The impact of smoking exposure on genomic alterations in muscle-invasive bladder cancer

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Background

- Smoking exposure: Most important risk factor for developing muscle-invasive bladder cancer (MIBC)
- Incidence of MIBC and lung cancer correlates to smoking status (current versus never smoker)
- Duration (years) of smoking exposure
- Number of cigarettes smoked per day
- Carcinogenic toxins similar to cigarette smoke administered to rodents to model the effects of smoking on the development of MIBC

Aim:

- To investigate genomic alterations in MIBC and the patient smoking status
- To compare these findings with lung adenocarcinoma (LAC) and
to compare with the biological characteristics of chemically induced MIBC in rodents

Material & Methods

Datasets from the public domain (MIBC and LAC):
- TCGA and MSK-IMPACT from cbioportal.org
- MSK-IMPACT dataset
  - Genomic data: Genomic DNA sequencing data
  - Mutation count in Signature 5*
  - Total mutational burden
  - RNA sequencing
- MSK-IMPACT dataset
  - Genomic data: Genomic DNA sequencing data
  - Total mutational burden
  - RNA sequencing

Outcome measurements

Effects of smoking exposure on:
- Patient outcomes
- Mutational burden

- Signature 5*
- Molecular subtypes

Genomic data:

- MSK-IMPACT dataset
  - Total mutational burden
  - Mutation count in Signature 5*
- Genomic DNA sequencing data

- TCGA dataset
  - Ref. level: Lifelong non-smoker
  - Current/former/never

Mutation count (n=382)

Mutation count (n=283)

Mutation count (n=290)

Mutation count (n=614)

TP53 mutations (n=382)

TP53 mutations (n=382)

TP53 mutations (n=290)

TP53 mutations (n=283)

Mutation counts vs. pack years

Contrast:

No association with smoking and mutational burden in bladder cancer but in Lung adenocarcinoma

Contrast:

Positive correlation in lung adenocarcinoma but not in bladder cancer

Results

Bladder Cancer TCGA

Bladder Urothelial Carcinoma from MSK-IMPACT

Lung adenocarcinoma from Pan Lung Cancer TCGA

Smoking status and molecular subtype

GSC subtypes

Lund subtypes

No association with smoking and molecular subtypes

Contrast:

Chemically induced bladder cancers in rodents show a Basal-like or Urobasal B phenotype

Signature 5*

Disease-free survival

Signature 5* is associated with smoking. We found no association of Signature 5* and molecular subtypes.

Conclusions

- Impact of smoking exposure on genomic alterations in MIBC not obvious
- In contrast to LAC: Higher mutational burden and enrichment of mutations in known oncogenes (e.g. TP53) in smokers
- Cigarette smoke contains over 4000 compounds, which may prevent a direct comparison to rodent models that are induced by a single toxin.

References