Erbb3 is Not Required for Tumorigenesis by Mutant *EGFR*

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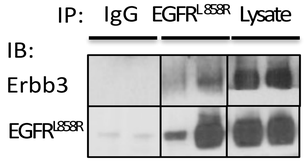
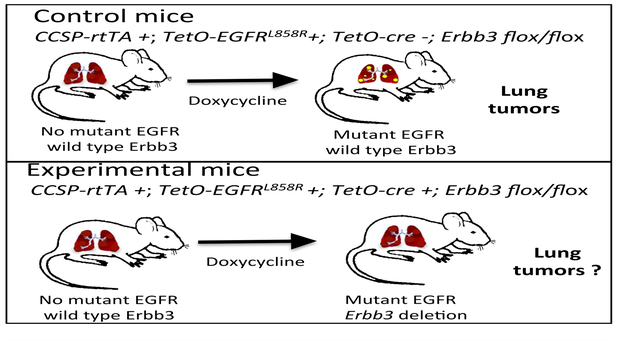
Background

Lung cancer is the leading cause of cancer-related death in the USA and worldwide. Mutations in the Epidermal Growth Factor Receptor (EGFR) are found in 15% of lung adenocarcinomas. Tumors bearing *EGFR* mutations are sensitive to treatment with specific tyrosine kinase inhibitors (TKIs) and show radiographic responses in about 70% of cases. However, it is not known why the remaining 30% of the tumors do not respond to these drugs, and patients who initially respond to TKI treatment eventually develop drug resistance on average within a year. Mutant *EGFR*-induced signaling is initiated by the formation of EGFR homodimers or heterodimers with other members of the EGFR family (ERBB2, ERBB3 or ERBB4). Here the role of EGFR family members in the tumorigenic process driven by mutant *EGFR* was studied using genetically engineered mouse models.

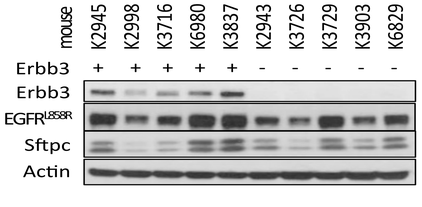
Transgenic mutant EGFR interacts with Erbb3



Experimental strategy



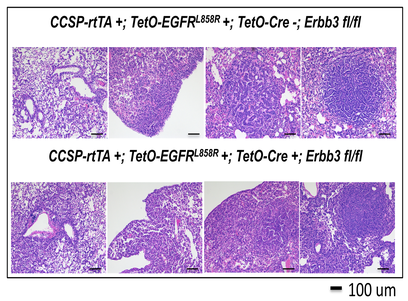
Efficient deletion of *Erbb3* in transgenic mice



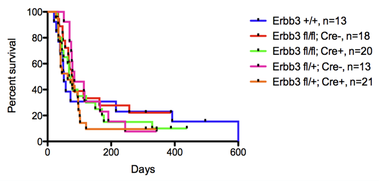
Summary of Key Findings

A tetracycline-inducible transgenic model was used to test the requirement for Erbb3 in mutant EGFR-induced lung tumorigenesis. In this model, deletion of *Erbb3* had no effect on tumorigenesis induced by mutant *EGFR*, suggesting that it is not required to initiate tumorigenesis. Tumors that develop in the absence of *Erbb3* remain sensitive to TKIs. Analysis of the biochemical consequences of *Erbb3* deletion revealed increased levels of phosphorylation of EGFR and Erbb2 in tumors arising in the absence of *Erbb3*. Acute loss of *ERBB3* in lung cancer cell lines with *EGFR* mutations led to modest effects on cell viability possibly due to activation of parallel signaling pathways. Together these data suggest that recruitment of compensatory pathways may overcome the need for Erbb3 in tumorigenesis driven by mutant *EGFR*. Knowledge of the role EGFR heterodimerization partners play in mutant *EGFR*-driven lung cancer can help guide the selection of which EGFR family members to target in the treatment of this disease.

Deletion of *Erbb3* does not affect tumorigenesis induced by mutant *EGFR*

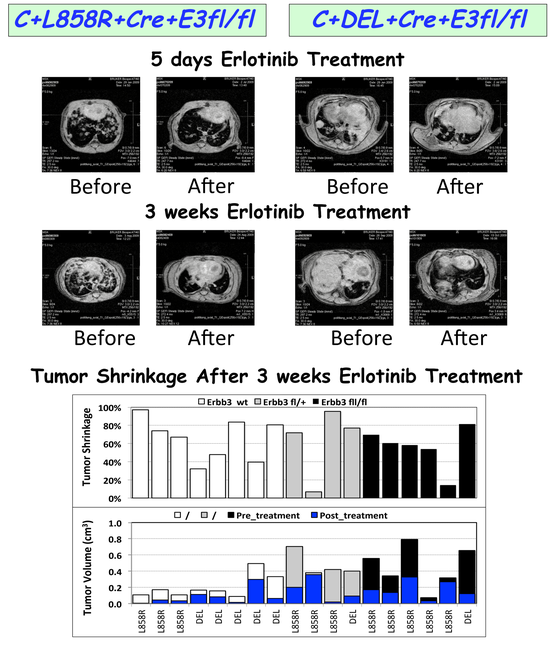


Mutant EGFR drives lung tumor formation in the presence and the absence of *Erbb3*

