ASU Complex Adaptive Systems
ARIZONA STATE UNIVERSITY

BIO 302:
MARCH 4 & 6, 2014

WEEK 8 LECTURE 1:
CANCER AS A COMPLEX ADAPTIVE SYSTEM

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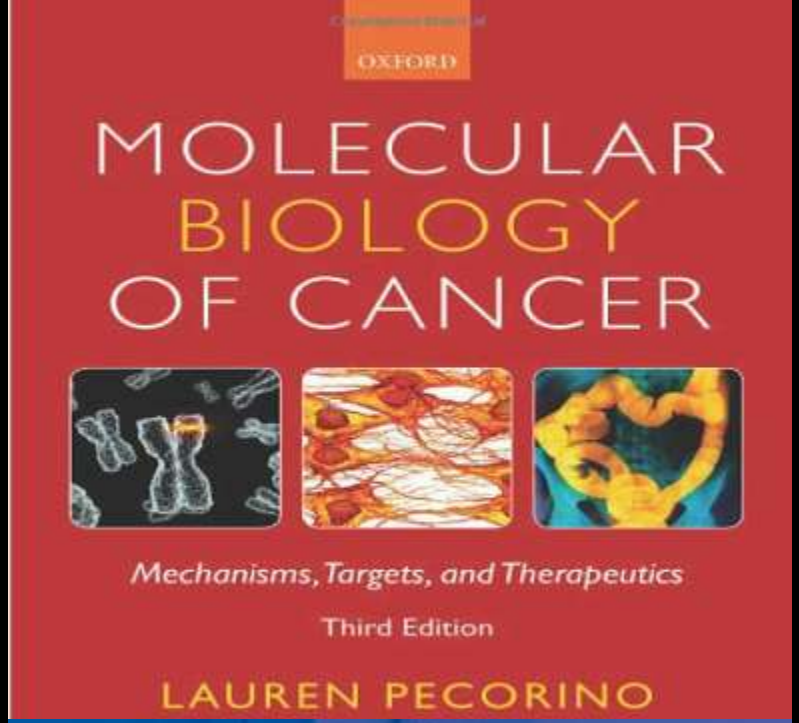
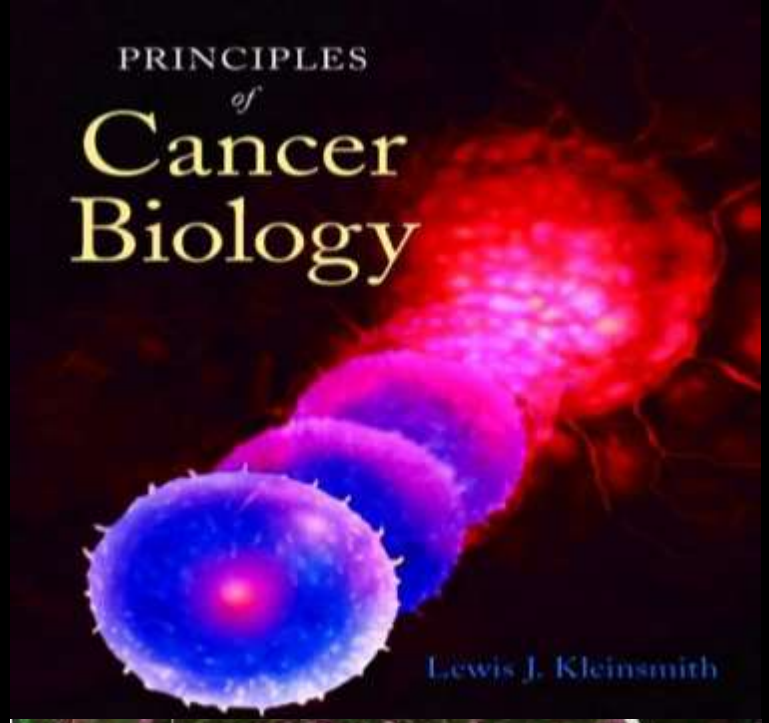
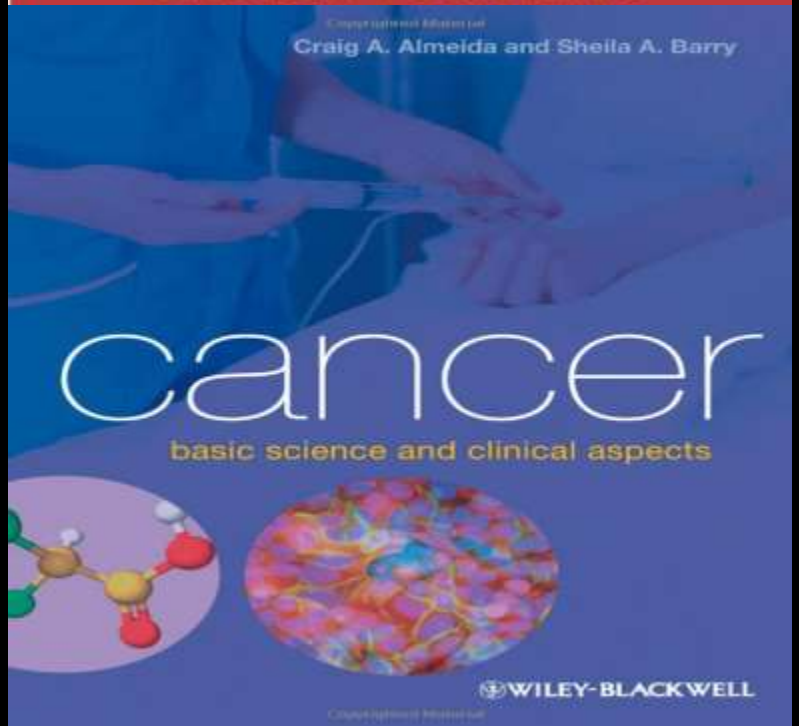
Cancer as a Complex Adaptive System (CAS)

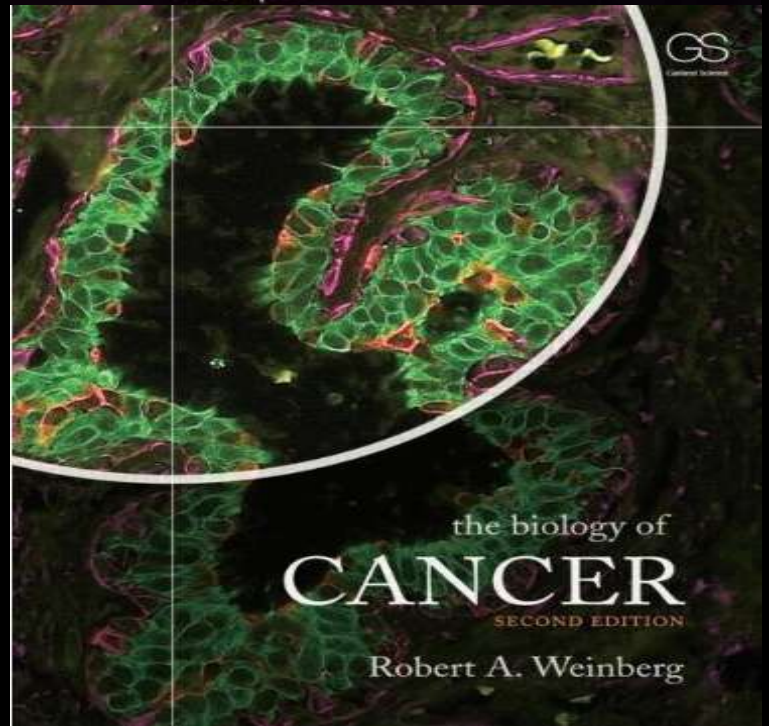
Lecture 1

- genotoxic insult(s), mutations and genome instability in cancer (drivers)
- the progressive evolution of phenotypic heterogeneity in different clones within tumors
- selection pressures on clonal fitness, adaptation and the evolution of the metastatic process
- tumor progression as a complex co-evolutionary interaction between dynamic changes in tumor behavior and host responses


OXFORD
MOLECULAR BIOLOGY OF CANCER
Mechanisms, Targets, and Therapeutics
Third Edition
LAUREN PECORINO


PRINCIPLES of Cancer Biology
Lewis J. Kleinsmith


Craig A. Almeida and Sheila A. Barry
cancer
basic science and clinical aspects
WILEY-BLACKWELL


GS
the biology of
CANCER
SECOND EDITION
Robert A. Weinberg

Genotoxic Insult(s), Mutations and Genome Instability: The Drivers of Tumor Initiation and Progression

The Lengthy Timeframes for Progression in Different Human Cancers

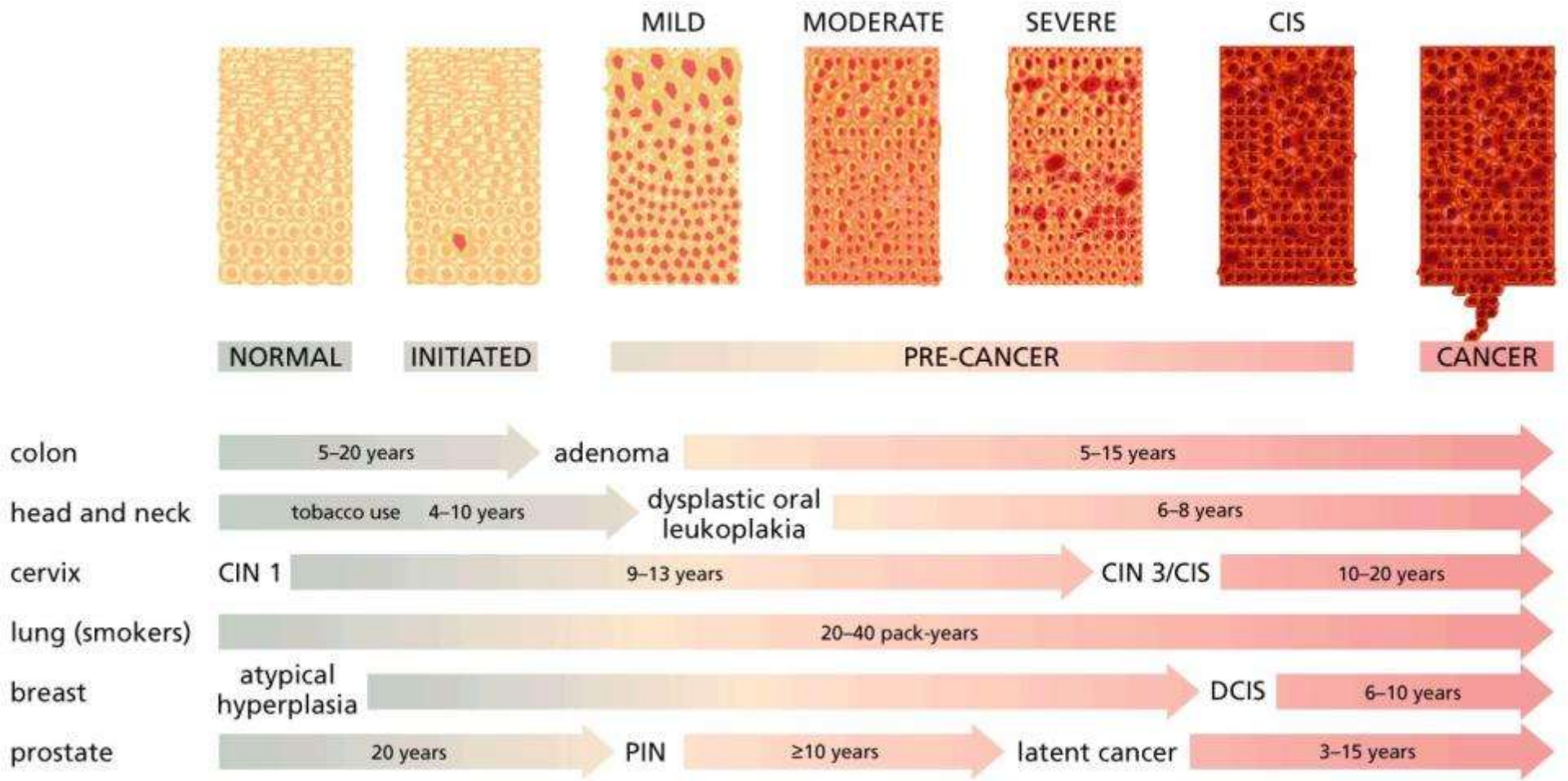
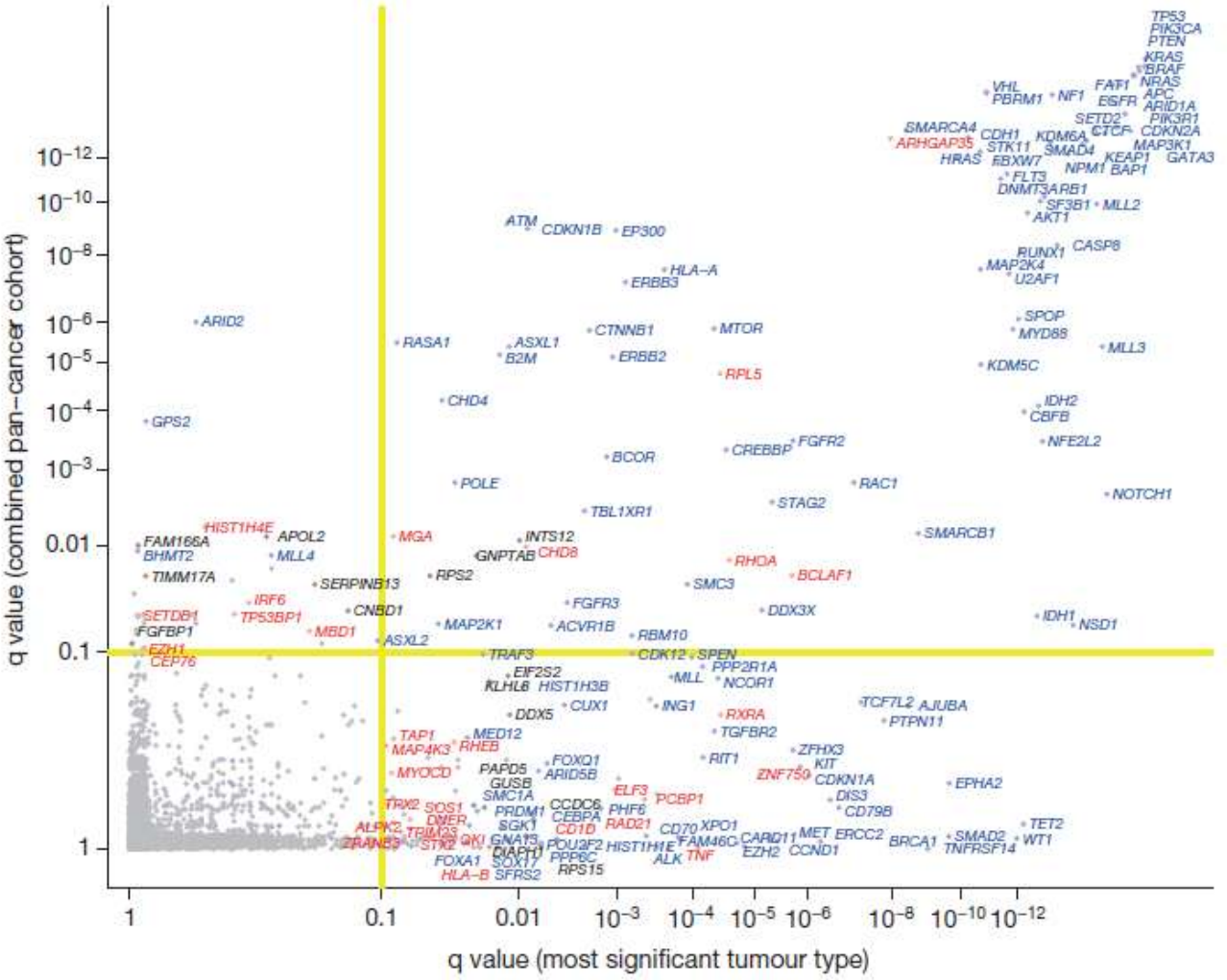


Figure 11.8a The Biology of Cancer (© Garland Science 2014)

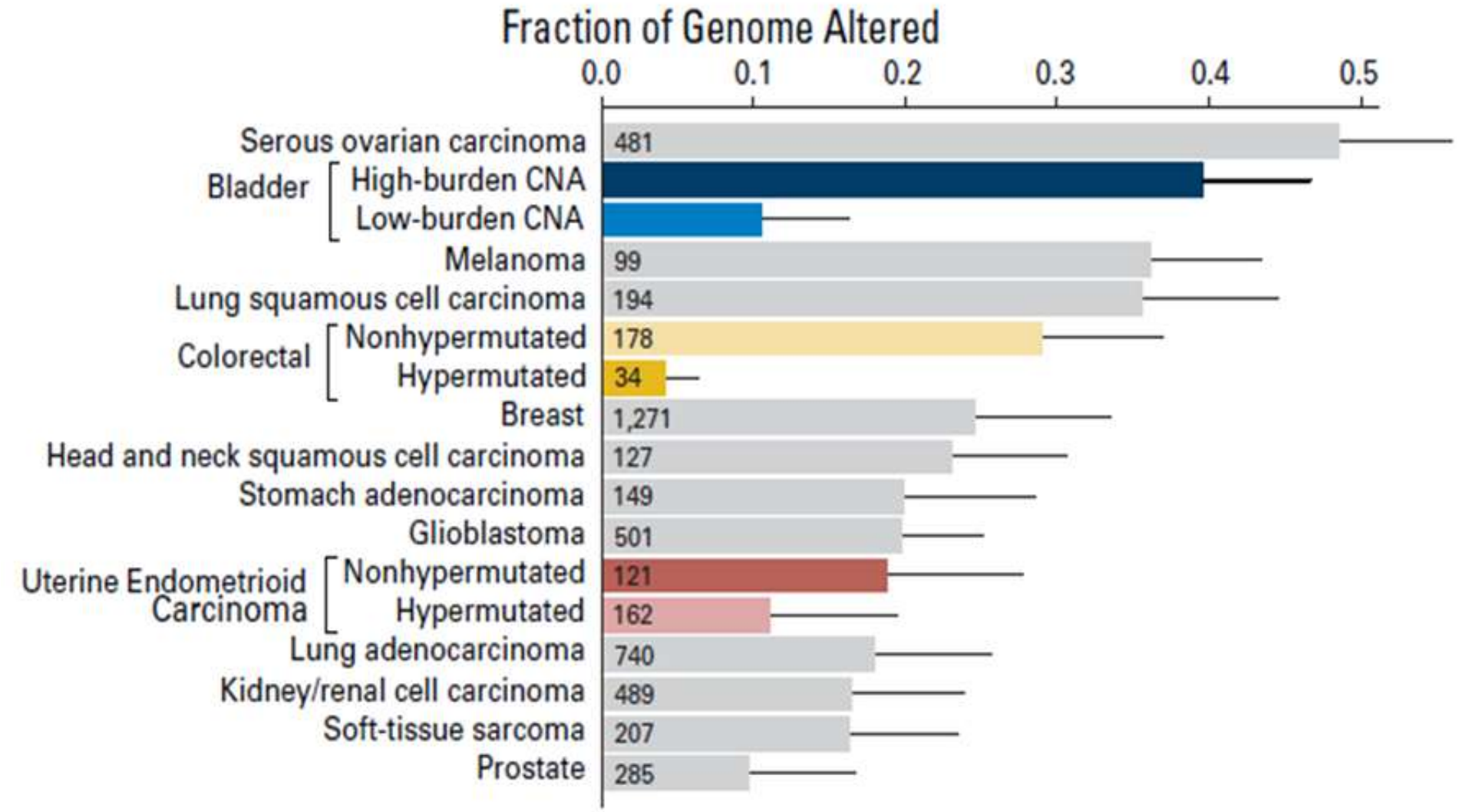
Cancer Genomes: A Formidably Complex Catalog of Genomic Changes and Molecular Network Disruptions

Cancer Genes Identified in 4,742 Human Tumors



M. S. Lawrence et al. (2014) Nature 505, 495

Copy Number Alteration in 5135 Tumors from 14 Solid Tumor Types



From: G. Iyer et al. (2013) JCO 31, 3133

Genotoxic Insult(s), Accumulation of Mutations and Progressive Genome Instability

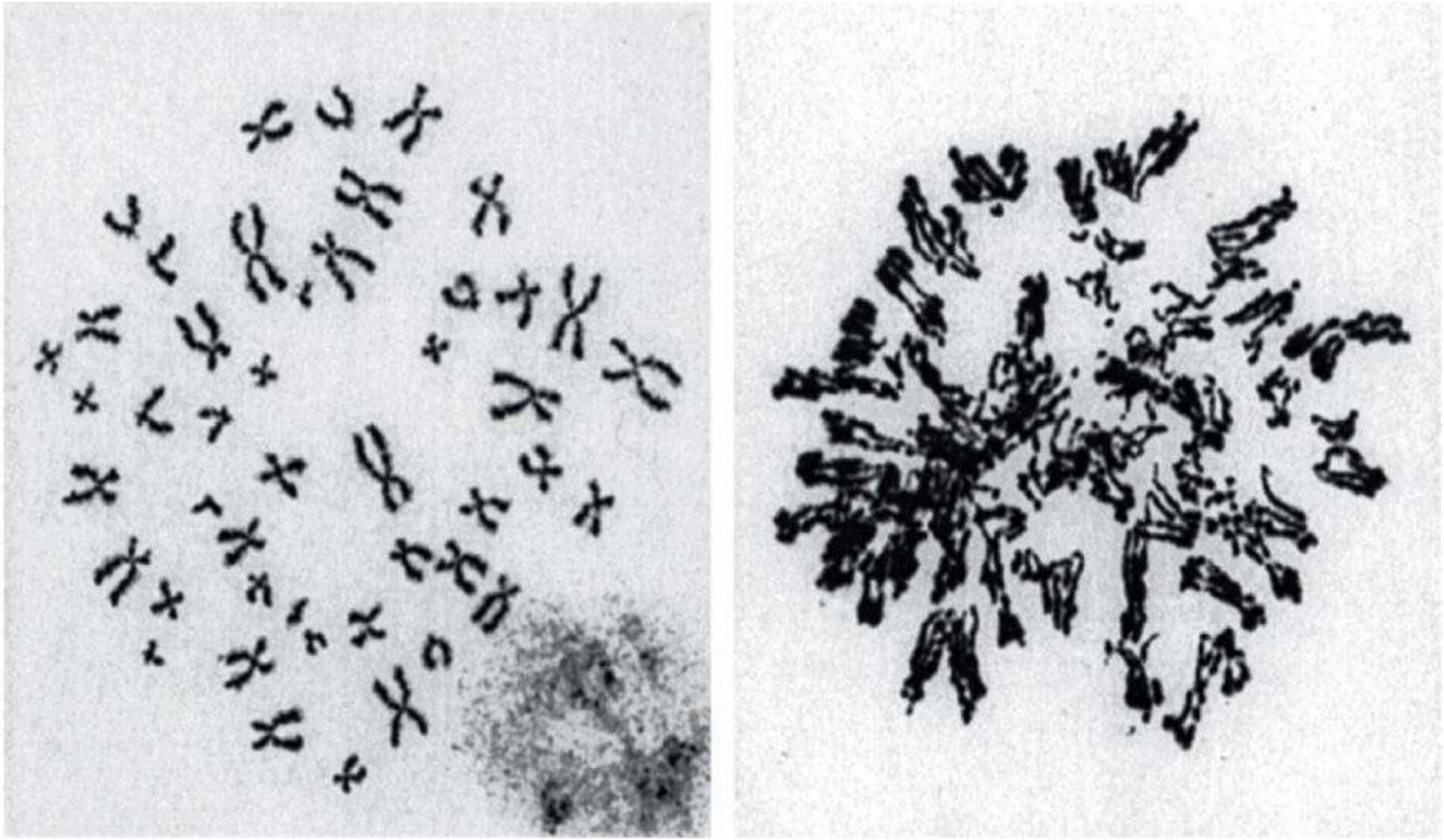
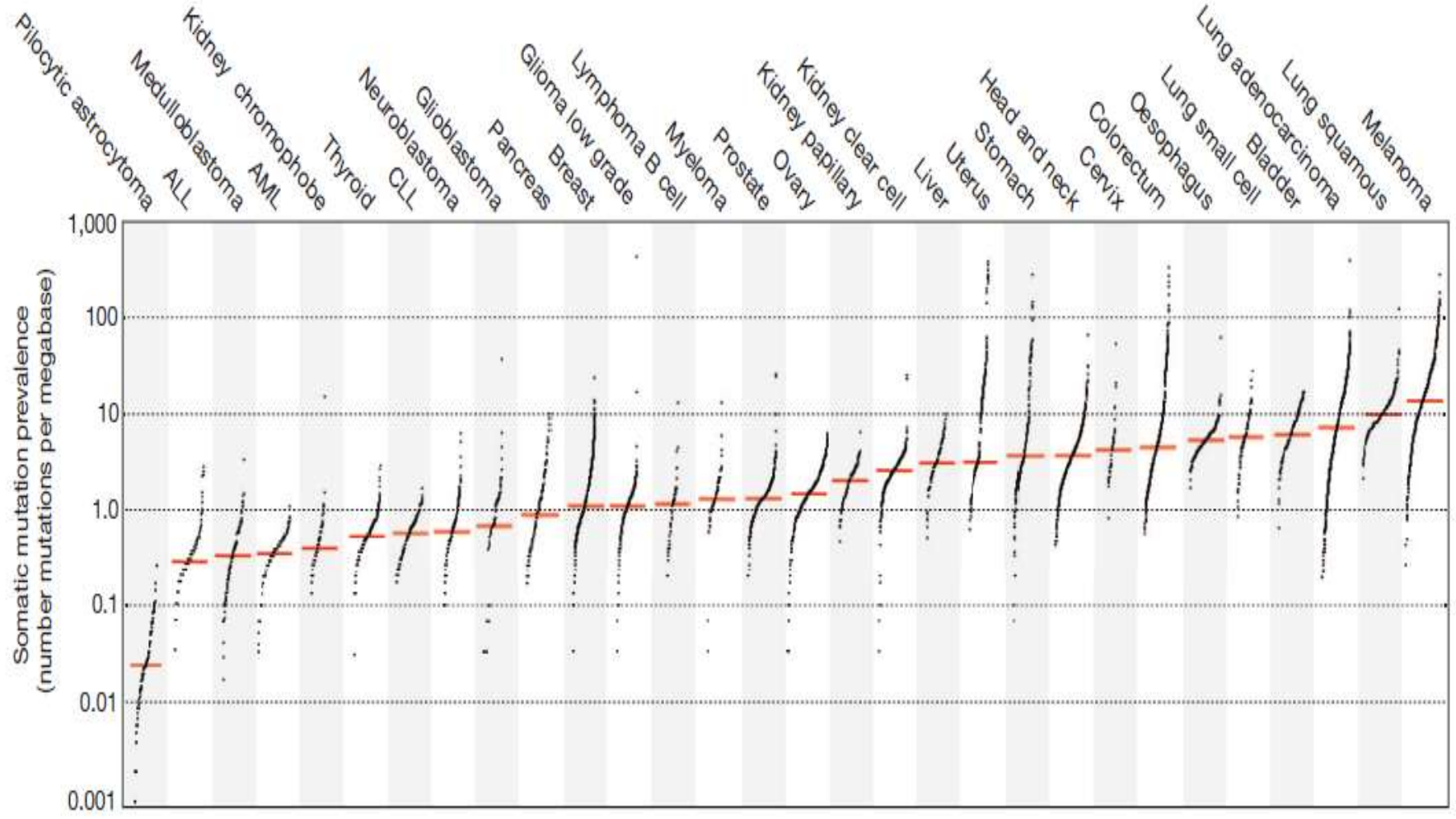


