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Neuroendocrine Cells in Benign and Malignant Prostate Tissue: Morphogenesis, Proliferation, and Androgen Receptor Status

Helmut Bonkhoff*

Institute of Pathology, University of the Saarland, Homburg/Saar, Germany

BACKGROUND. The presence of neuroendocrine (NE) differentiation in benign and neoplastic prostate tissue has attracted increasing attention in contemporary prostate cancer research.

METHODS. The present review focuses on the proliferation and androgen receptor (AR) status of NE phenotypes and their morphogenetic origin in benign and malignant prostate tissue.

RESULTS. Recent data have documented phenotype relation between NE cells and other cell lineages in benign and malignant prostate tissue indicating their common origin. NE cell types (as defined by the most commonly used endocrine marker, chromogranin A) do not show evidence of cell proliferation and consistently lack the nuclear AR in both benign and malignant conditions.

CONCLUSIONS. Prostatic NE cells most likely derive from local stem cells and represent terminally differentiated and androgen-insensitive cell populations in benign prostate tissue. The frequent occurrence of NE differentiation in prostatic adenocarcinoma obviously reflects the differentiation repertoire of its stem cells. Neoplastic NE cells devoid of nuclear AR constitute an androgen-insensitive cell population in prostate cancer. Furthermore, the absence of proliferation activity may endow NE tumor cells with relative resistance toward cytotoxic drugs and radiation therapy. *Prostate Supplement 8:18–22, 1998.*

KEY WORDS: **neuroendocrine differentiation; prostate; prostate cancer; androgen receptor; proliferation; morphogenesis; prognosis**

INTRODUCTION

The prostate gland harbors a large number of neuroendocrine (NE) cells whose morphogenetic origin and functional role are poorly understood. In recent years it has become increasingly evident that prostatic NE cells produce a variety of neurosecretory products with growth promoting activities, including serotonin, calcitonin, and parathyroid hormone-related peptides [1–3]. These regulatory peptides may act through lumencrine, endocrine, paracrine, and autocrine mechanisms and are probably involved in normal growth, differentiation and secretory functions of the gland [1,2]. More information is currently available on potential clinical and prognostic implications of NE differentiation in prostate cancer. Immunohistochemical studies have shown that focal NE differentiation occurs in virtually all common prostatic adenocarcinomas [1,2]. Extensive and multifocal endocrine features are detected in approximately 10% of all prostatic malignancies. These tumors tend to be more aggressive and resistant to hormonal therapy [1–3]. The most common eutopic hormones produced by NE cancerous cells include serotonin, thyroid stimulating hormone-like peptide, parathyroid hormone-related peptide, somatostatin, calcitonin, calcitonin gene related peptide and bombesin/gastrin- related peptide [1–3]. Some of these regulatory peptides can affect tumor cell proliferation in vitro, as documented for bombesin, calcitonin, and parathyroid hormone-related peptide in prostatic cancer cell lines [4–6]. Several recent

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*Correspondence to: Helmut Bonkhoff, Institute of Pathology, University of the Saarland, 66421 Homburg/Saar, Germany.

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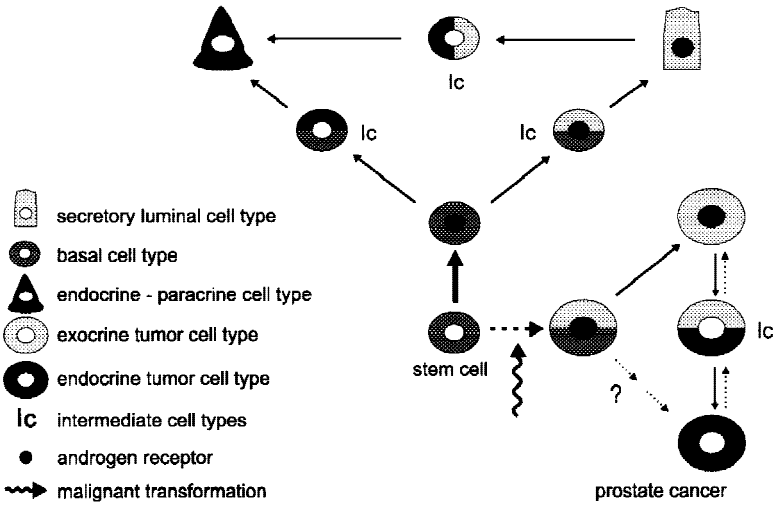

Fig. 1. Morphogenesis of endocrine cell types in benign and malignant prostate tissue. The differentiation pathways illustrated in this model are deduced from the occurrence of intermediate cell types (Ic) identified in benign and malignant human prostate tissue [10].

clinical studies suggest that NE differentiation predicts tumor progression after total prostatectomy and radiation therapy [7–9].

