

Background

The neurotrophin tyrosine kinase receptors NTRK1 (TRKA) and NTRK2 (TRKB) are involved in proliferation and survival of neurons during development (1).

Although weak to undetectable by immunohistochemical methods in normal lung, increased expression of NTRK1 and/or NTRK2 is reported in lung cancer (2-5).

In neuroblastoma, increased expression of NTRK1 is associated with a significantly improved prognosis (6).

This positive relationship may also hold true in lung cancer; however, the prognostic significance of NTRK1 and NTRK2 expression is presently unknown.

Here we define the relationship between NTRK1 and NTRK2 expression and patient outcome in over 680 lung cancer cases.

Design

Normal control tissues and 686 individual lung cancer cases with clinical outcome data in tissue microarray (TMA) format are examined.

TMA's are immunostained for NTRK1 and NTRK2 using commercially available antibodies (1:350 dilution of monoclonal anti-human NTRK1 clone 14G6 and 1:25 dilution of monoclonal anti-human NTRK2 clone 80G2; Cell Signaling Technology), automated immunostaining and standard protocols.

Positive immunostaining is defined as circumferential membranous staining in any amount of tumor cells (Figure 1).

Statistical analyses are performed on SPSS v16.0.

Results

NTRK1 and NTRK2 immunostaining in lung cancers

Positive NTRK1 and NTRK2 immunostaining is seen most frequently in squamous carcinoma of lung (Figure 1, Table 1).

Positive NTRK1 and NTRK2 immunostaining is strongly correlated to squamous lung carcinoma (NTRK1: Kendall τ -b = 0.729, $p < 0.05$ and NTRK2: Kendall τ -b = 0.526, $p < 0.05$).

Aside from adenosquamous and large cell neuroendocrine, positive NTRK immunostaining is rare in other carcinoma subtypes (Table 1).

NTRK1 and NTRK2 immunostaining in control tissues

NTRK1 and NTRK2 immunostaining in this study is mostly consistent with previous reports (4,7,8):

- NTRK1 immunostaining is strongly positive in normal epidermis and absent in colon carcinoma and normal lung (Figure 2 A-C).
- NTRK2 immunostaining is positive in breast carcinoma and weakly cytoplasmic (negative) in normal lung (Figure 2 D,E).

NTRK2 immunostaining has been reported in normal epidermis (7); however, no staining was observed in this study (Figure 2 F).

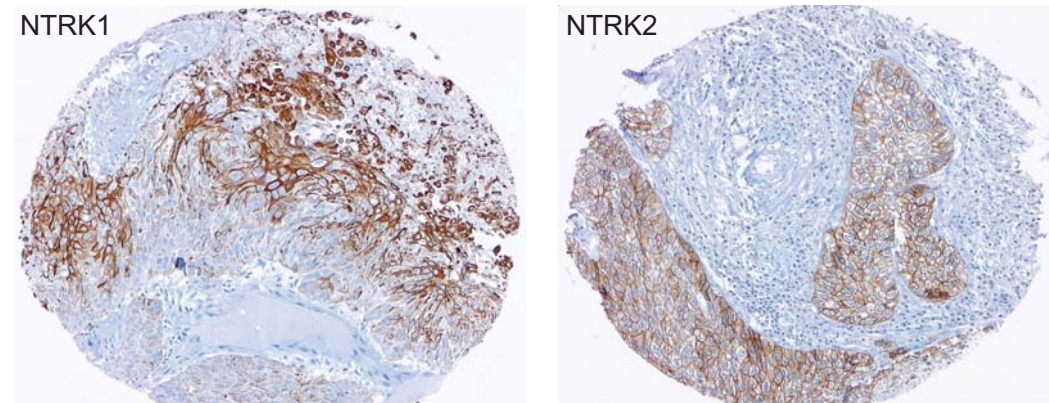


Figure 1. Representative images of positive NTRK1 and NTRK2 immunostaining in squamous cell carcinomas of lung (20x objective).

Tumor type	Total Cases	NTRK1 (TRKA)			NTRK2 (TRKB)		
		IHC Score	IHC Score	% Positive	IHC Score	IHC Score	% Positive
Squamous	268	204	64	76%	135	133	50%
Adenocarcinoma	236	11	225	5%	11	225	5%
Carcinoid	93	1	92	1%	1	92	1%
Large cell	55	6	49	11%	4	51	7%
Small cell	12	0	12	0%	0	13	0%
BAC	8	0	8	0%	0	8	0%
LCNEC	6	0	6	0%	2	4	33%
Pleomorphic	5	0	5	0%	0	5	0%
Adenosquamous	3	2	1	67%	1	2	33%

BAC: Bronchioloalveolar carcinoma, IHC: immunohistochemical, LCNEC: Large cell neuroendocrine carcinoma

Table 1. Frequency of positive and negative NTRK1 and NTRK2 immunostaining in lung carcinomas by histological subtype.

