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Cyclic GMP-dependent protein kinase II promotes chondrocyte hypertrophy and skeletal growth

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Skeletal growth is achieved by endochondral ossification in the growth plate cartilage with orderly columnar arrays of resting, proliferative, and hypertrophic zones of chondrocytes. Cyclic GMP-dependent protein kinase II (cGKII) is a kinase that lies downstream of the C-type natriuretic peptide (CNP)/GC-B pathway which is essential for skeletal growth in both humans and rodents. We found that a naturally occurring mutant rat KMI that lacks the kinase domain of cGKII exhibits dwarfism due to the impaired hypertrophic differentiation of growth plate chondrocytes [1]. cGKII caused attenuation of the transcriptional function of Sox9, an inhibitor of chondrocyte hypertrophy, through inhibition of nuclear entry. However, inhibition of the nuclear entry was independent of the phosphorylation of Sox9 itself, suggesting that other phosphorylation targets of cGKII are important.

The cGKII-deficient (cGKII-/-) mice also showed dwarfism with an elongated growth plate due to impairment of chondrocyte hypertrophy [2]. A screen using a kinase substrate array identified glycogen synthase kinase-3β (GSK-3β) as a principal phosphorylation target of cGKII. Phosphorylation of GSK-3β caused its inhibition and this was associated with enhanced hypertrophic differentiation of cultured chondrocytes. cGKII-induced chondrocyte hypertrophy was suppressed by co-transfection with a phosphorylation-deficient mutant of GSK-3β at Ser9 (GSK-3β^{S9A}). Analyses of mice with compound deficiencies in both protein kinases (cGKII-/-;GSK-3β+/-) demonstrated that growth retardation and elongated growth plate caused by cGKII deficiency were partially alleviated by haploinsufficiency of GSK-3β. cGKII and GSK-3β were

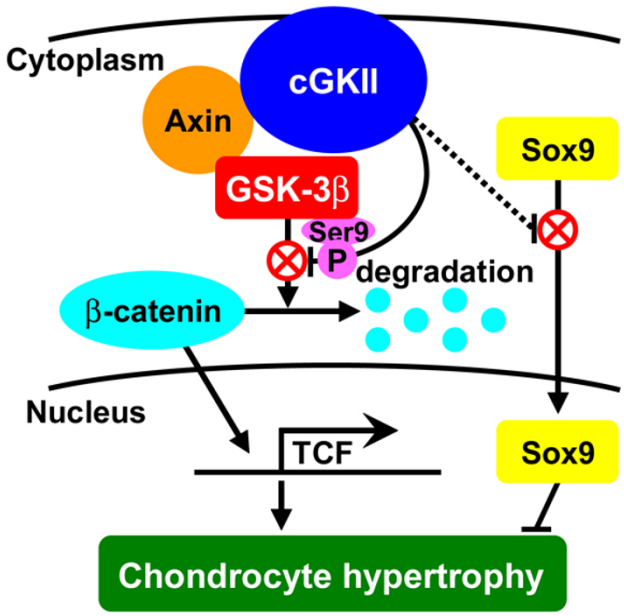

Figure 1

co-localized in prehypertrophic chondrocytes of the growth plate with β-catenin, whose level was decreased in the cGKII-/- mice. Overexpression of cGKII increased the accumulation and transactivation function of β-catenin in ATDC5 cells, which were blocked by co-expression of GSK-3β^{S9A}. Figure 1.

Conclusion

Hypertrophic differentiation of growth plate chondrocytes during skeletal growth is promoted by Ser9 phosphorylation and inactivation of GSK-3β, as well as the Sox9 transcriptional inhibition, by cGKII.

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