REVIEW ARTICLE

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Parathyroid gland angiogenesis in secondary hyperparathyroidism: an overview

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ABSTRACT

Secondary hyperparathyroidism is a common complication of chronic kidney disease. Increased parathyroid hormone synthesis and secretion is associated with parathyroid hyperplasia. The exact mechanism involved in parathyroid gland hyperplasia is still poorly understood. The hyperplasia observed during the development of secondary hyperparathyroidism necessarily needs the support of an angiogenic process.

There are limited data evaluating the angiogenic process of the parathyroid glands in patients with parathyroid proliferative lesions. Our results suggest that the parathyroid gland in patients with secondary hyperparathyroidism has a significant expression of neovessels and an increased expression of the angiogenic factors b-FGF and VEGF-A.

In this article, we review the evidence which supports the importance of angiogenesis in primary and secondary hyperparathyroidism.

Key-Words:
Angiogenesis; parathyroid gland hyperplasia; secondary hyperparathyroidism.

INTRODUCTION

Normal parathyroid cells are characterised by an extremely low turnover. Their mean life span has been estimated, using the expression of cell cycle-associated nuclear antigen Ki-67, to be approximately two years in adult rats and twenty years in adult humans[1].

Under physiological steady-state conditions, at least in normal adult life, the rate of parathyroid cell apoptosis should equal that of proliferation and therefore be comparably low[1].

Primary and secondary hyperparathyroidism are two pathological conditions with chronic increase in PTH secretion. There is clear evidence that this overproduction of PTH is accompanied by an increase in parathyroid gland size[2,3,4]. This feature is not exclusive to parathyroid glands and occurs in most endocrine organs, in which secretory overactivity is generally associated with hypertrophy and/or hyperplasia.

In the normal parathyroid gland, the cells are relatively quiescent and very few cells proliferate. In secondary hyperparathyroidism the mineral and hormonal imbalances, particularly low serum calcium, high serum phosphorus, low $1,25(OH)_2D_3$ and uraemia lead to polyclonal and oligoclonal parathyroid cell proliferation, parathormone (PTH) gene expression and to increased PTH secretion[5].

Angiogenesis is the process of new blood vessel development from preexisting vasculature. Under normal circumstances, the microvasculature is maintained in a quiescent state. Angiogenesis is a very complex, tightly regulated process which occurs only

rarely in the adult vascular apparatus. It is a dynamic integrated process involving basement membrane degradation, endothelial cell proliferation and migration and capillary tubule formation. Wound healing and the menstrual cycle are physiological conditions associated with increased angiogenesis.

Angiogenesis is a necessary event for tumour growth and metastasis, and antiangiogenic therapy represents an important and promising strategy for cancer treatment. Antiangiogenic agents are designed to attack the tumour vessels and prevent the blood supply from providing the necessary nutrients for tumour growth[6].

Dysregulation of angiogenesis with excessive blood vessel formation has also been implicated in such pathological, nontumoural conditions as rheumatoid arthritis, psoriasis, endometriosis and diabetic retinopathy[7,8].

The angiogenic phenotype depends on the balance of proangiogenic growth factors such as vascular endothelial growth factor (VEGF) and inhibitors, and interactions with the extracellular matrix, allowing for endothelial migration.

VEGF-A plays an important role in the physiological and pathological angiogenesis. This growth factor induces proliferation and migration of endothelial cells[9] and increases endothelial permeability by inducing fenestrations in the endothelium[10]. VEGF also inhibits apoptosis of endothelial cells in newly formed vessels[11].

Fibroblast growth factors are polypeptide growth factors which show potent mitogenic activities for cells of mesodermal and neuroectodermal origin. The family of fibroblast growth factors (FGFs) regulates many developmental processes, including brain patterning, branching morphogenesis and limb development[12]. Fibroblast growth factor (FGF)-2, also called basic FGF (bFGF), is another potent angiogenic factor produced by endothelial, stromal and tumoural cells as well as being released from the extracellular matrix. FGF-2 stimulates proliferation of endothelial cells[13,14].

