

INVITED EDITORIAL

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Neuroendocrine cells in the normal, hyperplastic and neoplastic prostate

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Abstract Neuroendocrine cells can be demonstrated in normal, hyperplastic and neoplastic prostatic tissues. The products secreted by these cells can be used as tissue and/or serum markers but may also have biological effects. Neuroendocrine cells in prostate cancer most probably do not contain the androgen receptor and are therefore primarily androgen independent. Some of the neuropeptides secreted by the neuroendocrine cells may act as growth factor by activation of membrane receptors in an autocrine-paracrine fashion or by ligand-independent activation of the androgen receptor in neighboring non-neuroendocrine cells. Evidence is accumulating from experiments with tumor models that neuropeptides indeed can influence the growth of prostatic tumor cells. Future research on neuroendocrine differentiation may answer some questions concerning the biological behavior of clinical prostatic tumors.

Key words Neuroendocrine differentiation · Prostate Neoplasm · Androgen sensitivity · Neuropeptide Experimental models

In most developed countries prostate cancer has become the most prevalent tumor in men and in these countries its mortality is only surpassed by that due to lung cancer [74, 106]. Much research done in the field of prostate cancer is directed towards the identification of factors involved in tumor progression and the change from androgen dependency towards independency. Neuroendocrine differentiation is a possible factor which has received increasing attention during the past few years [74].

Neuroendocrine (NE) cells are also known as APUD (amine precursor uptake and decarboxylation) cells or endocrine-paracrine cells [77]. The concept of NE/APUD cells was worked out by Pearse and coworkers from the diffuse endocrine epithelial organ concept of Feyrter [42, 77]. The APUD system consists of a group of apparently unrelated endocrine cells located in endocrine and non-endocrine tissues, which share a number of cytochemical, ultrastructural and functional characteristics [77]. In more detail, the endocrine/NE system consists of: the classical endocrine organs (e.g., adrenals, parathyroid gland), clusters of endocrine cells (e.g., pancreatic islets of Langerhans), dispersed epithelial endocrine cells (e.g., gastrointestinal NE cells), neurons and ganglia and the paraganglion system [39].

The clinical aspects of NE differentiation in prostatic carcinoma have been reviewed in more detail in a number of papers by Di Sant'Agnesse [30–32]. This review will therefore emphasize the experimental aspects: the role of NE cells in androgen insensitivity, tumor growth and progression. Nevertheless, some clinical data will be provided to better understand the concept and the questions that emerge from it.

Neuroendocrine cells in the normal prostate

In normal prostatic epithelium, NE cells are found among the well-known prostate specific antigen (PSA) producing exocrine cells and basal cells (Fig. 1) [2]. Such cells were described for the first time by Pretl in 1944 as the argentaffin basal cells [84]. In this study the argentaffin cells were identified by silver staining procedures as well as autofluorescence techniques [84]. Prostatic NE cells are located in the glandular and ductal epithelium and they form only a small part of the epithelial cell compartment. They clearly belong to the "dispersed epithelial endocrine cell" type [39]. NE cells are found throughout the whole prostate although they are more abundant in the periurethral and ductal regions [23]. In the guinea pig prostate the num-

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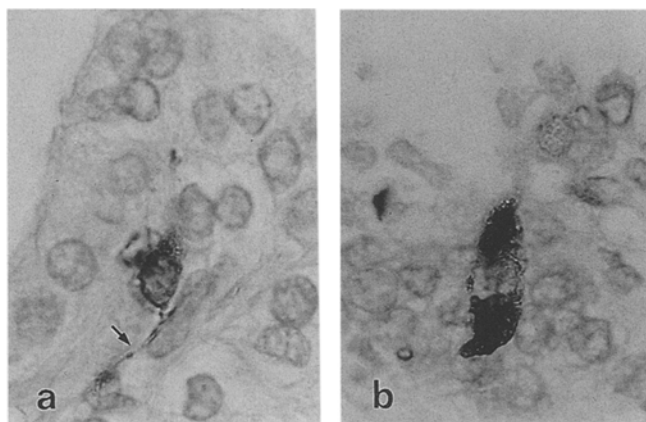


Fig. 1a, b Prostatic neuroendocrine cells. **a** Closed-type neuroendocrine cell with cytoplasmic process (*arrow*). **b** Open-type neuroendocrine cell. Chromogranin A staining with immunoperoxidase technique, nuclear counterstaining with hematoxylin, $\times 900$

ber of NE cells increases with age [38], a phenomenon which has not been described for humans [23]. NE cells in the glandular acini but not in the periurethral and ductal epithelium of the human prostate were found to disappear soon after birth and to reappear at puberty [23]. These findings suggest a direct or indirect effect of circulating androgens on the acinar NE cells but not on periurethral and ductal NE cells.

