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Cbl mutations (mt) as important mediators of oncogenic RTK signaling in NSCLC

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Disclosures

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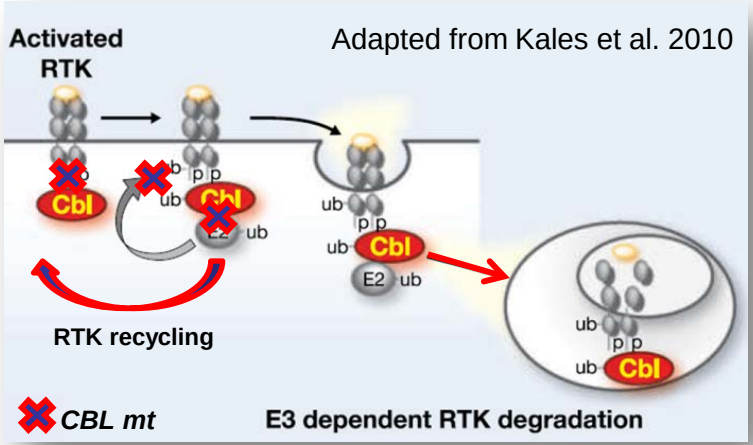
Background – Casitas B-lineage lymphoma (CBL)

- **An E3 ubiquitin ligase that negatively regulates a wide range of RTKs including many drivers of NSCLC**
- **Uncoupling CBL from its regulatory activities has oncogenic effects and its characterization in a large clinical data set is warranted.**

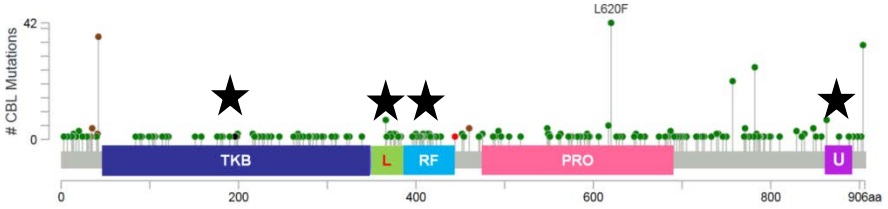


Study Design
• Genomic database queried for NSCLC tumors with CBL, NGS (Illumina NextSeq, 592 genes) • Additional data (as available) - RNA-sequencing, FISH, CISH, IHC
• CBL mt annotation- somatic mt databases used to categorize mt and SNPs • Statistics - associations tested by Fisher's exact test

(Kales, Ryan et al. 2010, Dikic and Schmidt 2007)

Results –Frequency, Variant Distribution and Clinical Characteristics

CBL frequency & variant distribution by functional domains

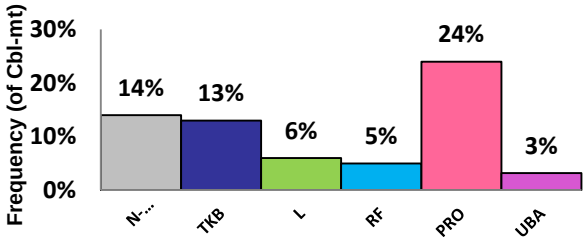


***CBL* mt rate (total n=8106):**

Overall: 5%

★**LOF: 1.4%**

Other: 3.6%



Clinical characteristics of patients by CBL mt status

Variable	LOF (n=110)	Other (n=298)	Wildtype (n=7698)	Total (n=8106)
Median Age (range)	67 (46-87)	66 (32-94)	68 (20-97)	68 (20-97)
Sex, n (%)				
Male	66 (60%)	153 (51%)	3847 (50%)	4066 (50%)
Female	44 (40%)	145 (49%)	3851 (50%)	4040 (50%)
Tumor Histology, n (%)				
Adenocarcinoma	90 (82%)	234 (79%)	5923 (77%)	6247 (77%)
Squamous cell cancer	20 (18%)	58 (19%)	1650 (21%)	1728 (21%)
Adenosquamous, mixed	-	6 (2%)	82 (1%)	88 (1%)
Other, NOS	-	-	43 (1%)	43 (1%)
Specimen Site, n (%)				
Primary	60 (55%)	176 (59%)	4337 (56%)	4573 (56%)
Distant Metastasis	50 (45%)	122 (41%)	3361 (44%)	3533 (44%)

