Cancer Biology I
BIO-471
Fall Semester

Teachers:

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ISREC @EPFL
Institut Suisse de Recherche Expérimentale sur le Cancer

EPFL

Galina Glousker

galina.glousker@epfl.ch

- Saint-Petersburg State University

Studies in Biology of the Cell

- Hebrew University of Jerusalem

PhD (with Dudy Tzfati): Telomeropathies

- EPFL

Postdoc (with Joachim Lingner): DNA damage at telomeres

Staff Scientist (with Joachim Lingner)

Joachim Lingner – brief biography

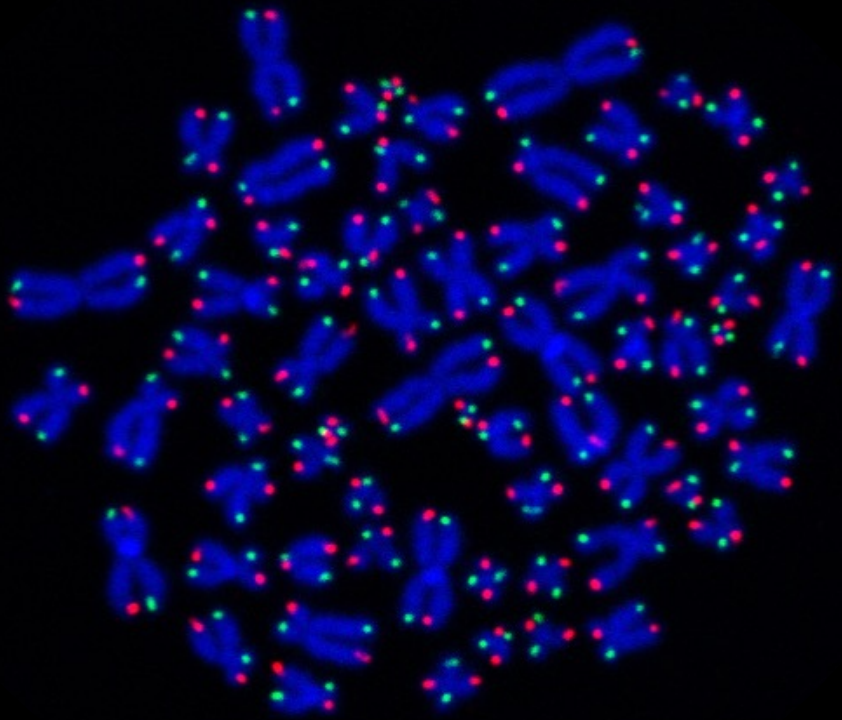
- Biozentrum of the University of Basel
Studies in Biology II
PhD (with Walter Keller): RNA processing

- HHMI, University of Colorado, Boulder
Postdoc (with Thomas Cech): Telomerase

- Group Leader at ISREC, Professor at EPFL:
Telomeres and telomerase in health and disease
(https://www.epfl.ch/labs/lingner-lab/)

Lingner-lab

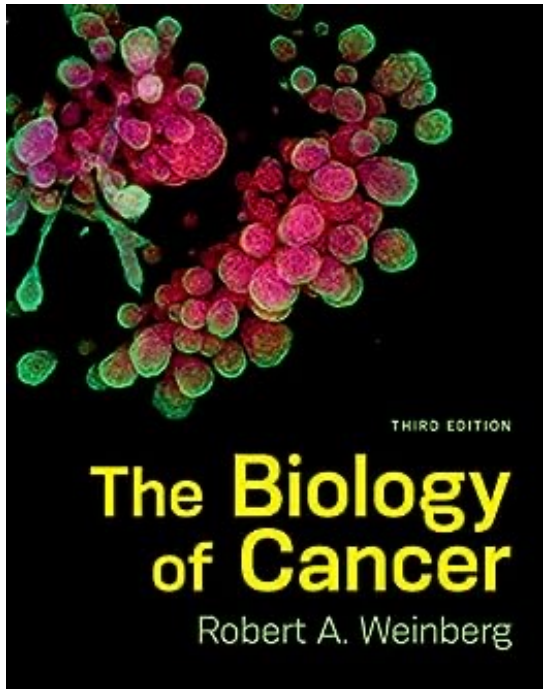
Telomeres and telomerase in health and disease



Readings

THE book:

Robert A. Weinberg
The Biology of Cancer
W. W. Norton & Company; Third edition (July 1, 2023)



On Moodle for this week:

- Hallmarks of Cancer: The Next Generation
Douglas Hanahan and Robert A. Weinberg. Cell **144**, 646-674, 2011
- Principles of Cancer Therapy: Oncogene and Non-Oncogene Addiction.
Ji Luo *et al.*: Cell **236**, 823-837, 2009

More literature to be indicated and placed weekly on Moodle

Cancer Biology I :

- 2h + 3h lectures/exercises every week.
- Mondays at 14:15-16:00: **lectures** in room **AAC132**
- Wednesdays 13:15-16:00: **short lectures / introduction to exercises and exercises** in room **CE1103**.

- You will form **groups** to discuss and answer within your group all the questions. You may create and interact via zoom or in person as convenient for you. At approximately 3 pm, individual groups present and discuss the answers that have been assigned to their group in front of the class.
- Group formation (maximally **5/group**): **inscribe in 1 of the 5 groups** via https://framadate.org/8Vgos7nr4uoNeGNJ
- **Understanding of the exercises is essential for passing the exam!**

Cancer Biology I :

Topics covered

Week 1:

- Lecture 1 (Monday 14:15-16:00: room **AAC132**): **Hallmarks of cancer – an overview; DNA damage**
  (Chapters 2, 4, 7 (Weinberg book))
- Exercises: Wednesday 13:15-16:00: room **CE1103** **Oncogenes and tumor suppressor genes**

Week 2:

- Lecture 2 (Wednesday 13:15-16:00: room **CE1103**):
  p53, genome instability and DNA repair of DNA double strand breaks; Synthetic lethality

Week 3:

- Lecture 3/Exercises: **DNA repair and the DNA damage response**

Week 4:

- Lecture 4/Exercises: **p53 and apoptosis**
  (Chapters 9 (Weinberg))

Cancer Biology I :

Topics covered

Week 5:

- Lecture 5/Exercises: **Telomeres and cellular senescence**

  (Chapters 10 (Weinberg))

Weeks 6:

- Lecture 6/Exercises: **CDKs and G1/S control**

  (Chapter 8 (Weinberg book): pRb and control of the cell cycle clock)

1 Week semester break

Week 7, Monday:

- Monday: **Q & A session: discussion of your questions**

  (to be submitted via email to me in advance during week 6!!!)

- **Wednesday October 30, 2024: exam (contrôle continu)**

Cancer Biology I :

Topics covered

Weeks 8-14: Elisa Oricchio

- **Major signaling pathways involved in cancer**
- **Genomic cancer analysis and rational cancer therapies**

- **Week 14: exam (contrôle continu)**

Cancer Biology I :

Objectives

- Introduction to the basic cellular processes that underlie the initiation and progression of cancer

- Become familiar with experimental approaches that can be applied to cancer research and biological research in general (**exercises**)

Cancer Biology II : Spring Semester

Teachers: Joerg Huelsken, Michele de Palma

Topics

- interactions of cancer cells with their environment
  - tumor-angiogenesis
  - inflammation
  - adaptive and innate immunity and cancer-induced immune suppression
- cancer metabolism
- cancer stem cells
- metastasis

Week 1, lecture 1 and exercises:

Hallmarks of cancer – an overview

Oncogenes and tumor suppressor genes

For further details, see:

- Chapters (Weinberg book) 2, 4, 7

and

- The Hallmarks of Cancer: The Next Generation Douglas Hanahan and Robert A. Weinberg Cell **144**, 646-674, 2011
- Cancer Genome Landscapes B. Vogelstein et al., Science 339, 6127, 1546-1558, 2013

What is cancer?

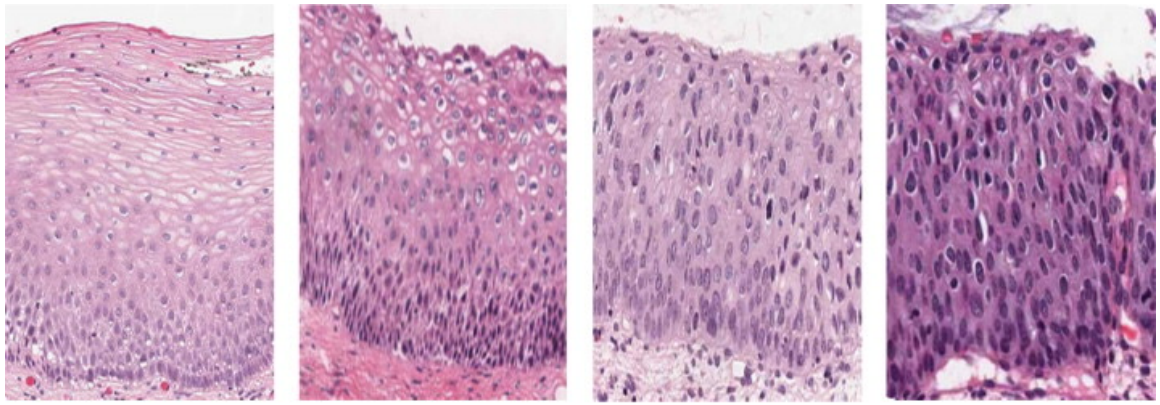
- A disease in which some of the body's cells grow uncontrollably and spread to other parts of the body:

  - **Neoplasm** (new growth)**:** abnormal growth of tissue often forming a **tumor** (or not: leukemia).

Tumor characteristics

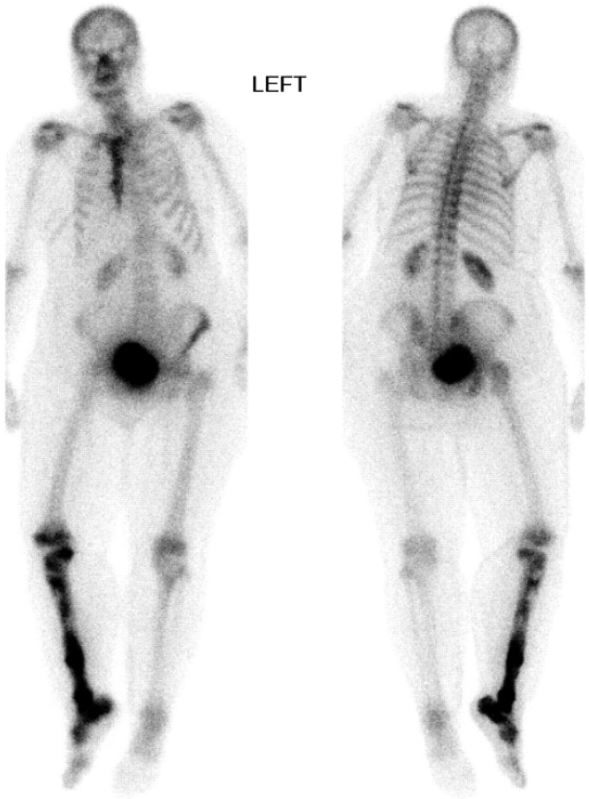
	benign	malignant
growth	growth locally, slow, expansive, often encapsulated	invades nearby tissue and forms metastases, rapid, nonencapsulated
metastases	No	Yes
recurrence after removal	No	frequent
histological findings	Relatively normal	Abnormal to varying degree
cytological findings	Normal	Varying degrees of anaplasia (reversion of differentiation)
mitoses	Absent	Usually numerous and abnormal
systemic effects	Rare	Usual

Tumor progression



CIN grading label examples. (a) Normal, (b) CIN 1, (c) CIN 2, and (d) CIN 3.

De et al., 2013



Dewdney and Selvarajah
Anticancer Research July 2010, 30 (7) 2949-2951;

Types of cancer

80% of all cancers are carcinomas

Cell type	Tissue	Derived tumors
Epithelial	Breast (milk secretion) Liver (bile secretion) Skin Linings of stomach, gut, bladder, lung, uterus	Adenocarcinomas (from secretory tissue) Sqamous carcinomas (from protective linings)
Connective tissue	Cartilage Bone Muscle Blood vessel	Chondrosarcomas Osteosarcomas Rhabdomyosarcomas Angiosarcomas
Blood forming	Bone marrow	Lymphomas, erythroleukemias, lymphocytic and myelogenous leukemias
Nerve	Peripheral nervous system (spinal cord, ganglia, adrenal cortex) Central nervous system (notably brain)	Neuroblastomas Gliomas, astrocytomas, medulloblastomas, neuromas, schwannomas

How many normal cells give rise to a tumor?

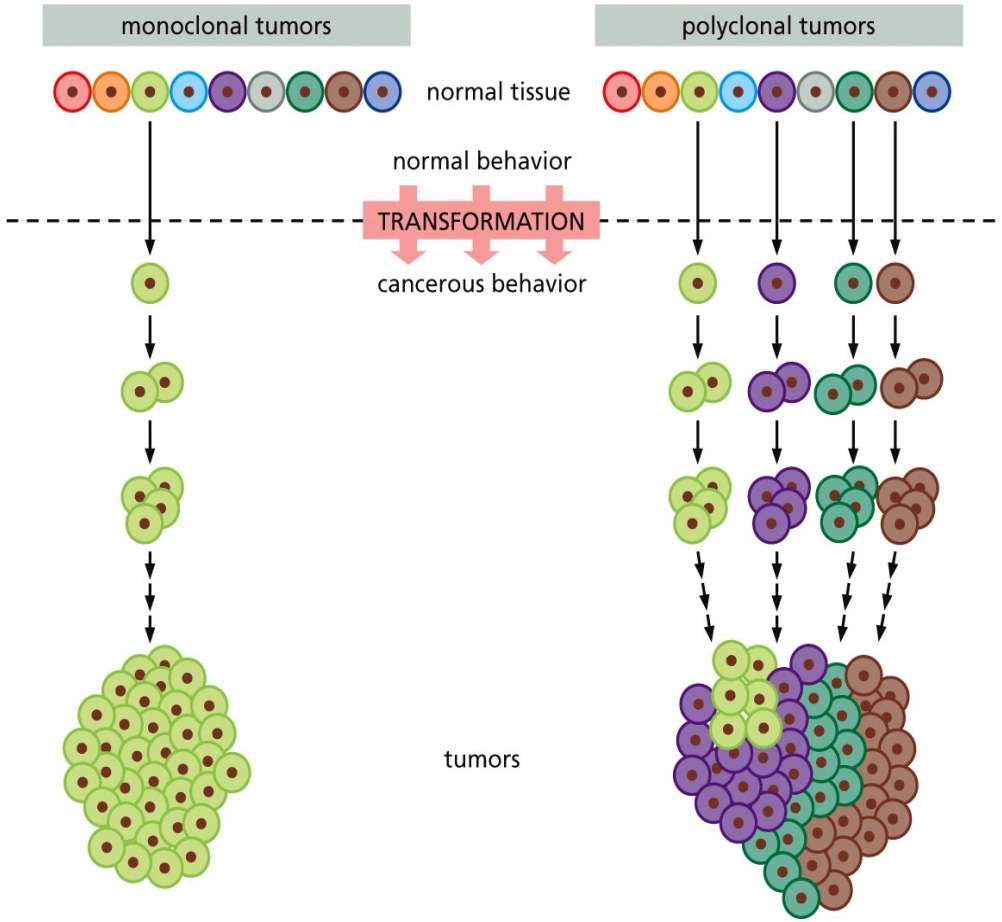


Figure 2.19 The Biology of Cancer (© Garland Science 2014)

X-Chromosome Inactivation Patterns

M – X chromosome inherited from the mother
P – X chromosome inherited from the father

The adult female body is made of patches of cells with active maternal (Mp) or Paternal (Pm) X chromosome

First shown in 1965 for leiomyomas (benign tumors of the uterine wall)

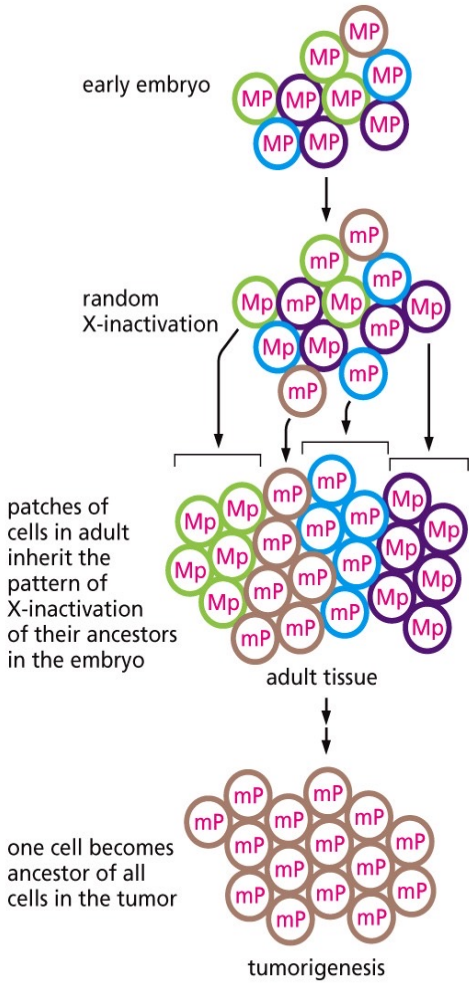


Figure 2.20a The Biology of Cancer (© Garland Science 2014)

