Parathyroid Hormone Related Protein - A Skeletal Biomarker – A Review

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Abstract

The discovery of Parathyroid hormone-related protein (PTHrP) was through its structural and functional homology with parathyroid hormone. It is secreted by cancers and it interacts with parathyroid hormone receptors in kidney and bone to cause humoral hypercalcemia of malignancy and paraneoplastic syndrome and plays an important role in cellular differentiation and proliferation, embryonic development, transepithelial calcium transport and in the regulation of smooth muscle contraction.Its intracrine, paracrine and endocrine modes of action play a central role in organogenesis and drives numerous physiologic and pathologic conditions.It is initially translated as a preprohormone which is posttranslationally processed to yield a family of mature secretory forms. The aminoterminal portion of the molecule is homologous to parathyroid hormone.As PTHrP plays a vital role in the regulation of endochondral bone development it was surmised that it could also serve as an ideal biologic skeletal maturity indicator to detect peak pubertal growth spurt.

Keywords: *parathyroid hormone, endochondral, parathyroid hormone related protein*

Introduction

Parathyroid Hormone–related protein (PTHrP) is a protein member of the parathyroid hormone (PTH) family secreted by mesenchymal stem cells and occasionally by cancer cells and that multiple steps in skeletal morphogenesis is regulated by PTHrP and Indian hedgehog protein (Ihh).PTHrP plays an important role in placental calcium transfer, fetal development, epithelial cell growth and smooth muscle relaxation in addition to its parathyroid hormone-like actions.[1]

PTHrP is a paracrine factor expressed throughout the body whose structure is not closely related to that of PTH as it is a product of a separate gene with the exception of a short N-terminal region. It is a poly hormone comprising of a family of distinct peptide hormones. It acts like a growth factor, calciotropic hormone, myorelaxant and as a developmental regulatory molecule.

Rizzoli R et al [2] (1992) reported that PTH and PTHrP by interacting with a structurally identical receptor displayed a common spectrum of action on the transport of mineral elements in kidney and bone and in-vivo, PTH/PTHrP increased the renal tubular reabsorption of calcium and similarly reduced the inorganic phosphate (Pi). An increase in both bone resorption and renal calcium reabsorption is the causative factor of the hypercalcemic effect of PTHrP brought about by the stimulation of the renal transport of calcium. They also speculated that biphosphonate therapy can inhibit the PTHrP-stimulated bone resorption and that PTHrP appeared to less stimulate bone formation than PTH. PTHrP elicited a 2-fold increase of cAMP production in cultured mammary cells isolated from lactating rats.

Riond JL et al[3] (1995) opined that PTHrP played an important role in calcium homeostasis as it stimulated the calcium transfer through the placenta and maintained a concentration gradient between the maternal blood and the fetus thereby contributing to as an important fetal growth factor. Its exact and principal function in lactation has yet not been determined despite the fact that it is produced in large quantities in the milk. It has been reported tofoster the development of the mammary gland and to stimulate the secretion of magnesium, calciumand phosphate in milk.

Wu TL et al[4] (1996) in their study defined a novel, highly conserved mid-region secretory form of PTHrP

which was biologically active as also confirmed the fact that PTHrP was a prohormone.

Philbrick WM et al [5] (1996) reported that PTHrP is a prohormone that is posttranslationally cleaved by prohormone convertases to yield a complex family of peptides, each with its own receptor and that the PTHrP gene is expressed not only in a vast majority of normal tissues during fetal and/or adult life but also in cancers. PTHrP plays predominantly a paracrine and/or autocrine role in normal circumstances in contrast to an endocrine role in humoral hypercalcemia of malignancy. Its physiological functions include 1) regulation of transepithelial (placental, renal, mammary gland, oviduct) calcium transport, 2) differentiation, proliferation and regulation of organ and tissue development, and 3)regulation of smooth muscle (intestinal, vascular, bladder, uterine) tone. The authors in their review have discussed the normal physiological functions of PTHrP, with emphasis on its discovery, gene structure and cDNAs, and the posttranslational processing of the initial translation products.

Wysolmerski JJ and Stewart AF[6] (1998) opined that PTHrP was responsible for humoral hypercalcemia of malignancy alongwith its role in normal development and adult physiology. Their review focused on studies of the past two years namely: (1) the role of PTHrP as an intracrine regulator of cell growth and cell death; (2) mechanisms of action of the various secretory forms of PTHrP and elucidation of the posttranslational processing pattern of PTHrP (3) the advances in understanding the roles of PTHrP in the vascular smooth muscle tone and proliferation, materno-fetal calcium transfer across the placenta and regulation of pancreatic islet mass; and (4) the emergence of PTHrP as a critical developmental factor in skeleton,mammary glandand epidermis.

