The genomic landscape of RAS-driven tumours

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Barcelona, Spain 13-14 March 2015
DISCLOSURE

No conflicts of interest to declare
GLOBOCAN Projection for 2030 in Europe

Incidencia: 4,000,000 nuevos casos de cáncer

30% RAS-mutados

1,200,000 casos RAS-mutados
OUTLINE

1. RAS family members and their mutations
2. Prognostic and predictive role of RAS mutations
3. Downstream to RAS
4. RAS is guilty but he is not the only one
OUTLINE

1. *RAS* family members and their mutations
2. Prognostic and predictive role of *RAS* mutations
3. Downstream to *RAS*
4. *RAS* is guilty but he is not the only one
# RAS-oncogenic mutations from COSMIC catalogue

**Incidence per year in USA of RAS mutations in human cancers**

<table>
<thead>
<tr>
<th>Primary Tissue</th>
<th>KRAS (%)</th>
<th>HRAS (%)</th>
<th>NRAS (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>71</td>
<td>0</td>
<td>&lt;1</td>
<td>71</td>
</tr>
<tr>
<td>Colon</td>
<td>35</td>
<td>1</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>Small intestine</td>
<td>35</td>
<td>0</td>
<td>&lt;1</td>
<td>35</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>26</td>
<td>0</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Endometrium</td>
<td>17</td>
<td>&lt;1</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Lung</td>
<td>19</td>
<td>&lt;1</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Skin (melanoma)</td>
<td>1</td>
<td>1</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Cervix</td>
<td>8</td>
<td>9</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>5</td>
<td>10</td>
<td>1</td>
<td>16</td>
</tr>
</tbody>
</table>

- **Pancreas**: 95% total
- **Colon**: 45% total
- **Small intestine**: 45% total
- **Biliary tract**: 45% total
- **Endometrium**: 35% total
- **Lung**: 35% total
- **Skin (melanoma)**: 35% total
- **Cervix**: 35% total
- **Urinary tract**: 35% total

---

*Stephen AG, Cancer Cell 25, March 17, 2014*
# RAS family oncogenic mutations

from COSMIC catalogue

## Incidence per year in USA of RAS mutations in human cancers

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<td>18</td>
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<td>10</td>
<td>1</td>
<td>16</td>
</tr>
</tbody>
</table>

*Stephen AG, Cancer Cell 25, March 17, 2014*
**KRAS-oncogenic mutations**

from COSMIC catalogue

Incidence per year in USA of *KRAS* mutations in human cancers

<table>
<thead>
<tr>
<th></th>
<th>All KRAS</th>
<th>G12C</th>
<th>G12D</th>
<th>G12V</th>
<th>G13D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>60,000</td>
<td>5,700</td>
<td><strong>25,000</strong></td>
<td>15,700</td>
<td><strong>13,600</strong></td>
</tr>
<tr>
<td>Lung</td>
<td>45,600</td>
<td><strong>23,000</strong></td>
<td>9,200</td>
<td>11,900</td>
<td>1,500</td>
</tr>
<tr>
<td>Pancreas</td>
<td>32,200</td>
<td>1,000</td>
<td><strong>19,500</strong></td>
<td>11,500</td>
<td>200</td>
</tr>
<tr>
<td>Total new cases/year</td>
<td>137,800</td>
<td>29,700</td>
<td>53,700</td>
<td>39,100</td>
<td>15,300</td>
</tr>
</tbody>
</table>
RAS family codon mutations

Isoform specific pattern

Cancer specific pattern
Mucinous Adenocarcinoma

Lung Carcinoma

Mucinous Adenocarcinoma
KRAS mutation: histotype association

East Asian Lung Carcinoma

- **AAH/AIS**: preinvasive lesions
- **MIAs**: minimally invasive adenocarcinomas
- **Invasive Carcinoma**
  - **LEP**: lepidic
  - **ACN**: acinar
  - **PAP**: papillary
  - **MP**: micropapillary
  - **SLD**: solid
  - **IMA**: invasive mucinous adenocarcinoma

