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Cancer Biology I-PATHG4500 FALL 2025

COURSE DIRECTORS

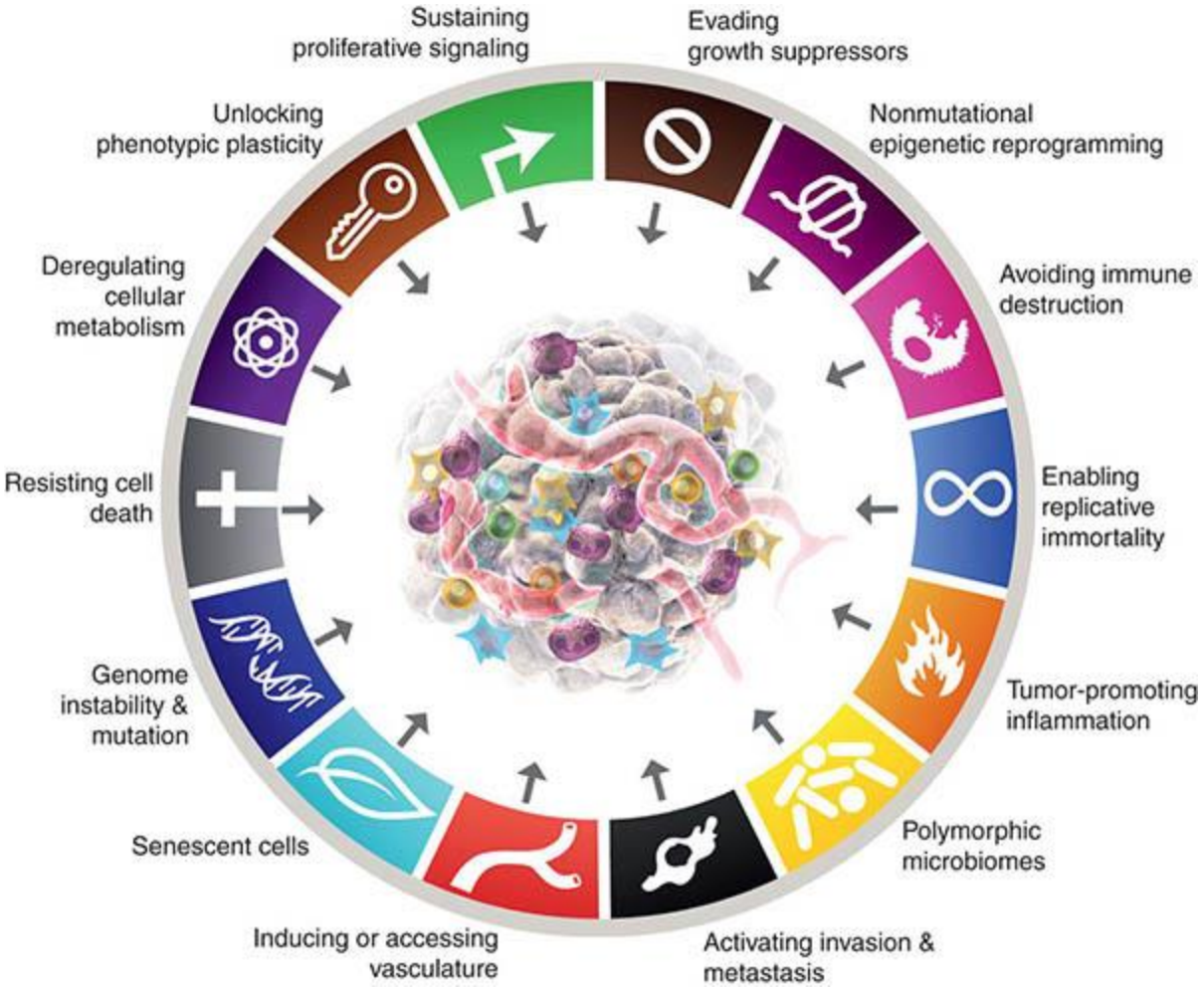
CHRISTINE CHIO

TERESA PALOMERO

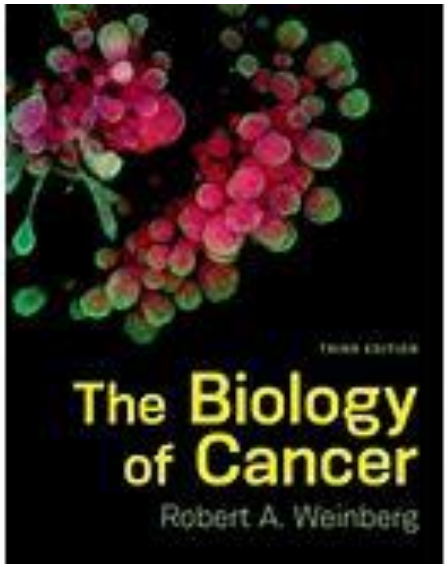
STAVROULA KOUSTENI

tp2151@cumc.columbia.edu
ic2445@cumc.columbia.edu
sk2836@cumc.columbia.edu

Cancer Biology I PATHG4500



Cancer Biology I PATHG4500-MATERIALS



Recommended Textbook

The Biology of CANCER

Robert A. Weinberg

Third Edition (2023)

Course Materials will be uploaded in CourseWorks and in the Course Website:

https://www.vagelos.columbia.edu/departments-centers/institute-cancer-genetics/courses

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Cancer Biology I PATHG4500-FACULTY

Cancer Biology I PATHG4500 EVALUATION

Mid-term and Final Exams: both "**take-home, open book**" essay-format; about one week's time to complete each exam

Attendance to classes is recorded and could impact final scores (QR code)

1.Exam Scores

The final exam grade is calculated based on performance in both assessments (midterm and final). The combined total score is prorated to account for the different number of questions in each exam.

