Cell Communication and Signaling BioMed Central

Meeting abstract

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Nuclear-mitochondrial crosstalk – role in aging processes

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from 12th Joint Meeting of the Signal Transduction Society (STS). Signal Transduction: Receptors, Mediators and Genes
Weimar, Germany. 29–31 October 2008

Published: 26 February 2009

Cell Communication and Signaling 2009, **7**(Suppl 1):A54 doi:10.1186/1478-811X-7-S1-A54

This abstract is available from: http://www.biosignaling.com/content/7/S1/A54

Numerous diseases share common pathways with aging processes. Therefore, it is important to understand the mechanisms of aging and senescence on a cellular level. Environmental stressors such as sun light and diet are known to induce oxidative stress and advance aging processes. Mitochondrial and nuclear dysfunction and increased oxidative stress contribute to the onset of replicative senescence. We investigated several proteins, which are known to play a role in aging processes: telomerase reverse transcriptase (TERT), matrix metalloproteinase 1 (MMP1) and grainyhead like 3 (GRHL3). TERT is exported from the nucleus under conditions of oxidative stress and replicative senescence. The Src-kinase family via phosphorylation of TERT mediates this export. We identified the tyrosine phosphatase Shp-2 as a negative regulator of this export. Overexpression of Shp2 inhibited nuclear export of TERT. This inhibition was dependent on the catalytic activity of Shp2. Ablation of Shp2 increased tyrosine phosphorylation of nuclear TERT and subsequently led to loss of nuclear telomerase activity. Recently, we also discovered TERT in the mitochondria. There, TERT binds to mitochondrial DNA and protects it against UV light induced damage. TERT also reduced ethidium bromide-induced mitochondrial DNA damage. Mitochondrially targeted TERT, but not nuclear targeted TERT revealed the most prominent protective effect on H2O2-induced apoptosis. Mitochondria isolated from hearts of second generation TERT knock-out mice showed reduced respiration demonstrating for the first time a heart phenotype of these mice. A central mechanism in exogenous skin aging is the increased proteolytic degeneration of dermal matrix fibers of connective tissue due to increased MMP1 activity. UVA, UVB and IRA irradiation induced MMP1 expression and activity. After IRA-irradiation reactive oxygen species are generated from the mitochondrial respiratory chain leading to increased MMP-1. The gene regulatory potential of IRA was assessed by microarray analysis. Cluster analysis suggested additional pathways to be involved, e.g. Calcium- and mTOR-signalling. TNFa is increased in serum of CAD patients, induces senescence and apoptosis of endothelial cells and decreases their migratory capacity. Recently, we discovered the transcription factor GRHL3 as a TNFa regulated gene. GRHL3 deficient mice show defects in cell migration. Therefore, we investigated the role of GRHL3 in endothelial cell migration. Overexpression of GRHL3 increased endothelial nitric oxide synthase activity and cell migration. Moreover, nitric oxide increased endogenous levels of GRHL3, suggesting a positive feedback loop of nitric oxide on GRHL3. Thus, GRHL3 plays an important role in the increase of nitric oxide bioavailability and could therefore serve as a new anti-aging therapeutic. In conclusion, we identified intracellular mechanisms, which regulate three important candidate proteins in aging processes.