Molecular correlates with PSMA expression in primary prostate cancer

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Background

Prostate cancer (PCa) is clinically and biologically heterogeneous

PSMA PET has improved characterization and localization, but not all tumors express PSMA

Variations in intratumoral PSMA levels may reflect differential cancer biology and susceptibilities to treatments

Objectives

Query molecular profiles from multiple cohorts of treatment naïve PCa to discover and validate cell pathways and treatment susceptibilities associated with PSMA RNA abundance (*FOLH1*).

Methods

Prospective trial of 55 patients who underwent PSMA PET prior to prostatectomy with RNA profiling to correlate PSMA RNA with SUVmax

Discover & validate pathways associated with PSMA in large cohorts of primary PCa: TCGA, n=491 and GRID, NCT02609269, n=2612.

Validation of pathway associations and clinical outcomes via orthogonal assessments and independent cohorts

Conclusions

PSMA levels reflect differential PCa biology

In treatment naïve PCa, low PSMA tumors are relatively resistant to ADT and radiotherapy.

Results

Fig 1

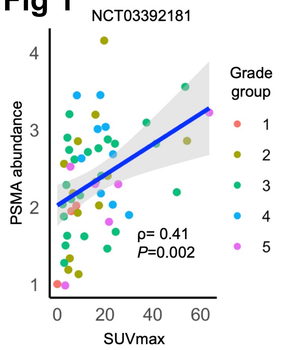


Fig 2

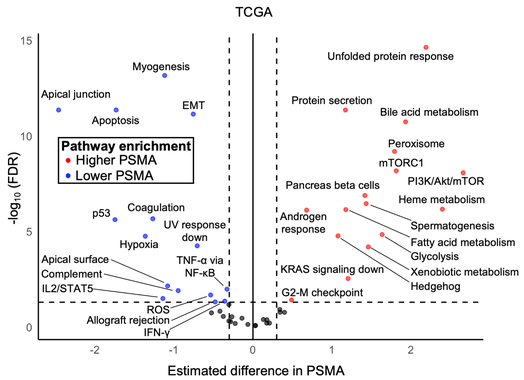


Fig 3

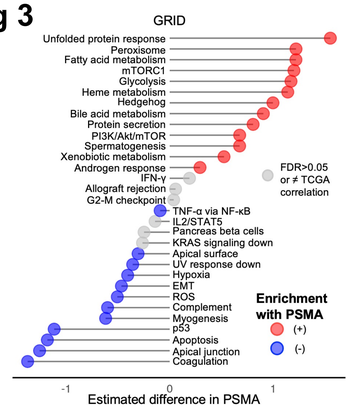
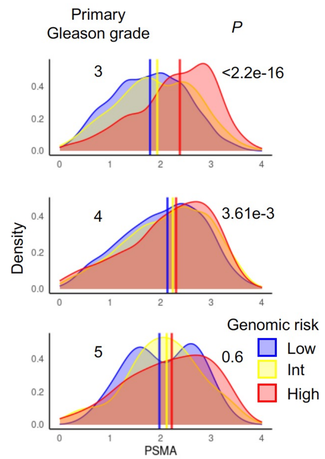


Fig 6



PSMA RNA abundance correlates with SUVmax, establishing RNA levels as a proxy for PET metrics (**Fig 1**)

Using multivariable linear regressions, TCGA was used to discover pathways associated (**Fig 2**) with validation in GRID (**Fig 3**)

Fig 4

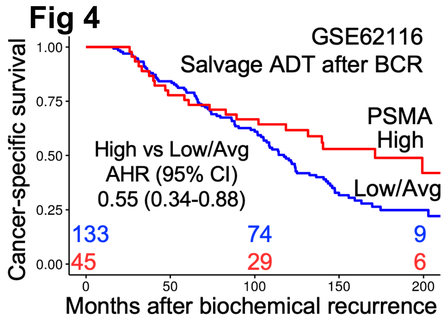


Fig 5

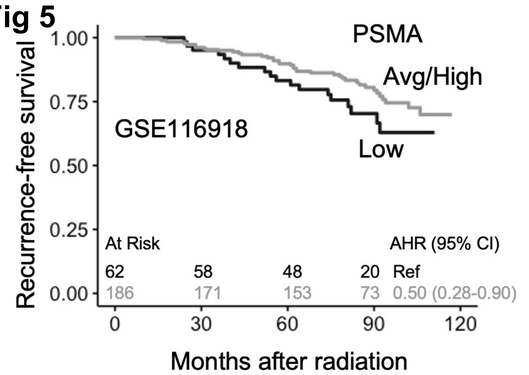
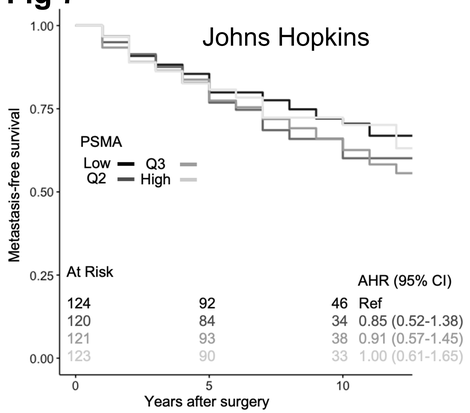


Fig 7



PSMA high tumors:
Enriched for androgen response pathways (**Fig 2-3**). Associated with longer cancer-specific survival after BCR following prostatectomy managed with salvage ADT (**Fig 4**).

PSMA lower tumors:
Enriched for markers of cancer stem cells (ROS, EMT, hypoxia, and angiogenesis; **Fig 2-3**). Associated with increased recurrences after radiotherapy (**Fig 5**).

PSMA was not associated with tumor grade group, stage (primary vs nodal), or cribriform histology (not shown).

PSMA was associated with high genomic risk only for tumors with primary pattern 3 and 4 (**Fig 6**). In a largely high-grade surgery cohort, PSMA did not predict outcomes (**Fig 7**)

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