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Commentary

Parathyroid Hormone-Related Protein Receptor Signaling in Chondrocyte Hypertrophy during Endochondral Ossification

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DESCRIPTION

Endochondral ossification represents the primary mechanism of long bone formation and growth, involving the coordinated differentiation of chondrocytes through proliferative, hypertrophic, and mineralization stages. Parathyroid Hormone-related Protein (PTHrP) and its Receptor (PTH1R) play key roles in regulating chondrocyte differentiation and preventing premature hypertrophy. This investigation examined the molecular mechanisms through which PTHrP-PTH1R signaling controls chondrocyte hypertrophy during endochondral bone formation.

Primary chondrocytes were isolated from the growth plates of 2-week-old rat tibiae using sequential enzymatic digestion with collagenase and dispase. Cells were cultured in high-density micromass cultures or monolayer conditions using Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum, ascorbic acid, and insulin-transferrin-selenium. Chondrogenic differentiation was assessed through Alcian blue staining for proteoglycan production and immunofluorescence for collagen type II expression.

PTHrP treatment (1 nM-100 nM) significantly inhibited chondrocyte hypertrophy in a dose-dependent manner, as evidenced by reduced cell size and decreased expression of hypertrophic markers including collagen type X, alkaline phosphatase, and Matrix Metalloproteinase-13 (MMP-13). Quantitative PCR analysis revealed that PTHrP treatment reduced Col10a1 expression by 73%, Alpl expression by 68%, and Mmp13 expression by 81% compared to untreated controls.

Cyclic Adenosine Monophosphate (cAMP) measurements demonstrated that PTHrP treatment rapidly elevated intracellular cAMP levels, with peak concentrations reached within 10 minutes of treatment. The cAMP response was blocked by PTH1R antagonists, confirming receptor-mediated signaling. Protein Kinase A (PKA) activity assays revealed sustained PKA activation following PTHrP treatment, with peak activity occurring 30 minutes post-treatment and remaining elevated for 4 hours.

Transcriptional analysis using reporter assays demonstrated that PTHrP-cAMP-PKA signaling suppressed the activity of hypertrophic gene promoters. The Col10a1 promoter showed 64% reduction in activity following PTHrP treatment, while the Mmp13 promoter displayed 58% suppression. Chromatin Immunoprecipitation (ChIP) analysis revealed that PTHrP treatment enhanced cAMP Response Element-Binding protein (CREB) binding to regulatory elements within these promoters, correlating with transcriptional suppression.

Calcium signaling measurements using Fura-2 fluorescence revealed that PTHrP treatment modulated intracellular calcium dynamics in chondrocytes. Baseline calcium levels were reduced by 23%, while calcium transients in response to ATP stimulation were attenuated by 45%. These calcium changes correlated with altered expression of calcium-binding proteins including calmodulin and S100 proteins, suggesting that PTHrP influences calcium homeostasis during chondrocyte differentiation.

In vivo studies using PTHrP-deficient mice confirmed the essential role of PTHrP in growth plate organization. PTHrP knockout mice exhibited accelerated chondrocyte hypertrophy, with 67% reduction in proliferative zone height and 89% increase in hypertrophic zone height compared to wild-type littermates. Bone formation was accelerated but disordered, resulting in shortened long bones and abnormal trabecular architecture.

Rescue experiments using local PTHrP administration to PTHrP-deficient mice partially restored normal growth plate organization. Osmotic pump delivery of PTHrP (50 μg/kg/day) for 2 weeks increased proliferative zone height by 43% and reduced hypertrophic zone height by 34%. These structural improvements were accompanied by restored expression of proliferative zone markers including Sox9 and collagen type II.

Mechanistic studies revealed that PTHrP signaling intersects with other important regulatory pathways including hedgehog and FGF signaling. PTHrP treatment enhanced expression of *Gli1* and *Ptch1*, key components of hedgehog signaling, while modulating FGF receptor expression. These interactions suggest

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that PTHrP functions as a central coordinator of multiple signaling pathways during chondrocyte differentiation.

CONCLUSION

PTHrP-PTH1R signaling serves as a critical brake on chondrocyte hypertrophy during endochondral ossification through cAMP-PKA-mediated transcriptional regulation. The suppression of hypertrophic gene expression and modulation of calcium signaling demonstrate the multifaceted mechanisms through which PTHrP maintains growth plate organization. These findings provide important insights into skeletal development and suggest therapeutic targets for treating growth disorders and cartilage-related diseases.