Morphologically, two types of prostatic NE cells can be recognized: a closed type separated by other cells from the lumen (Fig. 1a) and an open type reaching to the glandular lumen (Fig. 1b) [37]. The closed type often has dendritic cytoplasmic processes interdigitating between neighboring cells [37]. Prostatic NE cells are ultrastructurally characterized by so-called dense core granules or neurosecretory granules [36]. Based on the variations in the ultrastructural morphology of the granules a greater heterogeneity of NE cells has been suggested [36].

The heterogeneity of this cell type is also apparent from the variety of products (biogenic amines or peptide hormones) which they secrete. Chromogranin A and B (CgA and CgB), secretogranin II, neuron-specific enolase (NSE) and serotonin (5-HT) are found in most, if not all, prostatic NE cells [3, 8, 37, 90]. A small number of these cells also contain calcitonin (CT) and related peptides such as calcitonin gene related peptide (CGRP) and katacalcin [27, 29, 35, 40, 94]. In addition, somatostatin (SMS) [27, 34], bombesin/gastrin-related peptide (GRP) [29], β -chain midportion of thyroid-stimulating hormone [1, 4], glycoprotein hormone α -chain [41] and parathyroid hormone related protein have been found [50].

The chromogranins are acidic glycoproteins which are widely expressed in NE cells [112]. Various biologically active peptides can be released from the CgA and CgB molecules by enzymatic action [68, 112]. A third chromogranin (chromogranin C) is now known as secretogranin II [48, 112]. Most of the immunohistochemical studies on NE differentiation have been performed with antibodies specific

for CgA or 5-HT. NSE (γ -enolase, a subtype of the glycolytic enzyme enolase) was thought to be an exclusive marker of endocrine and NE cells, but it has been shown that NSE is secreted by a large variety of other cell types [49].

The heterogeneous morphology of the neurosecretory granules and the diversity of secreted products suggest that these cells exert a number of distinct functions, which so far have been virtually unknown. In parallel with functions of NE cells in more extensively studied systems (i.e., lung, pancreas and adrenals), a role of these cells in growth and differentiation, and in maintenance of homeostasis has been suggested [47, 99, 111]. Some of the neuropeptides share growth factor activity (reviewed in [25, 92, 105]). Relatively high levels of CT, GRP/bombesin and SMS have been found in human semen [45, 88, 98]. Exposure to salmon-CT (sCT) decreased sperm motility in vitro [44]. Furthermore, sCT also increased the secretion of prostatic alkaline phosphatase by rat ventral prostate explants in a dose-dependent manner [61]. These studies indicate that prostatic NE cells might also have some exocrine functions.

According to Feyrter's original concept of the diffuse endocrine organ, all NE cells throughout the body were thought to originate from the neural crest [59]. However, nowadays a local origin of the NE cells in most tissues is suggested and has been proven, for example, in colorectal epithelium [59]. A multidirectional differentiation has been postulated for normal tissues as well as for tumors arising in these tissues (reviewed by DeLellis [28]). In a recent immunohistochemical study, some prostatic NE cells expressed basal cell specific cytokeratins and a few NE cells in hyperplastic glands displayed immunoreactivity for PSA [8, 17]. These observations suggest a common differentiation pathway of prostatic secretory, NE and basal cells and it is now generally accepted that prostatic NE cells indeed originate from the prostate. It may be hypothesized that the basal cell layer contains the prostatic stem cells and that these cells give rise to both the exocrine and NE phenotypes of the glandular epithelium.

