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

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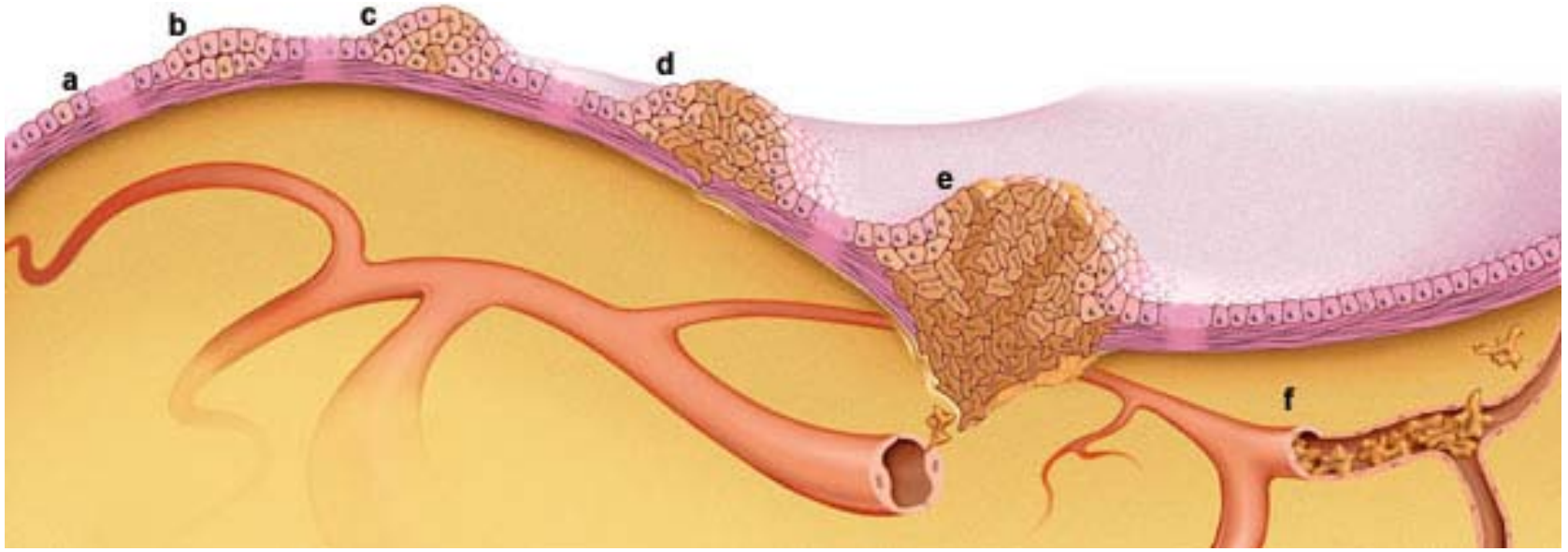
Cancer : a progressive disease



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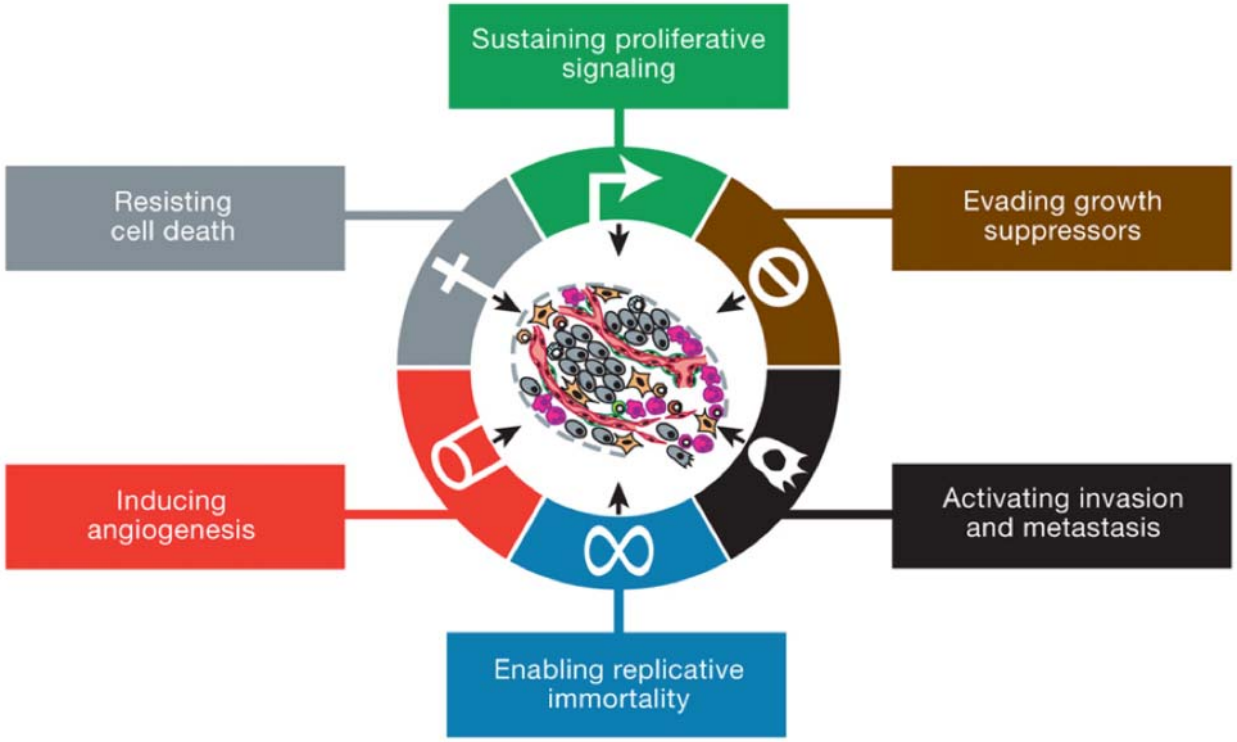
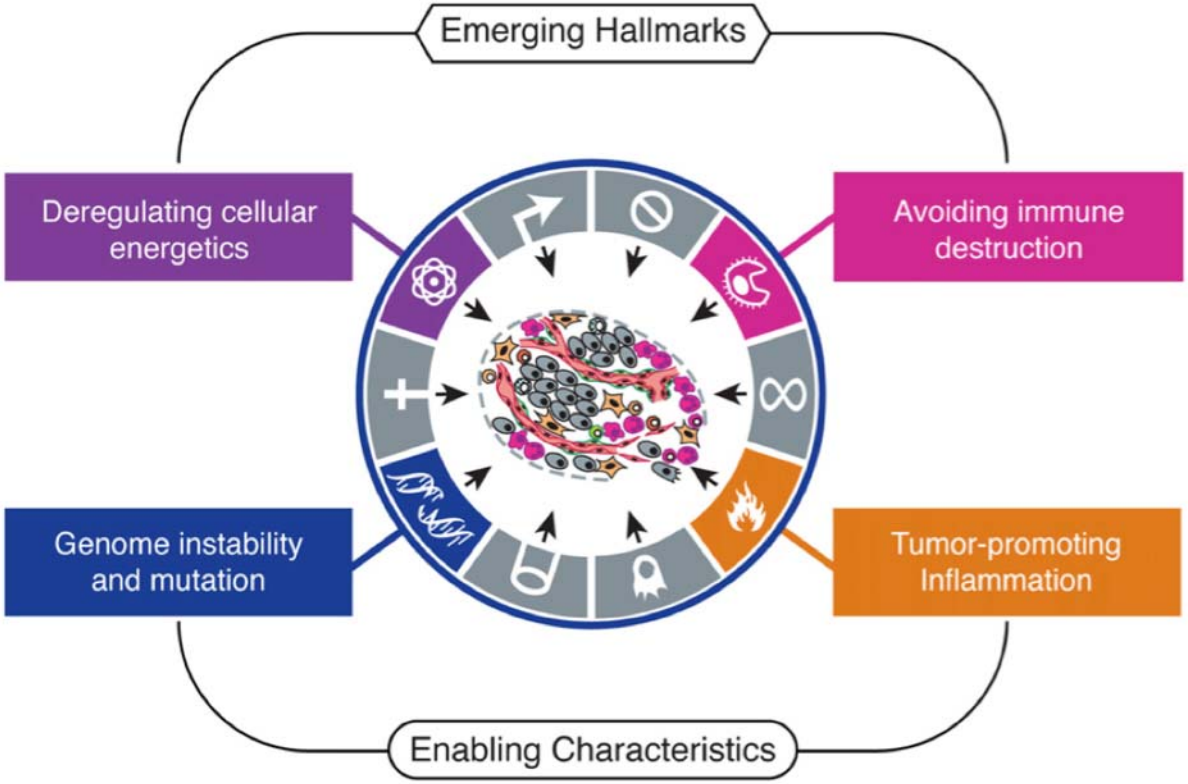
Hallmarks of Cancer 2000