Figure 8.5a The Biology of Cancer (© Garland Science 2014)

The Prevalence of Somatic Mutations Across Human Cancer Types

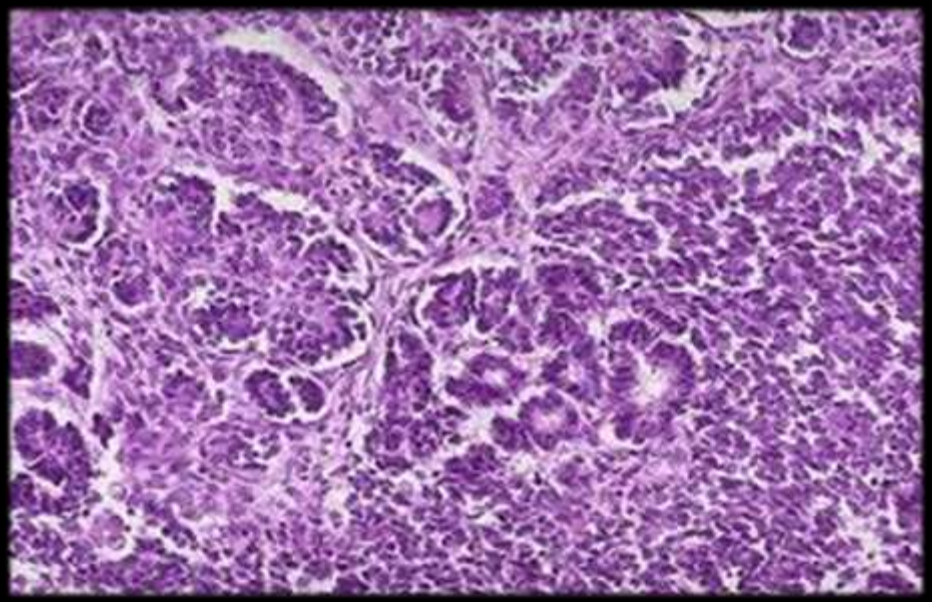


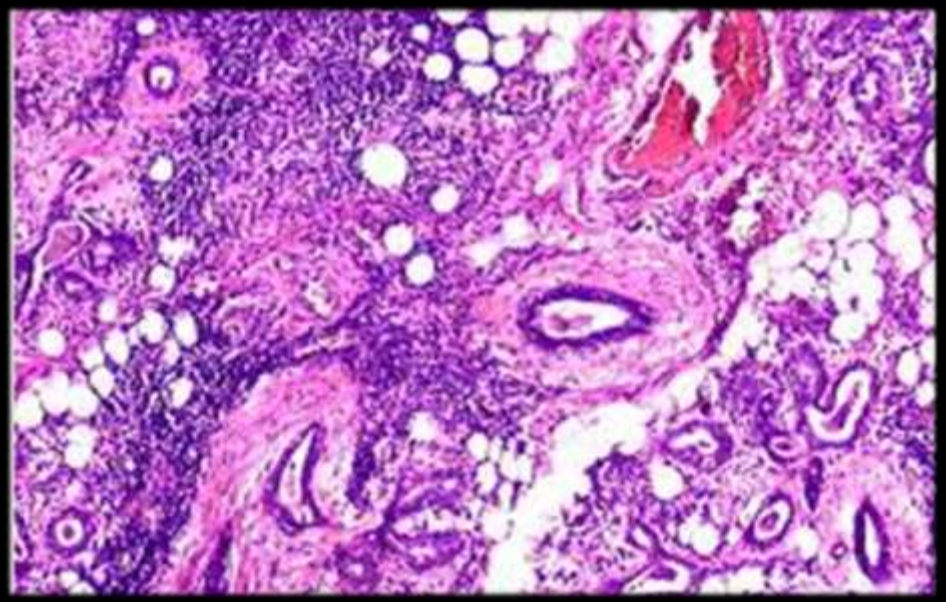
From: L. B. Alexandrove et al. (2013) Nature doi:10.1038/nature12477

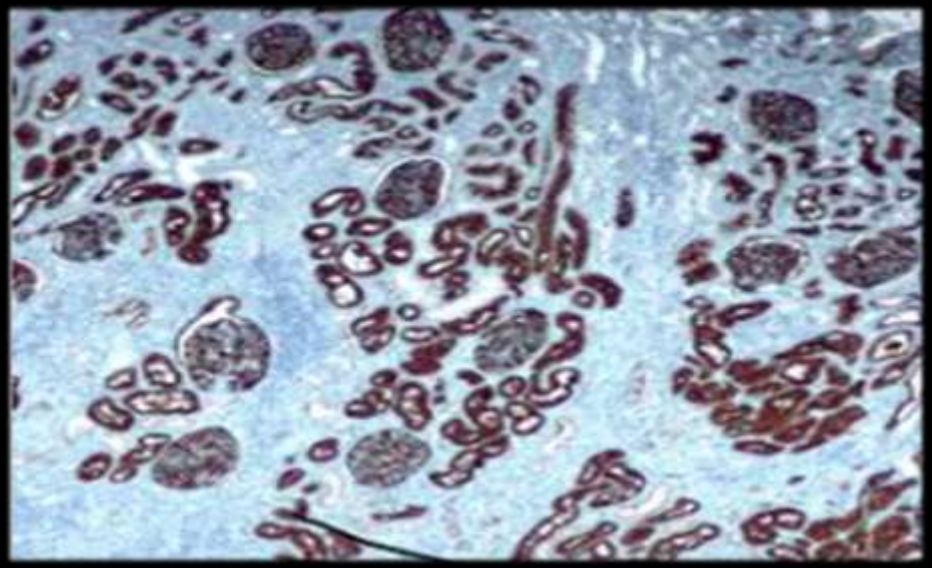
Somatic Mutation Prevalence in Different Cancers
Nature (2013) doi.1038/nature 12477

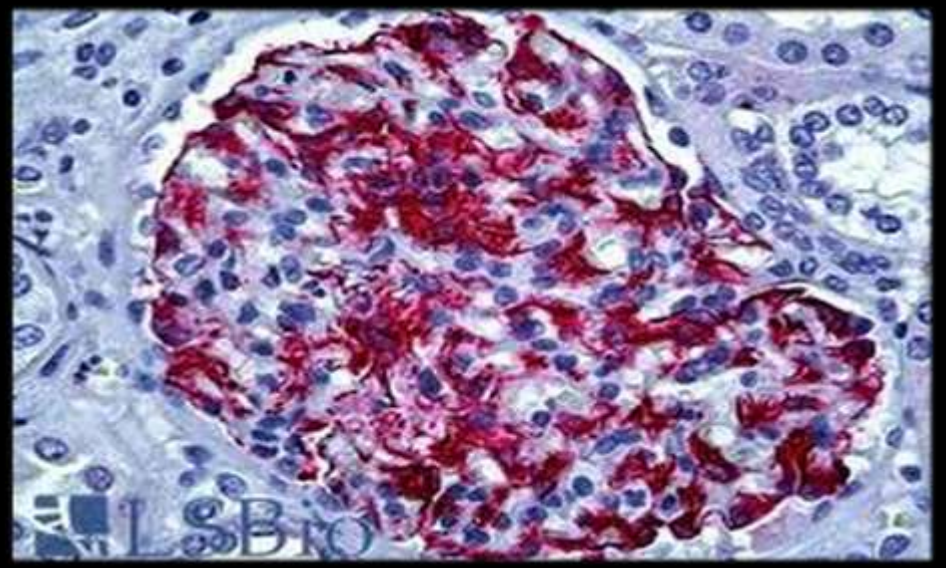
- survey of 5 million mutations from over 7000 cancer cases from 30 different cancer types
- highly variable mutation load
  - 0.001 per DNA megabase (Mb) to 400 per Mb
- childhood cancers carry fewest mutations
- cancers related to chronic mutagenic exposure exhibit highest mutation burden
  - lung cancer (tobacco expose), malignant melanoma (UV exposure)

Histopathologic Classification of Disease





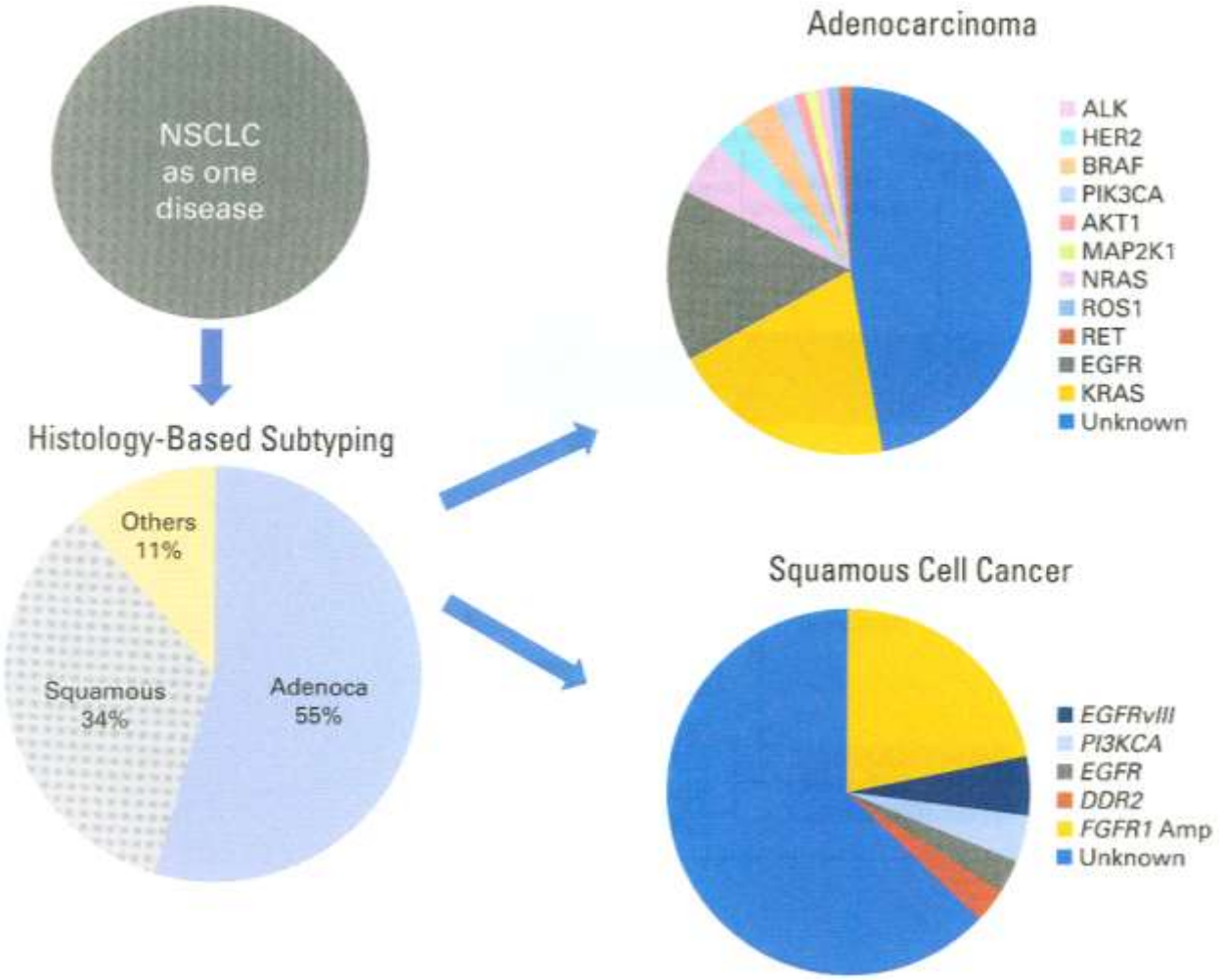




The Shift from Cancer Diagnosis by Histopathology to Molecular Profiling of Perturbed Gene Networks and Altered Molecular Signaling Pathways

Different Tumor Subtypes Arise in the Same Cell Lineage via Different Genomic Perturbations and Alterations in Molecular Signaling Networks

The Evolution of the Classification of Non-Small Cell Lung Cancer (NSCLC)

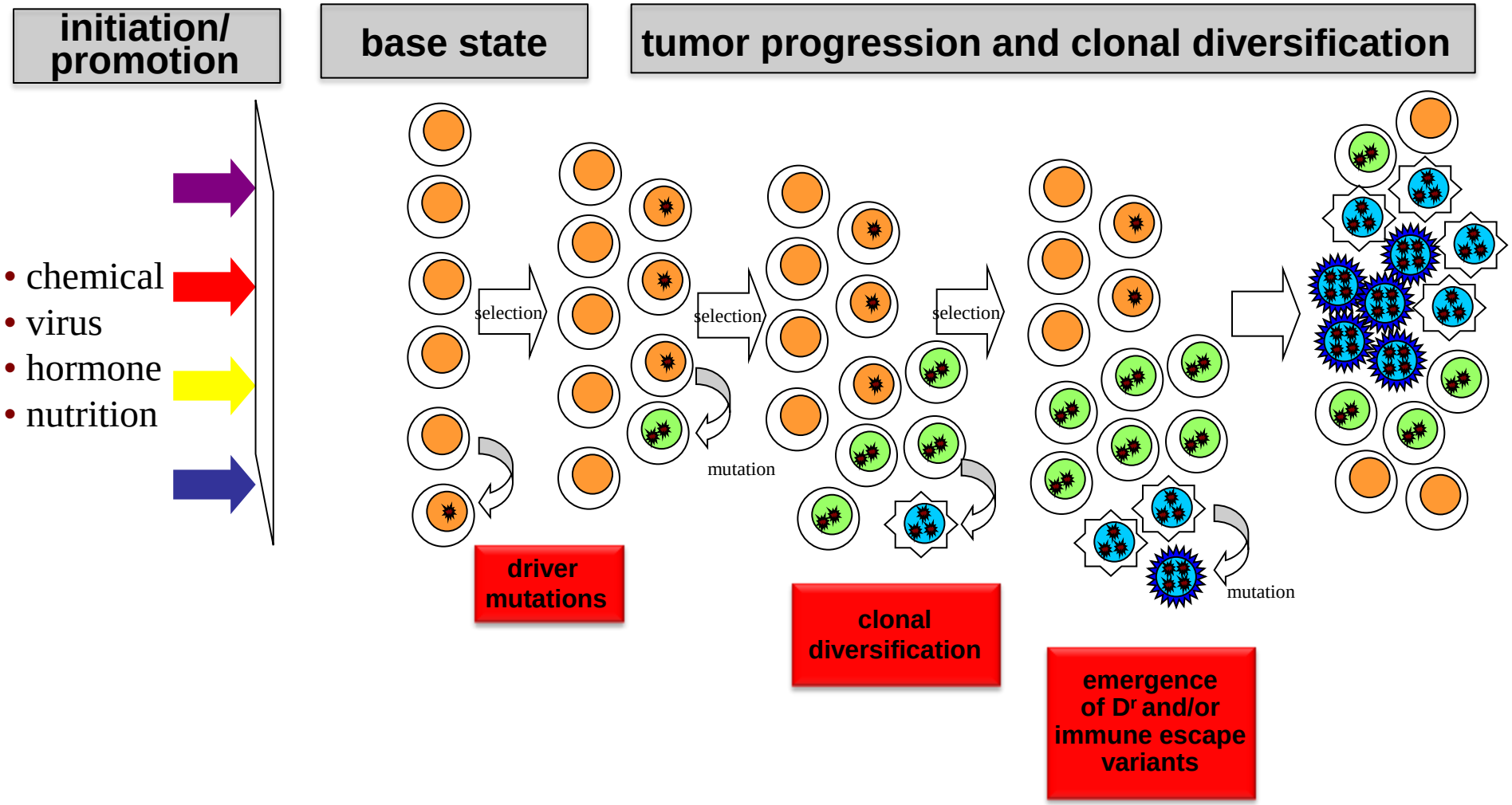


From: T. Li et al. (2013) JCO 31, 1039

Emergence of Different Tumor Cell Clones and Subclones with Tumor Progression

continued accumulation of genomic alterations generates cancer cell clones and subclones with different genomic alterations and phenotypes (heterogeneity)

Emergence of New Clones With Different Phenotypes (Heterogeneity) During Tumor Progression



Adapted from A. Barker and K. Buetow

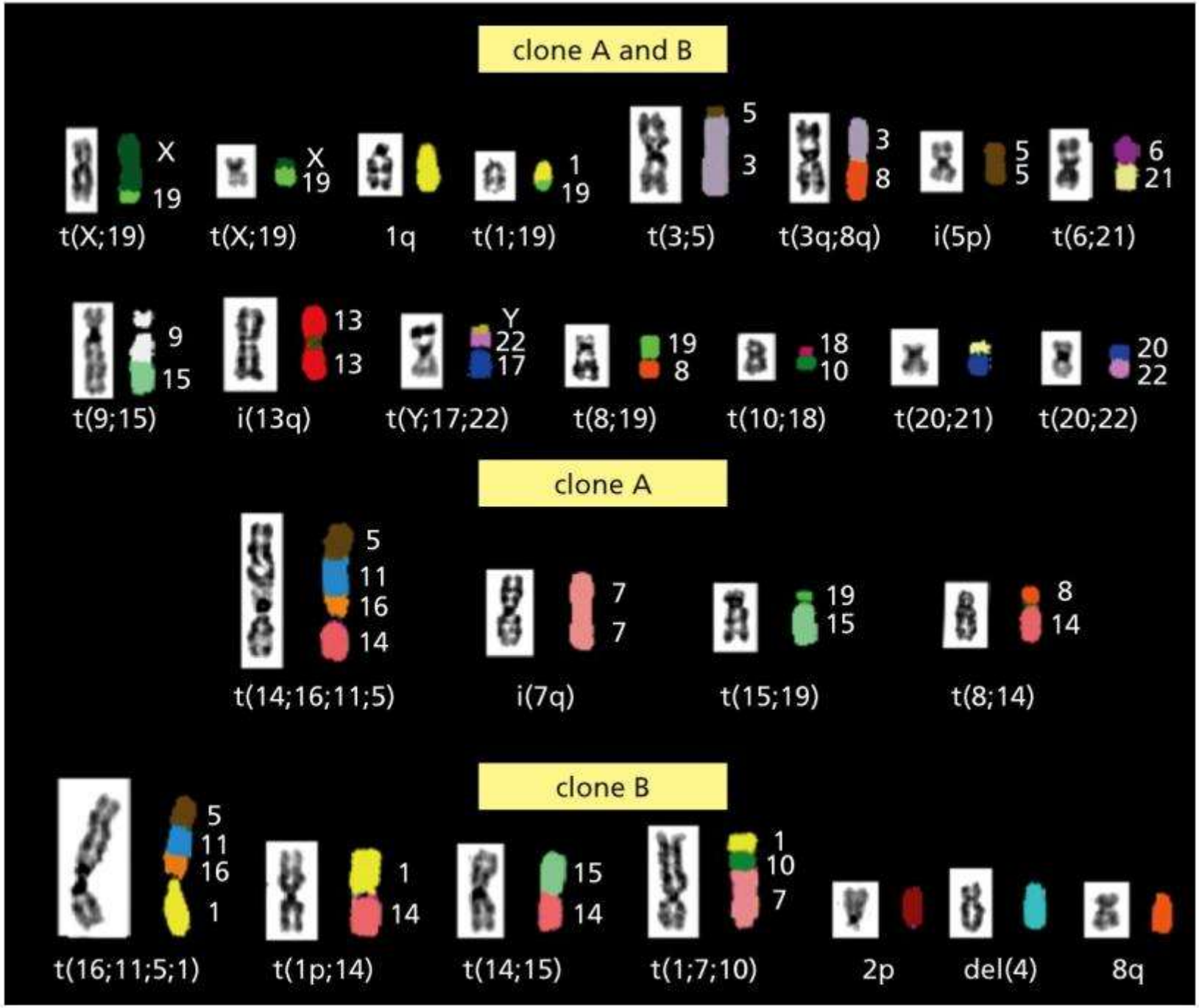
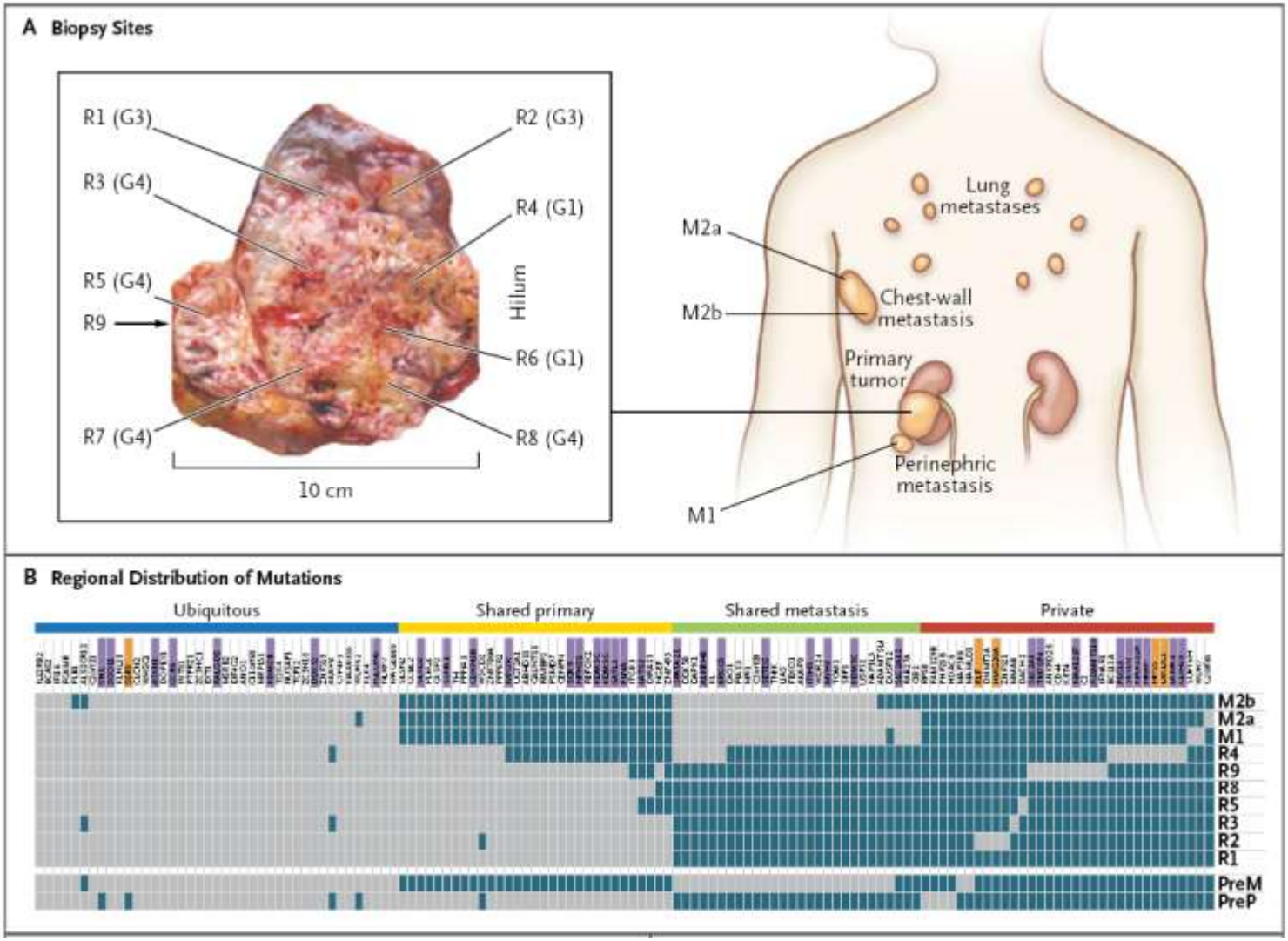