Multiple Myeloma

A cancer of plasma cells

Plasma cells produce antibodies

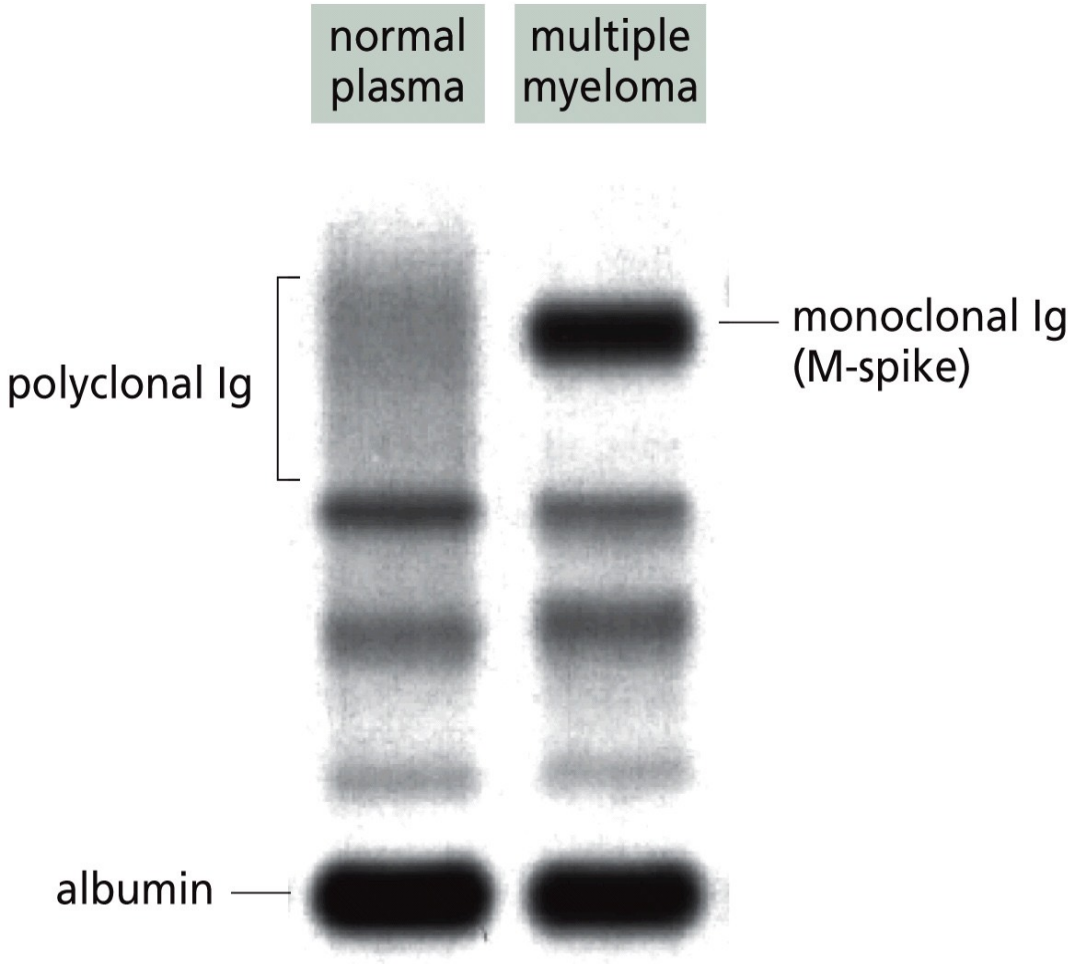
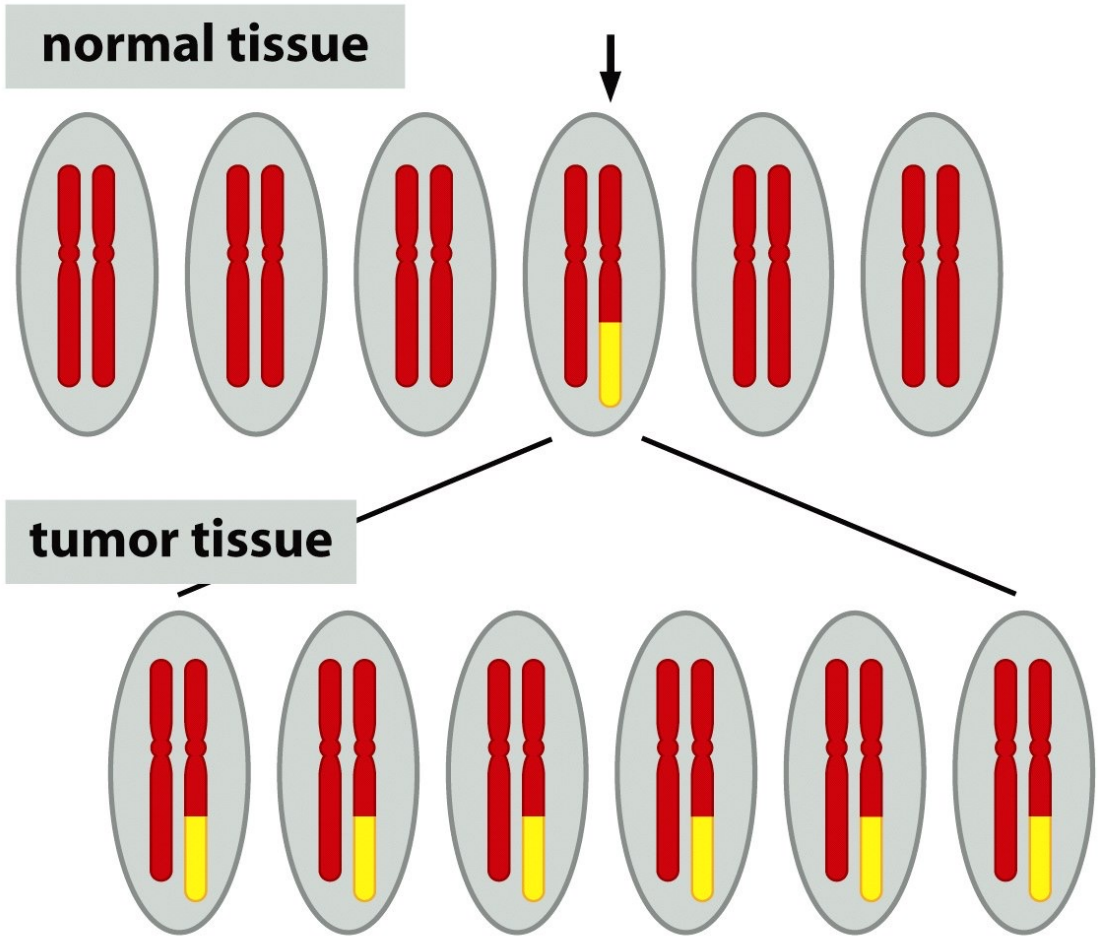


Figure 2.21a The Biology of Cancer (© Garland Science 2014)

Rare translocation



Philadelphia Chromosome in CML

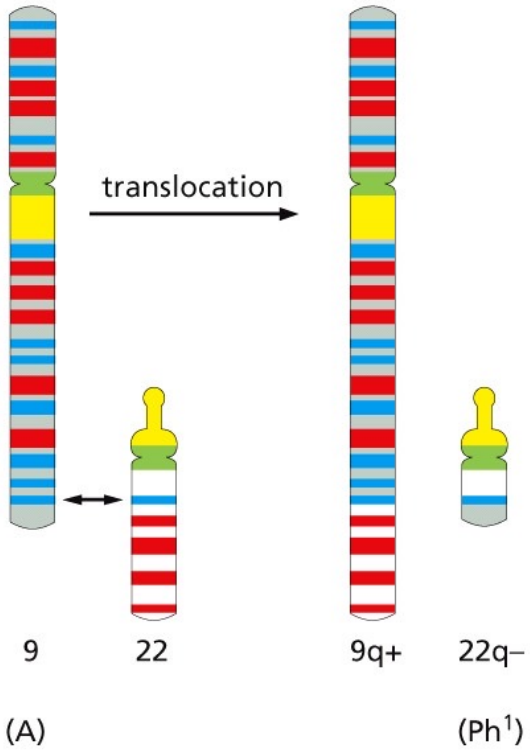
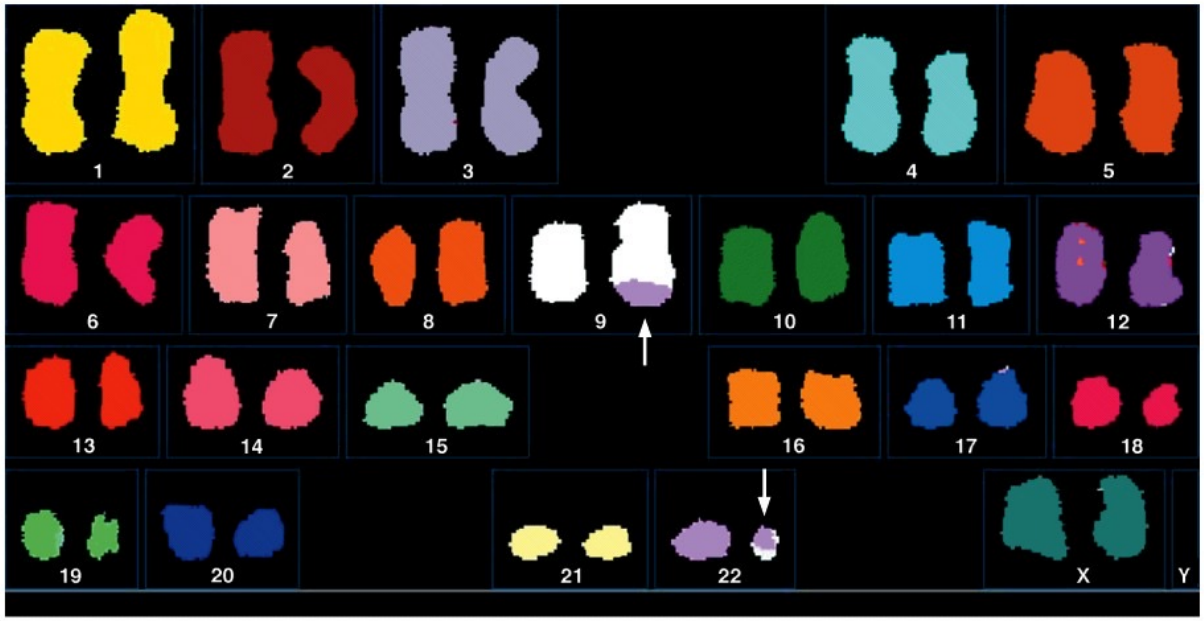


Figure 2.26 The Biology of Cancer (© Garland Science 2014)



(B)

Spectral Karyotyping (SKY) analysis

- In more than 90% of the patients
- ABL1 gene on chr 9 is fused to BCR on chr 22 >>> BCR-ABL oncoprotein with abnormal TK activity

Intratumoral Heterogeneiety

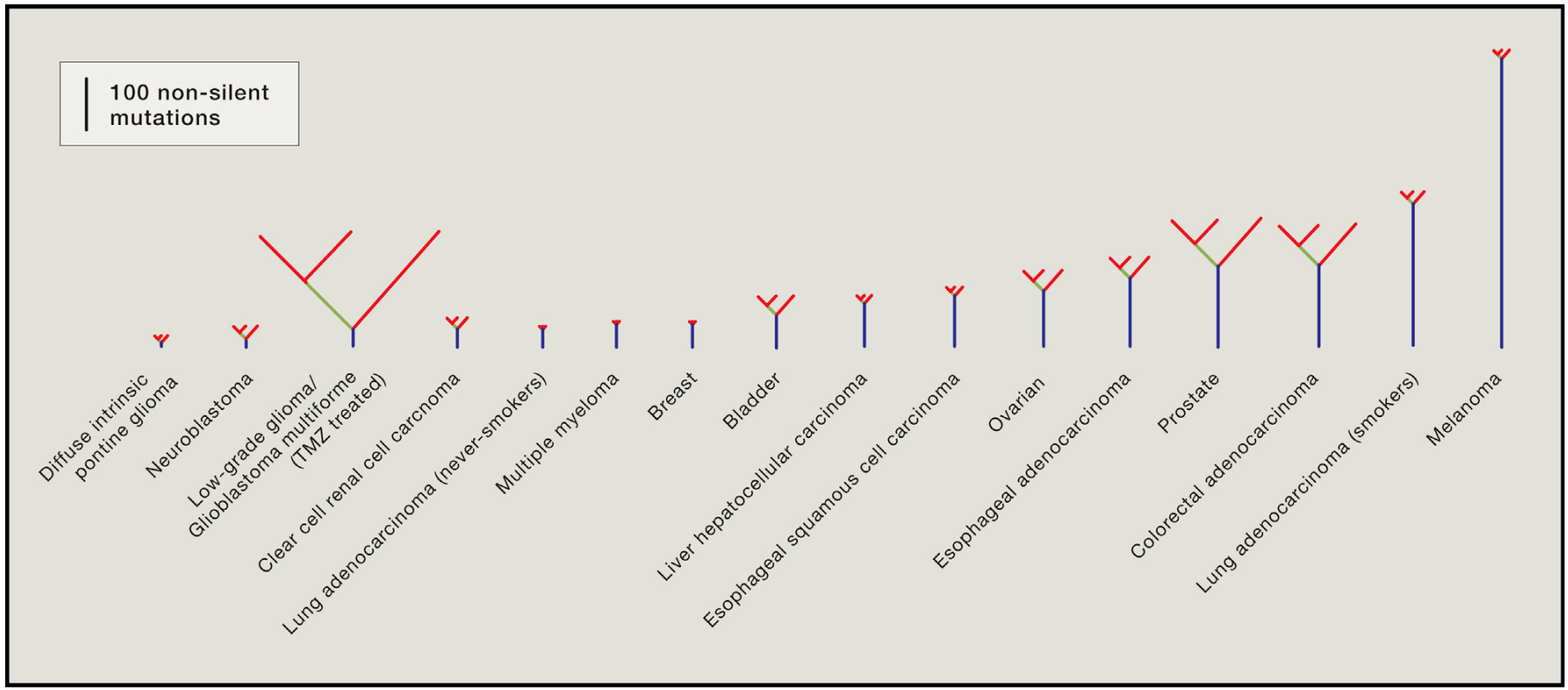
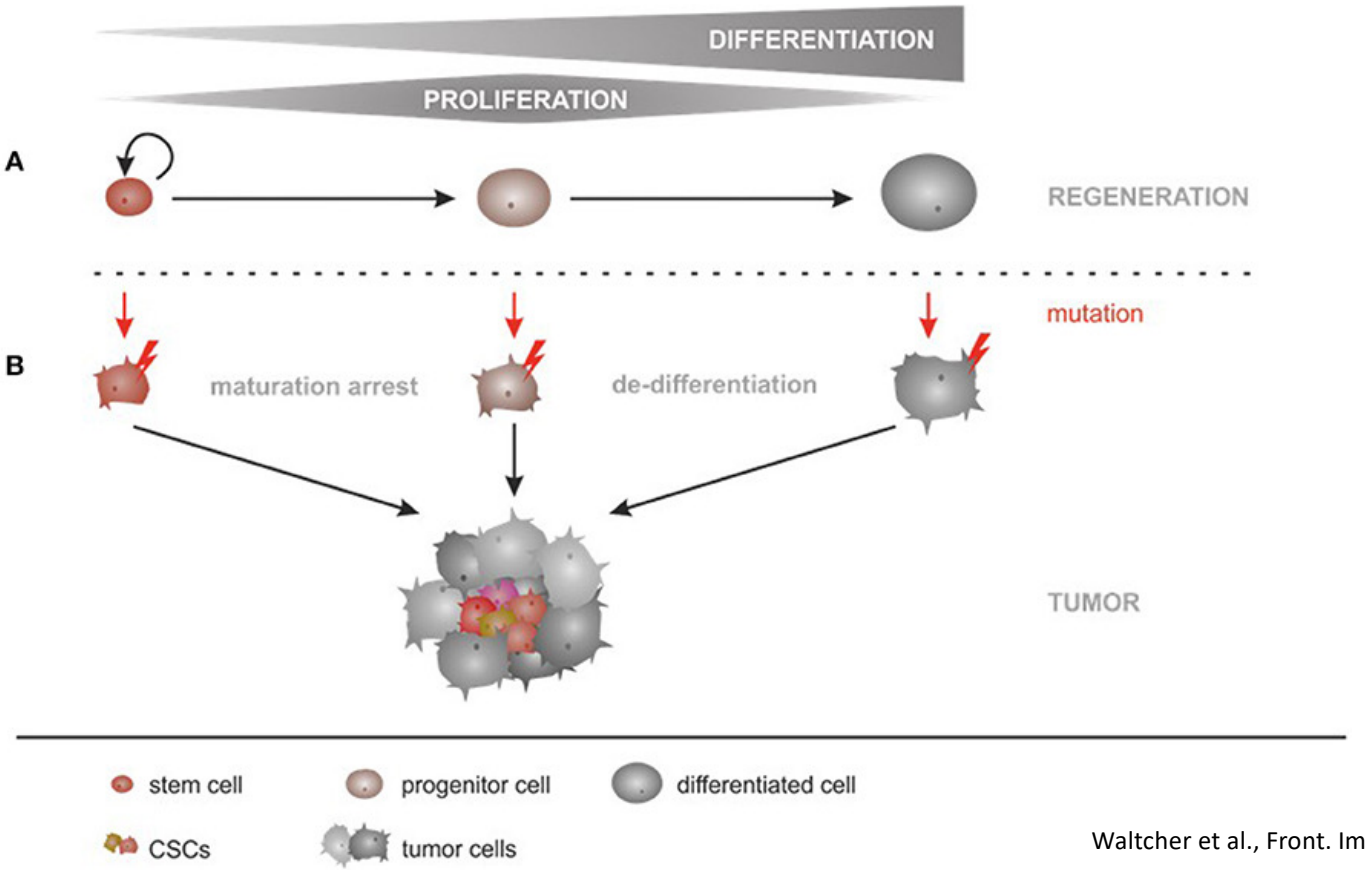


Figure 2. Evolutionary Trees Illustrating Intratumor Heterogeneity across Cancer Types
For each cancer type, the mean number of clonal and subclonal non-silent mutations are depicted as trunks (blue) and branches (yellow and red), respectively.

From McGranahan and Swanton, Cell **168**, 613 (2017)

Cancer stem cells

Tumors contain different cell types



Waltcher et al., Front. Immunol. 11(2020)

Cancer stem cells

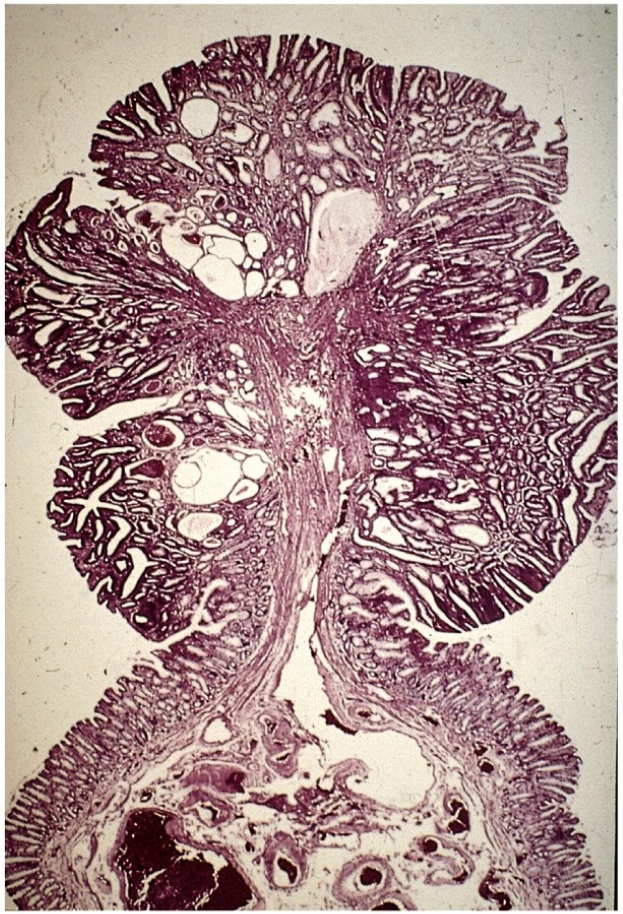
- Have the ability to efficiently seed new tumors upon inoculation into recipient host mice (tumor initiating cells)

- a subpopulation of cancer cells that
  - can initiate a tumor
  - possess self-renewal capacity
  - can contribute to heterogeneous lineages of cancer cells in the tumor

- CSC are more resistant to chemotherapeutic treatments

How many events make a tumor cell?

