Letter to the Editor

Cancer Research

Intraprostatic Steroidogenic Enzymes – Letter

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We read with interest the report by Hofland and colleagues evaluating the expression of steroidogenic enzymes in castration-recurrent prostate cancer (CRPC; ref. 1). Their analysis of cell lines, xenografts, normal prostate tissue, lymph node metastases, and locally recurrent CRPC tissues identified transcripts encoding steroidogenic enzymes involved in the conversion of circulating adrenal androgens in CRPC. In contrast, they detect the simultaneous expression of CYP17A and HSD3B1, required for the *de novo* synthesis of androgens, in only 19 of 88 samples. Based on these observations, the authors suggest that *de novo* intratumoral steroidogenesis plays a limited role in resistance to androgen deprivation. The limited detection of CYP17A and HSD3B1 is in contrast with our detection of these enzymes in CRPC metastases, as well as our demonstration that LNCaP synthesizes DHT *de novo* (2–4).

Several important differences in methodology may underlie the observed differences. First, the tissues evaluated by Hofland and colleagues did not include any bone or soft tissue metastatic CRPC. The original impetus for our study was the biology of distant metastases, as acquisition of metastatic potential likely changes tumor progression and potentially androgen synthesis, and may differ between recurrent primary tumors and distant CRPC metastases. Therefore, low CYP17A or HSD3B1 expression in nodal metastases (prior to resistance), or in CRPC primary tumors is not surprising and does not preclude detection in distant metastases.

Second, the primers utilized by Hofland and colleagues to amplify CYP17A and HSD3B1 are located 1,300 bp upstream of the 3′ mRNA terminus (our primers are within 300 bp of the 3′ ends). The generation of cDNA via oligo-T12 priming of total RNA does not produce transcripts longer than 600 bases, and the use of primers located more 5′ compromises sensitivity of transcript detection. This is consistent with their observation that these transcripts were seen more frequently when using ABI primer sets located more 3′ on the mRNA transcripts. We agree that the expression of these transcripts is low, with the cycle thresholds for CYP17A and HSD3B1 in the CRPC tissues we examined ranging from 31 to 36 (data not shown).

Importantly, the low CYP17A transcript expression observed by Hofland and colleagues in LNCaP underscores the point that transcript expression may not always reflect protein levels. Although transcript levels for CYP17A in LNCaP may be low, *de novo* dihydrotestosterone synthesis clearly occurs in this model, demonstrating that low transcript levels maintain protein expression and enzymatic activity (4). We and others have also shown that CYP17A protein expression is present in clinically localized and in CRPC tumor specimens (Fig. 1A; refs. 5, 6). The demonstration of protein expression corroborates the data regarding transcript expression in these tissues.

Despite these differences, we believe both data sets are consistent with the conclusion that intratumoral androgen synthesis is heterogeneous within CRPC tumors. A heatmap depiction of steroidogenic enzyme expression in our original data set (samples clustered by expression of these transcripts) shows three subsets of CRPC tumors (Fig. 1B). Approximately one-third of these samples have simultaneous expression of transcripts encoding the range of enzymes needed for *de novo* androgen synthesis. A second subset primarily expresses 17BHSD3 and AKR1C3 (necessary for conversion of adrenal androgens to dihydrotestosterone), whereas the third subset shows only increased expression of AR, suggesting amplified signaling independent of steroidogenesis.