Neuroendocrine cells in the hyperplastic prostate

The presence of NE cells in hyperplastic prostatic tissue has been demonstrated using silver staining techniques [10, 57]. In one study, up to 16 out of 20 hyperplastic nodules displayed NE differentiation [10]. However, in another study it was found that hyperplastic nodules in general contained less argentaffin NE cells than the adjacent normal epithelium [57]. This was confirmed in a recent study using immunohistochemistry with a 5-HT antibody and chromatographic quantification of the 5-HT content of tissue homogenates [20]. On the other hand, Abrahamsson et al. [3] found more NE cells in hyperplastic prostatic tissue than in normal glands as defined by immunoreactivity for 5-HT, thyroid-stimulating hormone and CT. Aprikian et al. [8] found immunohistochemically defined NE cells in all investigated hyperplastic specimens, although their rela-

tionship with the adjacent normal glands was not studied. Whether or not neuroendocrine cells play a role in the pathogenesis of benign prostatic hyperplasia is not clear at the moment. The study of Cockett et al. [20] gives some support to this idea since they found more NE cells in small hyperplastic nodules than in normal prostate or large hyperplastic nodules. This suggests that the growth of the more immature small hyperplastic nodules is stimulated by NE products. Alternatively, the presence of NE cells may simply reflect an enhanced proliferative activity of glandular epithelial cells in prostatic hyperplasia.

Neuroendocrine cells in the neoplastic prostate

NE cells can be identified in prostate cancers (Fig. 2), although the percentage of tumors with NE cells varies in the literature from about 10% to almost 100%. This variation partially reflects the development of techniques used to identify NE cells. An extensive recently published study indicated that NE cells are present in about 60% of prostate cancers [8]. Two papers on the argentaffin cells in the hyperplastic and neoplastic prostate were published in the 1970s [10, 57], but only recently have NE cells in prostate cancer gained increasing attention.

According to Di Sant'Agnesse [31], the term NE differentiation in prostate cancer includes the pathological categories small cell prostate cancer (SCPC), prostatic carcinoid, adenocarcinoma with scattered NE cells and mixed tumors of these three types. A relatively small proportion of prostatic adenocarcinomas with NE differentiation contain NE cells with large eosinophilic granules. This phenomenon was termed Paneth cell like change [6]. Very recently it has been suggested that these cells be renamed "NE cells with large eosinophilic granules" [6, 33]. Obviously, the tumors with this type of NE cell also fit in the category of prostate cancer with NE differentiation. From a clinical point of view, prostate cancer with evidence of eutopic or ectopic production of neuroendocrine hormones and/or markers and prostatic malignancies associated with paraneoplastic syndromes linked to NE differentiation should also be included in the definition [31].

Undifferentiated small cell cancers, also referred to as NE carcinomas, occur in various organs, but most often in the lungs. SCPC is a relatively rare disease, accounting for $\pm 1-5\%$ of all prostate cancers, and has been described in a few larger studies [76, 86, 91, 104]. It is a highly malignant disease with a mean survival time of 7-17 months [76, 104]. In about half of the patients the small cell component is preceded by a common adenocarcinoma, suggesting that at least in a number of patients the small cell carcinoma arises in a common adenocarcinoma. In line with this suggestion, a number of mixed tumors have been found [76, 104]. Not all SCPC showed NE differentiation, however [86]. Prostatic carcinoid is a very rare entity. Only some case reports have been published as yet [7, 43, 67, 101, 109, 110]. Carcinoids occur especially in the digestive system (appendix) and they are in general relatively

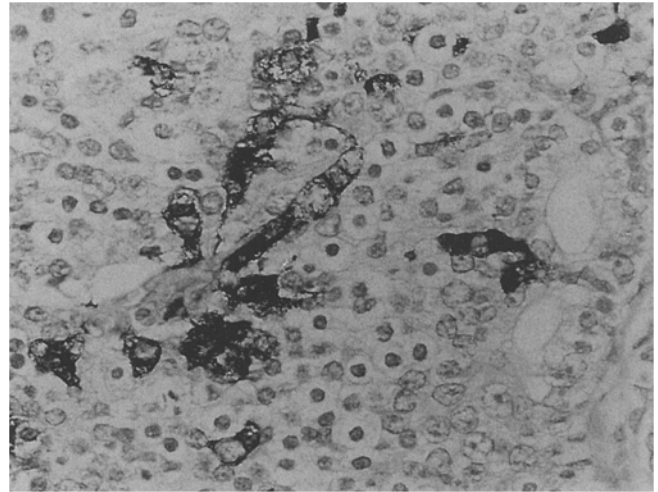


Fig. 2 Prostatic adenocarcinoma with neuroendocrine cells. Chromogranin A staining with immunoperoxidase technique, nuclear counterstaining with hematoxylin, $\times 175$

benign [46]. It appears that prostatic carcinoid tumors behave more aggressively [31, 101], although detailed studies with follow-up data are lacking. Mixed carcinoid-adenocarcinoma tumors have been found and it has been suggested that carcinoid formation in a hormonally treated adenocarcinoma might be a selective effect of the treatment [101].