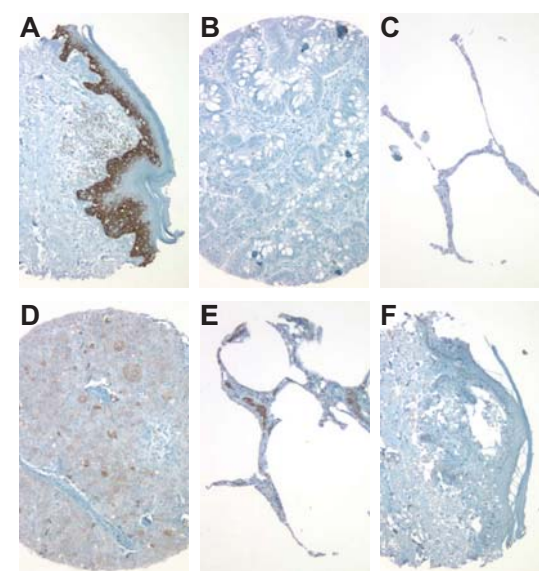


Figure 2. NTRK1 and NTRK2 immunostaining in control tissues. NTRK1 is expressed in normal skin (A), but not colon carcinoma (B) or normal lung (C). NTRK2 is expressed in breast carcinoma (D), stains weakly in normal lung (E) and is absent in normal skin (F).

Results (continued)

NTRK2 immunostaining correlates with positive patient outcome

There is no statistically significant correlation between positive NTRK1 immunostaining and disease specific survival (Log rank test: $\chi^2 < 0.0001$, $p = 0.994$) or overall survival (Log rank test: $\chi^2 = 0.131$, $p = 0.717$).

There is a significant positive correlation between positive NTRK2 immunostaining and:

- ⇒ improved disease specific survival (Figure 3 A, log rank test: $\chi^2 = 13.4$, $p = 2.5 \times 10^{-4}$)
- ⇒ improved overall survival (Figure 3 B, log rank test: $\chi^2 = 8.9$, $p = 2.8 \times 10^{-3}$)

Positive NTRK1 and NTRK2 immunostaining is not frequent enough in other lung cancer subtypes to achieve statistically reliable correlations with patient outcome.

Conclusions

Positive NTRK1 and NTRK2 immunostaining is associated with squamous lung carcinoma.

Positive NTRK2 immunostaining predicts significantly improved disease specific and overall survival in squamous cell carcinoma of lung.

- may warrant consideration as a clinical prognostic marker

NTRK2 immunostaining appears restricted to neoplastic squamous epithelium, suggesting a role in pathogenesis.

- may identify a patient subset that responds to NTRK signaling inhibition.

Disclosure

There are no potential commercial or financial conflicts of interest between the authors and subject of this study.

There is no off-label use of investigational products associated with the subject of this study.

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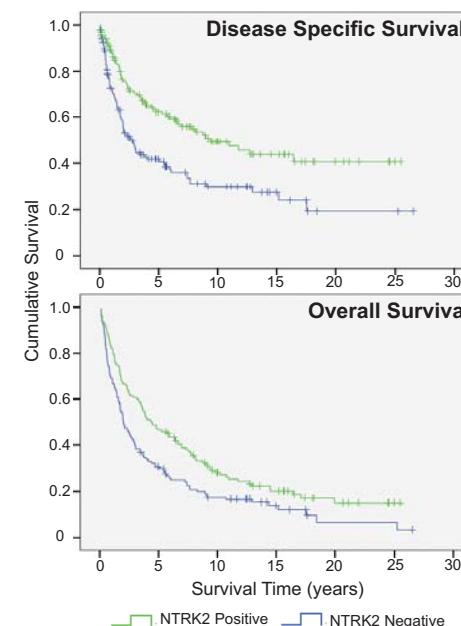


Figure 3. Kaplan-Meier plots of disease specific and overall survival in patients with NTRK2 positive (green) and negative (blue) squamous lung carcinomas.