Neuroendocrine differentiation in human prostate tissue: is it detectable and treatable?

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INTRODUCTION

Until recently the available publications on neuroendocrine (NE) differentiation in the prostate were few compared with the voluminous literature related to NE cells in other organs, e.g. the gastrointestinal tract and lung. This situation has begun to change, with a marked increase in the number of publications related to NE differentiation in prostatic carcinoma. Nonetheless, research on the prostatic NE system is still in its infancy. Very little is known about the specific role that these cells have in the prostate, or their relationship to the pathogenesis, growth and prognosis of prostatic diseases. In this review we present some of the information that is known about NE cells and differentiation in the prostate. We then speculate on the potential role of NE differentiation in prostate carcinoma and how this differentiation may be clinically analysed and treated.

PROSTATIC NE CELLS: ORIGIN AND LOCATION

NE cells, in addition to basal and secretory cells, represent the third epithelial cell type of normal prostatic tissue [1]; all three cell types share a common origin from pluripotent stem cells. The stem-cell model, as defined by Bonkhoff and Rembumer [2], distinguishes three compartments in the prostatic epithelium: (i) the stem-cell compartment which is androgen-independent and unresponsive to androgen; (ii) the proliferation compartment of androgen-independent but androgen-responsive cells; and (iii) the differentiation compartment derived from committed basal cells, giving rise to androgen-independent NE cells, androgen-responsive basal cells and androgen-dependent secretory cells.

NE cells of the urethro-prostatic region were first described by Pretl in 1944 [3]. They represent a minor epithelial cell population which is present in the normal, hyperplastic and dysplastic prostate. NE cells are located in all regions of the human prostate at birth, but rapidly decrease in the peripheral prostate after birth and then reappear at puberty [4]. After puberty, the number of NE cells seems to increase until an apparently optimum level is reached, which persists from 25 to 54 years old [5]. The relationship of age beyond puberty to the number and distribution of these endocrine-paracrine cells has not been definitively assessed, but in the guinea pig these cells in the peripheral prostate increase markedly with adult age [6]. Studies on adult human prostates indicate that NE cells are more frequent in the periurethral ducts than in the peripheral parts of the gland [7]. Others [8,9] also described the presence of NE cells in the stroma of fetal and infantile prostates.

There are two morphological types of prostatic NE cells, i.e. open flask-shaped cells with long slender extensions reaching the lumen, and closed cells with no luminal extension [10]. Both cell types have a complex appearance with irregular dendrite-like processes extending between adjacent epithelial cells.

NE cells are further characterized by the presence of cytoplasmic dense core granules, and ultrastructural studies have shown these constitutive NE cell organelles to be markedly heterogeneous in size and form, suggesting the existence of several cell variants [10]. Abrahamsson et al. [1] summarized the histological and cytological patterns of NE cells in the prostate gland as: 'Ideally, a NE cell is defined as a cell of neuronal or epithelial type that fulfills all or most of the following criteria: it contains secretion granules; its secretion is essentially directed towards the blood; the secretion granules store peptide hormones and or biogenic amines; it is often argynophil or even argentaffin, and is immunoreactive to antiserum against neurone-specific enolase (NSE) or chromogranin A or other so-called NE markers.'

Immunocytochemical studies show that the androgen receptor is not expressed in prostatic NE cells, suggesting that they may function independently of androgen regulation [11].

PROSTATIC NE CELLS: FUNCTION

The function of NE cells in the prostate is unknown, but it is hypothesized that they may be involved in regulating the growth and differentiation of the developing prostate, and in regulating secretory processes in the mature gland. This hypothesis is based on three factors: (i) the morphology of the NE cells; (ii) the known function of the NE secretory products; and (iii) the analogy with the known physiology of NE cells in the peripheral system.

