Reviewer’s report

Title: Immunohistochemical analysis of ezrin-radixin-moesin-binding phosphoprotein 50 in prostatic adenocarcinoma

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Reviewer: Kenneth Iczkowski

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This well-written paper by Bartholow et al. describes how EBP50 protein has different expression in benign, HGPIN, primary cancer, and metastatic cancer tissues. It also does a good job explaining the biology of this protein and studies of its expression in other cancers.

While it is an interesting discovery that expression is highest in HGPIN, goes down somewhat in primary cancer, and goes way down in metastatic cancer, it remains uncertain whether the immunoreactivity in primary prostate cancer is predictive of co-existing or future metastatic potential. This lessens the value of the findings, making the findings just correlative rather than prognostic.

The addition of immunostaining results on primary prostate cancer with known biochemical failure, or with known metastatic outcome, versus known non-failure or known non-progression outcome, would greatly strengthen the paper.

An example of this is a paper on EZH2 protein (Varambally S et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. Nature 2002;419:624-9.) The authors examined the increase in this protein by staining 23 primary prostate tissues among 1023 tissue microarray elements from men who died of metastatic prostate cancer. A resource for studying this for EBP50 would be the CPCTR (www.cpctr.info/tma.html) which has, for 21 patients, both the primary and the metastatic lymph node lesion. Since stage and grade do not correlate with staining, is weak staining in the primary cancer tissue predictive of future/concurrent metastasis? Or is staining in the primary tissue relatively strong, and weak staining is solely a function of being in a metastatic site? The authors could demonstrate this without the CPCTR by just using up to 10 primary prostate cancers in which a history positive for metastasis is known, and comparing staining intensity with primary cancer tissue in those men known to have only localized non-progressing cancer.

Figure 2 should be omitted. This is because we have a mean staining of 139, 131, and 137 for stages 2, 3, and 4 respectively, and these groups consist of 39 men, 37 men, and 27 men respectively. The difference between stages 2 and 3, although statistically significant, is not meaningful or logical. The fact that this may be a statistical fluke is handled satisfactorily in the Discussion, but it doesn’t deserve its own Figure.

Lastly, I wouldn’t make too much of the membranous versus cytoplasmic distinction, as I cannot appreciate such a difference between Fig. 4C (benign)
and Fig. 4E (cancer); and the staining in metastases is too faint to determine whether it is cytoplasmic or membranous--giving the impression of 0/36 cases with cytoplasmic staining which may not be valid.

Minor issues:
Abstract line 2 The data was--> were
Introduction line 4 over diagnoses--> one word
paragraph 4 line 3 et al, --> et al.
paragraph 5 line 2 and line 3 over expressed--> one word; also in Discussion page 11
last paragraph line 2 series 11 cases --> series of 11 cases
Methods line 7 35 cases of HGPIN--> just say cases of ISOLATED HGPIN (no accompanying cancer diagnosed)
How many cases on the microarray were duplicate only rather than triplicates?
Page 9, third-last line. co-accompanying--> coinciding, or coexistent
Discussion: Fig. 1 belongs to the Results section, not the Discussion.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.