*LOF = TKB, L, RF and UBA

Benign (presumed germ-line) SNPs: H42dup, L620F, A757T, P782L, V904I

Lollipop mutation mapper: Gao et al. 2013

Results – Rate of Concurrent oncogenic MAPK alterations in NSCLC

	MAPK Alteration	CBL-LOF	CBL-other	CBL-WT	*P*-value LOF vs. WT	*P*-value Other vs. WT
Mutations	ERBB4	5%	1%	0.2%	<0.001	
	ERBB3	4%	1%	0.3%	<0.001	
	EGFR	5%	16%	12%		<0.001
	KRAS	20%	26%	28%		
	HER2	1%	3%	2%		
	METex14	1%	1%	2%		
	BRAF V600E	2%	0.7%	2%		
Fusions	ROS1	1%	0%	0.6%		
	ALK	2%	2.6%	2.5%		
	RET	1.3%	0.9%	0.3%		
	EGFR amp.	2%	4%	2%		<0.05
	No MAPK Driver	57%	44%	52%		

- Mutations in CBL are not mutually exclusive events with oncogenic drivers
- ERBB3/ERBB4 mt → CBL LOF
- EGFR → CBL mt in other domains
- Proline-rich domain is involved in interactions with proteins containing SH3 domains, such as Grb2

(Jiang and Sorkin 2003)

Results – Case Highlights & Translational Significance

Pt.	Driver - % MAF	Gender	Age	Stage at Diagnosis	Biopsy Site	*CBL* Protein Change % MAF	Functional Domain	CBL mt *de-novo* or acquired?	Treatment
1	EML4-ALK Variant 3b	F	67	IV	Pleura	H398N-63%	RF	*de-novo*	
2	EML4-ALK	M	47	IIIA	Lung	Y371D-15%	L	*de-novo*	
3	*EGFR* Exon19del -40% + T790M -15%	F	55	IV	Ovary	S407C-28%	RF	acquired	1st gen EGFR TKI
4	*EGFR* S768I -49% + G719A -47%	M	78	IIIB	Lymph Nodes	S216G-55%	TKB	*de-novo*	
5	CD74-ROS1	M	75	IV	Media-stinum	C396R-8%	RF	*de-novo*	
6	KIF5B-RET	F	65	IV	Bone	WT	-	-	
			67		Lymph Node	c.100833_1026 del52 - 17%	L	acquired	Platinum/ Pemetrexed
7	*ERBB4* R396K 48%	F	67	IIIA	Lung	C372X -16%	Truncated protein	*de-novo*	
8	"No-Driver" EGFR-Amplification (>75 copies by CNA)	M	57	IV	Lung	E366fs -32%	Truncated protein	de-novo	

CBL LOF Mutations:

Facilitates Resistance?

Pre-existing genomic landscape for bypass signaling → resistance?

Help identify the RTK "drivers" for Rx guidance?

(Vaishnavi, Schubert et al. 2017)

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Conclusions

- CBL mts occurred in ~5% of a large cohort of NSCLC, 1.4% are LOF
- CBL mts are not mutually exclusive events with oncogenic drivers, some patterns for co-occurrence
- CBL LOF mts were found in the de-novo and post-treatment settings → Role in acquired and pre-existing genomic landscape that facilitate bypass signaling upon therapeutic insult?
- Future work includes – impact of CBL LOF on response to treatment with TKIs and further characterization of other CBL mts

TAKE HOME MESSAGES

- CBL interactome = under-studied node of RTK signaling
- CBL mutations may uncover nodes of de-regulated signaling, responsible for:
  - Hidden drivers of cancer
  - Acquired resistance mechanisms
  - Bypass signaling embedded in the pre-existing genomic landscape