Cagatay Günes et al., Madridge J Cancer Stud Res. 2016
http://dx.doi.org/10.18689/2640-5180.a1.004

madridge CONFERENCES

International
Cancer Study & Therapy Conference

April 4-6, 2016 Baltimore, USA

Telomerase sensitizes mammalian cells to aneuploidy-induced transformation by alleviating telomere replication stress

Cagatay Günes[1,4]*, Jitendra K Meena[1], Johann M Kraus[2], Sarah-Fee Katz[3], Andre Lechel[3], Hans A Kestler[1,2] and **Karl L Rudolph[1]**
[1]Leibniz Institute of Age Research, Fritz Lipmann Institute, Germany
[2]Institute of Neural Information Processing, Ulm University, Germany
[3]Department of Gastroenterology, Ulm University, Germany
[4]Department of Urology, Ulm University, Germany

In humans and mice, most autosomal monosomies and trisomies are not compatible with organismal survival. It was shown that aneuploidy impairs cellular proliferation, survival, and spontaneous immortalization. In contrast, aneuploidy is a hallmark of cancer cells indicating that aneuploidy survival mechanisms must exist in cancer cells. We used a genome-wide, stable iRNA screening and identified a large set of gene knockdowns with a novel role in aneuploidy induction strongly associating with recurrent gene mutations in human cancers. In mouse hematopoietic stem cells in vivo and in primary human cell cultures, aneuploidy inducing gene knockdowns result in telomere replication stress, premature senescence, or stem cell depletion. These aneuploidy-induced checkpoints were abrogated by endogenous expression of telomerase in stem cells and by up-regulating telomerase in primary human cells. We show, that aneuploidy inducing gene knockdowns replace the requirement of iatrogenic introduction of oncogenic Ras for the malignant transformation of human cells. Current studies focus on elucidating the mechanisms that induce telomere replication stress in response to aneuploidy and the mechanism how telomerase suppresses aneuploidy-induced senescence.