<table>
<thead>
<tr>
<th>Genes</th>
<th>AAH/AIS</th>
<th>MIA</th>
<th>LEP</th>
<th>ACN</th>
<th>PAP</th>
<th>MP</th>
<th>SLD</th>
<th>IMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-negative</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>57</td>
<td>19</td>
<td>3</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td>PIK3CA*</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>RET</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>ALK</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>27</td>
<td>7</td>
<td>1</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>BRAF</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>HER2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>KRAS</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>26</td>
<td>5</td>
<td>2</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>EGFR</td>
<td>4</td>
<td>16</td>
<td>58</td>
<td>356</td>
<td>118</td>
<td>17</td>
<td>60</td>
<td>6</td>
</tr>
</tbody>
</table>
KRAS mutation: histotype drives diagnostic workflow

**Lung Adenocarcinoma**

- **AAH / AIS**
  - Mutation Testing not recommended

- **MIA**
  - **EGFR**

- **Invasive**
  - **EGFR**

- **IMA**
  - **KRAS** (ALK, EGFR)

  - **Non-mucinous never-smoker**
    - **ALK**
      - (RET, KRAS for solid)

  - **Non-mucinous ever-smoker**
    - **KRAS**

  - **Minor mucinous**
    - **ALK**

Hu H, Onco Targets Ther. 2014 Aug 13;7
OUTLINE

1. RAS family members and their mutations
2. Prognostic and predictive role of RAS mutations
3. Downstream to RAS
4. RAS is guilty but he is not the only one
KRAS mutations: Prognostic significance
Colorectal Cancer

Codon 12 mutations associated with shorter TTP

![Graph showing time to recurrence for different KRAS mutation types. Wild-type 62%, Codon 12 30%, Codon 13 8%.]

P < 0.001

WT 13

WT 12

P = 0.26

Blons H, Ann Oncol. 2014 Dec; 25(12)
KRAS mutations: Prognostic significance
Lung Cancer
312 resected stage I cancers
KRAS mutations: the only independent predictor of shorter OS (p = 0.001) and DFS (p < 0.0001) at multivariate analysis.
KRAS mutations: Prognostic significance
Lung Cancer

312 resected stage I cancers

DFS

p = 0.031

OS

p = 0.17

Codon 12
Other codons (13/61)
**KRAS** mutations: Prognostic significance

Lung Cancer

312 resected stage I cancers

**DFS**

G12C/G12V

All other mutations

\[ p = 0.027 \]

**OS**

\[ p = 0.06 \]
OUTLINE

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Advanced Lung Cancer: anti EGFR prediction

KRAS status does not affect response

A

Exon 19 deletion
L858R mutation

B

EGFR + / KRAS WT
EGFR WT / KRAS +
EGFR WT / KRAS WT

<table>
<thead>
<tr>
<th></th>
<th>EGFR + / KRAS WT</th>
<th>EGFR WT / KRAS +</th>
<th>EGFR WT / KRAS WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>47</td>
<td>41</td>
<td>83</td>
</tr>
<tr>
<td>RR</td>
<td>68%</td>
<td>0</td>
<td>5%</td>
</tr>
<tr>
<td>Median TTP (months)</td>
<td>13.1</td>
<td>3.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Median OS</td>
<td>24.5</td>
<td>13.0</td>
<td>11.8</td>
</tr>
</tbody>
</table>

< .001
< .0001
< .002
Locally Advanced Lung Cancer: anti EGFR prediction

Erlotinib is detrimental in KRAS mutated
Early Stage Resected Lung Cancer: anti EGFR prediction

KRAS status cannot be recommended to select patients for adjuvant chemotherapy

Shepherd JCO 2013
Colorectal Cancer: molecular classification

- KRAS mutated
- NRAS mutated
- PIK3CA mutated
- RAF mutated
- Quadruple-negative
New scenarios in EGFR targeting in CRC

The Lancet Oncology

Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis

Wendy De Roock MD a, Bart Claes MSc b, David Bernasconi MSc c, Jef De Schutter MSc a, Bart Biesmans MSc a, Prof George

1022 tumours treated with cetuximab

KRAS 40%
BRAF 5%
NRAS 3%
PIK3CA 15% (4% ex 20)

are significantly associated with a low response rate
Colorectal Cancer: anti EGFR prediction

**KRAS-G13D** respond to Cetuximab as Wild Type tumors

**Figure 1.** Overall Survival: Predictive Analysis by KRAS Status for Patients Receiving Any Cetuximab-Based Therapy vs No Cetuximab