Blood supply is essential for the normal function and control of hormone feedback loops of endocrine glands which are typically vascular organs.

The hyperplasia observed during the development of secondary hyperparathyroidism necessarily needs the support of an angiogenic process. There are limited data evaluating the angiogenic process of the parathyroid glands in patients with parathyroid proliferative lesions. A regulatory effect originated in vascular parathyroid tissue raises the possibility of using angiogenic inhibitors to prevent gland hyperplasia or induce apoptosis and gland involution by simply reducing the vascular support necessary for the maintenance of parathyroid tissue metabolic functions.

In this article, we review the compelling evidence that supports the importance of angiogenesis in primary and secondary hyperparathyroidism.

PARATHYROID GLAND ANGIOGENESIS

Parathyroid gland transplantation with implantation of the parathyroid tissue in the muscle structures of the forearm is a relatively common surgical procedure. The implanted tissue develops its own vascularisation and is capable of maintaining function.

In 1984 Saxe *et al.*[15] used an established *in vivo* model to test for the ability of human parathyroid tissues from patients with clinical diagnoses of adenoma and hyperplasia to evoke angiogenesis. Pieces of parathyroid tissue from each patient were placed on the irises of rabbits, and the investigators were able to observe that both adenomatous and hyperplastic human parathyroid tissue demonstrated angiogenesis with approximately the same frequency.

Carter *et al.*[16] used a three-dimensional intact microvessel angiogenesis system to evaluate the role of VEGF in the stimulation of angiogenesis by human parathyroid cells. They treated freshly isolated rat microvessels, embedded in a three-dimensional collagen I matrix with fragments of human parathyroid tissue or isolated parathyroid cells and used Gs-1 lectin, a marker for rat endothelium, and image analysis to assess linear growth of the microvessels. Parathyroid production of VEGF was determined with rt-PCR. They were able to observe that parathyroid tissue expresses low levels of VEGF mRNA, which was significantly upregulated on explantation. The increased VEGF expression was shown to be essential to drive parathyroid-induced angiogenesis

in their model, even though the angiogenesis induced exceeded the levels expected for an isolated effect of the VEGF-A, suggesting that other factors could be implicated in the process[16]. One of those factors, basic fibroblast growth factor, synergises with VEGF in the endothelial cell culture[17]. Interestingly, the presence of bFGF and its receptor has already been identified in parathyroid adenomas, in primary and also secondary PTG hyperplasia[18].

De La Torre *et al.*[19] demonstrated increased angiogenesis in parathyroid proliferative lesions compared with normal glands and also suggested a proangiogenic role of bFGF in parathyroid tissue. They analysed microvascular density, lymphatic vascular density, and expression of angiogenic and lymphangiogenic growth factors in thirteen normal parathyroid glands, 77 parathyroid adenomas, and seventeen primary parathyroid hyperplasia. Immunohistochemistry was used for CD34 and LYVE-1, specific markers for vascular and lymphatic endothelium, respectively, and also for the vascular endothelium growth factors VEGF-A, VEGF-C, and bFGF. Microvascular density was higher in primary parathyroid hyperplasia and parathyroid adenomas than normal parathyroid glands. In contrast, bFGF expression was higher in parathyroid hyperplasia than parathyroid adenomas and normal parathyroid glands. bFGF scores and microvascular density were significantly correlated. Lymphatic vascular density did not differ among groups, and VEGF-C expression was unrelated to lymphatic vascular density. There was no relationship between microvascular density and tumour behaviour (adenoma size, PTH, or calcium)[19].

