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Morphogenetic concepts of normal and abnormal growth in the human prostate

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Benign prostatic hyperplasia and prostate cancer are multifactorial disease processes, involving a growing number of biochemical, genetic and epigenetic factors. The present review focuses on current morphogenetic factors implicated in normal and abnormal growth in the human prostate.

Benign orostatic growth

The cellular diversity of basic cell types making up the prostatic epithelium (secretory luminal cells, basal cells and endocrine-paracrine cells) suggests the existence of pluripotent stem cells, presumably located in the basal cell layer. This concept derives from a series of biological properties of basal cells, including: i) their differentiation potency to give rise to secretory luminal and endocrine cells; ii) their proliferative function in normal and hyperplastic conditions; iii) their androgen independence; and iv) their ability to respond to circulating androgens, which is required for the differentiation process to secretory luminal cells (1, 2). Currently, two functional compartments can be defined within the prostatic epithelial cell system. The proliferation compartment is androgen independent and consists of basal cells. The secretory epithelium constitutes the differentiation compartment, which is androgen dependent but which has a limited proliferative capacity (2). The growth rate within the proliferation compartment is regulated by a network of growth factor receptors (e.g., EGF-R, pl8sSrbu, p180e~3) and Bcl-2, preventing basal cells from androgen dependent programmed cell death (1). Differentiation processes within the prostatic epithelial cell system involve a delicate balance between circulating androgens and estrogens. The phenotypic change from basal cells to secretory luminal cells is triggered by androgens, while estrogens block this process, leading to basal cell hyperplasia (1). The age-related decrease of androgens in the aging male, together with stromal derived growth factors may increase androgen gene expression in the basal cell layer (proliferation compartment), making basal cells more sensitive to the low levels of bioavailable androgens. This hormonal imbalance results in glandular hyperplasia by accelerating the differentiation process from basal cells to secretory luminal cells (1, 2).

Premalignant lesions

High-grade prostatic intraepithelial neoplasia (HGPIN) is considered to be the most likely precursor of peripheral zone cancer (3). This premalignant condition reflects severe proliferation and differentiation disorders within the prostatic epithelial cell system. The basal cell layer loses its proliferation function, whereas secretory luminal (dysplastic) cells acquire increased proliferative activity (1). These premalignant proliferation disorders are associated with aberrant expression of growth factor receptors (p1 **85erbB-2,pl 8Qerb** e-3, c-met) and tumor suppressor genes (nm23 Hi) restricted to basal cells in normal and hyperplastic conditions (1). In addition, the apoptosis suppressing Bcl-2 oncoprotein is overexpressed in approximately 20% of HGPIN, which is associated with markedly decreased levels of the nuclear androgen receptor in the dysplastic epithelium (1). This abnormal Bcl-2 process induces severe differentiation disorders by protecting the differentiation compartment from apoptotic cell death. The resulting increased life span of the transformed cells, together with the high proliferation rate, provides an environment in which genetic instability can occur. The most common numerical alterations detected in HGPIN so far include the loss of 8p, lOq, 16q, 18q and the gain of chromosomes 8q and 7, indicating that genes on these chromosomes may play a role in early phases of prostatic cancerogenesis (4). While virtually all phenotype and genotype data support the premalignant nature of HOPIN, the role of atypical adenomatous hyperplasia as a precursor of transition zone cancer is less well established. In particular, the morphogenesis of small acinar adenocarcinoma remains poorly understood (5).

Pathopenesis 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 (6). This process is associated with the loss of a number of hemidesmosome-forming proteins and associated adhesive molecules, including collagen VII, 33 and y2 subchains of laminin 5, and ct6j34 integrins. Being retained in benign acini and HOPIN, it is quite clear that the loss of these hemidesmosome-forming proteins represents a key step in the progression of HGPIN to early invasive cancer. It is well established that common prostatic adenocarcinoma produces newly formed basement membranes to invade the host tissue (6). Invasive tumor cells are separated from the stroma by distinct periacinar and pencellular basement membrane and express associated integrins that mediate affachment to these basement membrane-like matrices. This particular tumor-host relation is maintained through the various stages of the disease, including high-grade lesions, metastases and therapy-induced changes. Recent *in situ* hybridization analysis also suggests that the basement membrane-forming process increases with tumor progression. Neoplastic basement membrane differ from their normal counterparts in their differential susceptibility to pepsin treatment, and lack hemidesmosome-associated laminin 5, collagen VII and type IV collagen ct5 and ct6 chains. Their functional significance for the process of stromal invasion has also been demon-

strated *in vitro,* showing that prostate cancer cell lines generally require reconstituted basement membrane (Matrigel) to be tumorigenic in athymic mice. In summary, de *novo* synthesized basement membrane and adhesion via specific receptors significantly contributes to the ability of prostate cancer to penetrate the extracellular matrix during stromal invasion and metastasis (6).

