Characterizing the molecular landscape of early onset and average onset prostate cancer

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BACKGROUND

- Prostate cancer (PC) has a median onset age of 66, however, recent evidence suggests an increase in incidence of PC diagnosis in males <55 years of age.
- Family history and increased mutational burden has been associated with early onset PC (EOPC), nonetheless, comprehensive molecular and immune signatures that cluster in EOPC and average onset PC (AOPC) is poorly understood.
- Here, we characterized EOPC and AOPC, and their association with molecular and immune signature.

METHODS

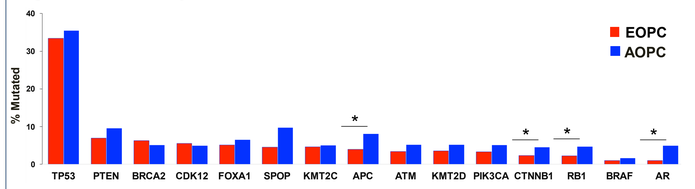
- 5,305 PC samples were tested by NGS (592, NextSeq; WES, NovaSeq), WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ).
- PC Patients with age <55 and ≥65 was classified as EOPC and AOPC, respectively.
- Microsatellite-instability (MSI) was tested by fragment analysis, immunohistochemistry (IHC), and next generation sequencing (NGS).
- Tumor mutational burden (TMB) totaled somatic mutations per tumor (high≥10 mt/MB).
- Androgen receptor (AR) signature and Neuroendocrine Prostate Cancer (NEPC) score calculated based on expression level of previously defined genes (Hieronymus *et al*. 2006, Beltran *et al*. 2016).
- Pathway enrichment was determined by GSEA (Broad Inst).
- RNA-deconvolution using QuantiSEQ was used to assess immune cell infiltration in the tumor microenvironment.
- Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons (q < 0.05).

Table 1: Patient demographics

	Count (N)	Median age (range)
EOPC	575	51 [35 - 54]
AOPC	4730	72 [65 - >89]

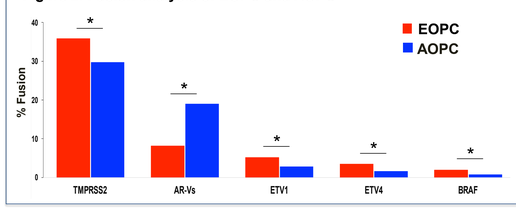
RESULTS

Figure 1. Mutation analysis of EOPC and AOPC



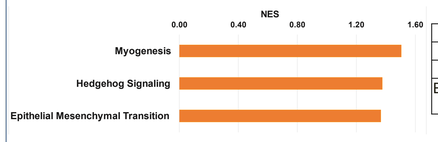
EOPC had but lower frequency of APC (4% vs 8%), *CTNNB1* (2.4% vs 4.6%), *RB1* (2.3% vs 4.7%) and *AR* (1% vs 4.9%) mutation, compared to AOPC (*p<0.05).

Figure 2. Fusion analysis of EOPC and AOPC



EOPC had higher frequency of *TMPRSS2* (35.8% vs 29.7%), *ETV1* (5.2% vs 2.8%), *ETV4* (3.4% vs 1.6%), and *BRAF* (1.9 vs 0.7%) fusions compared to AOPC (*p<0.05).

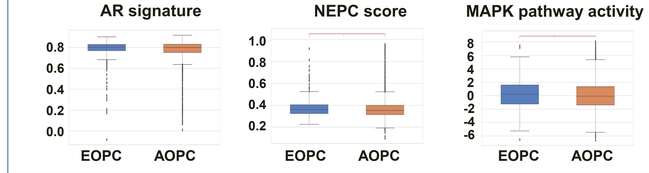
Figure 3. Gene set enrichment analysis (GSEA) of the EOPC and AOPC tumors



Term	FDR	NES
Myogenesis	0.00	1.50
Hedgehog Signaling	0.09	1.38
Epithelial Mesenchymal Transition	0.09	1.37

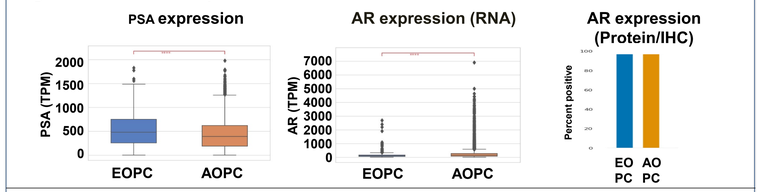
EOPC had had pathway enrichment of cancer associated signaling, A positive NES imply EOPC tumors are enriched with gene set.

