40 Morphogenesis of Prostate Cancer

HELMUT BONKHOFF, PhD

The three epithelial cell types of the prostatic epithelium—secretory luminal cells, basal cells, and neuroendocrine cells—arise from a common pluripotent stem cell in the basal layer through transit-amplifying cells that display intermediate phenotypes. The cellular diversity of the prostatic epithelium is maintained through a network of hormonal control, growth factors, and interactions with the basement membrane. Severe differentiation and proliferation disorders occur during the malignant transformation of the prostatic epithelium. In high-grade prostatic intraepithelial neoplasia (HGPIN), basal cells lose their proliferative capacity while luminal cells acquire increased proliferative activity. This process is associated with an abnormal expression of oncogenes (erbB-2, erbB-3, and c-*met*), the apoptosis-suppressing Bcl-2, and the classic estrogen receptor α (ERα). Conversely, the ERβ which mediates chemopreventive effects of phytoestrogens is partially lost in HGPIN. Neoplastic progression to invasion is associated with loss of cell adhesion proteins and formation of new tumor-associated basement membranes, which provide a matrix for invasion. Common prostatic adenocarcinoma is composed of exocrine cell types expressing prostate-specific antigen and cytokeratins 8 and 18, as well as androgen receptors (Ars), making exocrine tumor cells androgen responsive even in androgen-insensitive stages of the disease. The only phenotype of common prostatic adenocarcinoma lacking the nuclear AR shows neuroendocrine differentiation. These endocrine tumor cells do not proliferate or undergo apoptosis, indicating that such tumor cells are androgen-insensitive and escape radiation therapy and other cytotoxic drugs. In addition, endocrine tumor cells secrete a number of endocrine growth factors that can maintain proliferative activity in exocrine tumor cells through a paracrine mechanism. After androgen deprivation therapy, prostate cancer cells acquire estrogen and progesterone receptors and may use the pertinent steroids to survive in an androgen-deprived milieu. This warrants clinical trials to test the efficacy of antiestrogens in the medical treatment of advanced prostate cancer.

40.1. INTRODUCTION

Prostate cancer is one of the most commonly diagnosed cancers in North America and Europe. Despite its clinical magnitude and the recent progress made in molecular biology, the pathogenesis of prostate cancer remains poorly understood. This reflects several factors including the complex composition of the prostate gland by different anatomical, cellular, and functional compartments (Figs. 1 and 2); the heterogeneous and multifocal nature of prostate cancer; the limited number of established cell lines for in vitro studies; and the lack of suitable animal models that faithfully recapitulate all stages of disease progression. This chapter focuses on current morphogenetic factors implicated in the development of prostate cancer and tumor progression. The concepts discussed herein refer to recent data obtained in human prostate tissue.

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40.2. CELLULAR BIOLOGY OF PROSTATIC EPITHELIUM

The prostatic epithelium has a complex composition of three cell types differing in their hormonal regulation and marker expression (Fig. 2). The most prevalent phenotype consists of secretory luminal cells expressing prostate-specific antigen (PSA) and cytokeratins (CKs) 8 and 18 (Nagle et al., 1991; Xue et al., 1998). Basal cells, the second most important phenotype, maintain normal epithelial-stromal relation and express high-molecular-weight cytokeratins (Wernert et al., 1987; Bonkhoff, 1996). The third phenotype shows neuroendocrine differentiation. Neuroendocrine cells express chromogranins and secrete a number of neurosecretory products that may have growth-promoting properties (Di Sant'Agnese, 1992; Di Sant'Agnese and Cockett, 1996). Although these basic cell types clearly differ in their biological functions, they obviously share a common origin from pluripotent stem cells located in the basal cell layer (Bonkhoff, 1996a;

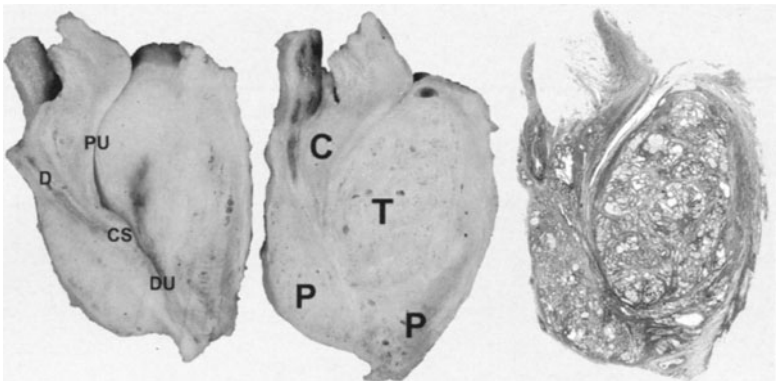

Fig 1. Zonal anatomy of prostate. The prostate of a 65-yr-old patient with benign prostatic hyperplasia (BPH) is shown. The prostate gland is composed of three anatomical zones. The central zone (C) located between ejaculatory ducts (D), and the proximal urethral segment (PU) accounts for about 25% of normal prostatic volume. Only about 10% of carcinomas arise in this zone. The transition zone (T) located around the proximal urethral segment accounts for about 5% of normal prostatic volume but steadily increases with age. Virtually all forms of BPH arise here. Transition zone cancer accounts for about 15–20% of prostatic adenocarcinoma and is commonly diagnosed in transurethral resection specimens from patients with BPH (incidental carcinoma). The peripheral zone (P) located around the distal urethral (DU) segment represents approx 70% of the normal gland. The majority (70–75%) of prostatic adenocarcinomas and high-grade prostatic intraepithelial neoplasias (HGPINs) arise in this zone. CS, colliculus seminalis.

