c-erbB-2 Oncogene Expression in Prostatic Intraepithelial Neoplasia: Mounting Evidence for a Precursor Role

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The search for the precursor of invasive prostatic adenocarcinoma has intensified in recent years, focusing on the spectrum of histopathologic changes referred to as high-grade prostatic intraepithelial neoplasia. This microscopic finding, considered to be the most likely precursor of invasive carcinoma (1), is characterized by cellular proliferations within pre-existing ducts and glands, with cytologic changes mimicking cancer, including nuclear and nucleolar enlargement. Prostatic intraepithelial neoplasia coexists with cancer in more than 85% of cases but retains an intact or fragmented basal cell layer, unlike cancer that lacks a basal cell layer (2). The clinical importance of recognizing prostatic intraepithelial neoplasia is based on its strong association with prostatic carcinoma. Prostatic intraepithelial neoplasia has a high predictive value as a marker for adenocarcinoma, and its identification in biopsy specimens of the prostate warrants further search for concurrent invasive carcinoma. Studies, to date, have not determined whether prostatic intraepithelial neoplasia remains stable, regresses, or progresses, although the implication is that it can progress (2). The identification of specific and consistent molecular changes in prostatic intraepithelial neoplasia, such as pl60\(^{erbB-3}\) and pl85\(^{erbB-2}\), adds further support to the expanding body of evidence indicating the premalignant nature of this lesion.

In this issue of the Journal, Myers et al. (3) describe immunoreactivity in paraffin-embedded archival tissue sections for p160\(^{erbB-3}\) and p185\(^{erbB-2}\) in the basal cells of the benign prostatic epithelium, in basal cells of prostatic intraepithelial neoplasia, in secretory luminal cells of prostatic intraepithelial neoplasia, and in carcinoma. This pattern of immunoreactivity for oncogenes in prostatic intraepithelial neoplasia and cancer is similar to that of other biomarkers in the prostate, including epidermal growth factor, epidermal growth factor receptor, type IV collagenase, Lewis Y antigen, transforming growth factor-\(\alpha\) (4), apoptotic bodies, and proliferating cell nuclear antigen (5). Increased cell proliferation is the most likely explanation for this phenotypic similarity of normal basal cells, prostatic intraepithelial neoplasia, and cancer, suggesting that the basal cells are the regenerative or stem cells of the prostate.

Other biomarkers show progressive loss with increasing grades of prostatic intraepithelial neoplasia and cancer and include markers of secretory differentiation such as prostate-specific antigen, secretory proteins, cytoskeletal proteins, glycoproteins, and neuroendocrine cells (6). These results indicate that there is progressive impairment of cell differentiation and regulatory control with advancing stages of prostatic carcinogenesis. Changes in cytoskeletal proteins in prostatic intraepithelial neoplasia may affect transport of cell products, accounting for the differences in secretory protein distribution. Virtually all studies to date of biomarkers have indicated that high-grade prostatic intraepithelial neoplasia is more closely related to carcinoma than to benign epithelium.

As members of the epidermal growth factor family and its associated oncoproteins, p160\(^{erbB-3}\) and p185\(^{erbB-2}\) reflect an increase in cellular proliferative activity when they are overexpressed. The c-erbB-2 (HER-2/neu) oncoprotein encodes a 185-kd transmembrane phosphoglycoprotein with 43% homology with epidermal growth factor receptor in extracellular sequences. The findings of Myers et al. (3) confirm and extend the results of other studies that indicate the presence of this oncoprotein in basal cells of the prostate and in the secretory luminal cells of high-grade prostatic intraepithelial neoplasia. Using TA1, a monoclonal antibody that recognizes the extracellular domain of the transmembrane oncoprotein, Ibrahim et al. (7) found a similar pattern of immunoreactivity for c-erbB-2 in frozen sections of prostatic intraepithelial neoplasia and prostate cancer. Using AB-3, a monoclonal antibody directed against the C-terminal end of the c-erbB-2 oncoprotein, Giri et al. (8) identified basal cell staining in normal and hyperplastic prostatic epithelium and in adenocarcinoma. Conversely, other studies of c-erbB-2 oncoprotein expression have found inconsistent patterns of immunoreactivity, probably resulting from differences in tissue preparation and fixation, immunohistochemical techniques, antibody specificity, and inter-
pretation of results (9-11); these results demonstrate the pitfall of interpreting negative immunohistochemical results without independent confirmation from other tests (4,11).

