Multi-cancer mutual exclusivity analysis of genomic alterations

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Mutually exclusive alterations in Cancer

Recurrent genomic alterations target specific pathways

Functional alterations targeting the same pathway frequently occur in a mutually exclusive manner

(TCGA, Nature, 2011)
MEMo: Mutual Exclusivity Modules

(Ciriello et al., Genome Res. 2011)
MEMo results on TCGA Datasets

MEMo has been applied to the following TCGA projects:

- **Glioblastoma Multiforme (GBM)**
  - Phase 2 338 samples
- **Serous Ovarian Cancer (OVCA)**
  - Updated dataset 384 samples
- **Colon and Rectum Adenocarcinoma (COAD)**
  - Non hyper-mutators 151 samples
- **Uterine Corpus Endometrioid Carcinoma (UCEC)**
  - Non serous / Non hyper-mutators 144 samples
- **Invasive Breast Cancer (BRCA)**
  - 463 samples

Mutually exclusive patterns of alteration identified in several oncogenic pathways:

- Rb - signaling
- p53 - signaling
- DNA repair
- PI(3)K/Akt signaling
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Mutually exclusive patterns of alteration identified in several oncogenic pathways:

- Rb - signaling
- p53 - signaling
- DNA repair
- **PI(3)K/Akt signaling**
Mutual exclusivity in PI(3)K/Akt

**GBM** (338 samples)

- **ERBB2**: 4%
- **EGFR**: 51%
- **PDGFRA**: 14.5%
- **MET**: 5%

- **PTEN**: 34%
- **PIK3CA**, **PIK3R1**, **PIK3CG**: 16%

- **Altered Samples**: 84%

**Colon and Rectum Adenocarcinoma**

- **IGF2**: 19%
- **PTEN**: 7%
- **PIK3CA**: 18%

- **Altered Samples**: 49%

**Endometrioid Carcinoma** (144 samples)

- **PIK3CA**: 49%
- **PIK3R1**: 19%

- **AKT1**: 3%

- **Altered Samples**: 67%

**Breast Carcinoma** (463 samples)

- **IGF2**: 2%
- **PTEN**: 5%
- **PIK3CA**: 22%
- **PIK3R1**: 3%

- **MAP3K1**: 8%

- **MAP2K4**: 7%

- **PAK1**: 8.5%

- **AKT1**: 3%

- **JNK / JUN** mediated apoptosis

- **Proliferation, Survival**

- **Altered Samples**: 66%
Mutual exclusivity in PI(3)K/Akt

**GBM** (338 samples)

- ERBB2
- EGFR
- PDGFRA
- PIK3CA
- PIK3R1
- PIK3CG
- PTEN
- MET

Altered Samples: 84%

**Colon and Rectum Adenocarcinoma** (151 samples)

- IGF2
- ERBB2
- PIK3CA
- PTEN

Altered Samples: 49%

**Endometrioid Carcinoma** (144 samples)

- AKT1
- PIK3CA
- PIK3R1

Altered Samples: 67%

**Breast Carcinoma** (463 samples)

- IGF2
- IGF1R
- ERBB2
- PIK3CA
- PIK3R1
- PTEN
- MAP3K1
- MAP2K4
- AKT1
- PAK1

Altered Samples: 66%
MEMo does not find PI(3)K/Akt modules

Search restricted to frequent events
MEMo does not find PI(3)K/Akt modules

Search restricted to frequent events

Are there low-frequency but functional events affecting this pathway?
Multiple Low-frequency events target PI(3)K pathway

24% Altered Samples
Breast Cancer (463 samples)

- IGF2: 2%
- ERBB2: 15%
- IGF1R: 4%
- PIK3CA: 22%
- PIK3R1: 3%
- MAP3K1: 8%
- MAP2K4: 7%
- PTEN: 5%
- AKT1: 3%
- PAK1: 8.5%

Altered Samples 66%

- Over-expressed
- Amplified
- Hom. Del.
- Mutated

Proliferation, Survival
JNK / JUN mediated apoptosis
Is the PI(3)K pathway altered by other means in Basal tumors?
• PTEN is down-regulated in Basal tumors

10% of Basal Tumors
• PTEN is down-regulated in Basal tumors
• Down-regulated samples show higher Akt phosphorylation

PTEN down-regulation activates Akt

10% of Basal Tumors
AKT3 is over-expressed in Basal Breast Cancer

30% of Basal Tumors

AKT3 mRNA expression distribution in Basal tumors

50% Altered Samples (BASAL Only)
Overall Extent of Alteration

PTEN
PIK3CA
ERBB2
PIK3R1
KRAS
IGF2
NRAS
PAK1
AKT1
MAP3K1
MAP2K4
AKT3
IGF1R
FGFR1
MET
PIK3CG
PDGFR
BRAF
EGFR
Conclusions

• MEMo systematically identifies **mutually exclusive** alterations targeting oncogenic pathways across multiple cancer types

• PI(3)K /Akt signaling is consistently altered in cancers, with different **extents of alteration**, and by **different mechanisms**

• Mutual exclusivity analysis **across multiple cancers** unveils the underlying heterogeneity of the disease, thus suggesting candidate **therapeutic targets in different subtypes**
Thanks!

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