Bonkhoff et al., 1996b, 1998b). This concept is based on the occurrence of intermediate differentiation among the three basic cell types making up the prostatic epithelium (Bonkhoff et al., 1994a; Xue et al., 1998), and some biological properties of basal cells (Bonkhoff, 1996a; Bonkhoff et al., 1996b, 1998b). Cell kinetic studies indicate that the proliferation compartment of the normal and hyperplastic epithelium is located in the basal cell layer (Bonkhoff et al., 1994b). Seventy percent of proliferating epithelial cells express basal cell–specific cytokeratins, while the remaining 30% of cycling cells are identified in secretory luminal cell types (Bonkhoff et al., 1994b). Chromogranin A (ChrA)–positive neuroendocrine cells lack proliferative activity and represent a terminal differentiated cell population within the prostatic epithelial cell system (Bonkhoff et al., 1991a, 1995b). It is therefore most unlikely that neuroendocrine cells present in the normal or dysplastic epithelium are precursors of prostate cancer cells with neuroendocrine features (Bonkhoff, 1998). In benign prostate tissue, apoptotic cell death is androgen regulated and mainly occurs in secretory luminal cells. Basal cells uniformly express the apoptosis-suppressing Bcl-2 oncoprotein, which obviously protects the proliferation compartment from programmed cell death (Bonkhoff et al.,1998a).

The cellular diversity of the prostatic epithelium is maintained through a network of hormonal control, growth factors, and adhesive interactions with the underlying basement membrane. The differentiation compartment of the prostatic epithelium is made up of secretory luminal cells that are androgen dependent but have a limited proliferative capacity (Bonkhoff et al., 1994b). Luminal cells strongly express the nuclear androgen receptor (AR). The proliferation compartment (basal cells) is androgen independent but harbors androgen-responsive target cells. In fact, subsets of basal cells express the nuclear AR at high levels (Bonkhoff et al., 1993b). Basal cells also contain the 5α-reductase isoenzyme 2, which is crucial for the dihydrotestosterone-forming process (Bonkhoff et al., 1996c). It is likely that androgen-responsive basal cells are committed to differentiate toward luminal cells under

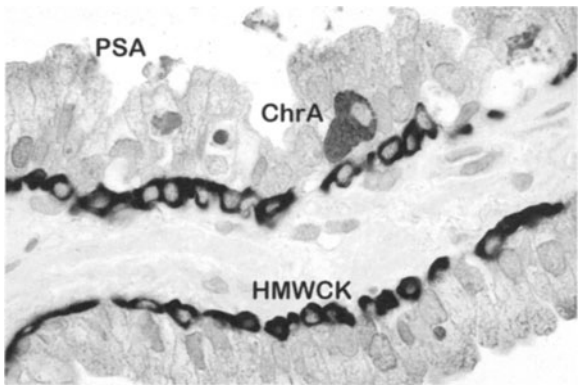

Fig. 2. Cellular composition of prostatic epithelium. The prostatic epithelium is composed of three basic cell types: secretory luminal cells, basal cells, and endocrine-paracrine cells. Simultaneous demonstration of PSA (secretory luminal cells), high-molecular-weight cytokeratins (HMWCK) (basal cells), and ChrA (endocrine cells).

appropriate androgen stimulation (Bonkhoff, 1996a; Bonkhoff et al., 1996b). This differentiation process is balanced by estrogens. Estrogen treatment leads to basal cell hyperplasia and atrophy of luminal cells by preventing basal cells to differentiate toward luminal cells (Bonkhoff, 1996a; Bonkhoff et al., 1996b). This process is mediated by the classic estrogen receptor α (ERα), which is expressed in stromal and basal cells but not in secretory luminal cell types (Bonkhoff et al., 1999b). On the other hand, the new ERβ is expressed extensively in luminal cells and at lower levels in basal cells (Fixemer et al., 2003). The ERβ binds phytoestrogens with high affinity and is a promising target for chemoprevention of BPH and prostate cancer (Chang and Prins, 1999; Steiner et al., 2001). It has been shown that ERβ knockout mice develop BPH with age, indicating that a functional ERβ protects the prostatic epithelium from hyperplastic changes (Krege et al., 1998).