The most common pattern of NE differentiation in prostate cancer is a prostatic adenocarcinoma with scattered NE cells. The number of NE cells within an adenocarcinoma varies from patient to patient and their presence may have prognostic significance [5, 18, 21, 22, 26]. Some authors found a relationship between the tumor grade and the number of NE cells [4, 5], but others did not [8]. NE cells were identified in about 50% of lymph node and bone metastases of prostatic adenocarcinomas [9]. This proves that NE cells are an intrinsic component of the adenocarcinoma and are not derived from preexistent benign glands. The presence of NE cells in metastatic lesions had no prognostic value [9]. Serum levels of CgA showed a 60% correlation with the immunohistochemical staining of this protein, and the presence of metastatic disease was better predicted by serum CgA levels than by tissue immunoreactivity [70]. The possible correlation between tumor grade and the number of NE cells in a tumor may well account for part or all of the reported prognostic value of NE differentiation, which would indicate that the number of NE cells just reflects the level of dedifferentiation of a tumor. This possibility can be investigated with long-term clinical follow-up studies using multiple regression analysis.

Secretion products and hormone sensitivity

NE cells in prostatic tumors are most often recognized by their immunoreactivity for NE markers (CgA, NSE) or eu-



Fig. 3 Androgen receptor (AR) and chromogranin A (CgA) double labeling in a benign prostatic gland. Nuclear AR staining with immunofluorescence technique (FITC, originally green). CgA staining with alkaline phosphatase technique (originally red fluorescence signal). Most epithelial cells display a strong AR positivity (*arrowheads*). The triangular-shaped closed-type neuroendocrine cell (*arrow*) is AR negative. $\times 250$ (Reproduced from [60] with kind permission)

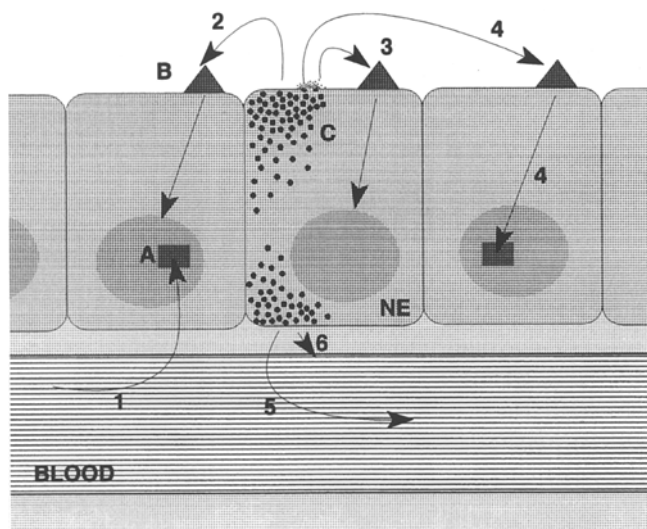


Fig. 4 Influence of a neuroendocrine (NE) cell on neighboring non-NE cells (working hypothesis). 1 actions of androgens mediated by the nuclear androgen receptor (A), 2, 3, 4 action of neuropeptides released from the neurosecretory vesicles (C) of the NE cell, 2 paracrine stimulation of neighboring non-NE cell by activation of neuropeptide receptor, 3 autocrine stimulation, 4 ligand-independent activation of androgen receptor in non-NE cell, 5 systemic action of neuropeptides secreted into the blood (paraneoplastic symptoms), 6 stromal effects of neuropeptides

topic bioactive peptides (5-HT, CT, SMS and others). In addition to the eutopic peptide products, a number of ectopic peptides have been found, for example, adrenocorticotrophic hormone (ACTH), leu-enkephalin and β -endorphin [4]. Expression of these factors, especially ACTH, might cause a paraneoplastic syndrome as occasionally found in prostate cancer patients (reviewed by Matzkin and Braf [65]). In high-grade tumors with marked NE differen-

tiation, CgB replaced CgA expression by NE cells [90]. This implies that in immunohistochemical studies CgA as well as CgB immunoreactivity has to be assessed.

