Inhibitor-sensitive fibroblast growth factor receptor mutations in lung squamous cell carcinoma

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Squamous cell carcinoma of the lung: a disease without treatment options

- Adenocarcinoma of the lung has seen many targeted therapy advances in the past decade (EGFR, EML4-ALK, ERBB2), while
- Squamous cell carcinoma had few targets and no targeted therapies—and the clinical burden is great

ARTICLE

Comprehensive genomic characterization of squamous cell lung cancers

The Cancer Genome Atlas Research Network*
FGFR events in the TCGA Lung Squamous Cell Carcinoma sequencing project

- ~10% focal amplification of FGFR1
- ~8% mutation across the four receptors
  - 3% FGFR2, 3% FGFR3
- Not significantly mutated across the dataset
FGFR2 and FGFR3 mutations are observed in lung SqCC
FGFR2 and FGFR3 mutations do not repeatedly co-occur with other events except TP53 mutation.
FGFR2/3 mutations are transforming in an anchorage-independent growth assay
FGFR2/3 transformation can be blocked by FGFR inhibitors
Loss of transformation correlates with loss of phosphorylation
Cells exhibiting dependency on the FGFR pathway are sensitive to FGFR inhibitors.
A clinical case

FGFR2 mutation in the coding sequence at p.P253R
An *FGFR2*-positive tumor regresses upon pazopanib treatment
Conclusions

- FGFR2/3 mutations observed in lung SqCC are sufficient to drive transformation in the NIH-3T3 cell line model, and the transformation phenotype can be reversed by FGFR small molecule inhibition.
- Ba/F3 cells dependent on FGFR2/3 signaling for proliferation can be growth inhibited by FGFR small molecule inhibition.
- A clinical success confirms that these findings provide a rationale for further study of patients with FGFR events in their tumors.
- TCGA data have been used effectively to find new driving, targetable events in tumors (though these events do not always meet the threshold of statistical significance).
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FGFR biology

Table 1
Ligand specificities of FGFR isoforms

<table>
<thead>
<tr>
<th>FGFR isoform</th>
<th>Ligand specificity</th>
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<tbody>
<tr>
<td>FGFR1b</td>
<td>FGF1, -2, -3 and -10</td>
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<tr>
<td>FGFR1c</td>
<td>FGF1, -2, -4, -5 and -6</td>
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<tr>
<td>FGFR2b</td>
<td>FGF1, -3, -7, -10 and -22</td>
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<tr>
<td>FGFR2c</td>
<td>FGF1, -2, -4, -6, -9, -17 and -18</td>
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<tr>
<td>FGFR3b</td>
<td>FGF1 and -9</td>
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<tr>
<td>FGFR3c</td>
<td>FGF1, -2, -4, -8, -9, -17, -18 and -23</td>
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<tr>
<td>FGFR4</td>
<td>FGF1, -2, -4, -6, -8, -9, -16, -17, -18 and -19</td>
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Disulfide bonding observed in ECD mutations to Cys

FGFR2 dimer

FGFR3 dimer

unreduced

FGFR3 monomer

reduced

actin