Understanding the Molecular and Cellular Mechanisms That Underlie the Conversion of EGFR Mutant Lung Adenocarcinomas to Small Cell Lung Cancer Upon Treatment with Tyrosine Kinase Inhibitors

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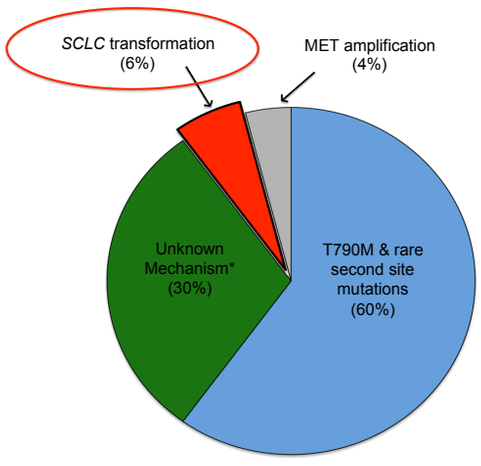
BACKGROUND

- Somatic mutations in the *E*pidermal *G*rowth *F*actor *R*eceptor (EGFR) are seen in approximately 15% of lung adenocarcinomas
- Mutant EGFR lung cancers are sensitive to tyrosine kinase inhibitor (TKI) treatment
- Resistance emerges on average 10-14 months after initiation of TKI treatment
- Phenotypic switch from lung adenocarcinoma to *S*mall *C*ell *L*ung *C*ancer (SCLC) is seen in 6% of acquired resistance cases[1]

Frequency of acquired resistance mechanisms to EGFR TKIs



*includes epithelial-mesenchymal transition (present at an uncertain prevalence)

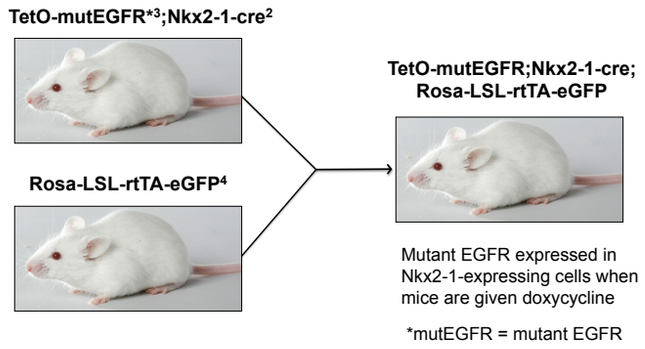
- EGFR mutant SCLC is sensitive to chemotherapies used to treat SCLC

OBJECTIVE

To understand the cellular and molecular mechanisms underlying the transformation of mutant EGFR lung adenocarcinomas to SCLC upon TKI treatment.

EXPERIMENTAL STRATEGY

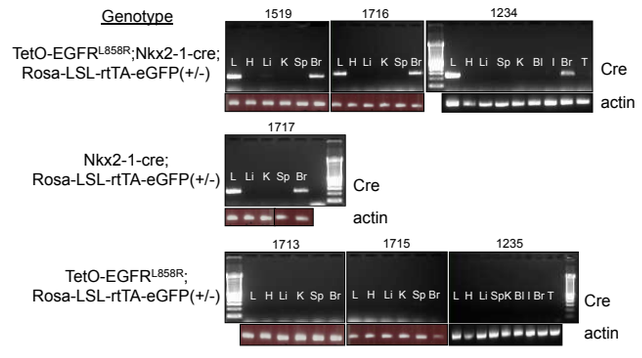
- Nkx2-1 is a lineage-specific transcription factor involved in lung morphogenesis
- Nkx2-1 expression is common in lung adenocarcinomas and SCLC
- Mutant EGFR expression is targeted to Nkx2-1-expressing cells in the mouse lung
- Expression of mutant EGFR is directed to a wide variety of cell types in the lung