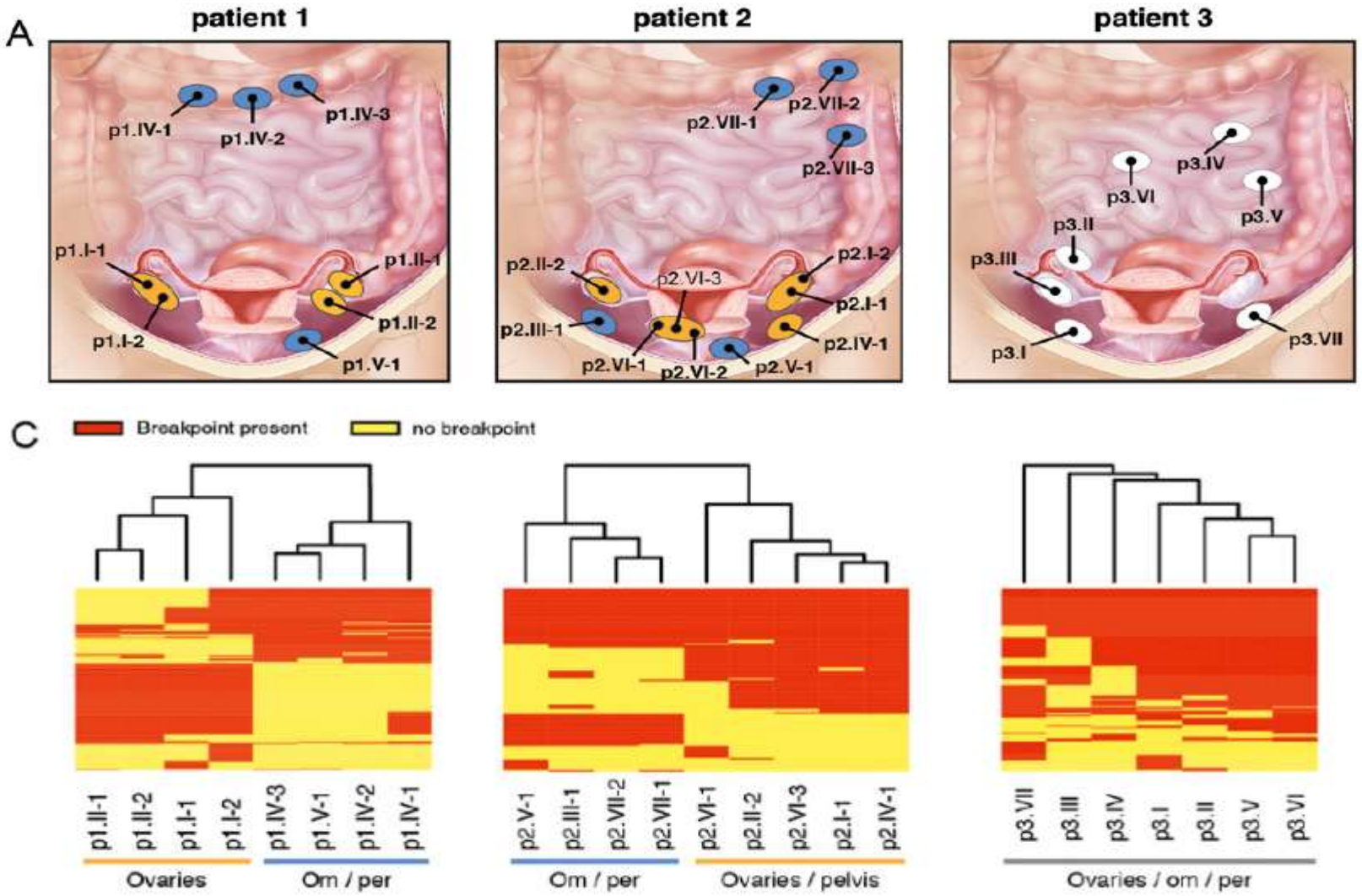
Figure 10.40 The Biology of Cancer (© Garland Science 2014)

Intratumor Genetic Heterogeneity in Multiple Regions of Primary Clear Cell Tumor and Three Metastases (Perinephric and Chest Wall) in RCC



From: M. Gerlinger et al. (2012) NEJM 366, 883

Intra-Lesional Variation in Somatic Gene Rearrangements in Three Treatment-Naïve Stage III/IV Epithelial Ovarian Cancer Patients



Adapted From: M. Hoogstraat et al. (2014) Genome Res. 24, 200

Clonal Heterogeneity in Cancer

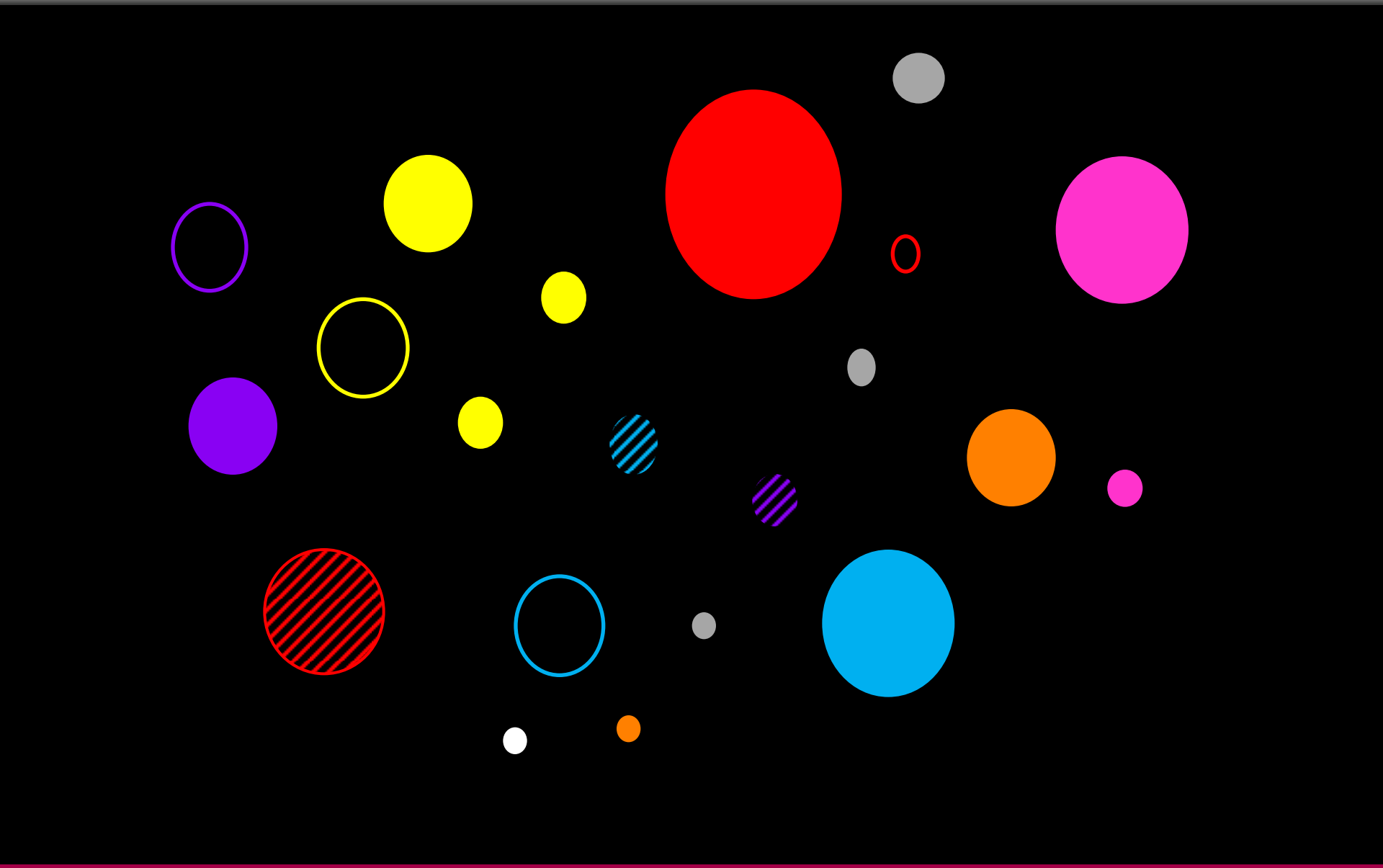
- intratumoral (same patient)
  - ‘zonal’ heterogeneity in primary tumor
  - presence of different clones in separate metastases
- inter-patient variation (same subtype of tumor in different patients)

Genome Instability in Cancer

- continued accumulation of genomic alterations and generation of clones and subclones with different genomic alterations and phenotypes

CLONAL HETEROGENEITY IN CANCER: THE LARGEST OBSTACLE TO SUCCESSFUL THERAPY

Tumor Cell Heterogeneity:
The Omnipresent and Greatest Challenge in Cancer Therapy



Tumor Cell Heterogeneity:
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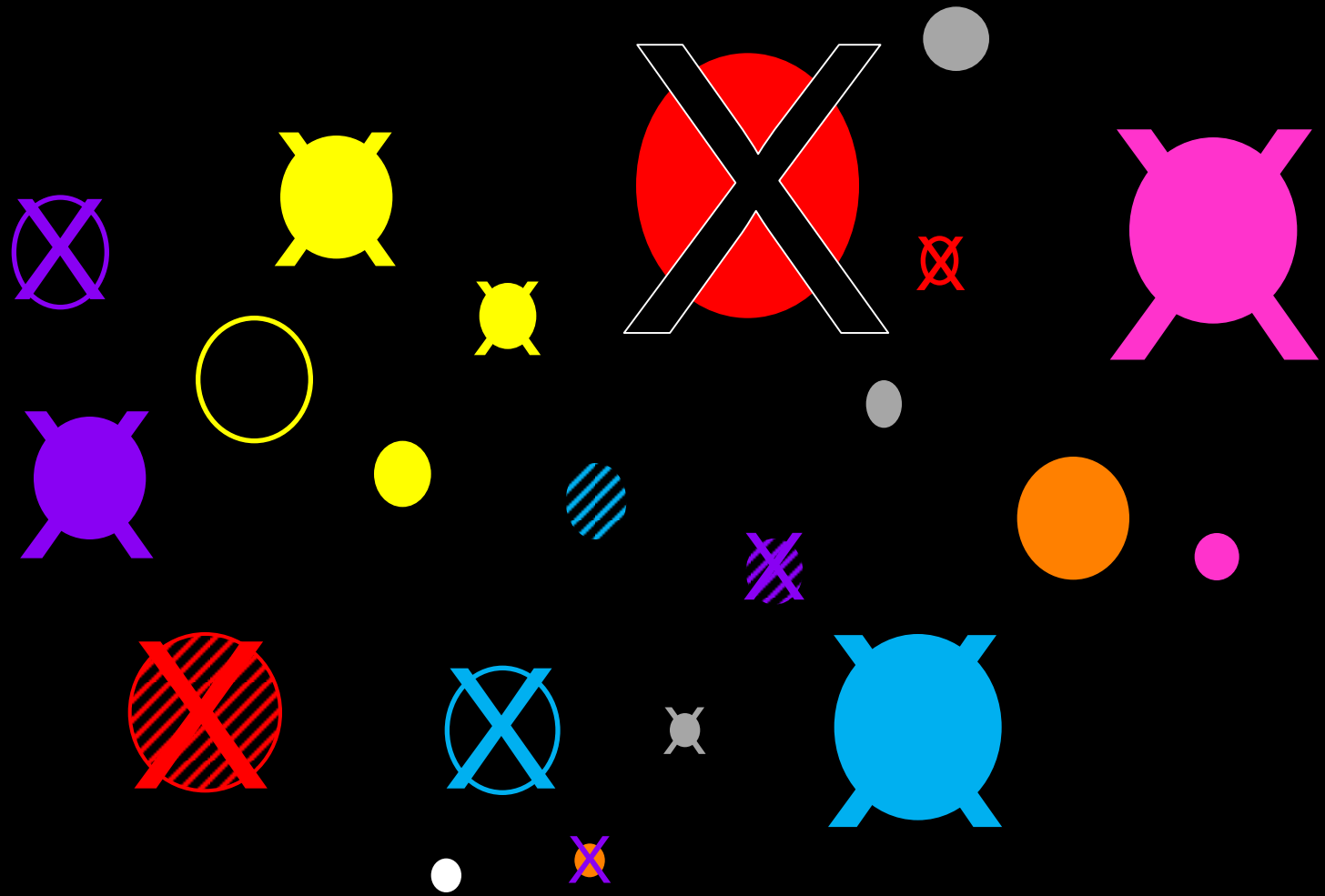
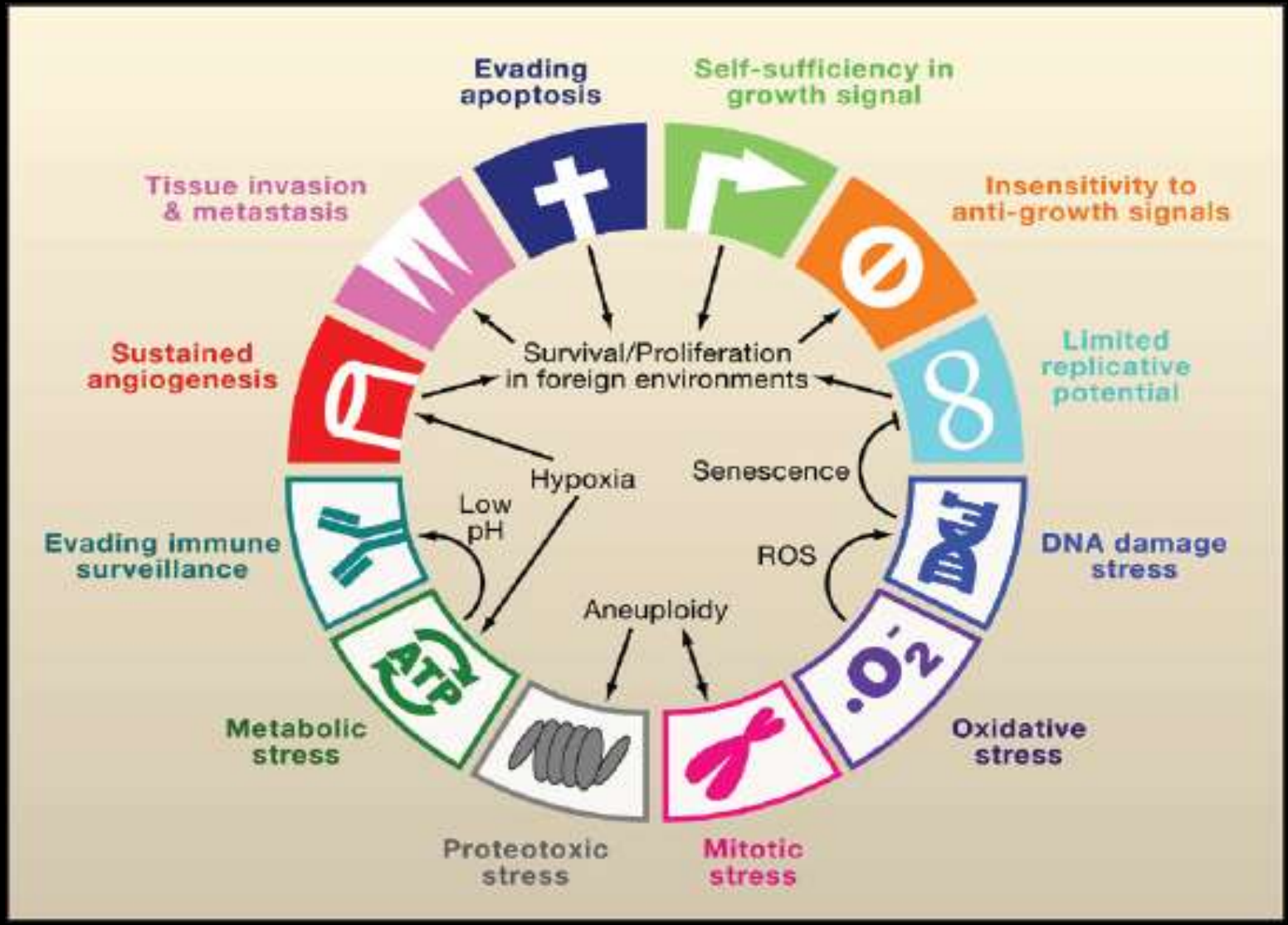


More details Lecture Week II

Cancer as an Evolutionary Process
Clonal Selection (Fitness): Robustness, Adaption and Evolvability

- continuous acquisition of heritable genetic variation in individual tumor cells and generation of clonal progeny
- action of natural selection on the resulting phenotypes (selection and fitness)
- cumulative acquisition and selection of traits that confer autonomous unlimited replication, high survival and eventual progression to invasion and disseminated metastasis

The Complex Phenotypes for Cancer Cell Survival and Metastasis



From: J. Luo et al. (2009) Cell 136, 823

Genome Instability in Cancer

- tumor initiation and progression via accumulation of mutations and other genomic alterations that confer selective growth advantage
- driver mutations
- passenger mutations

Making Sense of Cancer Genomic Data

driver mutations

- oncogenes
- suppressor genes

Cancer

Oncogene Activation

- overdrive of positive growth signals

Tumor Suppressor Gene Inactivation

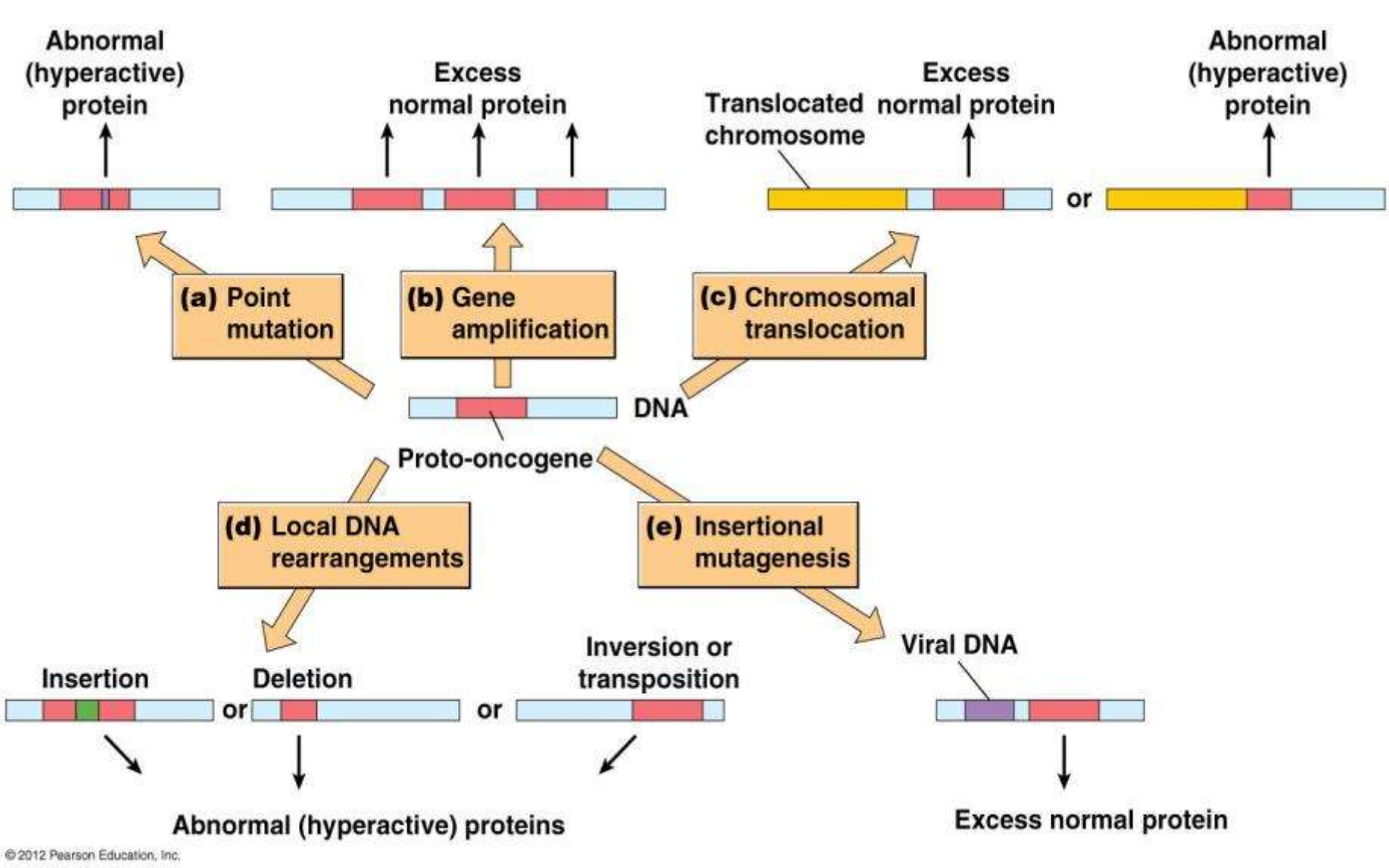
- escape from growth control signals for natural tissue homeostasis

