Landscape of Delta-like-ligand 3 (DLL3) Expression Across Neuroendocrine Neoplasms (NENs)

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Background

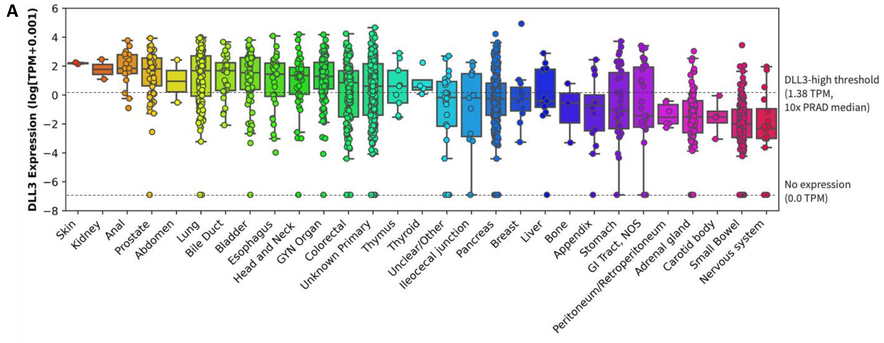
- Delta like ligand 3 (DLL3) is a cell surface protein and emerging therapeutic target in neuroendocrine carcinomas.
- The clinical and molecular features associated with DLL3 expression across cancer types are not well defined.
- Recent studies indicate that ~77% of neuroendocrine prostate cancers (NEPC) overexpress DLL3, as compared to metastatic castration resistant prostate cancers of the adenocarcinoma subtype (12.5%) or localized prostate tumor or prostate tissue (<1%).
- Similarly in small cell lung cancer (SCLC) and other neuroendocrine carcinomas, DLL3 is highly expressed and an emerging target.
- There are several ongoing clinical trials of drugs targeting DLL3 in neuroendocrine carcinomas, including T cell engagers and BiTE therapies.
- Defining the genomic landscape and aberrant signaling activity in DLL3-overexpressing neuroendocrine carcinomas will help elucidate regulators of DLL3 expression and may help improve patient selection for DLL3-targeted drugs.

Methods

- DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing was performed on 1589 patient samples at Caris Life Sciences (Phoenix, AZ).
- DLL3-high NENs were defined using a threshold TPM 10x the median expression of DLL3 in prostate NENs.
- Centralized pathology review was done on NENs from prostate (n = 64), lung (n = 122), and bladder (n = 64).
- Immune cell fractions were inferred via quanTIseq (Finotello, 2019).
- Statistical significance was determined using $\chi 2$ or Fisher's exact tests, with Benjamini-Hochberg correction for multiple comparisons.

Results

Figure 1. (A) Differential expression of DLL3 across NENs from various primary tumor sites, with summary metrics reported in Table 1. (B-D) Comparison of DLL3 expression in NENs vs Adeno for prostate, bladder, and lung sites



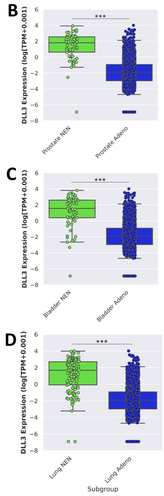


Table 1. DLL3 expression by primary site

Cancer type	Median DLL3 (TPM)	N Total	N w/ 0 TPM DDL3	% w/ 0 TPM DDL3	N w/ DLL3-High	% w/ DLL3-High
Skin	8.998175	2	0.0	0.00	2	100
Kidney	7.348750	2	0.0	0.00	2	100
Anal	6.323540	17	0.0	0.00	14	82.35
Prostate	6.105810	66	1.0	1.52	50	75.76
Abdomen	5.960443	2	0.0	0.00	1	50
Lung	5.400185	122	2.0	1.64	87	71.31
Bile Duct	5.374540	27	0.0	0.00	20	74.07
Bladder	4.691435	66	1.0	1.52	51	77.27
Esophagus	4.251460	32	0.0	0.00	22	68.75
Head and Neck	3.859390	43	1.0	2.33	31	72.09
GYN Organ	3.609865	118	1.0	0.85	90	76.27
Colorectal	2.353520	141	8.0	5.67	80	56.74
Unknown Primary	1.853830	294	12.0	4.08	161	54.76
Thymus	1.833560	9	0.0	0.00	5	55.56
Thyroid	1.726960	4	0.0	0.00	3	75
Unclear/Other	0.843033	25	4.0	16.00	9	36
Ileocecal junction	0.820018	11	1.0	9.09	4	36.36
Pancreas	0.772417	232	10.0	4.31	85	36.64
Breast	0.770587	11	0.0	0.00	3	27.27
Liver	0.662014	13	1.0	7.69	5	38.46
Bone	0.571393	3	0.0	0.00	1	33.33
Appendix	0.478279	16	1.0	6.25	4	25
Stomach	0.347639	38	2.0	5.26	12	31.58
GI Tract, NOS	0.238579	30	5.0	16.67	12	40
Peritoneum/Retroperitoneum	0.232515	6	0.0	0.00	0	0
Adrenal gland	0.220075	89	7.0	7.87	11	12.36
Carotid body	0.217635	4	0.0	0.00	0	0
Small Bowel	0.134410	150	14.0	9.33	12	8
Nervous system	0.099808	16	2.0	12.50	3	18.75

