

Distinct AR dependent transcriptional program in ETS fusion negative prostate cancer

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Background: The Androgen receptor (AR) regulated ETS family gene rearrangement (ETS+) is an early event in prostate cancer (PCa) pathogenesis that has been identified by our group and others to show racial variation with >70% of African American men (AA) men lacking ETS fusion (ETS-) prostate tumors. Given that ETS- tumors also demonstrate AR dependent growth, we determined if there are distinct AR regulated transcriptional programs in PCa pathogenesis based on ETS status by analyzing the expression pattern of AR target genes between ETS- and ETS+ tumors.

Methods: We analyzed three large PCa datasets (TCGA; N=333 including 43 AAs; and Decipher GRID_retrospective; N=635 including 127 AAs; and a validation set, GRID_prospective; N= 5925;). ETS+ status was assigned to samples with overexpression of ERG, and ETS family (ETV1-5, and FLI1). All others were assigned ETS-. The differential expression of biomarker genes by ETS status was evaluated using false-discovery-rate adjusted (q) Mann-Whitney U test and fold-change cut-off. Gene-set enrichment analysis (GSEA) was used to evaluate biologic differences by ETS status. A Principal Component Analysis (PCA) model was used to generate ETS classification based on expression pattern of known AR dependent genes within the Hallmark database. AR dependent pathway analysis was evaluated using gene ontology analysis.

Results: Within TCGA and GRID databases, the ETS- molecular subtype accounted for 50% of all PCa cases, with approximately 75% of these being of AA origin. In an unsupervised PCA model using the Hallmark database gene expression profile, we observed that AR regulated gene expression alone was able to independently separate out PCa samples based on ETS status in both datasets. Next, several genes that are differentially expressed based on ETS status in either TCGA (1423 genes; 6.9%) or GRID (3047 genes; 6.6%) databases were identified, of which 413 overlapping genes were found to be differentially expressed. In a GSEA, different sets of non-overlapping androgen response genes were identified from genes that are upregulated only in ETS- tumors compared with genes that are upregulated only in ETS+ tumors. Of these, metabolic pathway genes were preferentially enriched in ETS- samples. Using publicly available AR CHIPseq expression data, we identified 133 AR target genes that are differentially regulated in an ETS specific manner. The AR target genes that are preferentially dysregulated in ETS- tumors were identified within specific pathways involved in metabolic processes, and non-canonical WNT pathway.

Conclusion: These findings indicate that different AR target genes are activated in both ETS+ and ETS- PCa. The AR target genes identified in ETS- tumors enable us to address the apparently conflicting data on AR activity in ETS- PCa. Our data provides strong evidence to suggest that ETS- tumors utilize a distinctly different AR dependent transcriptional program for tumor progression.

Conflict of Interest: There are no conflicts of interest to disclose

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