Tumor-cell intrinisic capabilities

Hanahan and Weinberg 2000, Cell

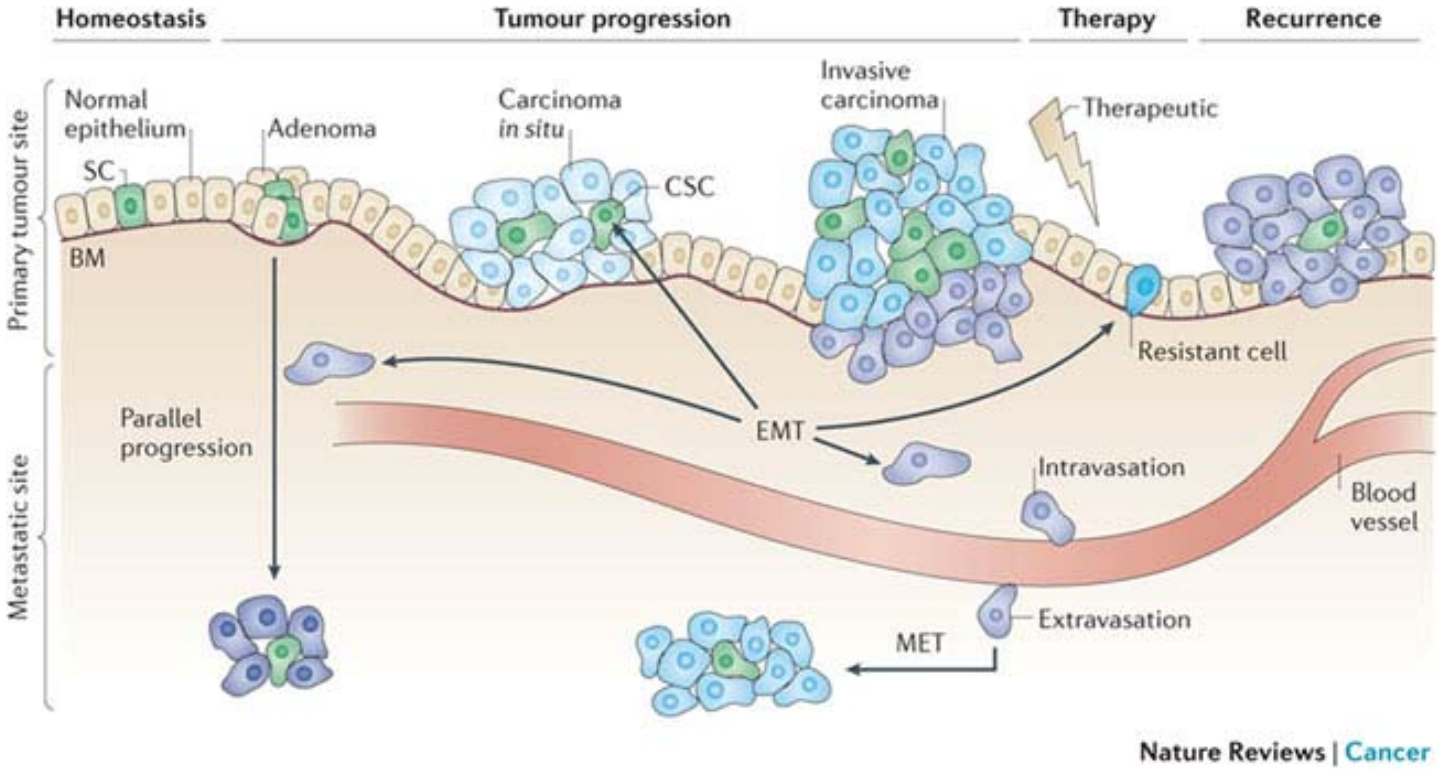
New Hallmarks, 2010



Tumor-cell extrinsic/cooperative capabilities

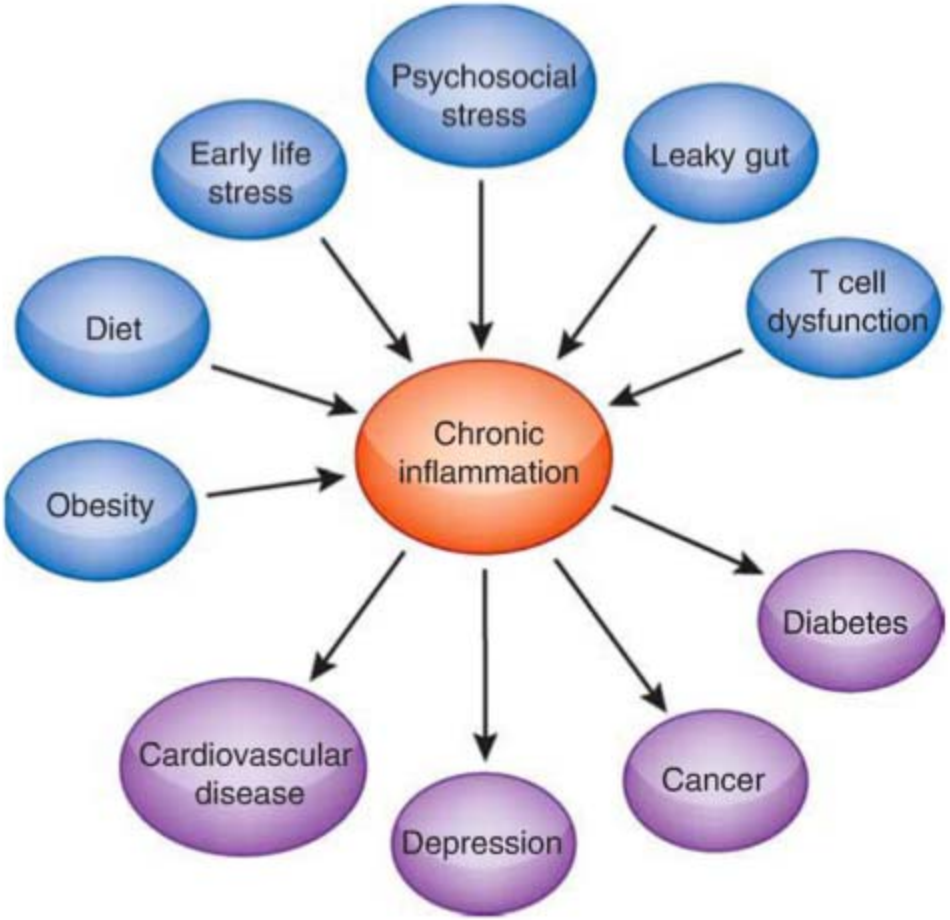
Hanahan and Weinberg 2012, Cell

Cell-cell interactions guiding tumour progression



De Craene and Berckx 2013 Nature Reviews Cancer 13: 97

Chronic Immuno-inflammation



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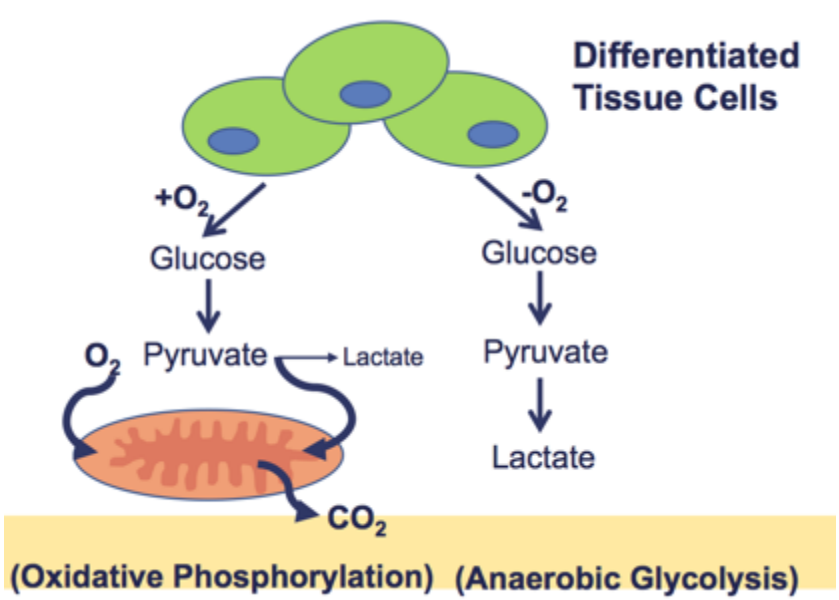
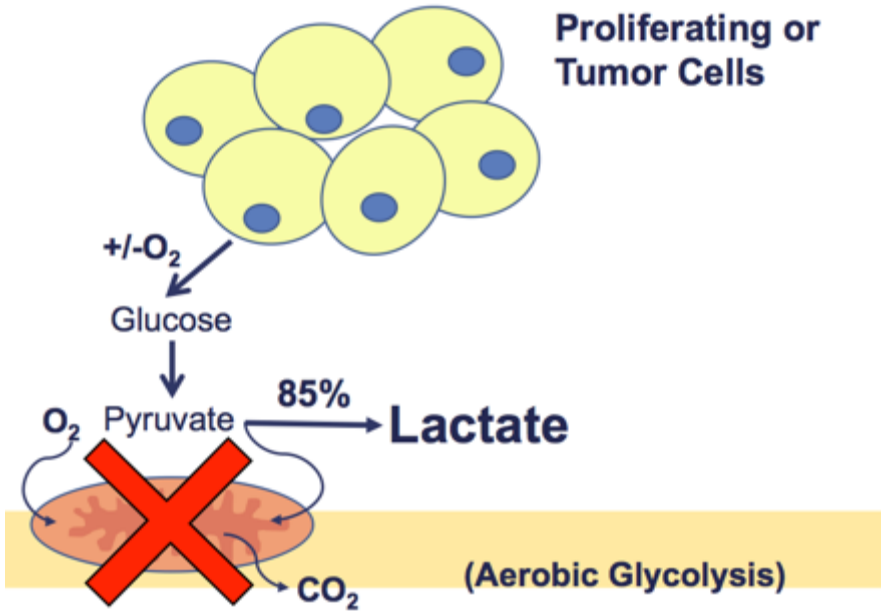
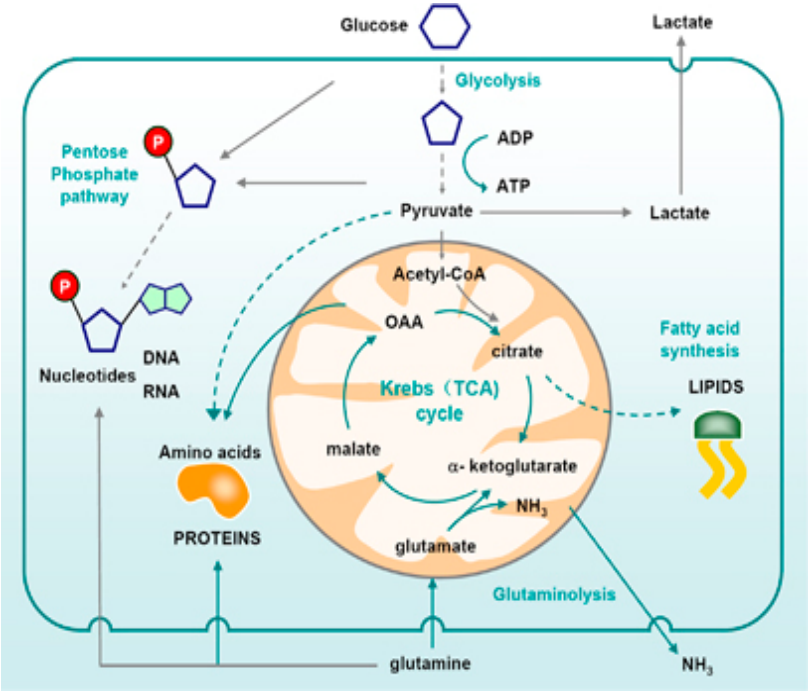
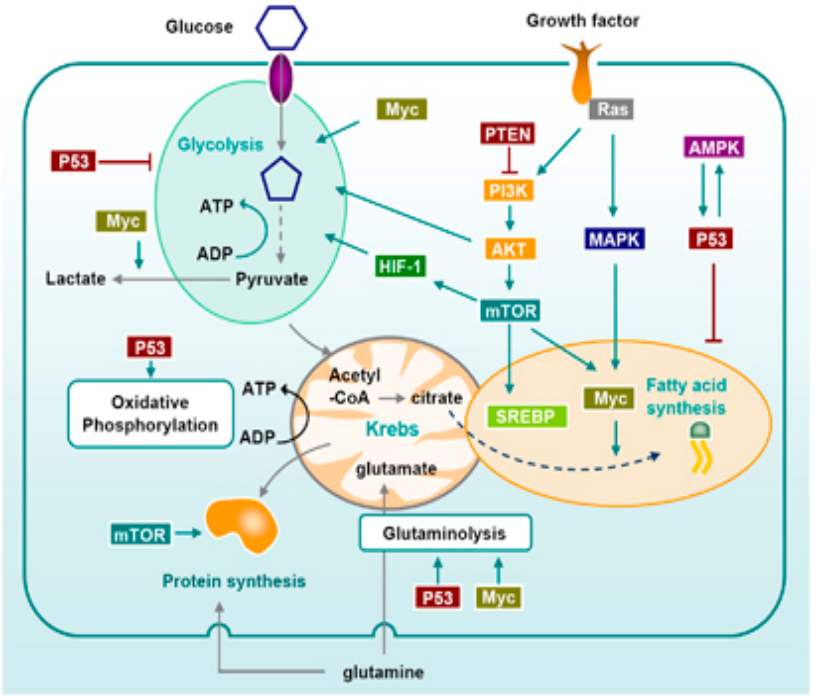
Proliferation metabolism





Reprogramming energy metabolism in cancer





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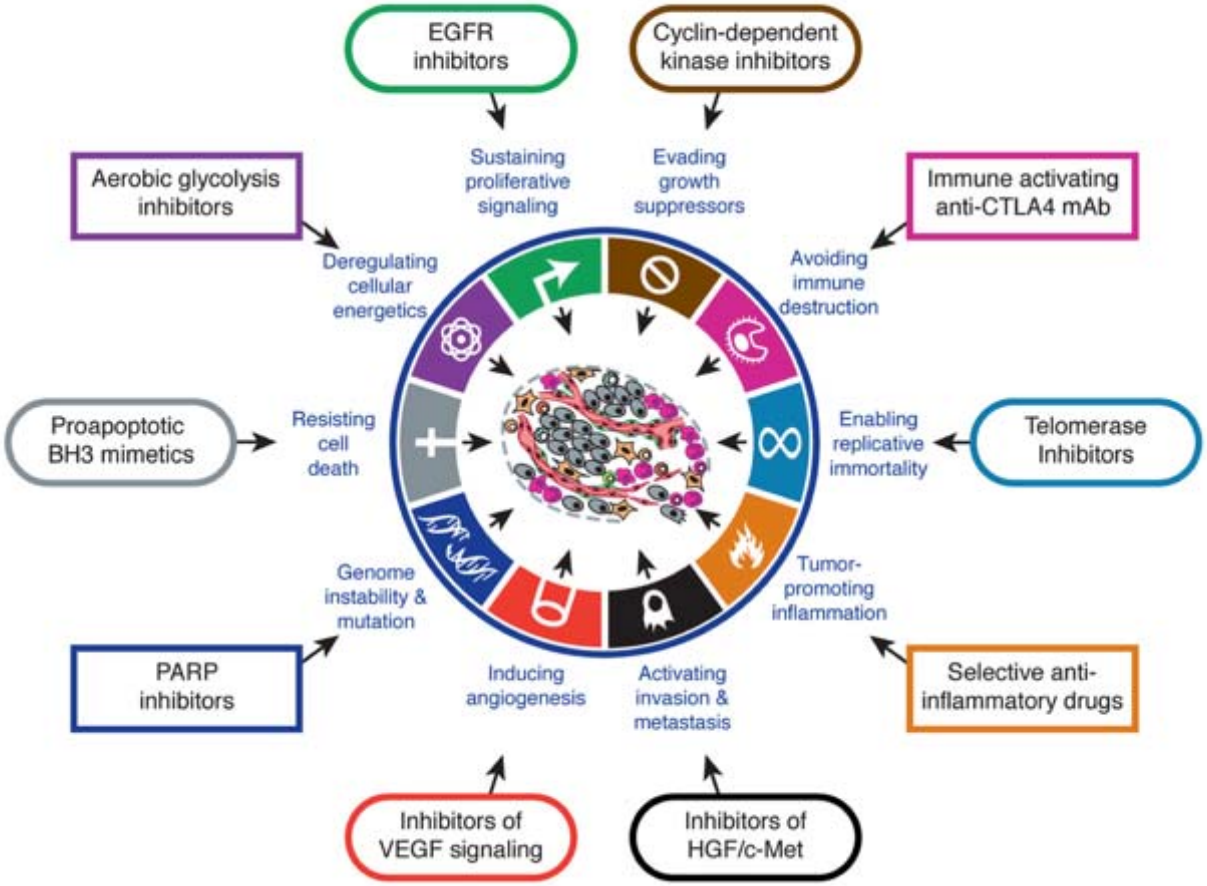
Hallmarks of cancer