Figure 2. Real-world overall survival for all NENs, as well as prostate, lung, and bladder NENs

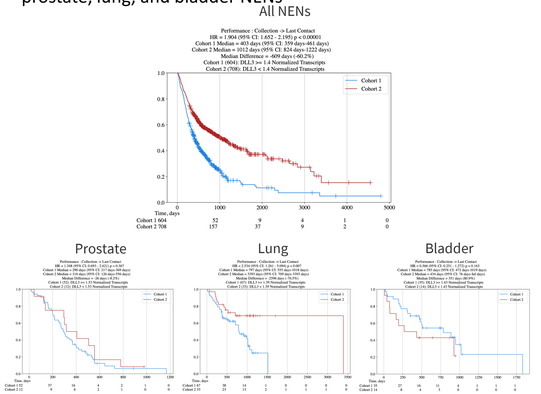


Figure 3. DLL3 expression by pathologic grade in lung NENs

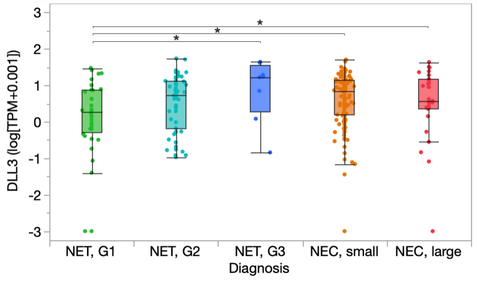


Figure 4. Differential gene expression in DLL3-Hi vs -Lo

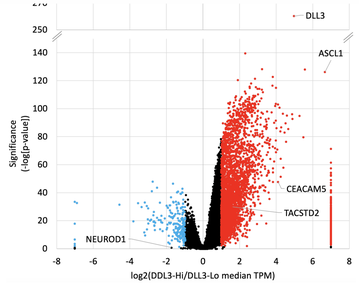


Figure 5. 10 most prevalent genomic alterations in DLL3-Hi vs -Lo, along with TMB-High and genome-wide LOH (gLOH)

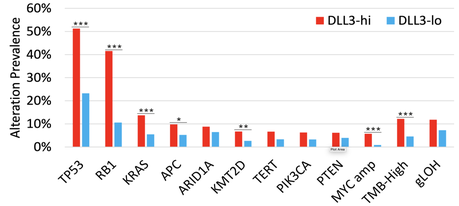


Figure 6. Correlation between expression of DLL3 and genes related to neuroendocrine phenotypes

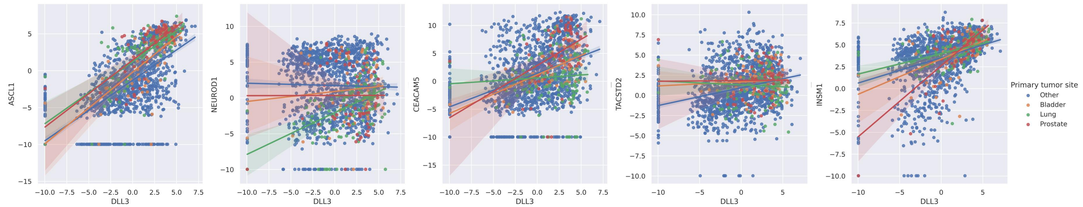
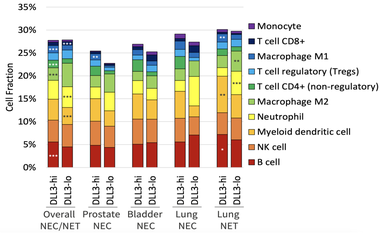


Figure 7. Tumor microenvironment composition



Conclusions

- High DLL3 expression is associated with poor overall survival, advanced pathologic grade, and distinct immune landscape.
- Further development of DLL3-targeted therapies for high grade NENs is warranted.

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The presenting author, Dr. A. Crymes, has no conflicts of interest to declare.

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