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# Immunostains for b-catenin in Diagnostic Pathology.

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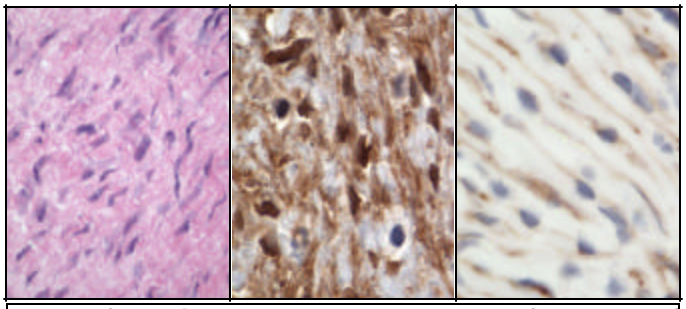
β-catenin is a cytoplasmic protein normally located immediately beneath the cell membrane. It binds to E-cadherin (a membrane protein), forming the E-cadherin-catenin complex. This E-cadherin-catenin complex is critical for a number of cellular processes, including normal embryonic development, regulation of cell differentiation, maintenance of normal tissue architecture, and controlling cell-to-cell adhesion. Normally, the APC (adenomatous polyposis coli) gene serves to downregulate β-catenin levels in the cell, through a series of steps that eventually phosphorylate a specific area of the β-catenin gene. However, when mutations occur in the β-catenin gene or in the APC gene, increased amounts of β-catenin collect within the cell, and the protein eventually accumulates within the nucleus (rather than occurring just below the cytoplasmic membrane as with normal cells). As such, nuclear localization of β-catenin can be viewed as a surrogate marker of mutations in the β-catenin gene, APC gene, or related genes involved in maintaining normal β-catenin levels. Abnormalities in β-catenin are thought to play an important role in the development of a variety of human cancers, particularly colorectal cancer. This month, we review the utility of immunostains for β-catenin in diagnostic surgical pathology.

Probably the most common use of β-catenin immunostaining at the current time is in confirming a diagnosis of **fibromatosis**, and assisting in distinction from mimics, such as gastrointestinal stromal tumor (GIST) and sclerosing mesenteritis. To my knowledge this application of β-catenin was first reported at the 2002 USCAP meeting by Montgomery and colleagues, who subsequently published their work in the American Journal of Surgical Pathology later that year. In this study, 11 cases of GIST, 5 cases of sclerosing mesenteritis, and 10 cases of mesenteric fibromatosis were studied. None of the cases of sclerosing mesenteritis or GIST demonstrated nuclear expression of β-catenin. In contrast, 9 of 10 cases of fibromatosis demonstrated appreciable nuclear immunoreactivity with β-catenin. Interestingly, 2 of 5 cases of sclerosing mesenteritis showed focal expression of CD117, and 60% of cases of mesenteric fibromatosis show expression of CD117 (using the CD117 antibody marketed by DakoCytomation), causing potential confusion with GIST. The reactivity of cases of fibromatosis with β-catenin is not surprising, as a number of studies have shown that fibromatoses frequently have mutations in the APC/β-catenin pathway, eventually resulting in accumulation of β-catenin protein within the nuclei of the neoplastic cells. At the 2003 USCAP meeting, Arnell et al confirmed these findings, identifying nuclear expression of β-catenin in 90% of 20 cases of sporadic deep fibromatosis, but in none of 11 cases of keloid, hypertrophic scar, or surgical scar.



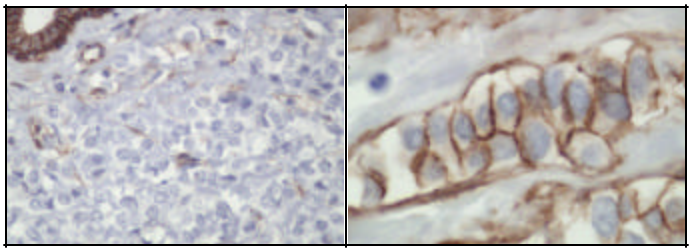
*H&E (left) and b-catenin immunostain (center) from a case of mesenteric fibromatosis. Note strong nuclear staining of nuclei. In contrast, the nuclei are negative on the b-catenin immunostain from a case of sclerosing mesenteritis (right).*

