Abstract # 1524

Tumor mutation burden and PD-L1 expression in SDH/FH mutated solid tumors

CONTRIBUTING RESEARCHERS

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BACKGROUND

Succinate Dehydrogenase and Fumarate Hydratase (SDH/FH) - deficient tumors are characterized by succinate/fumarate accumulation and resultant pseudohypoxia that drives malignant transformation.[1-3] It has been shown recently that HIF-1a stabilization due to hypoxia can lead to upregulation of the PD-1 ligand, *PD-L1*. In this study, we explored tumor mutation burden (TMB), gene expression of *PD-L1*, and expression of other immune checkpoint- associated genes in a diverse cohort of human tumors harboring *SDH A, B, C, D* and *FH* mutations.

METHODS

- Retrospective analysis was performed on 3461 paired tumor/normal whole exome sequences (WES; ~150x coverage) from the NantHealth clinical case database
- 42 clinical cases with potentially pathogenic variants (pPV) in *SDHx* and *FH* were identified. Variant pathogenicity was assessed by multiple factors including driver gene status, variant class (e.g. Missense), PhastCons conservation score, and population allele frequency
- TMB was measured by counting all somatic-specific non-synonymous exonic mutations. In 2739/3461 cases that also had whole transcriptomic RNA-seq (~200x10^6 reads per tumor) data, immune checkpoint expression was calculated

RESULTS

Figure 1. **Distribution of samples with potentially pathogenic somatic variants in SDH and/or FH.** The highest counts are seen in lung, breast, and colon cancers.

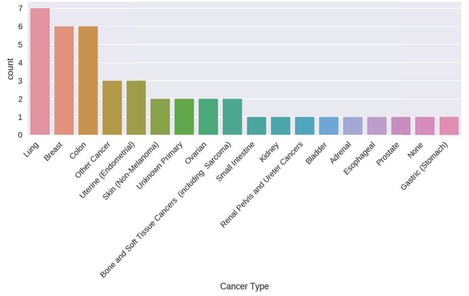
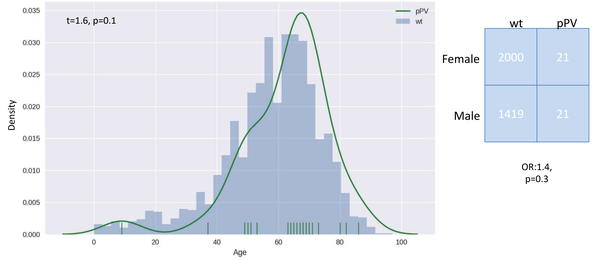


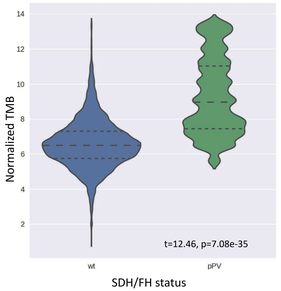
Figure 2. **Presence of SDH/FH pPV variants by age (left) and gender (right).** There was no significant association between patient age or gender and the observation of pPV.

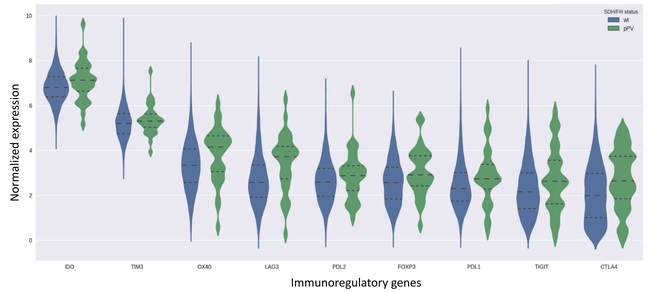


	wt	pPV
Female	2000	21
Male	1419	21

OR:1.4, p=0.3

Figure 3. **TMB and SDH/FH status and expression of immuno-regulatory genes.** Tumor samples with pathogenic or potentially pathogenic SDH/FH variants (pPV) have higher TMB (left) & expression of checkpoint-related genes.





Tests of differential significance

gene	t	p	adj. p
LAG3	3.57	0.0004	**0.0033**
CTLA4	2.92	0.0036	**0.0161**
FOXP3	2.45	0.0143	**0.0384**
OX40	2.39	0.0171	**0.0384**
TIGIT	2.24	0.0249	**0.0447**
IDO	2.12	0.0343	**0.0460**
PDL1	2.10	0.0357	**0.0460**
PDL2	1.51	0.1313	0.1477
TIM3	1.37	0.1715	0.1715

KEY FINDINGS

- Differential TMB and immuno-regulatory gene expression was observed between SDHx/FH pPV vs. WT cases
- TMB was positively correlated with the presence of *SDH/FH* mutations ($p < 0.001$)
- High *PD-L1* expression significantly correlated with the presence of *SDH/FH* mutations ($p < 0.05$)
- *CTLA4*, *IDO*, *LAG3*, *FOXP3*, and *OX40* expression was significantly higher in SDH/FH mutated samples ($p < 0.05$)

CONCLUSIONS:

We report for the first time an association between both increased TMB and increased *PD-L1* expression with the presence of *SDH/FH* mutations in a variety of tumors. These key associations suggest that a higher TMB – specifically in the presence of SDH/FH mutation and resultant deficiency - may drive evolutionary pressure for the selection of clones with a PD-L1 high phenotype. This observation supports a potential therapeutic role for inhibition of PD-1/PD-L1 pathway in SDH/FH deficient tumors.

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2. Eijkelenkamp, K, Osinga, TE, Links, TP, Horst-Schrivers, ANA. Clinical implications of the oncometabolite succinate in *SDHx*-mutation carriers. *Clin Genet.* 2019; 1–15. https://doi.org/10.1111/cge.13553
3. Miettinen M, Lasota J. Succinate dehydrogenase deficient gastrointestinal stromal tumors (GISTs) - a review. *Int J Biochem Cell Biol.* 2014;53:514–519. doi:10.1016/j.biocel.2014.05.033

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