Cancer: Unchecked Proliferation

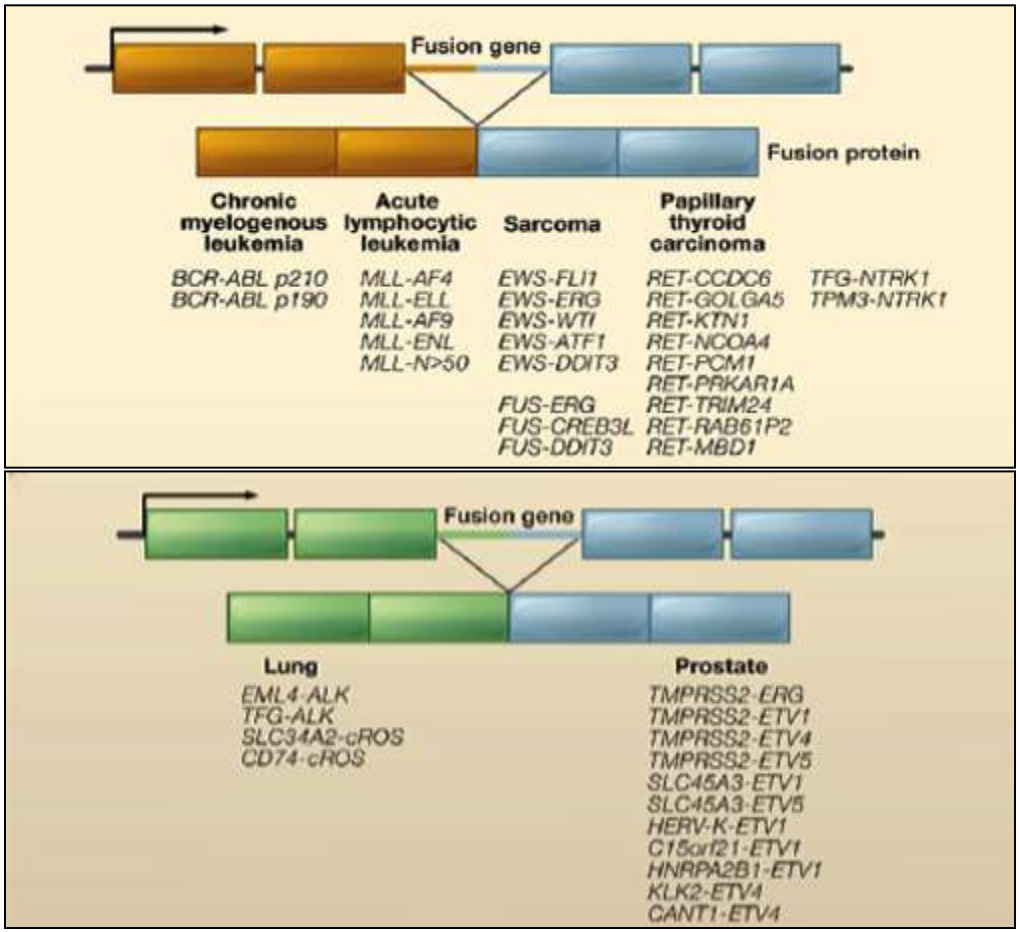
Oncogene Activation and Oncogene "Addiction"

- "activating" (gain-of-function) mutations in proto-oncogenes
- freedom from the negative feedback that impose control on proliferation in normal tissues
- prototypic examples: RAS, PI3-kinase, MYC, RAF

Multiple Mechanisms for Activation of Oncogenes



Chromosomal Rearrangements and Gene Fusions in Cancer



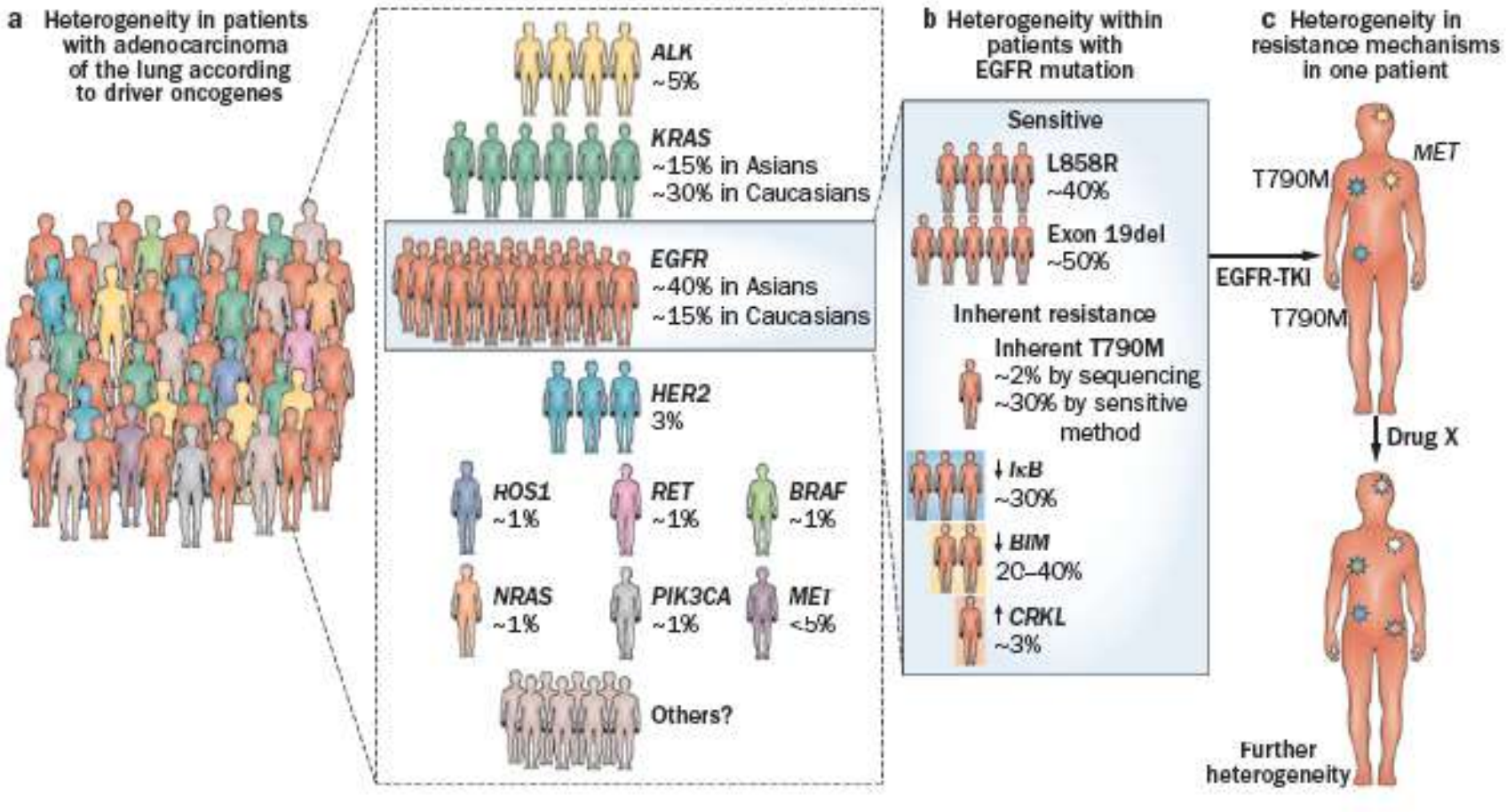
- **fusion of oncogenes with a second gene**

Adapted From: T. H. Rabbitts et al. (2009) Cell 137, 391

Activation of Different Oncogenes in Cancers Arising in the Same Cell Type

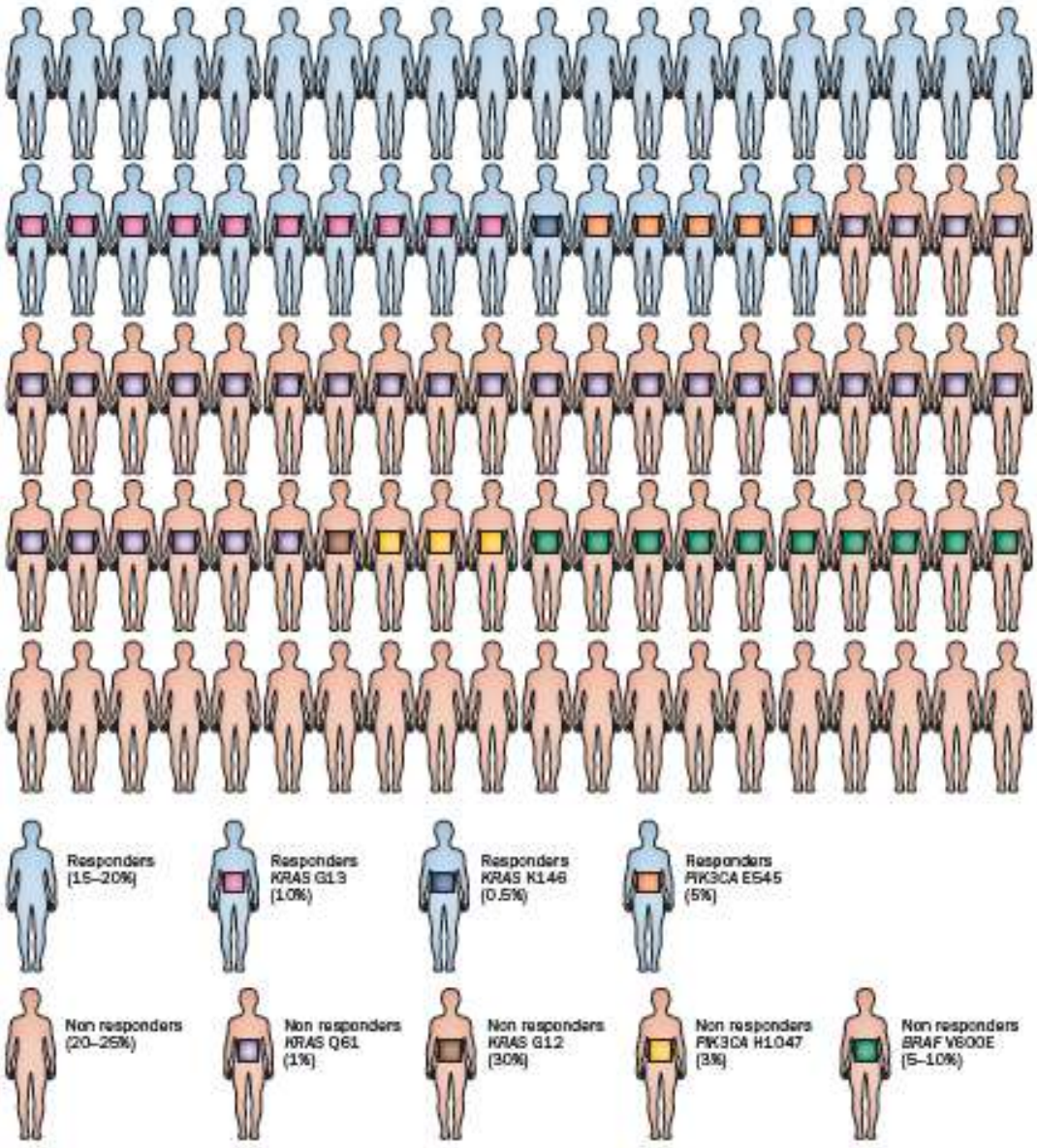
(Tumor Subtypes)

Heterogeneity of Driver Oncogenes in NSCLC



From: T. Mitsudomi et al. (2013) Nat. Rev. Clin. Oncol. 10, 235

Frequencies of Molecular Alterations in CRC and Responsiveness to Cetuximab or Panitumumab



From: M. Martini et al. (2012) Nature Rev. Clin. Oncol.

Two Classes of Tumor Suppressor Genes

gatekeepers

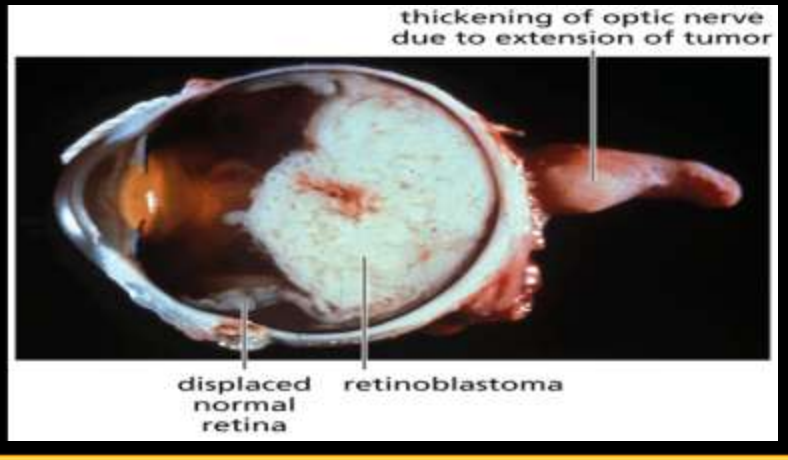
- normally act to restrain cell proliferation
- loss of function mutations can lead to excessive proliferation/tumor formation
  - e.g. RB, NF2, TP53 and PTEN

caretakers

- normally function in DNA repair and chromosome sorting
- loss of function mutations contribute to genomic instability
  - e.g. APC, BRCA1, BRCA2

Cancer Predisposition Genes

Retinoblastoma (RB)



Adenomatosis Polyposis Coli (APC)

BRCA 1 and 2 as Tumor Suppressor Genes: Different Mutations May Confer Different Risks

- substantially increased lifetime risks of breast and ovarian cancers but only small risk of increased pancreatic cancer
- loss-of-function mutations in central gene region confer higher risk of ovarian cancer versus breast cancer than mutations at gene end regions

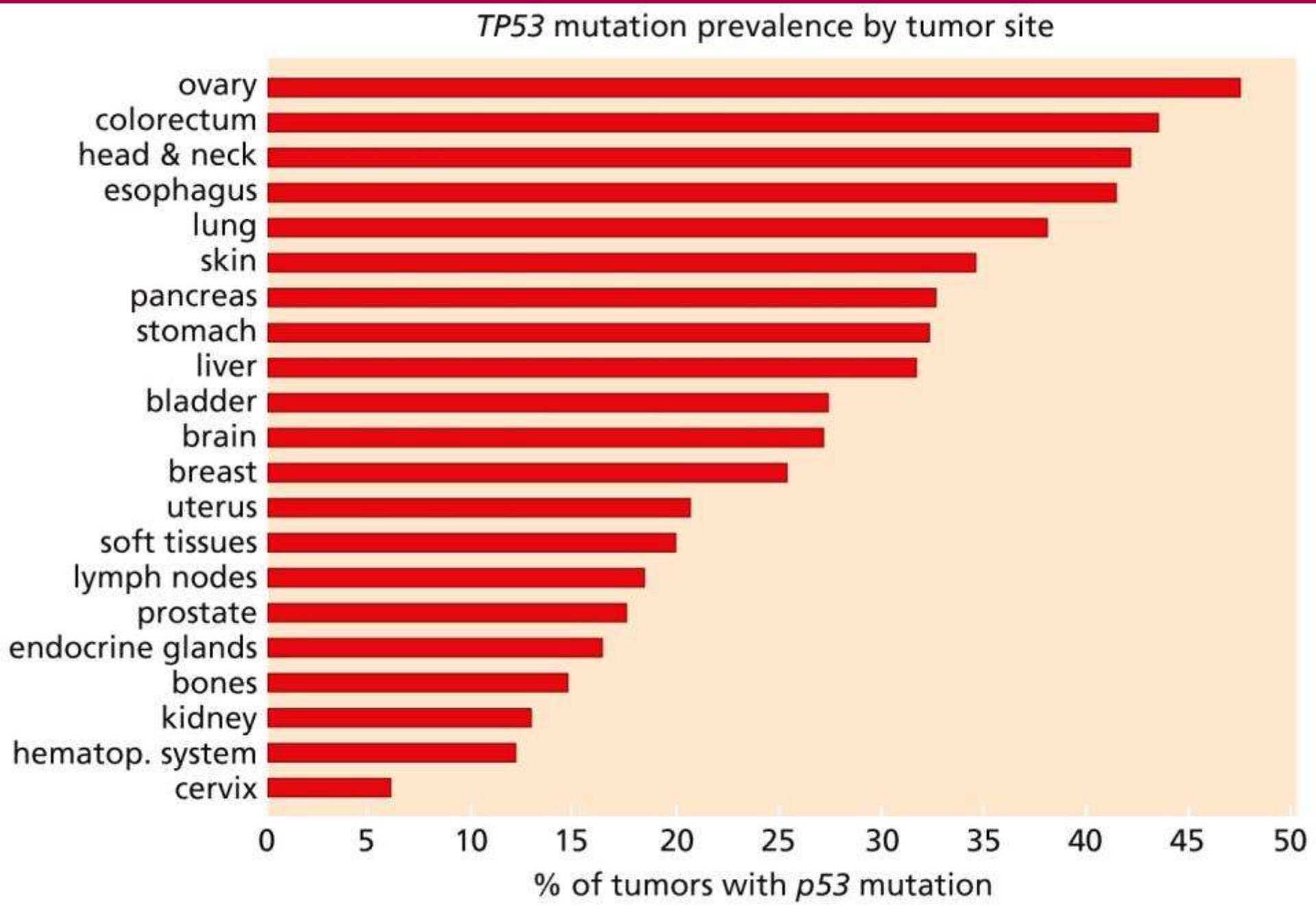


Figure 9.4 The Biology of Cancer (© Garland Science 2014)

Making Sense of Cancer Genomic Data

driver mutations

- oncogenes
- suppressor genes

passenger mutations

- changes in genome and gene regulatory networks that are not causal for cancer initiation and progression
- accumulate with increasing genome instability as tumor progresses
- may still contribute to adaptive survival advantage
  - drug efflux transporters

How Does Genome Instability Generate the Complex Behavior (Phenotypes) of Tumor Cells?

Immunoevasion, Metastasis and Drug Resistance as the Three Most Clinically Relevant (and Dangerous) Phenotypes in Cancer Cell Behavior

Understanding the Altered Molecular Signaling Networks that Drive These Aspects of Tumor Behavior and as Targets for Diagnostics (Dx) and Therapeutics (Rx)

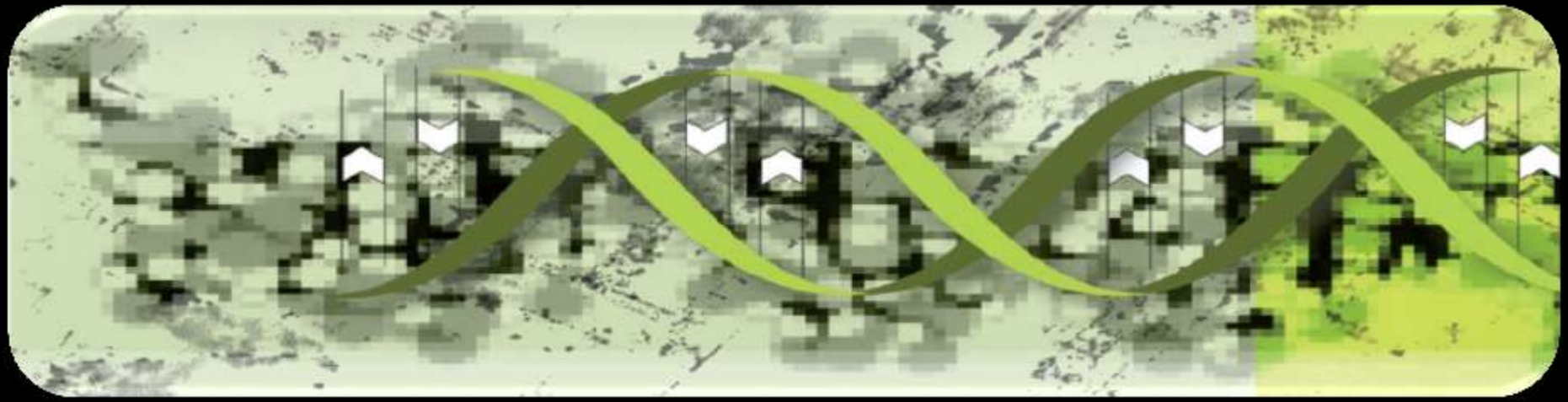
Molecular Medicine

Defining Disease Mechanisms at the Molecular Level

Mapping the Disruption of Molecular Signaling Networks

Profiling Altered Patterns of Information Flow
in Signaling Pathways and Understanding Their Contribution
to Disease Requires A Systems-Based Approach

Genes For ….
The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective



The Over-Simplified Perspective That Whole Exome-and Whole Genome-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis and Transform Treatment Options

Profiling Changes in Biological Signaling Networks in Cancer: Understanding Cancer Requires a Holistic "Systems" Approach

- genome sequence data alone will not provide a sufficiently complete picture for either Dx or Rx decisions
  - need to understand cancer as a complex multi-component process

- mapping disruption in signaling pathways requires profiling of multiple aspects of both genotypic and phenotypic changes

Elucidation of Disease Mechanisms Will Require More than Genome Sequence Information: The Need for Comprehensive Knowledge of Disruption of Gene Regulatory Networks

primary genome sequence

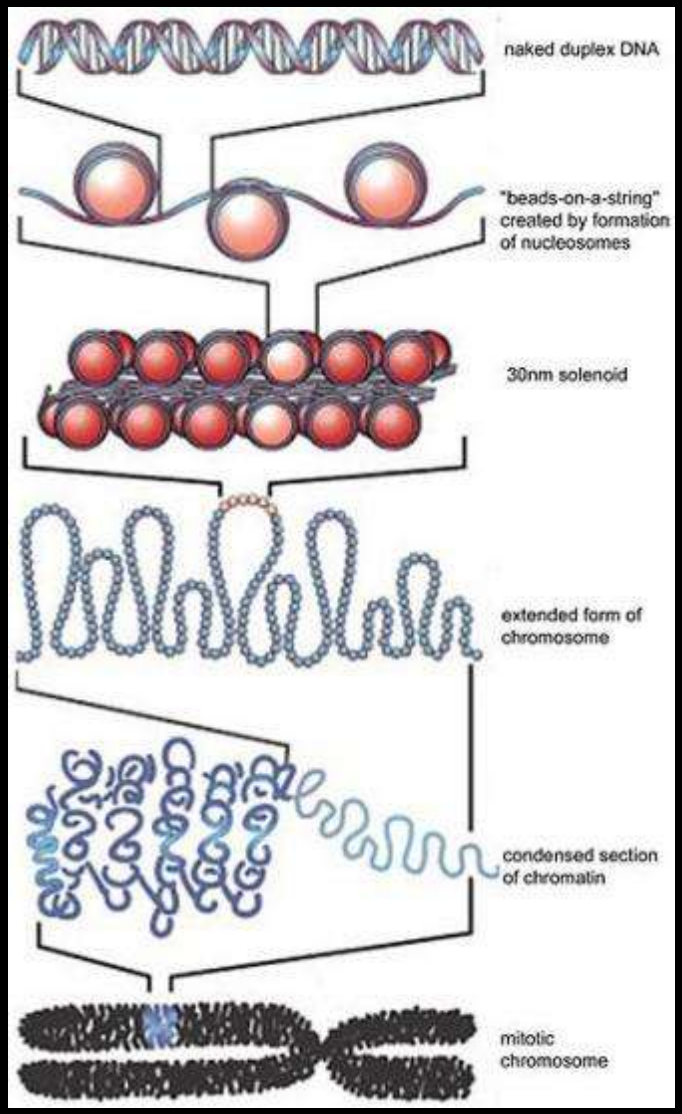
- mutations
- amplifications, deletions, copy number variation
- chromosomal translocations
- aneuploidy

epigenetic modifications

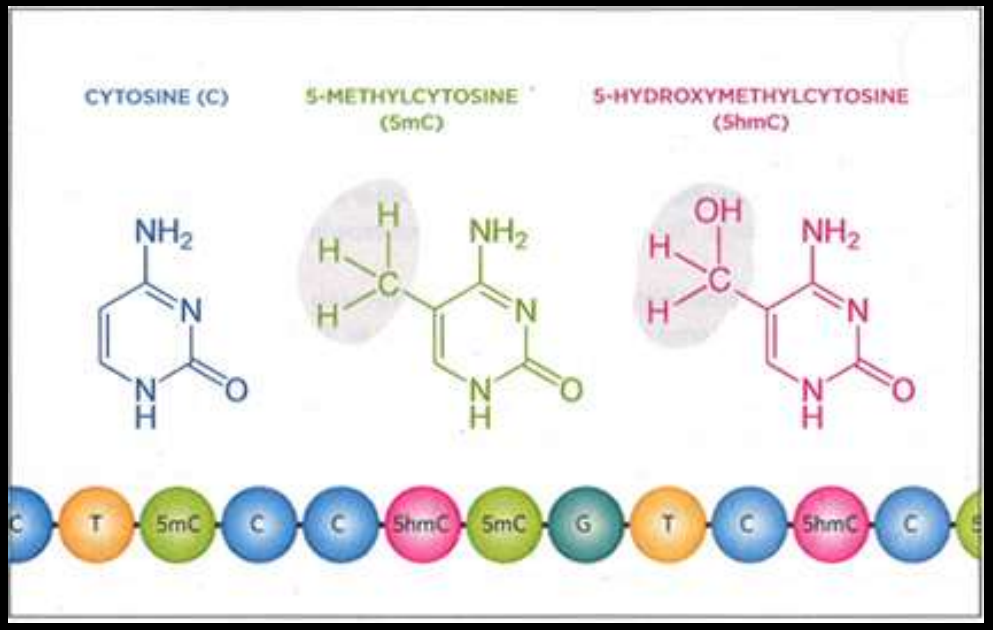
the non-coding transcriptome and gene regulation

