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Review

Paratharmone related protein (peptide): A novel prognostic, diagnostic and therapeutic marker in Head & Neck cancer

S. Sen [a], P. Dasgupta [b,*], G. Kamath [c], H.S. Srikanth [c]

[a] Unit-III, department of surgical oncology, Chittaranjan national cancer institute, 37, S.P. Mukherjee Road, 700026 Kolkata, West Bengal, India
[b] Baraniya cooperative society, Flat No. F2, AL/1/C/14, action area 1A, street no. 22, Newrown, 700156 Kolkata, West Bengal, India
[c] Department of oral medicine and radiology, Sri Hasanamba dental college and hospital, Vidyanagar, 573202 Hassan, Karnataka, India

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ABSTRACT

Parathyroid hormone-related protein (PTHrP) is a promising modality of assessment of different critical features of cancer. It is a protein member of parathyroid hormone family, secreted by certain physiologic cells and by malignant tumors in an increased amount. Recent studies have confirmed that PTHrP massively contributes to malignant behaviour of oral cancers-cell proliferation, migration and invasiveness. Strong correlation was found between PTHrP overexpression and local bone invasion and percentage of tumor cells in metastatic nodes. Normal range of PTHrP in serum is 0.7–2.6 ρmol/litre. Its down-regulation blocks cell cycle of cancer cell lines and inhibits cell proliferation and colony formation. PTHrP can be used as a diagnostic aid, prognostic marker and excellent research arena for designing novel anti-neoplastic drugs.

1. Introduction

Head and Neck cancers are the sixth most common cancers in the world, and oral cancers account for almost 80–90% of all head and neck carcinomas. With better understanding of pathogenesis of oral squamous cell carcinoma (OSCC) and improved treatment modalities, survival rates of OSCC have improved over the past 10 years. However, about 50% patients still die within 5 years of diagnosis [1]. As is known, many physical, chemical and immune-mediated factors are involved in pathogenesis of OSCC that act as critical factors in the functional outcome of the disease. Advanced OSCC frequently invades bones causing local bone destruction, pain, hypercalcemia, fractures, distant metastases, etc. that have become major clinical issues [2]. Thus, the understanding of the molecular mechanism of local bone invasion, distant metastasis and cell proliferation in OSCC needs to be addressed to assess the prognosis of the disease and possibly formulate a targeted treatment modality.

In this context, Parathyroid hormone-related protein (PTHrP) is a promising modality of assessment of the different critical features of cancer. It is a protein member of the parathyroid hormone family, secreted by certain physiologic cells and by some malignant tumors in an increased amount [3].

2. Materials and methods

A Pubmed and Google scholar search was conducted to review the literature in English language using the keywords: Parathormone related protein, Parathormone like protein, Head and neck squamous cell carcinoma and Oral squamous cell carcinoma. Articles were included from the year 1980 to 2016. Further, a manual search of articles was done for the same. The results not representing the topic of search were excluded. The articles were analyzed for the history of PTHrP, its structure and functions in malignancies.

3. Discussion

3.1. History

Decades of intensive research in this field bore fruit when, in 1941, Fuller Albright, based on clinical observation in a single patient with hypercalcemia due to renal cell carcinoma, postulated that tumors might produce a hormone of parathormone family, that may have parathormone like functions [3]. In 1980s it was found that patients with hypercalcemia of malignancy frequently had increased nephrogenous cyclic Adenosine Mono Phosphate (cAMP) and had a circulating factor that increased adenylate cyclase activity in cultured bone cells or renal membranes in much the same manner that parathormone did, but was clearly not

* Corresponding author.
E-mail address: drpaulami@yahoo.co.in (P. Dasgupta).

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parathormone [4,5]. Thus, it was concluded that a parathormone-like-factor was produced by tumors associated with hypercalcemia. Later, PTHrP, a peptide having close homology in the N-terminal sequence to parathormone was discovered [6].

PTHrP was first isolated by T.J. Martin et al. in 1987 in the University of Melbourne in a lung cancer cell line [7]. In 1990s, it was found out that PTHrP was not only produced by OSCC and other tumors exhibiting humoral hypercalcemia of malignancy (HHM), but also by non-hypercalcemic tumors and was responsible for local osteolysis [6]. Up to 1990s it was thought that HHM was due to a circulating factor (PTHrP) and localized osteolysis was either due to local cytokines, or as a direct effect of tumor cells [8]. Now, it is clear that PTHrP may act as circulating factor when produced in increased amounts by tumors, thus causing HHM and also act as a local factor when produced by metastatic tumor cells in bone microenvironment causing osteolytic metastasis [6].

3.2. Synthesis

PTHrP is secreted by normal tissues, though in negligible amount, but its secretion may be up regulated by many folds in case of tumors. The expression of PTHrP is regulated by Calcium–sensing Receptor (CaR) signaling in normal epithelial and cancer cells [1].