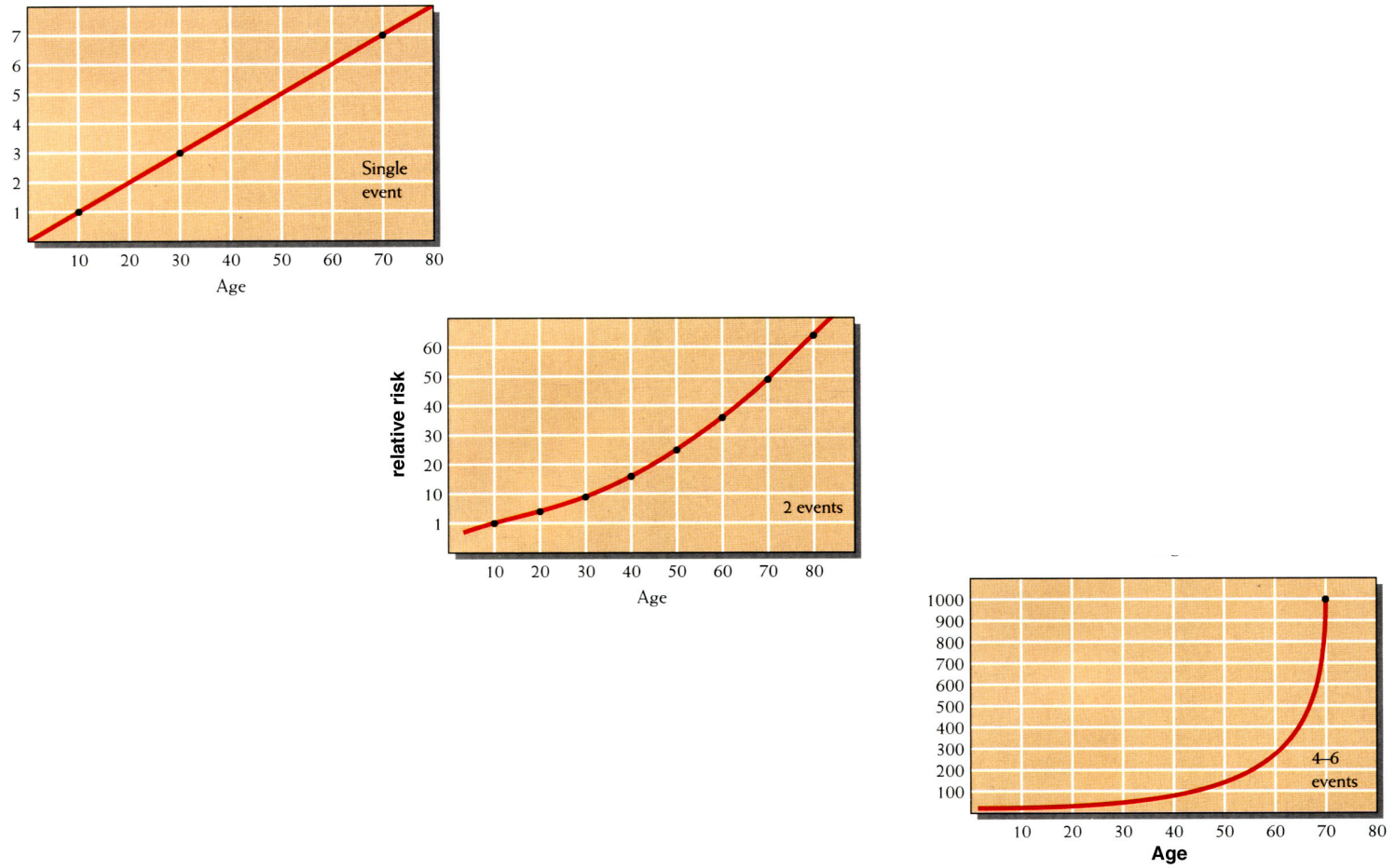
(A)



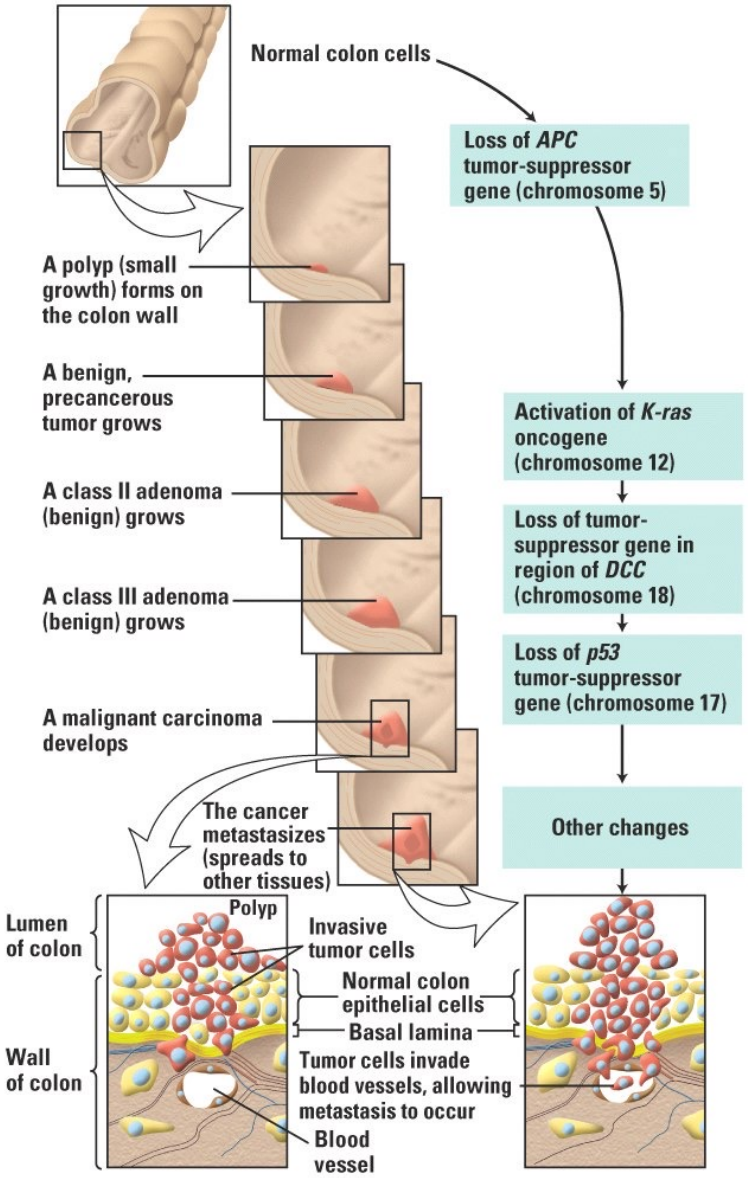
(B)

1 mm

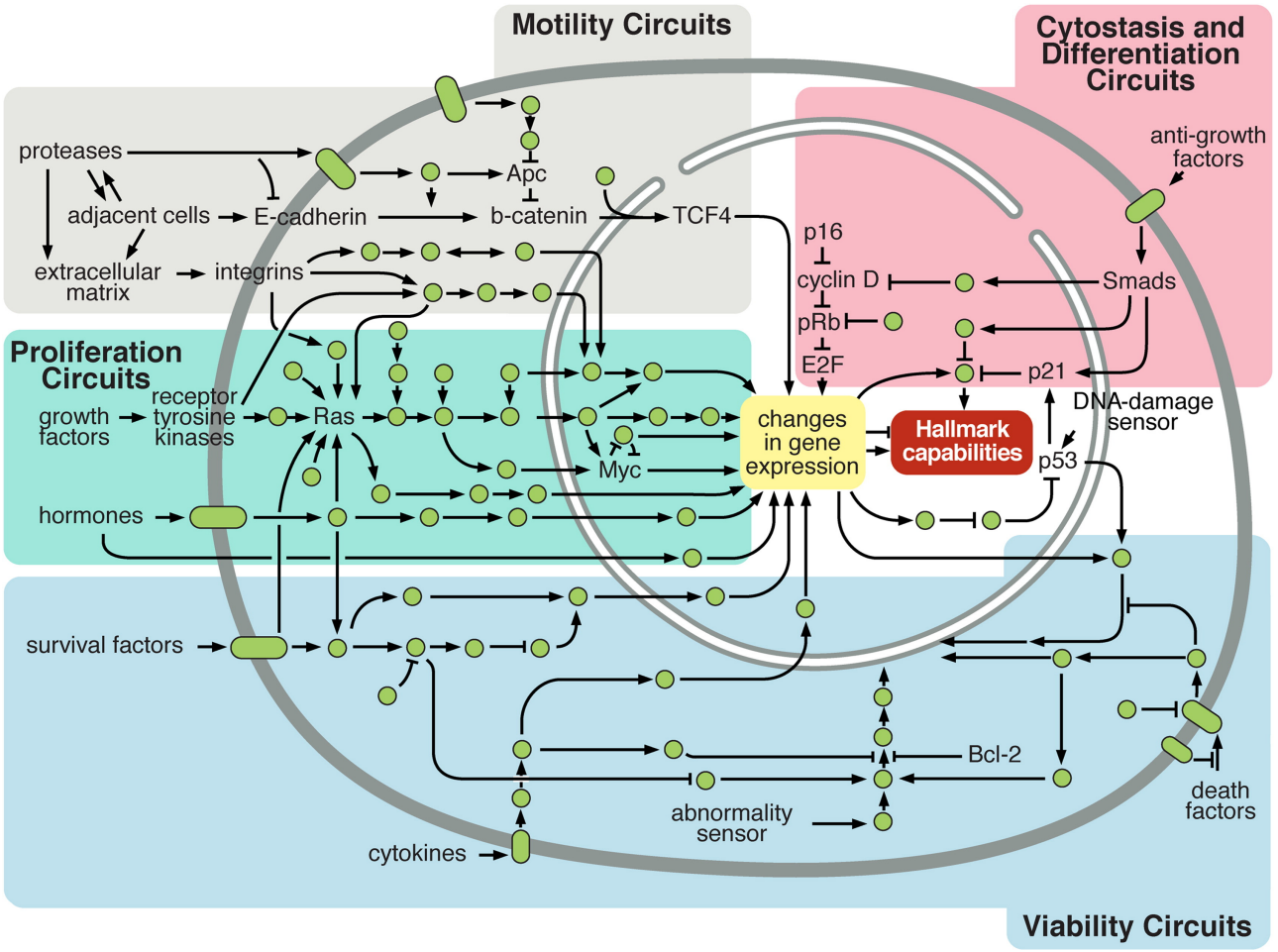
Predicted rates of colon cancer



Steps of cancer development



Disruptions in how many circuits makes a cell cancerous?

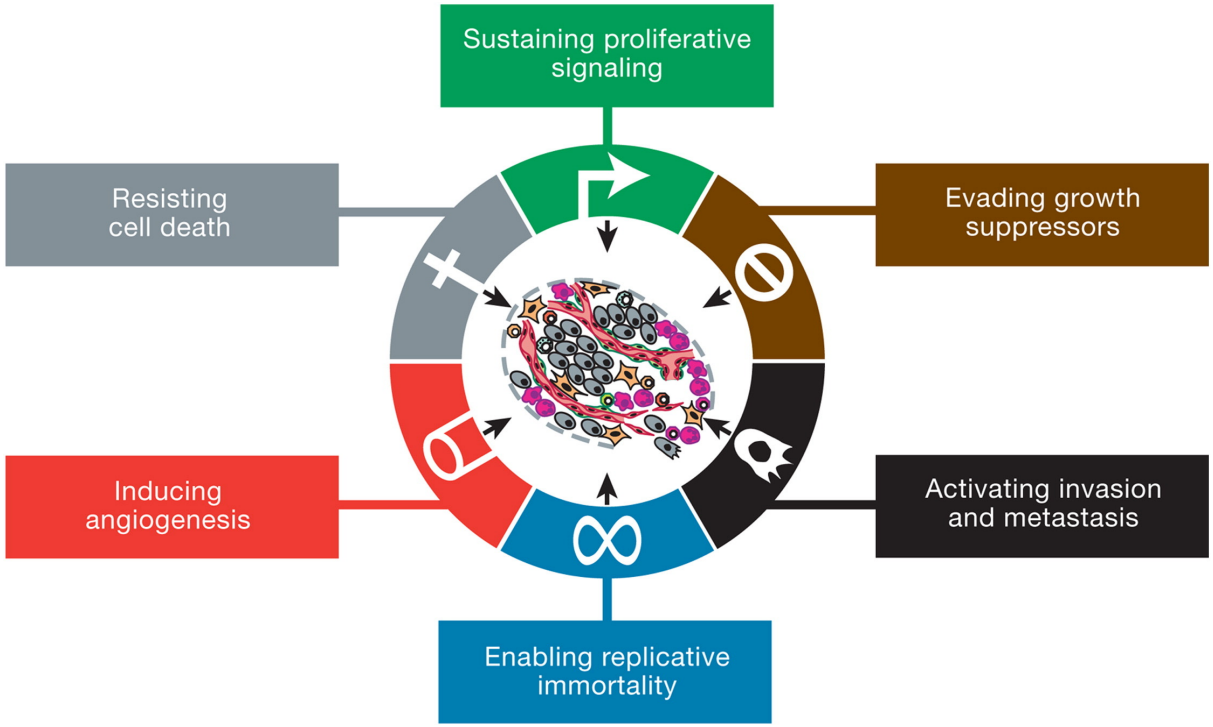


Hanahan and Weinberg, Cell, 2011

Hallmarks of cancer

Hanahan and Weinberg 2000/2011:

- six essential alterations in cell physiology that collectively dictate malignant growth - acquired capabilities – are shared in most tumors



Hanahan and Weinberg, Cell, 2011

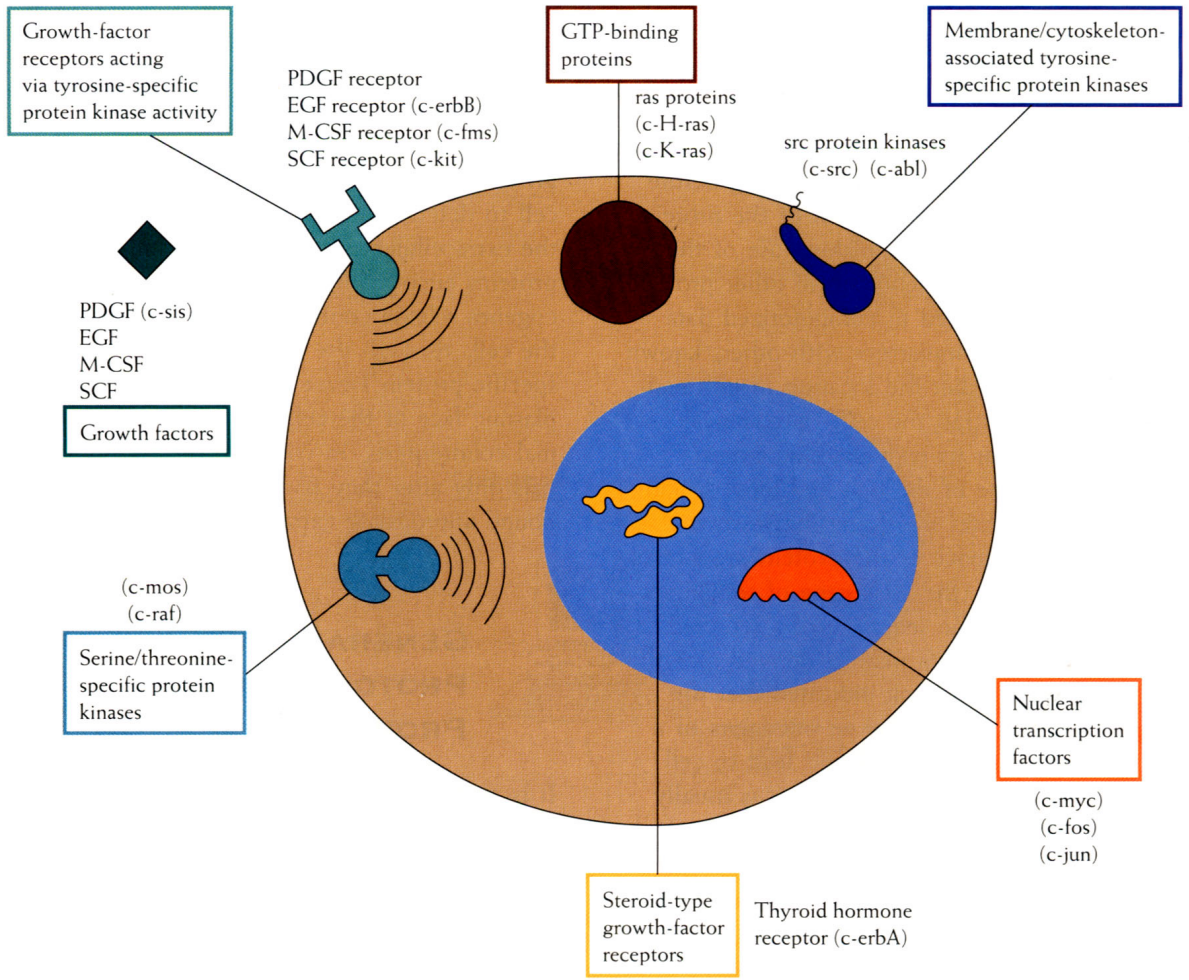
1. Sustaining Proliferative Signaling

- Normal cells require mitogenic growth signals to proliferate
  - transmitted through transmembrane receptors, which bind diffusible growth factors or cell-to-cell adhesion/interaction molecules

- Cancer cells can:
  - produce growth factor ligands themselves
  - send signals to stimulate normal cells to supply them with growth factors
  - upregulate the levels of growth factor receptors
  - activate components of signaling pathways operating downstream of these receptors