<table>
<thead>
<tr>
<th>G13D</th>
<th>Other mutations</th>
<th>Wild Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>P &lt; 0.001</td>
<td>P = 0.49</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

The no cetuximab group for all patients from the pooled data set is the best supportive care group from the CO.17 trial.
Colorectal Cancer: anti EGFR prediction

Resistance

Primary

Acquired

Response

Quadruple-negative

Dienstmann et al. 2014 ASCO Educational Book
1. RAS family members and their mutations
2. Prognostic and predictive role of \textit{RAS} mutations
3. Downstream to \textit{RAS}
4. \textit{RAS} is guilty but he is not the only one
The landscape of RAS-driven pathway

[Diagram of the RAS pathway with key components and interactions]

- RAF → MEK → ERK
- PI3K → AKT → PDK1 → RAC
- RALGDS → PLD, RAL, FORKHEAD
- PLCε → PKC → Ca²⁺

Key processes:
- Survival
- Transcription
- Cytoskeletal signals
- Translation
- Vesicle transport
- Cell-cycle progression
- Calcium signalling
Mechanism of resistance

Sensitive state

RTK

RAS

BRAF(V600E)

MEK

ERK

Resistant state

\( \uparrow \)RTK

\( \uparrow \)RAS

\( \downarrow \)NF1

\( \uparrow \)BRAF(V600E)

\( \uparrow \)BRAF(V600E)

\( \uparrow \)CRAF

\( \uparrow \)TPL2

\( \downarrow \)MEK

\( \downarrow \)ERK

Mechanism

- RTK upregulation
- RAS mutation
- NF1 loss
- BRAF(V600E) splicing variants
- BRAF amplification
- CRAF overexpression
- MEK mutations
- TPL2 overexpression

Increased RAF dimerization and increased activation of ERK signalling

Increased activation of ERK signalling

Samatar AA, Nat Rev Drug Discov. 2014 Dec;13
RAF FAMILY

BRAF mutations:
- Melanoma
- Non-small cell lung cancer
- Colorectal cancer
- Bile duct cancer
- Hairy-cell leukemia

Table 1 | Correct numbering of the important amino acids in B-RAF

<table>
<thead>
<tr>
<th>Original assignment</th>
<th>Correct assignment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>M116</td>
<td>M117</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>R187</td>
<td>R188</td>
<td>Equivalent of R89 in C-RAF where it is required for RAS binding</td>
</tr>
<tr>
<td>I325</td>
<td>I326</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>S364</td>
<td>S365</td>
<td>Phosphorylation site, possibly by AKT/PKB and PKA; forms core of 14-3-3 binding motif</td>
</tr>
<tr>
<td>S428</td>
<td>S429</td>
<td>AKT/PKB phosphorylation site</td>
</tr>
<tr>
<td>K438</td>
<td>K439</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>T440</td>
<td>T440</td>
<td>AKT/PKB phosphorylation site; mutated in cancer</td>
</tr>
<tr>
<td>S446</td>
<td>S446</td>
<td>N-region phosphorylation site; equivalent to S338 of C-RAF</td>
</tr>
<tr>
<td>D449</td>
<td>D449</td>
<td>Equivalent of Y341 of C-RAF</td>
</tr>
<tr>
<td>V459</td>
<td>V459</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>R462</td>
<td>R462</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>I463</td>
<td>I463</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>G464</td>
<td>G464</td>
<td>First glycine of the glycine-rich loop; mutated in cancer</td>
</tr>
<tr>
<td>G466</td>
<td>G466</td>
<td>Second glycine of the glycine-rich loop; mutated in cancer</td>
</tr>
<tr>
<td>F468</td>
<td>F468</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>G469</td>
<td>G469</td>
<td>Third glycine of the glycine-rich loop; mutated in cancer</td>
</tr>
<tr>
<td>K475</td>
<td>K475</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>N581</td>
<td>N581</td>
<td>Catalytic asparagine; mutated in cancer</td>
</tr>
<tr>
<td>E586</td>
<td>E586</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>D587</td>
<td>D587</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>D594</td>
<td>D594</td>
<td>Aspartic acid of the “DFG” motif; mutated in cancer</td>
</tr>
<tr>
<td>E595</td>
<td>E595</td>
<td>Phenylalanine of the “DFG” motif; mutated in cancer</td>
</tr>
<tr>
<td>G596</td>
<td>G596</td>
<td>Glycine of the “DFG” motif; mutated in cancer</td>
</tr>
<tr>
<td>L597</td>
<td>L597</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>T599</td>
<td>T599</td>
<td>Activation segment phosphorylation site; mutated in cancer</td>
</tr>
<tr>
<td>V600</td>
<td>V600</td>
<td>Most commonly mutated residue in cancer</td>
</tr>
<tr>
<td>K601</td>
<td>K601</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>S602</td>
<td>S602</td>
<td>Activation segment phosphorylation site</td>
</tr>
<tr>
<td>R682</td>
<td>R682</td>
<td>Mutated in cancer</td>
</tr>
<tr>
<td>A728</td>
<td>A728</td>
<td>Located within C-terminal 14-3-3 binding motif; mutated in cancer</td>
</tr>
<tr>
<td>S729</td>
<td>S729</td>
<td>Phosphorylation site and core of 14-3-3 binding motif</td>
</tr>
</tbody>
</table>