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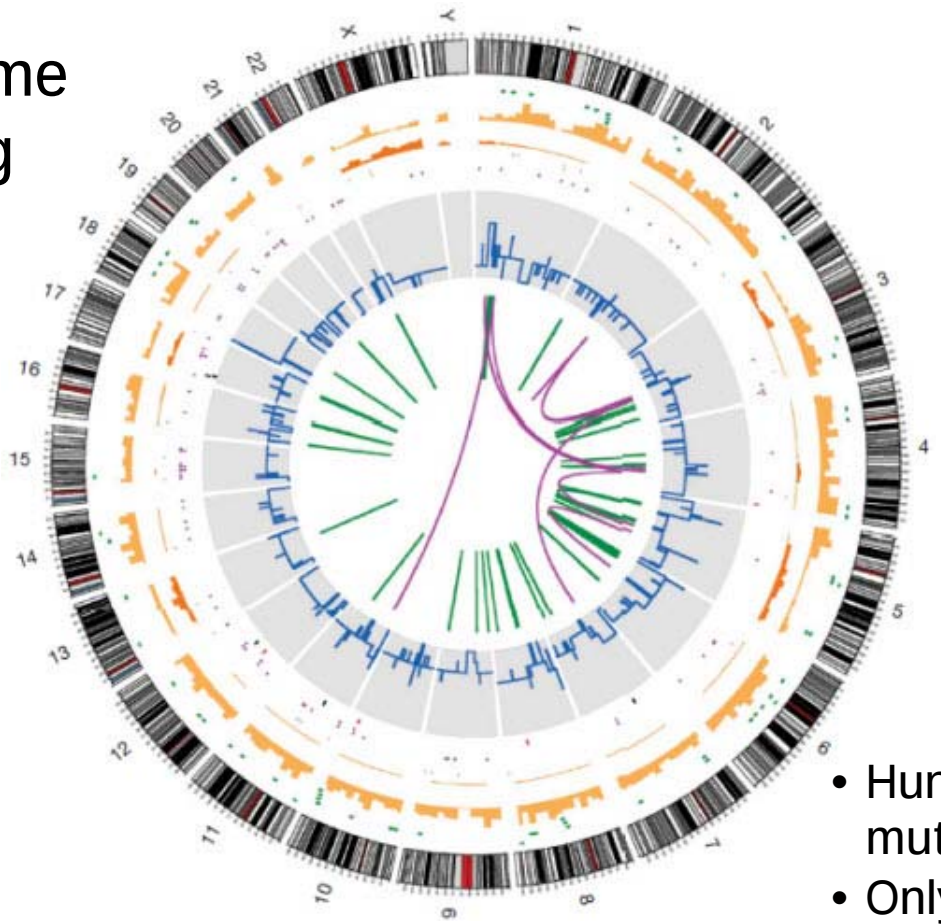
How Many Mutations in Cancer?

Whole-Genome Sequencing SCLC



- Hundreds to thousands of mutations /cancer cell
- Only a few may be « drivers », others are likely to be « passengers »

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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 »

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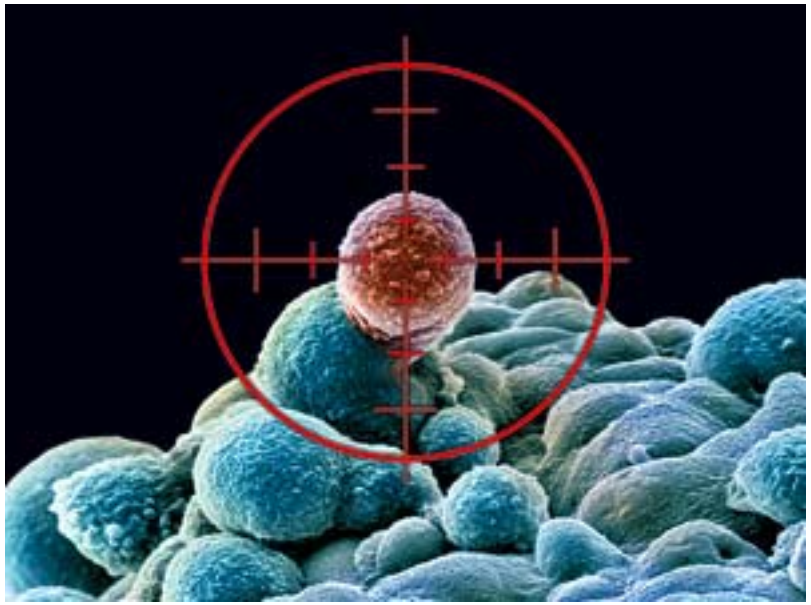
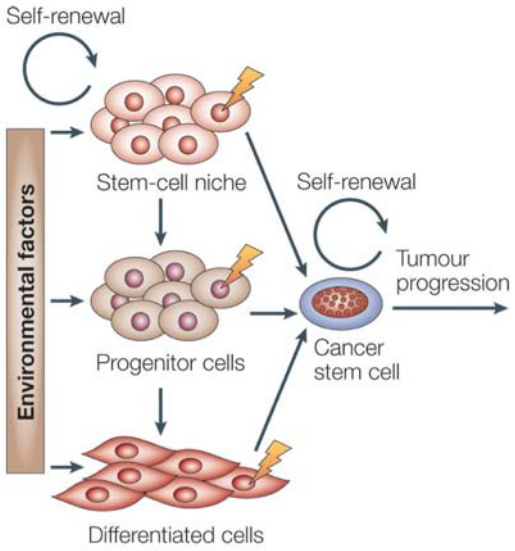
Cancer Initiating Cells

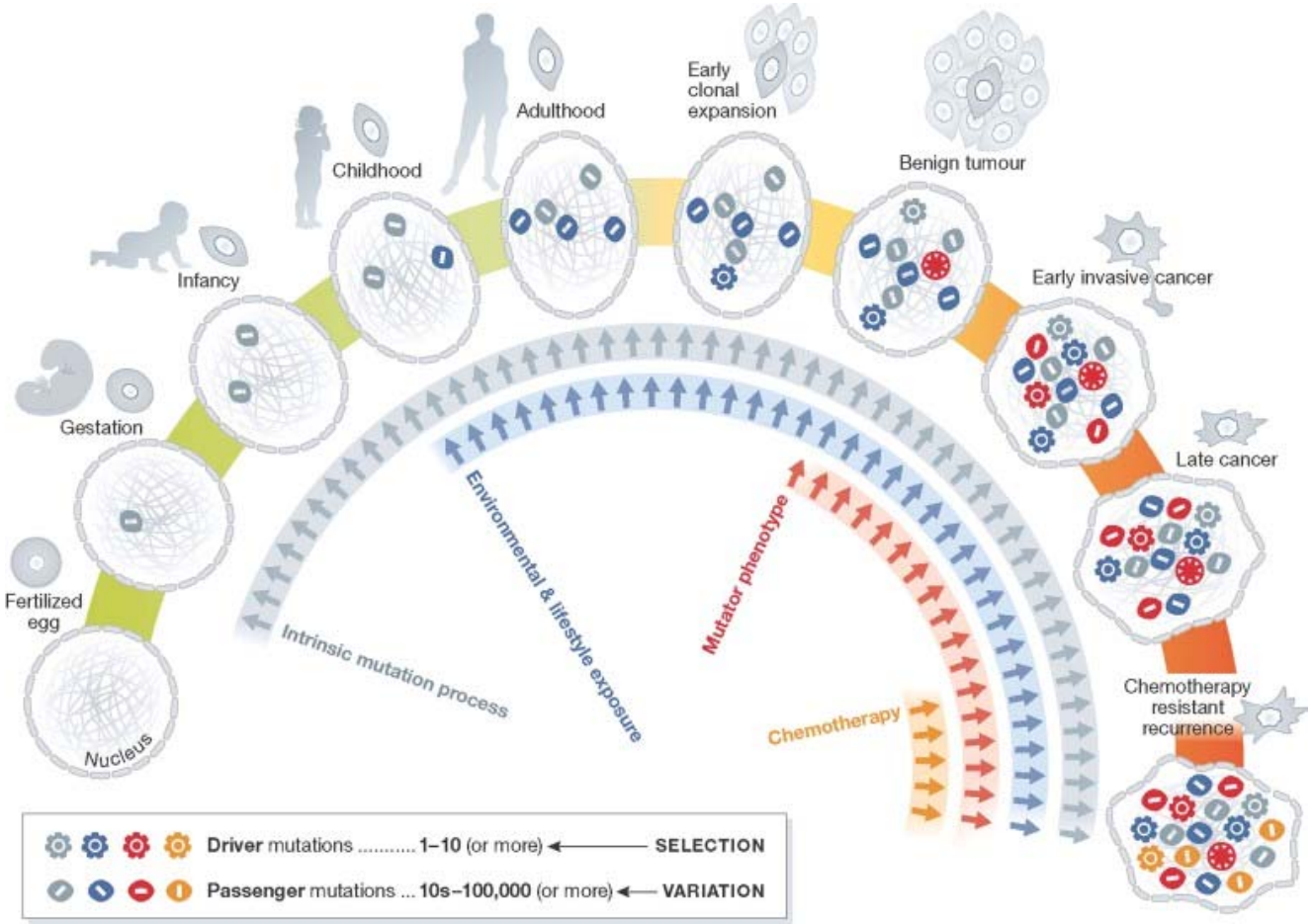




The « Cancer Stem Cell » Paradigm

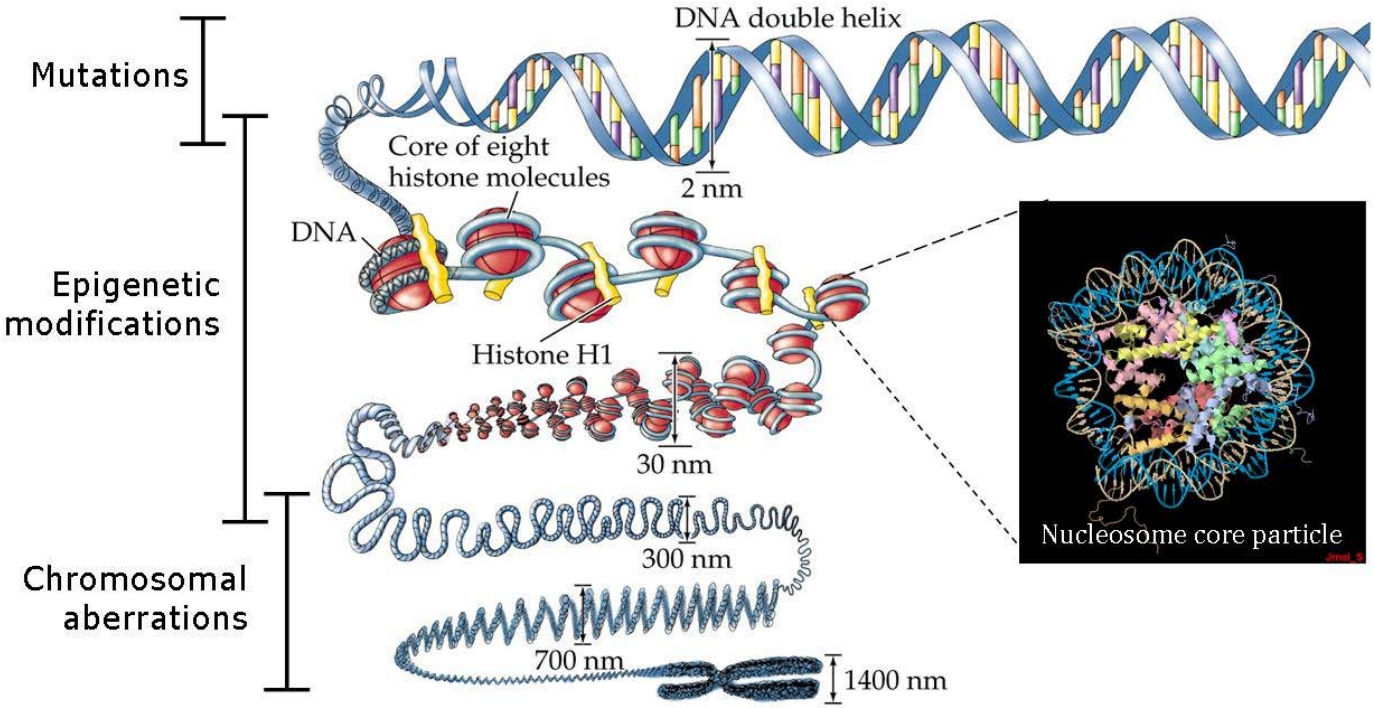
Bjerkvigt et al 2005 Nature Cancer Reviews 5:899

