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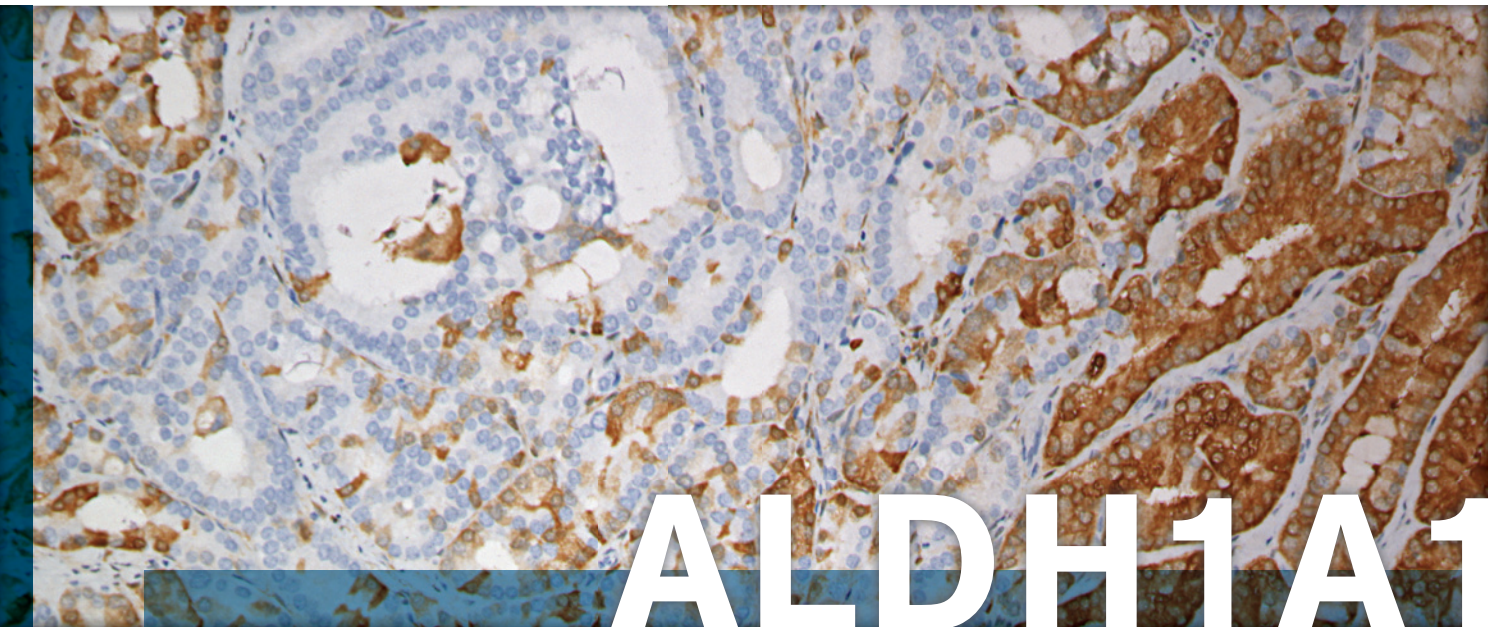
ALDH1A1 as a Marker of Stem Cells in Prostate Cancer: Correlation with Gleason Scores & Tumor Stage and Relevance for Patient Outcome

Ryan Bremer, Ph.D., David Tacha, Ph.D.; Biocare Medical, LLC, Concord, CA



Marker of Stem Cells in Prostate

As Presented at USCAP 2011, Abstract #761

Background

Mounting evidence supports the role of cancer stem cells (CSCs) in several malignancies, including prostate cancer (CaP). In particular, the high tumorigenicity and self-renewal capacity of CSCs contribute to their role in the recurrence and metastasis of tumors.[1] Specific markers of CSCs are potentially valuable as diagnostic tools and predictors of disease progression.

ALDH1A1, a member of the aldehyde dehydrogenase (ALDH) family of enzymes, has been shown to be a useful marker of CSCs. ALDH1A1 is responsible for the oxidation of retinal to retinoic acid, a key signaling molecule in stem cells, with roles in self protection, differentiation and expansion.[2]

Expression of ALDH1A1 is associated with poor patient outcomes in several cancers, including breast, lung, and bladder.[3,4,5] Experiments *in vitro* and *in vivo* have demonstrated the capacity of ALDH1A1+ CSCs to initiate tumors that resemble the heterogeneity of the parental tumor cells.

