Modern Pathology (2008) 21, 1058–1059

www.modernpathology.org

Letter to the Editor

Modern Pathology (2008) **21,** 1058; doi:10.1038/modpathol.2008.31

To the editor: We read with interest the article by Esposito *et al*[1] that appeared in the January 2007 edition of your journal. It essentially corroborates our 2004 study on 27 examples of the same lesion that established the morphologically hybrid nature of tubulolobular carcinomas with an immunophenotype more similar to tubular carcinoma than lobular carcinoma (Wheeler *et al*).[2] When a tumor is being evaluated for expression of an antibody and the results are compared with those of another study, it is important to apply the same methodologies. As pointed out in one of our previous studies (Bratthauer *et al*),[3] the high-molecular weight cytokeratin clone 34βE12 is not by itself suitable for the distinction of classic lobular neoplasia from ductal or hybrid neoplastic lesions and that it is of value only when used in tandem with E-cadherin immunostains. This earlier report also pointed out that for immunohistochemical staining of 34βE12, a heat retrieval form of antigen recovery was used—not the proteolytic enzyme digestion performed in the study by Esposito *et al*.[1] Although it is possible that the subset of lobular, tubulolobular, and tubular carcinomas used in Esposito *et al*'s[1] study may have reacted differently with 34βE12 compared to the cases we reported, comparisons are valid only when exactly the same methodologies are used. It would be of interest to repeat the high-molecular weight cytokeratin (34βE12) assay on Esposito *et al*'s[1] tumor samples with a pH 6.0 heat retrieval pretreatment to see if the results are any different than those obtained using enzyme digestion.

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Modern Pathology (2008) **21,** 1058–1059; doi:10.1038/modpathol.2008.24

***In reply*:** We thank Mr Bratthauer, Dr Wheeler and Dr Tavassoli for their comments on our article.

The methodology that we use for 34βE12 antibody is different from that used by Wheeler *et al*,[1] beginning with section thickness. We do not use 6 μm sections for any immunostaining procedure in contrast to the study by Wheeler *et al*. Indeed, it is not uncommon for a multitude of protocols to exist for any given antibody across laboratories.

The methodology that we use in our laboratory has been optimized and validated against tissues and controls with the Benchmark XT (Ventana Medical Systems, Tuscon, AZ, USA), and the results have been quite satisfactory in our diagnostic experience. We have not optimized 34βE12 antibody in our laboratory for detecting lobular carcinomas, because 34βE12 is an antibody that detects a high-molecular-weight cytokeratin that ultrastructurally correlates with the presence of tonofilaments. Tonofilaments are present in carcinomas of any duct derivation in addition to squamous cell carcinomas.[2] We detected 34βE12 in 50% of lobular carcinomas (10 cases examined) *vs* 80% in the paper by Wheeler *et al* (5 cases examined). The paper by Wheeler *et al* also clearly demonstrates that 34βE12 is not useful in the distinction of tubulolobular (93% positive) *vs* lobular carcinomas (80% positive). E-cadherin alone is a superior antibody for the distinction of ductal *vs* lobular phenotypes.

It was not the intent of our paper to discuss the usefulness of 34βE12 in making the diagnosis of lobular carcinoma. Rather, our goal was to demonstrate

the ductal immunostaining patterns, specifically of E-cadherin and p120 catenin, both of which are biological markers for the E-cadherin/catenin complex. Ours is the first study to demonstrate the membrane-dominant ductal phenotype immunostaining pattern of p120 catenin in tubulolobular carcinomas. The cytoplasmic p120 catenin immunostaining pattern that we described in lobular neoplasia was absent in the tubulolobular group and present in the lobular carcinomas. P120 catenin and E-cadherin are equally sensitive and specific (100%)[3] and far superior to 34βE12 for the distinction of ductal *vs* lobular phenotypes.

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