Genetic basis of cancer

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Disclosure conflicts of interest speaker

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<th>relationships with companies</th>
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Cancer is a genetic disease

true
false
Cancer is a genetic disease although mostly not heritable
human body

chromosomes in nucleus

cells

DNA

genetic code

Organismal damage (cancer)

Cellular damage

DNA damage (mutations)

Radboudumc
Tumorigenesis is a multistep process.

- **APC/β-catenin** leads to an aberrant crypt focus.
- **KRAS** leads to an early adenoma.
- **TP53, PIK3CA, loss of 18q** leads to a late adenoma.
- EGFR, COX2 indicates increasing chromosomal instability (CIN).

CIN = chromosomal instability

Pino and Chung, Gastroenterology 6, 2010
Tumour heterogeneity

Marusyk et al., Nature Rev Cancer 2012
The branching architecture of clonal evolution in cancer

Greaves and Maley, Nature 2012
Multiregion sequencing of metastasized renal carcinoma

B Regional Distribution of Mutations

Gerlinger et al, NEJM 2012
The cancer genome

- ideogram
- insertions and deletions
- heterozygous variants
- homozygous variants
- coding variants
- copy number variants (CNV)
- loss of heterozygosity
- intrachromosomal rearrangements
- interchromosomal rearrangements
- & epigenetic changes
Tumorigenesis and tumor progression

**Intrinsic factors**
- mutations in proto-oncogenes
  - e.g. EGFR/KRAS/BRAF/MET/KIT
- mutations in tumor suppressors
  - e.g. TP53/RB/PTEN

**External factors**
- viral infection (HPV, HCV, EBV, etc)
- hypoxia and angiogenesis
- chronic sublethal cell damage
- growth factors
- inflammation
Accumulation of mutations during life

1. DNA fails to copy and repair accurately

2. External factors
   Radiation, chemicals
Repair mechanisms

- Alkylating agents
  - Oxygen radicals
  - Spontaneous reaction

- X-rays

- UV light
  - Polycyclic aromatic hydrocarbons (PAHs)
  - Replication errors
  - Hydroxyurea (Hu)
  - Anti-tumor agents

- IR

- Single strand breaks
  - 8-Oxoguanine
  - Single strand breaks

- Uracil
  - Abasic site

- 6-4 photoproducts
  - Bulky adducts
  - Cyclobutane pyrimidine dimers

- A-G mismatch
  - T-C mismatch
  - Small insertion
  - Small deletion

- Interstrand crosslink
  - Double strand breaks (DSB)

- Direct Reversal
  - Single Strand Break Repair (SSBR)

- Base Excision Repair (BER)

- Nucleotide Excision Repair (NER)
  - Global Genomic Repair (GG-NER)
  - Transcription-Coupled Repair (TC-NER)

- Mismatch Repair (MMR)

- DSB Repair (DSBR)
  - Non-homologous End-Joining (NHEJ)
  - Homologous Recombination (HR)

- Checkpoint Signaling
  - Cell Cycle Arrest
Somatic mutational signature

The combined set of mutation types generated by a single biological process

Example: signature

Spontaneous deamination of 5-methylcytosine

 Mutation signatures in human cancers

- CpG
- APOBEC
- HRD
- Tobacco mutagens
- UV exposure
- POLE

30 different validated signatures described
The lung cancer genome

Drivers & Passengers:

5-10 driver mutations & 100-1000 passenger mutations
Targetable activating mutations in lung cancers

- EGFR activating mutation
- MET amplification
- ALK rearrangement

Principles of clinical cancer genetics
Driving mutations in NSCLC

Mutual exclusive driving mutations

Tumor Mutational Burden

more nonsynonymous mutations
more neopeptides
more effective immune response
more benefit from checkpoint inhibitors
Colorectal cancer and mutational load may be associated with Lynch syndrome.

> Chromosomal instability

Yaeger et al, Cancer Cell 2018
Underlying mechanisms and therapeutic options

Hanahan and Weinberg, Cell 2011
Unravelling genetic make-up of cancer

- Understand tumour biology

- Selection of therapeutic strategies
  - Targeting signal transduction pathways
  - Increase immune response by checkpoint inhibitors
  - Use of PARP inhibitors in tumours with homologous recombination defects
  - Recognize resistance mechanisms

- Recognition of putative genetic tumour risk syndromes
  - Microsatellite instability
  - Homologous recombination scars
  - Specific mutational signatures
  - Presence of specific pathogenic variants ...
Role of tumour testing in GENTURIS

• Analysis of tumour DNA to unravel germline and somatic mutations simultaneously (e.g. BRCA1 / BRCA2 in ovarian cancer)

• Explore effect of germline variants (variant classification):
  • microsatellite instability
  • homologous recombination scars
  • mutational signature

• Detection of mosaics due to postzygotic mutations (e.g. APC)

• Analysis for somatic mutations to reduce a priori risk of genetic disease (e.g. biallelic somatic mutations reduce chance of Lynch syndrome)

• Analysis of LOH or 2nd hit mutations (variant classification)
Understanding genetic basis of cancer

prevention

therapy