



Oral Abstract

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Cyclic GMP-dependent protein kinase II (cGKII) controls hypertrophic differentiation of chondrocytes through phosphorylation and inactivation of GSK-3 β

Y. Kawasaki, F. Kugimiya, H. Chikuda, T. Ikeda, S. Kamekura, F. Yano, T. Saito, A. Higashikawa, M. Ushita, K. Nakamura, U.I. Chung and H. Kawaguchi

Orthopaedic Surgery & Tissue Engineering, University of Tokyo, Japan

cGKII is a kinase that lies downstream of the C-type natriuretic peptide/GC-B pathway which is essential for skeletal growth in both humans and rodents. A naturally occurring mutant rat KMI that lacks the kinase domain of cGKII is known to exhibit dwarfism due to the impaired hypertrophic differentiation of growth plate chondrocytes. To investigate the mechanism underlying the kinase activity of cGKII, the present study initially performed screening of its phosphorylation targets and found that glycogen synthase kinase-3 β (GSK-3 β) was strongly phosphorylated and inactivated by cGKII. In cultured mouse chondrogenic ATDC5 cells, type X collagen (COL10) mRNA level was induced by the cGKII overexpression and by an addition of lithium chloride, a selective inhibitor of GSK-3 β . The cGKII-induced COL10 expression was attenuated by co-transfection of a constitutively active mutant GSK-3 β , which was confirmed not to be phosphorylated by cGKII. We then examined the involvement of GSK-3 β in the cGKII action in vivo. cGKII-deficient ($-/-$) mice exhibited skeletal growth retardation with an enlarged growth plate due to the impairment of chondrocyte hypertrophy. Although GSK-3 β $-/-$ mice were embryonically lethal, GSK-3 β $+/-$ mice developed and grew normally. When we generated the compound-deficient mice (cGKII $-/-$;GSK-3 β $+/-$), both the impaired growth and the enlarged growth plate seen in cGKII $-/-$ mice were significantly restored, indicating that sufficient GSK-3 β is needed for suppression of the chondrocyte hypertrophy by the cGKII deficiency. We conclude that cGKII controls skeletal growth by hypertrophic differentiation of growth plate chondrocytes through phosphorylation and inactivation of GSK-3 β .