2. Attendance Bonus

Bonus points based on attendance are added as follows:

- **Attendance over 60%**: +1% to final grade
- **Attendance over 70%**: +2% to final grade
- **Attendance over 80%**: +4% to final grade
- **Attendance over 90%**: +6% to final grade

This attendance bonus is added to the final exam score to reward consistent participation. Excused absences that were notified to course directors (attendance to scientific meetings, medical exemptions etc) have been counted as present in the final score.

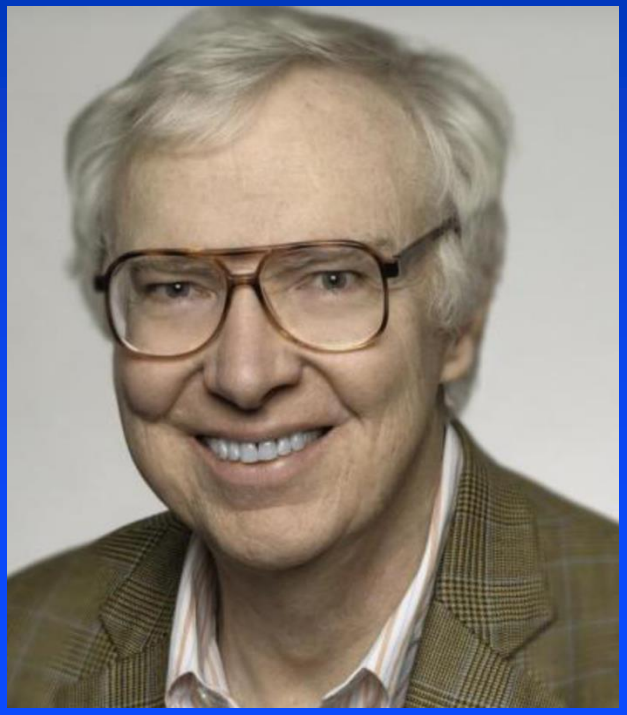
3. Grade Adjustment (Top Score Benchmark)

Final score will be adjusted based on the highest score in the class.

Letter scores are assigned based on the following: A+ (97–100), A (93–96), A- (90–92), B+ (87–89), B (83–86), B- (80–82), C+ (77–79), C (73–76), C- (70–72), D+ (67–69), D (65–66), D- (below 65).

Introduction to Cancer Biology

Lecturer: Richard Baer, Ph.D.
rb670@cumc.columbia.edu



Basic tenets of cancer biology

- Acquisition of the malignant phenotype occurs genetically (or epigenetically).
- Most cancers have a clonal origin.
- Cancer development is a multistep process.
- Each step results from a specific genetic or epigenetic alteration.
- Cancer results from the accumulation of multiple genetic alterations.
- Each step of tumor evolution is subject to clonal selection.
- Some genetic alterations represent rate-limiting steps on the path to cancer.
- The genetic alterations associated with malignancy are induced principally by viruses, chemicals, radiation, and random errors.

Basic tenets of cancer biology

→ Acquisition of the malignant phenotype occurs genetically (at the DNA level) or epigenetically (especially histone modifications).

- Most cancers have a clonal origin.
- Cancer development is a multistep process.
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- Cancer results from the accumulation of multiple genetic alterations.
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Basic tenets of cancer biology

- Acquisition of the malignant phenotype occurs genetically.

→ Most cancers have a clonal origin.

  - within an evolving clone of tumor cells, the malignant phenotype is heritable.

