging telomere dysfunctional mice. To analyze the *in vivo* role of p53 in this context  $TERC^{-/-}$  mice were crossed conditional, intestine-specific TRP53-knock out mice. Our study shows that intestinal deletion of TRP53 did not induce an obvious intestinal phenotype of aging  $TERC^{+/-}$  until 12 months. In contrast TRP53 deletion significantly shortened the lifespan of  $TERC^{-/-}$  TRP53 $^{-/-}$  animals (mean lifespan: 8 months) compared to  $TERC^{-/-}$  TRP53 $^{+/+}$  (mean lifespan: 9,5 months,  $p=0,0002$ ). This reduction correlated with earlier appearance of crypt atrophy and weight loss but was not associated with cancer formation. Deletion of the TRP53 gene resulted in accumulation of DNA damage and increase in apoptosis in the intestine of telomere dysfunctional mice. Gene expression analysis revealed an increase in inflammatory signalling in the intestinal compartment of  $TERC^{-/-}$  TRP53 $^{-/-}$  compared to  $TERC^{-/-}$  TRP53 $^{+/+}$  mice. Our results provide first experimental evidence that p53 induction has a protective function preventing accumulation of damaged cells and organ degeneration induced by aging in the context of telomere dysfunction.