Kadmon et al. demonstrated elevated CgA serum levels in 12 out of 25 patients with metastatic, hormone-insensitive prostate cancer [55]. Moreover, in 4 of these 12 patients PSA levels were in the normal range. Serum levels of NSE were found to be increased more often in patients with hormone refractory tumors (10/46) than in patients with hormone-sensitive tumors (2/89) [103]. Abrahamsson et al. studied NE differentiation in repeated biopsy specimens of patients treated with hormonal therapy or with radiotherapy [5]. They found mostly an increasing number of NE cells during follow-up paralleled by dedifferentiation and hormonal escape (i.e., progression) of the tumor. These results raise the question whether NE cells in prostate tumors are androgen sensitive or not. NE cells in benign and malignant prostatic tissues contained rarely, if at all, androgen receptor immunoreactivity (Fig. 3) [16, 60]. In another study, using a different antibody for the androgen receptor, prostatic NE cells generally expressed the androgen receptor [71]. Very recently the authors of the latter study confirmed the findings of the former two studies [33], leading to the conclusion that NE cells in the normal or neoplastic prostate do not contain the androgen receptor. It has been shown that the androgen receptor content of a prostatic tumor does not predict androgen (in)sensitivity [87, 107]. It is, however, unlikely that androgen receptor negative tumor cells will respond to androgen withdrawal. Therefore, NE cells in prostate cancer most probably form a primarily androgen-insensitive tumor cell population.

Growth modulation by neoplastic neuroendocrine cells

A number of peptides produced by NE prostatic tumor cells (5-HT, GRP/bombesin, CT, SMS) exhibit growth factor activities mediated by a membrane receptor. This may represent a way of paracrine or autocrine growth modulation [25, 92, 111]. Most of the prostatic adenocarcinoma cells surrounding NE cells contain the androgen receptor, even in androgen refractory carcinomas [16, 60]. It was found in COS cells transfected with steroid hormone receptors that dopamine activated several steroid hormone receptors (progesterone, estrogen, vitamin D and thyroid hormone β -receptors) in a ligand-independent fashion [83]. In this way NE tumor cells might influence the growth of neighboring non-NE tumor cells by androgen-independent activation of the androgen receptor in a paracrine manner. It is, however, not known yet if the androgen receptor can be activated similarly by neuropeptides and, therefore, this should be studied first. It should be stressed that neuropeptides may enhance or inhibit growth, depending on the specific nature of the neuropeptide and properties of the target cell. Bonkhoff et al. found in an immunohistochemical study that proliferating cells in normal, hyperplastic and cancerous prostatic tissues were usually, but not necessar-

ily, located in the proximity of clusters of NE cells [15]. This supports the concept of paracrine growth regulation by prostatic NE cells.

The following hypothesis can be postulated: NE cells in a prostatic adenocarcinoma form a subset of primarily androgen-independent tumor cells which modulate the growth of neighboring non-NE tumor cells by the secretion of neuropeptides in a paracrine manner (Fig. 4). Granted this hypothesis, one would expect that following androgen withdrawal the proportion of NE cells would increase. Abrahamsson et al. described in a group of 24 hormonally treated patients that the number of NE cells increased in time, although this was paralleled by dedifferentiation of the tumors (see above) [5]. Aprikian et al. were not able to confirm the observed increase in NE differentiation following short- or long-term hormonal therapy, however [8]. Larger follow-up studies on long-term androgen-depleted tumors with assessments of absolute and relative numbers of NE cells should confirm the occurrence of this phenomenon. Even if the NE cell population does not increase following androgen withdrawal, the secreted neuropeptides may still stimulate the surrounding non-NE cells by acting as "androgen substitutes." The secreted neuropeptides may also have effects on stromal cells (stromal-epithelial interactions), a possibility which has not been studied as yet.