NE cells were defined by Pearse [12] as 'APUD' to refer to chemical characteristics of 'amine precursor uptake and decarboxylation', common to the cells of this system. The NE prostate cells produce serotonin, chromogranin A, chromogranin B, secretogranin or chromogranin C, and a thyroid-stimulating hormone-like peptide. Other granules are present in smaller subpopulations of NE cells, e.g. a calcitonin-gene family including calcitonin, katacalcin and calcitonin gene-related peptide, parathyroid hormone-related protein (PTHrH), and αvCG-like peptide. Finally, some peptides are inconsistently present in some NE cells, e.g. bombesin, gastrin-releasing peptide or somatostatin. These regulatory peptides may act through lumecrine, endocrine, paracrine and autocrine mechanisms. The rather long dendritic processes of these cells suggest paracrine regulation. The open cell type may be related to lumecrine secretion, but more probably
reflects sampling of the luminal contents to relay regulatory signals to epithelial prostatic cells, to maintain homeostasis of the exocrine secretion.

Some of these products have growth factor activity; e.g. serotonin, calcitonin gene-related peptide, bombesin, others have neurosecretory inhibitory properties (somatostatin) and others may be involved in regulating secretory processes (serotonin, chromogranins, bombesin, PTHrP) [13].

The most predominant product of prostatic NE cells is chromogranin A, a member of a family of acidic secretory proteins found in the secretory granules of a wide variety of endocrine cells and neurones. The function of chromogranin A is still an open question [14]; it may have extracellular bioactivity and act as an autocrine paracrine regulatory agent in secretory processes. Moreover, chromogranin A may modulate peptide hormone processing because it has several dibasic sites, which possibly serve as competitive substrates for proteolytic enzymes [14].

Another secretory product commonly associated with prostatic NE cells is serotonin, a biogenic amine that mediates different functions by binding to several receptor subtypes [15]. Growth factor activity has been attributed to serotonin, it may also be involved in regulating morphogenesis, and it has been shown to regulate the secretion of peptide hormones from endocrine cells [16]. Serotonin may also serve as a neurotransmitter and vasoactive agent; in the male genital tract, neurotransmitters including serotonin may be 'permissive' for androgen action [17]. Finally, NSE is often expressed by prostatic NE cells and is sometimes referred to as a marker of NE differentiation [14].

Expression of angiogenic factors such as platelet-derived growth factor and basic fibroblast growth factor has been shown in NE tumours. Intense granular cytoplasmic staining for vascular endothelial growth factor (VEGF) was reported in a cluster of NE-like cells in prostate carcinoma, and a similar distribution of VEGF and chromogranin A-positive cells, suggesting co-expression in some cells [18]. Therefore NE cells in the prostate might modulate angiogenesis and thus influence prostate growth and differentiation. A subpopulation of NE cells was also intensely stained with TGF-α antibody; TGF-α has been reported to be expressed in various NE tumours [19].

**PROSTATIC NE CELLS: REGULATION**

Prostatic NE cells show no proliferative activity; prostatic epithelial cells characterized by chromogranin A consistently lack the proliferation-associated Ki-67 and MIB-1 antigens [20]. Thus an important question is how these prostatic NE cells are regulated.

NE cells in normal and neoplastic prostate are devoid of androgen receptors, indicating that they are androgen-insensitive, but they express EGFR and c-erbB-2. Iwamura et al. [21] described the expression of human EGF-Rs in prostatic NE cells, suggesting that EGF is significantly involved in the regulation of these cells. The same authors also reported the expression of PTHrP and its mRNA in prostatic NE cells; EGF regulates the secretion of PTHrP and PTHrP may be involved in the regulation of EGF on NE cells. In conclusion, it seems that NE cells in the prostate gland are directly modulated by some growth factors (EGF, TGF-α) and not by hormones. Moreover, epithelial secretory and basal prostate cells probably influence NE cells by cross-signalling at their junctions [21]. NE cell regulatory pathways may also involve the cell’s products (neuropeptides, i.e. serotonin).

Diaz et al. [22] reported that expression of the NE marker chromogranin A in the LNCaP and DU-145 human prostate cancer cell lines was up-regulated by interleukin-1β and interleukin-6, and down-regulated by interleukin-2. In particular, interleukin-6 may influence prostate cell growth modulating NE activity in the prostate gland. In the prostate, interleukin-6 induces the formation of neurite extensions, and morphological features associated with NE differentiation and enhanced expression of neuronal markers [23]. Some authors also report that NE cells in the prostate are innervated by autonomic efferent nerves, suggesting the regulation of these cells by the nervous system [10].