Immunohistochemical studies of these plasma membrane receptor proteins usually indicate membrane localization, although cases with cytoplasmic immunoreactivity have been described. Such findings may be due to protein synthesis or cytoplasmic internalization of the receptors; Grizzle et al. (4) suggest that different "rules" of interpretation of immunohistochemical staining apply in different sites, and cytoplasmic staining may be valid in prostate cancer.

The study by Myers et al. (3) is also noteworthy, since it is the first study to describe p160*erbB-3* overexpression in prostatic intraepithelial neoplasia and prostate cancer, a new and potentially useful biomarker. The mechanism of overexpression of p160*erbB-3* and p185*erbB-2* in prostate cancer is uncertain, but it does not appear to result from gene amplification (12,13). More likely, there is an increased rate of c-erbB-2 transcription, increased messenger RNA stability, or an increased amount of post-transcriptional processing (13).

The role of the c-erbB-2 and c-erbB-3 oncogenes in prostatic growth and differentiation is uncertain. Transfection of the rat neu-activated gene into the rat ventral prostatic epithelial cell line NBe-1.4 resulted in acquisition of a tumorigenic phenotype (14), indicating that this oncogene is involved in tumor growth. The expression of c-erbB-2 is regulated positively by androgens in vitro and in vivo, parallelizing expression of prostate-specific antigen (13). Interestingly, the luminal secretory cell layer of the benign prostatic epithelium and prostatic intraepithelial neoplasia is androgen dependent, and these cells are more sensitive to androgen loss than the androgen-independent basal cells. Prostatic intraepithelial neoplasia is ablated by androgen-deprivation therapy, probably as a result of accelerated programmed cell death (apoptosis), with subsequent exfoliation of cells into the glandular lumens (15). Consequently, androgen-deprivation therapy may be useful as an ablative or chemopreventive agent for prostatic intraepithelial neoplasia and perhaps for early prostate cancer (16).

The expression of c-erbB-2 is a potentially useful prognostic factor, particularly in the management of women with lymph node-positive breast cancer (17), and may be of value in the clinical management of prostate cancer. Considerable effort is currently directed at identifying preoperative factors that allow stratification of patients with prostate cancer into prognostically distinct groups; oncogene expression offers some promise in this regard. However, the predictive value of these and other molecular markers in the management of prostate cancer has not been validated, and results with c-erbB-2 have been contradictory. Overexpression of c-erbB-2 was found to be an independent, predictive marker of poor prognosis in two recent studies (18,19), but not in other studies (7,12,20,21). Ross et al. (21) described a positive association of c-erbB-2 expression with grade, aneuploid DNA content, and metastases in a series of 100 cases of prostate cancer, but they found that it offered no independent value in multivariate analysis. Other reports have not identified an association between c-erbB-2 expression and prostatic tumor grade (7,12,20), stage (12,20), progression (12), or p53 expression (20).

In addition to c-erbB-2 and members of the epidermal growth factor family, other oncogenes and tumor-suppressor genes may be clinically useful in prostate cancer, but these biomarkers are in the investigational stage. Mutations of cancer genes, such as ras oncogenes or the suppressor gene p53, have been found in only a minority of early prostate tumors (22-24) and apparently participate in later stages of prostatic carcinogenesis, with increased levels in high-grade metastatic tumors. Cytogenetic studies of short-term cultures of primary prostate cancers have revealed several chromosomal aberrations, such as deletion of chromosomes 1p and 10q (25), whereas studies of allelic loss have suggested a different set of chromosomal changes. Carter et al. (26) first reported nonrandom loss of chromosomes 10q and 16q in about 30% of prostate cancers, and other recent studies (27-29) revealed loss of at least one locus on the short arm of chromosome 8 in 46%-65% of prostate cancers.

Although little is currently known about oncogenesis of prostatic carcinoma, it probably occurs through the selection of several genetic changes, each modifying the expression or function of genes controlling cell growth or differentiation (30). Further studies are needed to evaluate the function and prognostic utility of oncogene expression in the normal, preneoplastic, and neoplastic prostate.

References


Note
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Add sliced bananas or peaches to your cereal.

Keep a tangerine, apple or banana on your desk for a midday snack. Pick one up from a sidewalk fruit vendor or convenience store on your way to work.

Don't hide fruits and vegetables in your crisper. Keep them visible on the top shelf in your refrigerator.

Serve kids a glass of 100% orange, grapefruit or tomato juice for breakfast.

Pour fruit juice in your ice cube tray and add toothpicks for homemade fruit pops.

Add more vegetables to your dinner tonight. Try chopped zucchini, cauliflower, carrots and green peppers.

Drink a glass of 100% fruit juice after a ball game or workout.

Pick up pre-cut vegetables or ready-to-eat salads at your supermarket's produce section or salad bar.