The recent developments in this field indicate that the concept of NE differentiation has potential implications in normal and neoplastic prostatic growth. The present review examines morphogenetic aspects of NE differentiation and discusses possible mechanisms by which neoplastic cells may affect prognosis of prostate cancer, particularly in relation to their proliferation and androgen-receptor status.

MORPHOGENESIS OF NE CELLS IN PROSTATE TISSUE AND PROSTATE CANCER

Along with secretory luminal and basal cells, NE cells represent the third epithelial cell type in benign prostate tissue. Although these basic cell types significantly differ in their marker expression and hormonal regulation, they obviously share a common origin from pluripotent stem cells. This concept is based on the occurrence of intermediate differentiation between these epithelial cell types [10]. Using double label techniques for phenotypic markers, we have observed intermediate cell types between secretory luminal, basal cells, and NE cells (Fig. 1). In particular, endocrine cells characterized by chromogranin A may simultaneously express basal cell-specific cytokeratins or prostate-specific antigen (PSA), a specific marker for secretory luminal cell types [10]. On the basis of these data, we have recently proposed a stem cell model for the organization of the prostatic epithelium, which accounts for many current aspects of benign prostatic growth [11,12]. There is increasing evidence that the human prostatic epithelium is composed of two functional compartments. The basal cell layer represents the proliferation compartment and most probably houses prostatic stem cells [11,13]. The differentiation compartment consists of secretory luminal cells that are androgen-dependent, but have a limited proliferative capacity [13]. Conversely, NE cells do not show proliferative activity. Prostatic epithelial cells characterized by chromogranin A consistently lack the proliferation-associated Ki-67 and MIB-1 antigens [14,15]. These data clearly indicate that NE cells are postmitotic and terminally differentiated cell populations in the human prostate. Another distinct feature of prostatic NE cells is the absence of detectable nuclear AR [16]. Chromogranin A-positive cells lack detectable levels of the nuclear AR, indicating that NE cells are androgen-insensitive [16,17]. The potential biological functions that NE cells may exert through endocrine, paracrine, and lumencrine mechanisms are obviously regulated by androgen-independent processes [16].

There is currently no convincing evidence that neoplastic NE cells originate from transformed NE cells of benign glands or premalignant lesions. It is most unlikely that tumor cells with endocrine features derive from terminally differentiated and postmitotic cell populations. Recent immunohistochemical data have shown that NE foci in prostatic adenocarcinoma harbor a significant number of amphicrine tumor cells expressing both endocrine (chromogranin A) and exocrine (PSA) markers [10]. The frequent occurrence of intermediate differentiation between exocrine and endocrine cell types strongly supports the concept that NE tumor cells derive from exocrine (PSA-positive) cell types during tumor progression [11]. Both cell lineages obviously share a common origin from pluripotent stem cells [11] (Fig. 1). Much more work is needed to define molecular mechanisms and regulatory fac-