- the increasing complexity of regulation of gene expression by diverse RNA species

The Epigenome: Reading The Second Genomic Code



- chromatin structure and access to DNA



- DNA methylation

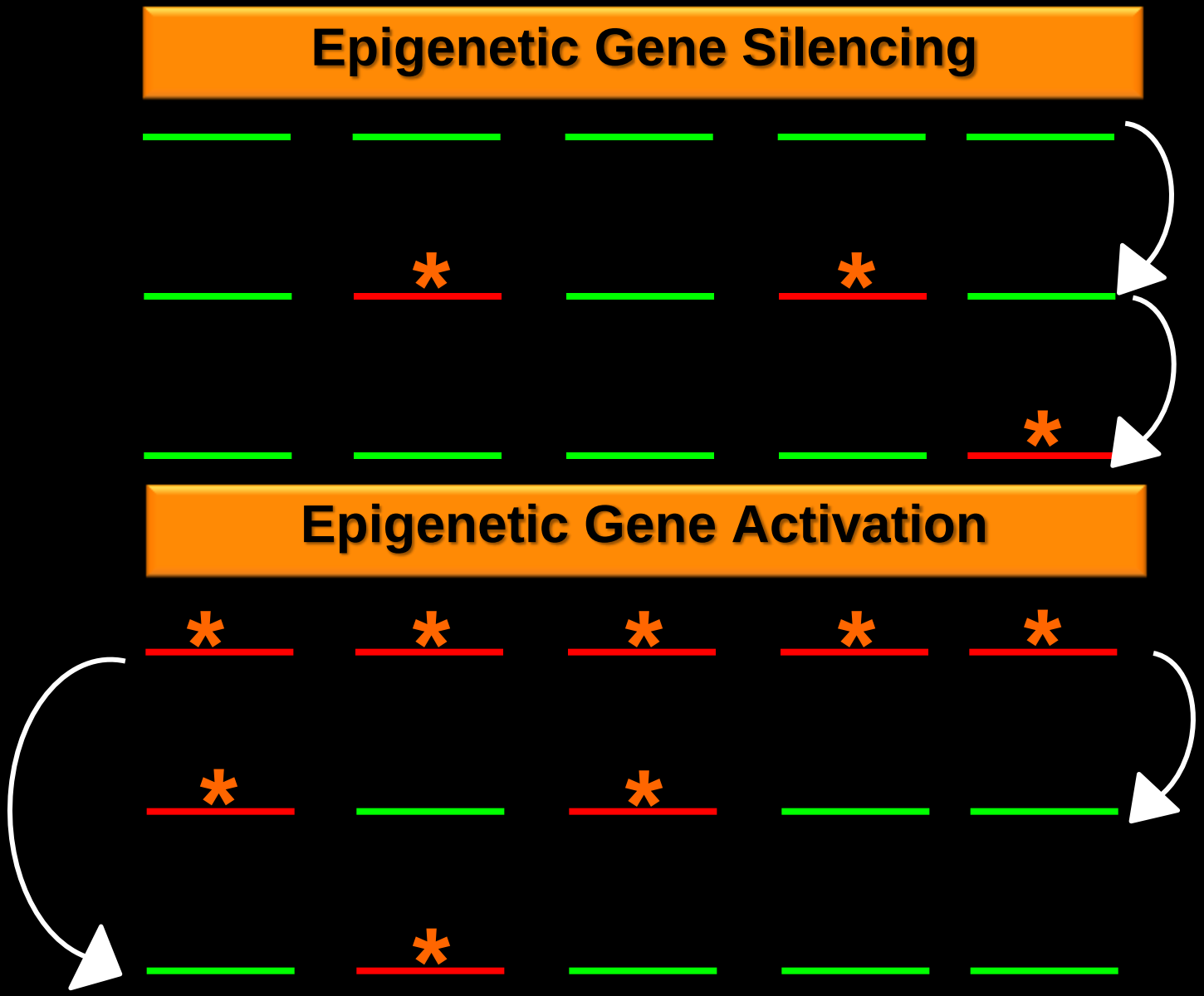
Epigenome

the epigenome

- dynamic modulation of gene expression without change in the primary sequence of nucleotide bases
- regulation of gene expression (activation, silencing) by modification of chromatin structure and histones
- dynamic changes in cytosine methylation

the epitranscriptome

- dynamic and reversible chemical modification of RNA
  - e.g. N6-methyladenosine



green line = expressed; red line = silent; * = DNA methylation

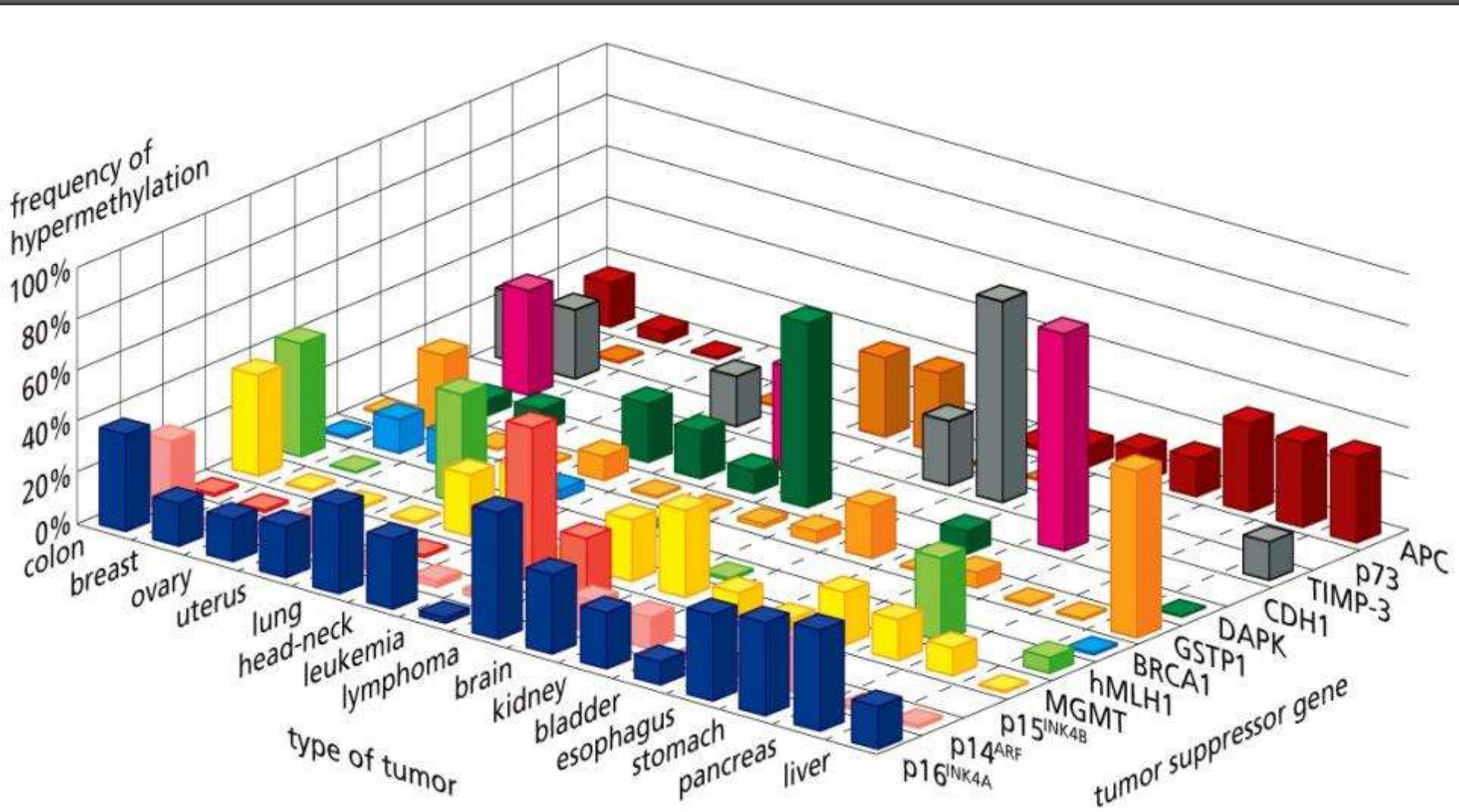
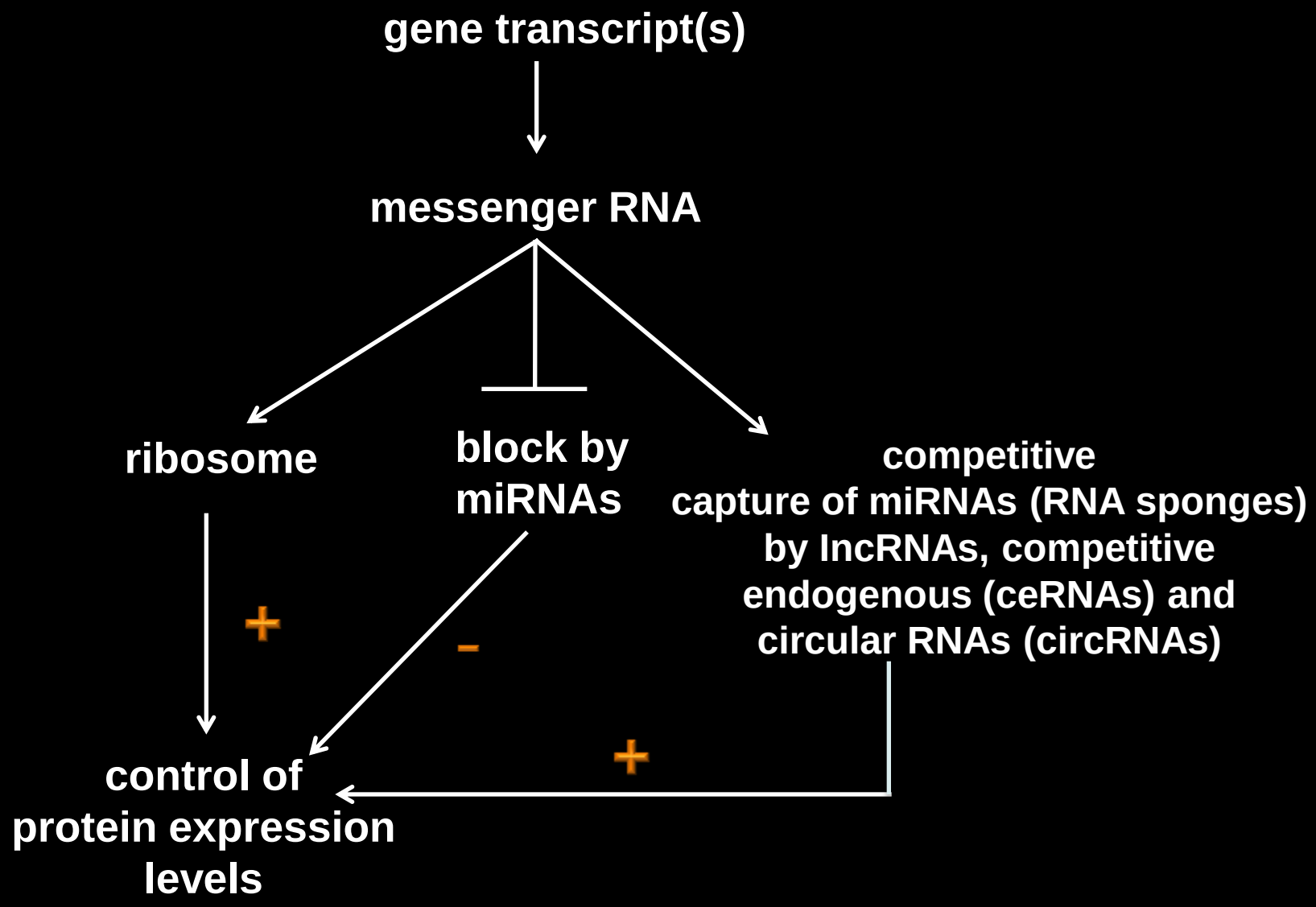


Figure 7.18 The Biology of Cancer (© Garland Science 2014)

Growing Recognition of the Complexity of the RNA Universe in Regulating Gene Expression

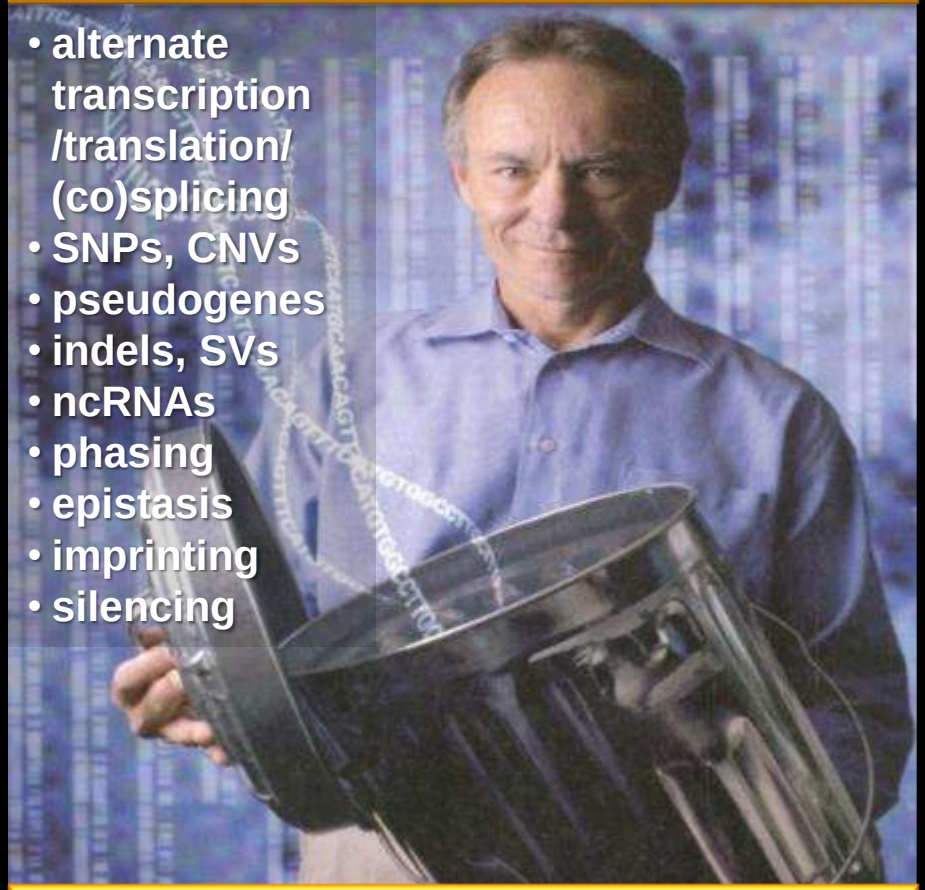
- pervasive transcription of >90% of the genome with less than 2% encoding protein-coding genes
- human transcriptome
  - 21,000 protein-coding genes
  - 9,000 small RNAs
  - 10,000-32,000 long non-coding RNAs (lncRNAs)
  - 11,000 pseudogenes
- extensive crosstalk and interactions between different RNA species

Post-Transcriptional Regulation of Gene Expression



Individual Variation, Genome Complexity and the Challenge of Genotype-Phenotype Predictions

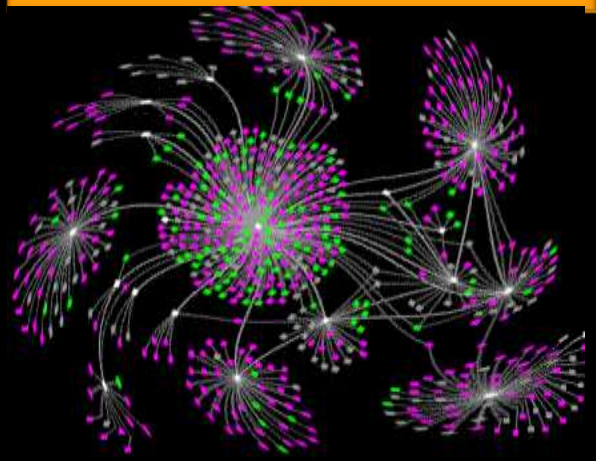
Junk No More: Pervasive Transcription



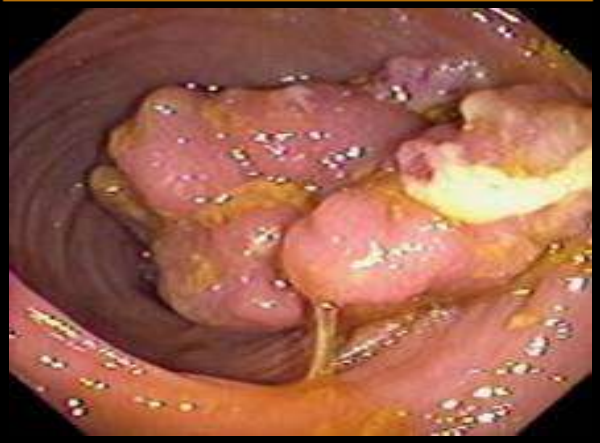
- alternate transcription /translation/ (co)splicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- ncRNAs
- phasing
- epistasis
- imprinting
- silencing

recognition of the complexity of genome organization and regulation

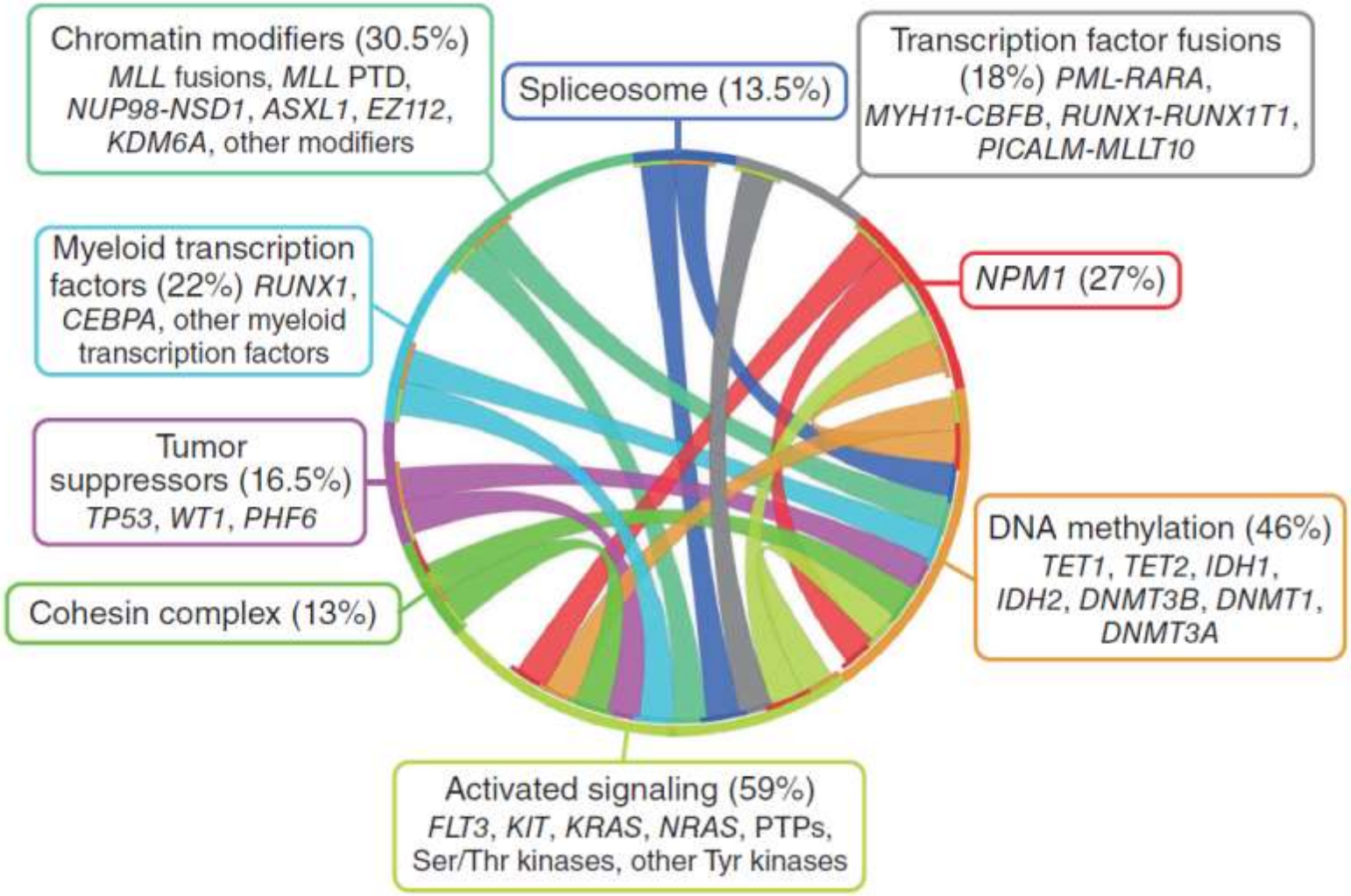
Cell-specific Molecular Interaction Networks



Perturbed Networks and Disease

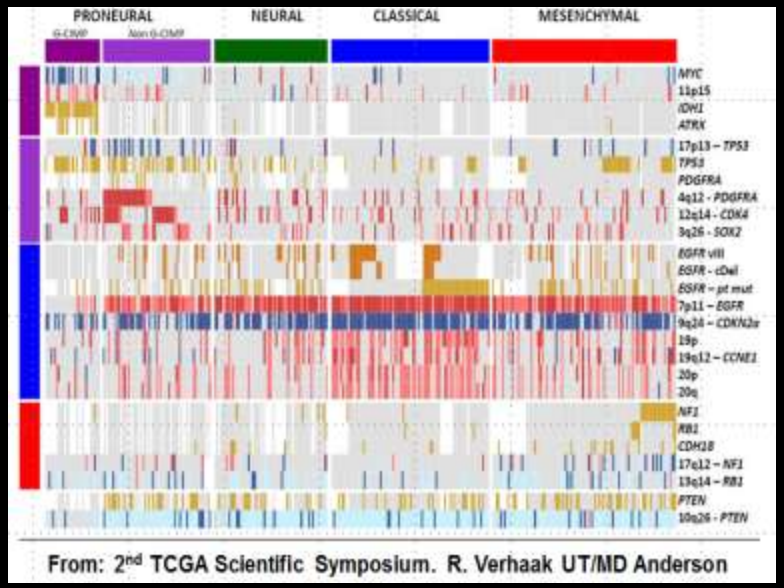


The Multiplicity of Genomic, Transcriptomic, Epigenomic and Signaling Pathway Alterations in AML Illustrate Why Genome Sequencing Alone is Only One Part of the Molecular Profile Needed for Guiding Diagnosis and Therapy

