《招待講演》

PTH-related Protein: A New Tumor Marker

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The syndrome of humoral hypercalcemia of malignancy (HHM) shares many similarities with primary hyperparathyroidism, including increased osteoclastic bone resorption, reduced renal calcium excretion, increased renal phosphorus excretion and increased nephrogenous cyclic AMP production. However, true ectopic PTH production has never been convincingly demonstrated in HHM. A number of biochemical and histomorphometric differences also exist between HHM and primary hyperparathyroidism, such as the absence of renal bicarbonate wasting with the subsequent hyperchloraemic acidosis seen in primary hyperparathyroidism, and reduced rates of bone formation and reduced intestinal calcium absorption compared with primary hyperparathyroidism.

A number of bone resorbing factors have been proposed as causes of HHM, including prostaglandins, prostaglandin-stimulating factors, cytokines, 1-25-dihydroxyvitamin D_3, and transforming growth factors. However, none of these factors have been able to reproduce the PTH-like adenylate cyclase-stimulating activity displayed by tumours associated with HHM. Therefore, it seems likely that PTH-like factors could account for most features of HHM. Evidence was produced that tumors produce a protein that acts through the PTH receptor but is immunologically distinct from PTH. We have recently purified and cloned a parathyroid hormone-related protein (PTHrP) implicated in HHM from a human lung cancer cell line (BEN). Full-length cDNA clones have been isolated and found to encode a prepro peptide of 36 amino acids and a mature protein of 141 amino acids. Eight of the first 13 amino-terminal residues were identical with human PTH, although antisera directed to the amino-terminus of PTHrP do not recognize PTH. The striking homology with PTH about the amino-terminal region is not maintained in the remainder of the molecule. PTHrP therefore represents a previously unrecognized hormone and may have arisen from the PTH gene by a process of gene duplication, yet remaining a distinct gene product.

Antisera raised against synthetic peptides corresponding to various parts of the PTHrP molecule have been developed and characterized. Highly specific antisera have been used in immunohistology to localize PTHrP consistently in squamous cell carcinomata, renal cortical carcinomata and in some breast cancers. In normal tissues, PTHrP has been immunohistochemically localized in keratinocytes and PTHrP-like activity has been extracted from ovine placenta and fetal ovine parathyroids.

The high incidence of hypercalcemia and of increased nephrogenous cyclic AMP in patients with squamous cell carcinoma of the bronchus point to the likelihood that plasma assays for PTHrP will be useful in the early diagnosis and follow-up of patients with this disease. The evidence for involvement of PTHrP in certain other cancers will also be discussed. Highly specific antisera are being used in development of plasma assays. It is likely that a two-site assay will be necessary in order to achieve sufficient sensitivity. This is the subject of current work, which includes studies of the predominant circulating forms of PTHrP.

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