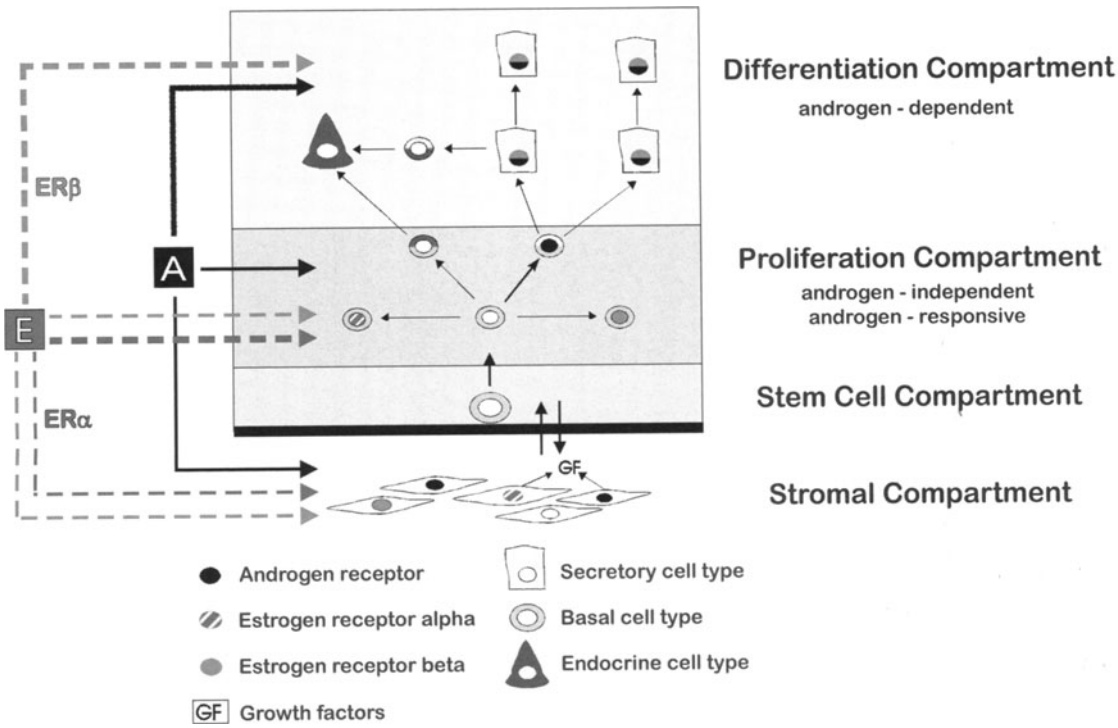

Fig. 3. Stem cell model for organization of the prostatic epithelium. Three functional compartments can be identified within the complex prostatic epithelial cell system. The differentiation compartment consists of secretory luminal cells that are androgen dependent but have a limited proliferative capacity. Luminal cells express high levels of the nuclear AR and the ERβ, which may exert antiproliferative effects on luminal cells. The basal cell layer is androgen independent and makes up the proliferation compartment. The proliferation function of basal cells is maintained by several growth factors (e.g., EGF), oncogenes (erbB-2, erbB-3, c-*met*), and tumor suppressor gene products (nm23-H1), while Bcl-2 protects basal cells from apoptotic cell death. The basal cell layer houses a small stem cell population that gives rise to all epithelial cell types through a process of intermediate differentiation. These differentiation processes depend on a delicate balance between estrogens and androgens. Estrogens prevent basal cell differentiation toward luminal cells, thus leading to basal cell hyperplasia and atrophy of luminal cells. When basal cells require androgens to give rise to androgen-dependent luminal cells, the turnover of the luminal epithelium depends on the presence of androgen-responsive target cells in the basal cell layer. The age-related decrease in circulating androgens may hypersensitize basal cells to the reduced levels of bioavailable androgens by upregulation of the nuclear AR in the basal cell layer. This may lead to glandular hyperplasia by accelerating the turnover of luminal cells from basal cells. Alternatively, other stroma-derived factors may be involved to control the differentiation process from basal to luminal cell types.

Besides estrogens and androgens, a number of nonsteroidal growth factors are involved in the regulation of benign glandular growth. Most growth factor receptors (e.g., epidermal growth factor receptor [EGF-R]), oncogenes (erbB-2, erbB-3, c-*met*, Bcl-2), and tumor suppressor genes (nm-23-H1) of the prostatic epithelium are expressed in basal cells (Bonkhoff et al., 1998b; Myers and Grizzle, 1996). The interplay among these factors may ultimately determine the growth fraction within the basal cell layer. On the other hand, differentiation processes within the prostatic epithelial cell system most likely depend on a hormonal balance between circulating androgens and estrogens (Bonkhoff, 1996a; Bonkhoff et al., 1996a, 1998b). Another important factor implicated in benign prostatic growth is the role of basal cells mediating adhesive interactions with epithelial basement membranes (Bonkhoff, 1998c). Prostatic epithelial cells require basement membrane components for their in vitro growth and differentiation (Fong et al., 1991). In human prostate tissue, basal cells exhibit polarized distribution of integrin receptors (α6β1, α2β1, α6β4) and hemidesmosome-associated proteins (BP180, BP220, HD1) (Bonkhoff et al., 1993a; Knox et al., 1994; Nagle et al., 1995). It seems likely that formation of stable hemidesmosomes and adhesive interactions with basement membrane contribute significantly to the integrity and biological functions of basal cells.