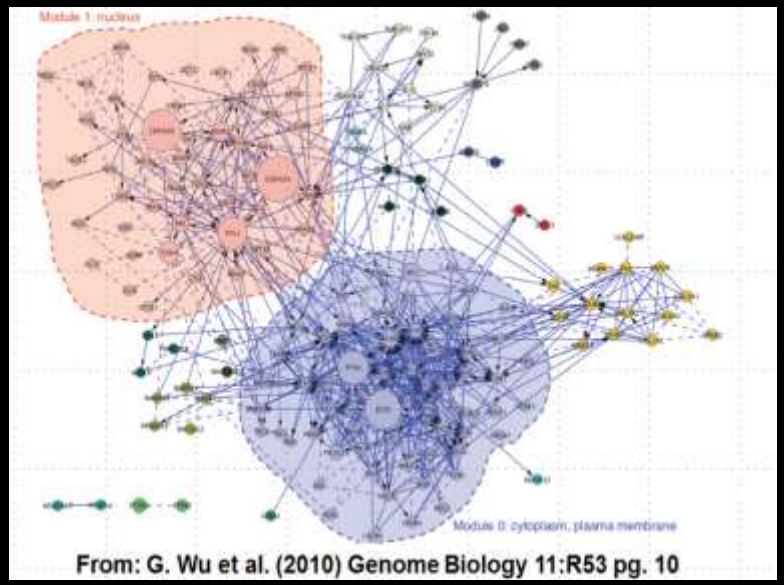


From: S-J. Chen et al. (2013) Nature Genetics 45, 586

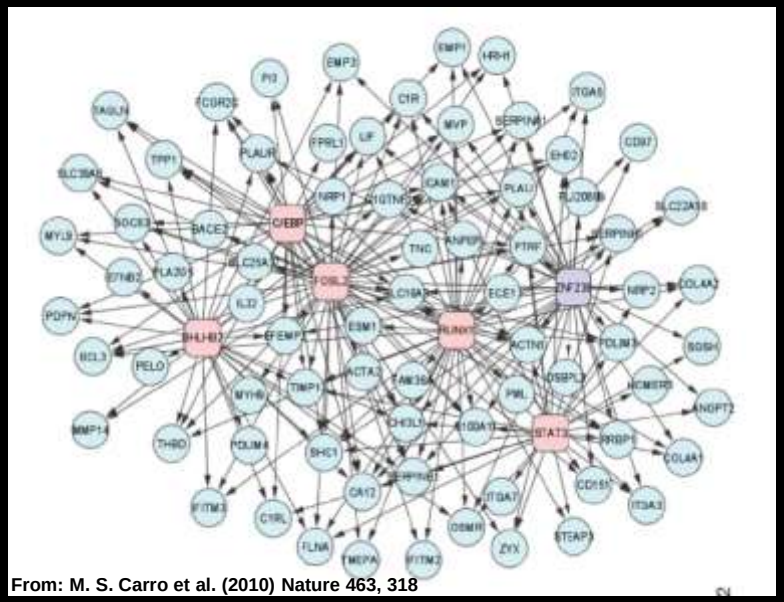
GBM Expression Subtypes and TF and miRNA-TF Regulatory Networks

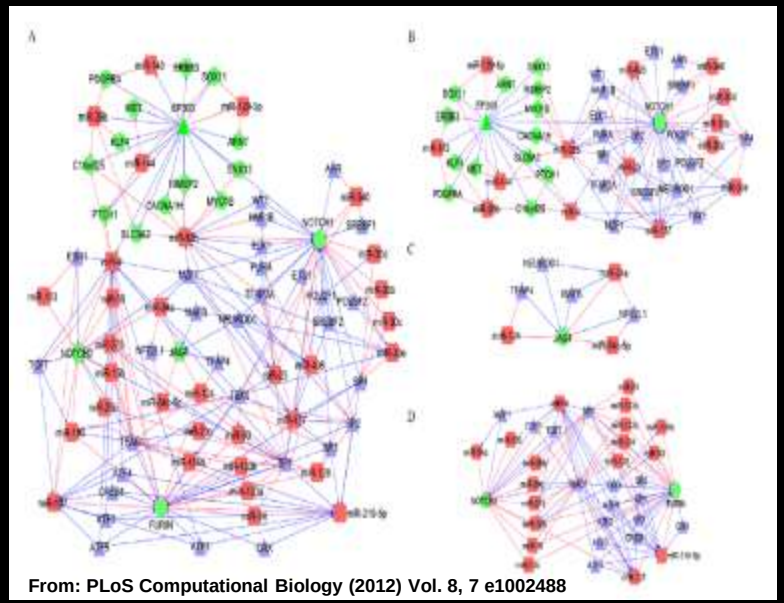


From: 2nd TCGA Scientific Symposium. R. Verhaak UT/MD Anderson

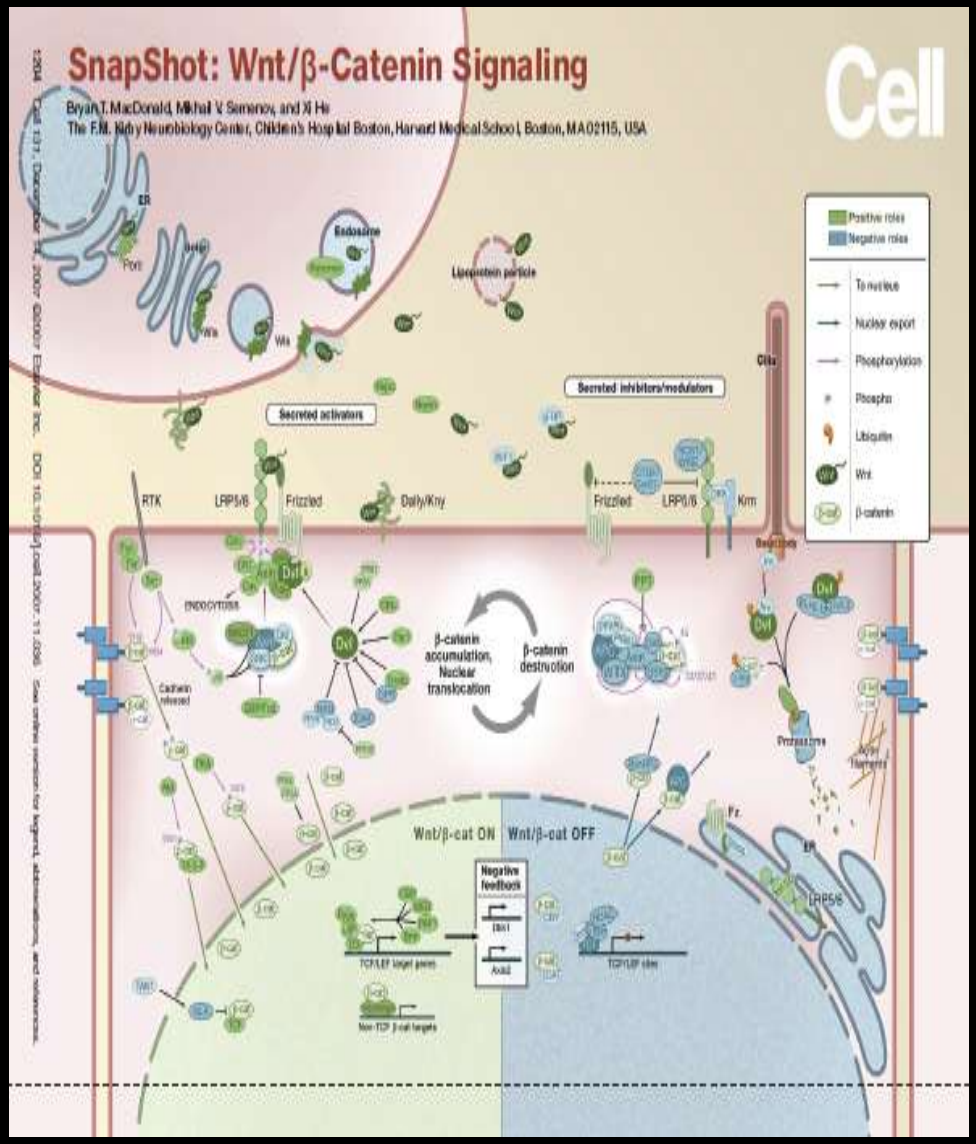


From: G. Wu et al. (2010) Genome Biology 11:R53 pg. 10


From: M. S. Carro et al. (2010) Nature 463, 318


From: PLoS Computational Biology (2012) Vol. 8, 7 e1002488

Canonical Molecular Signaling Networks and Pathways and Dysregulation in Disease



The Complex Ecology of Tumor Progression and Metastasis

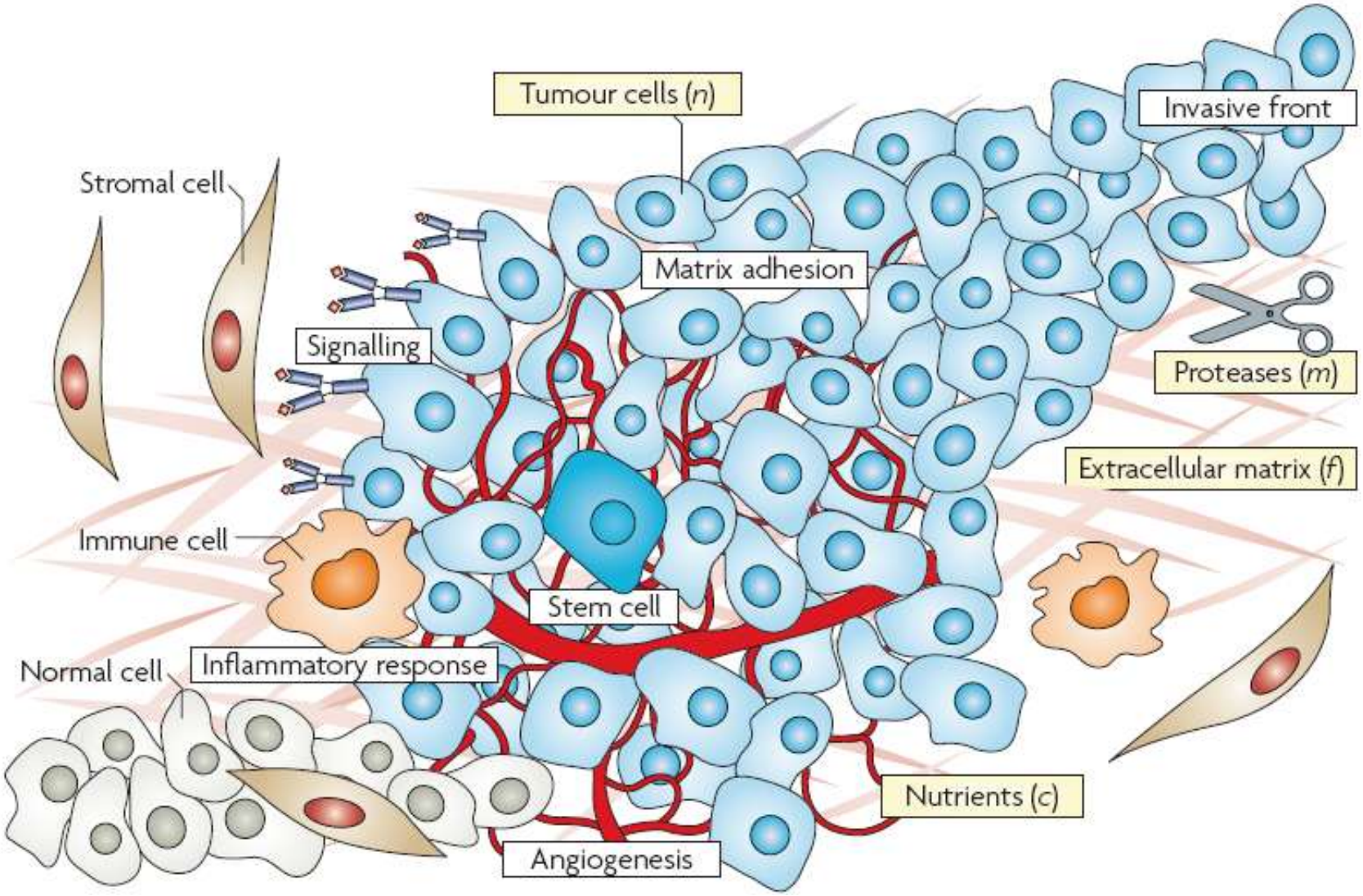
The Tumor Microenvironment:

Molecular Signaling Between Cancer Cells, Immune Cells and Tissue Components

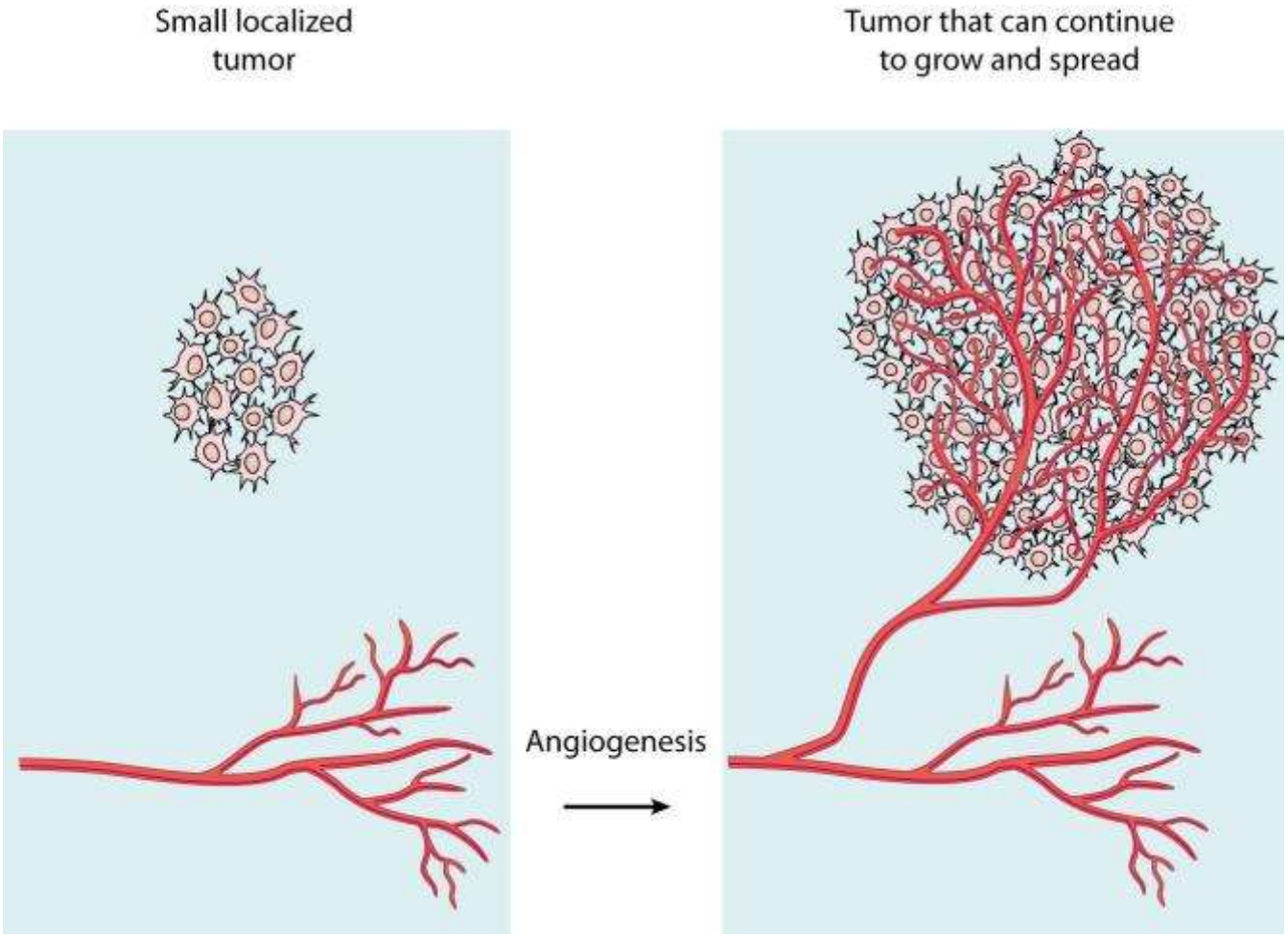
The Complex Ecology of Malignant Neoplasms

- multiple cell types and inter-cellular molecular communication activities in the tumor microenvironment(s)
- tumor cell-tumor cell interactions
- tumor cell-host stroma interactions
- tumor cell-host defense interactions
- tumor cell-host interactions in different body organ environments for successful metastasis
- effect of treatment(s) on tumor cells, host defense systems and the host microbiome

The Complex Microenvironment of Neoplasms



From: A. R. A. Anderson and V. Quaranta (2008) Nature Reviews Ca. 8, 227



Reprogramming Energy Metabolism in Cancer Cells
The Warburg Effect

- pioneering work of Otto Warburg (1927)
- normal dominance of oxidative metabolism under aerobic conditions (Krebs cycle)
- normal cells shift to glycolysis under anaerobic conditions
  - redirect pyruvate away from mitochondrial oxidation to reduce pyruvate to lactate
- tumor cells metabolize glucose to lactate in both aerobic and anaerobic environments
  - support survival and proliferation in microenvironments with limited oxygenation (hypoxia) due to impaired vascular supply

Reprogramming Energy Metabolism in Cancer Cells

- possible role of reactive oxygen species (ROS) released by tumor cells in causing tumor-associated host fibroblasts to switch to aerobic glycolysis
  - increased production of lactate and pyruvate as metabolites to fuel cancer cells
- similar reprogramming of adipocytes in fat tissue
  - production of free fatty acids (FFA) as tumor nutrients

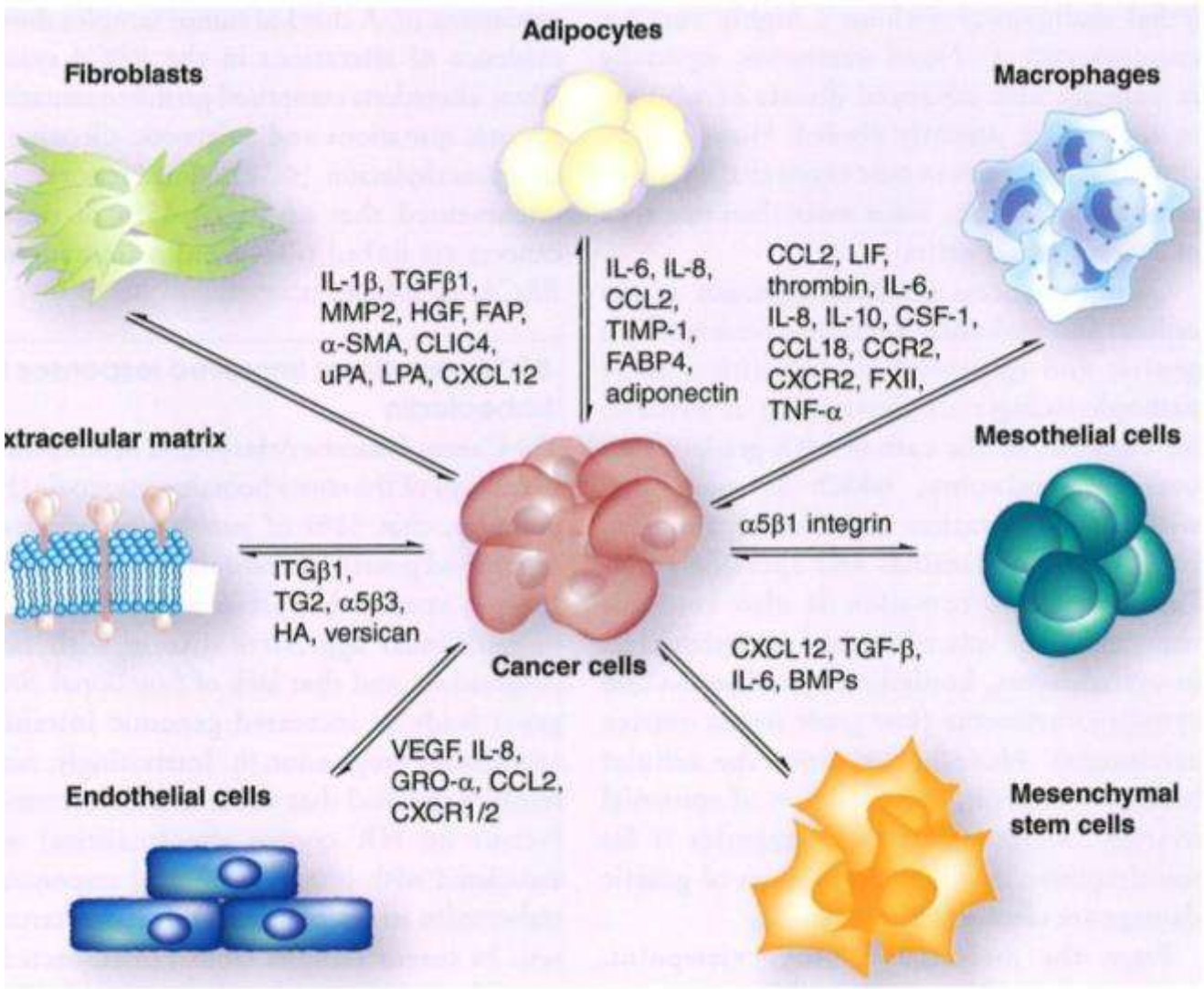
Pro-Inflammatory Host Responses and Promotion of Tumor Growth

- insufficient blood supply, hypoxia, increased acidity and impaired nutrient supply in growing tumors trigger necrosis and release of pro-inflammatory signals
  - stimulus to recruit host immune cells who then release further pro-proliferation signals exploited by tumor cells to promote survival and progression

The Tumor Microenvironment Hijacking: Host Responses by Tumor Cells to Promote Proliferation and Progression

- tumors secrete growth factors and chemoattractants for host inflammatory and immune cells
- pro-inflammatory cytokines released by these host cells promote tumor progression
  - suppress apoptosis
  - promote cell cycle progression/cell replication
  - angiogenesis
  - induce epithelial-mesenchymal transition (EMT) markers

The Tumor Microenvironment



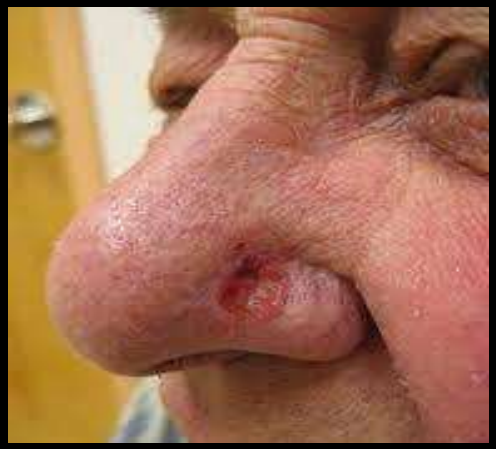
From: Ray-Coquard Future Oncol. (2013) 9, 12 Suppl. 1, 11

Tumor-Mediated Suppression of Host Anti-Cancer Immune Responses

- tumors recruit T regulatory cells (Treg) and myeloid-derived suppressor cells (MDSC)
- these host immune cells suppress the ability of cytotoxic killer T cells to detect and destroy tumor cells

More Details in Lecture Week II

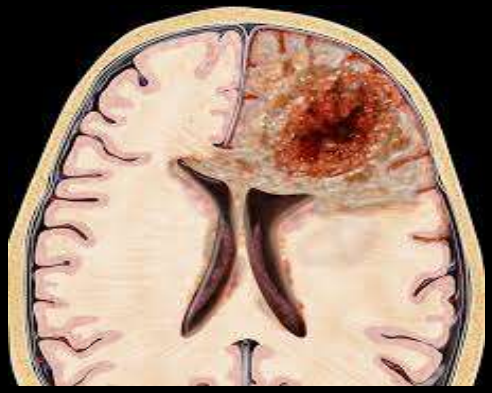
Invasion and Metastasis:
The Start of the Deadly Phase of Cancer Progression



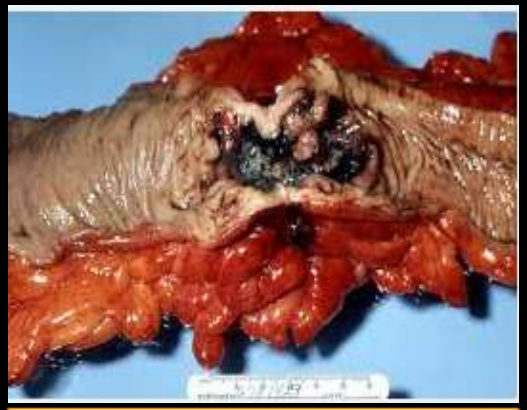
basal cell carcinoma

lung

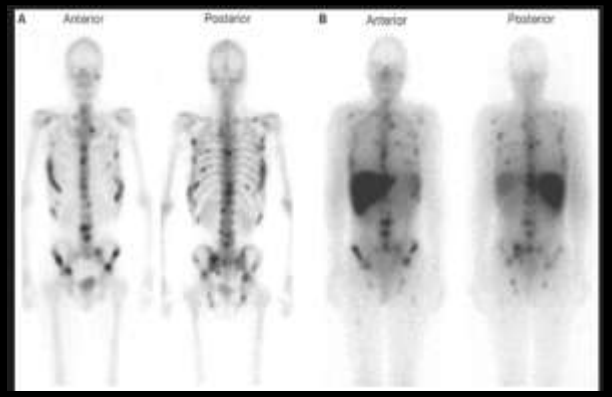
breast



glioblastoma



colorectal



prostate

Invasion Without Metastasis

Invasion and Metastasis

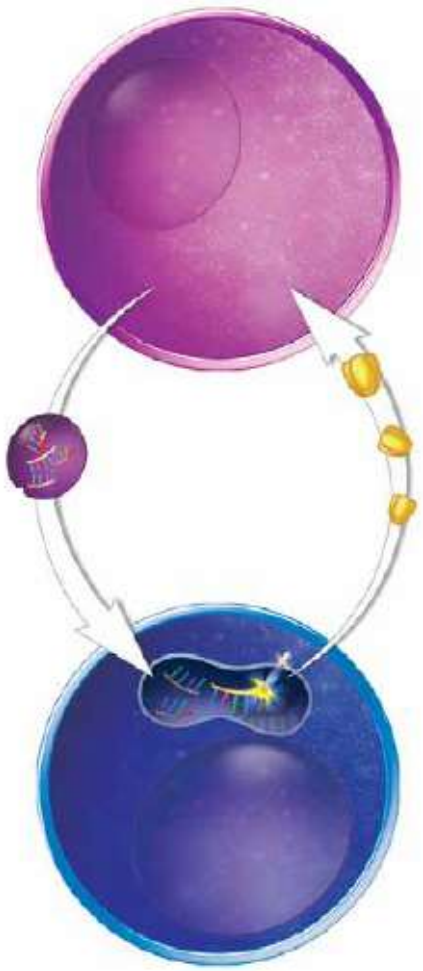
Macrophages and the Tumor Microenvironment

- tumor-associated macrophages (TAM)
- switch of macrophages from M1 to M2 phenotype in normal inflammation and then switch back
- in tumors and obesity macrophages remain in M2 state
- role of TAM in early steps in metastasis (intravasation)

A Perverse Molecular Conversation: Tumor Cell Signals That Stimulate Host Macrophages to Promote Tumor Growth and Spread

1. Cancer cell releases microvesicles that contain miRNA-21 and miR-29.

2. Macrophages take up the microvesicles releasing miR-21 and miR-29 into the cytoplasm where they are taken up by endosomes.

