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

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Keywords: Differential TMB and immuno-regulatory gene expression was observed between SDH/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.

Background: Succinate Dehydrogenase and Fumarate Hydratase (SDH/FH) - deficient tumors are characterized by succinate/fumarate accumulation and resultant pseudohypoxia that drives malignant transformation.1 It has been shown recently that HIF-1a stabilization due to hypoxia can lead to upregulation of the PD-L1 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 (“200x106 reads per tumor) data, immune checkpoint expression was calculated.

Results: TMB was positively correlated 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.

Figure 1. Distribution of samples with potentially pathogenic variants in SDH/A and 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.

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

Figure 4. Kaplan-Meier plot showing the survival rate of melanoma patients (TMB<10 vs. TMB>10).

Figure 5. Kaplan-Meier plot showing the survival rate of melanoma patients (pPV<10 vs. pPV>10).

Key Points:
* Differential TMB and immuno-regulatory gene expression was observed between SDH/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.