Specific neuropeptides

Serotonin

Serotonin (5-HT) is well known as a neurotransmitter and vasoactive peptide and some recent reports indicate that 5-HT also has growth factor activity [56, 93]. 5-HT stimulated DNA synthesis in hamster fibroblasts proved to be mediated by activation of the 5-HT_{1b} receptor [93]. This receptor is only expressed in rodents. Further experiments indicated that in humans 5-HT mediates the proliferation of smooth muscle cells mediated through activation of the 5-HT_{1d} receptor [56]. 5-HT might influence tumor growth indirectly by changing the local blood flow in a tumor due to its vasoactive action. It is very likely that 5-HT plays a role in the prostate since it is expressed by most if not all prostatic NE cells [3, 8, 37]. Unfortunately, it is as yet not known if human prostatic tumor cells contain 5-HT receptors and, if so, which subtypes. If prostatic tumor cells contain 5-HT receptors, 5-HT may also exert its effect by ligand-independent activation of the androgen receptor [83].

Bombesin/gastrin-related peptide

Gastrin-related peptide (GRP) is the mammalian analogue of the amphibian peptide bombesin [102]. GRP stimulated the growth of cultured normal bronchial epithelial cells in a dose-dependent manner [111]. In vitro studies with cultured pulmonary NE cells demonstrated that treatment with

GRP increased the number of NE cells and stimulated their 5-HT expression while treatment with 5-HT did not [99]. It has also been shown that GRP stimulated growth of small cell lung cancer cells [24]. This effect could be blocked in vivo by an antibody against GRP and in vitro by GRP analogues, which prevent binding of GRP to its receptor [24, 64]. In vitro studies with the androgen-independent prostatic cancer cell line PC-3 similarly showed a growth stimulatory action of GRP which could be blocked by an anti-GRP antibody [14]. Saturable GRP-binding sites were demonstrated on PC-3 cells, but no immunoreactivity for GRP was demonstrated in these cells, excluding an autocrine action of GRP [14]. The GRP antagonist RC-3095 was able to inhibit the growth of the androgen-dependent human xenograft PC-82, the Dunning R-3327H rat prostate tumor and the androgen-independent DU-145 and PC-3 prostatic in vitro cell lines [66, 80-82]. Saturable GRP-binding sites were demonstrated on cells of all these models. Altogether, evidence exists that GRP has a potential role in the growth of (neoplastic) prostatic tissue.

Calcitonin

The human (hCT) and salmon (sCT) subtypes of CT can be demonstrated in a subset of normal and neoplastic prostatic cells [4, 8, 27, 29, 35, 40, 94, 96]. In conditioned medium of cultures of prostate cancer cells, immunoreactive CT was found in a concentration fourfold higher than in cultures of BPH cells [94]. In vivo administration of sCT to rats induced ornithine decarboxylase (a key enzyme associated with cell cycle progression and growth) in a number of organs [73]. It should be realized that CT also inhibits the pituitary secretion of luteinizing hormone, which is an important hormone in the mediation of androgen secretion [62]. In addition, the secretion of prolactin, which influences the action of androgens on the prostate, was also found to be decreased by CT [12]. Therefore, a pituitary-mediated growth-inhibiting effect of CT on prostatic cancer growth is also expected. The direct growth-modulating effects of CT have been studied in a few tumor systems. T-47D breast cancer cells contained high-affinity receptors for CT, and in vitro growth of these cells was dose dependently inhibited by CT [51, 75]. Comparable results were found in cells of the human gastric carcinoma cell line KATO III [72]. Following CT administration, intracellular cAMP levels increased [51, 72, 75]. This increase was also found in four out of six renal adenocarcinoma cell lines and only these four cell lines were growth inhibited by CT administration [58]. In a panel of 13 small cell lung cancer cell lines, 2 contained CT and only 1 was able to bind CT while no growth effect upon CT administration was found [11]. It has recently been shown that sCT dose dependently increased the cAMP concentration and the DNA synthesis in cells of the in vitro human prostatic cancer cell line LNCaP [95]. The growth stimulatory effect of CT in LNCaP cells is at variance with the results from other non-prostatic tumor model systems [51, 58, 72, 75]. Therefore, the effects of CT have to be confirmed in additional stud-

ies using other prostatic tumor models including in vivo models because CT also has systemic effects which may influence prostatic tumor growth.