In summary, basal cells play a pivotal role in benign prostate growth. The basal cell layer houses pluripotent stem cells and maintains cell proliferation and normal epithelial-stromal relations (Fig. 3). Genetic and epigenetic factors interfering with the normal function of basal cells are therefore crucial for the development of prostate cancer.

40.3. DIFFERENTIATION AND PROLIFERATION DISORDERS IN EARLY PHASES OF PROSTATIC CANCEROGENESIS

HGPIN is the most likely precursor of prostate cancer (Bostwick, 1996; Montironi et al., 1996). This lesion usually arises in preexisting ducts and duct–acinar units of the peripheral zone and shares cytological features with intermediate and high-grade carcinoma but retains basal cell differentiation (Bostwick, 1996). Autopsy studies indicate that PIN precedes carcinoma by 10 yr and more. HGPIN is currently the most significant risk factor for prostate cancer. Its identification in prostatic biopsy specimens warrants further searches for concurrent cancer (Bostwick, 1996).

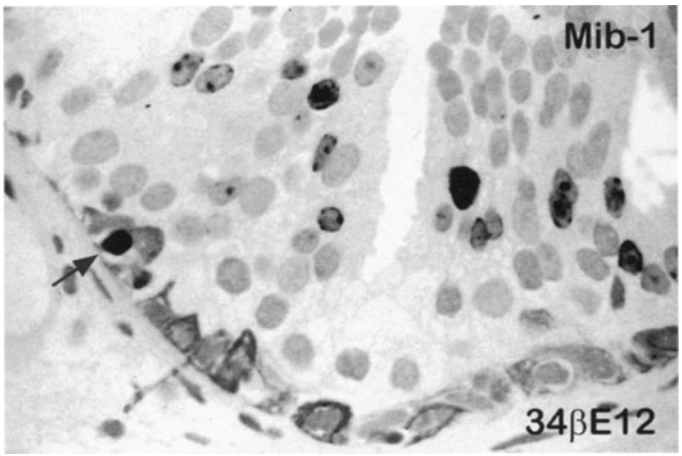

Fig. 4. Proliferation abnormalities detected in HGPIN. During the malignant transformation of the prostatic epithelium, the proliferation zone extends to secretory luminal cells (differentiation compartment). Less than 10% of cycling cells are identified in the basal cell layer (arrow), the proliferation compartment of the normal prostatic epithelium. Simultaneous demonstration of the proliferation marker Mib-1 and basal cell–specific cytokeratins (34βE12) in HGPIN.

Severe differentiation and proliferation disorders occur during the malignant transformation of the prostatic epithelium. In HGPIN, the basal cell layer (proliferation compartment) loses its proliferation function, whereas secretory luminal (dysplastic) cells acquire increased proliferative activity (Bonkhoff et al., 1994a). Less than 10% of cycling cells detected in HGPIN belong to the former proliferation compartment (Bonkhoff et al., 1994a) (Fig. 4). Extension of the proliferative zone to luminal cells in the differentiation compartment is a typical feature of well established premalignant lesions such as colorectal adenomas. The premalignant proliferation disorders encountered in HGPIN are associated with an aberrant expression of oncogenes (erbB-2, erbB-3, c-*met*) and tumor suppressor genes (nm23-H1) in the differentiation compartment of the transformed epithelium (Myers and Grizzle, 1996; Bonkhoff et al., 1998b). Restricted to basal cells in normal conditions, these biomarkers are implicated in the malignant transformation of the prostatic epithelium. In addition, severe regulatory disorders of the programmed cell death have been identified. At least 20% of HGPINs express high levels of the apoptosis-suppressing Bcl-2 oncoprotein in the differentiation compartment of the transformed epithelium and thus prevent dysplastic cells from the apoptotic cell death (Bonkhoff et al., 1998a). The resulting prolonged life-span of transformed cells, together with their high proliferation rate, provides an excellent environment in which genetic instability can occur. The most common genetic alterations in HGPIN include gain of chromosome 7, particularly 7q31; loss of 8p and gain of 8q; and loss of 10q, 16q, and 18q. The overall frequency of numeric chromosomal anomalies reported is remarkably similar in HGPIN and invasive cancer, suggesting that they have a similar pathogenesis (Qian et al., 1998; Foster et al., 2000).

Clinical studies suggest that HGPIN lesions are androgen dependent and generally regress after androgen deprivation (Bostwick, 1996). This observation obviously reflects the fact that most of these precursors express the nuclear AR and Bcl-2 as described in benign acini. Conversely, HGPIN with aberrant expression of Bcl-2 in the differentiation compartment tends to downregulate the AR, as documented by markedly reduced levels of detectable receptor proteins (Bonkhoff et al., 1998a). It is likely that such premalignant lesions escape the androgen-regulated programmed cell death and do not regress after androgen deprivation. Accordingly, Bcl-2 may be a promising biomarker to define the virulence of HGPIN.

