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A STING Operation in neuroendocrine neoplasms

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BACKGROUND

Significant advances have been made in the treatment of gastrointestinal (GI-) and pancreatic (P-) NENs. However, the use of immunotherapy is still limited, with most tumors considered immune "cold". The cGAS-STING signaling pathway has emerged as a critical mediator of inflammation and immune-mediated responses, with pathway agonists under development for enhancing immunotherapy. In this study, we evaluated associations between cGAS-STING pathway activity and the molecular and immune landscapes of GI- and P-NENs.

METHODS

DNA (592-gene or whole exome) and RNA sequencing (whole transcriptome) were performed on GI- (n=571) and P- (n=294) NEN specimens submitted to Caris Life Sciences (Phoenix, AZ). Immune-high (IH) and low (IL) groups were based on hierarchical agglomerative clustering of STING pathway genes (*CCL5, CXCL10* and *MB21D1*); a STING pathway score (SPS) was defined as the summation of z-scores of these genes. QuanTIseq analysis was used to estimate tumor microenvironment immune cell fractions. Statistical significance was determined using chi-square, Fisher's exact or Mann-Whitney U tests where appropriate and adjusted for multiple comparisons.

RESULTS

Median expression of somatostatin receptors (*SSTR*) 1 and 2 was reduced in the IH vs IL groups (Table 1). IH samples were enriched for TP53, RB1 and KRAS mutations (Table 1). Interestingly, while mutations in all three genes was associated with high SPS in P-NENs, multiple gene mutations did not significantly affect SPS in GI-NENs. IH tumors were associated with increased expression of immune checkpoint genes, including CD80, CTLA4 and IFNG (3.01-4.16-fold and 4.39-8.24-fold compared to IL in GI- and P-NEN, respectively; all $p<0.05$) and increased immune cell fractions, such as B-cells (GI- and P-NENs(%): 5 vs 4, $p<0.05$) and M1 Macrophages (GI-NENs(%): 2 vs 1, P-NENs: 1 vs 0; all $p<0.05$).

Table 1: Features associated with IH and IL groups.

Features	IH: GI-NENS (n=187)	IL: GI-NENS (n=384)	IH: P-NENS (n=83)	IL: P-NENS (n=211)
SSTR1 (median TPM)	2.11	3.18	2.96	5.3
SSTR2 (median TPM)	5.36	12.58	18.44	29.58
TP53 (% Prevalence)	57.61	29.24	41.46	23.79
RB1 (% Prevalence)	36.72	15.21	31.75	7.59
KRAS (% Prevalence)	23.66	11.78	22.89	6.64

CONCLUSIONS

Our results demonstrated that the cGAS-STING pathway activity identifies GI- and P-NENs with an immunogenic profile, which may be augmented by one or multiple mutations in *TP53, KRAS* and *RB1*. These results suggest combination of cGAS-STING agonists and immune checkpoint inhibitors may be effective in GI- & P-NENs and warrant further investigation.

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