Somatostatin

Abrahamsson et al. [4] found somatostatin (SMS) immunoreactivity in 12 out of 40 prostatic adenocarcinomas, a result that has not been confirmed by Aprikian et al. [8]. SMS receptors were found neither in 17 prostatic carcinomas nor in 2 BPH specimens [85]. On the other hand, binding sites for several SMS analogs were demonstrated in normal and neoplastic prostatic tissues [100]. A number of experimental studies concerning the growth-modulating effects of SMS in prostate cancer have been published. Several SMS analogs (sandostatin, somatuline, RC-160, RC-121) decreased without exception the growth of prostatic tumor models in vivo (Dunning R-3327 and R-3327H, PC-82, DU-145, PC-3) and in vitro (LNCaP) [13, 19, 54, 66, 69, 80, 82, 89, 97, 113]. In the Dunning R-3327H rat tumor the SMS effect potentiated the castration-induced growth inhibition even when the tumors became androgen independent [13]; however, this was not confirmed by others [97]. In experiments with heterotransplants of the androgen-independent PC-3 cell line, SMS was able to inhibit growth only if the tumors were small (10 mm³) [82]. Combination treatment of tumor models with an SMS analog and luteinizing hormone-releasing hormone (LH-RH) analog (D-TRP⁶ LH-RH) resulted in a stronger growth inhibition than treatment with only one of the components [54, 66, 89]. SMS-binding sites were demonstrated on cells of the PC-82 [66], Du-145 [80], PC-3 [82] and Dunning R-3327H [54] models. SMS and prolactin-binding sites were found to be downregulated in Dunning R-3327H tumors treated with analogs of SMS and LH-RH [54]. As noted above, prolactin may have a stimulating effect on prostate cancer, and the downregulation of the prolactin receptor by SMS might partially explain the growth-inhibiting effects of SMS. All these results strongly suggest a direct growth-inhibiting effect of SMS (analogs) in prostate cancer.

The effects of some of the neuropeptides on prostate cancer growth have been investigated quite extensively. The relationship with androgen levels and androgen receptor activity, the action of a combination of neuropeptides and the mechanisms of action are poorly understood at the moment. Furthermore, it is not clear whether the amounts of neuropeptides secreted by the NE cells are sufficient for biological activity on neighboring cells. For some of the neuropeptides, the presence of the corresponding receptor is not clear. Possibly other, as yet unknown, factors produced by prostatic NE cells may be even more important.

Neuroendocrine differentiation in prostatic tumor models

To enhance our knowledge of NE differentiation in prostate cancer, experimental models with NE cells are urgently

needed. A heterotransplantable model of a small cell prostatic carcinoma has been established [52, 53, 108]. An SCPC is biologically different from an adenocarcinoma and, therefore, this model is probably not useful for the study of the paracrine role of NE cells in prostatic adenocarcinoma. None of the available prostatic tumor models contains NE cells as defined by immunoreactivity for CgA, 5-HT, CT, SMS, NSE and thyroid-stimulating hormone, although two heterotransplantable human tumor models which were recently established in this laboratory contain CgA-positive cells (unpublished observation).

Possibly, NE differentiation can be induced in non-NE prostatic tumor models. Transfection of *v-ras*^H into DMS-53 small cell lung cancer cell line cells resulted in a cell line with increased NE features [63]. Transfection of both *c-raf-1* and *c-myc* oncogenes into SV-40-immortalized bronchial epithelial cells resulted in the generation of heterotransplantable large cell carcinoma cell lines with an NE phenotype [78, 79]. These studies indicate that NE differentiation can be induced and that it is associated with the expression of certain (proto-) oncogenes. Future experiments have to show if a similar approach can be applied to prostate cancer.

Conclusion

Knowledge about the function of NE cells in the human prostate and prostate cancer is limited. Evidence is, however, accumulating that NE cells and tumors with NE cells are related to the androgen-independent and poorly differentiated types of prostate cancer. However, at the moment it cannot be excluded that NE differentiation is only an epiphenomenon associated with dedifferentiation of a tumor. There is evidence that the secretion products of prostatic NE cells affect prostate cancer growth and possibly also affect tumor differentiation. Research directed towards identifying the role of NE cells in prostate cancer is likely to contribute to the understanding of the transition of androgen-dependent to androgen-independent prostate cancer.

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