The role of estrogens in the malignant transformation of the prostatic epithelium appears even more complex. Epidemiological and experimental data suggest that estrogens may exert cancerogenic and chemopreventive effects on the prostatic epithelium (Chang and Prins, 1999; Griffiths, 2000; Steiner et al., 2001). This apparent contradiction obviously reflects the presence of two distinct estrogen receptors (ERα and ERβ). In human prostate tissue, ERα gene expression is restricted to basal and stromal cells in normal conditions. In HGPIN, high steady-state levels of ERα mRNA are detected in the dysplastic epithelium (Bonkhoff et al., 1999b). At least 10% of HGPINs express the ERα at the protein level (Bonkhoff et al., 1999b). The estrogen-inducible PS2 has been identified in a significant number of benign and dysplastic prostate tissues from patients with locally advanced prostate cancer, but not in prostate tissue from patients without evidence of malignant disease (Bonkhoff et al., 1995a). These data suggest that the cancerogenic effects that estrogens may exert on the prostatic epithelium are mediated by the classic ERα. On the other hand, the ERβ binds phytoestrogens, which have antiproliferative and chemopreventive properties in animal models (Chang and Prins, 1999; Steiner et al., 2001). Expressed in luminal cell types at high levels in normal conditions, the ERβ is downregulated in HGPIN. At least 64% of these precursors reveal decreased or markedly decreased levels of the ERβ in the dysplastic epithelium (Fixemer et al., 2003). This indicates that the ERβ is a tumor suppressor that is partially lost during the malignant transformation of the prostatic epithelium.

In summary, virtually all phenotype and genotype data amassed in recent years suggest that HGPIN is the precursor of intermediate and high-grade cancer arising in the peripheral zone (Bostwick, 1996; Foster et al., 2000; Montironi et al., 1996). Conversely, the significance of atypical adenomatous hyperplasia (AAH) as a precursor of low-grade transition zone cancer is not well established (Montironi et al., 1996). Although the proliferative activity of AAH is increased compared with hyperplastic lesions, the proliferation zone and Bcl-2 expression are restricted to basal cells as described in benign prostate tissue (Bonkhoff et al., 1994b, 1998a). Thus, AAH does not reveal typical premalignant proliferation and differentiation abnormalities as found in HGPIN. Nevertheless, allelic imbalance may occur, indicating a genetic link between AAH and prostatic adenocarcinoma (Cheng et al., 1998). Much more work is needed to define the morphogenesis of low-grade transition zone cancer.

40.4. PATHOGENESIS OF STROMAL INVASION

Adhesive interactions in premalignant lesions do not differ significantly from those encountered in benign prostate tissue. Dramatic changes occur during early stromal invasion when the transformed epithelium loses basal cell differentiation (Bonkhoff, 1998c). This process is associated with the loss of a number of hemidesmosome-forming proteins and associated adhesive molecules, including collagen VII, β3 and γ2 subchains of laminin 5,

and α6β4 integrins (Knox et al., 1994; Nagle et al., 1995). It is quite clear that benign acini and HGPIN require these adhesive elements to maintain basal cell differentiation and normal epithelial–stromal relations. Alternatively, the inability of transformed cells to express hemidesmosome-associated proteins obviously presents a key step in the neoplastic progression of HGPIN to early invasive cancer.

Another important event in early stromal invasion refers to the synthesis of tumor-associated basement membranes (Bonkhoff et al., 1991b, 1992). Invasive prostate cancer cells produce basement membrane–like matrices to invade the host tissue, and express associated integrins (α6β1, α2β1) that mediate attachment to this newly formed matrix (Bonkhoff et al., 1991b, 1992, 1993a) (Fig. 5). This particular tumor–host relation encountered in prostate cancer is maintained through the various stages of the disease, including high-grade, metastatic, and recurrent lesions (Bonkhoff et al., 1991b, 1992, 1993). Neoplastic basement membranes differ from their normal counterparts in their differential susceptibility to pepsin treatment and lack hemidesmosome-associated laminin 5, collagen VII, and type IV collagen α5 and α6 chains (Bonkhoff et al., 1993a; Knox et al., 1994; Nagle et al., 1995). Recent *in situ* hybridization analysis showed that these basement membranes are produced by tumor cells and not by the host tissue (Pföhler et al., 1998). High steady-state levels of laminin and type IV collagen mRNA are detected in metastatic lesions when compared with primary tumors (Pföhler et al., 1998). This indicates that the basement membrane–forming process increases with tumor progression. Their functional significance for the process of stromal invasion has also been demonstrated in vitro, showing that prostate cancer cell lines generally require reconstituted basement membrane (Matrigel) to be tumorigenic in athymic mice (Bonkhoff, 1998c).

In summary, *de novo*–synthesized basement membrane and adhesion via specific receptors significantly contribute to the ability of prostate cancer to penetrate the extracellular matrix (ECM) during stromal invasion and metastasis (Bonkhoff, 1998c).

