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INTRODUCTION

Parathyroid Hormone-Related Protein: Not Just a Parathyrin Mimic but a Key Regulator of Diverse Tissues and Physiological Systems

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Prior to the cloning of parathyroid hormone-related protein (PTHrP), three clinical scenarios predicted its existence. First was humoral hypercalcemia of malignancy (HHM), in which the skeleton is resorbed by a circulating factor whose tissue source may not be within bone. Although HHM resembles many aspects of primary hyperparathyroidism, parathyroid hormone (PTH) is undetectable. Second was a consistent discrepancy in newborn cord blood: low to undetectable immunoreactive levels of PTH, but high levels of PTH-like bioactivity in cytochemical assays. Third was that hypoparathyroid and aparathyroid women normalize mineral homeostasis during lactation and become hypercalcemic unless their supplemental calcium and calcitriol are discontinued. All three scenarios display biochemical results that are consistent with a circulating PTH-like hormone that binds to the PTH receptor and mimics the actions of PTH.

Investigators focused on the cancer angle, and in 1987, three groups independently announced that they had cloned PTHrP from the picomolar or lesser amounts secreted from precious fragments of HHM-causative tumors. Soon enough, it became clear that increased circulating levels of PTHrP explained all three clinical scenarios. And to the chagrin of those researchers, they later learned that 1,000–10,000 times the amount of the elusive PTHrP had been more readily and cheaply recoverable from milk—whether in the local corner store, or produced by breastfeeding women!

In the elapsed decades, it has become clear that PTHrP is also expressed in many tissues, wherein it has key paracrine and autocrine roles to regulate diverse tissues and cells. We have surveyed a select number of those roles in the following articles:

Danks, Freeman and Martin provide an overview on the evolutionary origins and roles of PTHrP, PTH, and related gene products.

Wright and Guise explain how PTHrP is both a locally secreted factor that enables tumors to carve out a niche for themselves within the skeleton and a systemically secreted factor that can lead to its classic presentation in HHM.

Ohba and Chung detail the role that PTHrP plays in regulating the development of the endochondral skeleton.

Kovacs describes the adaptive roles that PTHrP has to regulate mineral homeostasis in the mother during pregnancy and lactation and in the offspring during fetal and early neonatal development.

Vasavada's colleagues explain how PTHrP is expressed within pancreatic beta cells and contributes to the regulation of insulin and glucose homeostasis.

Hiremath and Wysolmerski point out how PTHrP plays critical roles at all stages of breast development and physiology: from nipple bud to lactating breast and from normal to cancerous tissue.

Finally, Towler provides an overview of our understanding of PTHrP's role in regulating vascular smooth muscle and, thereby, blood pressure and vascular calcifications.

Through these articles, it should become clear that PTHrP is not simply a parathyrin mimic. Nor is it a jack-of-all-trades. Instead, it is a key regulator of diverse tissues and physiological systems. In each system, PTHrP may become a treatment target, whether it is to boost, reduce, or block PTHrP signaling as needed to address the underlying clinical disorder.

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