

# Abstract

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## Chronic oxidative stress compromises telomere integrity and accelerates the onset of senescence in human endothelial cells.

Kurz DJ, Decary S, Hong Y, Trivier E, Akhmedov A, Erusalimsky JD.

Department of Medicine, University College London, 5 University Street, London, WC1E 6JF, UK.

**BACKGROUND:** Replicative senescence and oxidative stress have been implicated in ageing, endothelial dysfunction and atherosclerosis. Replicative senescence is determined primarily by telomere integrity. In endothelial cells the glutathione redox-cycle plays a predominant role in the detoxification of peroxides.

**OBJECTIVE:** The aim of this study was to elucidate the role of the glutathione-dependent antioxidant system on the replicative capacity and telomere dynamics of cultured endothelial cells.

**METHODS:** Human umbilical vein endothelial cells were serially passaged while exposed to regular treatment with 0.1 microM tert-butyl hydroperoxide, a substrate of glutathione peroxidase, or 10 microM L-buthionine-[S,R]-sulphoximine, an inhibitor of glutathione synthesis.

**RESULTS:** Both treatments induced intracellular oxidative stress but had no cytotoxic or cytostatic effects. Nonetheless, treated cultures entered senescence prematurely (30 versus 46 population doublings), as determined by senescence-associated beta-galactosidase staining and a sharp decrease in cell density at confluence. In cultures subjected to oxidative stress terminal restriction fragment (TRF) analysis demonstrated faster telomere shortening (110 versus 55 bp/population doubling) and the appearance of distinct, long TRFs after more than 15-20 population doublings. Fluorescence in situ hybridisation analysis of metaphase spreads confirmed the presence of increased telomere length heterogeneity, and ruled out telomeric end-to-end fusions as the source of the long TRFs. The latter was also confirmed by Bal31 digestion of genomic DNA. Similarly, upregulation of telomerase could not account for the appearance of long TRFs, as oxidative stress induced a rapid and sustained decrease in this activity.

**CONCLUSION:** These findings demonstrate a key role for glutathione-dependent redox homeostasis in the preservation of telomere function in endothelial cells and suggest that loss of telomere integrity is a major trigger for the onset of premature senescence under mild chronic oxidative stress.

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