Phosphorylation of GSK-3beta by cGMP-dependent protein kinase II promotes hypertrophic differentiation of murine chondrocytes.

Abstract:

cGMP-dependent protein kinase II (cGKII; encoded by PRKG2) is a serine/threonine kinase that is critical for skeletal growth in mammals; in mice, cGKII deficiency results in dwarfism. Using radiographic analysis, we determined that this growth defect was a consequence of an elongated growth plate and impaired chondrocyte hypertrophy. To investigate the mechanism of cGKII-mediated chondrocyte hypertrophy, we performed a kinase substrate array and identified glycogen synthase kinase-3beta (GSK-3beta; encoded by Gsk3b) as a principal phosphorylation target of cGKII. In cultured mouse chondrocytes, phosphorylation-mediated inhibition of GSK-3beta was associated with enhanced hypertrophic differentiation. Furthermore, cGKII induction of chondrocyte hypertrophy was suppressed by cotransfection with a phosphorylation-deficient mutant of GSK-3beta. Analyses of mice with compound deficiencies in both protein kinases (Prkg2(-/-)Gsk3b(+/-)) demonstrated that the growth retardation and elongated growth plate associated with cGKII deficiency were partially rescued by haploinsufficiency of Gsk3b. We found that beta-catenin levels decreased in Prkg2(-/-) mice,
while overexpression of cGKII increased the accumulation and transactivation function of beta-catenin in mouse chondroprogenitor ATDC5 cells. This effect was blocked by coexpression of phosphorylation-deficient GSK-3beta. These data indicate that hypertrophic differentiation of growth plate chondrocytes during skeletal growth is promoted by phosphorylation and inactivation of GSK-3beta by cGKII.