Mechanism of parathyroid tumourigenesis in uraemia

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Abstract Clonal analysis has shown that in renal hyperparathyroidism (2-HPT), parathyroid glands initially grow diffusely and polyclonally after which the foci of nodular hyperplasia are transformed to monoclonal neoplasia. There is a great deal of information about genetic abnormalities contributing to the tumourigenesis of parathyroid neoplasia in primary hyperparathyroidism. It is speculated that allelic loss of the \textit{MEN1} suppressor gene and overexpression of cyclin D1 induced by rearrangement of the parathyroid hormone gene may be the major genetic abnormality in sporadic parathyroid adenoma but not in 2-HPT. The pathogenesis of 2-HPT, abnormality of the \(\text{Ca}^{2+}\)-sensing receptor (CaR) gene and the vitamin D receptor gene may possibly contribute to parathyroid tumourigenesis in 2-HPT. However, this is not yet clear and heterogeneous and multiple genetic abnormalities may be responsible for the progression of secondary parathyroid hyperplasia.

Introduction

It is well known that in chronic renal failure, hypocalcaemia, vitamin D3 deficiency, and phosphate retention stimulate parathyroid hormone (PTH) synthesis, PTH secretion, and proliferation of the parathyroid cells. Nevertheless, it is still not understood how these stimuli contribute to parathyroid cell hyperplasia in chronic renal failure. In our department, we performed parathyroidectomy in advanced renal hyperparathyroidism (2-HPT) refractory to medical treatment in 773 patients. We have been evaluating the histopathology and pathophysiology of 2-HPT using specimens which were obtained at operation to clarify the process and mechanism of parathyroid hyperplasia induced by uraemia. In this article, we focus on the proliferative process of parathyroid hyperplasia caused by uraemia as well as the possible genetic abnormalities contributing to parathyroid tumourigenesis.

Histopathology

Histopathological studies have shown that the characteristic histopathological findings of 2-HPT can be characterized as asymmetric enlargement, nodularity, and an increase in oxyphil/transitional oxyphilic cells. Parathyroid hyperplasia in 2-HPT can be divided into four types. Based on the relationship between glandular weight and hyperplastic pattern in our series, it is obvious that as the gland becomes heavier, the hyperplastic pattern changes the initial diffuse hyperplasia to early nodularity, and then to nodular hyperplasia and ultimately to a single nodule. It was confirmed that nodular hyperplastic parathyroid tissue has a greater growth potential than diffuse hyperplasia by image cytometric DNA analysis and immunohistochemical studies on proliferative cellular nuclear antigen and Ki67 [1]. Using clonal analysis by random inactivation of the X-chromosome-linked gene we found that diffuse hyperplasia proliferates polyclonally, whereas nodules of nodular hyperplasia grow monoclonally [2]. It is suggested that the cells in the nodules are transformed monoclonally possibly induced by some kind of genetic abnormality (‘genetic hit’). It is speculated that the genetic hit may occur randomly in the cells. This hypothesis would explain the asymmetric enlargement of parathyroid glands in 2-HPT. In diffuse hyperplasia, the genetic hit has not yet occurred, and the glands are small. Early nodularity is not long after the genetic hit, and the nodules are small. When the genetic hits occur in multiple cells in a gland, the cells have been proliferating aggressively and therefore made multiple nodules. If the genetic hit occurs in only one cell in a gland, the gland enlarges homogeneously in the same way as a primary adenoma (single nodular gland) (Figure 1).

Genetic abnormality in primary hyperparathyroid disease [3]

The gene responsible for the \textit{MEN1} suppressor gene was mapped to the long arm of human chromosome 11 [4]. More than half of the parathyroid tumours in \textit{MEN1} demonstrated loss of alleles from chromosome...
Diffuse hyperplasia

* Hit of genetic abnormality

Early nodularity in diffuse hyperplasia

Single nodular gland

Nodular hyperplasia

Fig. 1. Hypothesis for parathyroid hyperplasia in renal hyperparathyroidism. In diffuse hyperplasia, the genetic hit has not yet occurred. Early nodularity is not long after the genetic hit and the nodules are small. When the genetic hit occurs in multiple cells in the gland, the cells have been proliferating aggressively and there are many nodules in the gland. If the hit occurs in only one cell in the gland, the gland enlarges homogeneously (single nodular gland).