- Cancer development is a multistep process.
- Each step results from a specific genetic or epigenetic alteration.
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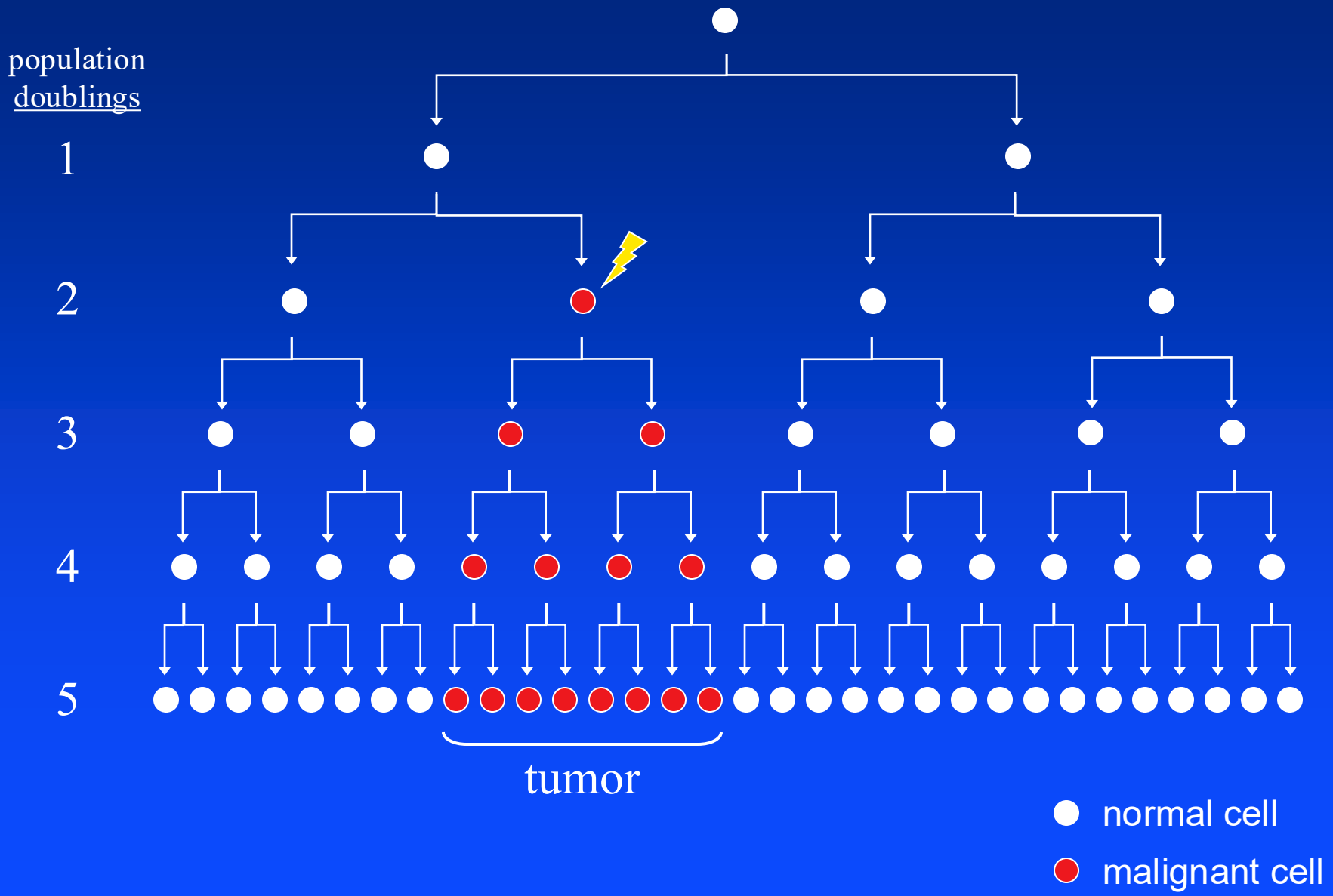
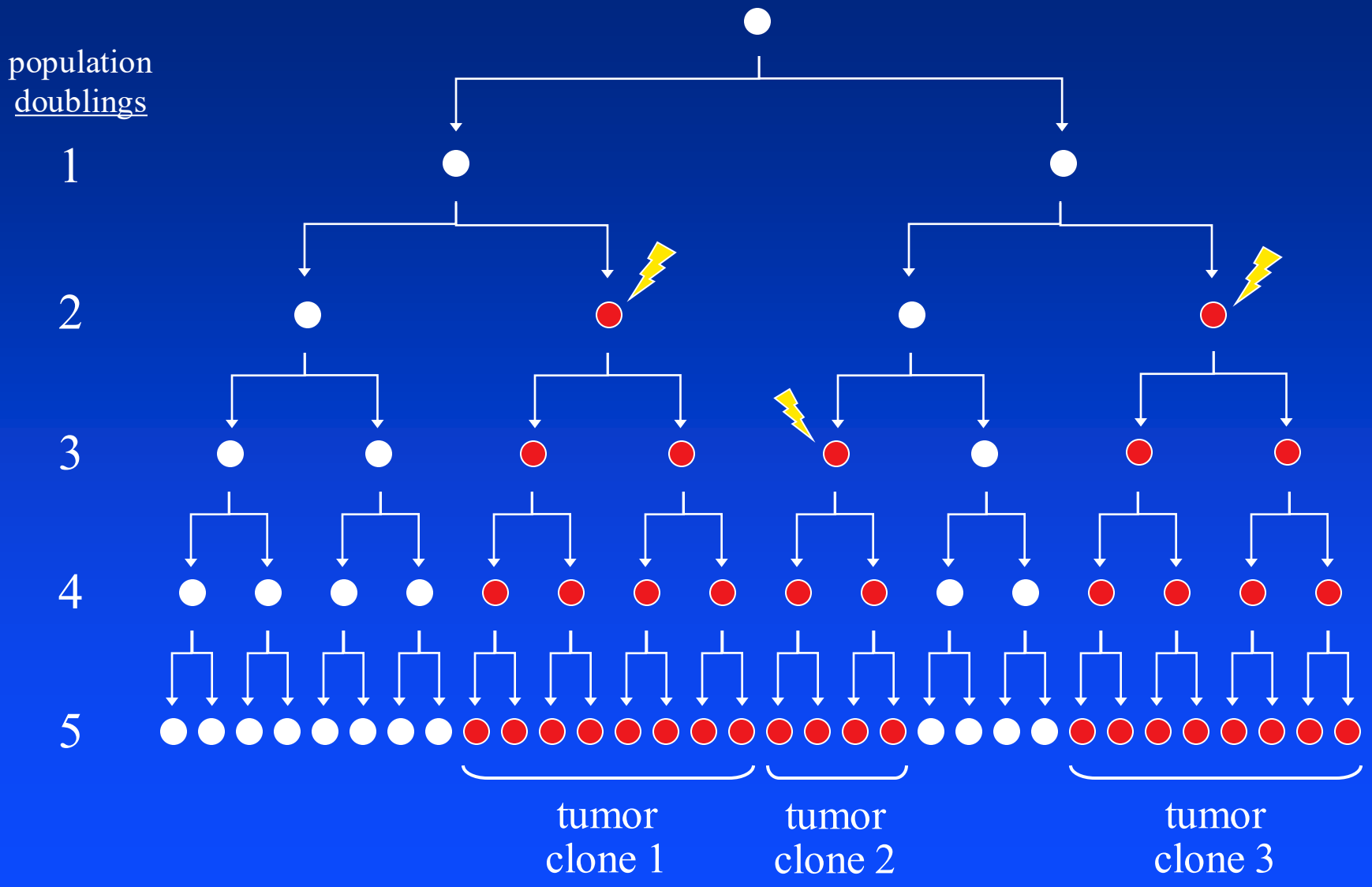
Most tumors have a clonal origin