In prostate cancer patients, ALDH1A1 expression has recently been shown to be associated with higher Gleason sums and advanced tumor stage.[6] Most importantly, ALDH1A1 expression is a predictor of prostate cancer patient outcomes. Patients with high expression of ALDH1A1 have significantly reduced overall and cancer-specific survival rates, compared to those with low expression of ALDH1A1 (P=0.0093 and P=0.0017, respectively).

Design

Tissue micro-arrays, with known Gleason sums and TNM staging, containing 169 samples of prostate adenocarcinoma were evaluated for expression of ALDH1A1 by immunohistochemistry, using a rabbit monoclonal antibody (Biocare Medical).

Positive ALDH1A1 staining was determined for each sample and classified as either "Negative or Low" (<10% of cells staining) or "High" (>10%) expression. The relationship between ALDH1A1 expression and Gleason sum was determined by assigning the samples into groups by Gleason sum (≤6, 7, ≥8) and correlating each group with the level of ALDH1A1 staining. Data were evaluated using a Pearson chi square test to determine statistical significance.

Results

In all, 37 of 169 (22%) total CaP cases exhibited high expression of ALDH1A1. Typically, positive staining was cytoplasmic, with some nuclear staining. Positive staining of normal prostate glands was observed rarely. Sporadic stromal staining was observed in all grades. Benign prostatic hyperplasia (BPH) and prostatic intraepithelial neoplasia (PIN) were negative for ALDH1A1 (Figure 1).

Results cont'd

A range of ALDH1A1 expression was observed in cases of all Gleason sums. For example, cases with Gleason sum 10 showed high expression, low expression or absence of ALDH1A1 (Figures 2-4). Similar levels of high expression were also observed in cases with Gleason sums of 4 (Figure 5) and 7 (Figure 6), as were low and negative staining in cases of these same Gleason sums (data not shown).

Samples with Gleason sums ≥8 demonstrated an increased frequency of high ALDH1A1 expression. Those with Gleason sums ≥8 had high expression of ALDH1A1 in 21 of 60 (35%) cases, whereas those with an intermediate Gleason sum of 7 showed high expression in 8 of 34 (19%) cases, and only 8 of 59 (12%) cases with Gleason sums ≤6 exhibited high expression of ALDH1A1. The anti-ALDH1A1 rabbit monoclonal antibody demonstrates a statistically significant correlation between ALDH1A1 expression and Gleason sum (P=0.002).

Additionally, high expression of ALDH1A1 was observed in 19 of 66 (29%) samples from patients with pathologic tumor stages ≥3, compared to 20 of 109 (18%) samples from patients where pT ≤2. Although an increased frequency of ALDH1A1 expression was observed with higher tumor stage, the difference was not statistically significant.

Conclusion

Evaluation of ALDH1A1 expression in CaP samples was readily performed using a rabbit monoclonal antibody and routine immunohistochemical procedures. Using an alternative antibody to ALDH1A1, previous reports of ALDH1A1 expression in CaP samples have been validated. Expression of ALDH1A clearly correlates with higher Gleason sums.

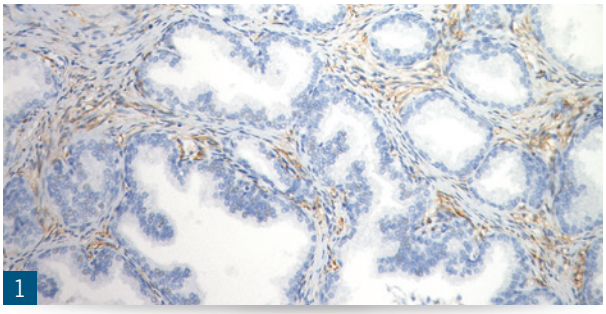
Considering its demonstrated effectiveness as a marker for cancer stem cells and a predictor of patient outcome, ALDH1A1 expression may be a useful diagnostic and prognostic tool for the evaluation of prostate cancer cases.

Table

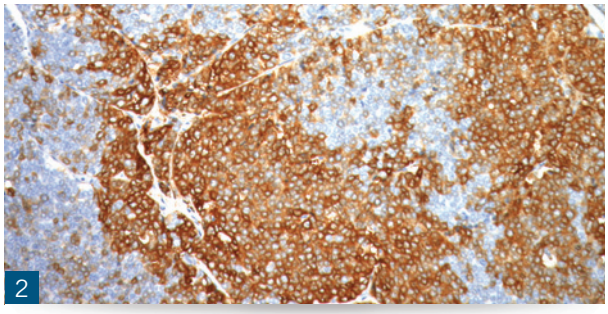
Gleason Sum	ALDH1A1 Expression		Total	% High Expression
	Neg or Low	High		
≤6	59	8	67	12%
7	34	8	42	19%
≥8	39	21	60	35%
Total	**132**	**37**	**169**	**22%**