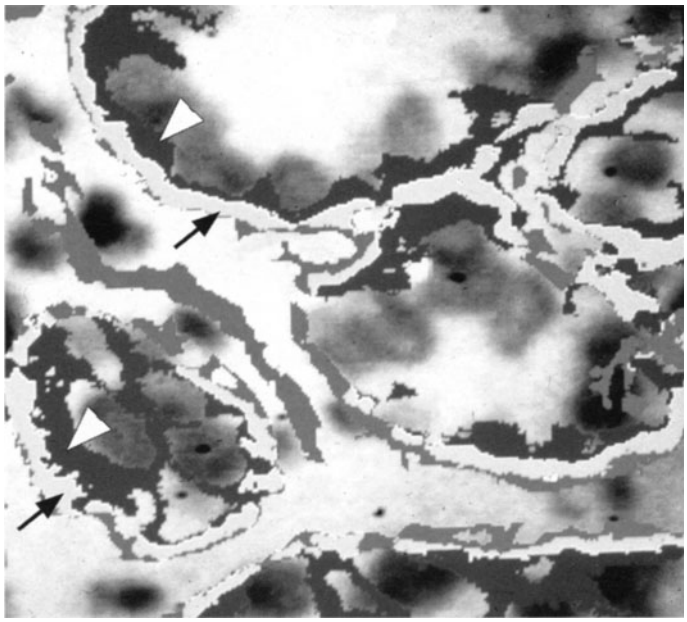

Fig. 5. Epithelial-stromal relation in prostate cancer. Invasive tumor cells are separated from the host tissue by pericellular and periacinar basement membranes expressing laminin and other basement membrane components. Pertinent receptors such as α6β1 integrins (arrowheads) mediate attachment to these newly formed matrices. Computer-assisted double staining reveals coordinate expression of the extracellular receptor domain and its corresponding ligand in basement membranes (arrows).

40.5. MORPHOGENETIC FACTORS IMPLICATED IN PROSTATE CANCER PROGRESSION AND HORMONE THERAPY FAILURE

Common prostatic adenocarcinoma is mainly composed of exocrine tumor cells that express PSA and CKs 8 and 18 and share phenotype similarity with secretory luminal cells of the normal prostatic epithelium (Nagle et al., 1991). These exocrine tumor cells generally express the nuclear AR and 5α reductase isoenzymes 1 and 2 in primary, metastatic, and recurrent lesions (Bonkhoff et al., 1993c, 1996c; Koivisto et al., 1998). This observation suggests that exocrine tumor cells are androgen responsive and maintain the dihydrotestosterone-forming process even in hormone-refractory stages of the disease. The continuous expression of the nuclear AR in androgen-insensitive tumors can be explained partially by AR gene amplification, which has been identified in at least 30% of recurrent lesions (Koivisto et al., 1998). The presence of the nuclear AR in prostate cancer tissue, however, does not imply androgen-dependent growth. Point mutations in the steroid-binding domain of the AR gene can seriously interfere with the normal function of the receptor protein (Koivisto et al., 1998; Culig et al., 2000). Mutant AR can bind estrogens and other steroids that maintain transcription of androgen-regulated genes even in the absence of androgens (Culig et al., 2000). AR gene mutations, however, are rather infrequent in prostate cancer. A significant number of hormone-refractory tumors have been reported to have apparently normal AR gene (Koivisto et al., 1998). Other factors are certainly involved in the multifactorial process of androgen insensitivity. Alternative pathways by which prostate cancer cells can escape androgen deprivation include their ability to acquire neuroendocrine differentiation (Bonkhoff, 1998d, 2001b) or to use estrogens for their own growth (Bonkhoff et al., 1999, 2000, 2001a).

40.5.1. NEUROENDOCRINE DIFFERENTIATION The second most prevalent phenotype encountered in prostate cancer shows neuroendocrine differentiation (Di Sant'Agnese and Cockett,1992; Di Sant'Agnese et al., 1996). Virtually all prostatic adenocarcinomas reveal at least focal neuroendocrine features as assessed by immunohistochemical markers such as ChrA. Tumors with extensive and multifocal neuroendocrine features (accounting for approx 10% of all prostatic malignancies) tend to be poorly differentiated, more aggressive, and resistant to hormonal therapy (Di Sant'Agnese, 1992; Di Sant'Agnese and Cockett, 1996). Several pathways have been described showing how neuroendocrine differentiation can affect tumor progression and hormone therapy failure (Bonkhoff, 1998d, 2001b). It has been shown that prostate cancer cells expressing ChrA consistently lack the nuclear AR in primary, metastatic, and recurrent lesions (Bonkhoff et al., 1993c) (Fig. 6). This clearly indicates that neuroendocrine phenotypes constitute an androgen-insensitive cell population in all stages of the disease. Neuroendocrine tumor cells most likely derive from exocrine phenotypes through a process of intermediate differentiation. This obviously reflects

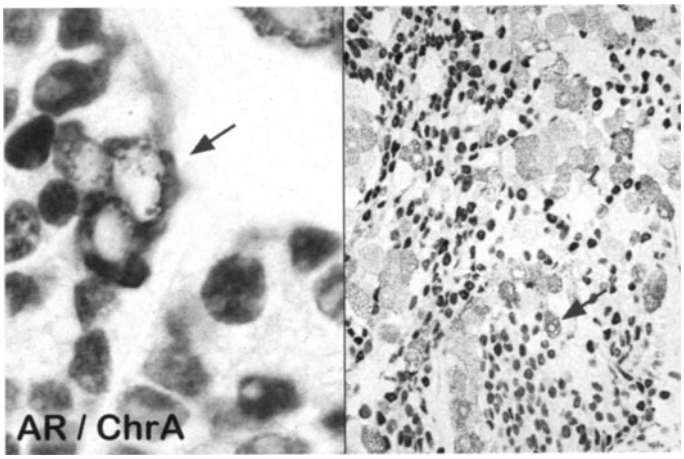

Fig. 6. AR status of endocrine and exocrine prostate cancer cells. AR expression is restricted to exocrine tumor cells. Neuroendocrine tumor cells identified by ChrA (arrows) consistently lack the nuclear AR in both primary (left) and recurrent (right) lesions.