- Many oncoproteins act by mimicking normal growth signaling

Protein products of proto-oncogenes



Normal cells have some defence mechanisms

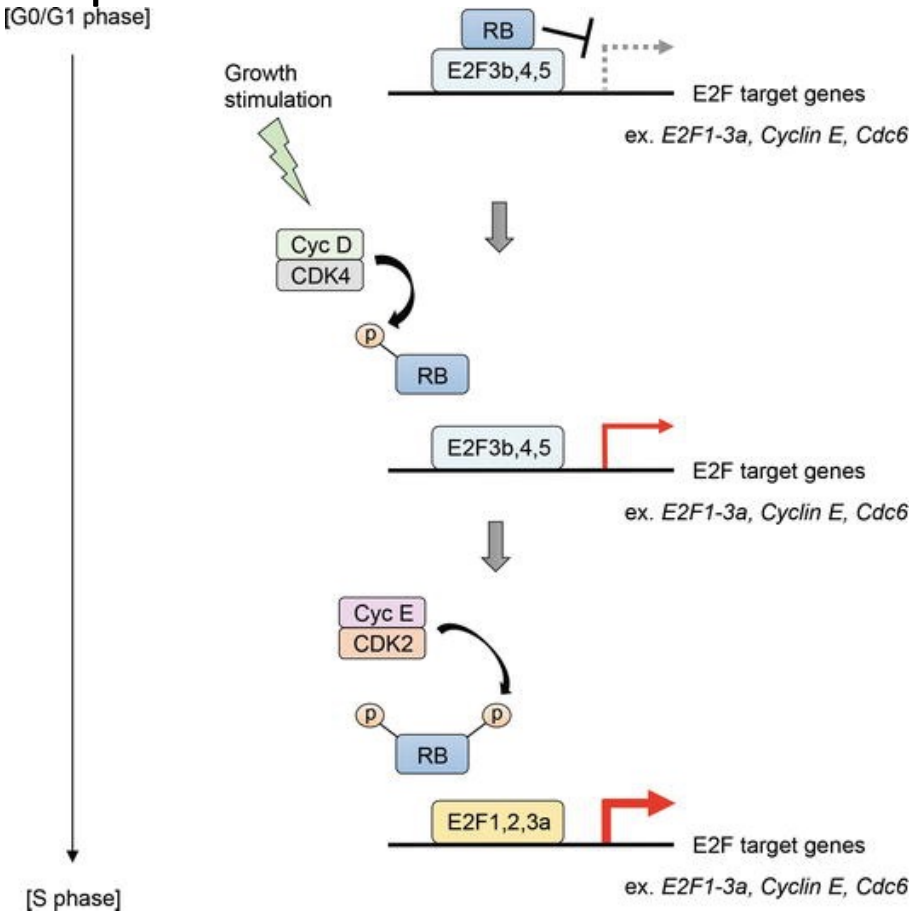
- Exessive proliferative signalling can trigger cell senescence and apoptosis:
  - cells expressing high levels of the Ras oncoprotein may enter into senescence; in contrast, cells expressing lower levels of this protein may avoid senescence and proliferate
- Intensity of oncogenic signaling in cancer cells is a compromise between maximal mitogenic stimulation and avoidance of antiproliferative defenses
- Some cancer cells may adapt to high levels of oncogenic signaling by disabling their senescence- or apoptosis-inducing circuitry

2. Evading Growth Supressors

- Mediated by deregulation of tumor supressors:
  - pRB (retinoblastoma associated)

    Signal is received from outside of the cell

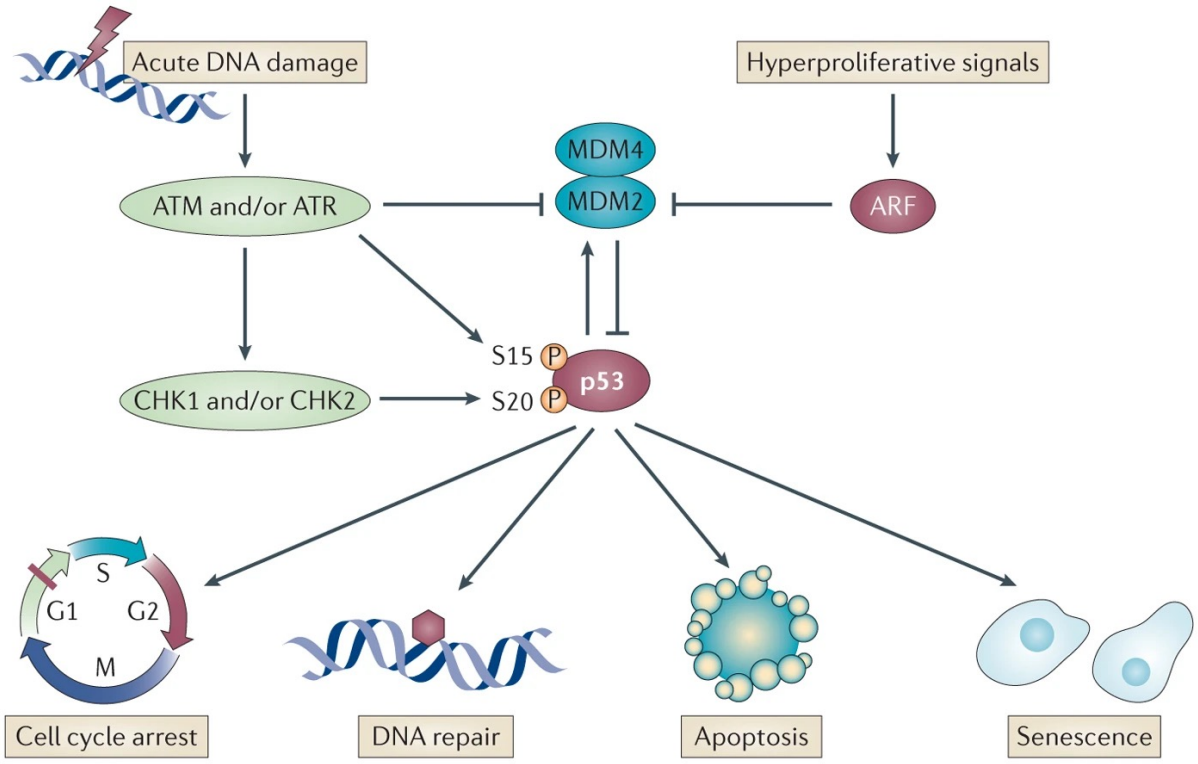
    Control of the cell cycle



Kurayoshi et al., InTech., (2018)

2. Evading Growth Supressors

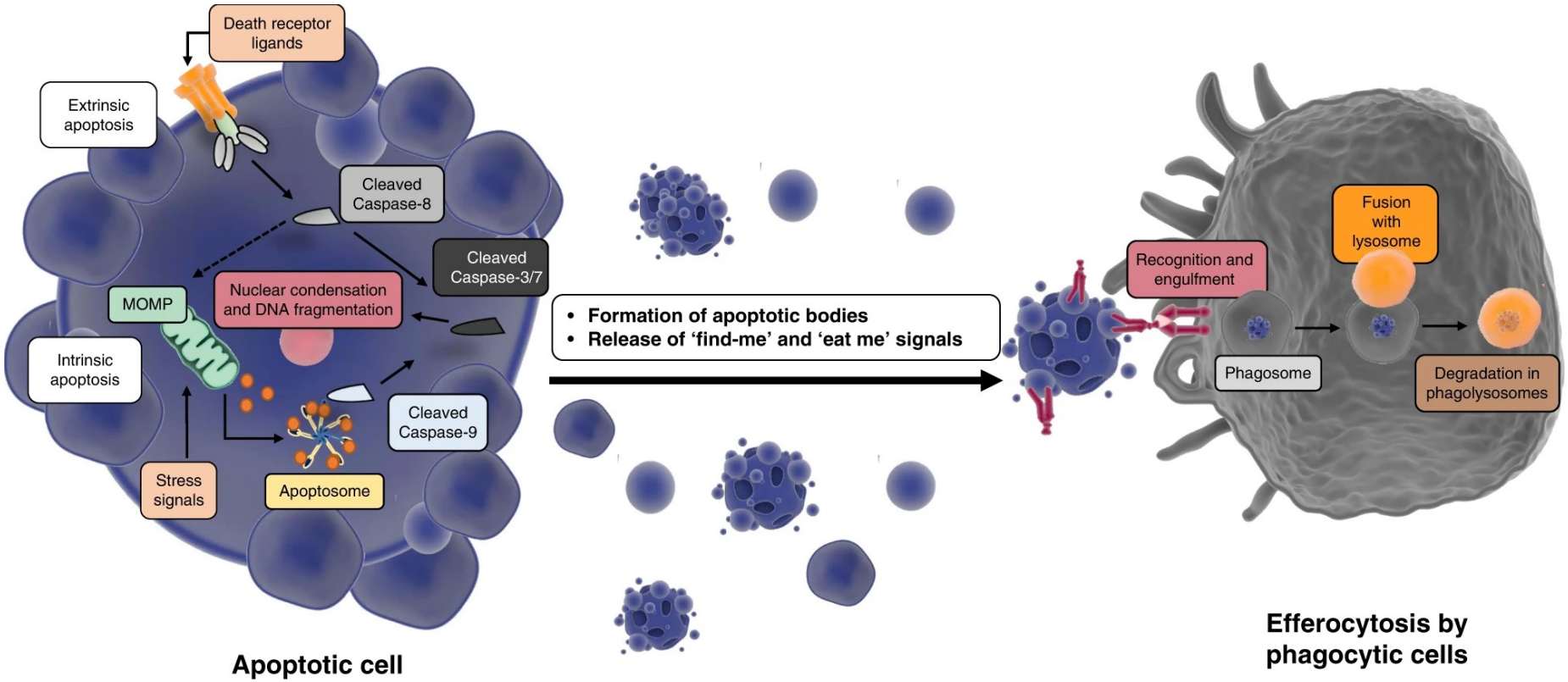
- Mediated by deregulation of tumor supressors:
  - p53
    - Receives information from stress and abnormality sensors within the cell
    - If damage is excessive, can induce cell cycle arrest and apoptosis



Bieging et al., *Nat Rev Cancer* **14**, 359–370 (2014)

Nature Reviews | Cancer

3. Evading Apoptosis



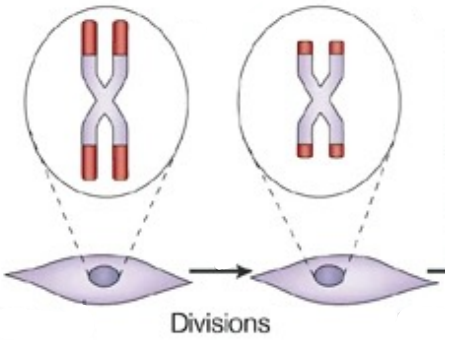
Nössing, C., Ryan, K.M. *Br J Cancer* **128**, 426–431 (2023)

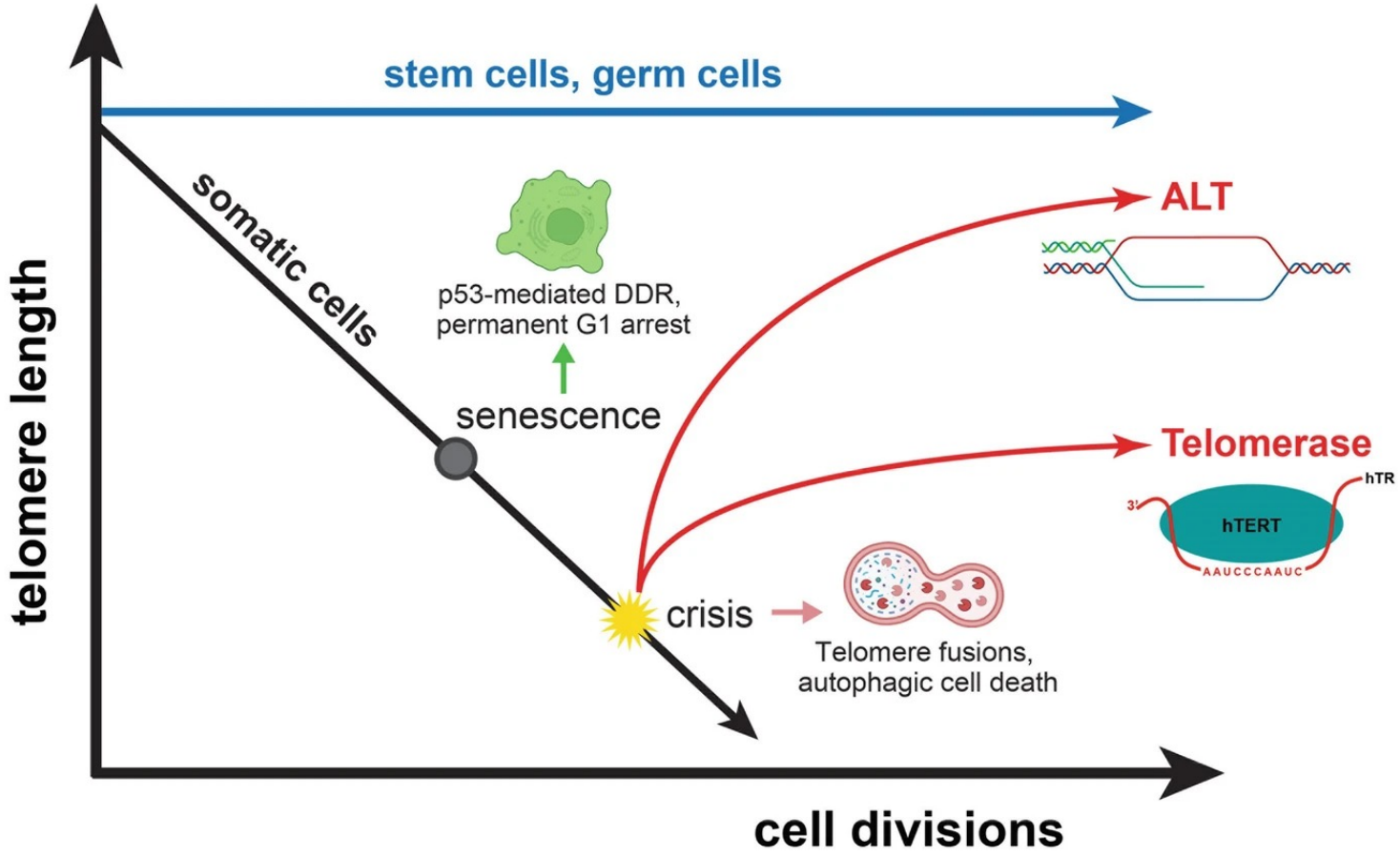
3. Evading Apoptosis

- Cancer cells evade apoptosis by
  - Loss of p53 tumor suppressor function, which eliminates this critical damage sensor from the apoptosis-inducing circuitry
  - Increased expression of antiapoptotic regulators (Bcl-2, Bcl-xL) or of survival signals (Igf1/2)
  - Downregulation of proapoptotic factors (Bax, Bim, Puma), or by short-circuiting the extrinsic ligand-induced death pathway.

Nössing, C., Ryan, K.M. *Br J Cancer* **128**, 426–431 (2023)

4. Limitless Replicative Potential

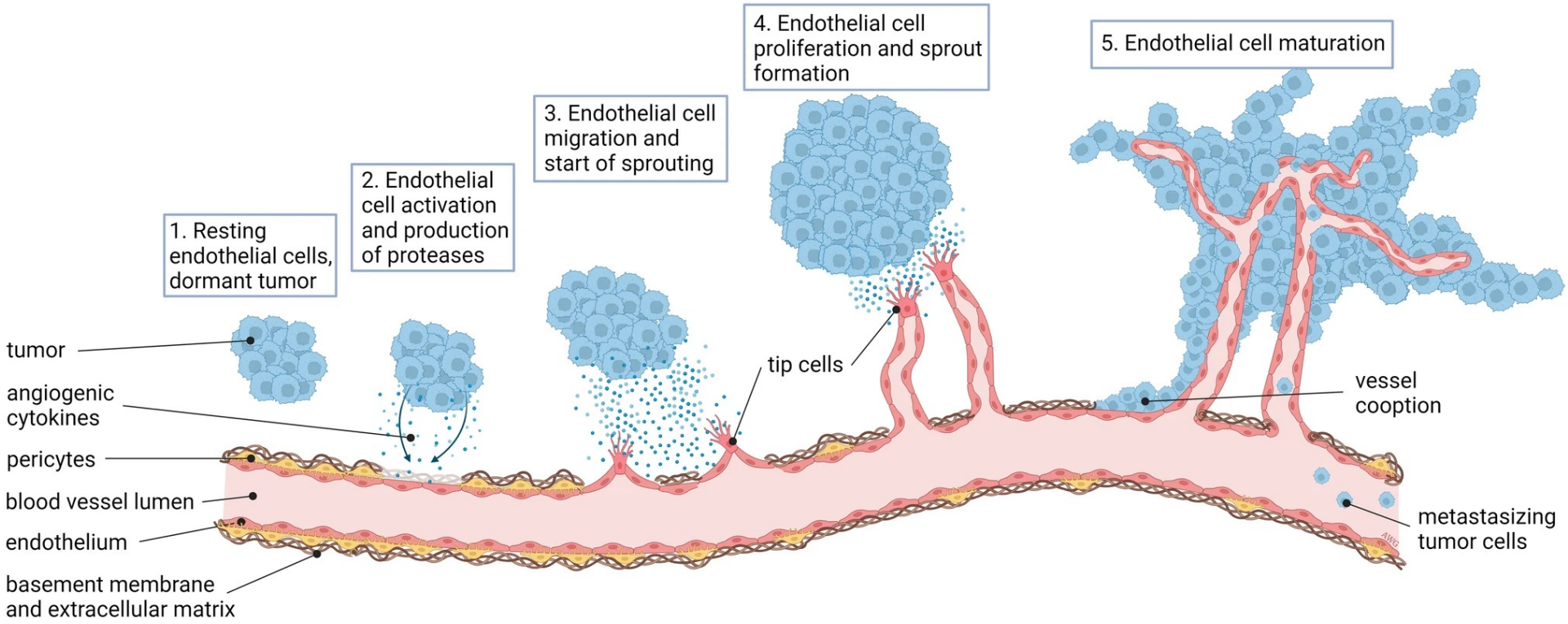




Cohen, S.B., Bryan, T.M. (2023). Handbook of Chemical Biology of Nucleic Acids. Springer, Singapore.