**DETECTING NE DIFFERENTIATION AND ACTIVITY IN THE PROSTATE**

Serum levels of NE markers, particularly chromogranin A, could reflect the NE activity of prostate carcinoma and be used during the follow-up evaluation of advanced prostate carcinoma. There is co-expression of NE markers and prostate markers such as PSA in prostate carcinoma cells [24]. Serum levels of chromogranin A, pancreastatin, chromogranin B and C were evaluated and compared as serum markers in the follow-up of patients with prostate cancer [25]. Chromogranin A appears to be the best marker of NE activity, but in some poorly undifferentiated tumours, chromogranin B is the major component and could be expressed in poorly differentiated carcinomas that almost completely lack chromogranin A and C. According to Wu et al. [26], in about half of patients with metastatic prostate cancer increases in serum chromogranin A precede that of PSA, suggesting that chromogranin A is an early marker of prostate tumour progression.

Increased serum levels of chromogranin A were more consistent in patients with androgen-insensitive prostate tumours [27] and there was a significant correlation between NE serum markers and distant metastases, but not with locally progressive disease [27]. Patients with tumours and who had high plasma chromogranin A or NSE levels were suggested to have a poorer prognosis, which is less recognized by tumour grading alone, than those not presenting with this type of differentiation [27].

Angelsen et al. [25] reported a correlation between the number of chromogranin A-positive NE cells and serum chromogranin A levels in patients with prostate cancer. Serum chromogranin A levels must be interpreted cautiously in patients with impaired renal function or in those receiving treatment for peptic ulcer with drugs such as omeprazole, as these particular situations can induce high serum chromogranin A levels [28].

In contrast to chromogranin A, the utility of measuring NSE in patients with advanced prostate cancer is uncertain. The incidence of high NSE levels in patients with prostate cancer was lower than that of high chromogranin A levels [28]. Cussenot et al. [28] found that high NSE levels are more frequent during hormonal escape, but they have no prognostic value compared with chromogranin A expression and have poor concordance with immunohistochemical data.

Ischia et al. [29] measured secretoneurin, a product of proteolytic processing of
chromogranin C in patients with prostate diseases. Mean secretoneurin serum levels were significantly higher in patients with hormone therapy-resistant prostate cancer than in patients with prostatitis, BPH and localized prostate cancer. There was a statistically significant correlation between secretoneurin and chromogranin A levels, but not between secretoneurin and serum PSA levels. However, the determination of NE markers in serum may not be specific for prostate activity and only the analysis of a very large stratified population may determine whether there is a significant serum marker of NE activity in prostate cancer.

Immunohistochemical staining for NE products in prostate cancer has been used by several authors (Fig. 1); di Sant’Agnese [30] noted that the immunocytochemical detection of serotonin, generic NE markers and specific peptides in prostate tissue may not be a very good indicator of ‘true’ NE differentiation and activity in prostate carcinoma. Perhaps the immunocytochemical detection of these products indicates storage, but not necessarily production and/or secretion of the products. Indeed, high levels of constitutive secretion of NE products may result in minimal storage and minimal immunostaining. In addition, the presence of NE products may not be sufficient for activity, as receptors for those products are needed to effect their actions. A more specific method to detect NE cell activity is to analyse the gene expression of chromogranin A in prostate tissue by semiquantitative RT-PCR [31] (Fig. 2).

However, there is a problem about the type of prostate tissue sample; evaluating prostate biopsy specimens for NE differentiation may not provide a complete analysis. The problem of obtaining specimens which represent the real extent of NE differentiation in the prostate was shown by Cohen et al. [32].

A relatively new method proposed to detect NE differentiation is total-body somatostatin-receptor scintigraphy (SRS) (Fig. 3). This method takes advantage of the over-expression of type II somatostatin receptors on the cell surface of most NE tumours. Some authors showed that positive SRS strongly predicts the presence of tumours with NE differentiation [33]. SRS is undertaken after an intravenous injection with $^{111}$In-pentetreotide, a radioactive somatostatin analogue. Planar images of the body are taken in anterior and posterior projections at 4 and 24 h after injection with $^{111}$In-pentetreotide. The images are analysed qualitatively and semi-quantitatively. With this technique, the presence of NE differentiation both at the primary (prostate) and metastatic sites of tumours can be detected. We described a case with prostate cancer, showing high serum PSA levels (86 ng/mL) and normal bone scintigraphy and CT findings [34]. Histological sections from the prostate biopsy were assessed for chromogranin A expression by immunohistochemistry and more than one focus with extensive staining for chromogranin A was detectable in the tumour cells. High chromogranin A plasma levels (126 ng/mL; normal <90) were detected by radio-immunoassay. The patient underwent an iliac bone marrow biopsy and the histology showed tumour cell clusters positive for PSA on immunohistochemical staining. Moreover, the patient underwent SRS and an intense focus of abnormal $^{111}$In-pentetreotide uptake was detected in the left part of the prostate, with other foci of lower intensity in the iliac crest bilaterally at 4 h after injection. Six months later a new conventional bone scan was positive, and similar areas of abnormal uptake were detected.

