REVIEW

Angiogenesis of endocrine gland tumours – new molecular targets in diagnostics and therapy

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Abstract

Angiogenesis is one of the key stages in the development of neoplastic tumours, in which a small group of mutated cells transforms into a large malignant tumour metastasising to the neighbouring tissues and organs. The studies on the significance of neoangiogenesis in the progression of endocrine gland neoplasms have recently become one of the most rapidly evolving branches of molecular endocrinology. The induction of angiogenesis has been demonstrated to result from the imbalance between positive and negative factors which control this process. Our paper presents the results of current studies on the role of factors such as molecular markers of angiogenesis (e.g. vascular endothelial growth factor and basic fibroblast growth factor), metalloproteinases (which regulate the decomposition of the extracellular matrix) and their inhibitors, and adhesive molecules (e.g. soluble vascular cellular adhesion molecule-1 and soluble intracellular adhesion molecule-1) in the pathogenesis and diagnostics of endocrine gland tumours in humans. Also, we discuss new therapeutic strategies for inhibiting the growth of neoplasms by blocking the formation of blood vessels using angiogenesis antagonists, which inhibit various stages of angiogenesis. More and more data are being accumulated suggesting that these preparations could, in the near future, be used in the pharmacotherapy of some endocrine gland neoplasms.

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Introduction

The term angiogenesis denotes the process of formation of new blood vessels from pre-existing small capillaries already present in the tissues and organs. This phenomenon accompanies some physiological processes such as wound healing, morphological changes observed within the female's reproductive organs during the menstrual cycle and formation of the placenta in pregnancy (1). Excessive formation of blood vessels can also be observed in a whole range of pathological processes connected with the development of rheumatoid arthritis, diabetic retinopathy, endometriosis, psoriasis and juvenile angiomas (2, 3). In 1963 Folkman *et al.* (4) observed that neovascularisation occurs during the formation and growth of solid tumours. The formation of new blood vessels within neoplasms, which provide the tumour tissues with oxygen and basic energetic compounds, is a complex process. It involves not only mutated tumour cells, but also endothelial cells, the basal membranes of the nearest capillaries and the stroma of the neoplasm (5, 6). This fundamental observation has become a stimulus for further studies on the role of angiogenesis

in the course of carcinogenesis. In later studies it has been demonstrated that the formation of new blood vessels is the turning point after which a small tumour, not exceeding 1–2 mm³ in size (*carcinoma in situ*) transforms into a large neoplasm metastasising to nearby tissues and capable of distant metastasising (7–9). For the last 30 years many competing scientific laboratories have been striving to answer the fundamental question of how mutated neoplastic cells control neoangiogenesis in order to determine how this process can be stopped. The molecular mechanisms and mediators of interactions taking place during angiogenesis in malignant tumours and during metastasis to other organs are becoming better understood. It is assumed that the key stimulus triggering angiogenesis is a defect in the genetic apparatus of a mutated cell, which results in the formation of the so-called angiogenic phenotype (10, 11). As a result of point mutations in oncogenes, constant and excessive production of angiogenic growth factors occurs, which stimulates endothelial cells to migrate and proliferate. In turn, mutations or deletions of suppressor genes lead to impaired synthesis of endogenous proteins, which function as inhibitors of angiogenesis. The vast

Table 1 Angiogenic growth factors.

Heparin binding growth factors	Vascular endothelial growth factor (VEGF) Basic fibroblast growth factor (bFGF) Platelet derived endothelial cell growth factor (PDGF) Hepatocyte growth/scatter factor (HGFSF) Pleiotrophin
Other growth factors	Transforming growth factors (TGF- α , TGF- β) Epidermal growth factor (EGF) Insulin-like growth factor-I (IGF-I)
Mediators of inflammation	Tumour necrosis factors (TNF- α TGF- β) Interleukins (IL-8, IL-3)
Hormones	Oestrogens Proliferin Substance P Erythropoietin
Adhesive molecules	Vascular cell adhesion molecule 1 (VCAM-1) Intracellular adhesion molecule 1 (ICAM-1) E-selectin