5. Sustained Angiogenesis

During tumor progression, an ‘‘angiogenic switch’’ is almost always activated and remains on, causing normally quiescent vasculature to continually sprout new vessels



Dudley, A.C., Griffioen, A.W.(2023) *Angiogenesis* **26**, 313–347

5. Sustained Angiogenesis

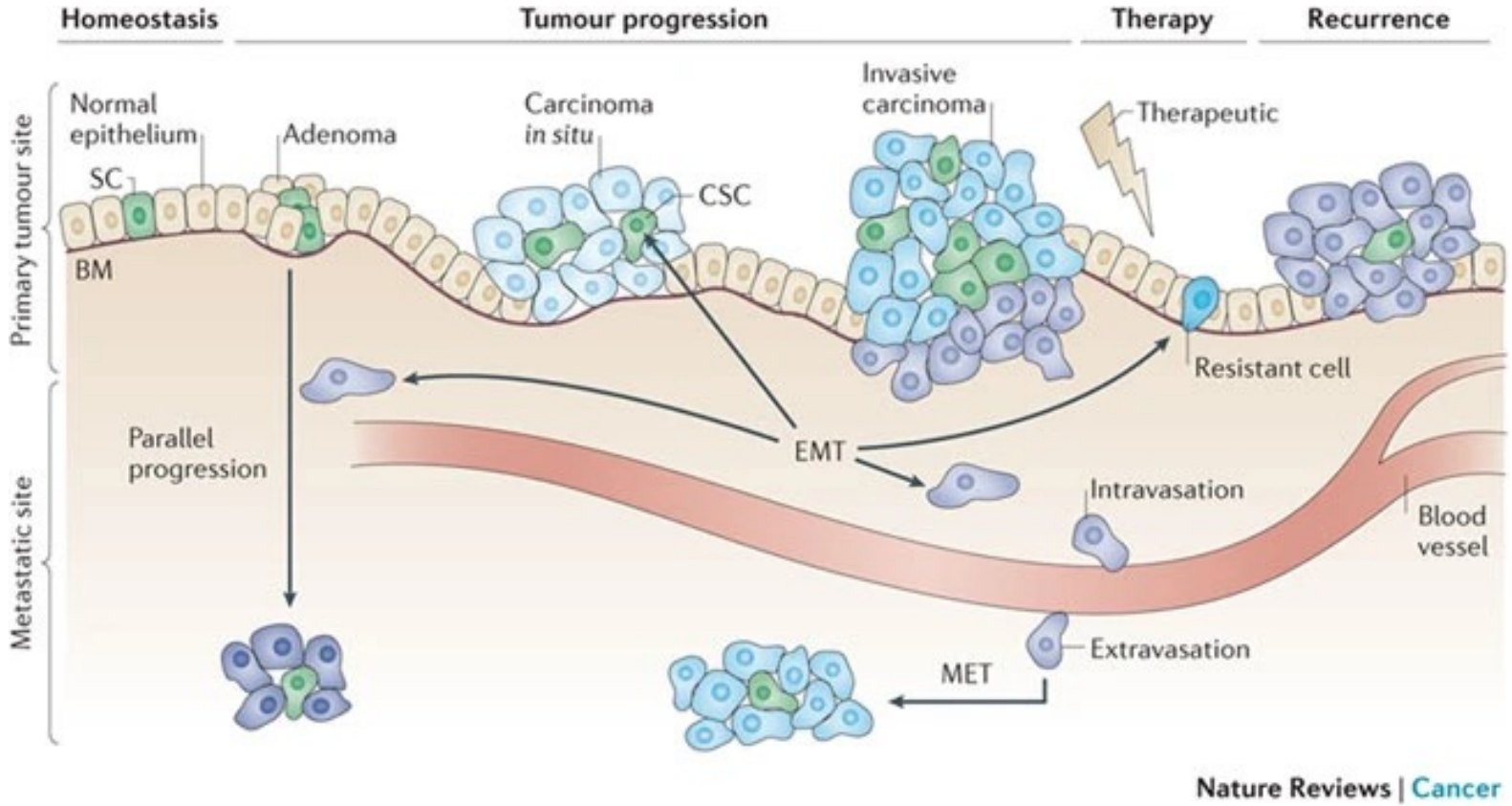
- Supply of oxygen and nutrients by the vasculature is crucial for cell function and survival.
- Incipient neoplasias must develop angiogenic ability.
- Angiogenic inducers and inhibitors:
  - Some tumors overexpress VEGF
  - Some lose expression of anti-angiogenic factors (TSP1).
- anti-VEGF antibodies impair neovascularization and growth of subcutaneous tumors (Bevacizumab)

6. Activating Invasion and Metastasis

- Distant settlements of tumor cells: Involves dissemination of cancer cells from primary tumor and successful colonization of distant tissue. Cause 90% of cancer deaths.
- Physical coupling of cells to their microenvironment. Altered cell-cell adhesion molecules (CAMs), integrins (link cells to extracellular matrix). Expression of proteases on the cell surface may facilitate invasion by cancer cells, into nearby stroma, across blood vessel barriers, and through epithelial cell layers.
- Best characterized alteration: loss (or mutation) of the cell-to-cell adhesion molecule E-cadherin.

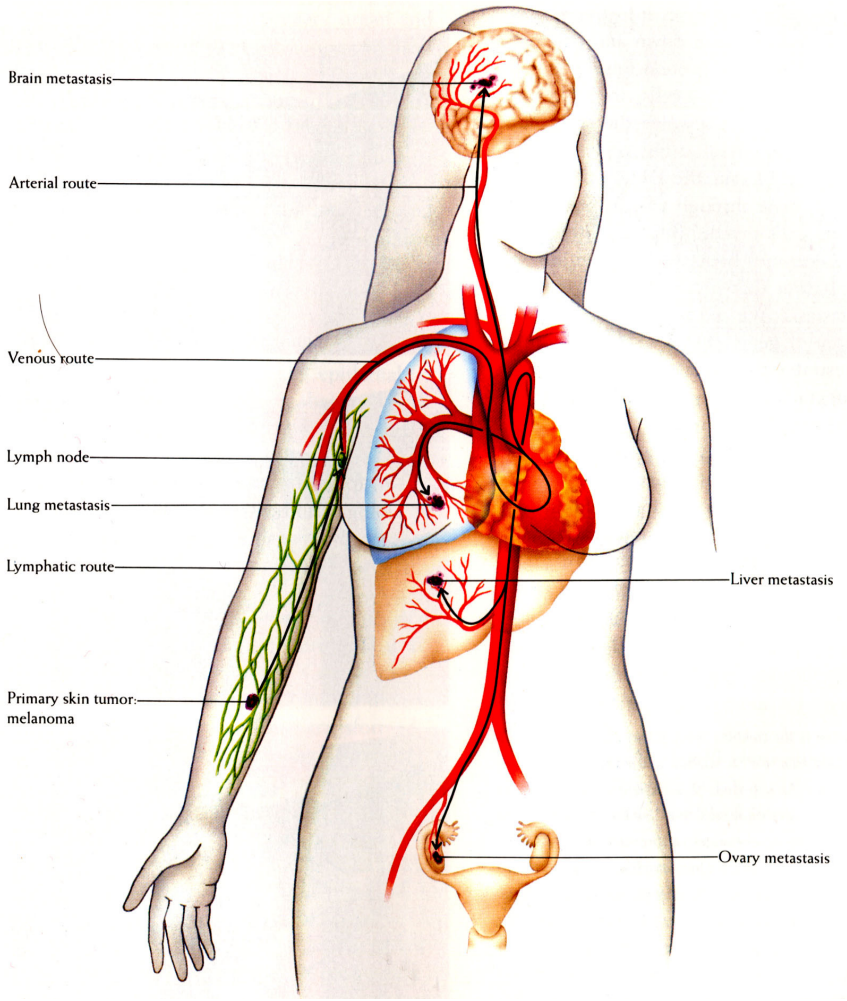
6. Activating Invasion and Metastasis

EMT, ‘‘epithelial-mesenchymal transition’’, is a developmental regulatory program



Craene, B., Berx, G. (2013) *Nat Rev Cancer* **13**, 97–110

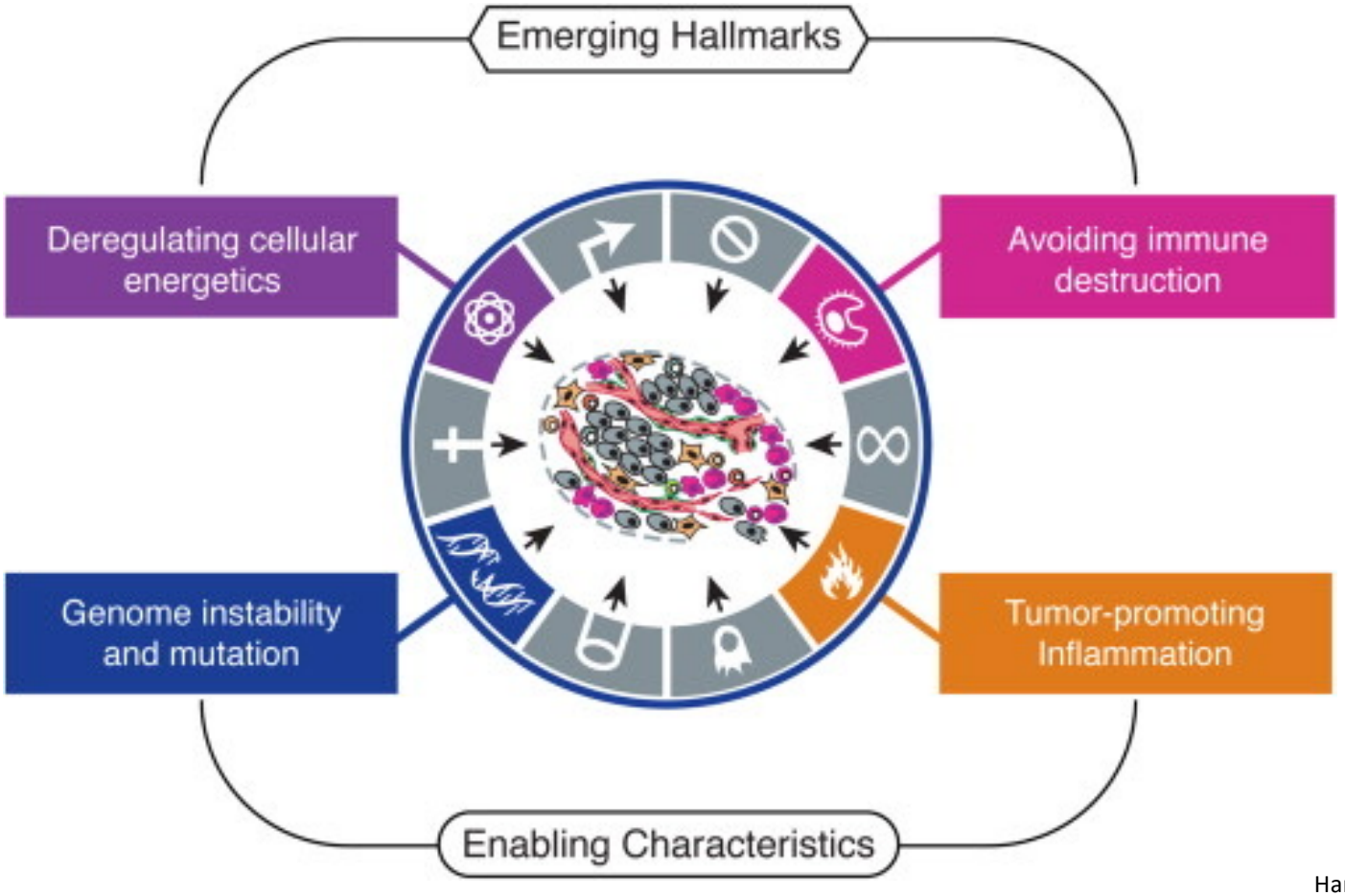
Metastatic spread of cancer



Metastasis and Prognosis in Colon Cancer

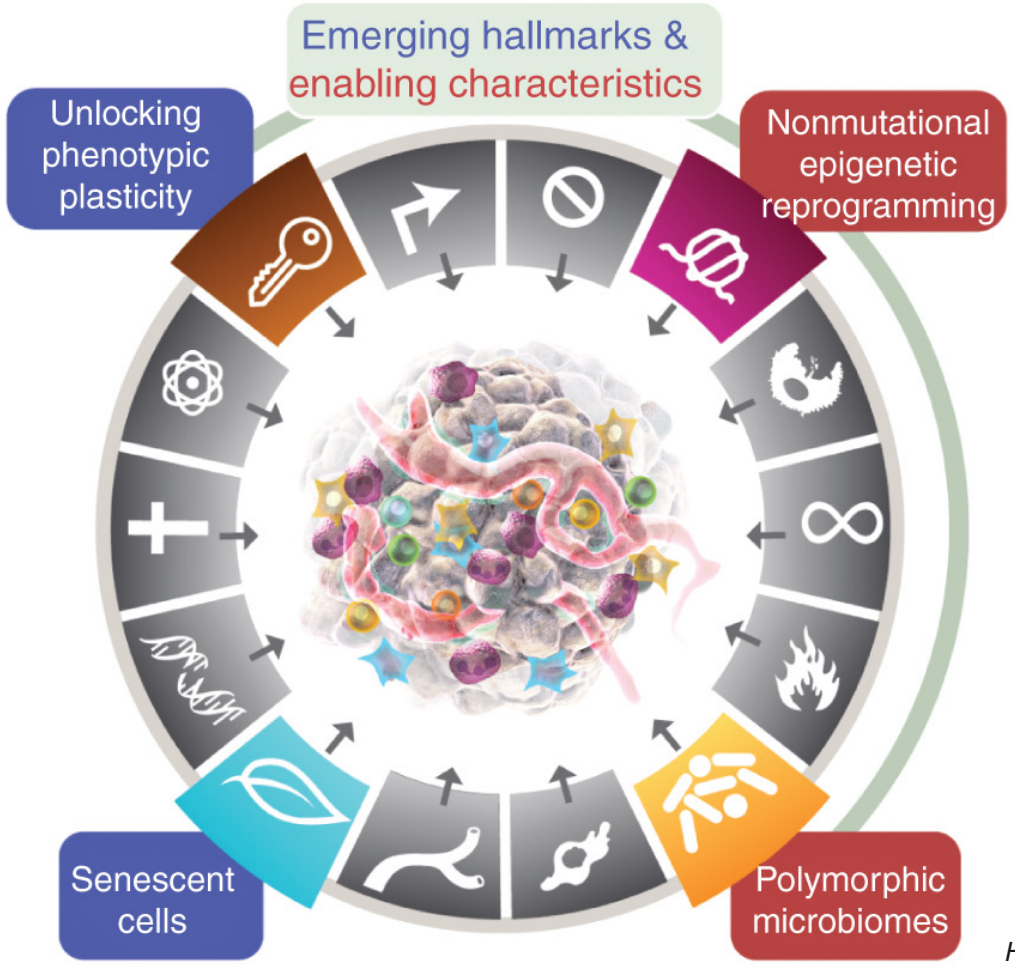
Description of carcinoma	**% of patients alive 5 years after diagnosis**
Limited to the mucosal lining of the gut	100
Extending down to underlying muscle layer but not penetrating through it; no lymph nodes involved	66
Extending down through the muscle layer, no cancer cells in nearby lymph nodes	53.9
Invading through the muscle wall and beyond, with occasional involved nearby lymph nodes	42.8
Invasion as above with cancer cells in many local lymph nodes	22.4
As above with distant metastatic spread to liver, lung, bones, the peritoneal membrane of the abdomen, and the brain	4