**NE CELLS IN BPH**

There are markedly fewer NE cells and NE secretory products in mature nodules of BPH. However, it was also noted that small, presumably proliferating hyperplastic nodules, and what appear to be growth foci in somewhat larger nodules, contained abundant NE cells [35]. Additional studies showed a correlation between the proliferating cell marker Ki-67 expression in proximate non-NE prostate cells and the number of NE cells in BPH tissue [36]. NE cells may be important also in the homeostasis of the glandular structure and in the first phase of BPH development.
NEUROENDOCRINE DIFFERENTIATION IN PROSTATE CANCER

NE CELLS IN PROSTATIC CARCINOMA

Three NE tumour phenotypes can be distinguished: (i) small cell NE carcinoma, accounting for 1–2% of prostatic malignancy; (ii) carcinoid-like tumours, also rare and poorly defined; and (iii) conventional prostatic adenocarcinoma with focal NE differentiation [10], which is very common.

Immunohistochemical studies show that focal NE differentiation occurs in virtually all common prostatic adenocarcinomas [10,24]. This differentiation takes the form of individual cells or clusters of cells with NE differentiation, scattered among a predominant population of non-NE malignant cells. Extensive and multifocal NE features are detected in ~10% of all prostatic malignancies [10,24]. These tumours tend to be more aggressive and resistant to hormonal therapy.

There is currently no convincing evidence that neoplastic NE cells originate from transformed NE cells of benign glands or premalignant lesions. Immunohistochemical data show that foci of NE in prostate adenocarcinoma harbour a significant number of amphicrine tumour cells expressing both NE (chromogranin A) and exocrine (PSA) markers [40]. The frequent occurrence of intermediate differentiation between exocrine and NE cell types strongly supports the concept that NE tumour cells derive from exocrine (PSA-positive) cell types during tumour progression [40]. As well as normal NE cells, malignant NE cells are unable to proliferate.

The most frequent products are serotonin and chromogranin A, but nearly all of the normal products of prostatic NE cells have been described in cells with NE differentiation in prostatic carcinoma. Some of the regulatory peptides produced by NE cells in the prostate can affect prostate adenocarcinoma cell proliferation in vitro, as documented for bombesin, calcitonin and PTHrP [11,38]. An increased proliferative activity of non–NE tumour cells in the vicinity of NE foci is probably related to these findings. NE cells may also contribute to cancer progression increasing the anti-apoptotic activity through a hyperexpression of Bcl-2 [39]. Bcl-2 increases as prostate cancer becomes androgen-independent and there is a proportional relationship between the tissue levels of bcl-2 and NSE in most prostate cancers [39,41]. Furthermore, malignant NE cells consistently lack the androgen receptor [42]; their activity may represent an independent cofactor unrelated to the carcinogenic activity of androgens.

It has been suggested that patients with prostate tumours presenting with high chromogranin A levels have a poor prognosis [43]. However, some studies showed no prognostic differences in tumours with and without high serum chromogranin A levels [32,44]. These studies did not stratify their patients for tumour grade. Interestingly, when only analysing patients with poorly differentiated tumours, focal NE differentiation is a more significant independent prognostic factor [45].