majority of results indicate that the initiation of angiogenesis is a result of an imbalance between pro- and anti-angiogenic factors, in particular of a decrease in the production of inhibitory proteins. Molecular studies on many neoplasms demonstrated that an important role in the formation of an angiogenic phenotype in a neoplasm is played by the activation of the vascular-endothelial growth factor (VEGF) gene which also occurs in physiological conditions of ischaemia (12, 13). So far it has been proven that oncogenes such as: *v-ras*, *K-ras*, *v-raf*, *src*, *fos* and *v-yes* act as strong inducers of cellular expression of VEGF, basic fibroblast growth factor (bFGF) and other angiogenic cytokines (14, 15). However, the key role in this process is played by mutation within the suppressor gene p53, responsible for apoptosis and the ability to secrete the strong endogenous glycoprotein inhibitor of angiogenesis – thrombospondin-1 (TP-1) (16). Mutations of the p53 gene block the inhibition of cellular proliferation and cause increased expression of VEGF. Cytokine VEGF-A is the strongest of the six known VEGF mitogens of vascular endothelial cells (17). This factor has been detected in many organs, such as brain, kidney, liver and spleen. Tissue transcription of VEGF mRNA is stimulated by various growth factors and cytokines, including platelet-derived endothelial cell growth factor (PDGF), tumor necrosis factor (TNF)- α , transforming growth factor (TGF)- β and interleukin-8 (IL-8). VEGF may thus mediate the activity of other angiogenic cytokines, listed in Table 1. So far, three types of receptors for VEGF have been identified (18). Two of them: VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1) are localized on endothelial cells, while the third one, Flt-4, is found on the surface of lymphatic endothelium, and is connected with the process of lymphangiogenesis.

From the group of over 40 factors inhibiting angiogenesis detected so far thrombospondin-1 seems to be the most important. This glycoprotein is one of the

essential components of the extracellular matrix (ECM). Its synthesis is regulated by the p53 gene (19). Mutation of this gene impairs the transcription of mRNA of thrombospondin-1 and releases the cascade of apoptosis. Inhibitors of angiogenesis, apart from their effect on programmed cellular death, influence the processes of transcription of growth factors in cancer cells, as well as transfer of signals in endothelial cells. They may also influence the migration of endothelial cells and expression of adhesive molecules called E-cadherins (20). The inhibitors of angiogenesis described so far are presented in Table 2.

In the cascade of neoangiogenesis an important stage is degradation and remodelling of the basal membrane of vessels and other elements which form the structure of the extracellular matrix. Neoplastic cells are able to invade due to the release of enzymes called metalloproteinases (MMPs), which catalyse the digestion of collagen type IV, forming the skeleton of basal membrane of vessels (21, 22). Increased activity of MMPs was seen in the course of many cancers (23–27). So far 26 MMPs have been described, and divided into 4

Table 2 Angiogenic inhibitors.

Natural fragments of proteins and polypeptide modulators	Angiostatin Endostatin aaAT (fragment of antithrombin 3) Prolactin (16 kDa fragment) Thrombospondin (TSP-1) Troponin I Interferons (INF- α , INF- β) Platelet factor-4 (PF-4) Interleukins (IL-12, IL-4) Tissue inhibitors of metalloproteinase (TIMP-1, TIMP-2)
Hormones	Testosterone Methoxyoestradiol Somatostatin Melatonin

groups: collagenases, gelatinases, stromelysins and the so-called membrane MMPs (28). The regulation of the expression of these endopeptidases is also controlled by some growth factors and cytokines. The activation of some MMPs necessitates plasmin. This peptide is formed in the course of conversion of plasminogen (PA) by urokinase (uPA) or tissue (tPA) activators of plasminogen. Plasmin demonstrates wide proteolytic activity towards such elements of ECM as fibrin, fibronectin, laminin and some proteoglycans (29).

In turn, natural inhibitors of MMPs are tissue inhibitors of metalloproteinases (TIMPs) and α 2-macroglobulin produced in the liver. There are four types of TIMPs, among which two are the most common: TIMP-1 and TIMP-2. Tissue expression of TIMPs is enhanced by some pro-inflammatory cytokines and retinoids. It has been demonstrated that some neoplasms become more invasive if the activity of MMPs prevails over the activity of tissue inhibitors.