Additional Hallmarks



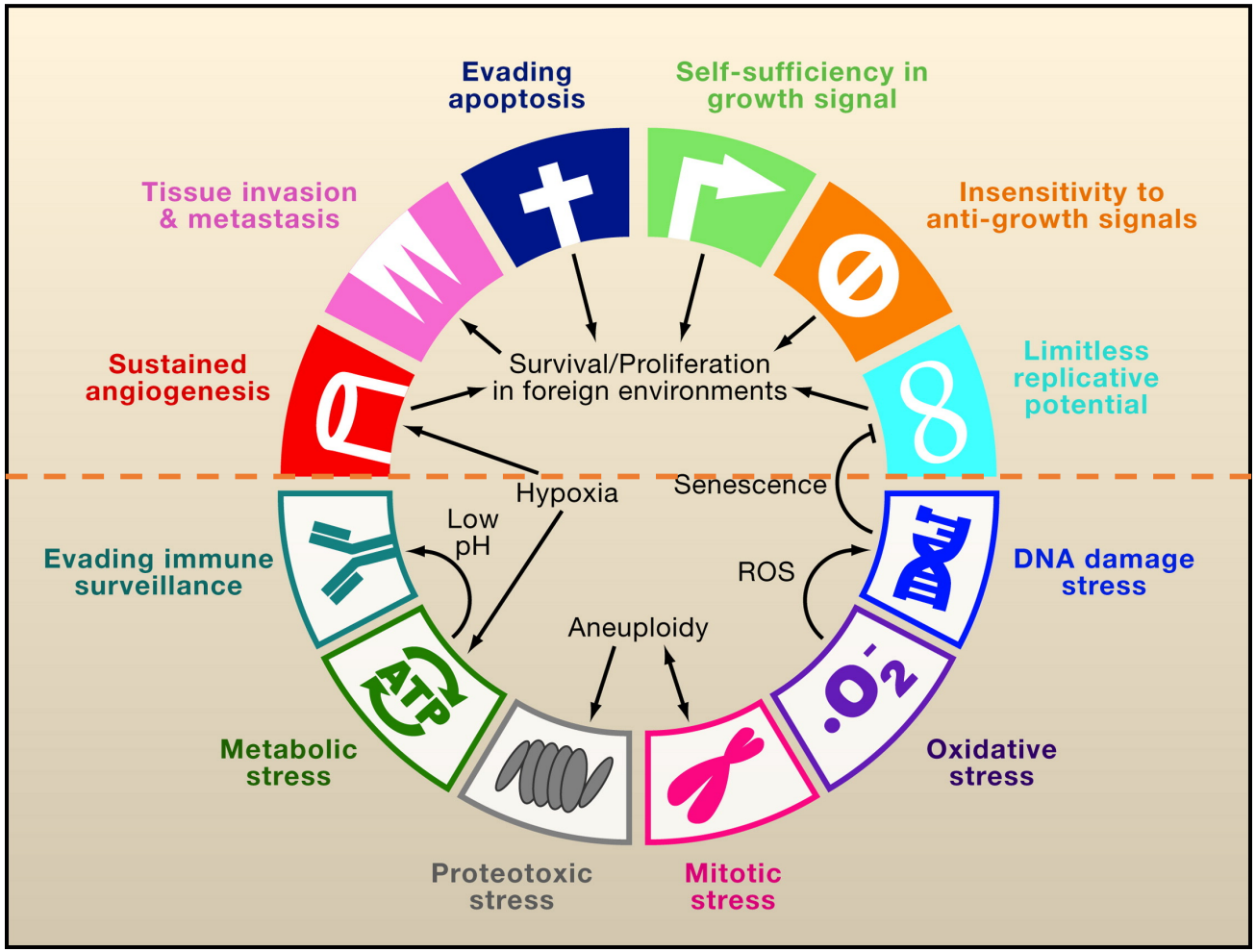
Hanahan and Weinberg, Cell, 2011

Additional Hallmarks



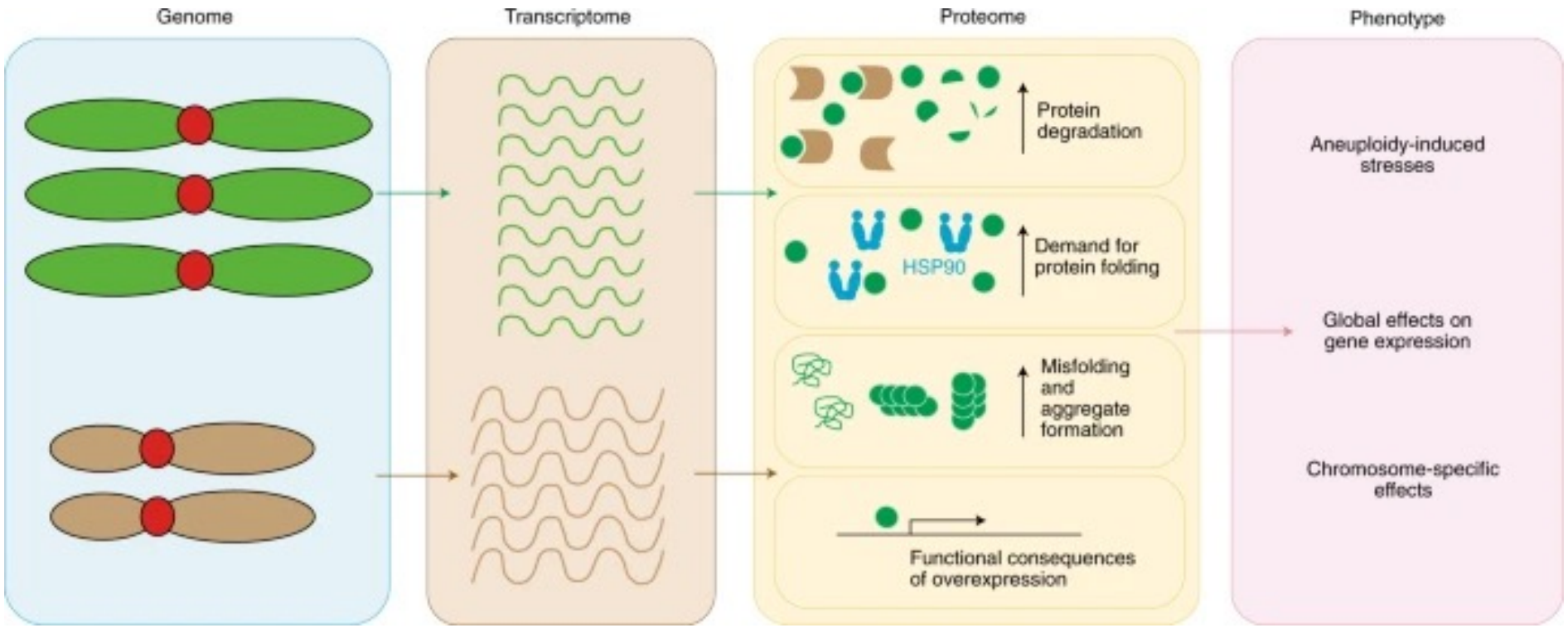
Hanahan, Cancer Discov (2022) 12 (1): 31–46.

Stress phenotypes of cancer cells



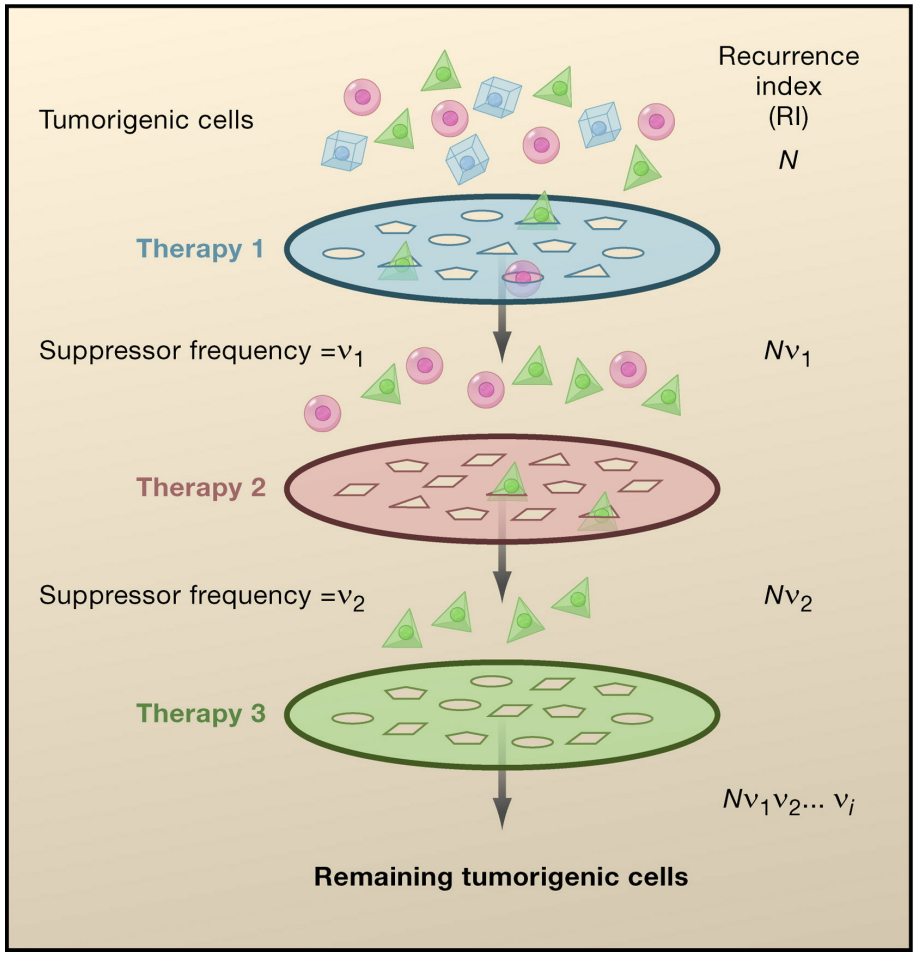
Luo, Solimini, Elledge Cell 2009 136, 823-837

Aneuploidy and Proteotoxic Stress



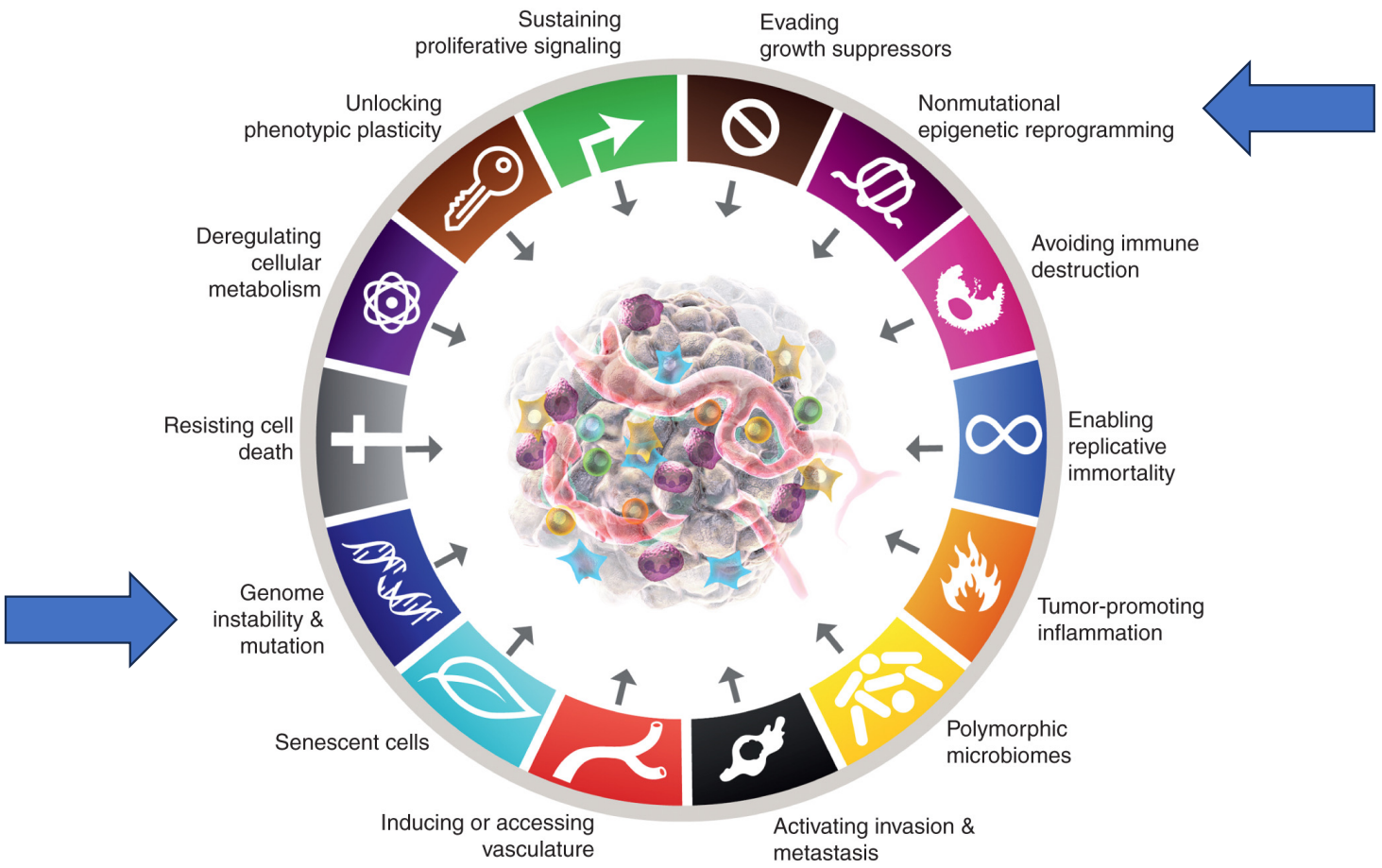
Addiction to heat shock proteins that promote protein folding

The Combinatorial Filter of Cancer Therapies



Luo, Solimini, Elledge Cell 2009 136, 823-837

Likelihood of accumulating >6 specific alterations in a single cell is very low



Genome and Epigenome Instability

Cancer cells often increase the rates of mutation (mutator phenotype):

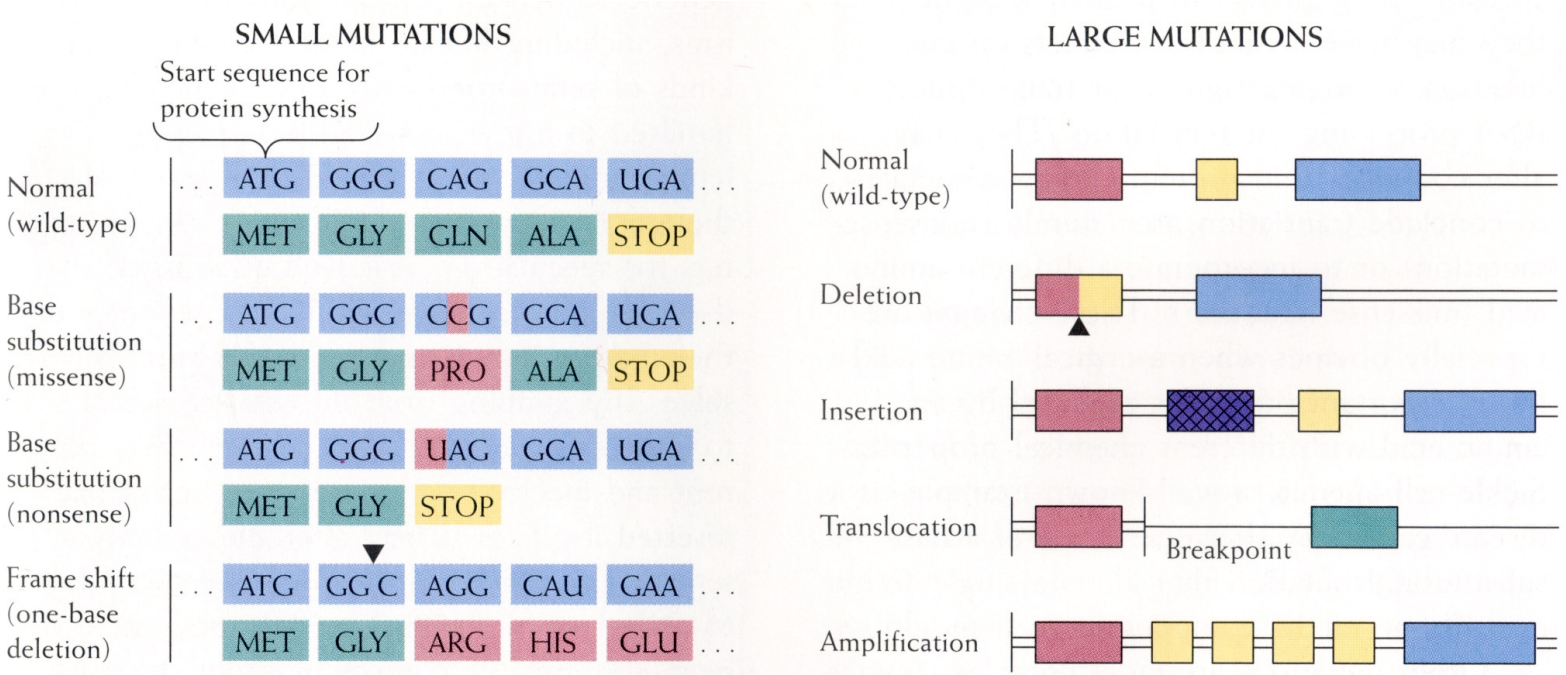
- increased sensitivity to mutagenic agents
- breakdown in one or several components of the genomic maintenance machinery
- accumulation of mutations can be accelerated by compromising the surveillance systems that normally monitor genomic integrity and force genetically damaged cells into either senescence or apoptosis

Caretaker genes

Increase the likelihood of cancer when mutated

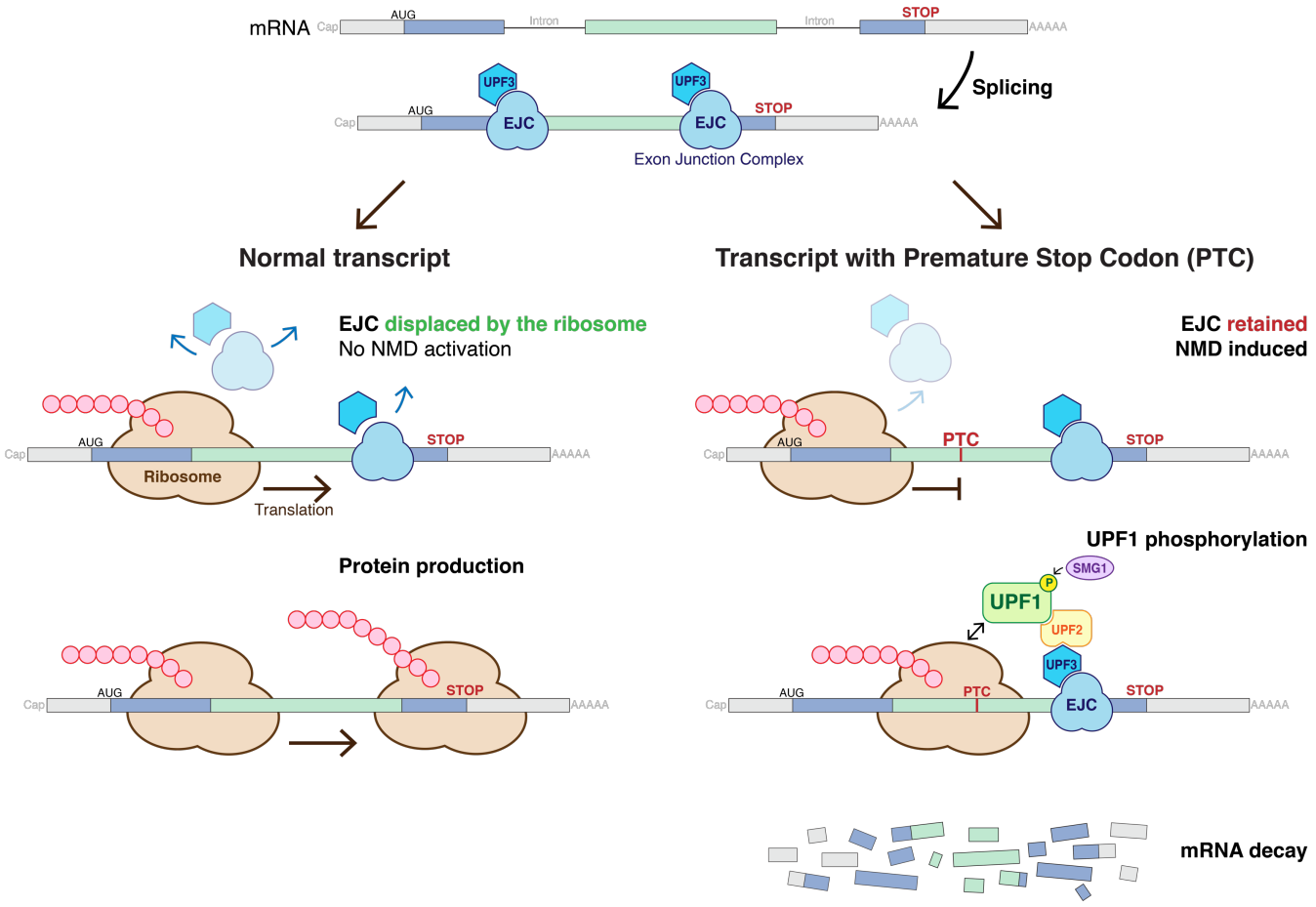
- detect DNA damage and activate the repair machinery
- directly repair damaged DNA
- Inactivate or intercept mutagenic molecules before they damage the DNA