Sequential accumulation of genetic changes

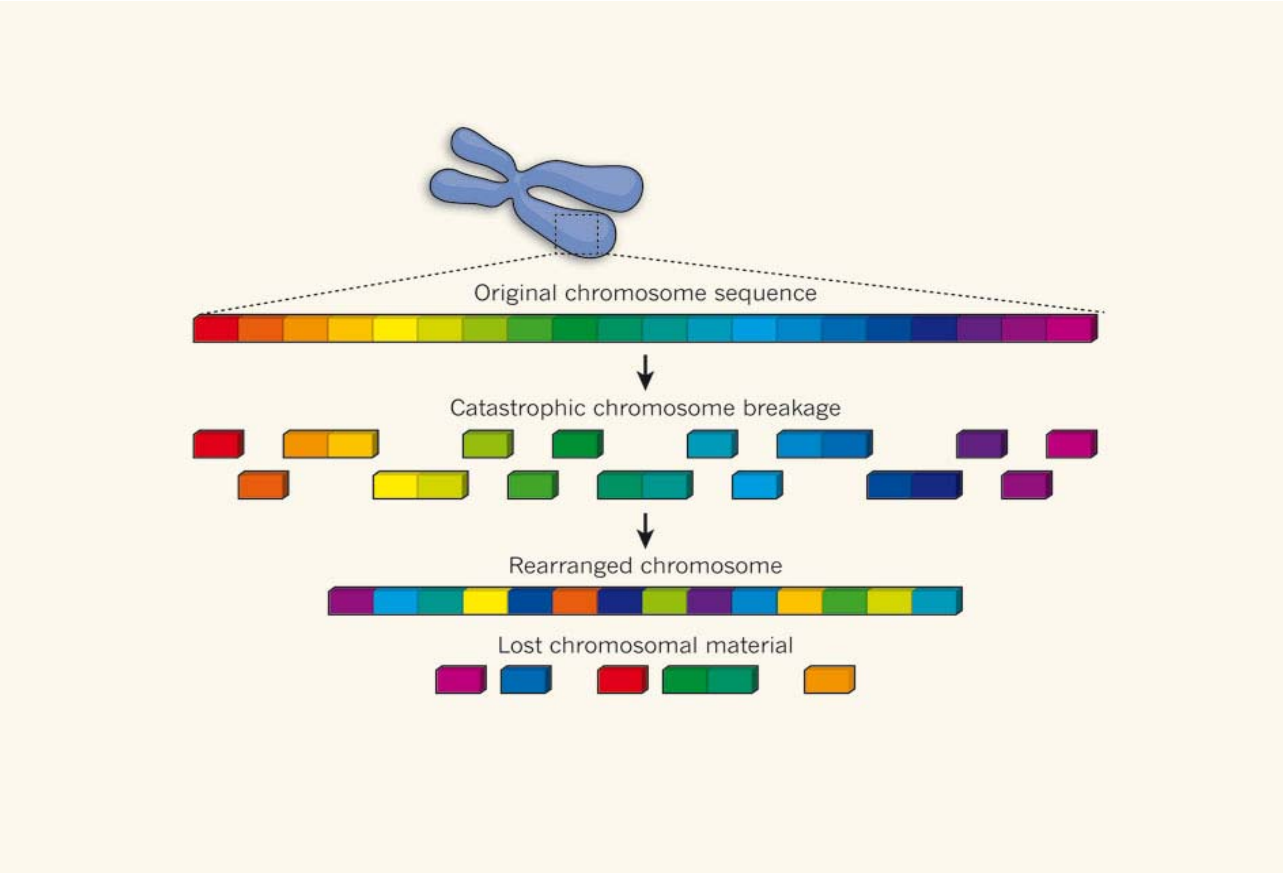


Stratton EMBO Mol Med 5:169

High order genome organization



Chromothrypsis



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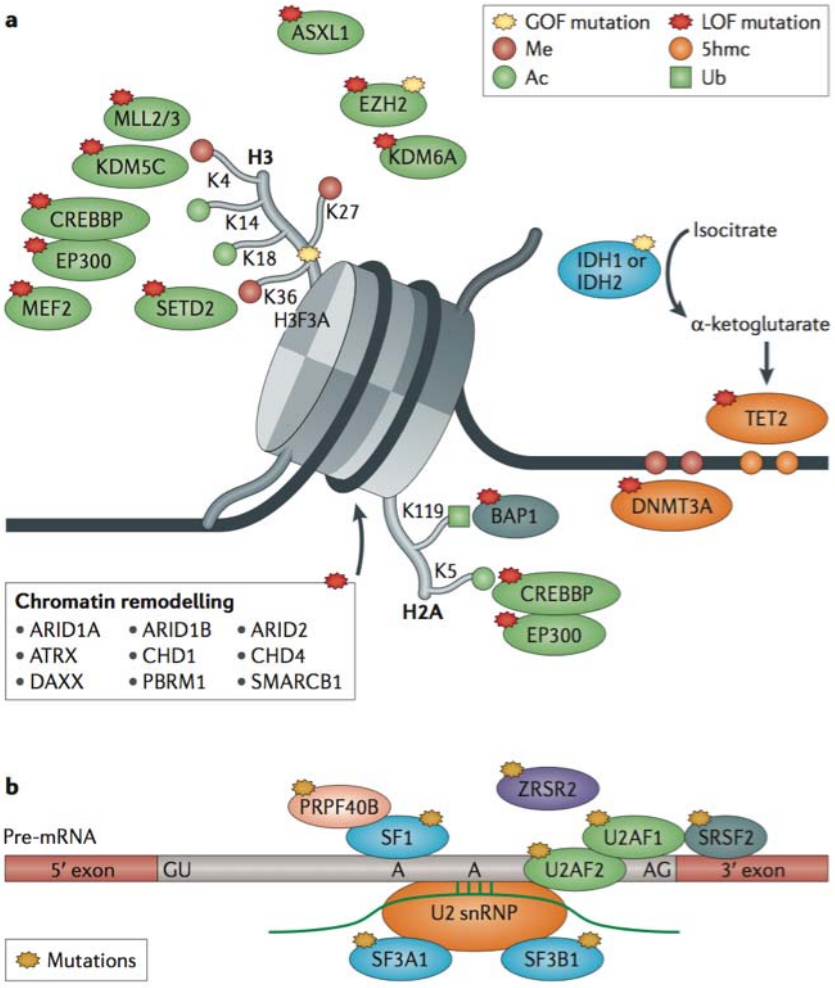
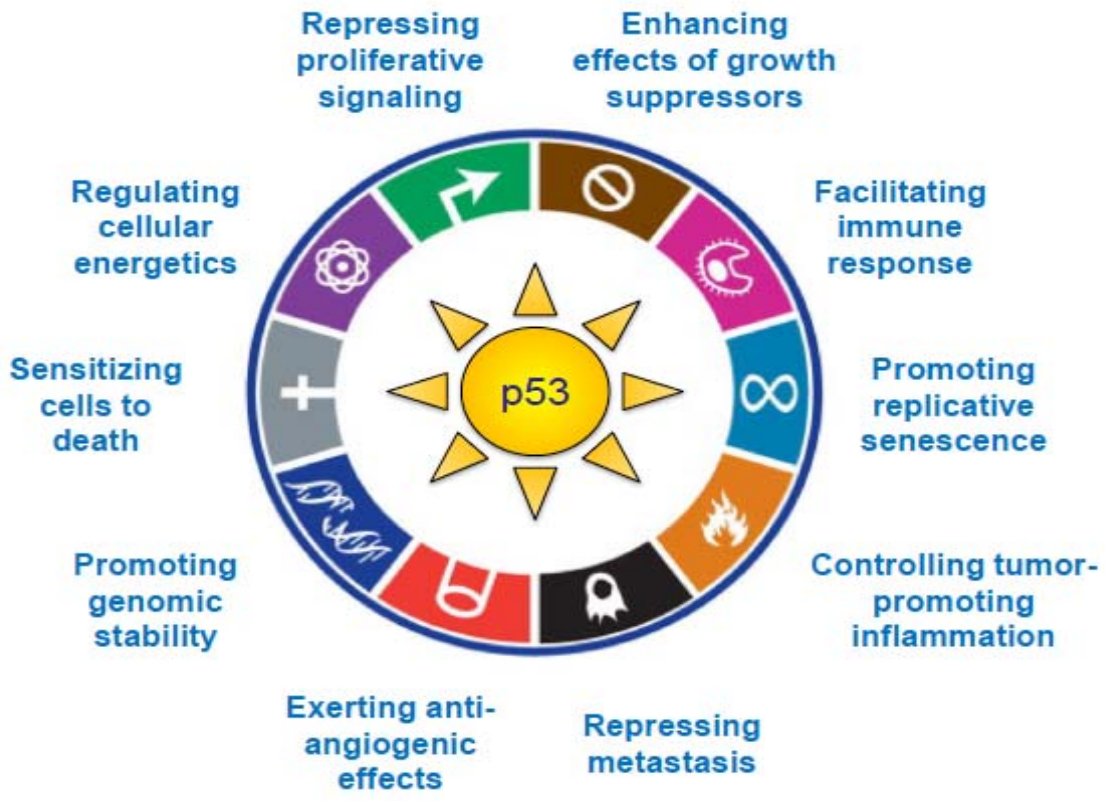
Mutations in epigenetic regulators



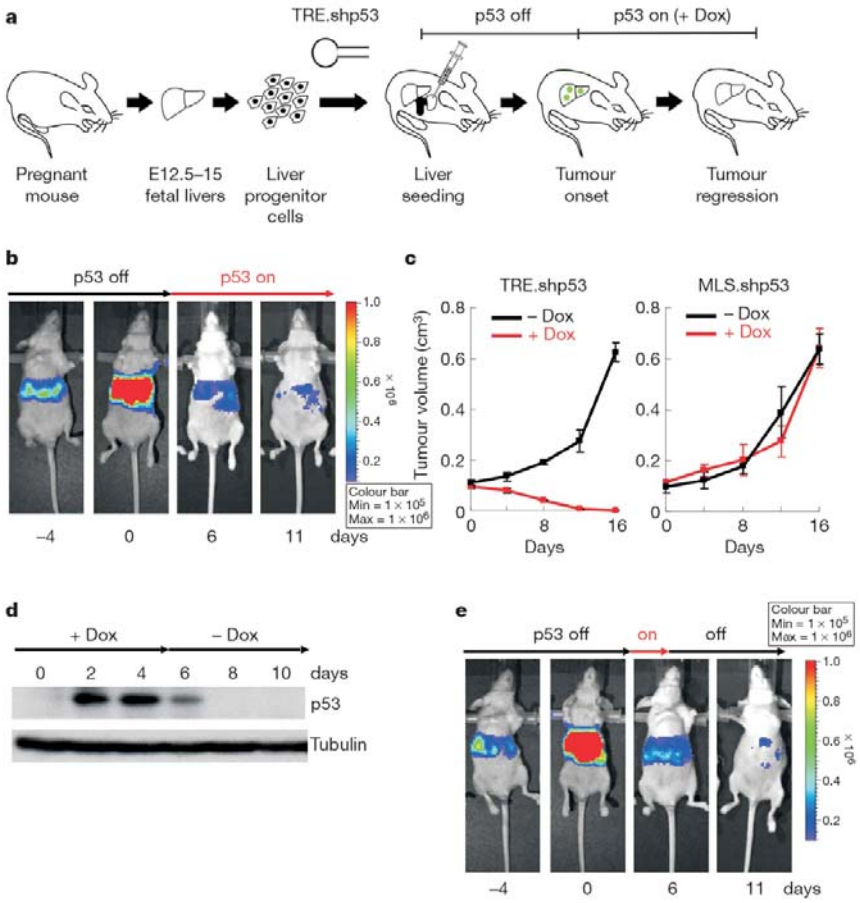
Watson et al
Nature Reviews
2013 14: 703

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



Xue et al. Nature 445: 656, 2007

Lung Carcinogenesis

The Clinical Lung Cancer Genome Project

RESEARCH ARTICLE

CANCER

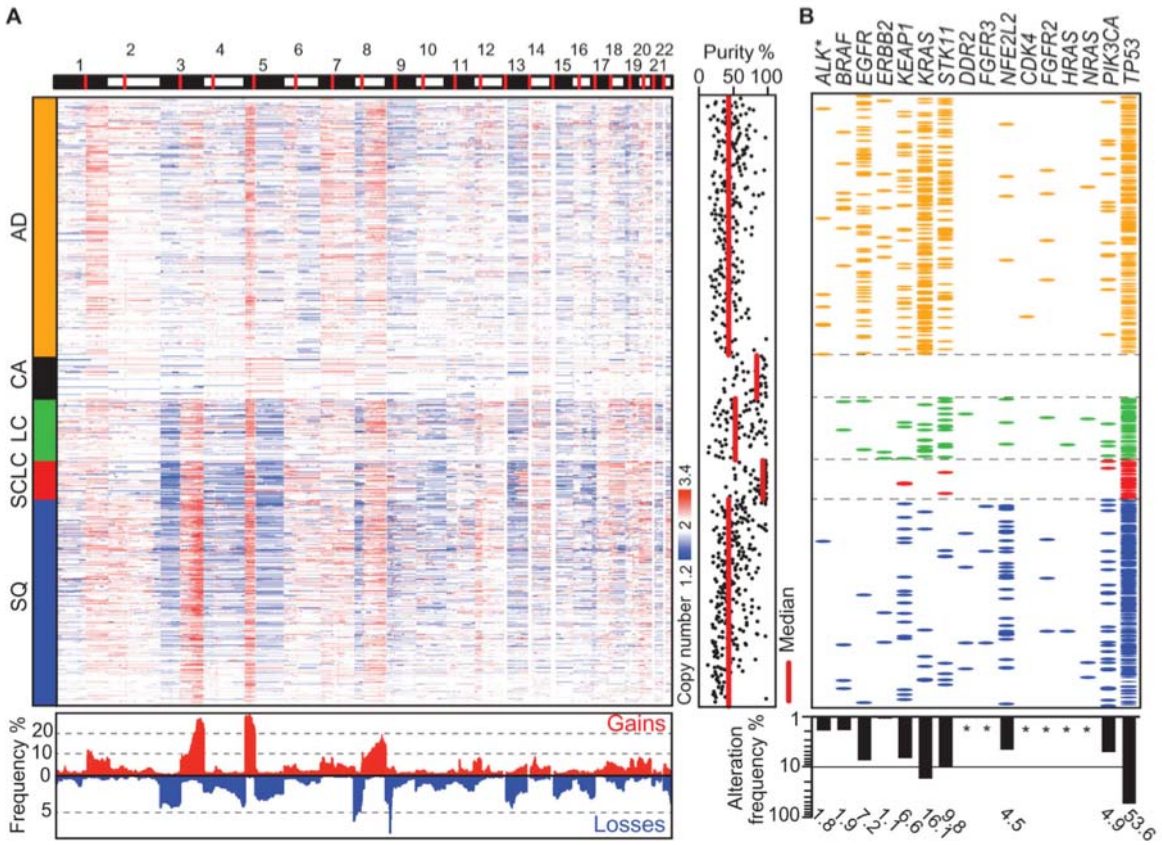
A Genomics-Based Classification of Human Lung Tumors

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.