About 10 years ago these studies were brought from the laboratories into leading oncological clinics, where first attempts at pharmacological evaluation of the efficacy of anti-angiogenic therapy were undertaken. The evaluation of tissue expression and measurements of adhesive molecules, angiogenic cytokines, metalloproteinases and their inhibitors has become an important element in the diagnostics and monitoring of therapeutic and surgical treatment of some neoplasms. In recent studies an increased expression or concentration of VEGF in serum or urine has been seen in such neoplasms as: gliomas, and breast, lung, stomach, pancreas, liver, bladder and ovary cancers (9). In some neoplasms an increased level of another important growth factor, bFGF has also been observed. Increase in the level of this cytokine has been found in over 90% of patients with colorectal carcinoma in the highly dynamic stage of the disease (30). Nguyen *et al.* (31) reported significant elevation in the level of this peptide in over 30% of patients with various types of solid tumours and in 45% of patients with distant metastases. Disturbed balance between proteolytic activity of MMPs and their natural inhibitors is a factor enhancing the development of malignant tumours (32). Increased expression of MMP-2 and MMP-9 was seen in patients with colorectal, breast, prostate and kidney cancer.

Increase in the proportions between MMP-2, MMP-7, MMP-9 and TIMP-1, TIMP-2 is significant for the degree of invasiveness of prostate and uterine cervix cancer (33, 34). The analysis of various publications on the role of VEGF, bFGF and metalloproteinases in the aetiology of tumours suggests that monitoring of their concentration in body fluids constitutes an important prognostic factor in any tumour. In recently published reports the blood level of VEGF has been suggested to correlate positively with the stage of advancement of neoplastic disease, size of primary

tumour, presence of metastases to surrounding lymphatic nodes and formation of distant foci (5).

In this review we present the latest developments in the studies of angiogenesis with particular stress on the role of this process in the regulation and control of the development of endocrine gland neoplasms.

Angiogenesis and neoplasms of endocrine glands

Endocrine glands are among the best vascularised organs in humans. So far there have been few literature reports on the problem of angiogenesis in endocrine glands and the role of this phenomenon in the pathogenesis of hormone-dependent neoplasms. It seems that standardised methods of evaluation of the density of blood vessels detected by specific antibodies against antigen markers of endothelial cells (CD31, CD34 and von Willebrandt factor) may be of significance in the diagnosis and prognosis of neoplasms of this type. Histological angiometric analysis of hormone-dependent breast tumours and prostate tumours revealed that the density of blood vessels in the tumour showed positive correlation with the number of metastases, size of primary tumour and number of involved lymphatic nodes in the vast majority of the studied patients (35, 36).

However, the results of studies based on the analysis of measurements of the density of capillaries within endocrine tumours (Table 3) are not so unequivocal. The pioneer studies of Jungenburg *et al.* (37) demonstrated negative correlation between the density of vessels and invasiveness of pituitary tumours in humans. The network of blood vessels in pituitary cancers and adenomas was less dense than in adjacent normal tissue of the glandular part of the pituitary. Erroi *et al.* (38) compared the density of vasculature in pituitary tumours and demonstrated a significantly lower degree in prolactin macroadenomas than in microadenomas and normal tissue. The results presented above are consistent with those of Turner *et al.* (39, 40) which were obtained from a large clinical material base, which also included somatotrophic and corticotrophic tumours. The same group of authors demonstrated a significantly higher degree of vasculature of invasive pituitary adenomas of prolactinoma type, which are strongly correlated with the expression of MMP-9 in the tumour tissue (41). It has also been found that the vascular density was higher in gonadotropinomas than in the non-tumoral anterior pituitary gland (42). The inhibitors of angiogenesis are effective in the suppression of growth of the experimental pituitary tumour (43, 44), and the levels of angiogenic cytokines VEGF and bFGF are elevated in the peripheral blood of patients with pituitary adenomas (45). However, Gorczyca & Hardy (46) in angiographic studies

Table 3 Angiogenesis in endocrine glands neoplasms.

Neoplasms	Summary	Literature
Experimental pituitary tumours	Decrease in vessels density by fumagilin, TNP-470 and batimast in prolactinomas	Stępień <i>et al.</i> (43) Mucha & Stępień (44)
Pituitary tumours	Impaired micro-and macrocirculation in adenomas as compared with normal tissue	Erroi <i>et al.</i> (38)
	Increase in density of vessels in gonadotropic tumours	Turner <i>et al.</i> (40, 41) Pawlikowski (42)
	Increased peripheral blood levels of bFGF and VEGF in patients with pituitary denomas	Komorowski <i>et al.</i> (45)
Anaplastic thyroid cancers	Impaired circulation as compared with differentiated tumours	Herrmann <i>et al.</i> (52)
Thyroid medullary carcinomas	Positive correlation between vessels density and clinical malignancy	Fontanini <i>et al.</i> (51)
Adrenal phaeochromocytoma	Positive correlation between degree of vascularisation and invasiveness	Liu <i>et al.</i> (53)
Adrenal cortex tumours	No correlation between vascularisation and clinical malignancy	Kołomecki <i>et al.</i> (55)

