Abs # 379

Genomic Profiling of the Tumors Harboring Activating EGFR Mutations

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INTRODUCTION

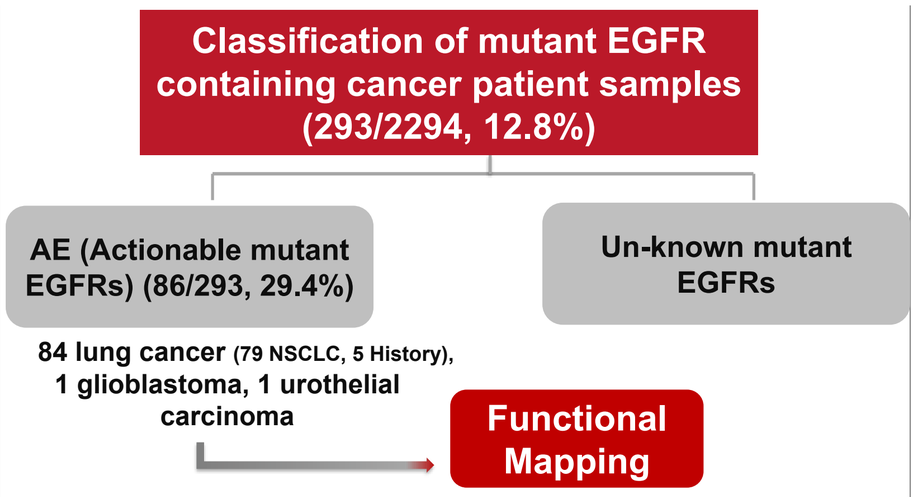
EGFR is a receptor tyrosine kinase of the HER/ERBB family and an oncogenic driver, especially for NSCLC, HNSCC and CRC. EGFR targeted therapies have been successfully used for treating cancer patients harboring activating EGFR mutations. However a main challenge is acquired drug resistance due to mutations or alternative signaling. While developing next generation drugs is a promising strategy, targeting other alternatives is also an attractive therapeutic option.

OBJECTIVES

The purpose of our study is to investigate the mutational landscape of the tumors harbored activating EGFR mutations and to pinpoint potential strategies for overcoming acquired drug resistance and for combinational therapies.

METHODS

CancerPlex, a NGS large panel test, which includes targeted, full-gene sequencing of over 400 genes, was applied to analyze a cohort of 2294 patient FFPE samples across majority of solid tumor types.



RESULTS

Table 1, Variants Associated with Activating EGFR Mutations

Pathway/Biological Function	Total Variant Number	TOP 1 Mutated Gene (variant number)	TOP 2 Mutated Gene (variant number)	TOP 3 Mutated Gene (variant number)
Receptors	227	PKHD1 (21)	ROS1 (20)	ERBB2 (16)
Genome and Epigenome Stability	246	ARID1A (27)	KMT2D (17)	XPC (14)
Wnt/beta-catenin	54	APC (9)	AXIN2, RNF43, (7)	BCL9 (6)
TP53/Apoptosis	45	TP53 (30)	NUMA1 (5)	NLRP1 (3)
PI3K/AKT/mTOR	43	PIK3CA (12)	RICTOR (7)	PIK3R2, TSC1, TSC2,(3)
NOTCH	39	NOTCH4 (9)	NOTCH2, SPEN, (8)	NOTCH1 (7)
Kinase	35	TNK2, TYK2, (8)	ABL1 (6)	JAK3 (4)
Rb1/Cell Cycle	24	NUP214 (5)	RB (4)	CCND1 (3)
Ras-Raf-Mek	23	NF1 (6)	RASA1 (5)	KIAA1804, RPS6KA2, (3)
Hedgehog	18	PTCH1, SMO, (5)	STK36 (4)	ETV4 (3)
TGFbeta	12	TFE3 (4)	SMAD4, TGFBR2, (3)	ACVR2A (2)
NFkB	9	IKBKB (3)	TNFAIP3, CARD11, (2)	BIRC3, REL, (1)
Phosphatases	6	PTPRT (5)	PTPRD (1)	

- Receptors at different classes and genes involving in genome and epigenome stabilities have the highest mutation rate in the context of activating EGFR mutations.
- PI3K/AKT/mTOR and Ras-Raf-MEK pathways have different mutation rate. Mutant variants are nearly 50% more in PI3K/AKT/mTOR than that in Ras-Raf-MEK.
- No KRAS mutation is found in the AE group, suggesting the mutual exclusivity of activating EGFR mutations and KRAS mutations, at least in NSCLC.
- Mutations are also found in the TP53/apoptosis and Rb/cell cycle pathways , but with higher variant numbers in the TP53/apoptosis axis.
- Strikingly, the number of mutant variants in the Wnt/beta-catenin pathway tops that in the PI3K and TP53 pathways, which suggest the importance of the Wnt/beta-catenin pathway in the activating mutant EGFRs signaling.

CONCLUSIONS

- Mutant EGFRs may magnify their oncogenic activities by disrupting genome and epigenome via recruiting more receptors into neoplastic transformation processes.
- Activating mutant EGFRs might preferentially utilize effectors in the PI3K pathway to transduce oncogenic signals.
- Targeting apoptosis could be another therapeutic strategy to increase efficiency of targeted EGFR therapies and to overcome drug resistance.
- Several recent publications demonstrated that the Wnt/beta-catenin pathway is abnormally activated in NSCLC and may be a main mechanism of the drug resistance to EGFR targeted therapies, as well as to radiotherapy and chemotherapy.
- Targeting the Wnt/beta-catenin pathway, in combination with EGFR targeted therapies, is a promising therapeutic strategy for the treatment and overcoming drug resistance of EGFR-driven tumors.

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