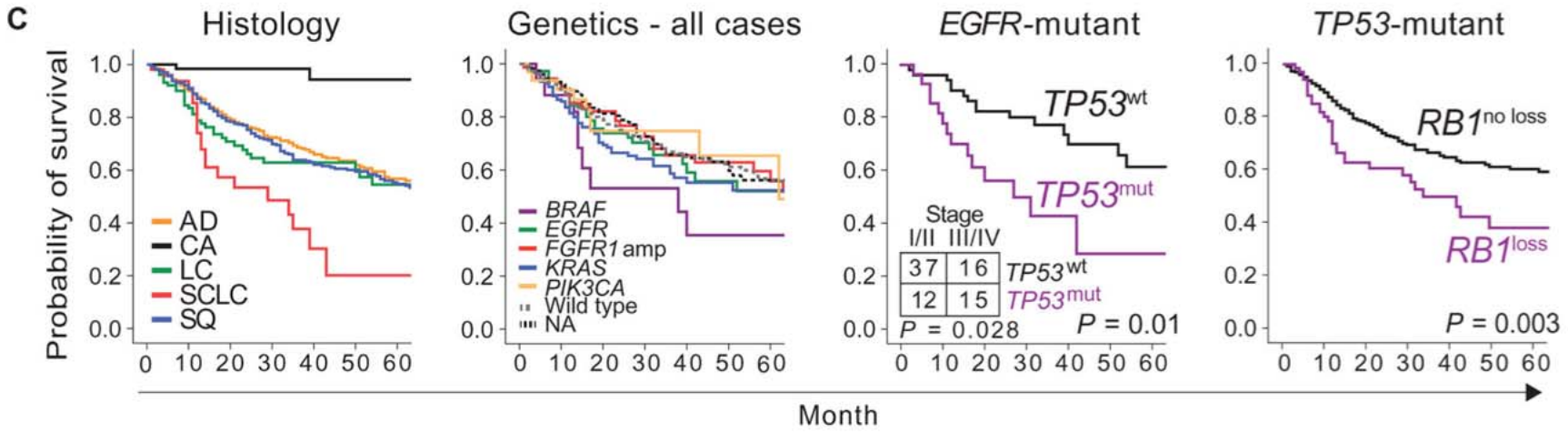
Sci Trans Med 2013 5: 209

Global View of Lung Cancer Genome



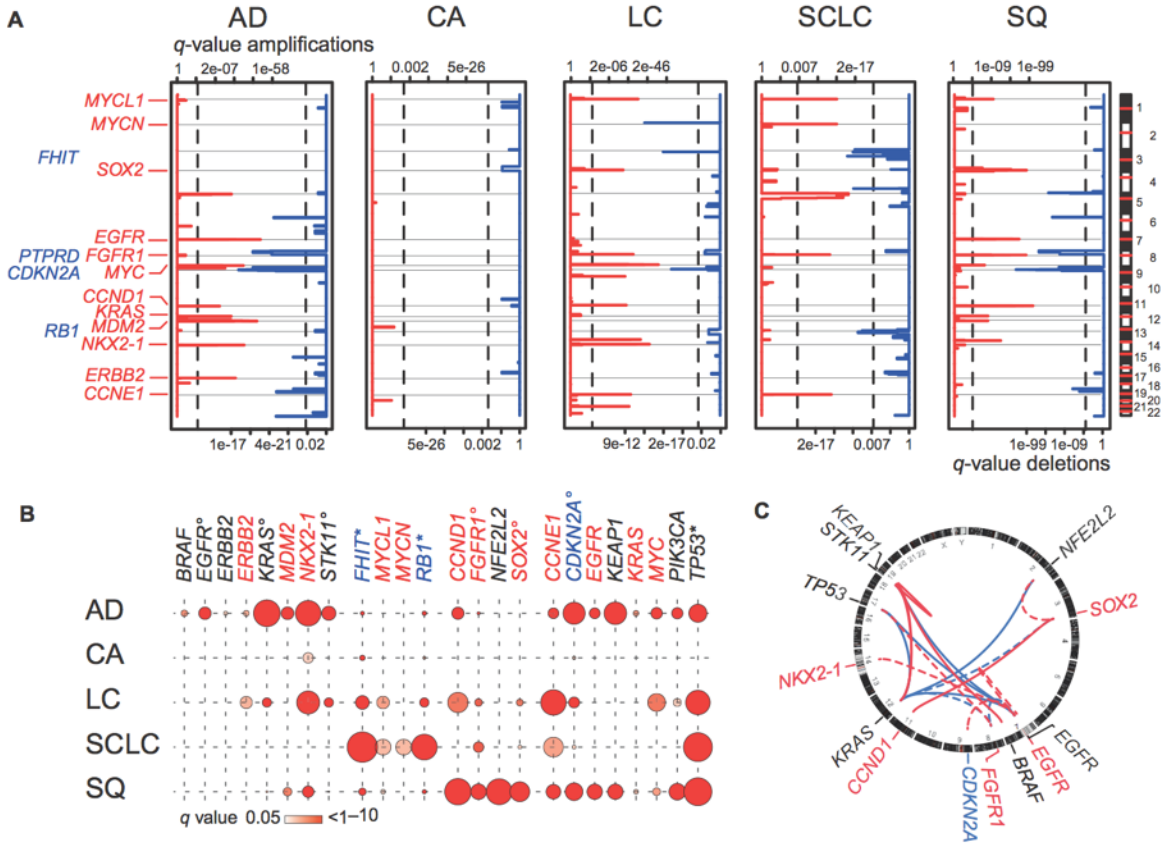
The Clinical Lung Cancer Genome Project Sci Trans Med 2013 5: 209

Overall Survival in LC patients



The Clinical Lung Cancer Genome Project Sci Trans Med 2013 5: 209

Histomolecular Classification of Lung Cancers



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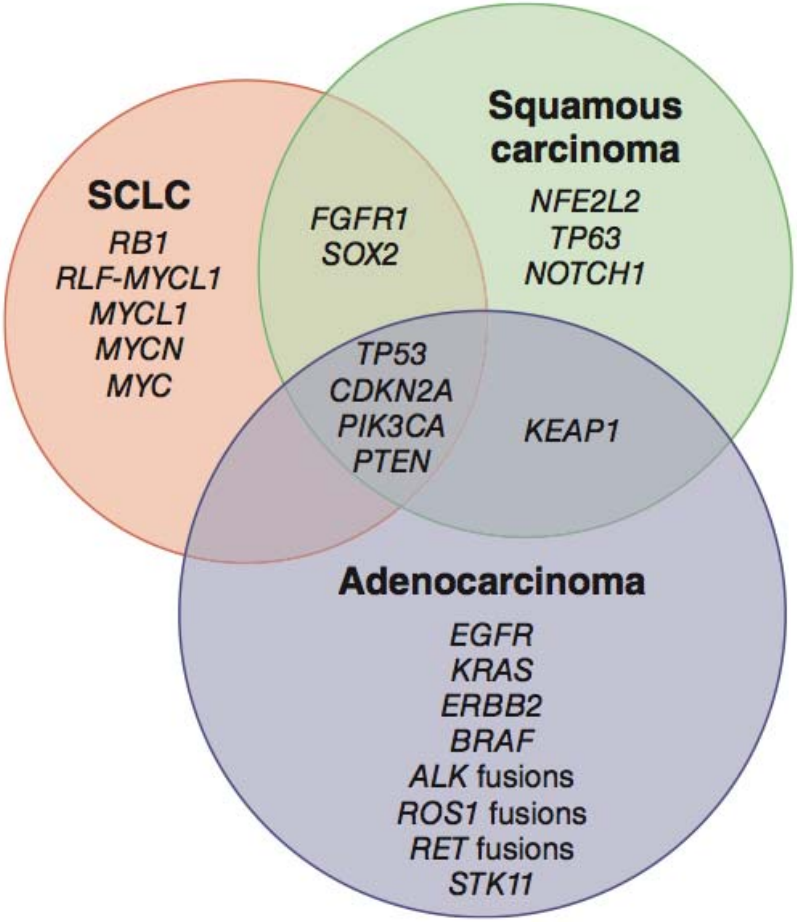
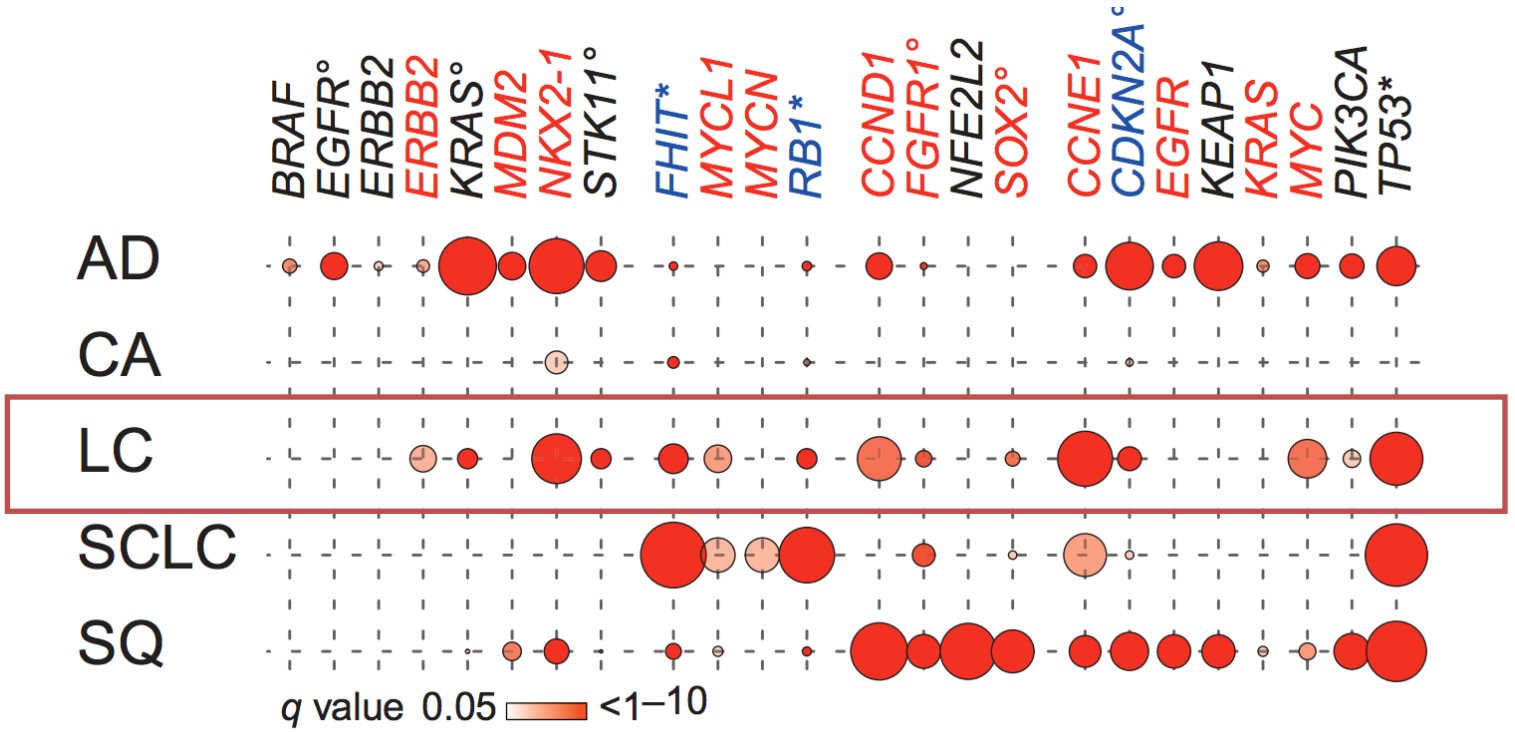
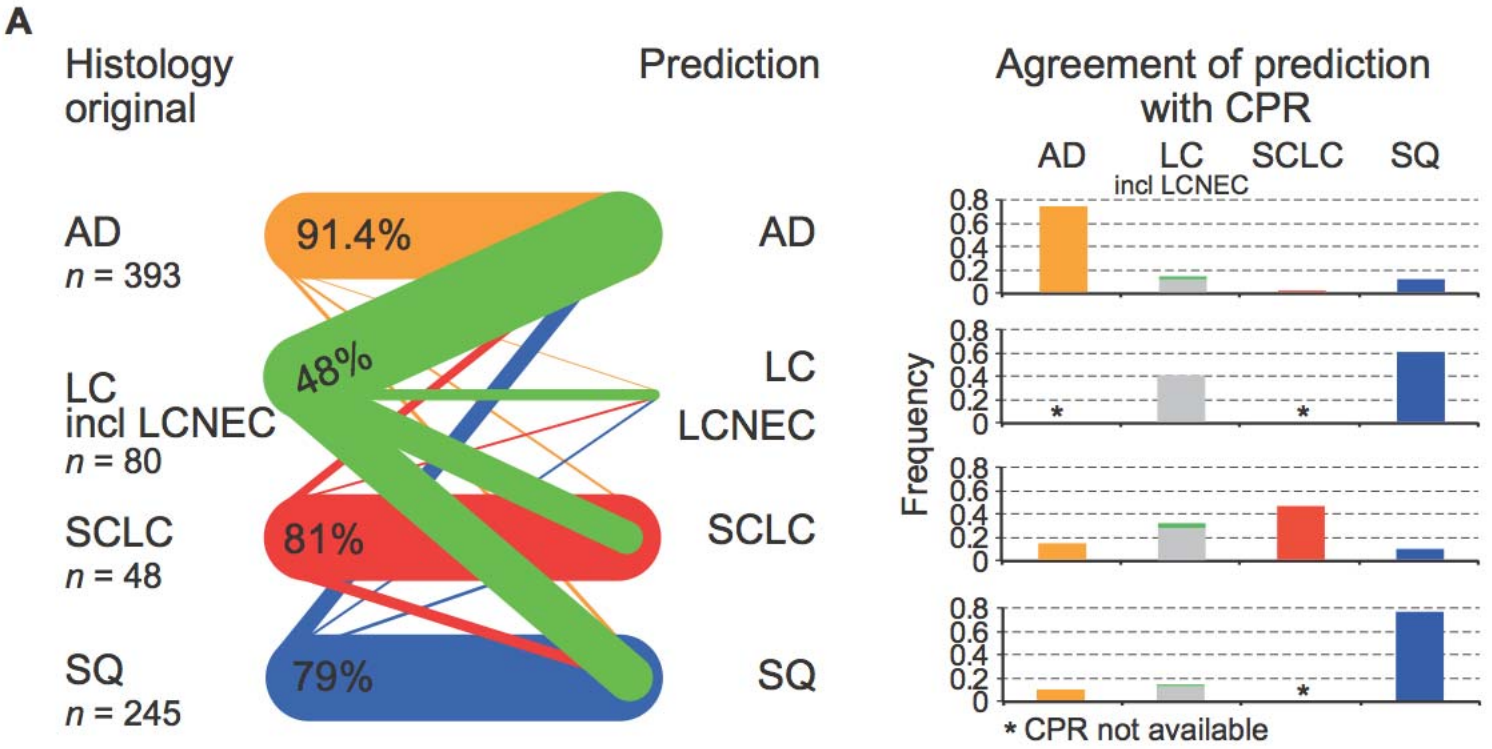
Genomic landscape of Lung Cancer