Genetic variations

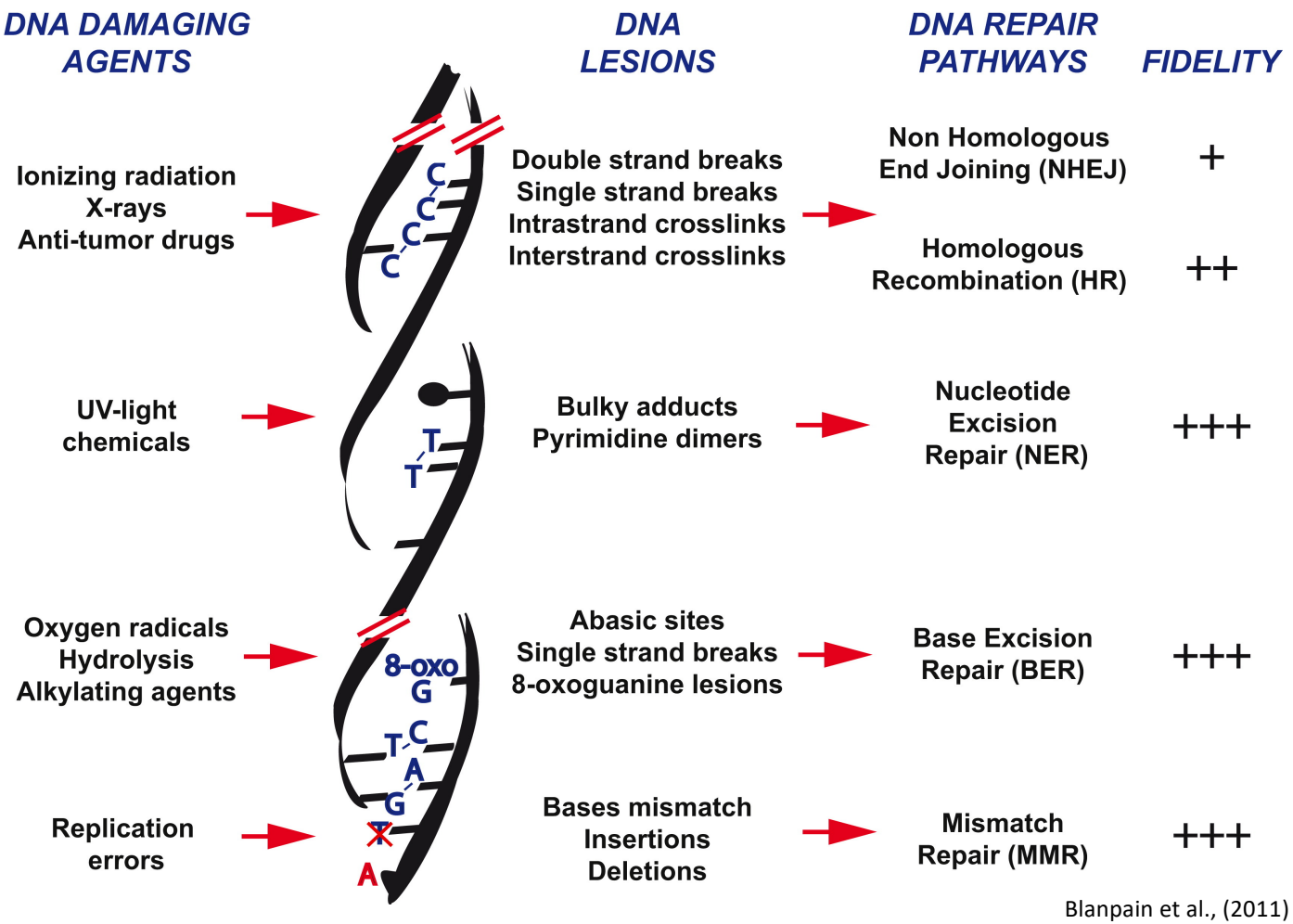


Genetic variation can take the form of small or large mutations in an organism's DNA, as the scheme above illustrates. Large mutations may involve the insertion of foreign, perhaps viral, genetic information (purple box) or the exchange of information by translocation between two chromosomes at a breakpoint. Small mutations result from changes in a single base (nucleotide) or codon (nucleotide triplet, dictating a particular amino acid in the protein product).

Nonsense-mediated mRNA Decay (NMD)



DNA Damage



Blanpain et al., (2011) Cell Stem Cell, Volume 8, Issue 1

DNA Replication Errors are Extremely Rare

- Mutation rate of $1/10^9$ per nucleotide per cell division
  - Copying mistake by DNA polymerases (delta and epsilon): $1/10^5$
  - 3'-5' proofreading overlook: $1/10^2$
  - Mismatch repair enzymes overlook: $1/10^2$

- 10-50 double-strand DNA breaks occur per S phase
- Human genome: 6.4 billion bp

Human cells can tolerate elevated mutation burdens

ARTICLES
https://doi.org/10.1038/s41588-021-00930-y

nature genetics

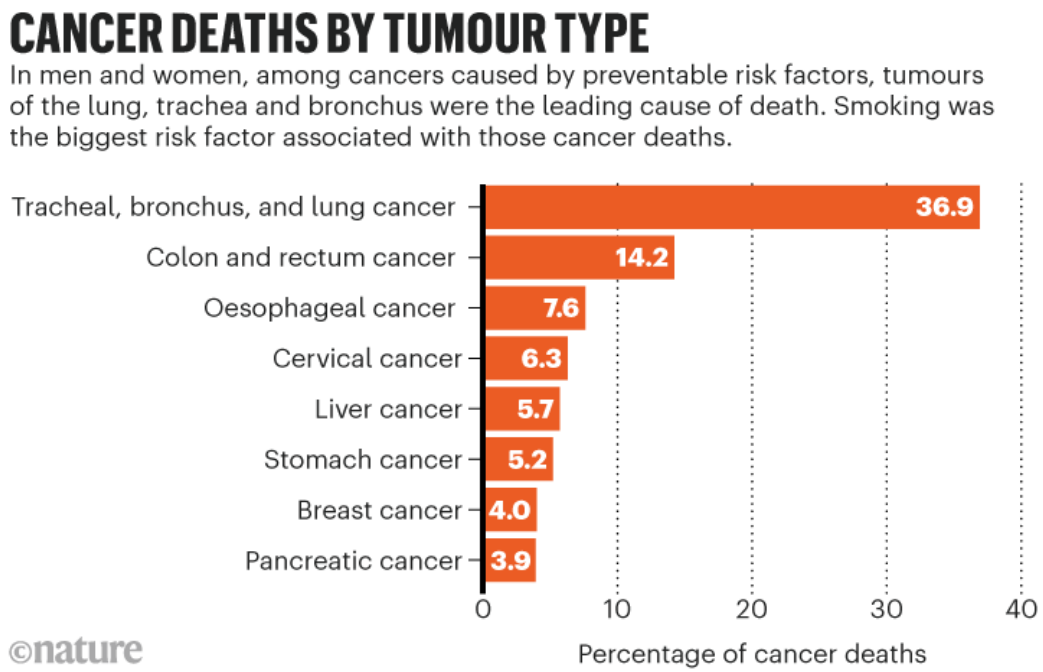
OPEN

Increased somatic mutation burdens in normal human cells due to defective DNA polymerases

Philip S. Robinson[1,2,7], Tim H. H. Coorens[1,7], Claire Palles[3,7], Emily Mitchell[1], Federico Abascal[1], Sigurgeir Olafsson[1], Bernard C. H. Lee[1,4], Andrew R. J. Lawson[1], Henry Lee-Six[1], Luiza Moore[1], Mathijs A. Sanders[1,5], James Hewinson[1], Lynn Martin[3], Claudia M. A. Pinna[3], Sara Galavotti[3], Raheleh Rahbari[1], Peter J. Campbell[1], Iñigo Martincorena[1], Ian Tomlinson[6,8] ✉ and Michael R. Stratton[1,8] ✉

Nature Genetics, 53, 1424 (2021)

Cancers Caused by Preventable Risk Factors

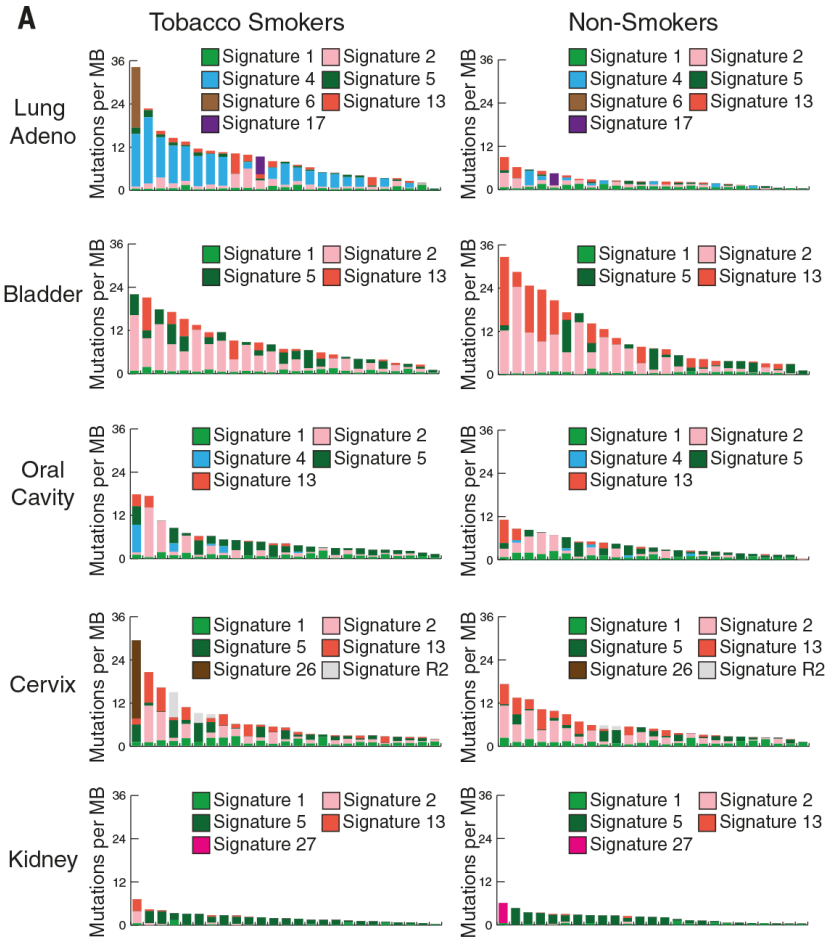


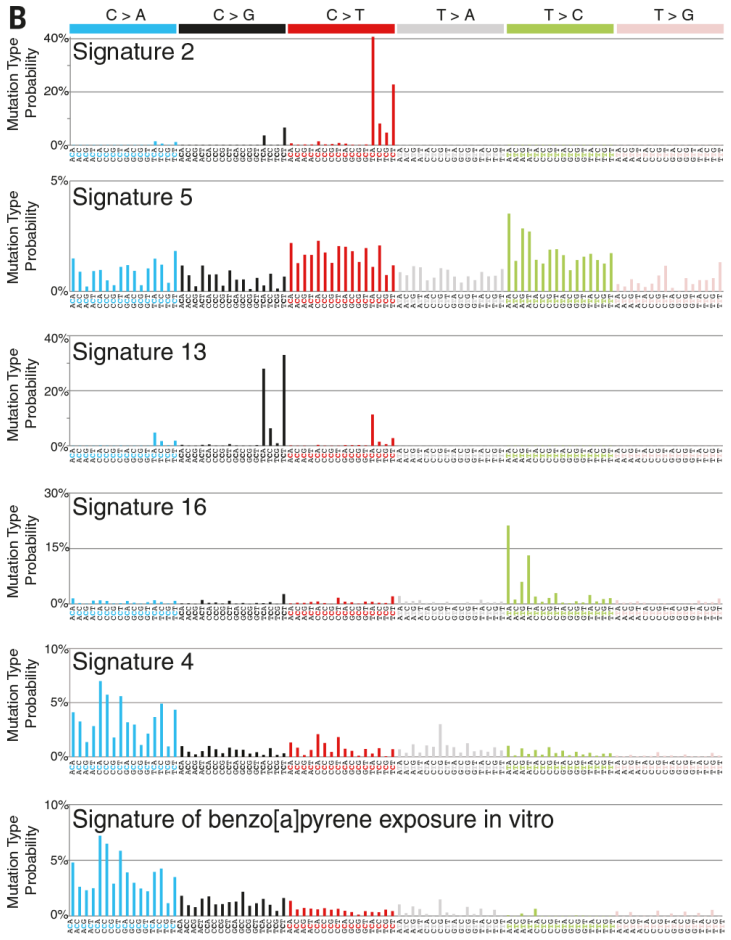
Source: Ref. 1

In 2019, half of all male deaths from cancer, and more than one-third in women, were due to preventable risk factors including tobacco and alcohol use, unhealthy diets, unsafe sex and workplace exposure to harmful products, such as asbestos.

Nature, 2022: doi: https://doi.org/10.1038/d41586-022-02355-x

Mutational Signatures of Tobacco Smoking





Alexandrov et al, Science 2016: 354, 618

DNA Lesions Generated by Endogenous and Exogenous DNA Damage

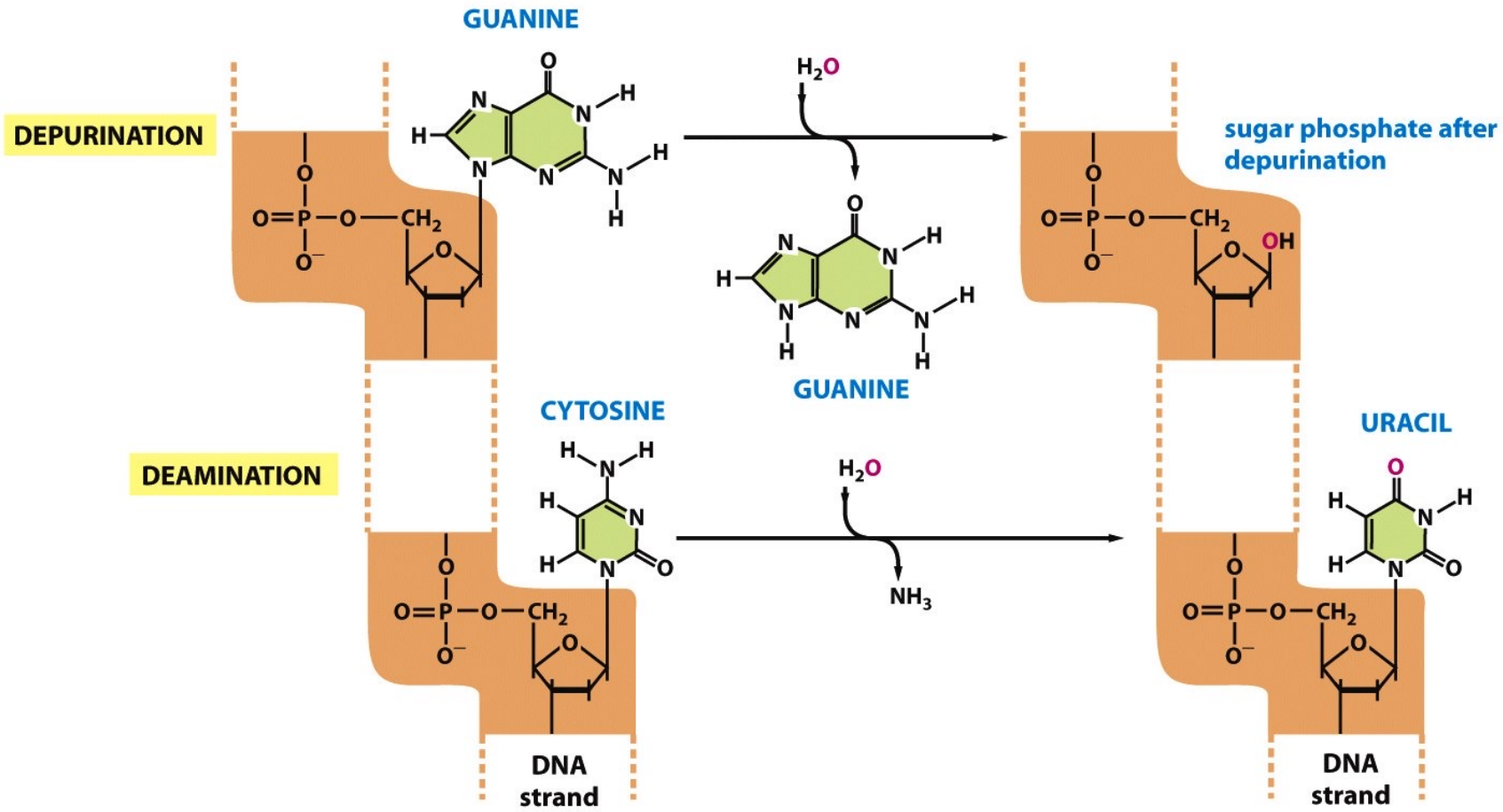
Table 1. DNA Lesions Generated by Endogenous and Exogenous DNA Damage

Endogenous DNA Damage	DNA Lesions Generated	Number Lesions/Cell/Day	
Depurination	AP site	10000[a]	
Cytosine deamination	Base transition	100–500[a]	
SAM-induced methylation	3meA	600[a]	
	7meG	4000[a]	
	O^6meG	10–30[b]	
Oxidation	8oxoG	400–1500[c]	
Exogenous DNA Damage	**Dose Exposure (mSv)**	**DNA Lesions Generated**	**Estimated Number Lesions/Cell**
Peak hr sunlight	—	Pyrimidine dimers, (6–4) photoproducts	100,000/day[d]
Cigarette smoke	—	aromatic DNA adducts	45–1029[e]
Chest X-rays	0.02[f,g,h]	DSBs	0.0008[i]
Dental X-rays	0.005[f,g,h]	DSBs	0.0002[i]
Mammography	0.4[f,g,h]	DSBs	0.016[i]
Body CT	7[f]	DSBs	0.28[i]
Head CT	2[f,g]	DSBs	0.08[i]
Coronary angioplasty	22[h]	DSBs	0.88[i]
Tumor PET scan (^{18}F)	10[h]	DSBs	0.4[i]
^{131}I treatment	70–150[h]	DSBs	2.8–6[i]
External beam therapy	1800–2000[j]	DSBs	72–80
Airline travel	0.005/hr[f]	DSBs	0.0002/hr[i]
Space mission (60 days)	50[k]	DSBs	2[i]
Chernobyl accident	300[l]	DSBs	12[i]
Hiroshima and Nagasaki atomic bombs	5–4000[k]	DSBs	0.2–160[i]

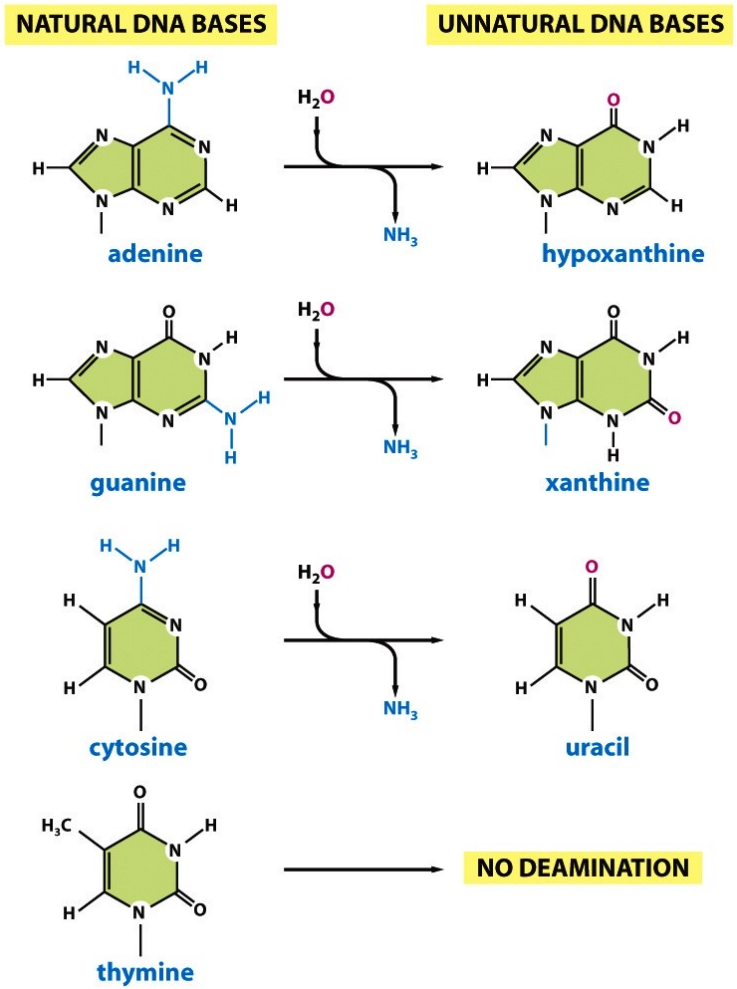
Type and number of DNA lesions are indicated. The number of lesions/cell has been estimated as described.

