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Meeting abstract

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Nuclear Shp-2 keeps telomerase reverse transcriptase in the nucleus – new potential anti-aging target

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Vascular diseases are associated with cellular aging, which is accompanied by telomere shortening counteracted in the nucleus by telomerase reverse transcriptase (TERT). Under conditions of oxidative stress TERT is exported from the nucleus and this export is mediated by Src-kinases via tyrosine phosphorylation of TERT. Nuclear export of TERT resulted in accelerated aging of endothelial cells. Therefore, the aim of this study was to determine a counterplayer for nuclear export of TERT.

In embryonic fibroblasts deficient in Src, Fyn and Yes, TERT nuclear export induced by oxidative stress is abolished. Fyn does not seem to play a role, because unlike Src and Yes it is not found in the nucleus. A putative regulator of this export is the tyrosine phosphatase Shp-2, which can regulate the activity of the Src-kinase family. We demonstrated that Shp-2 is localized in the nucleus and associated with TERT in endothelial cells. Overexpression of Shp-2 inhibited oxidative stress induced nuclear export of TERT and ablation of Shp-2 by siRNA reduced nuclear telomerase activity. This inhibition was dependent on the enzymatic activity of Shp-2 and on tyrosine 707 in TERT because overexpression of the dominant negative Shp-2 mutant (C459S) led to a reduction of TERT protein and telomerase activity, whereas telomerase activity in TERTY707F overexpressing cells was not altered by Shp-2. Thus, tyrosine 707 seems to be a critical target for regulation of TERT localization by Shp-2 mediated dephosphorylation. To establish a causal link between Shp-2, nuclear TERT and oxidative stress, we determined reactive oxygen species (ROS) formation in endothelial cells. Overexpression of Shp-2(C459S) (2.45 fold +/- 0.34 of Shp-2 wt) or ablation of Shp-2 by siRNA increased ROS levels (2.23 fold +/- 0.54 of scrambled siRNA). In contrast, keeping TERT in the nucleus by mutating tyrosine 707 or overexpressing Shp-2 wt reduced ROS formation (0.73 and 0.75 fold, respectively).

In summary, these data indicate that TERT is associated with nuclear Shp-2, Shp-2 acts as a negative regulator for nuclear export of TERT probably via regulating tyrosine 707 dephosphorylation of TERT and reducing ROS formation. Thus, increasing nuclear Shp-2 activity could be a useful tool to delay vascular aging processes.