Polyclonal tumors are rare



Basic tenets of cancer biology

- Acquisition of the malignant phenotype occurs genetically (at the DNA level).
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→ Cancer development is a multistep process.

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Phenotypic properties of cancer cells

- Loss of control over cell growth
- Failure of cellular differentiation
- Inappropriate resistance to cell death
- Acquisition of angiogenic capacity
- Evasion of host immunity
- Acquisition of metastatic potential
  - destruction of basal lamina
  - infiltration of local connective tissue
  - intravasation
  - extravasation
  - distal colonization

Basic tenets of cancer biology

- Acquisition of the malignant phenotype occurs genetically (at the DNA level).
- Most cancers have a clonal origin.
- Cancer development is a multistep process.

→ Each step attributable to specific genetic or epigenetic alterations.

- Cancer results from the accumulation of multiple genetic alterations.
- Each step of tumor evolution is subject to clonal selection.
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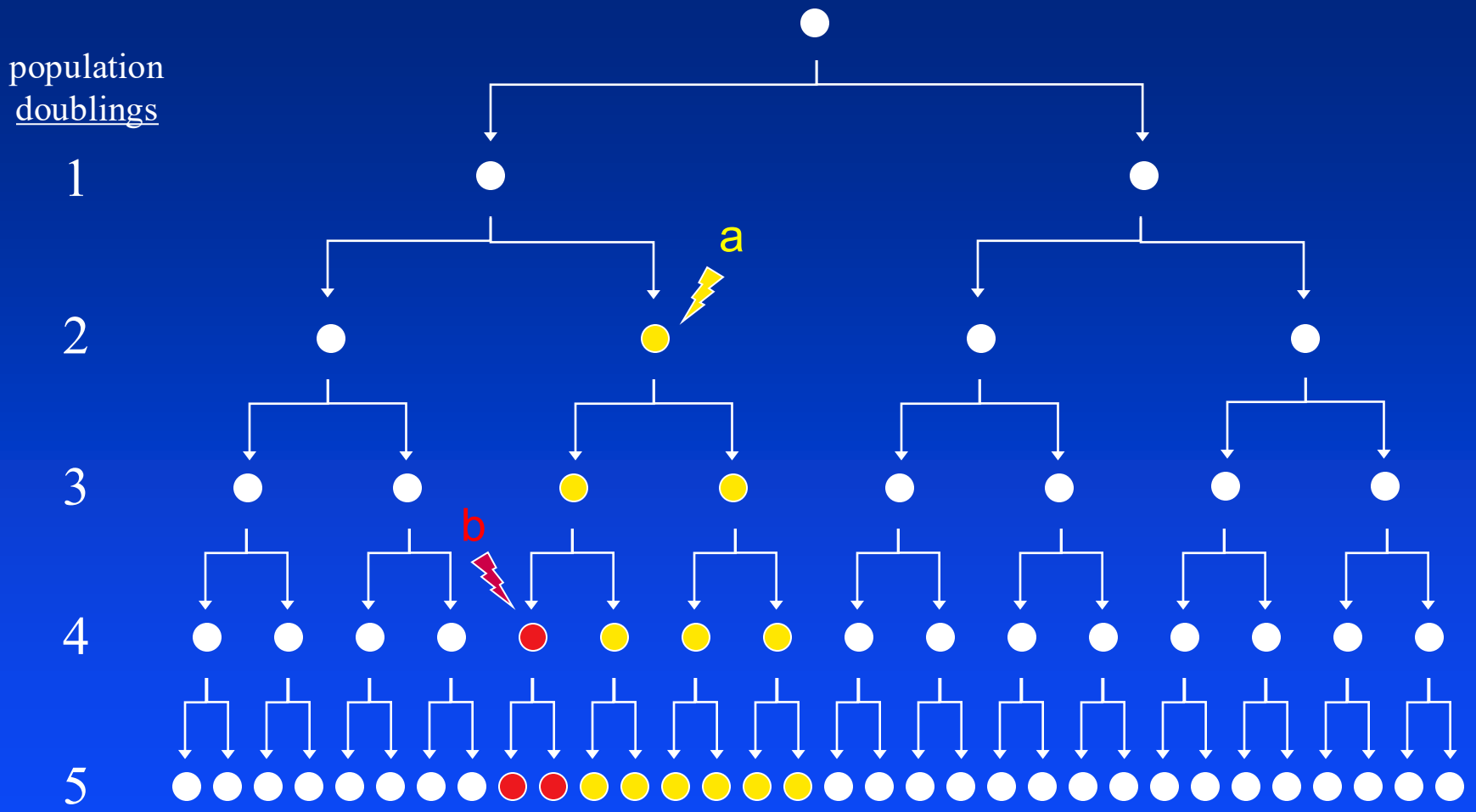
Multistep nature of cancer development



