Molecular Mechanisms of Lung Carcinogenesis

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Number of slides: 42
Overview

1. Molecular carcinogenesis: Hallmarks of cancer
2. Mechanisms that shape genetic cancer progression
3. A global view of lung cancer genomes
4. Clinical relevance
Cancer: a progressive disease
Hallmarks of Cancer 2000

Tumor-cell intrinsic capabilities

Hanahan and Weinberg 2000, Cell
New Hallmarks, 2010

Tumor-cell extrinsic/cooperative capabilities

Hanahan and Weinberg 2012, Cell
Cell-cell interactions guiding tumour progression

De Craene and Berckx 2013 Nature Reviews Cancer 13: 97
Chronic Immuno-inflammation
Proliferation metabolism

Differentiated Tissue Cells

+O₂
Glucose → O₂ → Pyruvate → Lactate → CO₂

(Oxidative Phosphorylation)

Anaerobic Glycolysis

Proliferating or Tumor Cells

+/-O₂
Glucose → Pyruvate → 85% Lactate → CO₂

(Aerobic Glycolysis)
Reprogramming energy metabolism in cancer
Hallmarks of cancer

- EGFR inhibitors
- Cyclin-dependent kinase inhibitors
- Immune activating anti-CTLA4 mAb
- Telomerase Inhibitors
- Selective anti-inflammatory drugs
- Inhibitors of VEGF signaling
- Inhibitors of HGF/α-Met

- Aerobic glycolysis inhibitors
- Proapoptotic BH3 mimetics
- PARP inhibitors
- Resisting cell death
- Deregulating cellular energetics
- Sustaining proliferative signaling
- Evading growth suppressors
- Avoiding immune destruction
- Enabling replicative immortality
- Tumor-promoting inflammation
- Genome instability & mutation
- Inducing angiogenesis
- Activating invasion & metastasis
How Many Mutations in Cancer?

- Hundreds to thousands of mutations per cancer cell
- Only a few may be "drivers", others are likely to be "passengers"

Whole-Genome Sequencing
SCLC

Pleasance et al 2010 Nature 463: 184
How does a cell accumulate so many mutations?

1. Not any cell can do it: stem/progenitor cells
2. It takes a lifetime (and more)
3. Cancer cells develop a « mutator phenotype »
4. Catastrophic genomic rearrangements may induce many mutations in one step
5. Many genes mutated in cancer are regulating chromatin dynamics and RNA processing/splicing (global alteration of genome expression)
6. *TP53* (encoding the p53 protein) operates as a critical « master gene »
Cancer Initiating Cells

The « Cancer Stem Cell » Paradigm

Bjerkvigt et al 2005 Nature Cancer Reviews 5:899
Sequential accumulation of genetic changes
High order genome organization
Chromothrypsyis
Mutations in epigenetic regulators

Watson et al
Nature Reviews
2013 14: 703
p53: integrating the « Hallmarks of Cancer »

Hainaut, « p53 in the clinics », 2012
Based on Hanahan and Weinberg, 2010
TP53 as « master gene »: experimental liver cancer

Lung Carcinogenesis
A Genomics-Based Classification of Human Lung Tumors

The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM)*†

We characterized genome alterations in 1255 clinically annotated lung tumors of all histological subgroups to identify genetically defined and clinically relevant subtypes. More than 55% of all cases had at least one oncogenic genome alteration potentially amenable to specific therapeutic intervention, including several personalized treatment approaches that are already in clinical evaluation. Marked differences in the pattern of genomic alterations existed between and within histological subtypes, thus challenging the original histomorphological diagnosis. Immunohistochemical studies confirmed many of these reassigned subtypes. The reassignment eliminated almost all cases of large cell carcinomas, some of which had therapeutically relevant alterations. Prospective testing of our genomics-based diagnostic algorithm in 5145 lung cancer patients enabled a genome-based diagnosis in 3863 (75%) patients, confirmed the feasibility of rational reassignments of large cell lung cancer, and led to improvement in overall survival in patients with EGFR-mutant or ALK-rearranged cancers. Thus, our findings provide support for broad implementation of genome-based diagnosis of lung cancer.
Global View of Lung Cancer Genome

