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NaPi2b expression in a large surgical Non-Small Cell Lung Cancer (NSCLC) cohort

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Background :

NaPi2b (SLC34A2) is a sodium-dependent phosphate transporter expressed in a high proportion of Non-Small Cell Lung Cancer (NSCLC), especially adenocarcinoma, and ovarian carcinoma cases, as well as some other tumour types.

A clinical trial of the NaPi2b-targeting antibody drug conjugate XMT-1536 is currently underway (NCT03319628).

This study investigates NaPi2b expression in NSCLC emphasising correlations to histology.

Methods:

Tissue Microarrays (TMAs) were constructed using triplicate 1mm cores from FFPE primary NSCLC tumours resected by lobectomy or pneumonectomy with curative intent at Austin Health, Melbourne, Australia. Pathology review identified the best site for coring of tumour blocks.

For IHC, TMAs were stained with an anti-human NaPi2b primary antibody (MERS67) on the Leica Bond RX autostainer and the H-score (0 – 300) calculated based on the percentage of tumour cells stained multiplied by the staining intensity (0 - 3+). The mean score of multiple cores was calculated. A high H-score was empirically defined as ≥50.

Results:

High NaPi2b expression was seen in 153/439 (35%) of cases of NSCLC, independent of histologic type. High NaPi2b expression was determined in 132/215 (61%) of adenocarcinoma cases, while only 12/178 (7%) of squamous cell and 9/46 (20%) of other histology cases (p < 0.001, chi-square) had high expression. (Table 1, Figure 1)

Table 1 NaPi2b Expression in a Cohort of Non-Small Cell Lung Carcinoma Cases

	NAPI2b		
Total (439)	H-score >50	H-score < 50	P value
Sex (%)			
M	82 (27.1%)	221 (72.9%)	<0.001
F	71 (52.2%)	65 (47.8%)	
Histology (%)			
Adenocarcinoma	132 (61.4%)	83 (38.6%)	<0.001
SqCC	12 (6.4%)	166 (93.6%)	
Other	9 (19.6%)	37 (80.4%)	
Smoking (%)			
No	20 (62.5%)	12 (37.5%)	0.001
Yes	133 (32.7%)	274 (67.3%)	
EGFR mutation (%)			
Mutant	18 (75.0%)	6 (25.0%)	<0.001
Wild Type	36 (22.2%)	126 (77.8%)	
KRAS mutation (%)			
Mutant	59 (71.1%)	24 (28.9%)	<0.001
Wild Type	35 (21.9%)	125 (78.1%)	

High scores were more frequent for females (52% vs 27%; p < 0.001), never smokers vs smokers (63% vs 33%; p < 0.001), EGFR mutation vs wt (75% vs 22%; p < 0.001) and KRAS mutation vs wt (71% vs 22%; p < 0.001). There were no significant differences in expression considering stage, primary tumour diameter, FEV1 (% predicted) or level of PD-L1 expression.

Considering adenocarcinoma subtypes (Table 2) , high NaPi2b was seen with 18/21 (86%) micropapillary, 35/61 (57%) solid, 3/13 (23%) mucinous, 54/84 (64%) acinar, 8/13 (62%) papillary, 3/3 (100%) lepidic and 3/9 (33%) adenosquamous.

Overall high NaPi2b was seen in 56/95 (59%) with poor risk subtypes (micropapillary, solid, mucinous) and 65/100 (65%) with good risk subtypes (papillary, acinar, lepidic).

Table 2 NaPi2b Expression in Lung Adenocarcinoma

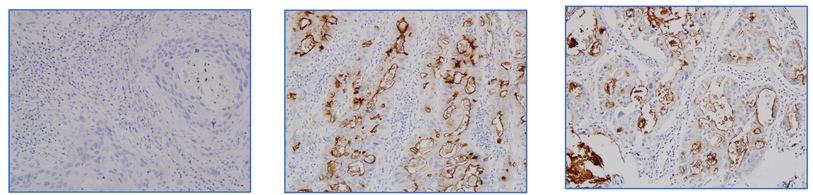
	NAPI2b		
	H-score > 50	H-score <50	Total
AD Micropapillary	18 (85.7%)	3 (14.3%)	21
AD Solid	35 (57.4%)	26 (42.6%)	61
AD Mucinous	3 (23.1%)	10 (76.9%)	13
AD Acinar	54 (64.3%)	30 (35.7%)	84
AD Papillary	8 (61.5%)	5 (38.5%)	13
AD Lepidic	3 (100%)	0	3
AD Mixed mucinous/non-mucinous	7 (100%)	0	7
Adenosquamous	3 (33.3%)	6 (66.6%)	9
AD Papillary-micropapillary	0	1	1
AD / LCNEC	0	1	1
AD NOS	1	0	1
MIXED AD - LCNEC	0	1	1
TOTAL	**132**	**83**	**215**

Considering patients with adenocarcinoma, high NaPi2b scores were seen in 16 of 20 (80%) of cases with EGFR mutations and 53 of 71 (75%) with KRAS mutations, as compared with only 17 of 39 (44%) with other mutations.

For the whole cohort, a high NaPi2b score was associated with improved overall survival on univariate analysis (median 58 months vs 36 months; HR 0.77 [95% CI 0.61-0.97], p=0.03), while for adenocarcinoma there was a trend for improved survival (median 54 months vs 35 months; HR 0.76 [95% CI 0.55-1.04], p=0.09), and for both high risk adenocarcinoma subtypes (micropapillary, solid) and good risk subtype (acinar), high NaPi2b expression was associated with a weak trend to better survival.

On multivariable analysis, NaPi2b remained the strongest predictor of improved survival (HR 0.77, 95% CI 0.58 - 1.02, p=0.07), though stage remained the only statistically significant variable.

Figure 1 Representative images of NaPi2b Immunohistochemistry on NSCLC of different types



A. Squamous Cell Carcinoma

B. Adenocarcinoma, Solid

C. Adenocarcinoma, Acinar

Conclusions:

In this large early stage surgical NSCLC cohort, a high level of NaPi2b expression was seen with adenocarcinoma histology and also across the range of adenocarcinoma subtypes. Female gender, never smokers, and KRAS or EGFR mutations were independently predictive of high-level expression.

For adenocarcinoma cases, 80% and 75% respectively with EGFR or KRAS mutations had high expression of NaPi2B.

For the whole cohort, high level expression was associated with improved overall survival.

There was a similar, but non-significant, trend for high level expression in adenocarcinoma cases to be associated with improved survival, which appeared to be the case for both high risk and good risk adenocarcinoma subtypes.

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