detected the presence of additional arteries (which were not part of the portal system) in 66% of their patients with microadenomas of this organ, while Farnoud *et al.* (47) observed changes characteristic for increased vasculogenesis in the basal membrane surrounding cells of pituitary tumours in humans.

In the pathogenesis of pituitary tumours the role and abnormal function of folliculo-stellate cells (FS) located, among others, in the anterior pituitary has been widely discussed (48). It is well established that the FS cells produce many kinds of signalling molecules, e.g. nitric oxide, bFGF, VEGF, follistatin and interleukin-6, and are responsive to central and peripheral stimuli (e.g. pituitary adenylate cyclase, vasoactive intestinal peptide, oestrogens, tumour necrosis factor α , transforming growth factor β and interferon- γ) (49). Although FS cells do not produce any pituitary hormones, their special tendency to surround endocrine cells with their long cytoplasmic processes suggests that they regulate endocrine cells by intracellular communication. It has been documented that paracrine communication plays an important role, not only in the regulation of hormone secretion, but also in the development, growth, differentiation and possibly also vasculature of the anterior pituitary (49, 50). The origin and differentiation of FS cells, particularly the possibility that FS cells are stem cells which have the potential to differentiate into endocrine cells, has also been suggested (48).

Within the studies on the degree of vasculature of other neoplasms of endocrine glands those concerning thyroid cancers and neoplasms of adrenal cortex and medulla are worth discussing. In undifferentiated and anaplastic thyroid cancers only the number of blood vessels in medullary carcinoma positively correlated with shortening of life-span of the studied patients

(51, 52). However, the quoted authors did not record the mean density of vessels in healthy tissue not affected by thyroid neoplasm. Liu *et al.* (53) analysed the density of blood vessels in 42 cases of benign and malignant phaeochromocytomas. The mean vasculature density factor in malignant tumours was twice as high according to these authors, and correlated with histological features of infiltration in the capsule and surrounding tissues, involvement of blood vessels and formation of metastases. Sasano *et al.* (54) demonstrated that endothelial cell proliferation is the most important factor in the evaluation of the invasiveness of adrenal cortex tumours. Similar conclusions may be drawn from morphological studies by Kołomecki *et al.* (55). The described discrepancies seem to be due to the differences in histological character of newly created endothelium, and in particular to the presence of the phenomenon of the so-called fenestrations. The presence of fenestrations in pituitary blood vessels determines their impaired sensitivity to the mitogenic activity of VEGF which increases permeability (56).

Angiogenic cytokines and their inhibitors in hormone-dependent neoplasms

Measurements of tissue expression and levels of VEGF, bFGF and other pro- and anti-angiogenic factors in body fluids of patients with hormone-dependent tumours are a relatively new issue (Table 4). For this reason, their diagnostic and prognostic value is not so well known as for other types of neoplasm. In oestrogen-induced prolactin-secreting pituitary tumours Banerjee *et al.* (57) observed increased expression of

Table 4 Hormone-dependent neoplasms with increased expression of VEGF and/or bFGF.

Breast cancer
Ovarian carcinoma
Hydatid mole
Uterine cervix carcinoma
Prostate cancer
Pituitary tumours
Adrenal medulla and cortex carcinomas
Thyroid cancers
Apudomas

VEGF, and Iuchi *et al.* (58) found positive correlation between the content of this factor and invasiveness of somatotrophic tumours in humans. However, Ishikawa *et al.* (59) suggested that angiogenic activity of human PTTG (pituitary tumour transforming gene) is mediated by bFGF. In our studies increase in the levels of serum VEGF and bFGF has been observed in patients with various adenomas of pituitary, as compared with normal subjects (45). Likewise, the activity of MMP-2 and MMP-9 in pituitary tumours (irrespective of their type) is higher than in normal tissue (60).

