Activation of telomerase and cyclooxygenase-2 in PDGF and FGF inhibition of C2-ceramide-induced apoptosis.

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Abstract

In the present study, the roles of telomerase and prostaglandin E(2) (PGE(2)) in platelet-derived growth factor (PDGF's) and fibroblast growth factor-2 (FGF-2's) effects against C(2)-ceramide-induced cell death were investigated. C(2)-ceramide reduced the viability of NIH3T3 cells in a condition without calf serum (CS) in accordance with decreasing telomerase activity according to the TRAP assay. The addition of CS significantly protected cells from C(2)-ceramide-induced apoptosis through increased telomerase activity, and the phosphorylations of PDGF and the FGF-2-like receptor in NIH3T3 cells were detected. Adding PDGF and FGF-2 decreased the cytotoxic effect elicited by C(2)-ceramide through stimulating telomerase activity, which was blocked by adding a telomerase inhibitor (TI). Activations of ERKs and JNKs were detected in PDGF- and FGF-2-treated NIH3T3 cells, and the telomerase activities induced by PDGF and FGF were respectively inhibited by the addition of the ERK inhibitor, PD98059, and the JNK inhibitor, SP600125. Accordingly, induction of cyclooxygenase-2 (COX-2) protein expression and PGE(2) production was detected in PDGF- and FGF-2-treated NIH3T3 cells, and the telomerase activities stimulated by PDGF and FGF were reduced by adding a specific COX-2 inhibitor, NS398, through a decrease in PGE(2) production. Incubation of cells with PGE(2) or the EP1 agonist, 17-PT, but not the EP2 agonist, sulprostone, the EP3 agonist, butaprost, or the EP4 agonist, PGE(1) alcohol, significantly enhanced the telomerase activity of NIH3T3 cells. PGE(2) protection of NIH3T3 cells against C(2)-ceramide-induced cell death was identified by the MTT and LDH-release assays, and it was inhibited by adding the EP1 antagonist, SC-19220. Ceramide metabolites including ceramide-1-phosphate (C1P) and sphingosine-1-phosphate (S1P), and a standard control of exogenous ceramide C(2)-dihydroceramide show no effect on the telomerase activity and viability of NIH3T3 cells. The involvement of COX-2/PGE(2)-mediated telomerase activation by PDGF and FGF-2 against C(2)-ceramide-induced cell death is first demonstrated herein.