Berruti et al. [46] analysed serum NSE and chromogranin A levels in patients with BPH, PIN, hormone-naive prostate cancer and hormone-refractory prostate cancer. High chromogranin A levels were noted particularly in 36% of patients with hormone-naïve disease and in 45% with hormone-refractory disease. There was no correlation between PSA and chromogranin A levels. The androgen-independent growth of prostate cancer can be caused by different mechanisms; one of these is receptor-specific paracrine or autocrine growth modulation of human prostatic cancer cells by neuropeptides secreted by NE cells. The role of NE cells and their secreted bioactive neuropeptides in the progression of human prostate cancer cells by neuropeptides secreted by NE cells. The role of NE cells and their secreted bioactive neuropeptides in the progression of human prostate cancer remains unknown.

NE DIFFERENTIATION AND HORMONE THERAPY

If NE cells are androgen-independent it would seem reasonable to suppose that: (i) androgen receptor-negative NE cells would increase in number despite hormonal suppression, and (ii) tumours with NE differentiation and androgen-receptor negativity may be resistant to hormonal manipulation.

Jongsma et al. [47] showed that the proliferation of prostatic cancer cell lines...
under conditions of androgen depletion can be modulated by neuropeptides which are known to be produced by NE cells, and the androgen suppression or depletion can lead to an induction of NE differentiation.

The NE component of prostate adenocarcinoma is resistant to hormone therapy; some studies showed that the number of NE tumour cells [47] and chromogranin A serum levels increase with escape of human prostate tumour from hormonal therapy [48,49]. Focal NE differentiation may help to identify patients who are more prone to endocrine therapy failure.

Ahlgren et al. [50] assessed the extent of NE differentiation in prostate cancer after 3 months of hormonal treatment. Radical prostatectomy specimens from patients randomized to 3-month neoadjuvant LHRH analogue treatment or to surgery alone were available for the analysis. Both the number of chromogranin A-positive cells and the proportion of NE-positive tumours were significantly greater (P < 0.003) in the neoadjuvant than in the control group. NE differentiation did not correlate with the decrease in serum PSA after hormonal therapy.

Currently we are analysing [31] serum concentrations and prostate gene expression (by RT-PCR) of chromogranin A and PSA in patients with prostatic cancer and BPH. In the latter, tissue samples for the analysis were obtained from radical prostatectomy. These patients will be progressively stratified on the basis of Gleason score and neoadjuvant LHRH-analogue therapy (3 or 6 months). In a few cases we found that in prostate cancers treated with LHRH analogue the serum chromogranin A levels were significantly (P < 0.01) higher than in the untreated group. On the contrary, serum PSA levels were higher in untreated than in treated patients. Chromogranin A and PSA mRNA were expressed in all prostate tissue samples analysed (both BPH and prostate cancer) with highest levels in prostate cancer tissue (P < 0.01). Considering treated and untreated prostate cancer cases separately, chromogranin A mRNA levels of treated cases were significantly higher (P < 0.05) than those of untreated prostate cancers. On the contrary, levels of PSA mRNA of untreated cases were significantly higher than those of treated cases.

Stratifying prostate cancer cases by Gleason score, the highest serum and mRNA levels of chromogranin A were in patients with a Gleason score of >7 and the difference between treated and untreated cases was more significant if limited to the analysis of these tumours. These results, if confirmed on larger and stratified populations, suggest that hormone therapy in prostate cancer induces different effects on PSA and chromogranin A.

The hypotheses that must be considered are: (i) chromogranin A may represent a useful marker to detect progression in poorly differentiated prostate cancer; (ii) chromogranin A may help in the analysis of androgen-independent growth and progression in prostate cancer; (iii) if chromogranin A mRNA expression reflects NE activity in the prostate, continuous androgen-suppression therapy seems to produce a hyperactivation of NE cells in the prostate. This may be one of the mechanisms by which prostate cancer progresses during hormonal therapy in an androgen-independent tumour. All these aspects would have significant implications for treating prostate cancer that is resistant to hormone therapy.

**NE DIFFERENTIATION IN PROSTATIC CARCINOMA: TREATMENT**

Many approaches to treating prostatic cancer rely on the responsiveness of this tissue to the androgen-oestrogen axis. However, a significant subset of prostate cancers involves the NE cells of this gland. These observations suggest an approach to therapy based on the growth characteristics of NE cells and the growth-regulating characteristics of NE products, e.g. chromogranins, PTHrP and other peptides. These approaches should be based on the NE regulatory axis, rather than (or in addition to) the gonadal regulatory axis.

