

Glutathione reverses the growth abnormalities of skin fibroblasts from insulin-dependent diabetic patients with nephropathy.

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Oxidative stress has been proposed as a possible pathogenic factor for diabetic complications. It is relevant in determining cell replicative capacity and life span, and in vitro antioxidant treatment is able to reverse the impaired proliferative activity of different cell types. It was recently demonstrated that cultured skin fibroblasts from insulin-dependent diabetic patients with nephropathy age prematurely and have a shorter life cell cycle. To test whether the growth phenotype of cells from patients with diabetic nephropathy was related to a lack of protection from oxidative stress, the effect of reduced glutathione (GSH) on cultured skin fibroblasts from 13 insulin-dependent diabetes mellitus (IDDM) patients with nephropathy (DN), 10 IDDM patients without kidney disease (D), and 10 nondiabetic control subjects (C), in normal (5 mM) glucose (NG) and high (22 mM) glucose (HG) medium was studied. After 6 to 8 passages, fibroblasts from DN showed impaired growth both in NG (mean \pm SD fold increase over baseline counts in DN 1.17 \pm 0.6 versus D 1.7 \pm 0.5 versus C 1.95 \pm 0.8; $P = 0.04$ by ANOVA) and in HG (mean \pm SD fold increase over baseline counts DN 1.16 \pm 0.41 versus D 1.89 \pm 0.66 versus C 2.24 \pm 0.9; $P = 0.003$ by ANOVA). GSH prevented the growth abnormalities of cells from DN restoring it to values similar to that of the other two groups (mean \pm SD fold increase over baseline counts NG \pm GSH: DN 1.68 \pm 0.9 versus D 1.78 \pm 0.49 versus C 1.99 \pm 0.7, $P = 0.6$; and in HG + GSH: DN 1.66 \pm 0.69 versus D 1.87 \pm 0.75 versus C 2.2 \pm 0.9, $P = 0.3$). Growth rates were not affected by the addition of GSH in fibroblasts from D and C. The treatment of fibroblasts from D and C with the inhibitor of the gamma-glutamylcysteine synthetase activity, L-buthionine-S,R-sulfoximine, resulted in growth impairment, and the addition to the culture medium of another antioxidant, superoxide dismutase, corrected the growth abnormalities in fibroblasts from DN. The impaired growth of cultured fibroblasts from IDDM patients with nephropathy is prevented by GSH and superoxide dismutase and is independent of prevailing glucose concentrations. This suggests that oxidative stress is an important mechanism of intrinsic cell dysfunction in these patients.

