Diagnostic Role of Immunohistochemistry in Prostate Cancer
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Prostate cancer is the most common extra-cutaneous malignancy and the second leading cause of cancer-related deaths in men in the United States.\(^1\) The accuracy of the pathologic diagnosis of this malignant tumor is critical for optimal patient care. Even though the diagnosis can usually be made on morphologic features such as growth pattern, nuclear atypia and the absence of basal cells, it is sometimes difficult to reach a firm diagnosis by routine histological study, in particular for small foci of cancer in needle biopsies.\(^2\) Not only is no single morphologic feature cancer specific, but many benign conditions can mimic prostate cancer. Therefore, the application of immunohistochemistry to distinguish prostate cancer from benign mimickers and to confirm the diagnosis becomes helpful and necessary, especially in equivocal cases.

The immunohistochemical diagnosis of prostate cancer largely depends on panels of markers because no absolutely specific and sensitive marker for prostate cancer has yet been discovered. These panels usually include at least one basal cell-specific marker and the prostate cancer-specific marker, alpha-methyl-CoA-Racemase (AMACR).

The most commonly used basal cell-specific markers in prostate cancer are high-molecular-weight cytokeratin (HMWCK) and p63. HMWCK is expressed in virtually all normal basal cells of the prostate with continuous intact circumferential immunostaining in most glands. There is no staining of luminal or stromal cells.\(^3\) At a large independent laboratory, Kahance et al found the application of HMWCK decreased the “atypical” diagnosis rate from 8.3% to 0.4%.\(^2\) Positive HMWCK immunoreactivity in suspicious or atypical glands almost always precludes a diagnosis of prostate cancer; however, negative staining must be interpreted with caution because HMWCK is formalin-sensitive and progressive loss of immunoreactivity can be seen in prolonged formalin fixation. Successful immunostaining requires optimal antigen retrieval. In addition, HMWCK positivity is typically discontinuous in a variety of benign lesions such as post-atrophic hyperplasia, atypical adenomatous hyperplasia and high-grade prostatic intraepithelial neoplasia (PIN). A newly described basal cell marker, p63, is characterized as a nuclear transcription factor that is important in the regulation of growth and development of epithelial organs, including the prostate gland. It shares a high structural homology with p53. The expression of p63 is limited to basal cells of prostate glands and exhibits a nuclear staining pattern. Almost all prostatic cancers of low and intermediate grade are negative for p63, while normal or hyperplastic prostatic glands show strong and diffuse p63 expression.\(^2,3\)
AMACR is a 382-amino-acid enzyme that plays a key role in the beta-oxidation of branched-chain fatty acids and fatty acid derivatives. Using quantitative polymerase chain reaction, messenger RNA of AMACR was found to be overexpressed in about 60% of prostate cancers, but low to undetectable in normal tissues. In 2001, Jiang et al investigated AMACR protein expression, using immunohistochemical methods, in 137 cases of prostate cancer and 70 cases of benign prostate specimens. They found AMACR immunostaining was strong in all prostate cancers with continuous dark diffuse cytoplasmic staining or circumferential apical granular staining pattern. In contrast, little or no immunoreactivity was observed in benign glands. Hence, AMACR is considered to be a useful immunohistochemical marker for prostate cancer. However, because of non-standardized immunostaining protocols, interpretation criteria and heterogeneous staining pattern, there is a wide variation in the sensitivity and specificity of AMACR immunoreactivity in prostate biopsies. In addition, AMACR expression has been demonstrated in high-grade PIN, atypical adenomatous hyperplasia/adenosis and nephrogenic adenoma. Therefore, AMACR positivity must be evaluated with caution. It is recommended that AMACR is best restricted to the evaluation of morphologically highly suspicious foci in which negative immunoreactivity of basal cell markers alone is insufficient to establish a diagnosis of cancer.

In summary, immunohistochemistry plays an important role in diagnosis of prostate cancer. It helps to differentiate malignant glands from benign lesions, especially for morphologically equivocal glandular alterations in small core biopsy specimens (see Table).

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<thead>
<tr>
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<th>Prostate cancer</th>
<th>Benign prostate gland</th>
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<tbody>
<tr>
<td>HMWCK</td>
<td>Negative</td>
<td>Positive in basal cells</td>
</tr>
<tr>
<td>P63</td>
<td>Negative</td>
<td>Positive in basal cells</td>
</tr>
<tr>
<td>AMACR</td>
<td>Positive</td>
<td>Negative*</td>
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*Note: AMACR can be positive in PIN, atypical adenomatous hyperplasia/adenosis and nephrogenic adenoma.

References