PKA, protein kinase A; PKB, protein kinase B.
Beyond BRAF mutations: translocations

38 cutaneous spitzoid lesions

BRAF

Wiesner T, Nat Commun. 2014;5:3116
**BRAF**

Beyond BRAF mutations: amplification/fusion genes

**44 pilocytic astrocytomas**

[Diagram showing genetic variations]
Beyond BRAF mutations: amplification/fusion genes
Activated B-RAF mutants

MEK

ERK

C-RAF

Impaired Activity B-RAF mutants

MEK

ERK

C-RAF
C-RAF (Raf-1): there is more than MEK activation

Allosteric MEK-Inhibitor

Lito P, Cancer Cell 25, 697–710, May 12, 2014
CRAF

Allosteric MEK-Inhibitor

Lito P, Cancer Cell 25, 697–710, May 12, 2014
**CRAF**

**Stronger Allosteric MEK-Inhibitor**

KRAS<sup>mt</sup>

- **CRAF**
- **MEK**

**PD0325901**

- **Time**
- **pERK**

**Trametinib**

- **Time**
- **pERK**

**CH5126766**

- **Time**
- **pERK**

**MEKi with dual allosteric effects**

- Block MEK kinase activity
- Prevent RAF activation of MEK:
  - Disrupt RAF-MEK complexes
  - Block in-complex phosphorylation

*ESMO*
ARAFT independent

RAFI-mediated ERK1/2 activation needs CRAF in RAS mutated cells

ARAFT dependent

RAFI-mediated ERK1/2 activation needs ARAF in a cell type–dependent manner
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RAS-networking

Not a “one man band”
The mutational landscapes of genetic and chemical models of *Kras*-driven lung cancer

Peter M. K. Westcott\(^1,2\), Kyle D. Halliwill\(^1,2\), Minh D. To\(^1\), Mamunur Rashid\(^3\), Alistair G. Rust\(^3\), Thomas M. Keane\(^3\), Reyno Delrosario\(^1\), Kuang-Yu Jen\(^4\), Kay E. Gurley\(^5\), Christopher J. Kemp\(^5\), Erik Fredlund\(^6\), David A. Quigley\(^1\), David J. Adams\(^3\) & Allan Balmain\(^1,7\)
The mutational landscapes of genetic and chemical models of *Kras*-driven lung cancer

Peter M. K. Westcott¹,², Kyle D. Halliwill¹,², Minh D. To¹, Mamunur Rashid³, Alistair G. Rust³, Thomas M. Keane³, Reyno Delrosario¹, Kuang-Yu Jen⁴, Kay E. Gurley⁵, Christopher J. Kemp⁵, Erik Fredlund⁶, David A. Quigley¹, David J. Adams³ & Allan Balmain¹,⁷
Somatic mutations affect key pathways in lung adenocarcinoma

