# A requirement for thioredoxin in redox-sensitive modulation of T-cadherin expression in endothelial cells

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T-cad (T-cadherin), a glycosylphosphatidylinositol-anchored cadherin superfamily member, is expressed widely in the brain and cardiovascular system, and absent, decreased, or even increased, in cancers. Mechanisms controlling T-cad expression are poorly understood. The present study investigated transcriptional regulation of T-cad in ECs (endothelial cells). Conditions of oxidative stress (serum-deprivation or presence of H(2)O(2)) elevate T-cad mRNA and protein levels in ECs. Reporter gene analysis, using serially deleted T-cad promoter stretches ranging from -99 to -2304 bp, located the minimal promoter region of T-cad within -285 bp from the translation start site. Reporter activity in ECs transfected with the -285 bp construct increased under conditions of oxidative stress, and this was normalized by antioxidant N-acetylcysteine. An electrophoretic-mobility-shift assay revealed a specific nucleoprotein complex unique to -156 to -203 bp, which increased when nuclear extracts from oxidatively stressed ECs were used, suggesting the presence of redox-sensitive binding element(s). MS analysis of the nucleoprotein complex unique to -156 to -203 bp after streptavidin-agarose pull-down detected the presence of the redox-active protein thioredoxin. The presence of thioredoxin-1 in a nuclear extract from oxidatively stressed ECs was demonstrated after immunoprecipitation and immunoblotting. Transfection of ECs with thioredoxin-1 small interfering RNA abrogated oxidative-stress-induced up-regulation of T-cad transcripts and protein. We conclude that thioredoxin-1 is an important determinant of redox-sensitive transcriptional up-regulation of T-cad in ECs.
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