Basic tenets of cancer biology

- Acquisition of the malignant phenotype occurs genetically (at the DNA level).
- Most cancers have a clonal origin.
- Cancer development is a multistep process.
- Each step results from a specific genetic or epigenetic alteration.

→ Cancer results from the accumulation of multiple genetic alterations.

  - most are acquired somatically, though some can be inherited.

- Each step of tumor evolution is subject to clonal selection.
- Some genetic alterations represent rate-limiting steps on the path to cancer.
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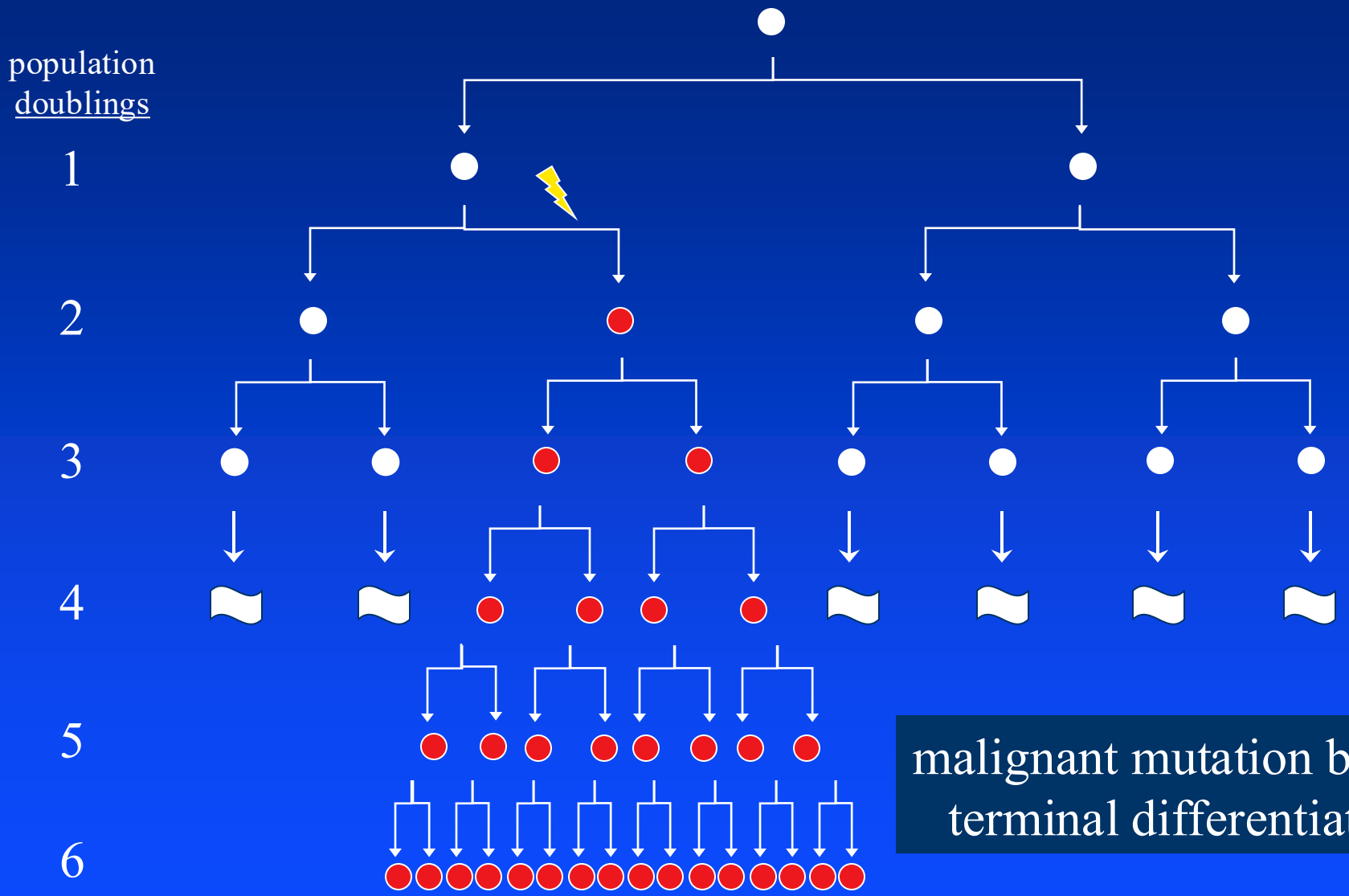
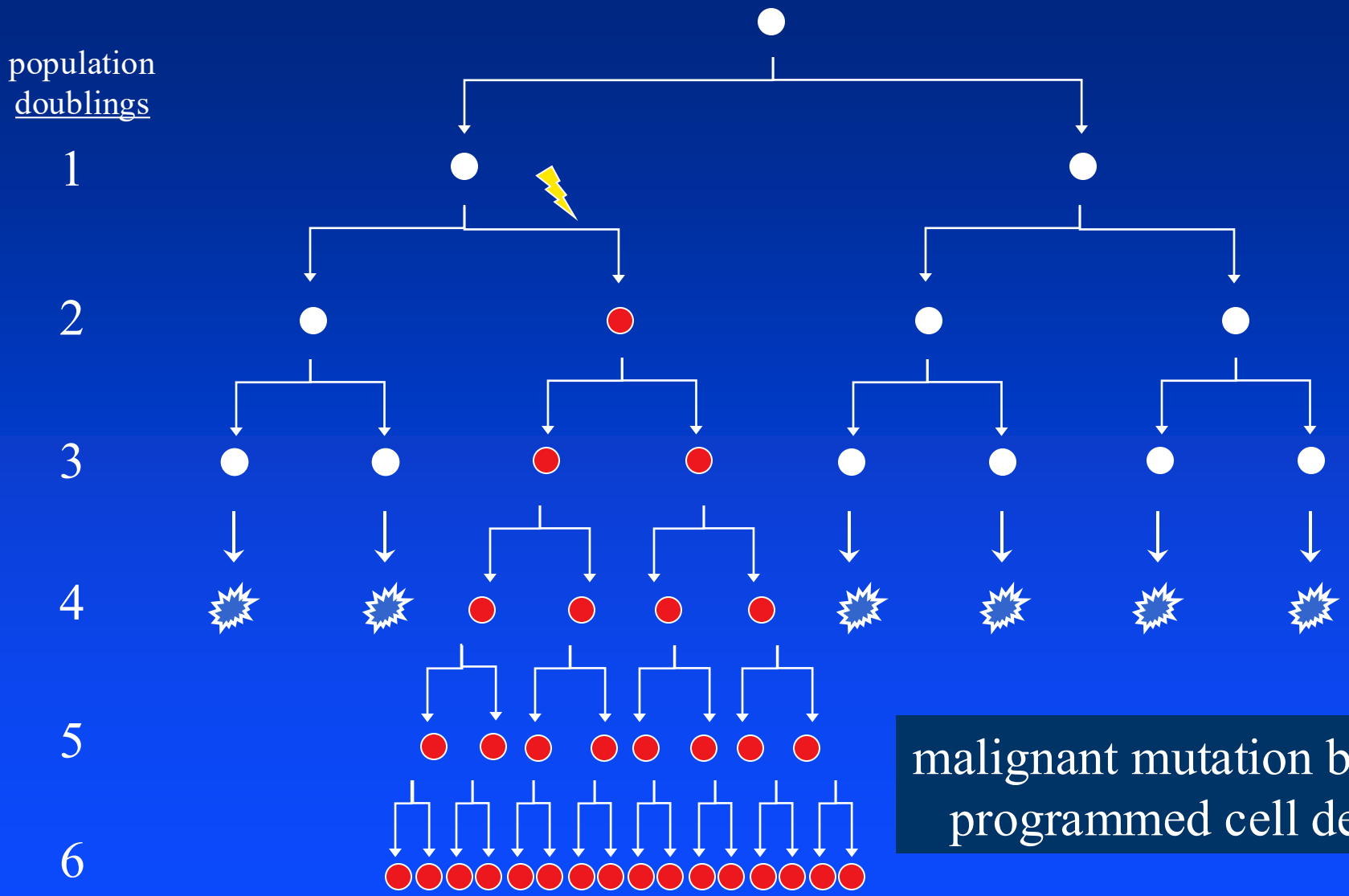
Selection for malignant clone - I