Implications of PhenotyPe heterogeneity in prostate cancer progression

The most common cell type encountered in prostatic adenocarcinoma shares phenotype similarity with secretory luminal cells *(e.g.,* prostate-specific antigens, cytokeratins 8, 18). These exocrine tumor cells generally express the nuclear androgen receptor and 5os reductase 1 and 2 in primary, metastatic and recurrent lesions (1). This observation suggests that exocrine tumor cells are potentially androgen responsive, and maintain the dihydrotestosterone-forming process even in hormone refractory disease. The continuous expression of the nuclear androgen receptor in androgen insensitive carcinomas is surprising, and involves a high level of androgen receptor gene amplification, which frequently occurs in recurrent prostate cancer (7). Nevertheless, recurrent tumors also reveal androgen receptor gene mutations, leading to an abnormal androgen receptor protein, responsive to estrogens and other steroids (7). Accordingly, the presence of the nuclear androgen receptor does not imply androgen dependence. An alternative pathway by which prostate cancer cells escape hormonal control refers to their ability to acquire neuroendocrine features (6). Virtually all common adenocarcinomas of the prostate show at least focal neuroendocrine differentiation. Tumors with extensive and multifocal neuroendocrine features (accounting for approximately 10% of all prostatic malignancies) tend to be poorly differentiated, more aggressive and resistant to hormonal therapy. Devoid of the nuclear androgen receptors, the neuroendocrine phenotype constitutes an androgen insensitive cell population in prostate cancer through the various stages of the disease (6). This particular phenotype derives from exocrine tumor cells, which reflects the differentiation repertoire of prostatic stem cells. Neuroendocrine differentiation predominantly occurs in the GO phase of the cell cycle and is lost when tumor cells reenter the cell cycle (1, 6). These cell kinetic properties make the neuroendocrine phenotype more resistant to cytotoxic agents and radiation therapy than exocrine tumor cells with proliferative capacity. This concept is supported by recent clinicopathological studies, showing that neuroendocrine differentiation predicts poor survival of advanced prostatic cancer after radiation therapy. The prognostic significance of neuroendocrine tumor cells in common prostatic adenocarcinoma most likely reflects their ability to secrete a series of regulatory products with growth promoting properties, including serotonin, bombesin and parathyroid hormone-related peptides. These regulatory peptides are able to maintain cell proliferation though the paracrine, androgen independent pathway (6). Thus, neuroendocrine differentiation can affect prostate cancer progression through several pathogenetic mechanisms.

In addition to androgen related pathways, estrogens have recently been recognized to play a role in the multifactorial process of endocrine therapy failure. Androgen deprivation therapy, widely used in the medical treatment of advanced prostate cancer, is known to increase the estrogenlandrogen ratio in cancerous tissue. This therapy-induced hormonal imbalance may have potential implications. We have recently shown that a substantial number of androgen independent and metastatic lesions express the classical estrogen receptor (ERos) at high levels. Tumor cells becoming estrogen responsive in an androgen deprived milieu may survive by using estrogens for their continuous maintenance and growth. This warrants clinical trials to test the efficiency of antiestrogens in the medical treatment of androgen independent prostate cancer expressing the nuclear estrogen receptor at significant levels.

Concluding remarks

Despite its clinical magnitude, the pathogenesis of benign prostatic hyperplasia and prostate cancer remains poorly understood. Knowledge of morphogenesis can significantly contribute to this issue.

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Atypical adenomatous hyperplasia, atypical small acinar proliferation and prostatic adenocarcinoma

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In the USA over 20,000 new cases of prostate cancer are diagnosed each year, accounting for more than 35% of all cancers affecting men and resulting in 40,000 deaths annually. As a consequence of active screening, pathologists are expected to detect cancer in increasingly small tissue samples.

Atypical adenomatous hyperplasia (AAH) and atypical small adnar proliferation (ASAP) are lesions that could be confused with prostatic adenocarcinoma (PCA) and are of great importance not only as sources of diagnostic pitfalls but also for the further clinical management of the affected patients. The nature of AAH is still unclear and it is controversially discussed as a putative precancerous lesion.

AAH (adenosis

AAH is a common lesion and is considered to be a benign glandular lesion with architectural features that could be confused with