Li Ding1,*, Gad Getz2,*, David A. Wheeler3,*, Elaine R. Mardis1, Michael D. McLellan1, Kristian Cibulskis2, Carrie Sougnez2, Heidi Greulich2,4, Donna M. Muzny3, Margaret B. Morgan3, Lucinda Fulton1, Robert S. Fulton1, Qunyuan Zhang5, Michael C. Wendl1, Michael S. Lawrence2, David E. Larson1, Ken Chen1, David J. Dooling1, Aniko Šabo3, Alicia C. Hawes3, Hua Shen3, Shalini N. Jhangiani3, Lora R. Lewis3, Otis Hall3, Yiming Zhu3, Tittu Mathew3, Yanru Ren3, Jiqiang Yao3, Steven E. Scherer3, Kerstin Clerc3, Ginger A. Metcalf3, Brian Ng3, Aleksandar Milosavljevic3, Manuel L. Gonzalez-Garay3, John R. Osborne1, Rick Meyer1, Xiaqi Shi1, Yuzhu Tang1, Daniel C. Koboldt1, Ling Lin1, Rachel Abbott1, Tracie L. Miner1, Craig Pohl1, Ginger Fewell1, Carrie Haieck1, Heather Schmidt1, Brian H. Dunford-Shore1, Aldi Kraja5, Seth D. Crosby1, Christopher S. Sawyer1, Tammi Vickery1, Sacha Sander1, Jody Robinson1, Wendy Winckler2,4, Jennifer Baldwin2, Lucian R. Chirieac6,7, Amit Dutt2,4, Tim Fennell2, Megan Hanna2,4, Bruce E. Johnson4, Robert C. Onofrio2, Roman K. Thomas8,9, Giovanni Tonon4, Barbara A. Weir2,4, Xiaojun Zhao2,4, Liuda Ziaugra2, Michael C. Zody2, Thomas Giordano10, Mark B. Orringer11, Jack A. Roth12, Margaret R. Spitz13, Ignacio I. Wistuba12,14, Bradley Ozenberger15, Peter J. Good15, Andrew C. Chang11, David G. Beer11, Mark A. Watson16, Marc Ladanyi17,18, Stephen Broderick17, Akihiko Yoshizawa17, William D. Travis17, William Pao17,18, Michael A. Province5, George M. Weinstein1, Harold E. Varmus19, Stacey B. Gabriel2, Eric S. Lander2, Richard A. Gibbs3, Matthew Meyerson2,4, and Richard K. Wilson1

ESMO

Ding et al. Nature 2008, 455:1069-75
26 significantly mutated genes in lung adenocarcinomas

188 primaries screened for 623 candidate genes

Lung cancer

Lung cancer

Each cancer holds from 4 to 29 mutated genes

Ding et al. Nature 2008, 455:1069-75
Lung cancer

Concurrent and mutual exclusion of mutations

Ding et al. Nature 2008, 455:1069-75
Mutations
Copy number alterations
Focal amplifications
Translocations

Comprehensive molecular characterization of human colon and rectal cancer. The Cancer Genome Atlas Network
Nature 2012, 487:330-7:
Colorectal cancer

32 somatic recurrently mutated genes

15

17

Comprehensive molecular characterization of human colon and rectal cancer. The Cancer Genome Atlas Network
Nature 2012, 487:330-7:
Mutated pathways in lung adenocarcinomas

RTK=90%

MAPK=60%

DNA repair=63%

PI3K-mTOR=37%

Ding et al. Nature 2008, 455:1069-75
Colorectal cancer

Pancreas cancer
Pancreas cancer

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Events Range</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>Locally rearranged</td>
<td>&lt;50 events</td>
<td>18%</td>
</tr>
<tr>
<td>Scattered</td>
<td></td>
<td>50 – 200 events widespread</td>
<td>39%</td>
</tr>
<tr>
<td>Unstable</td>
<td></td>
<td>&gt;200 events widespread</td>
<td>18%</td>
</tr>
<tr>
<td>Locally rearranged</td>
<td></td>
<td>50-200 events</td>
<td>25%</td>
</tr>
</tbody>
</table>

Legend:
- Intra-chromosomal rearrangement
- Inter-chromosomal translocation
- Duplication
- Tandem duplication
- Inversion
- Foldback inversion
- Deletion
- Amplified inversion

Waddell N, Nature. 2015 Feb 26;518(7540)
Pancreas cancer genes
Chromatin remodelling genes
DNA damage repair
Axon guidance genes
Other genes
Pancreas cancer
Pancreas cancer
Targetting-Ras…dream or reality?