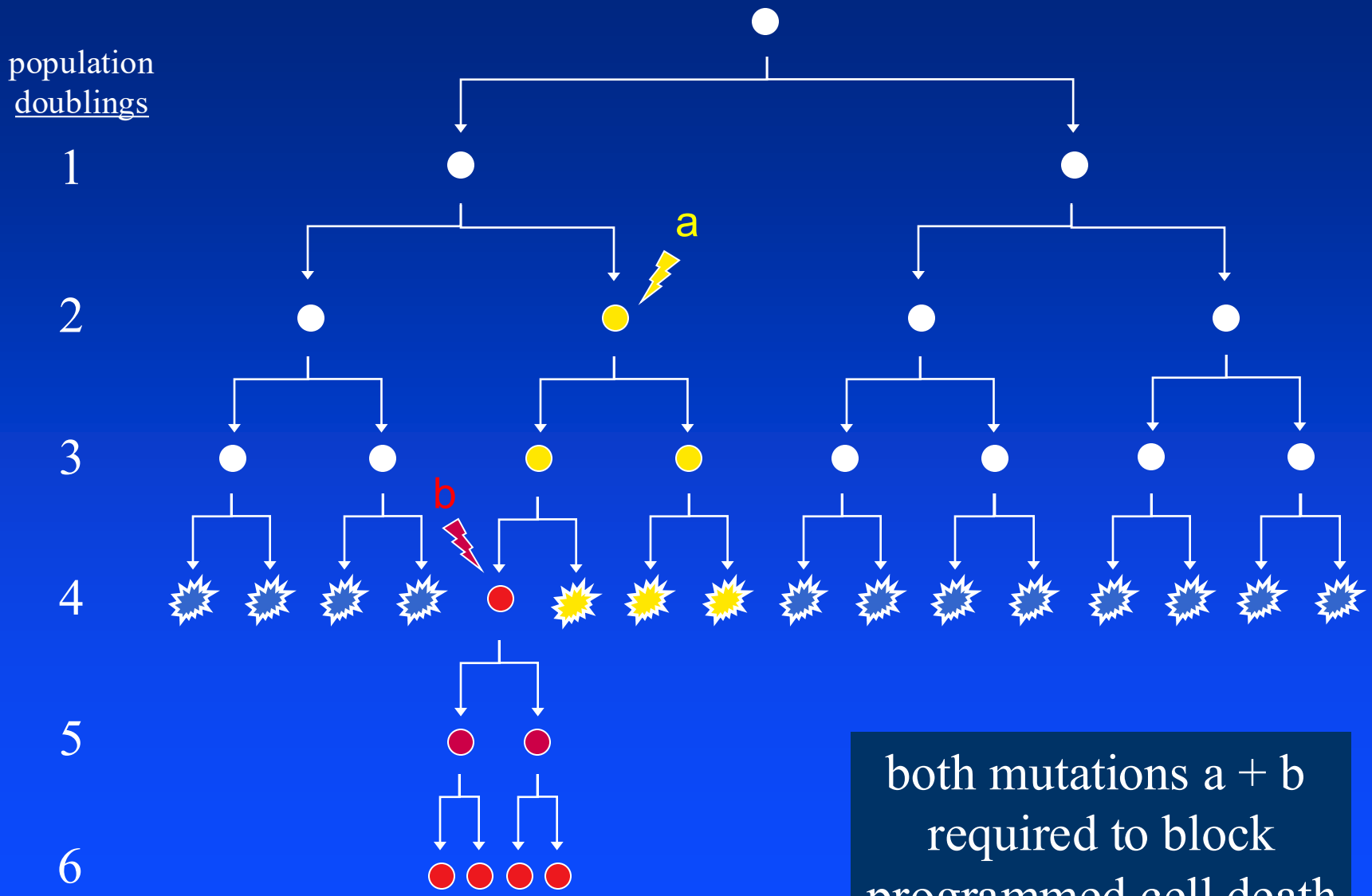
malignant mutation blocks terminal differentiation