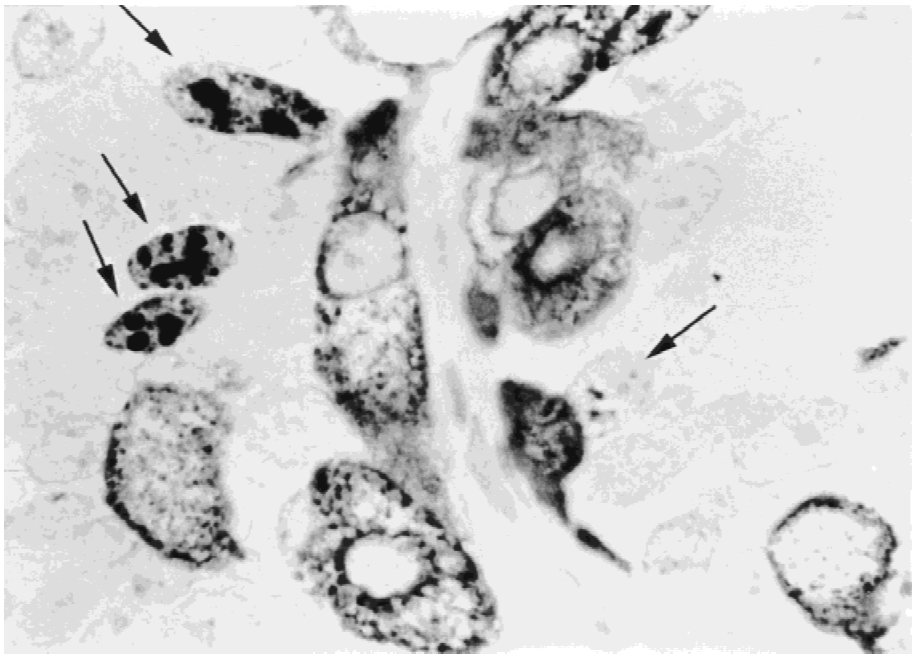

Fig. 2. Prostatic adenocarcinoma with endocrine differentiation. Simultaneous demonstration of chromogranin A and MIB-1. Endocrine tumor cells identified by chromogranin A lack proliferative activity as defined by MIB-1. Increased proliferative activity is detected in adjacent exocrine tumor cells labeled by MIB-1 *(arrows)*. ×1,000.

tors involved in the progressive emergence of NE cell clones in predominantly exocrine prostatic malignancies.

PROLIFERATION STATUS OF NE PHENOTYPES IN PROSTATE CANCER

Common prostatic adenocarcinomas with marked endocrine features tend to be poorly differentiated, more aggressive and resistant to hormonal therapy [1–3]. Surprisingly, neoplastic NE cells do not show evidence of cell proliferation (Fig. 2). We have recently shown that chromogranin A-positive tumor cells lack proliferation-associated MIB-1 and Ki-67 antigens that identify cycling cells in G1, S, and M phases of the cell cycle [14,15]. This clearly indicates that NE differentiation in common prostatic adenocarcinoma exclusively occurs in the G0 phase of the cell cycle and is lost when tumor cells reenter the cell cycle. Accordingly, the aggressiveness of prostate cancer with marked endocrine features can not be explained by proliferative capacities of the endocrine phenotype. Other regulatory mechanisms are likely to be involved in this process. It is well established that endocrine cell types in prostate cancer produce a variety of regulatory peptides with growth-promoting activities in vitro, including serotonin, bombesin, and parathyroid hormone-related peptide [1–3]. Using double label techniques in human tissue, we have noted increased proliferative activity in exocrine cells surrounding NE tumor cells [14] (Fig. 2). This frequent observation may reflect the regulatory impact of neurosecretory products on proliferation via paracrine mechanisms. Additional studies evaluating the differential expression of appropriate receptors for the various neurosecretory peptides are needed to support this concept.

The absence of proliferative activity in NE cell populations may also have therapeutic implications knowing that cytotoxic agents and radiation therapy predominantly affect cycling cancer cells. In prostatic adenocarcinoma, the proliferation compartment is composed by exocrine cell types, while NE tumor cells remain in a quiescent state (G0 phase of the cell cycle) [15]. It is likely that nonproliferating NE cells are more resistant to cytotoxic drugs and radiation therapy than cycling exocrine cells. Results of recent clinical studies lend credence to this concept. Grignon and coworkers in a prospective RTOG (Radiation Therapy Oncology Group) phase III trial have shown that the presence of NE differentiation in biopsy or transurethral resection specimens from patients with advanced prostate cancer is predictive of poor survival after external-beam radiation therapy [15].

