GSK-3? and GSK-3? proteins are involved in early stages of chondrocyte differentiation with functional redundancy through RelA protein phosphorylation.

Abstract:
Here we examine the roles of two isoforms of glycogen synthase kinase-3 (GSK-3), GSK-3? and GSK-3?, in skeletal development. Both isoforms were unphosphorylated and active in chondrocyte differentiation stages during SOX9 and type II collagen (COL2A1) expression. Although knock-out of both alleles of Gsk3a (Gsk3a(-/-)) or a single allele of Gsk3b (Gsk3b(+/+)) in mice did not significantly affect skeletal development, compound knock-out (Gsk3a(-/-); Gsk3b(+/+)) caused dwarfism with impairment of chondrocyte differentiation. GSK-3? and GSK-3? induced differentiation of cultured chondrocytes with functional redundancy in a cell-autonomous fashion, independently of the Wnt/β-catenin signal. Computational predictions followed by SOX9 and COL2A1 transcriptional assays identified RelA (NF-κB p65) as a key phosphorylation target of GSK-3. Among several phosphorylation residues in RelA, Thr-254 was identified as the critical phosphorylation site for GSK-3 that modulated chondrocyte differentiation. In conclusion, redundant functions of GSK-3? and GSK-3? through phosphorylation of RelA at Thr-254 play a crucial role in early stages of chondrocyte differentiation.

Zeitschriftentitel / Abkürzung:
J Biol Chem