Akt Inhibitors Attenuate Telomerase Activation by the PPAR-γ Agonist Pioglitazone in Endothelial Cells and Endothelial Progenitor Cells

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Background:
PPAR-γ agonists such as pioglitazone are used for the treatment of type II diabetes. In addition to their action as insulin sensitizers, PPAR-γ agonists mediate glucose-independent vascular effects. Endothelial senescence may be involved in the pathogenesis of vascular disease. Telomeres and telomere-associated proteins are key regulators of the cellular aging process and affect senescence, regeneration and survival. The study aimed to determine the effects of pioglitazone on vascular telomere biology.

Figure 1 Telomeres, T-Loop and shelterin complex

Telomeres represent protective caps at the ends of eukaryotic chromosomes. Telomere ends are organized as T-Loops which are stabilized by shelterin complexes. Telomere repeat-binding factor (TRF) 1 and 2 are the main components of the T-Loop structure.

Figure 2 Pioglitazone increases aortic telomerase activity and TRF2 expression in vivo

Effects of pioglitazone (20mg/kg p.d. daily) in C57/B16 mice for 30 days compared to vehicle-treated controls on (A) aortic telomerase activity determined by Telomerase Repeat Amplification Protocol and (B) TRF2 protein and mRNA expression. Western blots are normalized to GAPDH; n=6; *p<0.05; **p<0.01 vs. control animals.

Conclusion:
Pioglitazone treatment activates aortic telomerase and reduces senescence marker expression in vivo and in cultured endothelial cells, mononuclear cells and endothelial progenitor cells. PPAR-γ agonist treatment confers down-regulation of the mitochondrial death pathway and Akt is an upstream regulator of these effects. The findings suggest that pioglitazone improves endothelial stress resistance and counteracts endothelial senescence.