INTRODUCTION

In 1987, a second member of the parathyroid hormone (PTH) family, PTH-related protein (PTHrP), was identified and cloned (1). PTHrP is produced in many normal fetal (2-11) and adult (7,12-19) tissues, including several endocrine tissues, cartilage and bone, heart, vascular and other smooth muscle, skin, central nervous system, liver, kidney, and lung. The cell types that produce PTHrP encompass all three embryonic
germ layers and the extraembryonic trophoderm. The PTHrP gene is expressed in certain mesenchymal cells, but production of the protein typically is restricted to the epithelium of organs, while its receptor is often expressed in adjacent mesenchyme. During the past decade, investigations of PTHrP structure and functions have provided insights into new and novel actions of the PTH/PTHrP family leading to an appreciation of these molecules as important developmental and physiologic regulators. Although investigation of the functional significance of PTHrP gene expression in the lung has only recently begun in earnest, current evidence supports roles for the protein regulating pulmonary function, differentiation, and growth.

PARATHYROID HORMONE AND PARATHYROID HORMONE-RELATED PROTEIN: STRUCTURAL AND FUNCTIONAL RELATIONSHIPS

PTH is the principal hormonal regulator of calcium homeostasis in birds and mammals. By contrast, under physiologic conditions, PTHrP appears to act principally as a paracrine, autocrine, and intracrine factor. Overproduction of the protein by tumors, including all major lung cancer cell types (20–22) and, occasionally, benign tumors (23), led to the discovery of this second PTH family member. In this setting, PTHrP exerts classical endocrine effects on bone and kidney and induces the common paraneoplastic syndrome of humoral hypercalcemia of malignancy (HHM) (24,25). HHM is a frequent complication of squamous cell carcinoma of the lung and contributes substantially to morbidity and mortality of that disease. Fuller Albright first described HHM during a 1941 Massachusetts General Hospital clinical pathologic conference (26) in a discussion of a hypercalcemic and hypophosphatemic patient who had renal carcinoma and only a single bone metastasis. The systemic calcium and phosphate derangements resolved after irradiation of the tumor, prompting Albright’s proposal that the renal carcinoma secreted either PTH or a humoral PTH-like substance.

The biochemical similarities between primary hyperparathyroidism and HHM include hypercalcemia, hypophosphatemia (resulting from a reduced renal phosphate threshold), and increased nephrogenous adenosine 3',5'-cyclic monophosphate (cAMP) excretion (a hallmark of ligand interaction with proximal tubular PTH receptors) (27). In distinction from hyperparathyroidism, HHM patients show higher fractional calcium excretion, reduced circulating 1,25-dihydroxyvitamin D levels and, on bone histomorphometry, osteoclastic bone resorption with decreased osteoblastic activity, that is, bone formation “uncoupled” from bone resorption (28). These differences, as well as the findings that immunoreactive PTH (29) is suppressed in HHM and that the tumors lack detectable PTH mRNA (30), stimulated the search for a distinct molecule that could mimic certain PTH actions. Guided by sensitive in vitro bioassays, several research groups successfully purified a tumor-derived adenylyl cyclase-stimulating HHM factor from conditioned medium of a human lung squamous carcinoma cell line (BEN) (31) and renal carcinoma cells (32,33). Shortly afterward, cDNA clones that encode PTHrP were identified from lung (1) and renal (34,35) carcinomas. Over several years, the alternative names “PTH-like protein,” “HHM factor,” and “human hypercalcemia factor” have been discarded in favor of the designation PTHrP.

As predicted, circulating PTHrP is markedly elevated in HHM (22,36–39). The causal relationship between PTHrP and hypercalcemia has been demonstrated by the activity of PTHrP neutralizing antibodies reversing the hypercalcemia induced in animals by