Large Cell Carcinoma: a genetically mixed entity



Redefining Large Cell Carcinomas



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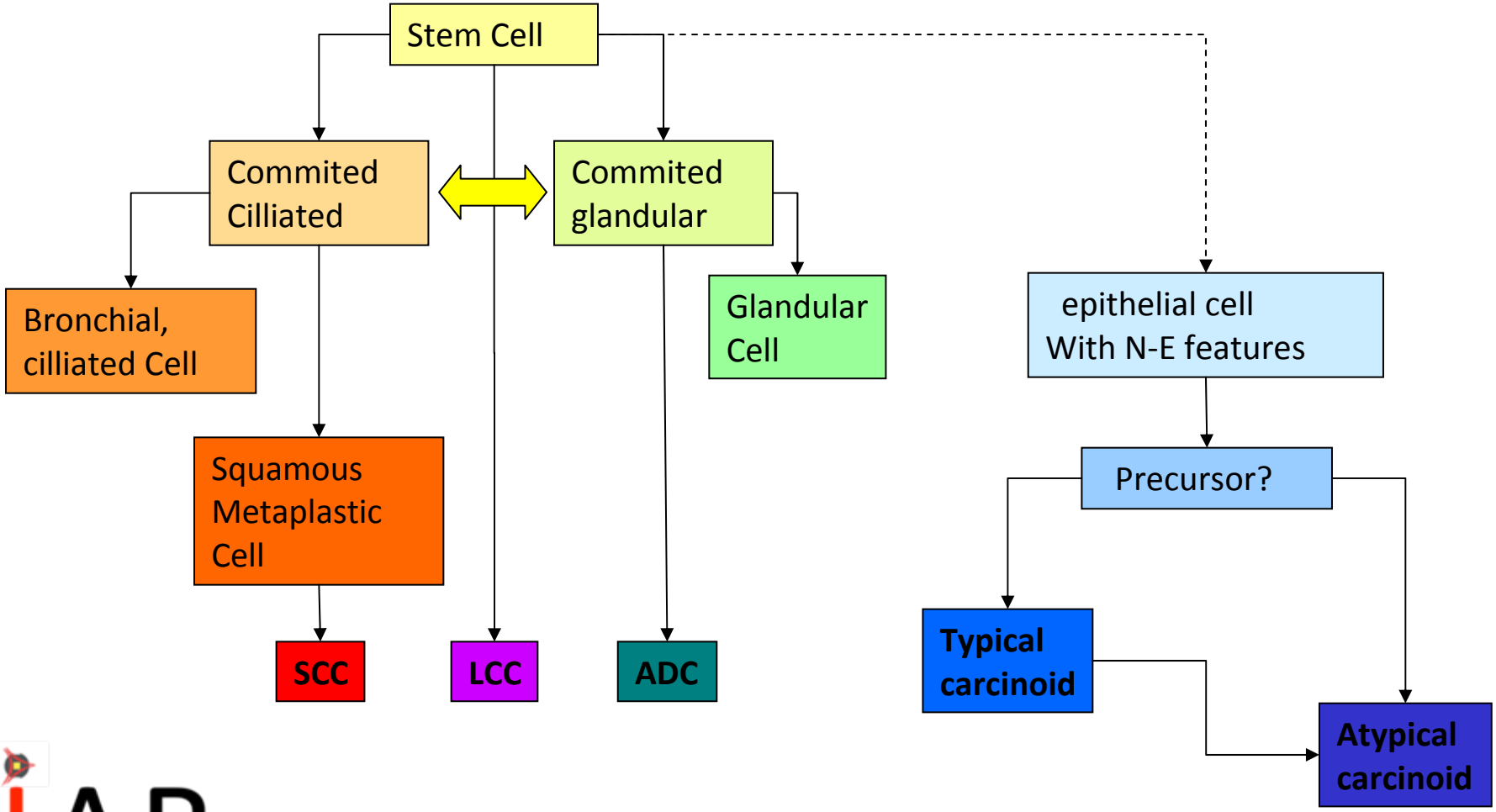
Cellular origin and histological differenciation



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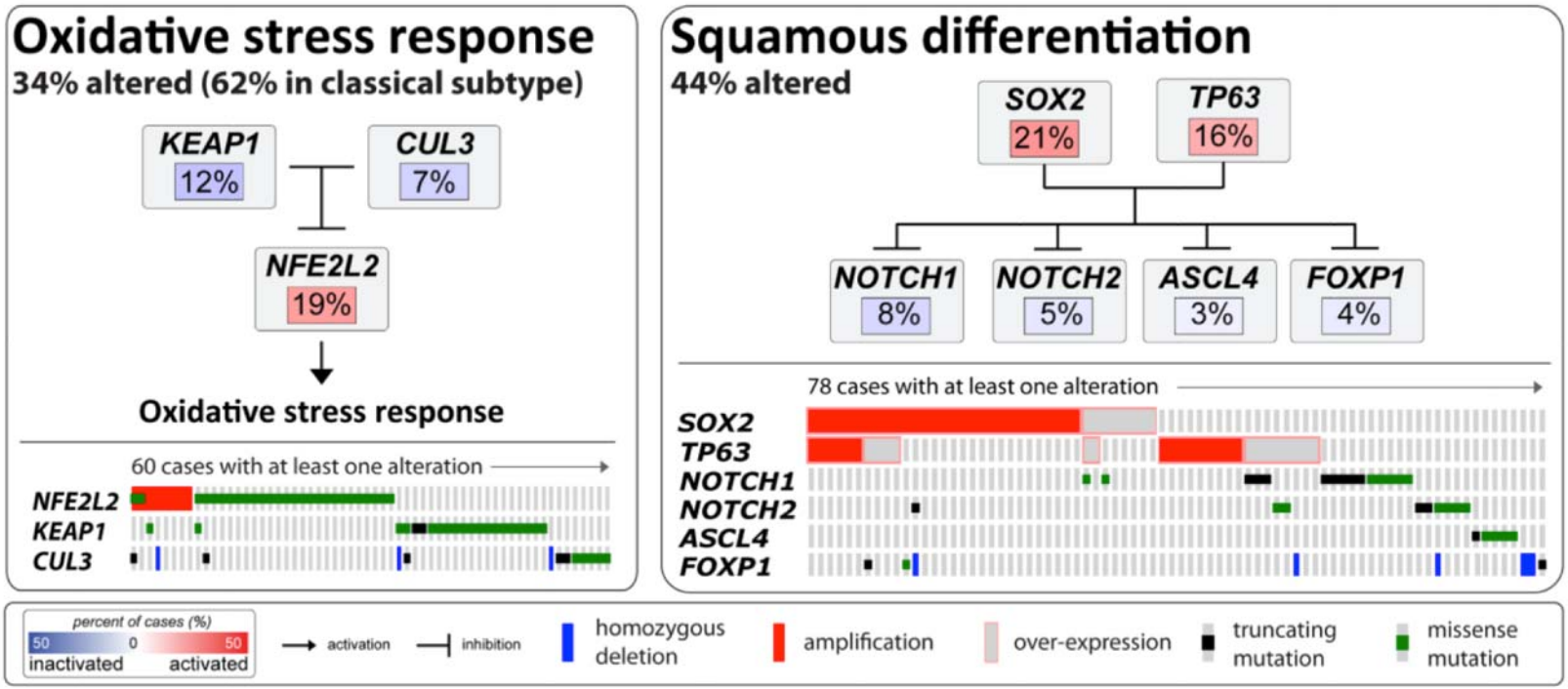
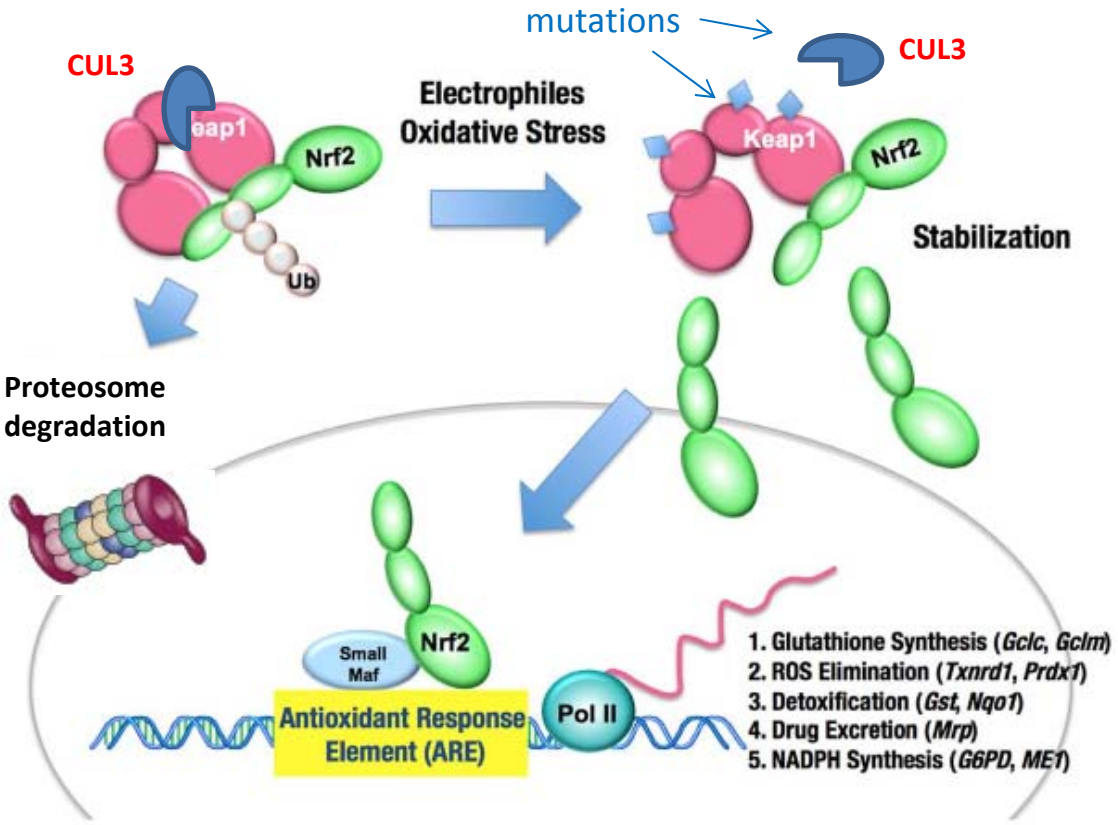
Somatically altered pathways in Squamous Cell Carcinomas