11, and it can be concluded that inactivation of both copies of the MEN1 locus may result in a monoclonal tumour component. Allelic loss of the MEN1 gene was found in 20–30% of sporadic parathyroid adenomas, and it is speculated that loss of the gene may be one of the genetic disorders responsible for parathyroid adenoma.

Arnold et al. showed that a DNA rearrangement had occurred at the PTH locus which conceivably placed a newly adjacent gene under the influence of the PTH regulatory element [5]. These genes encode a cyclin, called cyclin D1. It is reported that cyclin D1 is combined with cyclin-dependent kinase (cdk) and phosphorylate retinoblastoma gene products (pRB) and induces the G1–S transition in the cell growth cycle. Arnold et al. found rearrangement of the PTH gene in only about 5% of parathyroid adenomas [5]. In an immunohistochemical study, Hsi et al. recently found overexpression of cyclin D1 in 18% of primary parathyroid adenomas [6], and in our series, 40% of parathyroid adenomas over-expressed cyclin D1. In sporadic hyperparathyroidism, over-expression of cyclin D1 induced by PTH gene rearrangement has been suspected as one of major abnormalities for parathyroid tumourigenesis.

Recent reports have indicated that in sporadic parathyroid adenomas, frequent loss of heterozygosity was observed on chromosomes 1p, 6q, 11p, 11q, and 15q. The authors suggested the existence of a novel tumour-suppressor gene on these chromosomes that contributes to the pathogenesis of parathyroid tumourigenesis [7,8].

Crüns et al. demonstrated tumour-specific loss of the RB gene DNA in all parathyroid carcinomas and that 88% of the carcinomas had abnormal expression of pRB [9].

Genetic abnormality in sporadic primary hyperparathyroidism (apart from parathyroid carcinoma) has not yet been confirmed and it is suggested that heterogeneous abnormality contributes to parathyroid tumourigenesis.

Possible genetic abnormality in renal hyperparathyroidism [3]

Falchetti et al. found a loss of heterozygosity on chromosome 11, including the MEN1 gene, in only two markedly enlarged glands [10]. However, tumour-specific clonal loss of heterozygosity at 11q13 in uraemic patients has not been found by other investigators. It is speculated that abnormality of the MEN1 gene may not be a major abnormality in parathyroid hyperplasia in 2-HPT.

We could not find over-expression of cyclin D1 in secondary hyperplasia including single nodular glands although this had been detected in 40% of primary adenomas. Compared with diffuse hyperplasia, nodular hyperplasia showed significantly greater expression of cyclin D1, pRB, and Ki67. These results suggest that in 2-HPT, overexpression of cyclin D1 is not the genetic abnormality responsible for tumourigenesis and that some genetic changes seem to contribute to the expression of cyclin D1 and aggressive proliferation, both primarily and secondarily.

PTH secretion is abnormally regulated by Ca\(^{2+}\) both in vivo and in vitro in 2-HPT especially in nodular hyperplasia [1]. This can be explained by the finding that these receptors in nodular hyperplasia was significantly reduced, compared with that in diffuse hyperplasia in both mRNA and protein concentrations [11]. It is speculated that abnormality of the CaR gene may play a role in parathyroid tumourigenesis in 2-HPT. It is very interesting to note in the report of Farnebo
et al. [8] that they detected a loss of heterozygosity in chromosome 3q on which the CaR gene is located in about 10% of parathyroid tumours from uraemic patients.

Individuals with chronic renal failure appear to have a reduced number of vitamin D receptors and these receptors might be upregulated by calcitriol itself. It is suggested that a reduction of vitamin D receptors is one cause of progression in 2-HPT and might possibly explain the abnormal pathophysiology and proliferation of parathyroid cells. We found that the immunohistochemical expression of vitamin D receptors in nodular hyperplasia was significantly less prominent than in diffuse hyperplasia. It is possible that abnormalities in the mechanism of the vitamin D–vitamin D receptor complex contribute to parathyroid tumourigenesis either directly or secondarily.

It can be concluded that the genetic abnormalities contributing to parathyroid tumourigenesis in 2-HPT have still not been confirmed conclusively and that heterogeneous and multiple processes may be involved. We suspect that the genetic abnormalities may amplify the cyclin D1 gene and stimulate phosphorylation of pRB and induce G1–S transition.

References