Selection for the malignant clone - II



malignant mutation blocks programmed cell death

Selection for the malignant clone - III



both mutations a + b
required to block
programmed cell death

Basic tenets of cancer biology

- Acquisition of the malignant phenotype occurs genetically (at the DNA level).
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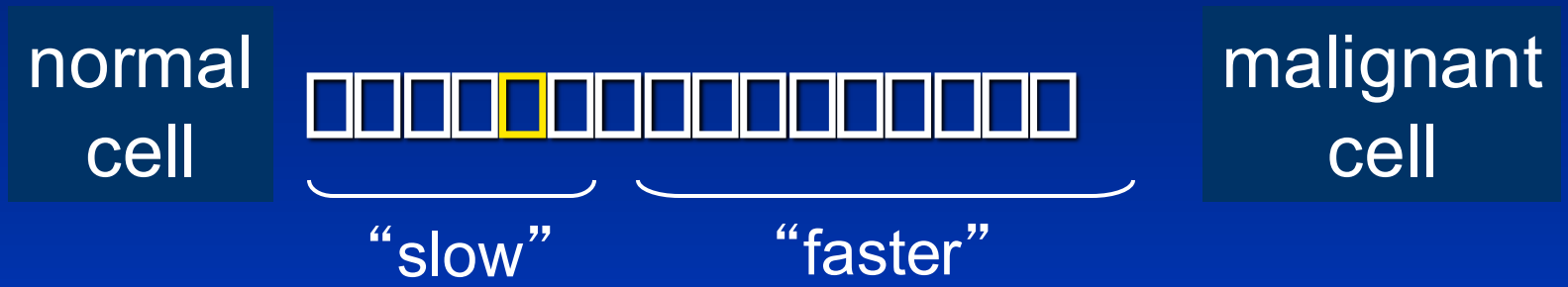
Rate-limiting steps in cancer development



possible rate-limiting steps:

- alterations that increase the rate of cell division
  - activation of the c-Myc oncogene
  - inactivation of the Rb tumor suppressor gene
- alterations that decrease genomic stability
  - inactivation of mismatch repair genes (hMSH2, hMLH1)
  - p53 mutations

Basic tenets of cancer biology

- Acquisition of the malignant phenotype occurs genetically (at the DNA level).
- Most cancers have a clonal origin.
  - within an evolving clone of tumor cells, the malignant phenotype is heritable.
- Cancer development is a multistep process.
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- Cancer results from the accumulation of multiple genetic alterations.
- Each step of tumor evolution is subject to clonal selection.
- Some genetic alterations represent rate-limiting steps on the path to cancer.

→ These alterations are induced principally by random errors, genome instability, viruses, chemicals, and/or radiation.

- What are the genetic targets of these tumorigenic agents ?