The Cancer Genome Atlas Network, Nature 2012 489: 519

NRF2 pathway: enhancing survival under oxidative stress



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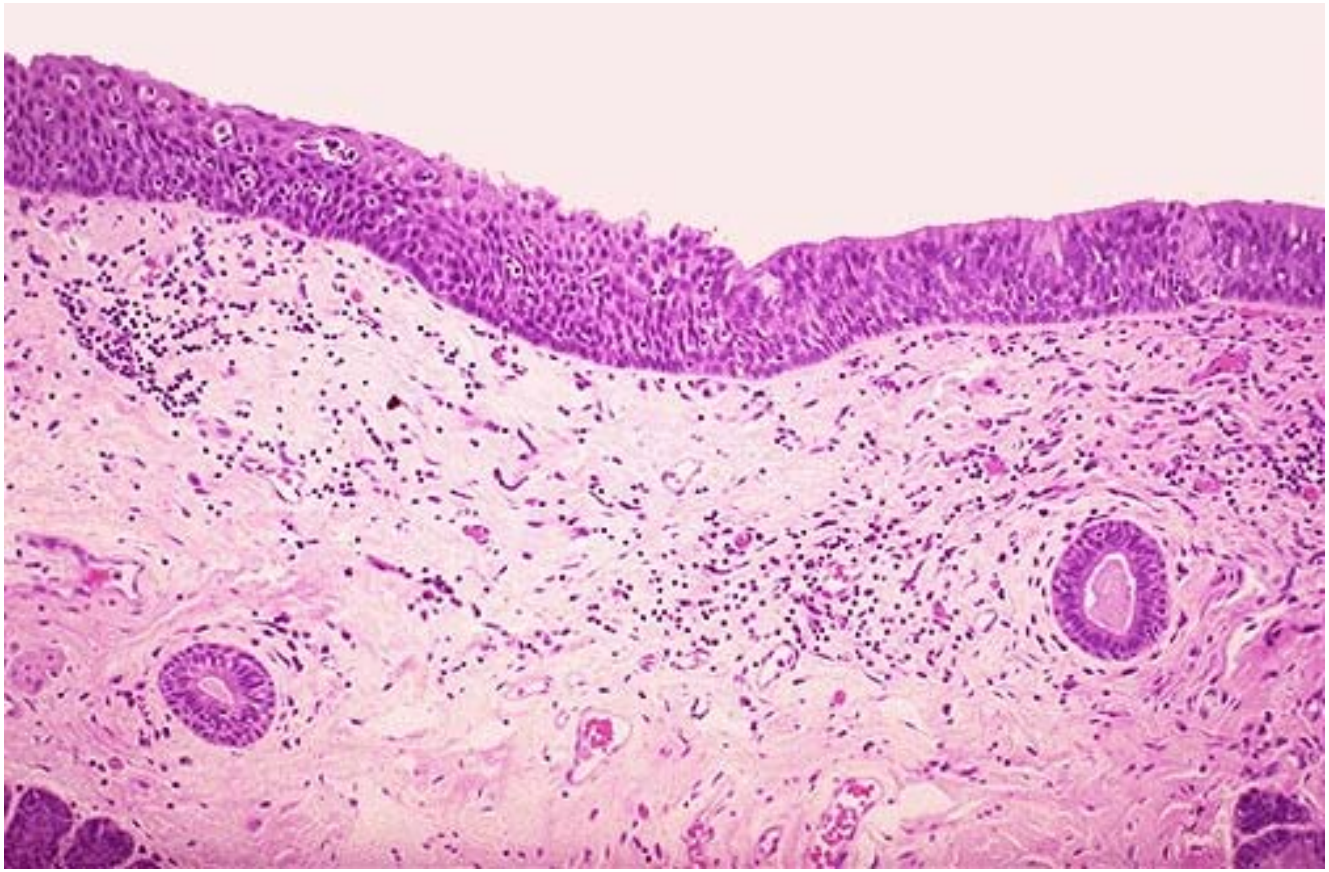
Tissue remodelling: Squamous metaplasia



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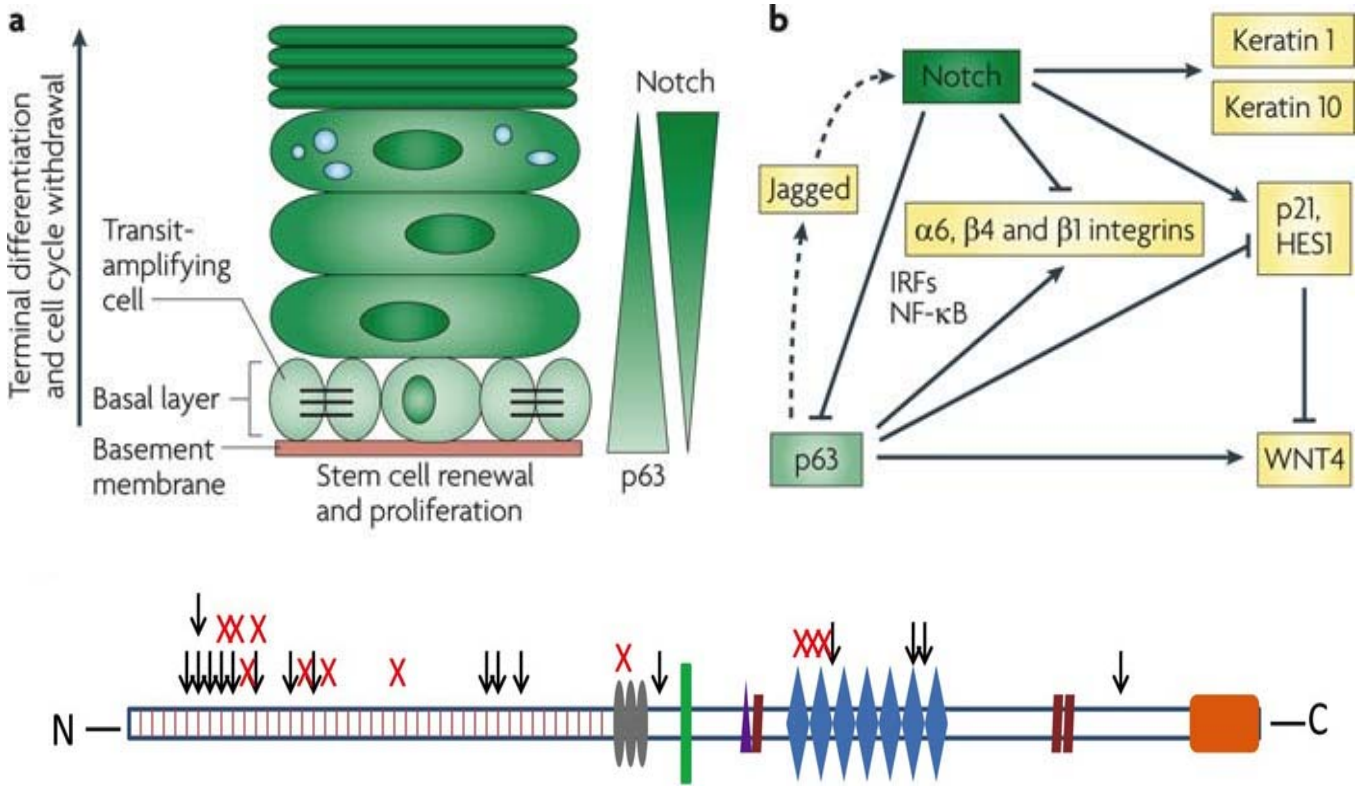
NOTCH: promoting squamous differentiation



Exome Sequencing of Head and Neck Squamous Cell Carcinoma Reveals Inactivating Mutations in NOTCH1. Agarawal, Myers et al., Science, 2011

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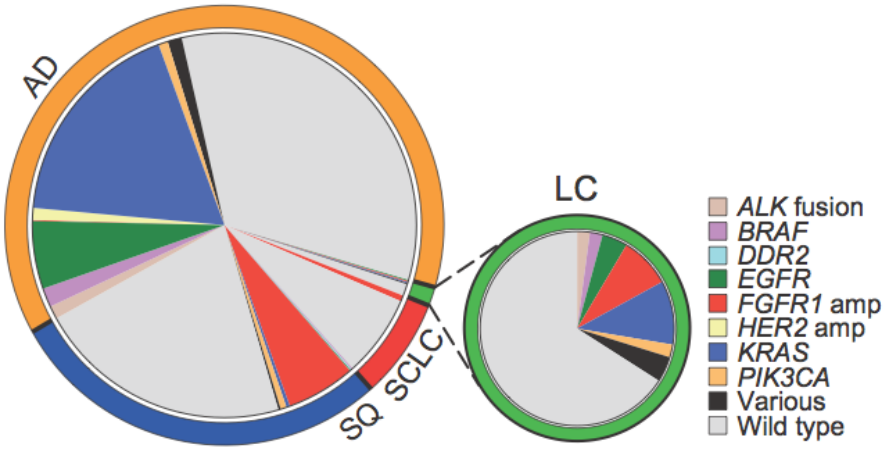
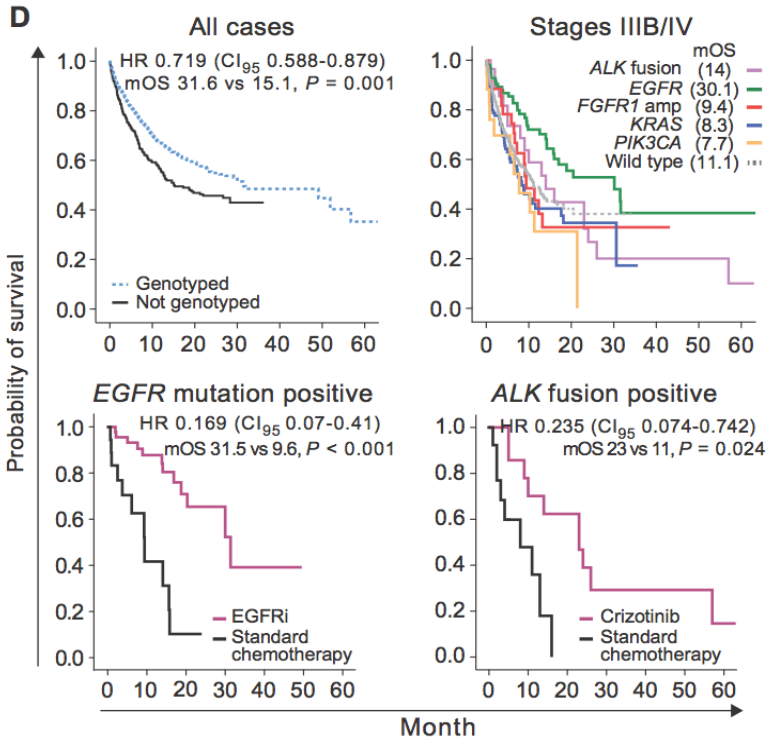
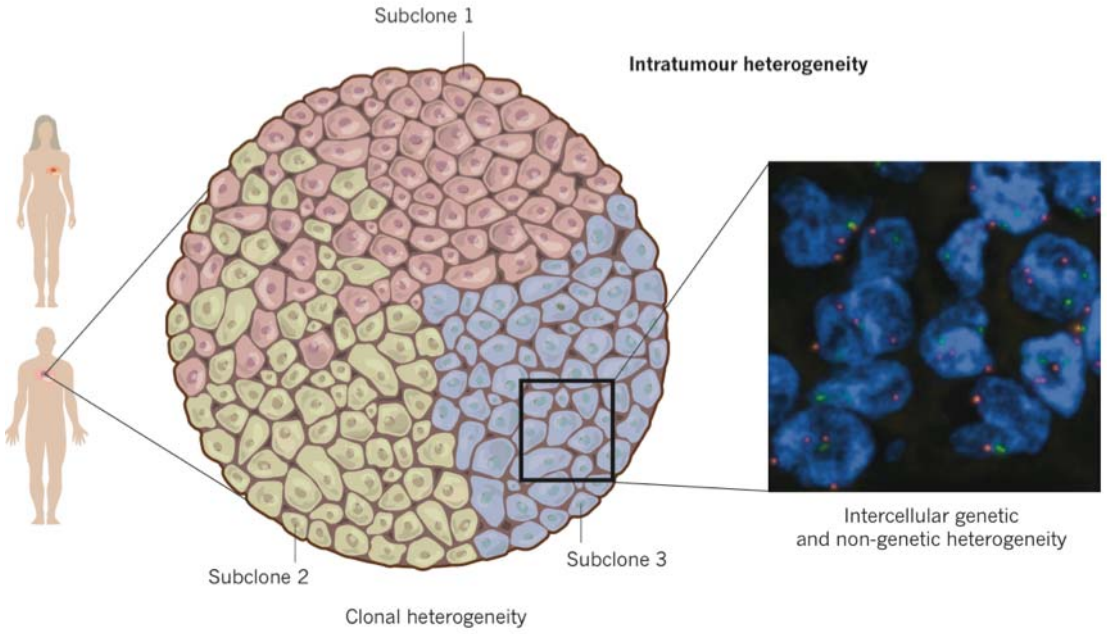
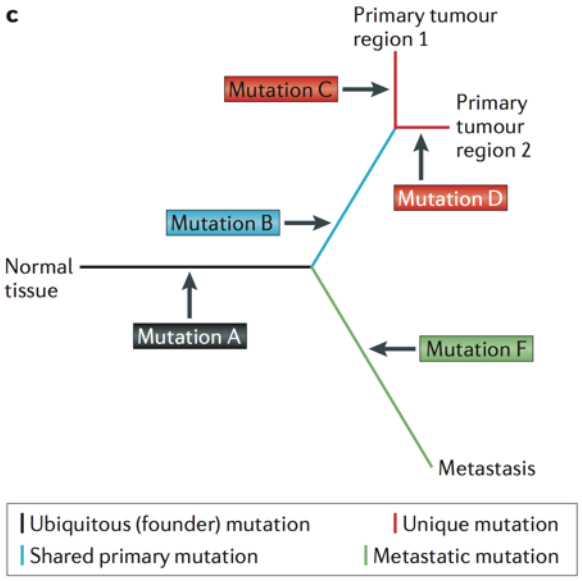
Clinically relevant genome alterations