CD105, also known as endoglin, is a tissue-specific 180 kDa transmembrane glycoprotein constitutively phosphorylated. CD105 is associated with proliferation and it is a hypoxia-inducible protein abundantly expressed in angiogenic endothelial cells[20]. It is predominantly expressed in endothelial cells and its promoter is strongly and selectively active in endothelial cells. Human microvascular endothelium and tissues with active angiogenesis, such as regenerating and inflamed tissues or tumours, have shown elevated levels of CD105 expression[21]. CD105 is a component of the receptor complex of Transforming Growth Factor (TGF)-β, a pleiotropic cytokine involved in cellular proliferation, differentiation and migration. It binds several components of the TGF-β superfamily. Interestingly, binding of TGF-β1 to CD105 reduces the levels of CD105 phosphorylation and the levels of CD105 expression modulate the effects of TGF-β1. The inhibition of CD105 expression enhances the ability of TGF-β1 to suppress growth, migration and capacity to form capillary tubes of cultured endothelial cells[21]. In the absence of TGF-β1, CD105 shows an anti-apoptotic effect in endothelial cells under hypoxic stress, suggesting a protective role of CD105 against pro-apoptotic factors.

Although the functional role of CD 105 is not fully understood, several findings suggest its involvement in angiogenesis and vascular development, and in maintaining vessel wall integrity.

The assessment of neovascularisation by CD105 staining has been found to represent a potential predictor of prognosis in different solid malignancies[21].

Another study focussed on parathyroid gland angiogenesis and examined immunohistochemical expression of CD105, VEGF and VEGF-R2 and its potential role in distinguishing parathyroid hyperplasia from neoplasia. Positive CD105 immunoreaction was significantly increased in parathyroid adenomas in comparison to primary and secondary hyperplasias. VEGF immunoreaction was more common in adenomas. In samples with secondary hyperplasia, VEGF-R2 immunoreactivity was positively linked with VEGF expression as well as with the apoptotic index of parathyroid cells. In secondary hyperplasia specimens, there was an inverse correlation between cyclin D1 immunoexpression and angiogenic indexes, such as CD105 and VEGF[22].

More recently the role of growth factors, such as insulin-like growth factor 1 (IGF-1), bFGF, VEGF, and transforming growth factor beta 1 (TGF-beta 1) on human parathyroid adenoma cell proliferation has been studied. The authors used parathyroid cell cultures prepared from six human adenomatous parathyroid glands that were surgically removed. IGF-1, bFGF, VEGF, and low-dose TGF-beta 1 promote cell proliferation, whereas high-dose TGF-beta 1 inhibits this phenomena[23].

Studying parathyroid glands from patients with secondary hyperparathyroidism, we sought to evaluate the angiogenesis and the expression of the angiogenic factors, bFGF and VEGF of hyperplastic glands in comparison to normal glands[24]. Twenty

one glands from haemodialysis patients with secondary hyperparathyroidism and eight normal human parathyroid glands encountered in surgical specimens of total thyroidectomy were used in our study. Cell proliferation was evaluated by immunohistochemical expression of the proliferation cell marker Ki67. Angiogenesis was evaluated by immunohistochemistry staining with anti-endoglin (CD105) antibody and the expression of angiogenic factors b-FGF and VEGF were determined by semi-quantitative analysis. We observed that the hyperplastic parathyroid tissue from chronic kidney disease patients with secondary hyperparathyroidism present an increased number of neovessels, accompanied by an increase in the angiogenic factors, VEGF-A and b-FGF[24].

There is very little data on the angiogenic process that occurs in the parathyroid glands from patients with primary and secondary hyperparathyroidism. The possibility of using angiogenic inhibitors to prevent parathyroid gland hyperplasia or induce apoptosis and gland involution by reducing the vascular support necessary for the maintenance of parathyroid tissue metabolic functions is of interest in our view.

Our data showed that parathyroid glands of patients with secondary hyperparathyroidism have an increased number of neovessels combined with an increased expression of angiogenic factors VEGF-A and b-FGF when compared to normal parathyroid glands. Studies using an animal model of secondary hyperparathyroidism are underway to evaluate the possible role of angiogenesis inhibitors in the prevention and treatment of parathyroid gland hyperplasia associated with secondary hyperparathyroidism.

Conflict of interest statement. None declared.

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