Wang et al have also advocated the use of β-catenin immunostains to assist in the **distinction of colorectal adenocarcinoma from primary adenocarcinoma of the urinary bladder**. In a 2001 paper published in the American Journal of Surgical Pathology, 17 primary adenocarcinomas of the urinary bladder (including 13 of enteric-type that were morphologically identical to colorectal adenocarcinoma) were compared with 16 colorectal adenocarcinomas secondarily involving the bladder, and also 10 conventional urothelial (transitional cell) carcinomas. 13 of the 16 (81%) colorectal adenocarcinomas demonstrated nuclear staining for β-catenin, but this was absent in all of the primary adenocarcinomas of the bladder and in all of the urothelial carcinomas. Cytoplasmic membrane staining was frequent, and did not assist in distinction of these tumors. Therefore, nuclear immunostaining with β-catenin in an enteric-appearing adenocarcinoma involving the bladder favors metastatic origin (particularly from the colorectum) rather than primary adenocarcinoma of the urinary bladder.

Other tumors that have been reported to show nuclear staining with β-catenin include **pilomatrixoma, some endometrial adenocarcinomas, melanoma, 61% of Barrett's esophagus-related adenocarcinomas, solid pseudopapillary tumor of pancreas, and classic pulmonary blastoma**. In cases studied at ProPath, I have also observed nuclear β-catenin in some cases of **metaplastic carcinoma of breast, adrenal adenoma, alveolar macrophages, cytotrophoblasts in placenta, normal prostate, cholangiocarcinoma, high-grade neuroendocrine carcinoma, gastric adenocarcinomas, solitary fibrous tumor, some hepatocytes, and hepatic adenoma.**

Finally, similar to E-cadherin, **loss of membranous reactivity with** b**-catenin occurs in lobular lesions of the breast**, and as such can aid in the distinction of lobular breast lesions from ductal lesions.

β-catenin has been available for several years in the ProPath immunohistochemistry laboratory, and as such is readily available for those who may need it for differential diagnostic problems such as those described above.



*Similar to E-cadherin, immunostains for b-catenin can aid in the distinction of lobular from ductal breast carcinoma. In lobular breast carcinoma, b-catenin does not show significant staining of the membrane (left), in contrast to ductal breast carcinoma (right).*

**References:**

1. Montgomery E et al: β-catenin immunohistochemistry separates mesenteric fibromatosis from gastrointestinal stromal tumor and sclerosing mesenteritis. Mod Pathol 15 (1): 19A (abstract #65), January 2002.
2. Montgomery E et al: β-catenin immunohistochemistry separates mesenteric fibromatosis from gastrointestinal stromal tumor and sclerosing mesenteritis. Am J Surg Pathol 26(10):1296-1301, Oct 2002.
3. Arnell PM et al: β-catenin expression in reactive and neoplastic fibroblastic proliferations. Mod Pathol 16(1): 8A (abstract #22), Jan 2003 .
4. Wang HL et al: Immunohistochemical distinction between primary adenocarcinoma of bladder and secondary colorectal adenocarcinoma. Am J Surg Pathol 25 (11): 1380-1387, Nov 2001.
5. Lazar AJF et al: Malignant pilomatrixomas are associated with mutations in exon 3 of CTNNB1, the gene encoding β-catenin. Mod Pathol 17(1), supplement 1, 95A (abstract # 390), Jan 2004.
6. Machin P et al: CTTNB1 mutations and β-catenin expression in endometrial carcinomas. Hum Pathol 33: 206-212, Feb 2002.
7. Demunter A et al: Loss of membranous expression of β-catenin is associated with tumor progression in cutaneous melanoma and rarely caused by exon 3 mutations. Mod Pathol 15(4): 454-61, Apr 2002.
8. Osterheld MC et al: β-catenin expression and its association with prognostic factors in adenocarcinoma developed in Barrett esophagus. Am J Clin Pathol. 117(3): 451-6, Mar 2002.
9. Tanaka Y et al: Usefulness of β-catenin immunostaining for the differential diagnosis of solid-pseudopapillary neoplasm of the pancreas. Am J Surg Pathol. 26(6): 818-20, Jun 2002.
10. Nakatani Y, Miyagi Y, Takemura T et al: Aberrant nuclear/cytoplasmic localization and gene mutation of β-catenin in classic pulmonary blastoma (CPB): Immunostaining for β-catenin is useful for distinguishing between CPB and blastomatoid carcinosarcoma (BCS). Mod Pathol 17(1), supplement 1, 341A-342A (abstract # 1441), Jan 2004
11.Yaziji H et al: β-catenin is as reliable as E-cadherin in the distinction between ductal and lobular tumors of the breast: A comparative study. Mod Pathol 17(1), supplement 1, 54A (abstract # 213), Jan 2004.

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