the differentiation repertoire of prostatic stem cells. In fact, neuroendocrine foci frequently harbor amphicrine cell types expressing both endocrine (ChrA) and exocrine (PSA) markers (Bonkhoff et al., 1994a). Despite their androgen insensitivity, neuroendocrine tumor cells have no proliferative capacity. It has been shown that neuroendocrine differentiation predominantly occurs in the G0 phase of the cell cycle and is lost when tumor cells reenter the cell cycle (Bonkhoff et al., 1991a, 1995b). Although neuroendocrine tumor cells lack proliferative activity, they may exert growth-promoting stimuli on adjacent (exocrine) tumor cells. Endocrine tumor cells secrete a number of neurosecretory products with mitogenic properties in vitro, including serotonin, bombesin, calcitonin, and parathyroid hormone–related peptides (Di Sant'Agnese, 1992; Di Sant'Agnese and Cockett, 1996). It is likely that these neuroendocrine growth factors can maintain cell proliferation of adjacent (exocrine) tumor cells through a paracrine (androgen-independent) mechanism.

Recent studies also indicate that neuroendocrine (ChrA-positive) tumor cells escape the apoptotic cell death, as assessed by DNA fragmentation assays (Bonkhoff et al., 1999a; Fixemer et al., 2003). The absence of proliferative and apoptotic activity in neuroendocrine phenotypes may have some therapeutic implications, since radiation therapy and other cytotoxic drugs mainly affect cycling cells. Given their cell kinetic features, it will be very difficult to kill neuroendocrine tumor cells by endocrine and other cytotoxic treatments currently available. Recent clinical studies lend credence to this concept. Elevated serum levels of ChrA in patients with prostate cancer correlate with poor prognosis and are scarcely influenced by either endocrine therapy or chemotherapy (Berruti et al., 2000).

40.5.2. ROLE OF ESTROGENS IN ANDROGEN-INSENSITIVE PROSTATIC GROWTH Since the time of Higgins, estrogens have been widely used in the medical treatment of advanced prostate cancer to reduce the testicular output of androgens. The recent discovery of the classical ERα and estrogen-regulated proteins such as the progesterone receptor (PR) and the heat-shock protein HSP27 clearly shows that prostate cancer cells can use estrogens for their own growth (Bonkhoff et al., 1999b, 2000, 2001a). In apparent contrast with breast cancer, the presence of the ERα and the estrogen-inducible PR and HSP27 is a late event in prostate cancer progression. The most significant levels of these markers are detectable in recurrent and metastatic lesions (Bonkhoff et al., 1999b, 2000, 2001a) (Fig. 7). This indicates that metastatic and androgen-insensitive tumors are estrogen responsive and can use estrogens for their maintenance and growth to survive in an androgen-deprived milieu. It is noteworthy that the expression of the ERα and PR in the normal prostatic epithelium is restricted to the basal cell layer, which is androgen independent, proliferative active, and harbors prostatic stem cells (Bonkhoff et al., 1998b). The reappearence of the ERα and PR in advanced and androgen-insensitive tumors suggests that prostate cancer cells expressing these steroid receptors recapitulate some biological features of basal cells or prostatic stem cells.

In apparent contrast with the classic ERα, the ERβ variant is expressed extensively in primary and metastatic lesions without any clear correlation with the histological grade or the pathological stage (Fixemer et al., 2003). Nevertheless, the ERβ is partially lost in androgen-insensitive stages of the disease, which may reflect the androgen dependence of ERβ gene expression in prostate cancer (Fixemer et al., 2003). Although the precise role of the ERβ in prostate cancer remains to be established, most studies suggest that the ERβ exerts anti-proliferative effects by counteracting the stimulating effects of the ERα (Krege et al., 1998; Chang and Prins, 1999; Steiner et al., 2001). Irrespective of possible explanations, the progressive emergence of the ERα and PR during tumor progression provides a theoretical background for studying the efficiency of antiestrogens and antigestagens in the medical treatment of advanced prostate cancer. The current morphogenetic factors implicated in prostate cancer development and progression are summarized in Fig. 8.

