Integrative genomic analysis of coincident cancer foci implicates PTEN alterations in ductal adenocarcinoma of the prostate

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Abstract

Background: Ductal adenocarcinoma of the prostate is an aggressive subtype, with high rates of biochemical recurrence and overall poor prognosis. It is frequently found coincident with typical acinar adenocarcinoma. The genomic features driving evolution to its ductal histology, and the biology associated with its poor prognosis, remain unknown. To characterize distinguishing features of ductal adenocarcinoma from coincident acinar adenocarcinoma foci from the same patient, we performed integrative genomic and transcriptomic analyses.

Methods: Laser microdissection was used to separately isolate acinar and ductal foci from ten prostatectomy specimens from subjects with treatment-naïve prostate cancer. DNA and RNA were extracted and used for mutational, copy number, expression, and pathway analysis.

Results: Mutational analysis and copy number estimates derived from exome sequence demonstrate each case of coincident ductal and acinar adenocarcinoma diverged from a common progenitor yet harbor distinct alterations unique to each focus. Androgen receptor (AR) expression, measured by RNA sequencing and immunohistochemistry, and its activity, measured by pathway analysis and expression of AR-regulated proteins, are similar in both histologies within each patient. Six of ten cases, however, harbor an alteration in the phosphatase and tensin homolog (PTEN) tumor suppressor gene, including a non-synonymous mutation, a small deletion, chromosomal deletion, and loss of heterozygosity. Strikingly, these alterations are exclusive to the ductal foci and a ductal-derived synchronous metastasis. These loss-of-function PTEN alterations are associated with loss of PTEN protein in ductal foci. Concomitant gain-of-function PI3K pathway activation is enriched in ductal relative to acinar adenocarcinoma.

Conclusions: Based on their shared genomic alterations, coincident ductal and acinar histologies arise from the same cell of origin, yet diverge early with distinct alterations unique to each. PTEN loss of function, and PI3K pathway activation, are enriched in ductal foci, potentially contributing to the histologic appearance and aggressive biology of this subtype. Given similar RNA and protein expression of AR and AR-regulated genes, this does not appear to include substantial effects on AR activity. It is not known if ductal features correlate with response to PI3K pathway inhibitors.

Conflicts of interest: none

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