Figures

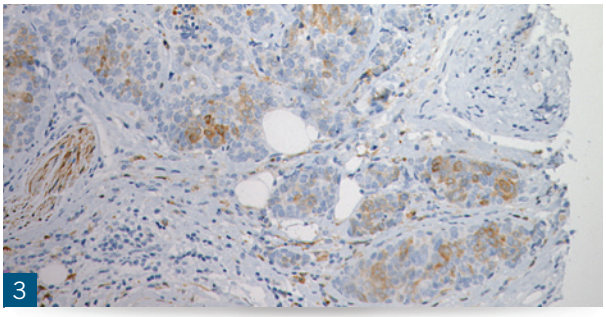
ALDH1A1 staining in prostate adenocarcinomas:



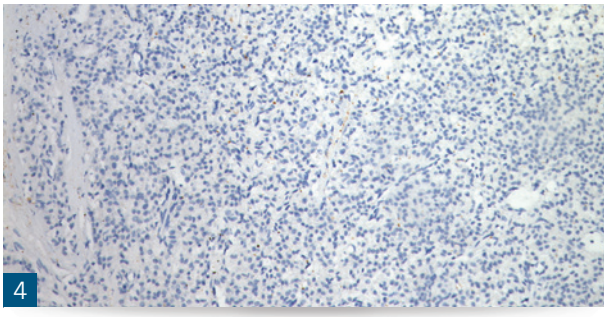
Negative ALDH1A1 staining in BPH and PIN



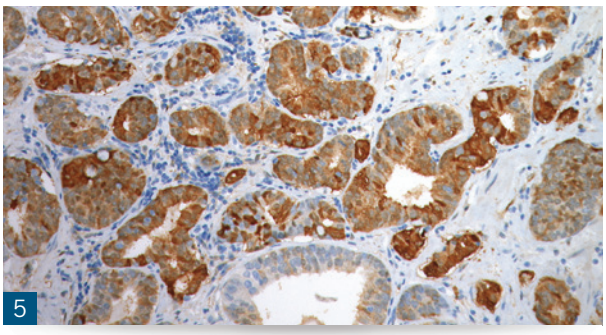
High Expression of ALDH1A1 in a case with Gleason sum 10



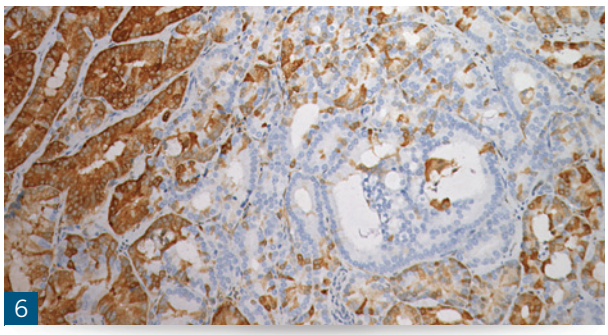
Low Expression of ALDH1A1 in a case with Gleason sum 10



Negative ALDH1A1 staining in a case with Gleason sum 10



High Expression of ALDH1A1 in a case with Gleason sum 4



High Expression of ALDH1A1 in a case with Gleason sum 7

References

1. Kelly K, Yin JJ. Prostate cancer and metastasis initiating stem cells. Cell Res 2008;18:528-537.

2. Ma I, Allan AL. The role of aldehyde dehydrogenase in normal and cancer stem cells. Stem Cell Rev and Rep 2010; online epub 20 Nov.

3. Ginestier C, Hur MH, Charafe-Jauffret E et. al. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. Cell Stem Cell 2007;1:555-567.

4. Jiang F, Qiu Q, Khanna A et. al. Aldehyde dehydrogenase 1 is a tumor stem cell-associated marker in lung cancer, Mol Cancer Res 2009;7:330-338.

5. Su Y, Qiu Q, Zhang X et. al. Aldehyde dehydrogenase 1 A1-positive cell population is encirched in tumor-initiating cells as associated with progression of bladder cancer. Cancer Epidemiol Biomarkers Prev. 2010 Feb;19(2):327-37.

6. Li T, Su Y, Mei, Y et. al. ALDH1A1 is a marker for malignant prostate stem cells and a predictor of prostate cancer patients' outcome. Lab Invest 2010;90:234-244.

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800.799.9499
4040 Pike Lane
Concord CA 94520

www.biocare.net