Highlights of “Integrated Genomic Characterization of Papillary Thyroid Carcinoma”

Plus Poster #100

Tom Giordano and Gad Getz, on behalf of the THCA AWG
Simple model of thyroid cancer progression

80-85% TCGA

MAPK pathway ↑
(e.g. via BRAF^{V600E})

PTC

MAPK pathway ↑↑

PDTC

MAPK pathway ↑↑↑

ATC

Follicular thyroid cell

PI3K–AKT ↑
(e.g. via RAS, PTEN, PIK3CA mutations)

FTA

FTC

PI3K–AKT ↑↑

PI3K–AKT ↑↑↑

PI3K–AKT ↑↑↑

Loss of differentiation

Mingzhao Xing, JHU
### 3 main histologic types of PTC

<table>
<thead>
<tr>
<th>Classical</th>
<th>Follicular Variant</th>
<th>Tall Cell Variant</th>
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</thead>
<tbody>
<tr>
<td><em>BRAF-V600E</em></td>
<td><em>RAS</em></td>
<td><em>BRAF-V600E</em></td>
</tr>
<tr>
<td><em>RET</em> fusions</td>
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Strong genotype - phenotype correlation
Cancer genes pre-TCGA

Translocations in RTKs (RET / NTRK1)

Frequent BRAF and RAS mutations

Infrequent PI3K genes (PTEN, PIK3CA, AKT1)

Cell growth, proliferation and survival
496 primary PTCs
391 on all major platforms

Plus 49 whole genome sequences done with PTCs without apparent driver mutations
Relative mutation frequency

Somatic mutation frequencies observed in exomes from 3,083 tumor-normal pairs.

Thyroid = 0.41 non-silent mutations per Mb

Somatic mutation frequencies observed in exomes from 3,083 tumor-normal pairs.

Lawrence et al. Nature 2013:499;214-218
Overview of somatic alterations

Mutations rate

Clinical info

Significant Mutations

Fusions

SCNAs

Driver summary
**EIF1AX**
Translation initiation factor 1A, X-linked

THCA:
6 mutations

COSMIC:
19 mutations
Endometrium, breast, colon, lung, esophagus, ovary and prostate

Uveal melanoma
20 mutations

Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3

Marcel Martin1,2, Lars Maßhöfer3, Petra Temming4, Sven Rahmann5, Claudia Metz5, Norbert Bornfeld5, Johannes van de Nes6, Ludger Klein-Hitpass7, Alan G Hinnebusch8, Bernhard Horsthemke9, Dietmar R Lohmann5,9 & Michael Zeschnigk5,9

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Fusions

- New *RET* partners
- Diverse *BRAF* fusions
- ALK fusions, diverse
  - *(EML4-ALK)*
- *ETV6-NTRK3*

Angela Hadjipanayis, Harvard
Katie Hoadley, UNC
Chip Stewart, Broad Institute
Even remaining 14 out of 402 ‘dark matter’ samples are not entirely dark
Common Drivers are clonal

Chip Stewart, Broad Institute
Challenges of THCA project

• Focused on papillary carcinoma
  – Indolent cancer type with 95% cure rate
  – No long term follow-up data (need 20 years)

• Relative low mutation density compared to other carcinomas
Two choices

• Report on a few new SSNVs, fusions, clusters, etc.

• Strive to tell a clinically-relevant story that leveraged the:
  – mutual exclusively of the drivers, \textit{BRAF} and \textit{RAS}
  – quiet nature of PTC genome
  – availability of multidimensional data
  – imagination of the AWG members
**BRAF^{V600E}-RAS Score (BRS)**

Giovanni Ciriello, Katie Hoadley, Yasin Senbagaoglu, Jim Fagin
**BRAF$^{V600E}$-RAS Score (BRS) defines a gradient between two PTC classes: BRAF$^{V600E}$-like (BVL) and RAS-like (RL)**

Giovanni Ciriello, Katie Hoadley, Yasin Senbagaoglu, Jim Fagin
BRAF^{V600E}-RAS Score (BRS)

Giovanni Ciriello, Katie Hoadley, Yasin Senbagaoglu, Jim Fagin
Silencing of iodine metabolism machinery by $BRAF^{V600E}$

Highly differentiated follicular cell

Loss of differentiation

Mingzhao Xing, JHU
Thyroid Differentiation Score (TDS)
16 gene signature

Jaegil Kim, Gordon Robertson, Chip Stewart, Lisa Iype
Signaling Differences between BVL and RL PTC

Giovanni Ciriello, Yasin Senbagaoglu, Jim Fagin
SuperCluster

Legend
BRAF-RAS score
-1 (BRAF) 0 (RAS) 1
Mutations
 Mutant  Wild type
Differentiation score
-4 0 2.5
Histology
 Classical  Follicular  Tail cell
Fol. Fraction
0% 100%

Rehan Akbani
Integrated MIR story leveraged the BRS, TDS, histologic type, and tumor grade, to demonstrate differences between clusters.
Overarching Conclusions

• RL-PTCs and BVL-PTCs are fundamentally different in their genomic, epigenomic and proteomic profiles

• Identified clinically relevant subgroups of BVL-PTCs
  — Potential role for miRs

• Propose a reclassification of thyroid cancer that more accurately reflects the genotypic and phenotypic differences of RAS- and BRAF\textsuperscript{V600E}-driven
We think TCGA THCA will be a landmark study
IMPACT

• Jim Fagin working on EIF1AX biology
• Working Group on FV-PTC
  – Yuri Nikiforov, Pittsburgh
  – International group of thyroid pathologists
  – Possible NCI support (R13)
• Biomarker study
  – Martha Zeiger, Hopkins
  – Hopkins, Mayo, Michigan and Cornell
  – 238 PTCs with central compartment LN dissections
  – BRAF + miRNA expression to predict LN positivity
TCGA Thyroid Analysis Working Group

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Entire TCGA Network

**Chip Stewart**
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