3.3. Structure and gene localization

PTHrP is a 141 amino acid polypeptide and is structurally similar to Parathormone. Human PTHrP is encoded by a single gene on the short arm of chromosome 12. The portions of both genes encoding the amino-terminal of secreted PTH and PTHrP are homologous. Thus, both peptides bind to the same receptor, which is why hypercalcemia is caused by PTHrP in HHM [9–12]. This gene causes changes in extracellular calcium concentration, and plays vital roles at local sites, such as bone, teeth and mammary glands [13].

4. Physiologic actions of PTHrP

4.1. Action on bone

Through animal models it was found that the amino-terminal of PTHrP coordinates the rate of chondrocyte differentiation and thus regulates the growth of long bones during development [14]. The growth plate consists of columns of proliferating and differentiating chondrocytes that expand to hypertrophic chondrocytes. PTHrP is secreted by immature chondrocytes at the top of the columns. This secretion occurs in response to Indian hedgehog (IHH), which is produced by differentiating hypertrophic chondrocytes [13]. PTHrP activates PTHR1 located on proliferating and prehypertrophic cells. Thus their proliferation is maintained and their rate of differentiation into hypertrophic cells is slowed down. This is how IHH and PTHrP act in a local negative feedback mechanism to regulate the rate of chondrocyte differentiation [14].

4.2. Action on developing teeth

Developing teeth are surrounded by bone and erupt through it into the oral cavity. Osteoclasts must resorb the bone overlying the crown of tooth for its eruption. Also, osteoblasts must form bone at the base of tooth to facilitate its eruption. PTHrP is produced by stellate reticulum cells, and it indicates the dental follicle cells to promote osteoclasts formation above the crypt. In the absence of PTHrP, these osteoclasts do not appear, leaving the tooth unerupted [15–17].

4.3. Action on mammary glands

In human fetuses, epithelial cells in the mammary bud produce PTHrP, which interacts with the PTHR1 expressed on the surrounding mesenchymal cells [13]. This communication is obligatory for proper differentiation of the mesenchymal cells, which prompts the development of the epithelial ducts [18]. Loss of PTHrP signalling results in detainment of development of mammary glands at bud stage. After embryogenesis, PTHrP is released from breast into circulation, and it regulates systemic calcium and bone metabolism during lactation. The maternal skeleton serves as a source of calcium for milk production, and thus bone loss has been found in nursing women [19]. Elevated levels of PTHrP is also associated directly with bone loss and resorption and inversely with bone mass [20,21]. Disturbance of *PTHrP* gene in mammary epithelial cells reduces circulating PTHrP levels, which in turn preserves bone mass. This confirms that lactating breast secretes PTHrP into circulation to increase bone resorption [22].

5. Mammary gland–Malignant cells analogy

Given the role of PTHrP in increasing bone resorption during lactation, it is not surprising that it also contributes to osteolysis in the setting of bone metastases [13]. Authors believe that similar, but more complex mechanisms are also involved in cancer. In solid tumors, it was found that PTHrP transcription is driven by Gli family members just like the mechanism that takes place in developing growth plates [23,24]. The cancer cells utilize this dormant developmental Hedgehog pathway to augment its expression of PTHrP, commence bone resorption, and form a centre for bone metastasis. The process is driven by TGF-β, the most plentiful growth factor in bone matrix, which is released into bone microenvironment when resorption takes place [25,26]. This leads to increased PTHrP expression and bone resorption. Bone resorption supports tumor cell growth and further release of active TGF-β from bone matrix [1]. This forms a vicious cycle between tumor cells and osteoclasts in metastatic cancer [8,27].

6. Studies on malignancies and PTHrP

6.1. Breast cancer

In 2003, Lindemann et al. proved that PTHrP appeared to function as an osteolytic factor associated with breast cancer metastases [28]. In breast cancers, PTHrP produced by cancer epithelial cells in an autocrine or paracrine mode induces local osteolysis causing HHM and bone metastases [29].

6.2. Renal cancer

Massfelder et al. found that PTHrP acts as an essential in vitro survival and growth factor for clear cell renal carcinoma lines. As the PTHrP receptors are inhibited by PTHrP-neutralizing antibodies, the cancer cell lines underwent apoptosis. It was also found that antibody treatment caused significant tumor regression in mice that might act as a promising treatment modality in renal cancer [30,31].

6.3. Medulloblastoma

In 2007,Gessi et al. found out evidence of increased secretion of PTHrP by medulloblastoma cells. Also, cell treatment with PTHrP antisense oligonucleotides resulted in a radical decrease of cell proliferation and inactivation of apoptosis. This suggested that PTHrP could promote tumor growth, shielding cells from apoptosis.

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