Ciccia and Elledge, (2010) Mol Cell, Volume 40, Issue 2

Depurination and Deamination



Deamination Yields Unnatural Bases



APOBEC3 proteins catalyze deamination reactions in ssDNA to target viruses and retroelements as part of the innate immune response.

However, **APOBEC3-mediated mutagenesis has also been observed in 70% of all cancer types and 50% of all cancer genomes! (***Nature* **607**, pages 799–807 (2022**).**

Deamination of 5-Methyl Cytosine Yields Thymine!

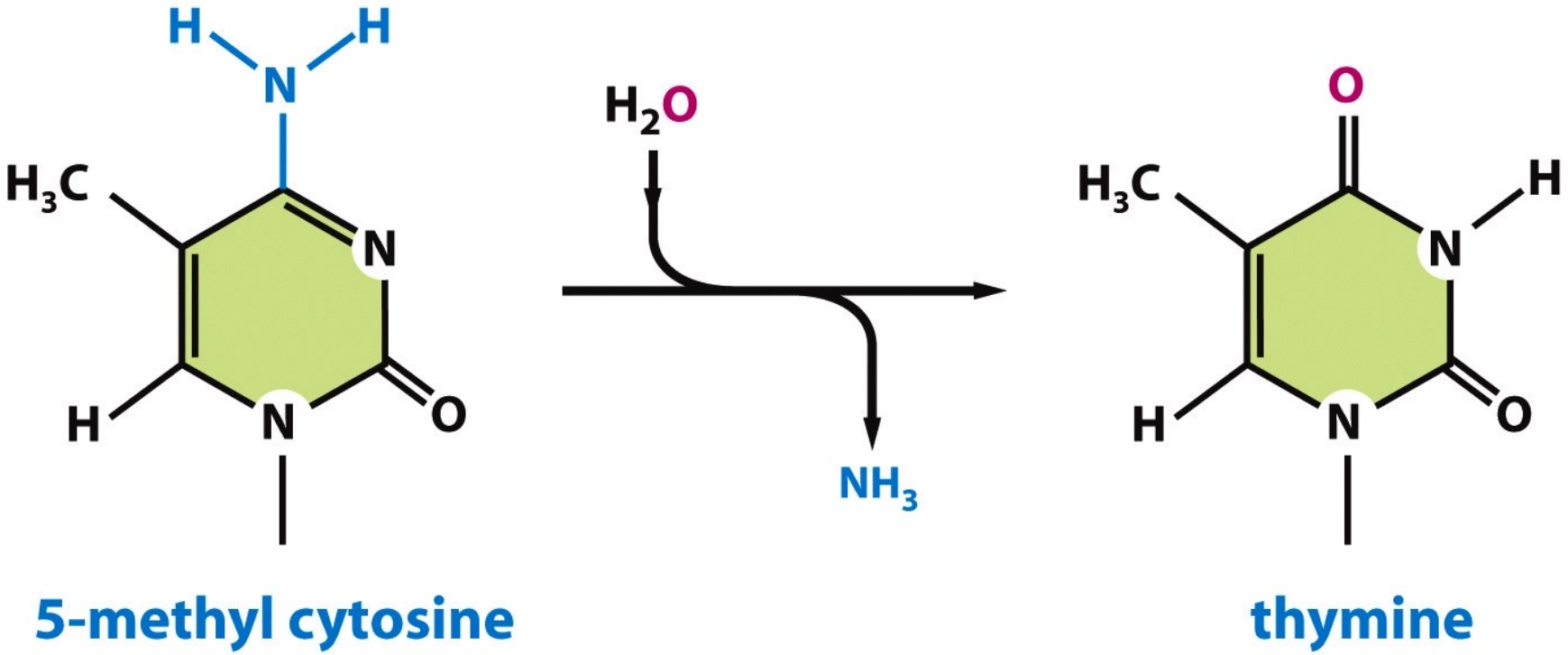


Figure 5-50b *Molecular Biology of the Cell* (© Garland Science 2008)

Thymine-Dimer: Caused by UV-light in the Skin

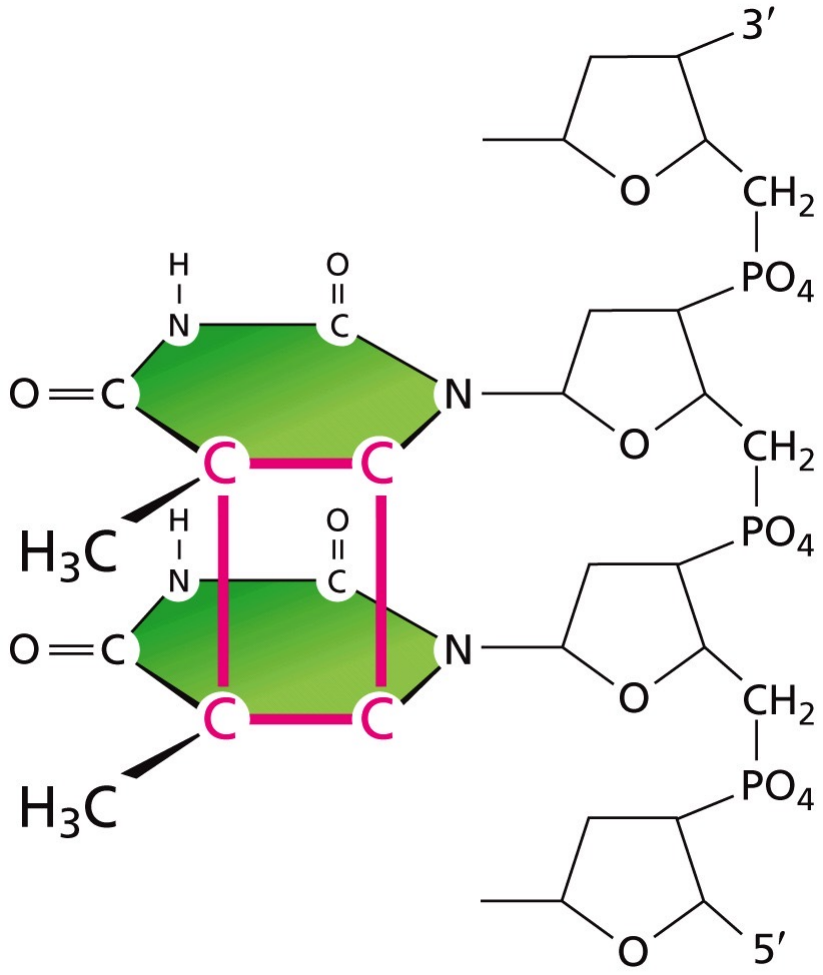


Figure 12.12a The Biology of Cancer (© Garland Science 2014)

6-4 Photoproducts of Pyrimidines

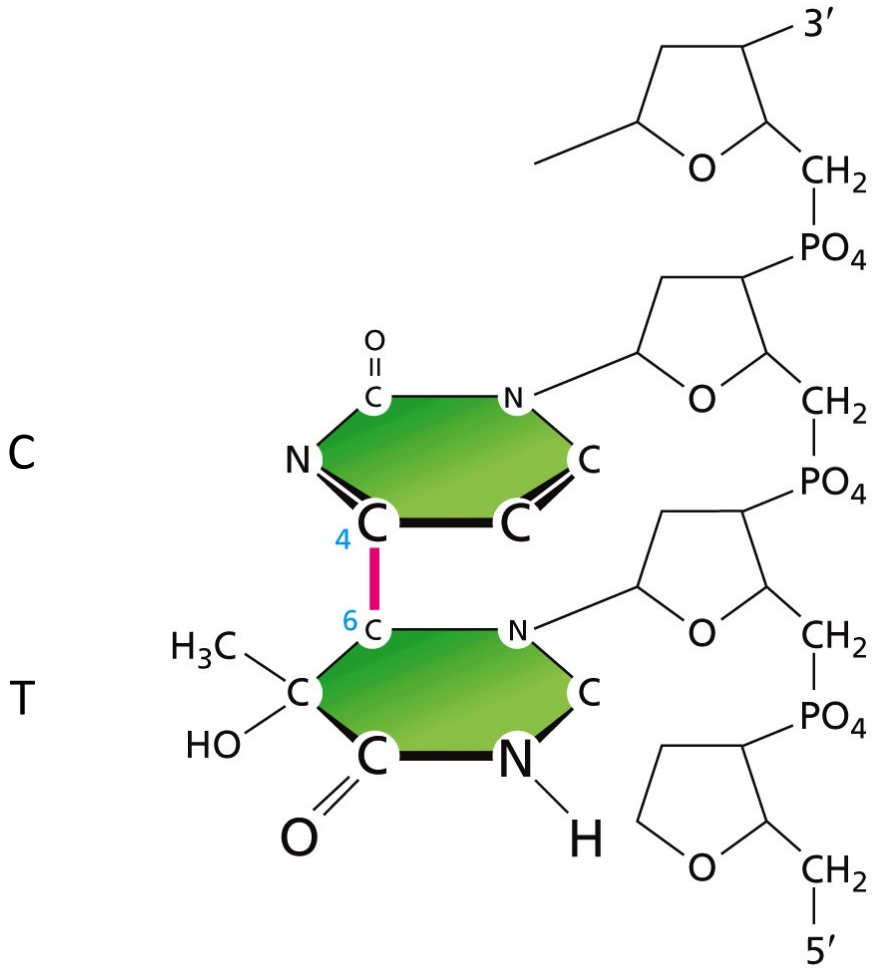
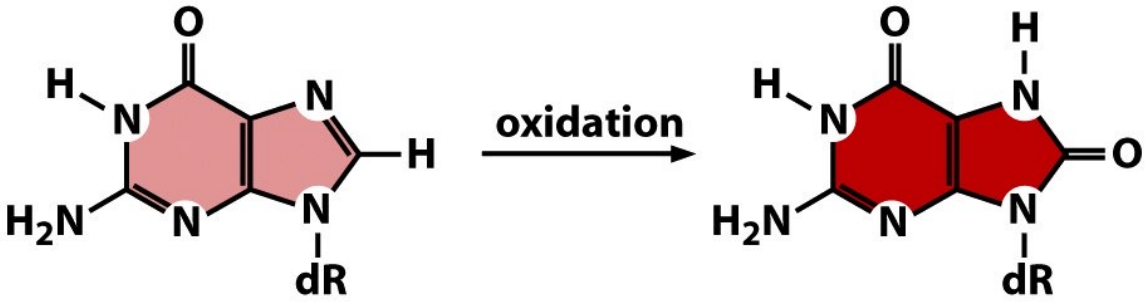
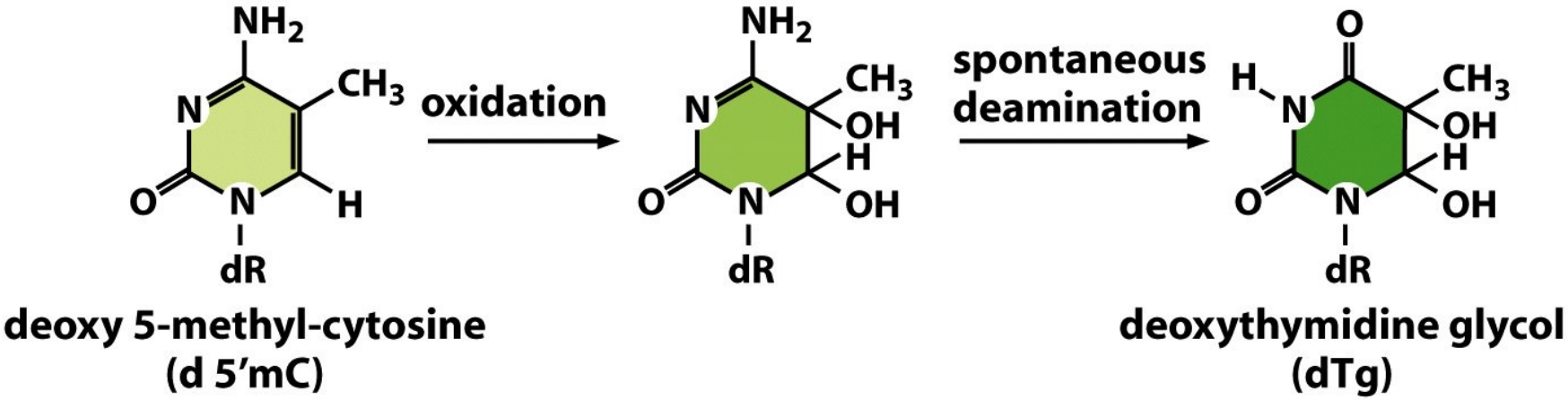


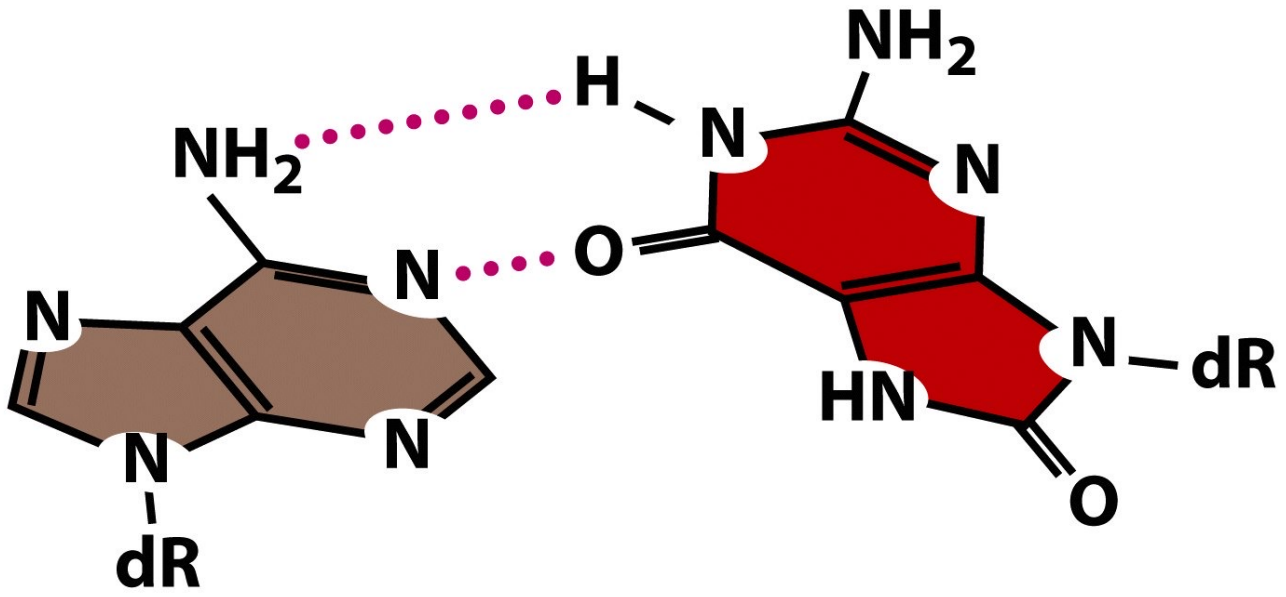
Figure 12.12b The Biology of Cancer (© Garland Science 2014)

Oxidation of DNA Bases





8-oxo-dG can mispair with deoxyadenosine during DNA replication



mispairing of 8-oxo-dG with deoxyadenosine (dA)

Ionizing Radiation (IR)

- Deposits energy to yield ionized molecules or reactive oxygen species (ROS) that then attack the DNA
- Causes base damage, DNA-protein cross-links, phosphate backbone damage, single-strand breaks, and double-strand breaks (DSBs)
- Cell killing by IR generally reflects the generation of DSBs, as these are difficult to repair
- Does not occur “often” but note that 200,000,000 gamma rays pass through your body every hour (these come from decay of naturally-occurring radioactive isotopes)
- Used in cancer therapy

Key concepts

- The vast majority of human tumors is monoclonal. But: genetic heterogeneity due to genetic instability may mask the true monoclonal origin

- The multiplicity of defenses may explain why cancer is relatively rare during human lifetime (more than 6 specific changes must occur to make out of a normal cell a tumor cell)

- Human cancers express a mutator phenotype

Exercise on Wednesday

- Please read the paper (Vogelstein et al. Cancer Genome Landscapes.Science339,1546-1558(2013).DOI:10.1126/science.1235122) to be discussed until Wednesday. During the exercises, you will have additional time to carefully analyze and discuss the paper and address the questions that you find on moodle.
- You should sign up and join one of discussion groups.

Group formation (maximally 5/group): inscribe via https://framadate.org/8Vgos7nr4uoNeGNJ

- At 3 pm, individual groups present and discuss the answers that have been assigned to their group in front of the class.