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P504S (α-Methylacyl-CoA-Racemase)

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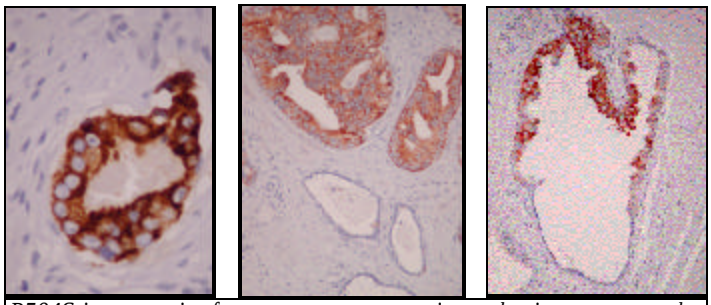
P504S is a gene recently found to show elevated expression in prostate cancers that were studied using cDNA library subtraction techniques in conjunction with microarray screening. This gene codes for a protein identified as α-methylacyl-CoA-racemase, an enzyme localized in mitochondria and peroxisomes that plays a role in the metabolism of fatty acids. Antibodies that have been raised to the P504S gene product have been the subject of a number of reports in the surgical pathology literature in the last several years, primarily with respect to their use as an aid in the interpretation of prostate biopsies.



P504S immunostains from a prostatectomy specimen, showing strong granular staining in a small malignant gland (left). In the middle frame, note the contrast between the positively-staining malignant glands (upper part of frame) and the adjacent negative benign glands (lower part of frame). The right frame shows a gland with partial involvement by high grade PIN, demonstrating P504S immunoreactivity only in the portion of the gland involved by PIN (upper part).

In November 2001, Jiang and associates (1) reported their results using a P504S monoclonal antibody on a study of 207 cases of prostate tissue, including 137 carcinomas and 70 cases of benign prostate. These investigators identified strong cytoplasmic granular staining in all of the prostate carcinomas (irrespective of Gleason grade), and 92% of these cases showed staining in >75% of the tumor cells. 88% of the benign prostate cases were negative for P504S, and those that were positive showed only focal and weak reactivity. Importantly, P504S was found to be negative in a number of conditions that may mimic prostate carcinoma in small biopsies, including basal cell hyperplasia, urothelial metaplasia, and atrophic glands As might be expected, P504S was also identified in high-grade PIN.

Atypical adenomatous hyperplasia (AAH) (a.k.a. adenosis or "atypical small acinar proliferation", ASAP) is a difficult area that has plagued nearly all diagnostic surgical pathologists at some time or another. Yang et al (2) reported their experience with P504S and high molecular weight cytokeratin immunostaining in a study of 40 cases of AAH (30 from prostatectomies and 10 from needle biopsies), and compared these with 20 cases of benign prostatic hyperplasia and 20 cases of prostate carcinoma. All 40 cases of AAH demonstrated patchy basal cells on high molecular weight cytokeratin immunostains (indicating the absence of invasive carcinoma), and P504S was negative in 82.5% (33/40) of cases of AAH. 7.5% (3 of 40) of cases of AAH demonstrated diffuse positive P504S staining, with focal staining noted in 10% (4 of 40) of cases of AAH. Interestingly, 2 of the 7 cases of P504S-positive AAH were associated with adjacent adenocarcinoma. All of the prostate carcinomas showed diffuse P504S immunostaining, and all cases of benign prostatic hyperplasia were negative.

More recently, Jiang et al (3) reported a study of 142 prostate needle biopsies stained with P504S and high molecular weight cytokeratin, including 73 cases with small (<1 mm) foci of prostate adenocarcinoma and 69 benign biopsies. In this study, all of the benign prostate biopsies (and all of the benign glands adjacent to areas of carcinoma) were negative for P504S.

In contrast, 94.5% (69/73) of the cases of prostate adenocarcinoma were positive with P504S (defined as continuous dark cytoplasmic or apical granular staining that was readily observed at low-power magnification,<100X). Weak fine granular background staining of epithelial and stromal cells which was not conspicuous at low-power examination was regarded as negative.

At the 2002 USCAP meeting, Beach et al (4) reported that 82% (144/176) of prostate carcinomas were positive with P504S, and 72% had staining in 11% or greater of the tumor cells. In 28% (73/259) of cases studied, obviously benign prostate epithelium showed focal, faint, non-circumferential luminal staining. All cases (59/59) of atrophy were negative, as were all cases of post atrophic hyperplasia (6/6), basal cell hyperplasia (1/1), and transitional cell metaplasia (11/11). Focal weak staining was noted in 5 of 7 cases that contained seminal vesicle epithelium.

A reasonable question that arises is whether or not P504S might serve as a marker of prostate origin in cases of metastatic carcinoma of unknown origin (similar to prostate specific antigen). However, several investigators have identified P504S in a number of non-prostate malignancies. In a study of 515 cases of malignant tumors (and 200 various normal human tissues), Jiang et al (5) found P504S in hepatocytes, renal tubular epithelial cells, and brush border of colonic mucosa. 81% (17/21) of hepatomas, 75% (18/24) of renal cell carcinomas, and 80% (20/25) of colorectal carcinomas were P504S positive. In addition, 31% (9/29) of urothelial carcinomas and 27% (4/15) of gastric adenocarcinomas were positive for P504S. 219 additional carcinomas including neuroendocrine carcinomas and carcinomas from the lung, breast, pancreas, bile duct, adrenal gland, salivary glad, ovary, thyroid, and endometrium were negative or rarely positive for P504S, and melanomas, squamous cell carcinomas, basal cell carcinomas, epithelioid sarcomas, synovial sarcoma, thymomas, and germ cell tumors were negative for P504S. Using a polyclonal antibody to the P504S gene product, Zhou et al (6) identified moderate to strong immunostaining in colorectal, prostate, ovarian, breast, bladder, lung, renal cell carcinoma, lymphoma, and melanoma, and also noted expression in the corresponding precursor lesions.

Using the ProPath multitumor sandwich block, we have observed P504S immunostaining in proximal renal tubules, colonic carcinoma, urothelial carcinoma, renal cell carcinoma, adrenal oncocytoma, breast carcinoma, hepatoma, liver cell adenoma, normal respiratory bronchial epithelium, prostate carcinoma, desmoplastic small round cell tumor, pancreatic islet cell tumor, and weak or focal positivity in lung carcinoma, cholangiocarcinoma, and clear cell carcinoma of the endometrium.

P504S is now available in the ProPath immunohistochemistry laboratory.

REFERENCES

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