

# Abstract

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## **Statins enhance migratory capacity by upregulation of the telomere repeat-binding factor TRF2 in endothelial progenitor cells.**

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**BACKGROUND:** Cultivation of endothelial progenitor cells (EPCs) leads to premature replicative senescence, limiting ex vivo expansion for potential clinical cell therapy. Recent studies have linked senescence to the dysfunction of telomeres, the "ends" of chromosomes, via the so-called mitotic clock or culture-induced stress. The purpose of this study was to elucidate a possible role of telomere biology in the functional augmentation of EPCs by statins.

**METHODS AND RESULTS:** Human EPCs were isolated from peripheral blood. Using flow cytometry after fluorescence in situ hybridization with a telomere-specific (C3TA<sub>2</sub>)<sub>3</sub> peptide nucleic acid probe (Flow-FISH), we found mean telomere length in untreated EPCs from healthy subjects to range between 8.5±0.2 and 11.1±0.5 kb with no change over 6 days of culture, excluding telomere erosion as one cause for premature senescence. Although mean telomere length did not differ between statin-treated and untreated EPCs, atorvastatin (0.1 micromol/L) and mevastatin (1.0 micromol/L) both led to a more than 3-fold increase in the expression of the telomere capping protein TRF2 (telomere repeat-binding factor), as shown by immunoblotting, whereas quantitative reverse transcription-polymerase chain reaction demonstrated no increase in TRF2 mRNA. Telomere dysfunction of EPCs was also paralleled by a 4-fold increase in the DNA damage checkpoint-kinase 2 (Chk2). Conversely, statin cotreatment or overexpression of TRF2 completely suppressed Chk2 induction. Finally, overexpression of a dominant negative mutant of the TRF2 protein abrogated statin-induced enhancement of migratory activity down to baseline values.

**CONCLUSIONS:** Ex vivo culturing of EPCs leads to "uncapping" of telomeres, indicated by the loss of TRF2. Statin cotreatment of EPCs prevents impairment of their functional capacity by a TRF2-dependent, posttranscriptional mechanism. This is the first time a beneficial effect of statins on telomere biology has been described.

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