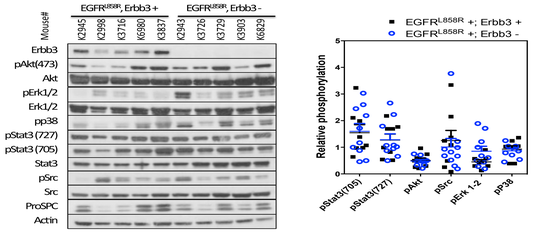


Deletion of *Erbb3* does not alter the latency of tumor formation

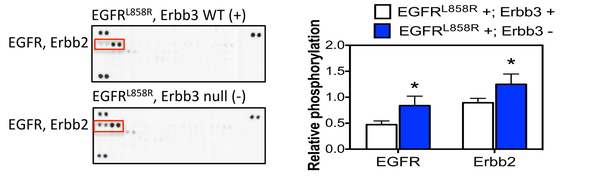
Lung tumors respond to TKI treatment in the absence of *Erbb3*



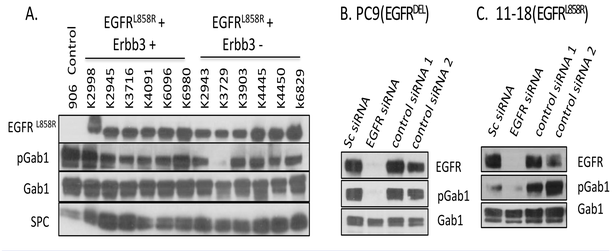
No significant changes in EGFR signaling pathways upon *Erbb3* deletion



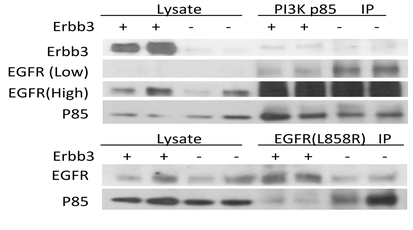
EGFR and Erbb2 phosphorylation are significantly increased in tumors without *Erbb3*



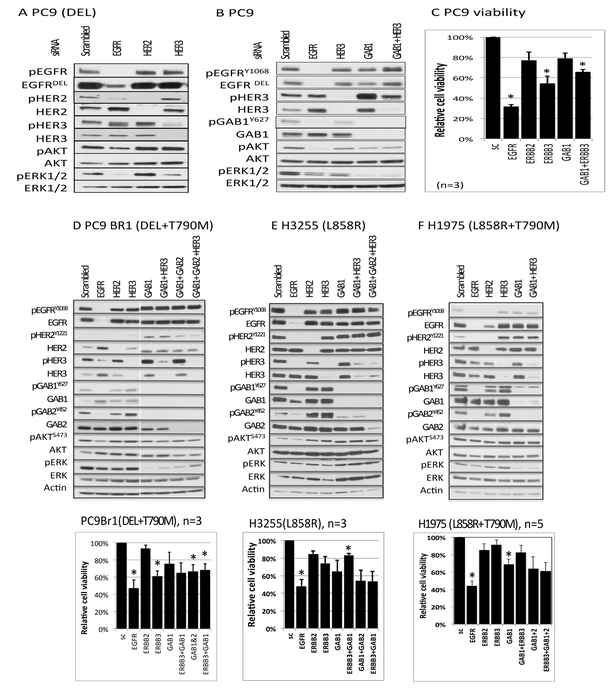
Phosphorylation of the GAB1 adapter by mutant EGFR



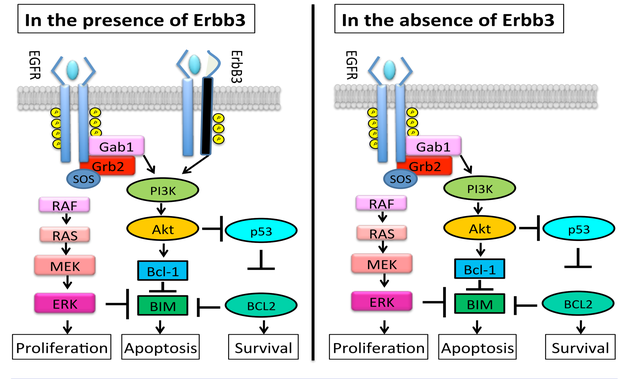
Mutant EGFR interacts with p85 in lung tumors in the absence of *Erbb3*



Activation of parallel signaling pathways upon loss of *ERBB3*



Proposed model



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