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VIRTUAL CONFERENCE

RSK2 Mutation-Driven MAPK Activation Sensitizes Sorafenib Treatment And Drives Cholesterol Metabolism In Hepatocellular Carcinoma

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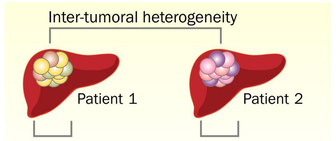
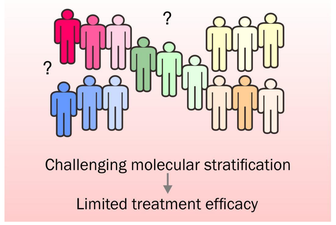
INTRODUCTION

- **HCC tumors are highly heterogeneous**



- **Extensive heterogeneity greatly hinders patient stratification and limits effective targeted therapy**



- **HCC development is mainly driven by loss-of-function mutations in tumor suppressor genes**

NGS-based mutation screens

Tumor suppressor genes	Oncogenes
TP53	*TERT*
ARID1A	*CTNNB1*
AXIN2	
TSC1/2	

Relevance of additional HCC-related genes identified by NGS-based screening remains to be clarified and characterized

AIM

NGS
1. To identify novel, recurrent and functionally important mutant genes in HBV-associated HCC

↓ *RPS6KA3* (RSK2)

HCC patient samples
2. To examine the clinical relevance of RSK2 mutation

↓

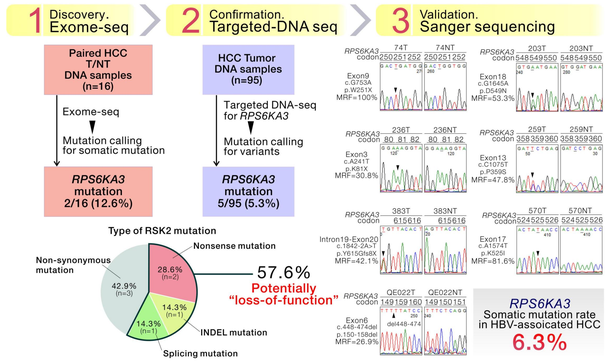
HCC cell line and xenograft models
3. To functionally characterize RSK2 mutation in HCC

↓

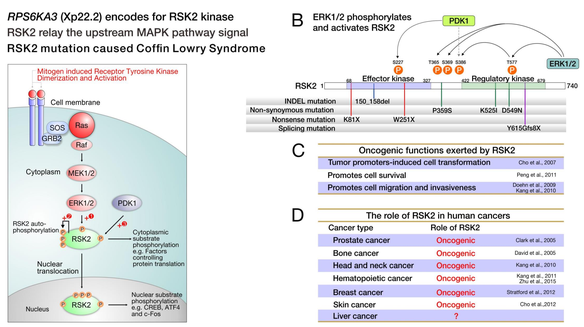
Functional implications
4. To assess the translational implication and underlying biological process of RSK2 mutation in HCC

RESULTS

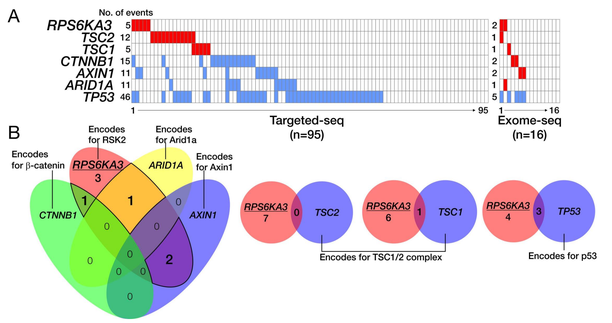
Somatic, loss-of-function RSK2 mutations in HCC



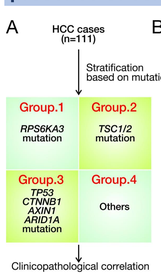
RSK2 is a direct downstream kinase phosphorylated and activated by MAPK



Limited co-occurrence of RSK2 mutations with known HCC-related mutations



RSK2 mutations were significantly associated with the presence of venous invasion