Shibata S et al [7] (2000) reported that severe abnormalities in endochondral ossification have been suggested by previous studies using PTHrP null mutant mice suggesting the fact that chondrocyte differentiation is affected by PTHrP. The authors found some deformities in the mandible that was formed via intramembranous ossification in the new born PTHrP-deficient mice. In the mandibular body a prominent bone crest to which the deep layer of masseter muscle was tendinously attached was observed alongwith the mandibular ramus being bent downwards. Active bone formation progressing along the tendon fibers of the masseter muscle was depicted with transmission electron microscope. The authors reported that the masseter muscle in the newborn PTHrP-deficient mice contained numerous type 2B fibers, an indicator of premature maturation of the masseter muscle, which was actually analysed using myosin ATPase staining. This premature maturation of the masseter muscle probably led to accelerated bone crest formation andbending of the mandibular ramus due to the increased tensile forces. These findings reiterated the fact that PTHrP was involved in the regulation of muscle development in normal animals.

Kindblom JM et al[8] (2002) opined that the rate of cartilage differentiation during skeletal morphogenesis in rodents was controlled by the Indian Hedgehog through a negative feedback involving PTHrP. However the role of PTHrP and Ihh in the regulation of human epiphyseal chondrocytes was unknown. Hence, they embarked on an immunohistochemistry study to detect the expression and localization of PTHrP and Ihhin the human growth plate at various pubertal stages by obtaining growth plate biopsies from patients subjected to epiphyseal surgery. They concluded that the levels of expression of PTHrP and Ihh were mainly in early hypertrophic chondrocytes and that they were higher in early stages of puberty than later. They concluded that PTHrP and Ihh could play an important role in the regulation of pubertal growth in humans.

Shibata S et al[9] (2003) found ectopic cartilage formation in the mandibular coronoid process in newborn mice when they analyzed PTHrP null mutant mice. This was the first report showing an "increase" of cartilage volume in contrast to smaller volumes of cartilage in many other previous studies involving PTHrP gene knockout mouse. Though small amount of cartilage temporally formed at d 7, coronoid secondary cartilage never formed from E 15 to d 4 in normal mice and was a similar observation for PTHrP-wild type mice too. It was therefore suggested that the secondary cartilage formation was advanced with PTHrP deficiency which was a novel role of PTHrP in chondrocyte differentiation. Increase in the number of multinucleated osteoclasts and abnormal expansion of bone marrow, an indication of abnormal bone modeling was observed in the coronoid process of the PTHrP-deficient mouse.These results indicated that

PTHrP was involved in chondrocyte differentiation and bone modeling. Immunohistochemical results of in situ hybridization of matrix protein mRNAs in the abnormal mandibular condylar cartilage revealed that this cartilage was proportionally smaller.

Rabie ABM et al[10](2003) evaluated and correlated the cellular dynamics of chondrocytes in condylar cartilage during natural growth and mandibular advancement with the pattern of expression of PTHrP by fitting 35-day-old Sprague-Dawley rats with functional appliances. To trace the mesenchymal cell differentiation, experimental animals with matched controls were labeled with bromodeoxyuridine 3 days before their death. Mandibular advancement increased the cartilage volume with an increase in the number of differentiated chondroblasts. Slowing of chondrocyte hypertrophy was associated with higher levels of PTHrP expression in the experimental animals. It was concluded that mandibular advancement promoted mesenchymal cell differentiation and triggered PTHrP expression, which retarded their further maturation to allow for more growth.

Gensure RC et al[11](2005)opined that PTHrP had important developmental roles whilePTH had a central role in the regulation of serum calcium and phosphate and that both peptides signalled through the PTH/PTHrP receptor (a class B G-protein-coupled receptor). Intermittent injection of PTH increased bone mass and thus provided a means to treat osteoporosis. This triggered a search for smaller peptide or non-peptide agonists that have efficacy at this receptor when administered non-parenterally.Deficiency or excess production of either peptide caused a variety of clinical syndromes.

