Small cell carcinoma genomics
A convergent but distinct pathogenesis

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Small cell genomics by way of exceptional responders

RESEARCH BRIEF

Synthetic Lethality in ATM-Deficient RAD50-Mutant Tumors Underlies Outlier Response to Cancer Therapy

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Bladder, cell lineage, or organ-specific differences?
Multi-modality sequencing of a rare histology

Mix of frozen and FFPE, primary untreated and post-treatment disease, patients with multi-histology disease or matched primary and metastatic specimen pairs

+ 500 retrospectively sequenced bladder and SCLC tumors for comparative analysis

Donahue TF, et al. *JCO Precis Oncol, in press*
Lee SH, et al. *Cell, in press*
High somatic mutational burden
A consistent story emerging...
APOBEC-driven
And not tobacco-associated mutagenesis

Pattern and frequency of key lesions

Obligate \textit{TP53}, \textit{RB1}, \textit{TERT}
Not absent but rare in urothelial

TP53+RB1

Different differences
Histology, organ, and cancer type

Potential therapeutic significance

46% of patients

http://oncokb.org/
High CNA burden was common
Driven by whole-genome doubling

WGD+ and biallelic missense TP53
Here, but not pan-cancer...

WGD pan-cancer, a digression
Common, but 46% of WGD in cancer arise in TP53-wildtype tumors
Timing of WGD can vary
Rather than absolute timing, relative to somatic mutations...
Waxing and waning APOBEC
Before or after WGD

Mixed histology tumors
Branching evolution, RB1 and TP53 are histology-specific and come after a founding driver

Obligate, but not the founder? 
Something else initially transforms and leads to clonal outgrowth?
Conclusions

• Small cell carcinomas of the bladder and lung have a convergent but distinct pathogenesis.

• Obligate likely early-arising lesions in \( RB1 \) and \( TP53 \)
  • Necessary but alone insufficient to drive small cell differentiation

• A founding driver along with other truncal driver mutations can precede histology-specific lesions in \( RB1 \) and \( TP53 \).
  • Small cell and urothelial bladder cancers have a shared cellular origin where the former represents de-differentiation from UC

• Overall, aside from \( RB1 \) and \( TP53 \) alterations, genomic alterations present in SCCB more closely resemble UC than small cell lung cancers, indicating that most alterations contribute to oncogenesis in an organ-specific manner rather than cell type-specific manner.
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