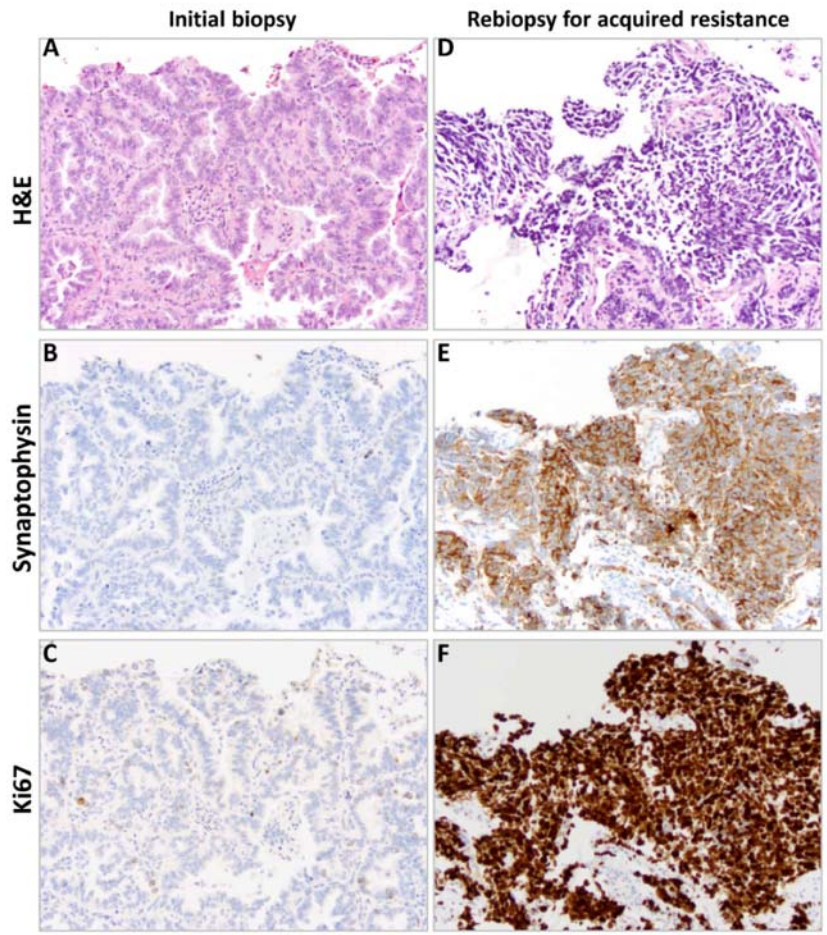
Tumour heterogeneity





Burell et al. Nature 2013 501:338

Histomolecular plasticity



Initial diagnosis:
Adenocarcinoma,
EGFR mutation (R858L)

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

Resistance mutations:
None
EGFR T790M
MET ampl

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Off-context gene expression: a new epigenetic paradigm

RESEARCH ARTICLE

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 Reyniès,[4] David G. Beer,[5] Jean-François Timsit,[1,2] Christian Brambilla,[1,2] Elisabeth Brambilla,[1,2] Saadi Khochbin[1]*

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.

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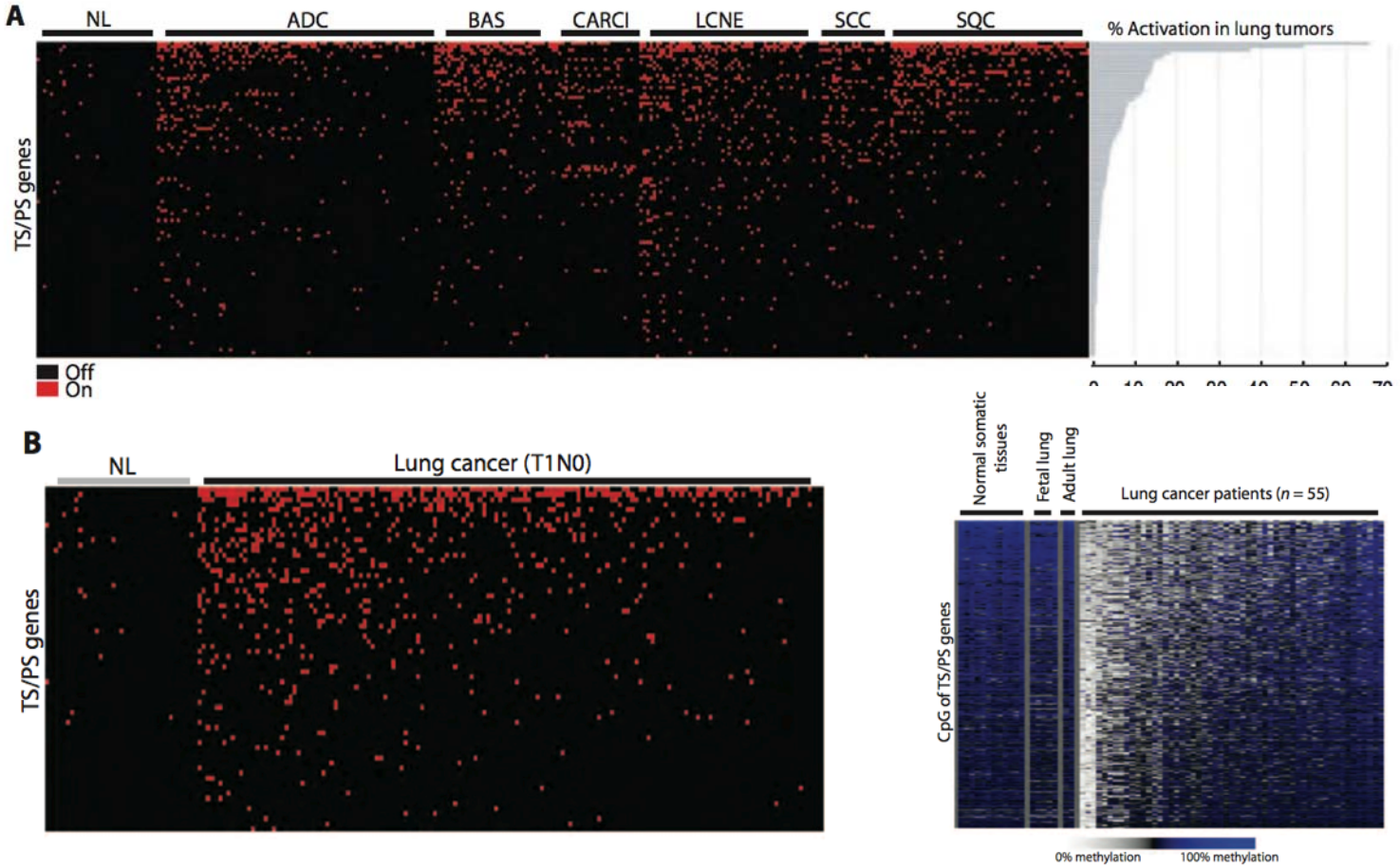
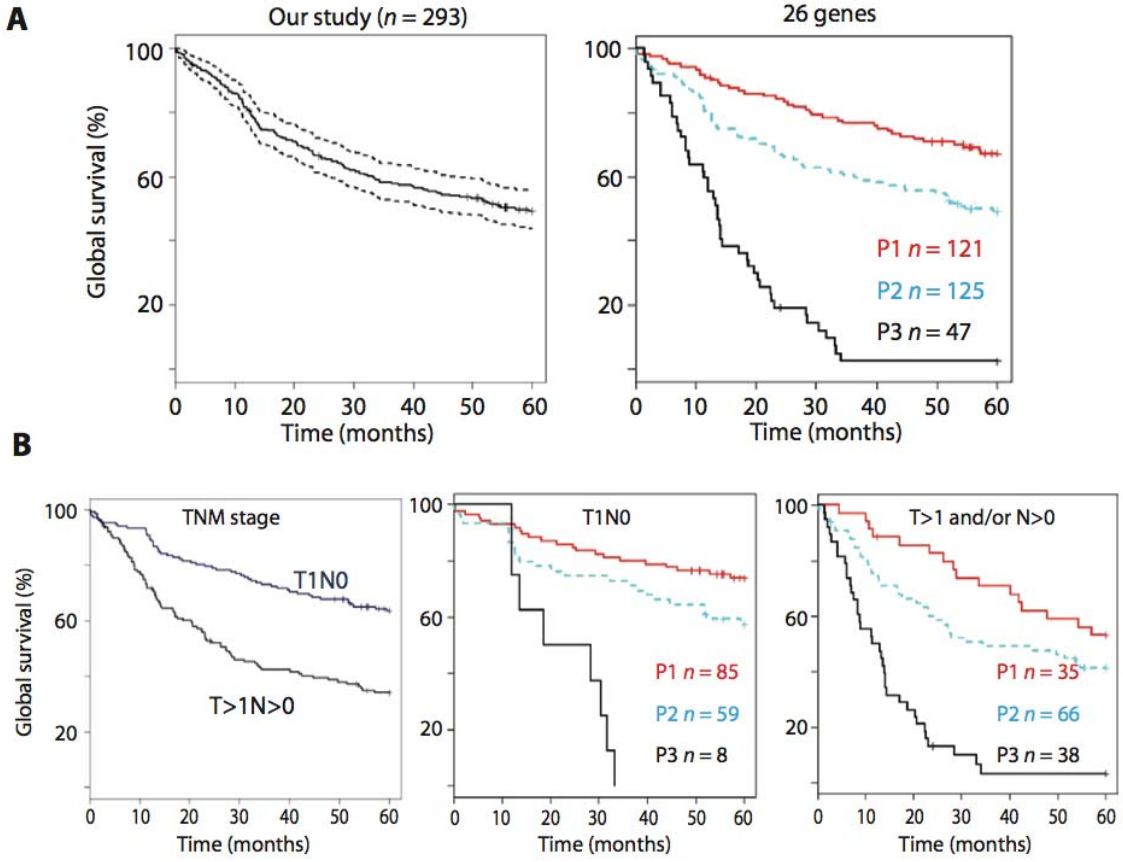
Testis and Placenta-specific (TS/PS) genes in Lung Cancer



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:

pierre.hainaut@ujf-grenoble.fr

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