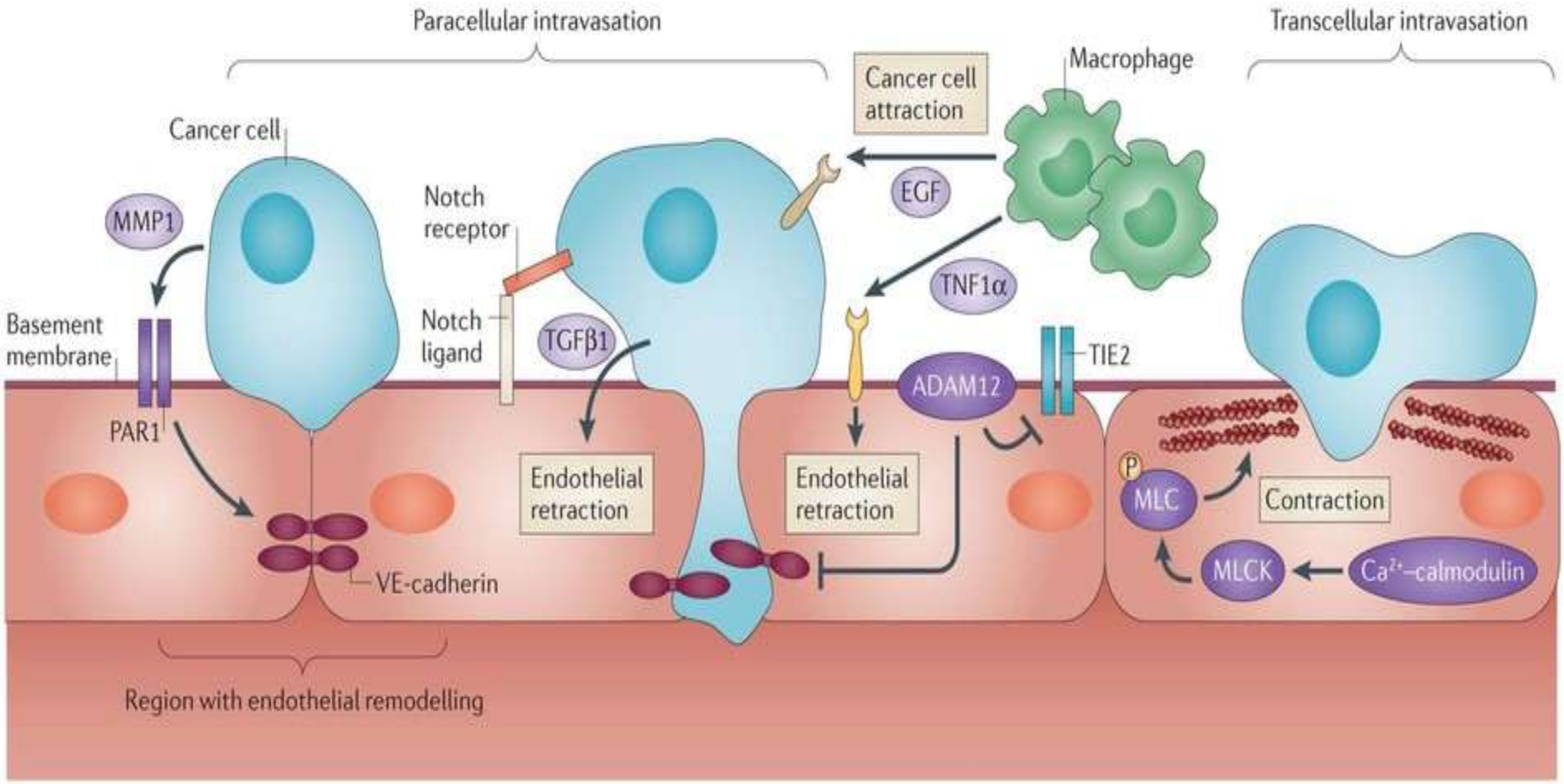


4. **Cancer cells** take up IL-6/TNFalpha, facilitating tumor invasion and metastasis.

3. In the endosome, miR-21 and miR-29 bind with toll like receptors, causing the macrophage to release interleukin 6 (IL-6) and tumor necrosis factor (TNF) alpha.

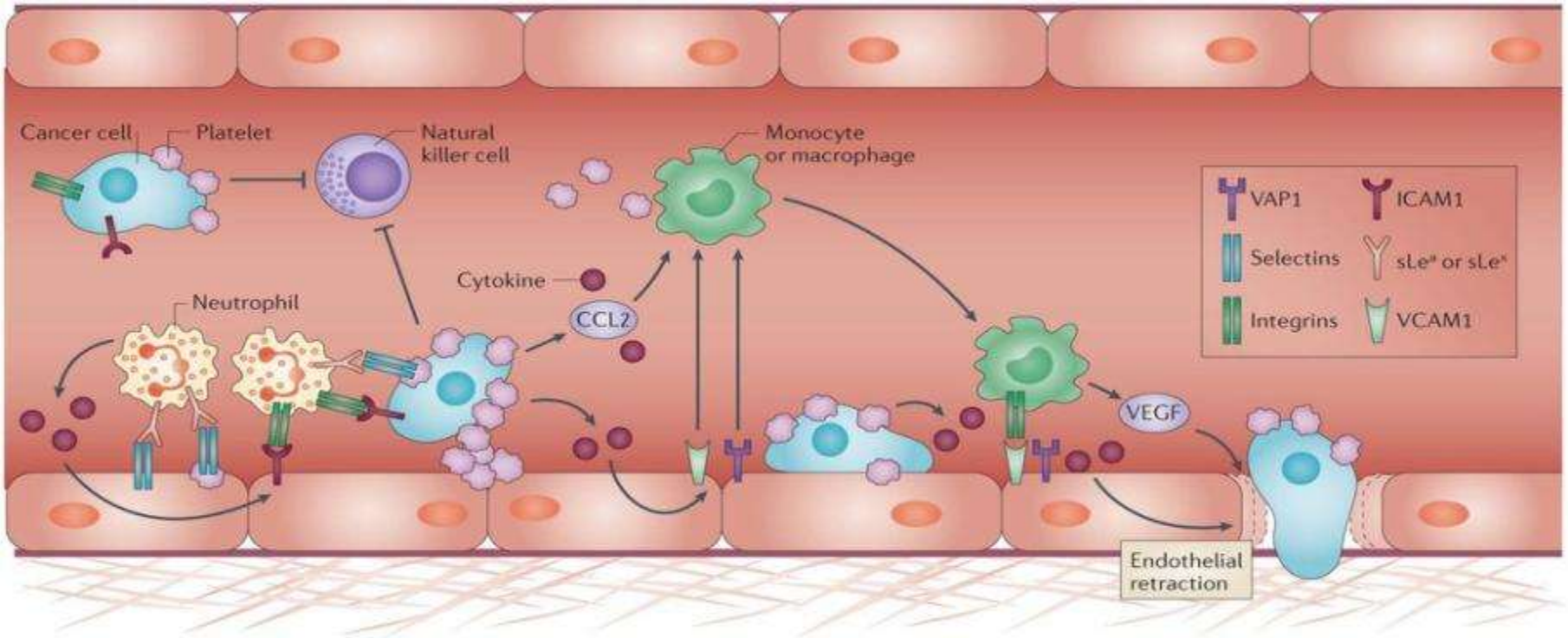
Adapted from Frontiers: OHSU James CCC Winter 2014

Entry of Metastatic Cancer Cells Into The Circulation (Intravasation) and Promotion by Tumour-Associated Macrophages



From: N. Raymond et al. (2013) Nature Rev. Cancer 13, 861

Tumor Cell- Platelet Interactions in Promoting Dissemination and Extravasation



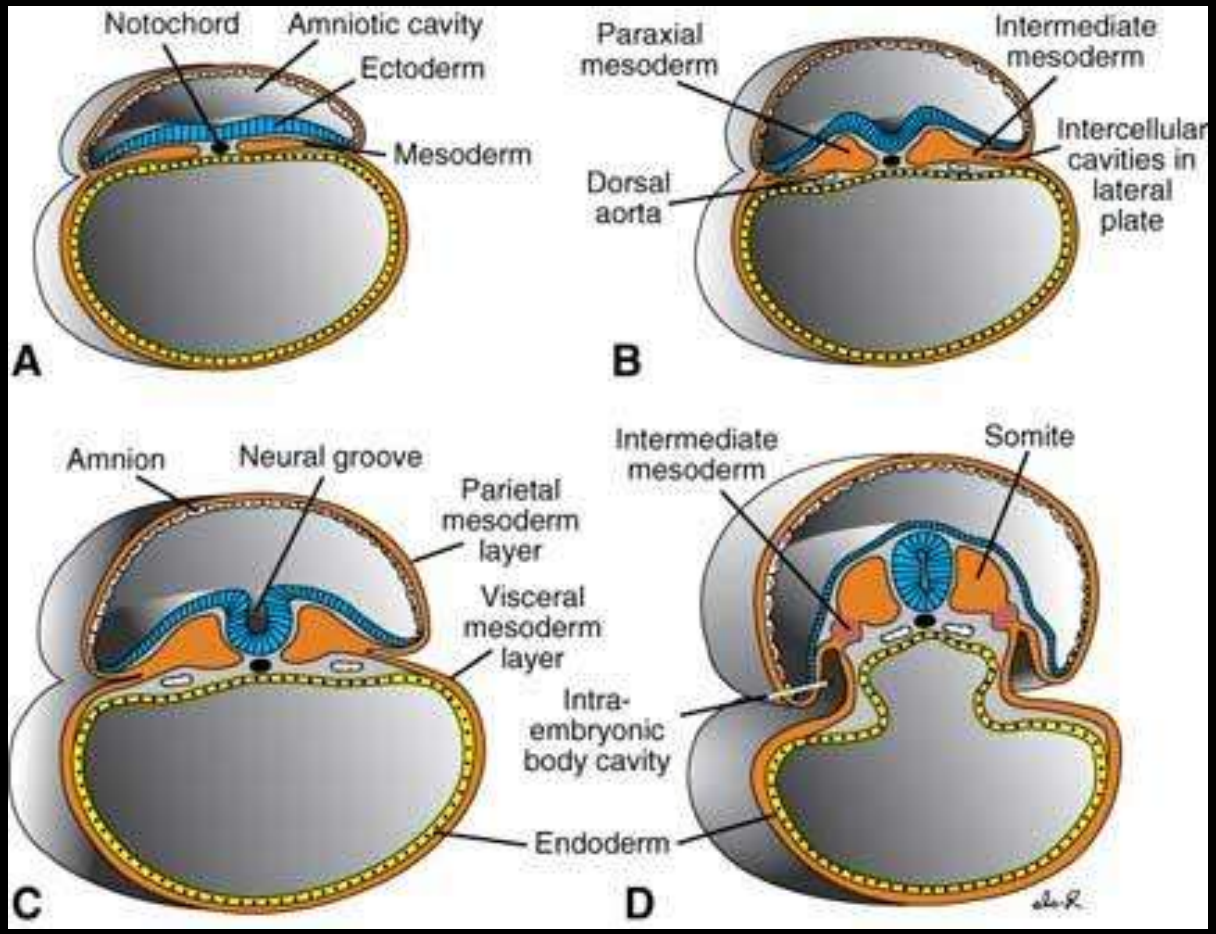
- **protect against lysis by NK cells; increase adhesion to endothelial cells; recruitment of WBC that release pro-inflammatory cytokines**

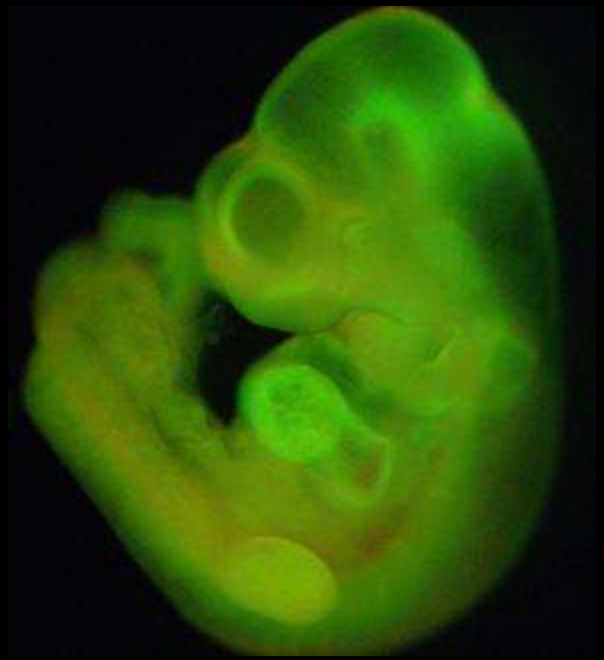
From: N. Raymond et al. (2013) Nature Rev. Cancer 13, 863

The Plasticity of Epithelial Cancer Cells:
Switching (Transition) Between Epithelial and Mesenchymal Phenotypes

Epithelial: Mesenchymal Transition (EMT) and Mesenchymal: Epithelial Transition (MET) as Core Features of Metastatic Spread and Tumor Dormancy

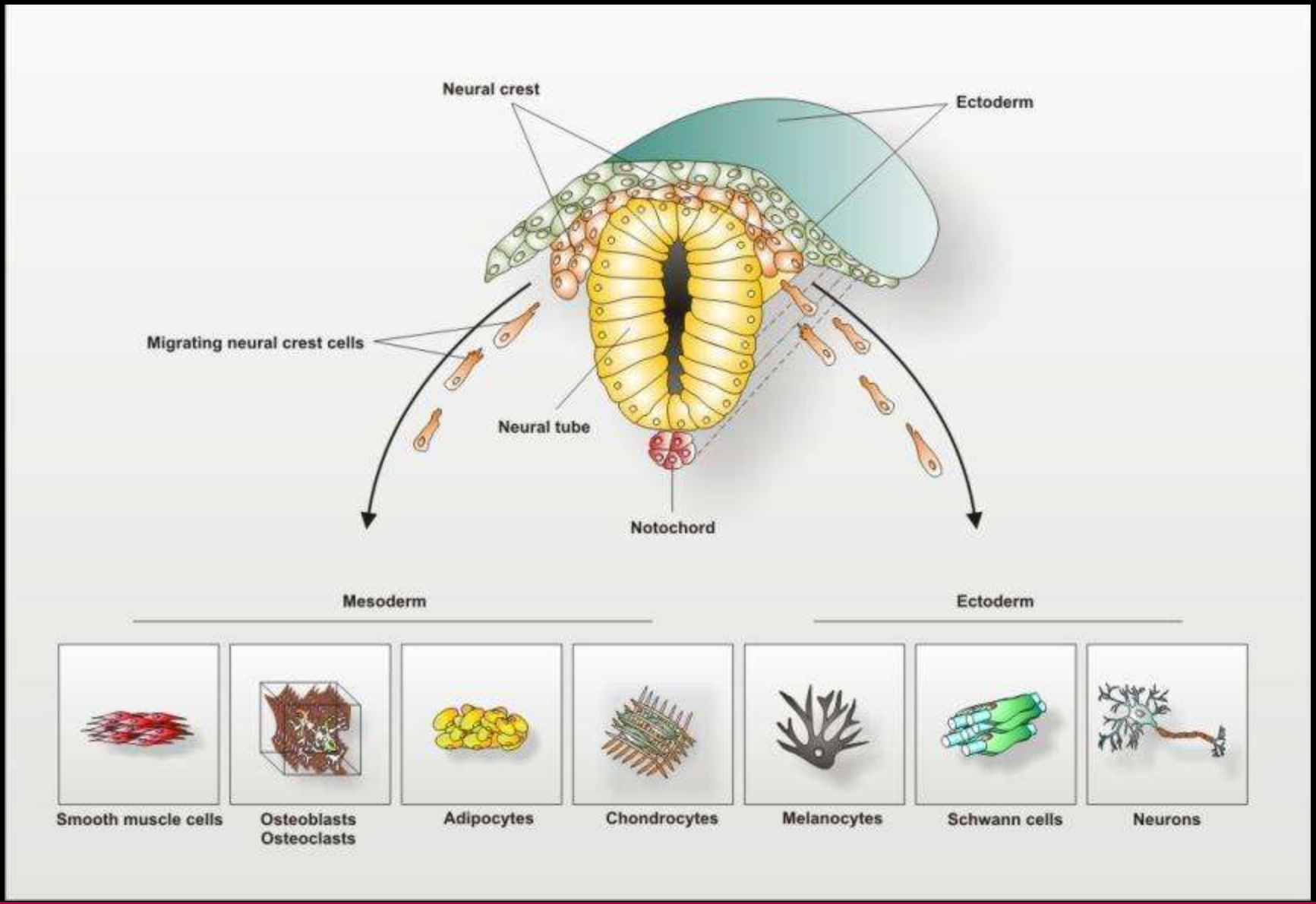
Formation of the Germ Layers in Embryogenesis: Endoderm, Mesoderm and Ectoderm





How to reset a cell https://student.societyforscience.org/article/how-reset-cell

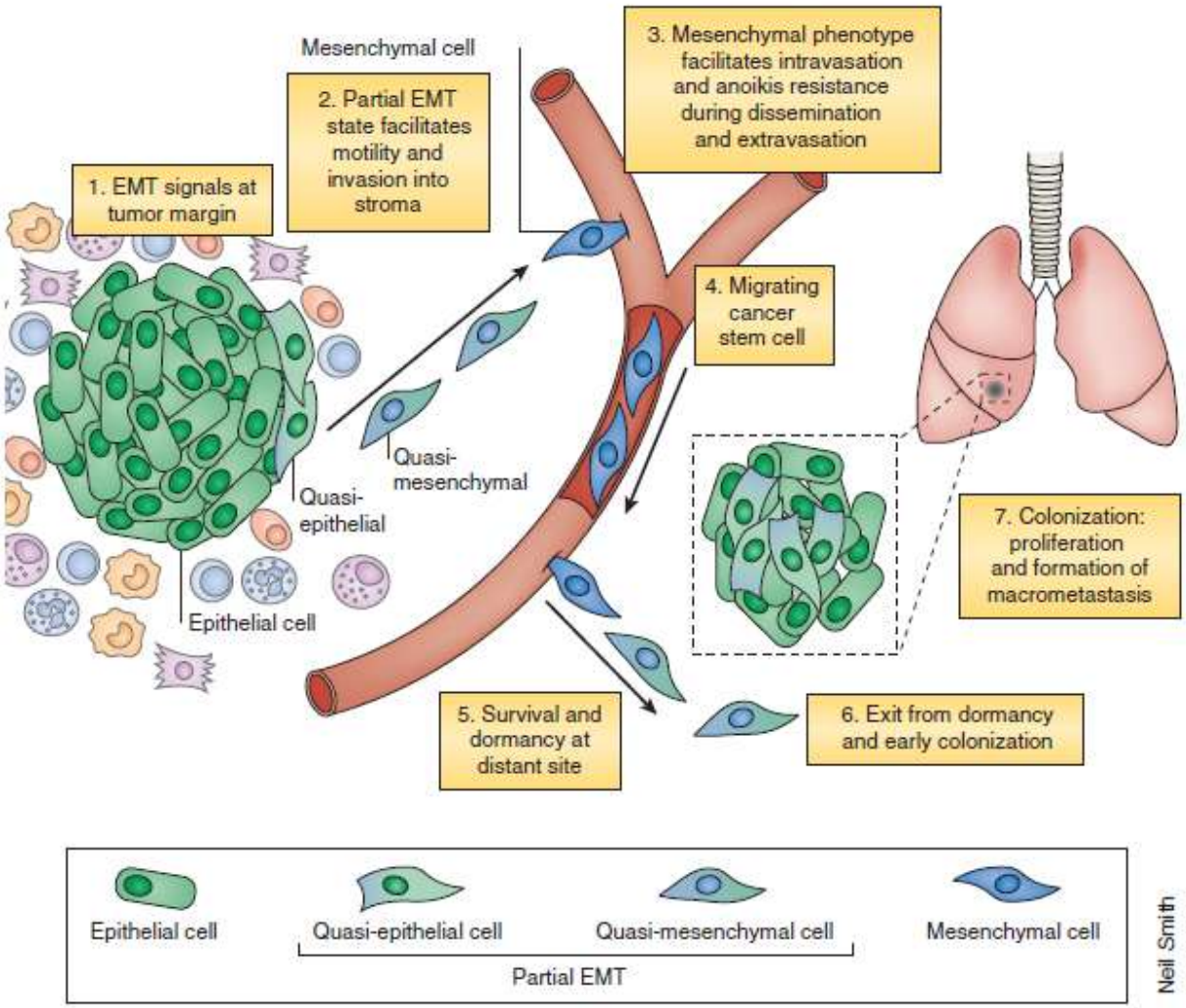
Migration of Neural Crest Cells and Formation of Different Cell Types in Multiple Body Locations



Epithelial (E)- Mesenchymal (M) Transition (EMT)

- acquisition of M-like properties by E cells
- physiological processes
  - migration of mesodermal cells during embryonic gastrulation
  - delamination of neural crest cells from dorsal neural tube
  - migration to multiple locations and subsequent differentiation into diverse cell lineages
- cancer
  - proposed crucial role in invasion and metastasis of epithelial malignancies
  - potential for repeated cycles of EMT and reversal (MET)

The Epithelial-mesenchymal Transition in the Invasion and Metastasis of Malignant Epithelial Cancers