Kronenberg HM [12] (2006) opined that PTHrP played a vital role in the regulation of endochondral bone development and that the chondrocytes and perichondrial cells at the ends of the cartilage mold established in fetal life synthesized PTHrP. It was surmised that this ligand then acts on PTH/PTHrP receptors on chondrocytes which profilerate and differentiate into post-mitotic, hypertrophic chondrocytes. PTHrP delays their further differentiation as they simultaneously keep proliferating. Chondrocytes that have just stopped proliferating synthesize Indian hedgehog (Ihh), required for the synthesis of PTHrP. The feedback loop between PTHrP and Ihh served to regulate the pace of chondrocyte differentiation and the sites where the osteoblasts first differentiated from the perichondrial cells. Stimulation of both Gs and Gq family heterotrimeric G proteins is due to activation of the PTH/PTHrP receptor. Genetic analyses demonstrated that, while Gq activation opposes, Gs activation mediates the action of PTHrP to keep chondrocytes proliferating. SOX9, phosphorylation of the transcription factor, Runx2 and suppression of synthesis of mRNA encoding the transcription factor all mediate PTHrP's actions to delay chondrocyte differentiation and regulate the pace of differentiation of growth plate chondrocytes in response to PTHrP.

Ng AFS et al [13](2006) opined thatadaptive changes in skeletal mass and architecture is as a result of mechanical loading that can invariably influence the biological behavior of the bone-associated cells and that the endochondral bone formation was controlled by SOX9 and PTHrP genes which regulated chondrocyte differentiation and delayed the maturation stage.280 Sprague-Dawley rats were randomly allocated into control and experimental groups and the mechanical loading was applied through a bite-jumping device in the experimental group to investigate the effects of repeated mechanical loading on bone. Together with the matched control the experimental animals were sacrificed on 10 different time points. PTHrP and SOX9 genes quantification using real-time RTPCR was done on RNA extracted from the mandibular condylar cartilage. Results showed that on the seventh day after mechanical loading PTHrP expression was increased and reached a peak level and subsequent to repeated mechanical loading another increment in its peak expression was observed. The expression of PTHrP was highly correlated with the SOX 9 expression, and its pattern of expression was similar after repeated mechanical loading. They concluded that repeated mechanical loading on the condyle triggered the expression of SOX9 and PTHrP, which in turn promoted condylar cartilage growth.

Broadus AE et al[14] (2007) opined thatPTHrP appeared to regulate subjacent bone cell populations at sites that included the periosteum and ligament/tendon insertion sites at surface of endochondral bones. In PTHrP-lacZ knockin mouse experiments it was observed that PTHrP/lacZ was also expressed in epiphyseal cartilage and that this structure contributed

to PTHrP-expressing chondrocyte populations to both growth-plate and articular cartilage postnatally and that in these locations the Indian hedgehog-PTHrP axis was fully deployed and particularly in articular cartilage it protected the joint space from invasion by mineralizing cells. A mechanical regulation of PTHrP at these sites was also confirmed.

McCauley LK, Martin TJ[15] (2012) opined that though great strides have been made in the understanding of PTHrP, yet much was needed to be discovered and investigated. They however concluded thatits intended temporal actions emerged as dichotomies of production and action in the menancing condition of cancer and that PTHrP undoubtedly "controlled the show" locally at the PTH/PTHrP receptor relative to PTH, the hormone regulating calcium homeostasis.

Hussain MZ et al[16] (2013)quantified serum PTHrP levels of 90 subjects at 6 cervical vertebral stages and correlated it to the 6 skeletal maturation stages to prove whether PTHrP could serve as an ideal biologic skeletal maturity indicator to detect peak pubertal growth spurt. They reported that in the late pubertal stages the mean serum PTHrP levels were significantly higher than in the early pubertal stages and thatthe Pearson correlation showed that serum PTHrP levels had a negative correlation with cervical vertebral maturation stages from the late pubertal to the postpubertal stages and a positive correlation from the prepubertal to the late pubertal stages. They questioned the validity of using serum PTHrP levels to predict peak growth velocity as these levels did not correlate with early pubertal stages characterized by maximum growth increments.

Conclusion

PTHrP is a protein identified from cancers that causes hypercalcemia and is credited for its ability to mimic parathyroid hormone. Its paracrine, endocrine, and intracrine modes of action play a central role in organogenesis and drives numerous physiologic and pathologic conditions. PTHrP is a key factor regulating the pace of endochondral ossification during skeletal development. Mandibular advancement solicits a cascade of molecular responses in condylar cartilage and hence PTHrP may serve as an ideal biomarker to help detect peak pubertal growth during the circumpubertal growth spurt to help treat functional jaw discrepancies.

Ethical Clearance – Not required since it is a review article

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Conflict of Interest – Nil

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