Genome Instability

- Tumor cells typically exhibit widespread genomic instability:
  - Chromosomal level (translocations, inversions, DMs, HSRs, etc.)
  - Sequence level (nucleotide substitutions, duplications, indels, etc.)
- Often caused by defects in specific DNA repair pathways: e.g.,
  - DNA break repair by homologous recombination
  - DNA mismatch repair
- Many other mechanisms of genome instability:
  - loss of cell cycle checkpoint control, replication stress, etc.
- Thus, cancer cells typically harbor many genetic lesions:
  - most are inconsequential: "Passenger mutations"
  - some promote tumorigenesis: "Driver mutations"
- What are the genetic targets of driver mutations?

Cancer genes

- What genes, when altered, promote cancer?
  - proto-oncogenes and tumor suppressor genes
- Some are altered in a restricted set of tumor types
  - e.g., the APC tumor suppressor in colorectal carcinoma
- Others are altered in a broad spectrum of tumor types
  - e.g., p53 tumor suppressor and the Ras proto-oncogenes
- The importance of tumor gene "pathways"
  - the Rb and p53 pathways

Proto-oncogenes vs. tumor suppressor genes

A proto-oncogene promotes cancer when its function is malignantly activated

- An activated proto-oncogene contributes to tumorigenesis by "gain-of-function"
- Thus, an activated proto-oncogene is genetically dominant at the cellular level
  - an activated oncogene can elicit a new phenotype (tumorigenesis) even in the presence of the corresponding wildtype allele

Proto-oncogenes vs. tumor suppressor genes

A tumor suppressor gene promotes cancer when its function is malignantly inactivated

- A tumor suppressor contributes to tumorigenesis by "loss-of-function"
- In most instances, an inactivated tumor suppressor gene is genetically recessive at the cellular level.
  - it will not promote tumorigenesis in diploid cells unless the other (wildtype) allele is also lost or inactivated
  - some exceptions:
    - dominant-negative p53 mutations
    - “haploinsufficient” tumor suppressor genes

Some prominent tumor pathways

pathways	oncogenes	tumor suppressor genes
Rb	Cyclin D1, CDK4, E2F	Rb, p16
p53	MDM2	p53, ATM, p21
AKT	PI3K, AKT, RAS	PTEN
Ras	HRAS, KRAS, NRAS, BRAF	NF1
hedgehog	SMO	PTCH1, PTCH2, SUFU
Wnt	Wnt1, β-catenin, TCF1	APC, AXIN1, SFRP1
BRCA		BRCA1, BRCA2, BARD1, PalB2

Cancer susceptibility syndromes

- Fewer than 10% of human cancers are heritable
- Hereditary syndromes of cancer susceptibility are usually caused by germline mutations of tumor suppressor genes.
  - Familial retinoblastoma: Rb
  - Li-Fraumeni syndrome: p53
  - Familial adenomatous polyposis coli: APC
  - Hereditary non-adenomatous c.c.: MLH1, MSH2
  - Familial breast and ovarian cancer: BRCA1, BRCA2

Recordings of Dr. Baer full lectures:

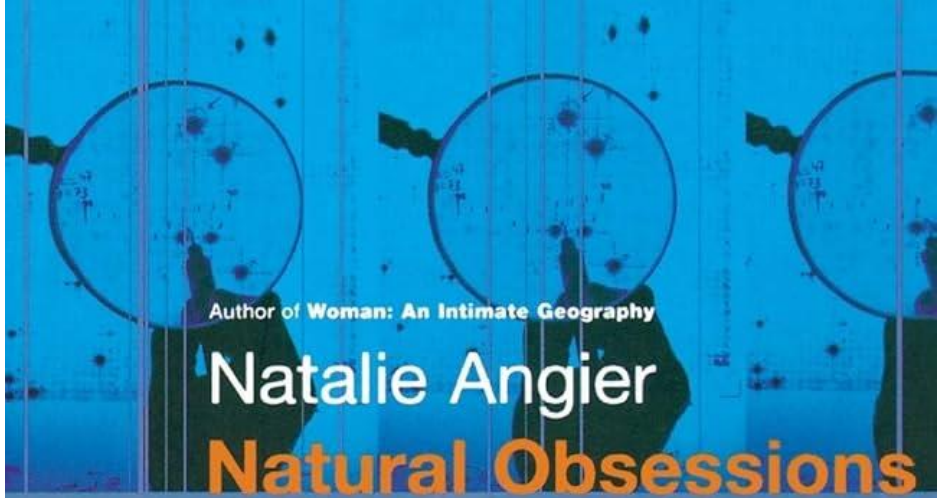
Lecture 1:

https://drive.google.com/file/d/1MFQvnaucaNieRRZlvE3lnf8SfIsSeKOO/view?usp=sharing

Lecture 2:

https://drive.google.com/file/d/1yMVcJsOD6tFPaB_nYvbFGrxCBiAPpcu3/view?usp=sharing

Midterm will be based on the contents of the full lectures



Author of **Woman: An Intimate Geography**

Natalie Angier

Natural Obsessions

striving to unlock the deepest secrets of the cancer cell

With a foreword by Lewis Thomas
and a new introduction by
the Pulitzer Prize–winning author

"A work of grand adventure, beauty,
and literature." — **Chicago Tribune**

MARINER BOOKS