From: W. L. Tam and R. A. Weinberg (2013) Nature Medicine 19, 1438

Principal Patterns of Metastatic Dissemination in the Major Epithelial Cancers

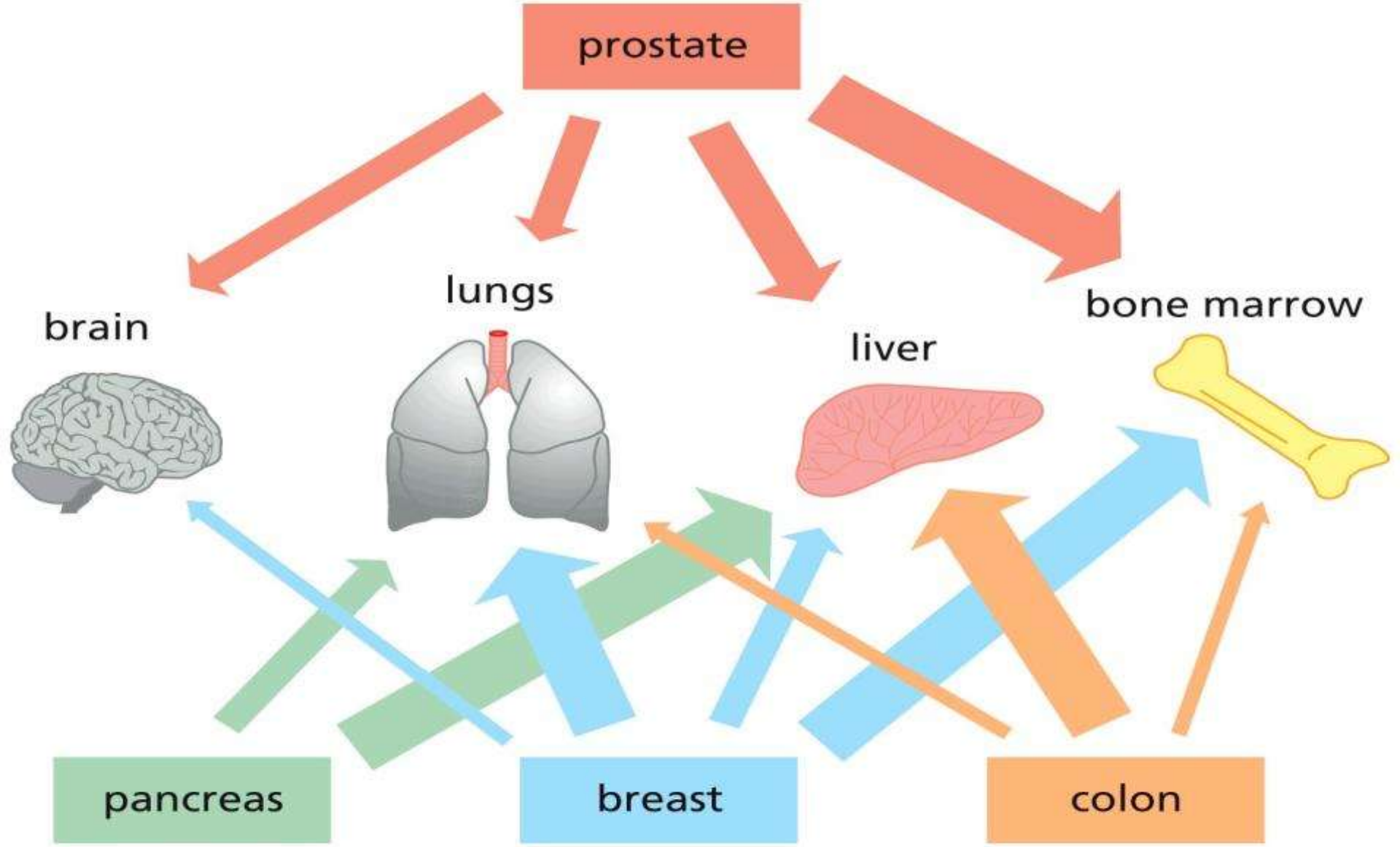


Figure 14.43 The Biology of Cancer (© Garland Science 2014)

“The Seed and Soil Hypothesis” of Metastasis

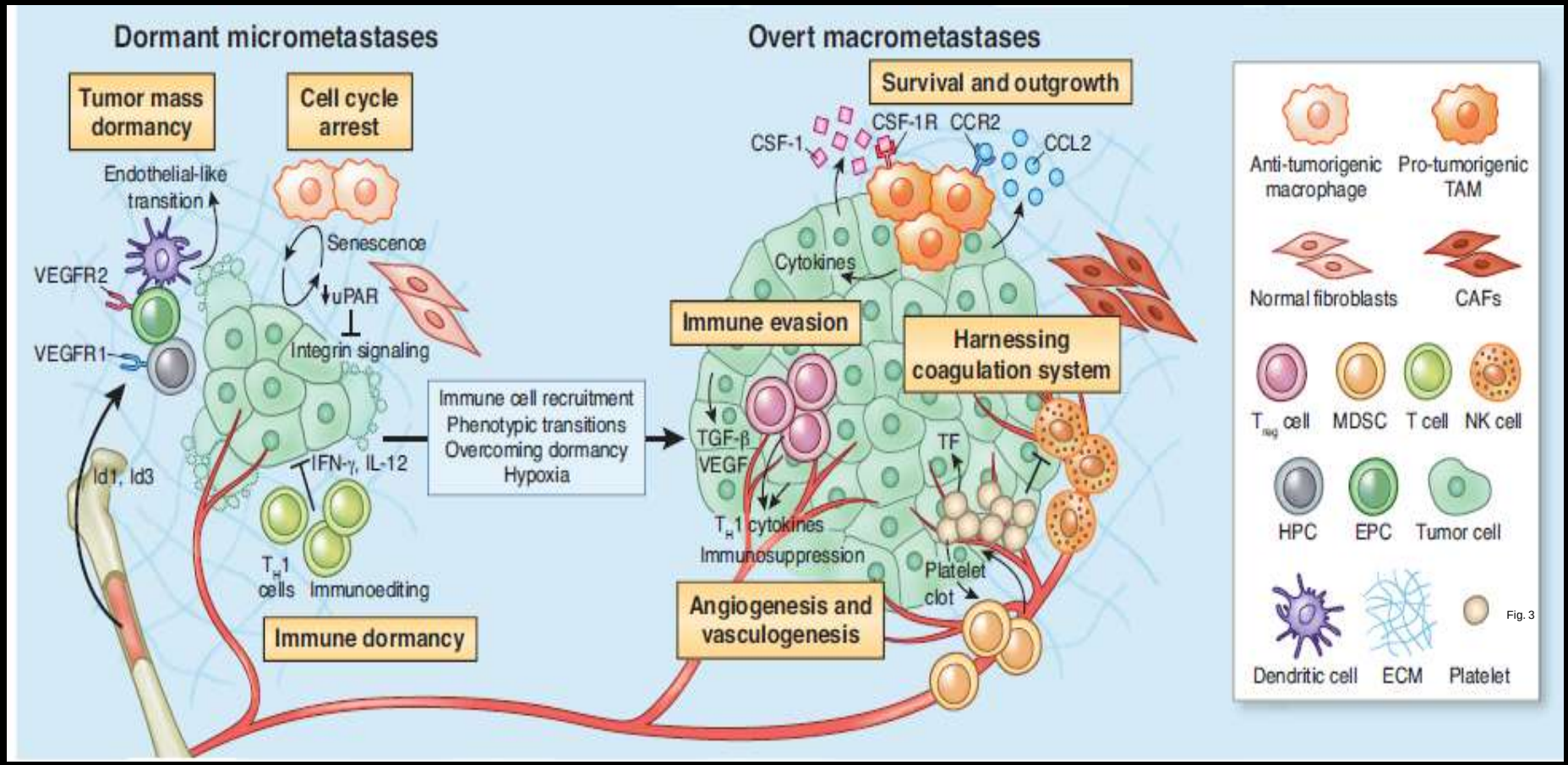
“When a plant goes to seed, its seeds are carried in all directions;
but they can only live and grow if they fall on congenial soil…
While many researchers have been studying ‘the seeds,’
the properties of ‘the soils’ may reveal valuable
insights into the metastatic peculiarities of cancer cases.”

Stephen´ Paget 1889

Cancer Metastasis: Key Questions

- what determines the different anatomic distribution of solid tumor metastases?
- is every cancer cell in a malignant tumor capable of causing metastases?
- is metastatic capability a property of only certain cell subpopulations/clones present in the primary tumor?
- do cells in metastases continue to spread (secondary metastases)?
- are future sites of metastatic colonization ‘primed’ by host cells to promote conditions for metastatic cell survival?

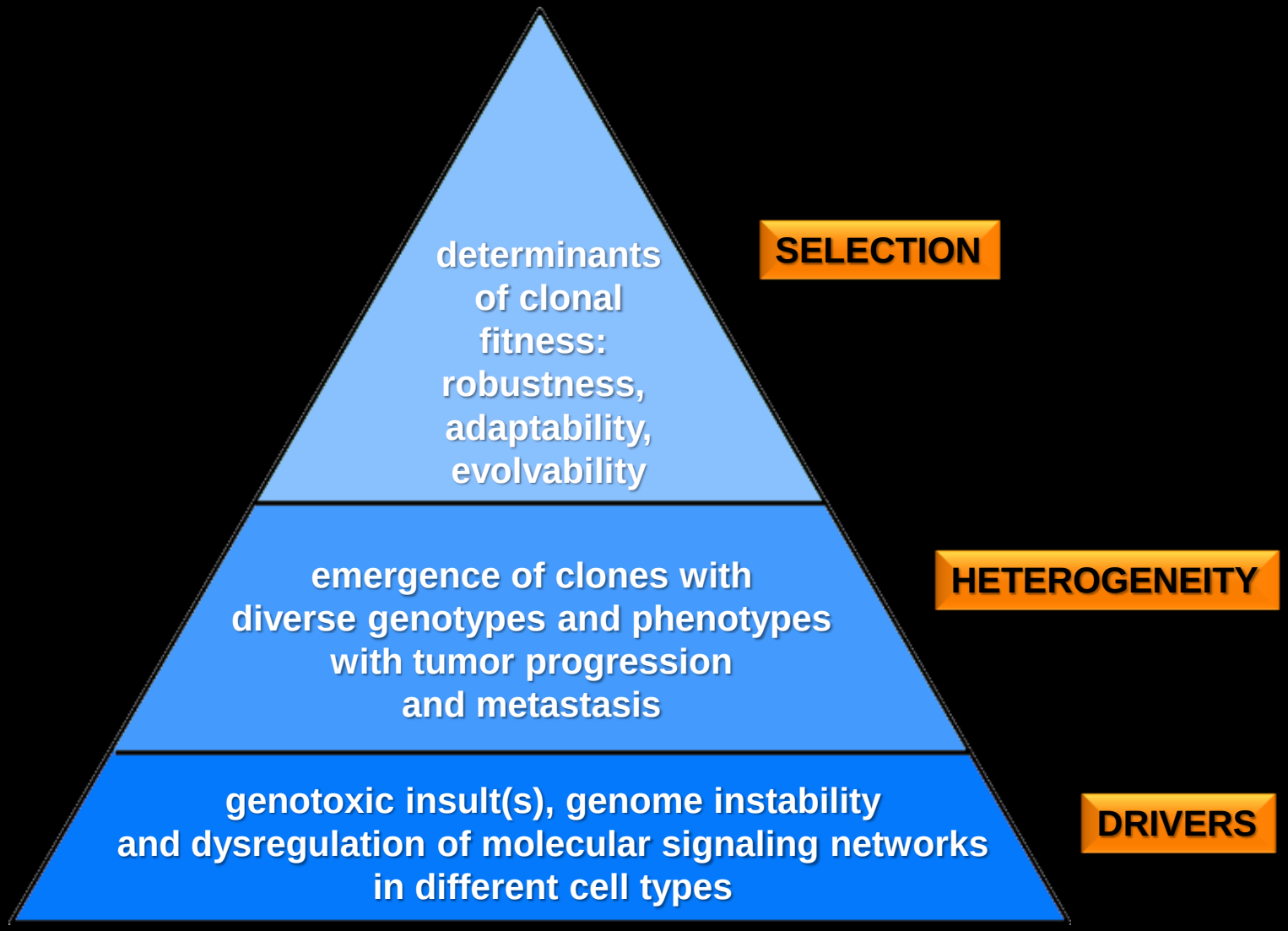
Tumor Dormancy Versus Metastatic Progression



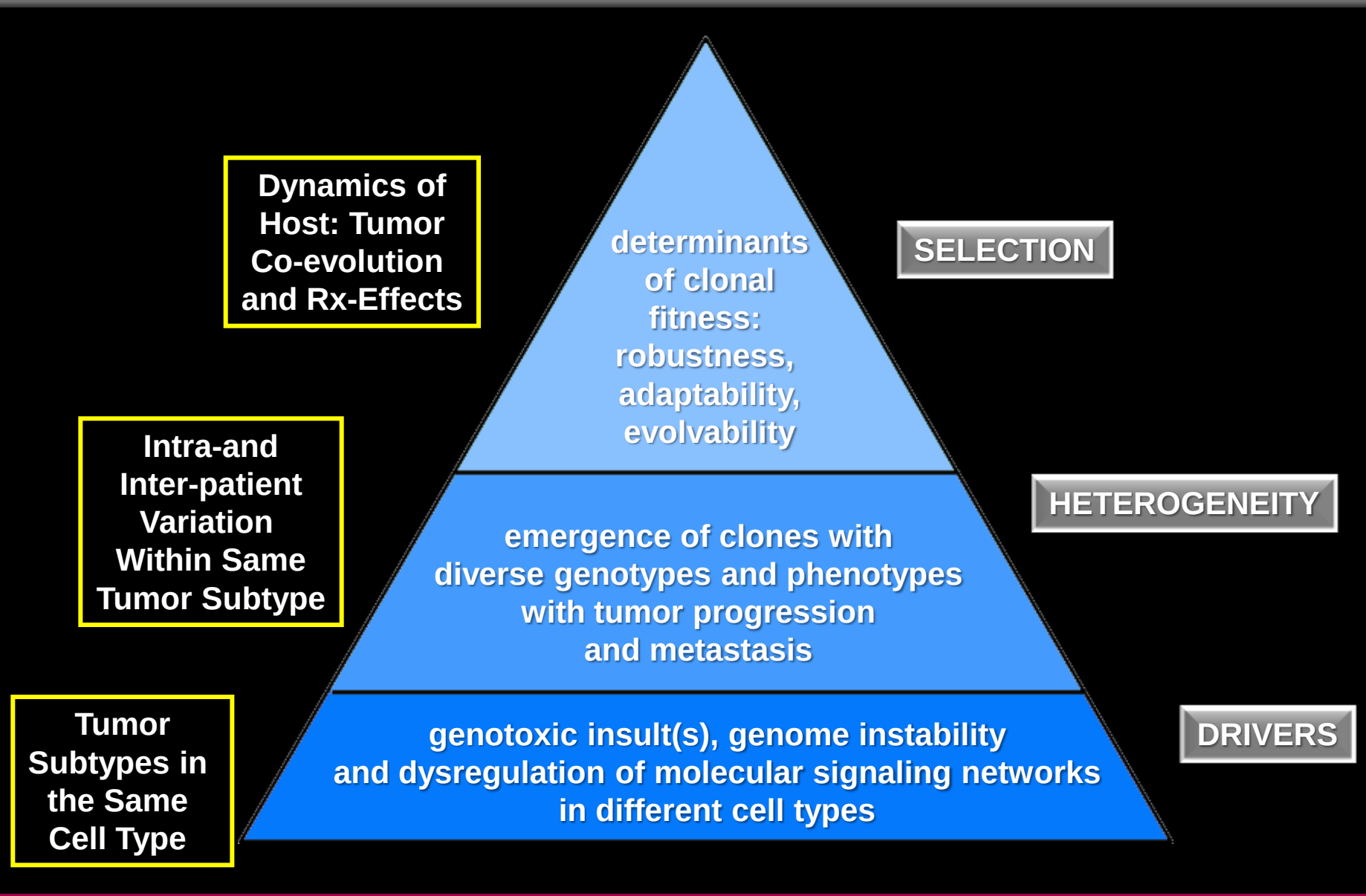
From: D. F. Quail & J. A. Joyce (2013) Nature Med. 19, 1423

Summary and Key Points

Cancer


determinants of clonal fitness: robustness, adaptability, evolvability
SELECTION
emergence of clones with diverse genotypes and phenotypes with tumor progression and metastasis
HETEROGENEITY
genotoxic insult(s), genome instability and dysregulation of molecular signaling networks in different cell types
DRIVERS

Cancer


Dynamics of Host: Tumor Co-evolution and Rx-Effects
Intra-and Inter-patient Variation Within Same Tumor Subtype
Tumor Subtypes in the Same Cell Type
determinants of clonal fitness: robustness, adaptability, evolvability
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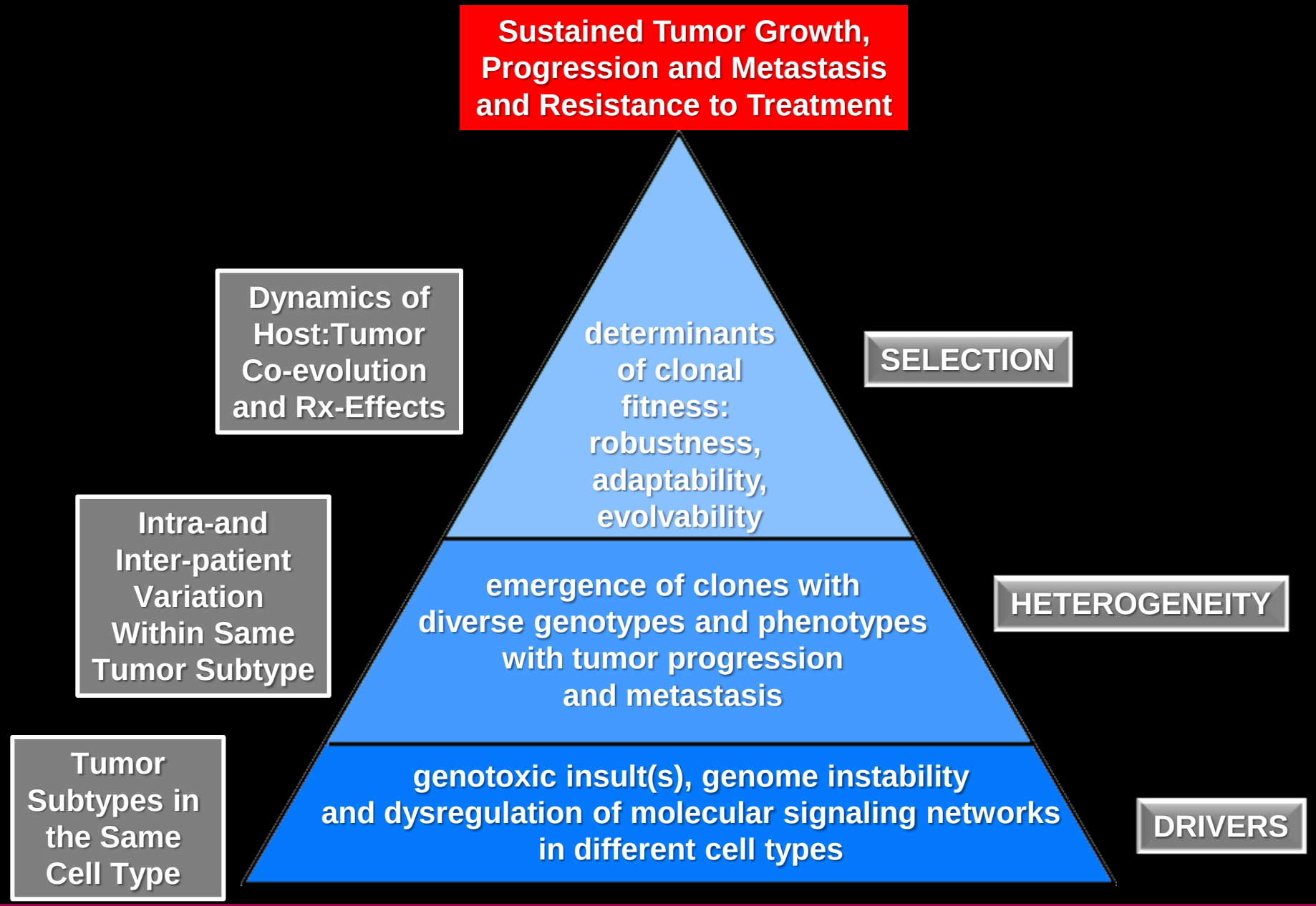
Cancer


Sustained Tumor Growth, Progression and Metastasis and Resistance to Treatment
Dynamics of Host:Tumor Co-evolution and Rx-Effects
determinants of clonal fitness: robustness, adaptability, evolvability
SELECTION
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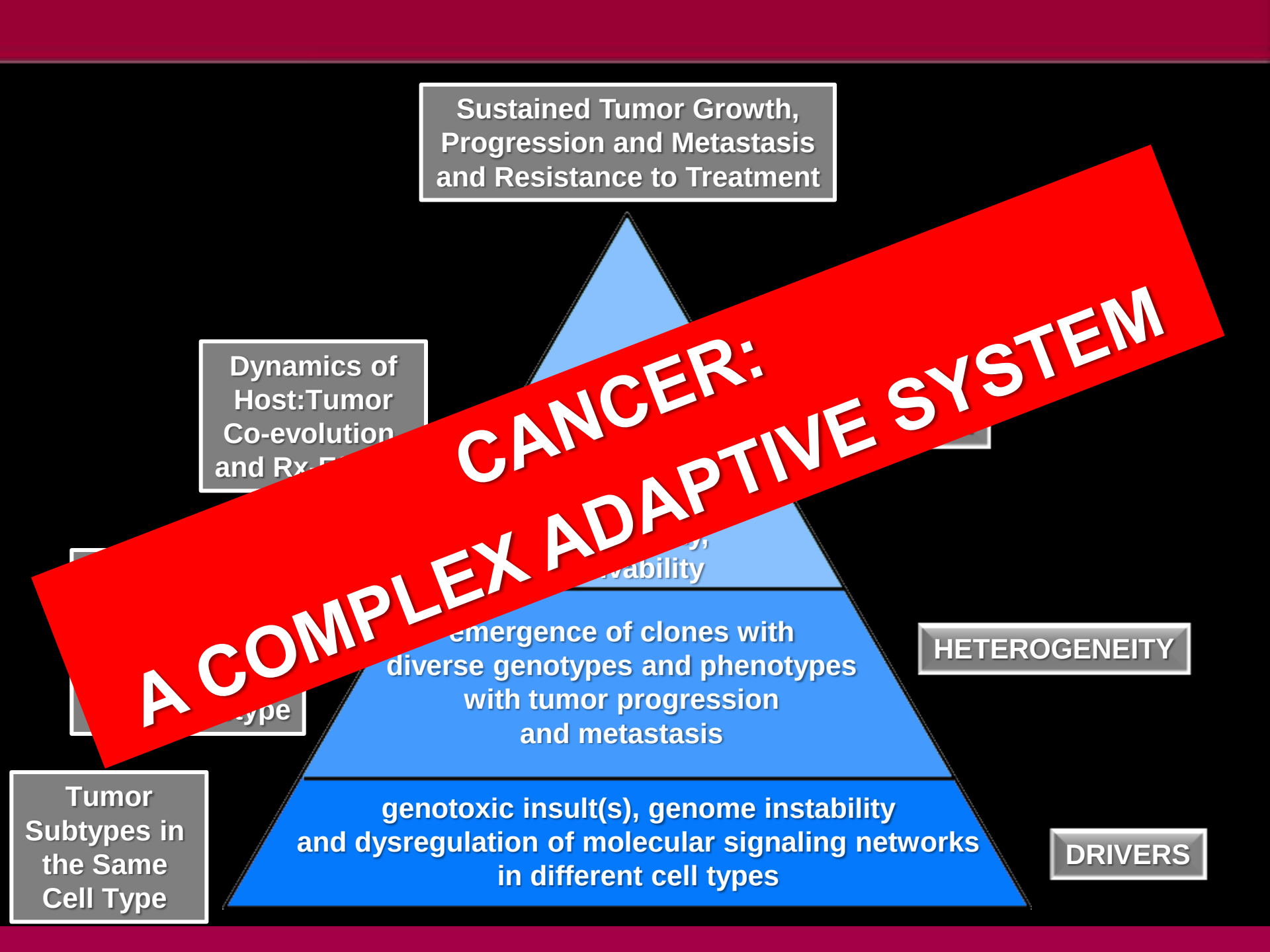
emergence of clones with diverse genotypes and phenotypes with tumor progression and metastasis
HETEROGENEITY
Tumor Subtypes in the Same Cell Type
genotoxic insult(s), genome instability and dysregulation of molecular signaling networks in different cell types
DRIVERS

The ‘Fitness’ of the Metastatic Clone: “The Decathlon Phenotype”

- survival in the primary tumor
- invasion of surrounding tissue
- epithelial-mesenchymal transition
- intravasation
- survival in the circulation
- extravasation
- colonization of new metastatic site
- mesenchymal-epithelial transition
- evasion of destruction by host immune defenses
- resist therapeutic assaults


Sustained Tumor Growth, Progression and Metastasis and Resistance to Treatment
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genotoxic insult(s), genome instability and dysregulation of molecular signaling networks in different cell types
DRIVERS
Tumor Subtypes in the Same Cell Type

Cancer as a Complex Adaptive System (CAS)

Lecture 2

- mapping the dynamics of the evolution of clones with genotypic and phenotypic differences (heterogeneity) during progressive tumor growth and metastatic spread
- how knowledge of the co-evolution of tumor behavior and host responses is essential to design improved diagnostic and therapeutic approaches in cancer