In summary, evidence implicating intratumoral androgen metabolism as a mechanism of progression in castration-resistant prostate cancers continues to accumulate. We find the examination of clinically localized prostate cancer specimens performed by Hofland and colleagues complementary to our demonstration of transcripts encoding steroidogenic enzymes in distant soft tissue CRPC metastases. We look forward to the continued evaluation of this intriguing mechanism and the clinical evaluation of novel agents targeting these pathways.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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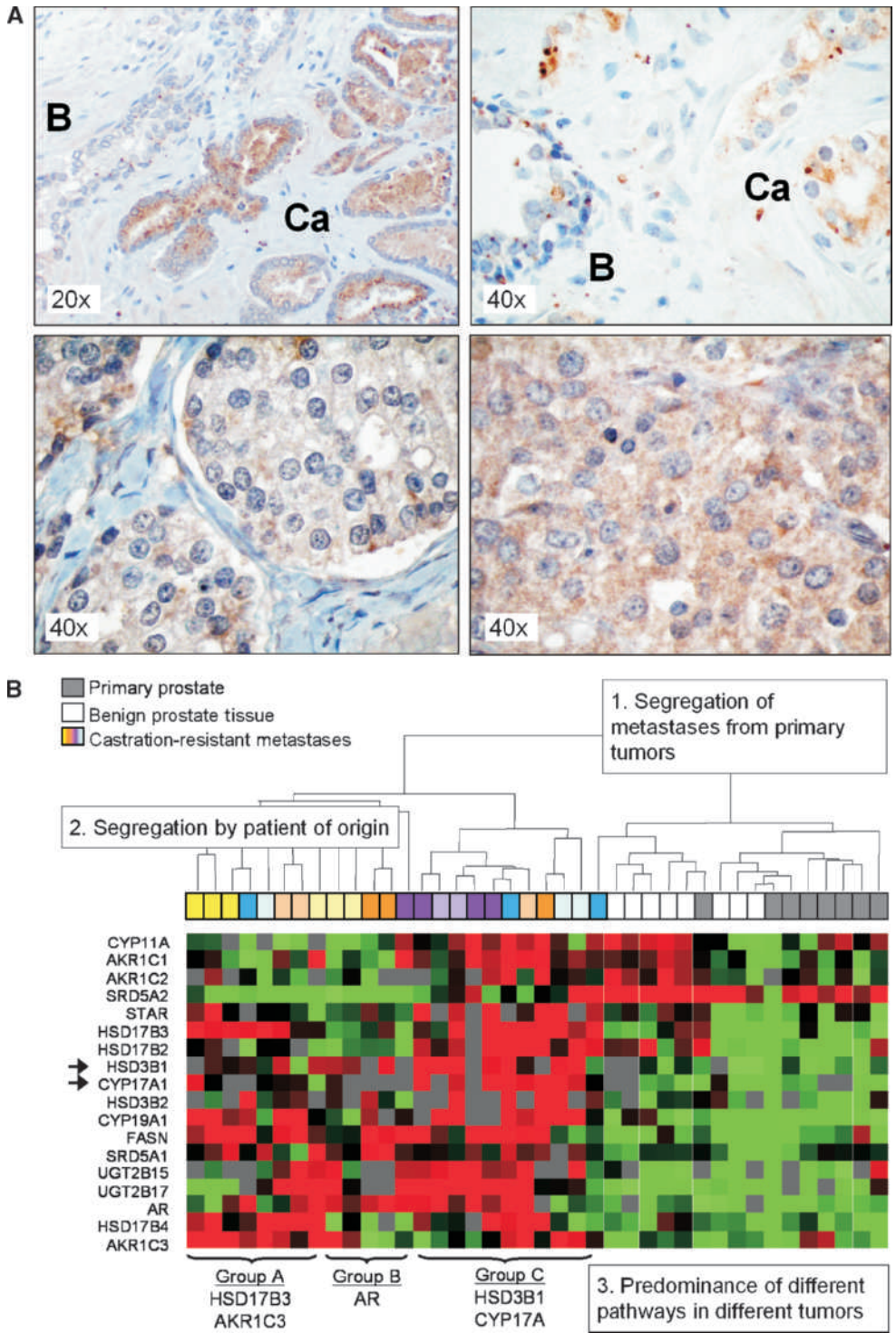

Figure 1. A, immunohistochemical staining for CYP17A expression (Santa Cruz SC-46085, 1:50) in two clinically localized prostate tumors (top), and two soft tissue CRPC metastases (bottom). Cytoplasmic staining of CYP17A is present in the primary prostate tumors (Ca) with little staining in adjacent benign glands (B), and is diffusely positive in the metastatic tumor cells. B, heatmap depicting expression of steroidogenic transcripts in benign prostate tissue, untreated primary prostate cancer, and distant soft tissue CRPC metastases. Samples are color-coded based on type of tissue and patient of origin and clustered based on relative transcript expression. The heatmap represents the range of relative staining from low (green) to high (red) with gray samples reflecting undetectable transcript expression.

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