Increased angiogenesis occurs in many pathological conditions in the thyroid, such as: development of goitre, Graves-Basedow disease, inflammation and neoplasms. In the 1990s Soh *et al.* (61) demonstrated increased expression of mRNA VEGF and increased release of VEGF in differentiated thyroid cancers, as compared with normal tissue. The authors also found that thyrotrophin (TSH) stimulated the release of VEGF. The intensity and characteristic distribution of anti-VEGF antibodies in immunohistochemical reaction in material obtained from patients operated for papillary thyroid cancer signifies local invasiveness and metastasising (62). Shingu *et al.* (63) demonstrated that the degree of tissue expression of bFGF closely correlates with clinical malignancy.

In our studies a significant increase in bFGF level in the blood plasma/serum of 22 patients with various forms of thyroid cancer was seen together with an unchanged level of VEGF (64). In the same group of patients we have detected, using the ELISA method, an increase in the level of soluble intracellular adhesion molecule-1 (sICAM-1) (in particular in anaplastic cancers) and of soluble vascular cellular adhesion molecule (sVCAM-1) in all studied forms of differentiated cancer. In the beginning of the 1990s Campo *et al.* (65) demonstrated increased expression of MMP-2 in the cells of papillary, follicular and medullary thyroid cancer.

Maruyama *et al.* (66) discovered elevated levels of MMP-2, MMP-9 and indeterminable levels of TIMP-2 in the serum of patients with papillary cancers. In benign adenomas the levels of MMP-2 and MMP-9 were similar to control values. These results are partly concordant with our observations, in which we

have also demonstrated an increase in the levels of MMP-3 and MMP-9 in medullary carcinomas (64).

Neoangiogenesis within the adrenal cortex and medulla during embryogenesis and regeneration is regulated by VEGF. The presence of VEGF mRNA was detected in both endothelial cells and in steroid hormone-producing cells of glomerular and trabecular zones. The production of VEGF in adrenal glands is regulated by adrenocorticotrophin (ACTH) (67). The appearance of the angiogenic phenotype has been suggested to be the key stage in the transition from benign adenoma to adrenal cortex cancer. In their studies de Fraipont *et al.* (68) demonstrated elevated levels of serum VEGF-A in cancers, compared with transitional forms and adenomas. On the other hand, the levels of TSP-1 determined in the same group of patients was highest in the group of benign adenomas and lowest in malignant cancers.

Increased expression of bFGF was observed in material sampled by biopsy from pheochromocytoma (69). In adrenocortical cancers Kjellman *et al.* (70) found increased expression of mRNA for MMP-2 and membrane type 1 matrix metalloproteinase compared with benign adenomas. Extensive studies by Kolomecki *et al.* (71) revealed that the blood concentration of VEGF and MMP-3 was significantly higher in patients with adrenal cortex carcinomas than in patients with benign hormonally inactive tumours. After surgical excision of the lesion the levels of VEGF and MMP-3 normalised and only increased again in the case of recurrence. The authors suggest that determination of the levels of VEGF and MMP-3 may be used as a potential marker of malignancy in tumours of incidentaloma type. The levels of bFGF, MMP-2, TIMP-2, MMP-8 and MMP-9 determined in the same material did not bring unequivocal results. Recently we have found that the levels of sVCAM and sICAM significantly increase in adrenal cortex cancers and that there is a positive correlation between the two studied adhesive molecules and VEGF level (unpublished observations).

The process of angiogenesis in the development of neoplasms in other endocrine glands is practically unknown. Fukuda *et al.* (72) demonstrated an increase in the expression of VEGF in the development of invasive forms of testicular seminoma in men and Tomito *et al.* (73) in their study on tumours originating from APUD cells (thyroid medullary carcinomas, adenomas and cancers of parathyroids, insulinomas) demonstrated significantly lower expression of MMP-1, MMP-2 and TIMP-1 in these tumours than in normal cells.

Perspectives of antiangiogenic treatment of neoplasms

Recruitment of endothelial cells by a tumour is an early event in angiogenesis, a process regulated at genetic

Table 5 Angioinhibitors tested in the Clinic.