Figure 4. AR signature, NEPC score and MAPK activation score (MPAS) in EOPC and AOPC tumors



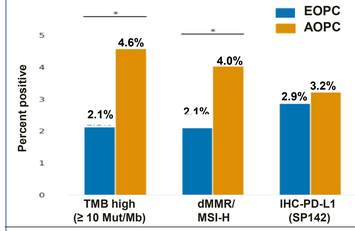
EOPC had higher median NEPC score (0.359 vs 0.353, q<0.05), higher MAPK pathway activity score (MPAS) (3-fold , q<0.05) but no difference in median AR signature (q=0.39) compared to AOPC.

Figure 5. PSA and AR expression in the EOPC and AOPC tumors



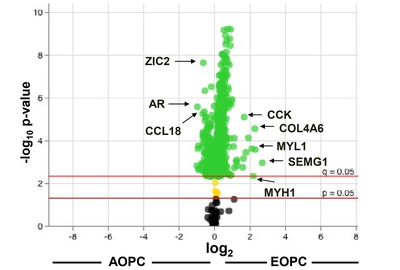
EOPC had higher expression of *PSA* (1.2-fold, p<0.05) and reduced *AR* expression (1.3-fold, p<0.01), however there was no difference in IHC-AR (p=0.65)

Figure 6. Immune markers in EOPC and AOPC tumors



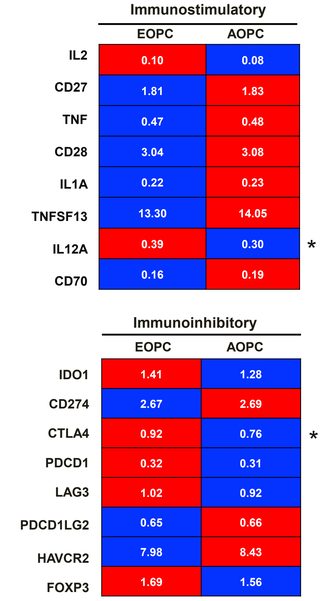
EOPC tumors had lower frequency of TMB high (2.1% vs 4.6%) and dMMR/MSI-H (2.1% vs 4.0%) compared to AOPC tumors, *p<0.05. There was no difference in IHC-PD-L1 between EOPC vs AOPC (p=0.65).

Figure 7. Differentially expressed gene in EOPC and AOPC tumors



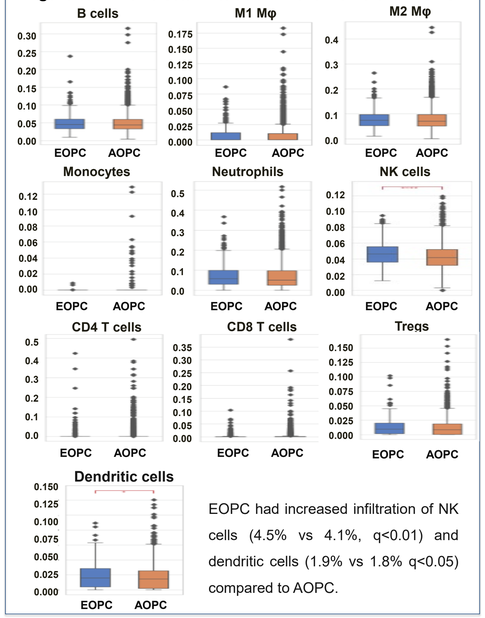
EOPC had higher expression of *CCK, COL4A6, MYL1, SEMG1, MYH1* (FC: 3.2-6.5, p<0.05) and lower expression of *ZIC2, AR, CCL18* (FC: 0.6-0.4, p<0.05) compared to AOPC.

Figure 8. Immune gene expression in EOPC and AOPC tumors



EOPC had higher expression of immunomodulatory genes (*IL12A, CTLA4*, FC:1.2, *p<0.05).

Figure 9. Immune cell infiltration in the EOPC and AOPC



EOPC had increased infiltration of NK cells (4.5% vs 4.1%, q<0.01) and dendritic cells (1.9% vs 1.8% q<0.05) compared to AOPC.

CONCLUSIONS

Our data suggest that EOPC is enriched in fusion events including *TMPRSS2*, *ETV1, ETV4* and *BRAF*. Distinct transcriptomic features seen in EOPC included neuroendocrine differentiation, MAPK activations, immunomodulatory gene expression, and increased infiltration of NK cells and dendritic cells, suggesting inherent molecular differences and differential tumor immune microenvironment in EOPC and AOPC.

AUTHOR INFORMATION