ANDROGEN RECEPTOR STATUS OF NE PHENOTYPES IN PROSTATE CANCER

Prostatic adenocarcinomas generally remain androgen-dependent in early stages, but invariably relapse to an androgen-insensitive disease after androgen withdrawal [18]. The underlying mechanisms responsible for the progression to androgen insensitivity are poorly understood. It is well established that androgen-dependent growth in prostatic malignancies re-

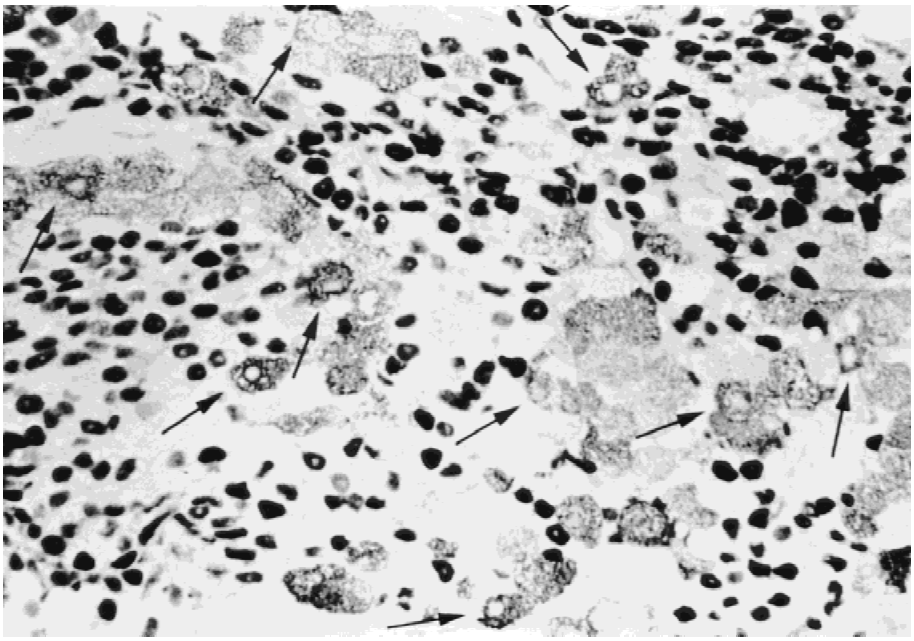

Fig. 3. Recurrent prostatic adenocarcinoma after hormonal therapy. Simultaneous demonstration of the nuclear androgen receptor (AR) and chromogranin A. Endocrine tumor cells defined by ChrA reactivity lack detectable levels of the nuclear AR *(arrows)*. Exocrine (ChrA negative) tumor cells strongly express the nuclear AR. ×400.

quires the nuclear AR and 5α-reductase, which is crucial for the dihydrotestosteron (DHT) forming process [18]. Surprisingly, recent data suggest that hormone resistant adenocarcinoma continues to express the nuclear AR and 5α-reductase isoenzymes 1 and 2 at high levels [19,20]. Possible molecular mechanisms responsible for the continuous expression of the nuclear AR in an androgen-deprived milieu involve a high level of AR gene amplification, which is common in recurrent tumors after androgen ablation therapy [21]. Immunohistochemical studies have shown that nuclear AR expression is restricted to exocrine cell types, whereas NE tumor cells consistently lack detectable AR reactivity [16,17]. This particular feature of NE cells is maintained in primary and recurrent disease after hormonal therapy (Fig. 3). The absence of detectable AR proteins in neoplastic NE cells clearly suggests that these cell populations are initially androgen insensitive and refractory to hormonal therapy. Although appropriate receptors for DHT are lacking, NE tumor cells express 5α-reductase isoenzymes 1 and 2 at high levels in poorly differentiated carcinomas and recurrent disease [20]. This indicates that other known substrates for 5α-reductase isoenzymes 1 and 2, including corticosteron and progesteron may be involved to control NE phenotypes in prostate cancer [20].

CONCLUSIONS

The present data on basic differentiation and proliferation processes within the prostatic epithelial cell system indicate that NE cells derive from prostatic stem cells located in the basal cell layer. The frequent occurrence of NE differentiation in common prostatic adenocarcinoma obviously reflects the differentiation repertoire of its stem cells. There are several mechanisms by which NE differentiation can affect the natural history and prognosis of prostate cancer. The absence of detectable nuclear AR strongly suggests that neoplastic NE cells are androgen-insensitive and escape hormonal control. The various neurosecretory products produced by NE tumor cells may induce proliferation of adjacent exocrine cells by paracrine mechanisms. The observation that NE differentiation occurs exclusively in the G0 phase of the cell cycle may indicate that NE cells are more resistant to radiation therapy and cytotoxic agents than proliferating exocrine cell populations. Together with recent clinical data, there are several lines of evidence that NE differentiation may have important implications in prostatic malignancies with significant endocrine features.

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