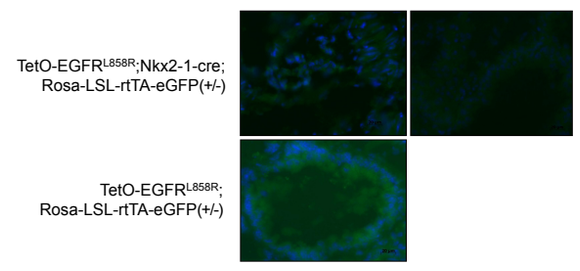
RESULTS

Nkx2-1 is expressed in most epithelial cells of developing lung buds of TetO-EGFR^{L858R};Nkx2-1-cre; Rosa-LSL-rtTA-eGFP(+/-) embryos (E11.5)

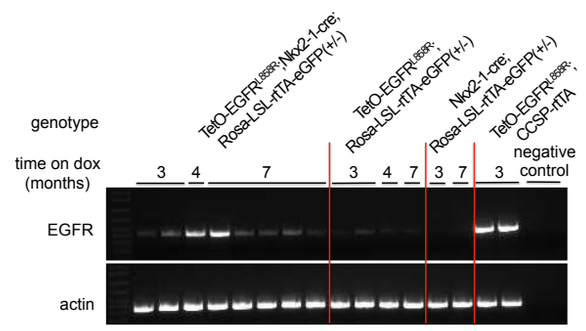
Cre expression is found only in Nkx2-1-cre+ mouse tissues that express Nkx2-1



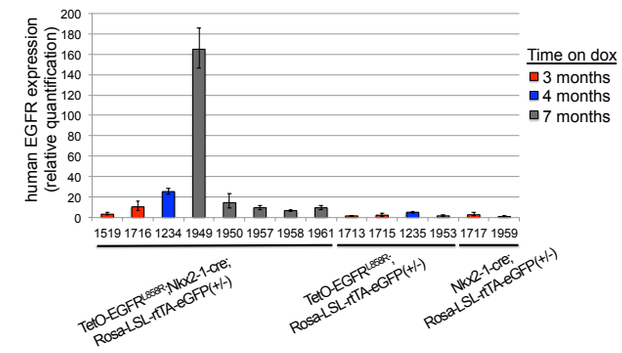
GFP-reporter expression is detectable at low levels in lungs of animals upon cre-mediated recombination



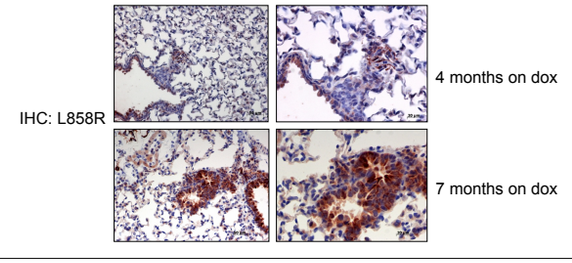
Mutant EGFR is detected in lung samples of TetO-EGFR^{L858R}+ animals



Mutant EGFR is expressed at variable levels in TetO-EGFR^{L858R}; Nkx2-1-cre;Rosa-LSL-rtTA-eGFP lung tissues



Mutant EGFR is expressed in lung tissue of TetO-EGFR^{L858R}; Nkx2-1-cre;Rosa-LSL-rtTA-eGFP(+/-) mice



CONCLUSIONS

- Preliminary data indicate suboptimal reporter and rtTA activity from the Rosa-LSL-rtTA-eGFP reporter strain
- Induction of mutant EGFR expression is much lower than observed in other mutant EGFR inducible mouse models used in our lab

FUTURE PLANS

- Confirm correct cre-mediated recombination by crossing the Nkx2-1-cre mouse to the Rosa-loxP-tdTomato-loxP-eGFP cre-reporter mouse
- Use an alternate rtTA reporter strain (CAGs-LSL-rtTA3IRESKate) to induce mutant EGFR expression

REFERENCES

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