The search for biomarkers to predict response to immunotherapies in NSCLC patients

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DISCLOSURE

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CONTENT

• Background
• Mutation burden and response to immunotherapies
• Gene/pathway alterations associated with response to immunotherapies
• Epigenetics – DNA methylation
• Link between epigenetics and immunotherapies
PRINCIPLE OF ANTI-TUMOR IMMUNITY

1. Killing of cancer cells (immune and cancer cells)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Release of cancer cell antigens (cancer cell death)

Chen et al., 2015
IMMUNOTHERAPIES ARE ...

• ... revolutionizing anti-cancer therapy
• ... active in multiple tumor types
• ... characterized by durable clinical benefit **in a subset of patients**

20 - 30%

**Urgent need for predictive biomarkers**

• PD-L1 expression (tumor cells / immune cells)
• Mutation burden / neoantigen expression
• Individual genes / pathways
• Epigenetic markers
MUTATION BURDEN - PREDICTIVE MARKER OF RESPONSE TO IMMUNOTHERAPIES?
MUTATION BURDEN (MB) IN VARIOUS HUMAN TUMOR ENTITIES

Schumacher et al., 2015
DETECTION OF MB: WHOLE EXOME SEQUENCING

A

- Genomic DNA
- DNA Shearing + end-adaptors
- Exome capture library
- Hybridization

Extract, purify and sequence

Raw data
QC
Alignment
SNP/InDel calling
Annotation
PEMBROLIZUMAB - MISMATCH-REPAIR DEFICIENT TUMORS

High number of somatic mutations correlates with response to treatment

Le et al., 2015
PEMBROLIZUMAB - NSCLC

Rizvi et al., 2015

High number of somatic mutations correlates with response to treatment

Feasible biomarker in clinical routine??

IPILIMUMAB - MELANOMA

Snyder et al., 2014
WHOLE EXOME SEQUENCING VS TARGETED SEQUENCING

Rizvi cohort

Snyder cohort

Highly comparable data between WES and Illumina TruSight Tumor 170 panel
DNA METHYLATION - PREDICTIVE MARKER OF RESPONSE TO IMMUNOTHERAPIES?
DNA METHYLATION

- Covalent addition of -CH$_3$ to carbon 5 of cytosine within CpG dinucleotide
- Reaction catalyzed by DNA methyltransferases (DNMT)
- Co-factor: S-adenosyl-L-methionine (SAM)
- Reversible process

Ku et al., 2011
**CPG ISLANDS**

- CpG-rich genomic regions of 0.5-4 kb in length
- Located in promoter region of ~ 60% of mammalian genes
- Usually unmethylated (exceptions: e.g. x-linked, imprinted genes)
- Tissue specific e.g. Cancer Testis Antigens

Nepomuceno et al., 2013
CANCER TESTIS ANTIGENS

- Large family of testis/placenta specific proteins
- Silenced by methylation in differentiated somatic cells
- Re-expressed various malignancies
- Recognized as non-self structures
- Induce immune response

Lifantseva et al., 2011
REDUCED CTA METHYLATION IN LUSC

- TCGA data
- Lung squamous cell carcinomas
- 372 primary TUs
- 43 matching NLs
- Infinium HumanMethylation450 BeadChip
CTA METHYLATION VS. EXPRESSION IN LUSC
IS REDUCED CTA METHYLATION / INCREASED CTA EXPRESSION A PREDICTIVE MARKER?
THANK YOU VERY MUCH FOR YOUR ATTENTION!!