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Mini-Review

Parathyroid hormone-related protein in human renal cell carcinoma

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Abstract

Parathyroid hormone-related protein (PTHrP), a polyprotein discovered in 1987, plays crucial roles not only in development and in various physiological events associated with normal life, but also in a number of pathological conditions such as cancer. PTHrP appears as the major causative agent in humoral hypercalcemia of malignancy (HHM) associated to a broad range of tumors. However, this is only one aspect of the multiple facets of PTHrP in cancer biology. Indeed, the complex growth factor-like properties of PTHrP has shed new light onto potential roles of this peptide in the regulation of tumor growth and invasion. Initial studies in breast, prostate and lung cancer and recent results in renal cell carcinoma (RCC) suggest such roles and highlight the therapeutic potential of PTHrP-targeting strategies in human cancer including RCC. In this review, the role of PTHrP in RCC tumorigenesis and its potential as a therapeutic target will be discussed.

Keywords: Renal cell carcinoma; Growth; Apoptosis; PTHrP, VHL tumor suppressor

1. Introduction

Parathyroid hormone-related protein (PTHrP) is a polyprotein derived from normal and malignant cells. In addition to its well-documented role in inducing humoral hypercalcemia of malignancy (HHM), a paraneoplasic syndrome associated to a broad array of cancers [1,2], PTHrP displays a variety of effects including the regulation of cell differentiation, proliferation and death [1,3]. The growth factor-like properties of PTHrP, together with the complex modulation of its expression by a number of growth and angiogenic factors including vascular endothelium-derived growth factor (VEGF) and tumor-derived growth factor-βTGF-β point toward potential roles for PTHrP in the regulation of tumor growth and invasion.

Conventional renal cell carcinoma (CRCC) represents 75% of all renal cell carcinomas (RCC) and is responsible for 2% of cancer-related deaths worldwide [4–6]. Functional inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene occurs in 40 to 80% of CRCC [7–9]. At the molecular level, VHL gene products (pVHL) are components of a ubiquitin–ligase complex involved in the down-regulation of several angiogenic and growth factors, such as VEGF

Abbreviations PTHrP, parathyroid hormone-related protein; RCC, renal cell carcinoma; VHL, von Hippel-Lindau; pVHL, VHL gene products; PTH1R, PTH1 receptor.

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and TGF-β, that contribute to RCC development and growth [10,11]. Current therapeutic strategies are only marginally effective against metastatic RCC, and adverse effects are common.

CRCC originates from the renal proximal tubular epithelium, a target tissue for PTHrP proliferation effects [12]. Early results published in 1990 and obtained in a single PTHrP-secreting CRCC cell line (SKRC-1) suggested that PTHrP might be involved in autocrine growth regulation of these cells [13]. Subsequent studies revealed that PTHrP is expressed in 95% of CRCC in humans, whether they are associated with hypercalcemia or not [14,15]. PTHrP expression was also observed in CRCC tumor cells in culture. More recently, PTHrP was shown to be an essential growth factor for RCC in various CRCC cell lines in vitro and in vivo and a new target for the VHL gene products [16,17]. All these studies identify PTHrP as new therapeutic target for CRCC in humans. This possibility will be discussed in this short review.

2. PTHrP as a polyprotein

PTHrP was discovered in 1987 as a PTH-like factor responsible for the hypercalcemic paraneoplastic syndrome, HHM, associated to a broad range of cancers in human and animals [1,2]. Indeed, when abundantly secreted by tumors, PTHrP mimics PTH effects and stimulates bone resorption and renal calcium reabsorption through an endocrine pathway. Both peptides signal through the same receptor, the PTH/PTHrP receptor (a class B G-protein-coupled receptor) called the type 1 PTH receptor, PTH1R [1,18]. The ability of both PTH and PTHrP to bind to a single receptor is explained by the limited amino-terminal sequence homology between both molecules allowing them to adopt similar conformation. In spite of sequence and conformational homologies, PTH and PTHrP are the products of distinct single genes present on chromosomes 11 and 12, respectively (Fig. 1).

The PTH gene consists of three exons and one promoter (Fig. 1). In all species tested to date,

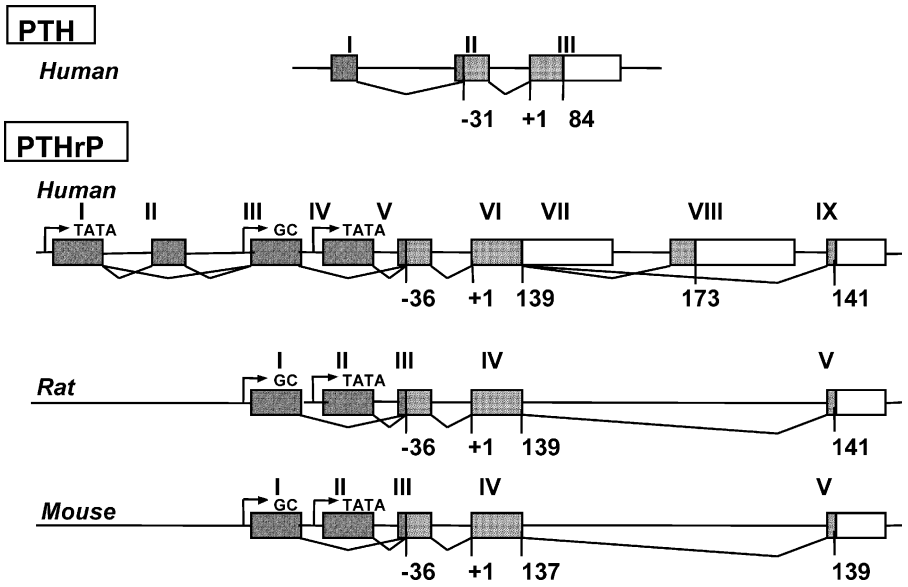

Fig. 1. Structure of the PTHrP gene. The panel shows examples of phylogenetic variations of the PTHrP gene in humans (chromosome 12) and rodents. Compared to the organization of the PTH gene in human (chromosome 11), the PTHrP gene has acquired much more complexity. Coding exons and 5′ and 3′ untranslated exons are represented in hatched boxes, dotted boxes and white boxes, respectively. Introns are represented by a line. The PTHrP gene promoters (three in human and two in rodents) are represented by the arrows above the sequences. Following 5′ and 3′ alternative splicing, represented by the broken lines below the sequences, and the use of the different promoters, various PTHrP mRNA isoforms are generated. These isoforms are translated into three PTHrP proteins containing 139, 141 or 173 amino-acids in humans depending on the cell or tissue-type. In rodents, only one PTHrP protein isoform is expressed containing 139 (mouse) or 141 (rat) amino-acids.