Mechanism of action	Preparation
Inhibitors of basal membrane decomposition, blockers of metalloproteinase activity	COL-3, marimastat, AG 3340, amilorid, BMS-275291
Inhibitors of endothelial cells adhesion and reconstruction of capillaries	minocycline, squalamine $\alpha_v\beta_3$ Ab, vitaxin, $\alpha_v\beta_5$ Ab, derivatives of benzodiazepines
Inhibitors of proliferation, migration, chemotaxis, stimulators of endothelial cell apoptosis	Endostatin, angiostatin, IFN- α , IFN- γ IL-12, TSP-1 α,γ , TNP-470, combrestatin, talidomide
Inhibitors of endothelial cell proliferation, blockers of growth factors	PF-4, octreotide, suramin and its analogues, FGF-2Ab, antisense-FGF-2, VEGF Ab, antisense-VEGF, SU 6668
Inhibitors of cyto-oxygenase	Aspirin, GH-RH antagonists, celecoxib, rofecoxib
Inhibitors of intracellular transmission of signals	Genistein, gleevec, EMD 121974

and epigenetic levels. Therefore, the inhibition of angiogenesis as a way of treating cancers was first suggested by Folkman in 1971 (74). The novelty of this approach lies not so much in direct destruction of tumour cells but in controlling their growth by blocking particular stages of neoangiogenesis of vessels which supply oxygen and nutrients to the tumour tissues. Clinical testing of angiogenesis inhibitors has accentuated the need for surrogate markers of tumour angiogenesis activity (75).

The main aims of blocking neoangiogenesis within neoplasms are: (1) neutralisation of endogenous stimulators of angiogenesis, stimulation of the production or administration of endogenous inhibitors; (2) inhibition of proliferation, chemotaxis and migration of vascular endothelium cells; and (3) prevention of damage to basal membrane of vessels, disintegration of extracellular matrix and release of growth factors stored in it. Many molecular targets may be achieved by directed anti-angiogenesis.

The most important target is VEGF, as blocking its synthesis, immunoneutralisation or impairing transduction of the signal from surface receptor to the inside of cell nuclei inhibits not only neoangiogenesis but also the development of the neoplasm itself and the spread of metastases (76, 77). Another group of anti-angiogenic preparations contains antagonists of adhesive molecules and their receptors. In particular, studies on the application of antibodies against $\alpha_v\beta_3$ integrin seem promising, as the antibodies bind with the fibronectin of the matrix and cause apoptosis of endothelial cells (78–80). Another promising group of preparations currently under investigation is the metalloproteinase antagonists, which prevent disintegration of the extracellular matrix (81–85), and inhibitors of tyrosine kinase and farnesyl transferase, which impair the transduction of the signal and development of the angiogenic phenotype by neoplastic tissue endothelium (86, 87).

Recently the first experimental attempts at applying gene therapy in 13 of 40 known angioinhibitors and antisense oligonucleosides, which block the activity of

the gene encoding VEGF, have been undertaken (88–90).

Clinical studies

Currently several endogenous inhibitors and numerous other preparations inhibiting angiogenesis are in stage I – III of clinical trials (Table 5). None of these preparations has been accepted for the treatment of endocrine gland neoplasms in humans so far. Evaluation of the clinical efficacy of potential anti-angiogenic drugs is time consuming and expensive. It requires implementation of the newest techniques of blood flow measurements in the tumour (colour Doppler) and measurements of metabolic changes using positron emission tomography (PET). Also, determination of the correlation between angiogenesis visualised by magnetic resonance imaging (MRI) and the density of vessels determined by immunohistochemistry in microscopic preparations seems to be of great importance. Clinical efficacy may also be evaluated by monitoring the levels of angiogenic cytokines (VEGF, bFGF) and their inhibitors (TP-1, angiostatin, endostatin) in body fluids in the course of treatment.

The studies conducted in animals, as no clinical data are yet available, suggest that a combination of several drugs affecting various stages of angiogenesis is more effective than any single preparation. The physiological oestrogen metabolite 2-methoxyoestradiol (91) and toremifene citrate (92) also have a strong anti-angiogenic effect and appear to be a new anti-tumour compound with strong potential for clinical application. It has also been demonstrated that combined administration of inhibitors of angiogenesis, chemotherapeutics and radiotherapy is more effective than each of these methods alone (75, 93). Novel approaches using combinations of somatostatin analogues with anti-angiogenic drugs or gene therapy are of particular interest and may lead to important advances in the management of some endocrine cancers in the not too distant future (94–96). These

preparations, it seems, do not cause drug resistance and their toxicity is relatively small. In the near future they will become valuable adjuvant therapeutic agents in the treatment of endocrine glands tumours.

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