Currently it is unknown how best to treat NE prostate cells. As these cells are post-mitotic and do not express androgen receptors, chemotherapy/radiotherapy and anti-androgen therapy probably are of little benefit; cytotoxic agents and radiation therapy predominantly affect cycling cancer cells.

Several of the peptides known to be expressed by NE cells in prostate cancer are potent candidates for drug therapy. NE carcinomas and foci of NE differentiation in carcinoma from various organ systems are known to express somatostatin receptors, which inhibit NE secretion and possibly NE growth [51]. Long-acting somatostatin analogues have had some positive effects on prostatic carcinoma [51,52]. This was initially thought to be an indirect effect by the action of somatostatin on central neurosecretory type cells, but it has recently been shown that there is also a more direct effect on prostate carcinoma [51]. Somatostatin analogues may inhibit NE tumour growth, directly interacting with somatostatin receptors that are present in both normal and malignant prostate cancer tissue.

**FIG. 4.** A possible treatment strategy for patients with prostate cancer in progression during hormonal therapy, based on chromogranin A determination. High or normal chromogranin A values are referred to serum levels and, if available, to mRNA expression on prostate tissue. CAB, complete androgen blockade.

How to treat?

- CAB
  - Biochemical and/or clinical progression
  - High chromogranin A and/or positive SRS
  - Normal chromogranin A and negative SRS
  - CAB + Long acting somatostatin analogue
  - - antiandrogen withdrawal
  - - modification of antiandrogen
  - - oestrogens
Bombesin is a small peptide produced by prostatic NE cells [10]. Because it is a potent mitogen bombesin may be useful in treating prostate cancer [42]. Bombesin antagonists inhibited the growth of a human small-cell carcinoma cell line both in vitro and in vivo [53]. Bombesin receptors have been detected on prostate carcinoma in vitro [54]. The bombesin antagonist RC-3095 inhibited the growth of Dunning R-3327 and AT-1 cells [53], but the remission produced by RC-3095 was of short duration, probably because of a down-regulation of the bombesin receptor.

Increasing evidence also indicates the presence of specific receptors for serotonin in prostate tissue. Moreover, some results suggested effects of selective serotonin receptor antagonists on the growth of human prostate carcinoma cell lines. The serotonin inhibitor pindobind inhibited the proliferation of androgen-independent tumour cell lines in a dose-dependent manner [55].

CONCLUSIONS

The study of the biology of NE prostate cells might answer questions about disease progression and hormone escape. The role of PSA has been questioned particularly in a subset of cases with hormone-refractory disease. Measuring NE markers might complement the PSA assay in selected cases of poorly differentiated and/or androgen-independent prostate tumours. The complementary information provided by NE markers with PSA is supported further by the presence of a correlation between chromogranin A and PSA levels. In these cases an increase in chromogranin A expression, despite low PSA levels, may indicate progression and a poor prognosis.

To clearly assess the prognostic significance of focal NE differentiation in prostate cancer, the most important criteria are the selection of cases on the basis of tumour Gleason score and concomitant or previous hormone therapies; moreover, the type, duration and intermittence of hormone therapy may be equally relevant.

The type of NE markers analysed is also important; this analysis is initially expected to be more accurate using radical prostatectomy specimens than prostate biopsy specimens. Different treatment strategies to affect NE differentiation in prostate cancer could be assessed. Our strategy is directed to patients initially undergoing hormone therapy; if there is tumour progression during complete androgen blockade we select how to modulate therapy on the basis of chromogranin A serum levels and/or chromogranin A mRNA expression (Fig. 4). In cases with high chromogranin A levels or positive findings on SRS, we combine hormone therapy with a somatostatin analogue. In cases with normal values for chromogranin A we continue with hormone therapy, modifying or suspending the anti-androgen used or adding oestrogens.

Further studies are needed to evaluate potential new therapeutic approaches which are directed against the NE component. It is possible that in the future, antagonist peptide growth factors, or antibodies to NE growth factors or their receptors, may be of use in treating prostate carcinoma with NE differentiation.

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Abbreviations: NE, neuroendocrine; NSE, neurone-specific enolase; PTHrH, parathyroid hormone-related protein; VEGF, vascular endothelial growth factor; SRS, somatostatin-receptor scintigraphy; PIN, prostatic intraepithelial neoplasia.