40.6. CONCLUSION

Prostate cancer is a complex disease process involving phenotype, epigenetic, and genetic factors. In each methodological approach, knowledge of prostatic heterogeneity, histology, and

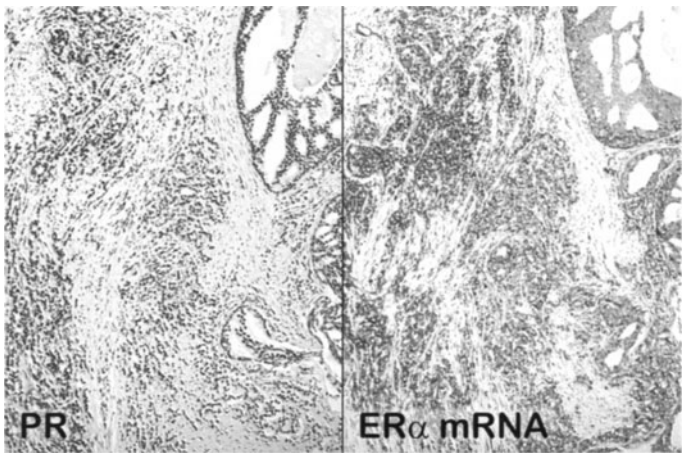

Fig. 7. ER and PR expression in recurrent prostatic adenocarcinoma. At least 30% of androgen-insensitive prostatic adenocarcinomas express the PR at significant levels (Bonkhoff et al., 2001a). The presence of the PR is associated with high steady-state levels of ERα mRNA. This indicates that such lesions have a functional ERα able to induce the PR.

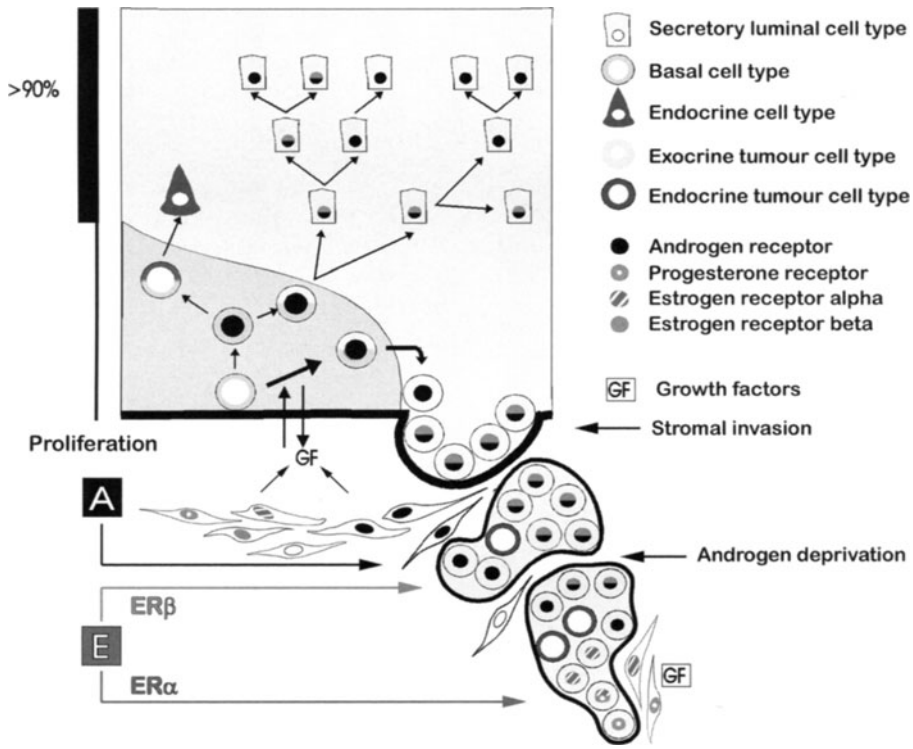

Fig. 8. Morphogenetic pathways implicated in prostate cancer development and tumor progression. Preinvasive phases of prostatic cancerogenesis are characterized by severe differentiation and proliferation disorders within the prostatic epithelial cell system (*see* text). Transformed precursor cells originating from the basal cell layer acquire exocrine features and produce an altered ECM. These newly formed (tumor-associated) basement membranes provide a supporting scaffold for penetration of the host tissue during stromal invasion and metastasis. Exocrine tumor cells (the most prevalent phenotype of prostatic adenocarcinoma) generally express the nuclear AR, 5α reductase isoenzymes 1 and 2, and the androgen-regulated ERβ. Thus, exocrine tumor cells remain androgen responsive even in hormone refractory stages of the disease. Point mutations in the steroid-binding domain of the AR gene, however, can seriously interfere with the normal function of the receptor protein. The progressive emergence of neuroendocrine tumor cells during tumor progression obviously reflects the differentiation potency of prostatic stem cells. Devoid of the nuclear AR, neuroendocrine tumor cells are androgen insensitive but produce neuroendocrine growth factors that can exert growth-promoting effects on adjacent exocrine tumor cells through a paracrine mechanism. The lack of proliferative and apoptotic activity in neuroendocrine tumor cells further contributes to their drug resistance. After androgen deprivation, prostate cancer cells acquire the ability to use estrogens and prosgestins for their own growth. The presence of the ERα and the estrogen-inducible PR in metastatic and recurrent lesions recapitulates some biological properties of basal cells and prostatic stem cells and provides a novel target for antiestrogens and antigestagens in the medical treatment of advanced prostate cancer.

morphogenesis is essential. This highlights the role of pathologists in contemporary prostate cancer research. The morphogenetic data reviewed here may provide a conceptual framework for studying the impact of biochemical and genetic factors on prostate cancer development and tumor progression.

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