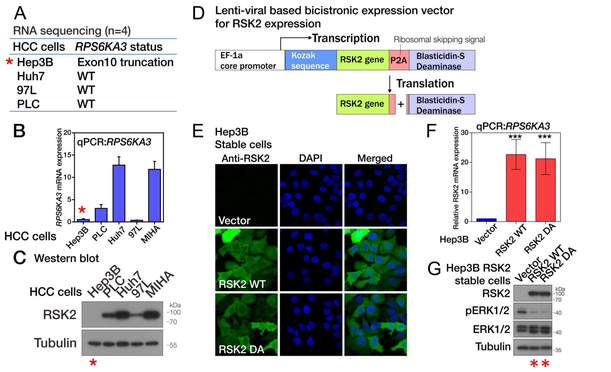


B

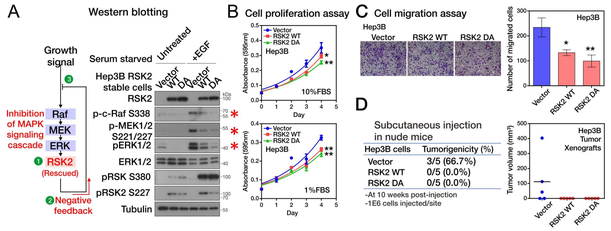
Parameters	*RPS6KA3* mutation (n=7)	*TSC1/2* mutation (n=17)	Known HCC driver mutation# (n=49)	Others (n=38)	*P**
Gender					0.116
Male	3 (42.9%)	14 (82.4%)	39 (79.6%)	25 (65.8%)	
Female	4 (57.1%)	3 (17.6%)	10 (20.4%)	13 (34.2%)	
Mean age (range)^	45 (36-51)	51.4 (24-68)	52.8 (29-72)	51.5 (24-74)	0.444
Tumor size					0.055
>5cm	5 (71.4%)	14 (82.4%)	29 (59.2%)	17 (44.7%)	
<=5cm	2 (28.6%)	3 (17.6%)	20 (40.8%)	21 (55.3%)	
Venous invasion					0.036*
Presence	5 (71.4%)	14 (82.4%)	27 (55.1%)	16 (42.1%)	
Absence	2 (28.6%)	3 (17.6%)	22 (44.9%)	22 (57.9%)	
TNM staging					0.072
I-II	2 (28.6%)	2 (11.8%)	18 (36.7%)	18 (47.4%)	
III-IV	5 (71.4%)	15 (88.2%)	31 (63.3%)	20 (52.6%)	

*Fisher exact test
^ANOVA test
#Cases that carry no *RPS6KA3* or *TSC* mutation but have mutations in any of *TP53*, *CTNNB1*, *AXIN1* and *ARID1A*

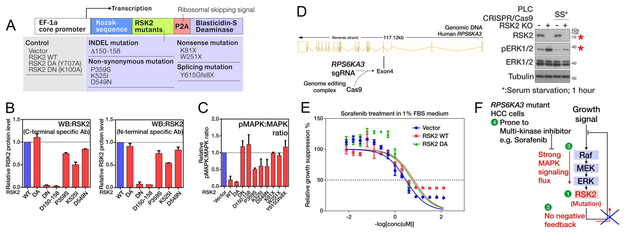
Establishment of a rescue model in the RSK2 null Hep3B cell lines



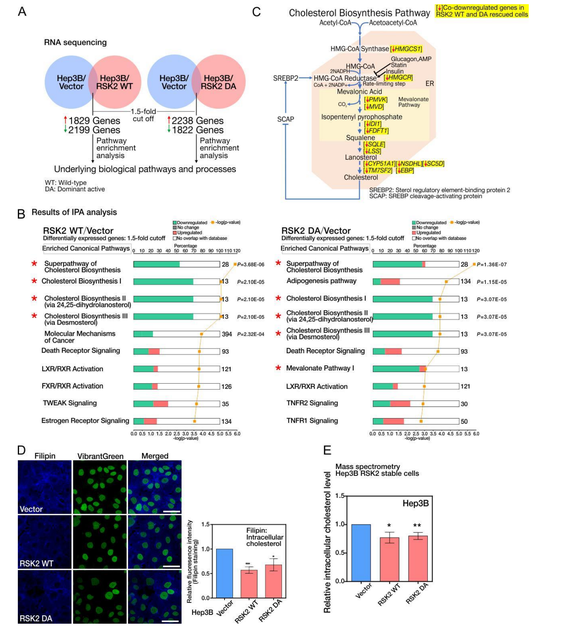
RSK2 rescued cells showed inactivation of MAPK signaling and reduction of the proliferative and migratory abilities when compared to RSK2-null HCC cells



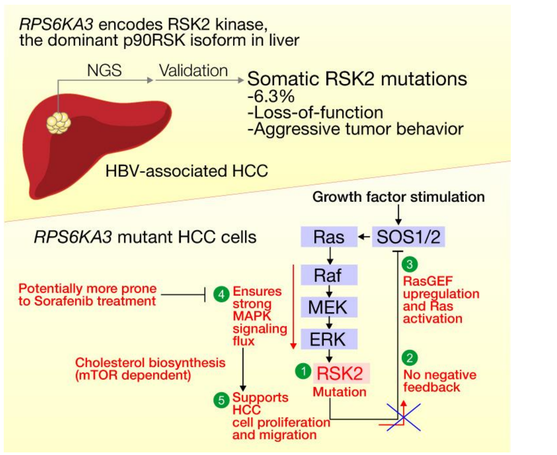
RSK2 mutants exhibited lower activity in negatively regulating the MAPK activity and the potential implication of RSK2 mutations and Sorafenib sensitivity



Downregulation of cholesterol biosynthesis in RSK2-rescued cells



SUMMARY



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