Overall Survival in LC patients
Histomolecular Classification of Lung Cancers

Genomic landscape of Lung Cancer

SCLC
- RB1
- RLF-MYCL1
- MYCL1
- MYCN
- MYC

Squamous carcinoma
- FGFR1
- SOX2
- NFE2L2
- TP63
- NOTCH1

Adenocarcinoma
- TP53
- CDKN2A
- PIK3CA
- PTEN
- KEAP1
- EGFR
- KRAS
- ERBB2
- BRAF
- ALK fusions
- ROS1 fusions
- RET fusions
- STK11
Large Cell Carcinoma: a genetically mixed entity
Redefining Large Cell Carcinomas

Cellular origin and histological differentiation

- Stem Cell
  - Commited Ciliated
    - Bronchial, ciliated Cell
      - Squamous Metaplastic Cell
        - SCC
  - Commited glandular
    - Glandular Cell
      - LCC
      - ADC
      - Atypical Carcinoid
    - epithelial cell With N-E features
      - Precursor?
      - Typical carcinoid
      - Atypical carcinoid
Somatically altered pathways in Squamous Cell Carcinomas

NRF2 pathway: enhancing survival under oxidative stress
Tissue remodelling: Squamous metaplasia
NOTCH: promoting squamous differentiation

Exome Sequencing of Head and Neck Squamous Cell Carcinoma Reveals Inactivating Mutations in NOTCH1. Agarawal, Myers et al., Science, 2011
Clinically relevant genome alterations
Tumour heterogeneity

Initial diagnosis:
Adenocarcinoma, EGFR mutation (R858L)

Diagnosis after relapse:
from TKI treatment SCLC,
R858L mutation present

Resistance mutations:
None
EGFR T790M
MET ampl
Off-context gene expression: a new epigenetic paradigm

**LUNG CANCER**

**Ectopic Activation of Germline and Placental Genes Identifies Aggressive Metastasis-Prone Lung Cancers**

Sophie Rousseaux,1* Alexandra Debernardi,1 Baptiste Jacquiau,1 Anne-Laure Vitte,1 Aurélien Vesin,1 Hélène Nagy-Mignotte,2 Denis Moro-Sibilot,2 Pierre-Yves Brichon,2 Sylvie Lantuejoul,2 Pierre Hainaut,3 Julien Laffaire,4 Aurélien de Reynies,6 David G. Beer,5 Jean-François Timsit,1,2 Christian Brambilla,1,2 Elisabeth Brambilla,1,2 Saadi Khochbin1*

Activation of normally silent tissue-specific genes and the resulting cell “identity crisis” are the unexplored consequences of malignant epigenetic reprogramming. We designed a strategy for investigating this reprogramming, which consisted of identifying a large number of tissue-restricted genes that are epigenetically silenced in normal somatic cells and then detecting their expression in cancer. This approach led to the demonstration that large-scale “off-context” gene activations systematically occur in a variety of cancer types. In our series of 293 lung tumors, we identified an ectopic gene expression signature associated with a subset of highly aggressive tumors, which predicted poor prognosis independently of the TNM (tumor size, node positivity, and metastasis) stage or histological subtype. The ability to isolate these tumors allowed us to reveal their common molecular features characterized by the acquisition of embryonic stem cell/germ cell gene expression profiles and the down-regulation of immune response genes. The methodical recognition of ectopic gene activations in cancer cells could serve as a basis for gene signature-guided tumor stratification, as well as for the discovery of oncogenic mechanisms, and expand the understanding of the biology of very aggressive tumors.
Testis and Placenta-specific (TS/PS) genes in Lung Cancer

Rousseaux et al 2013 Sci Trans Med 5 186
TS/PS genes: association with poor prognosis of Lung Cancer

Rousseaux et al 2013 Sci Trans Med 5 186
Thank you

To receive a copy of these slides (pdf) and list of key reference papers:

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