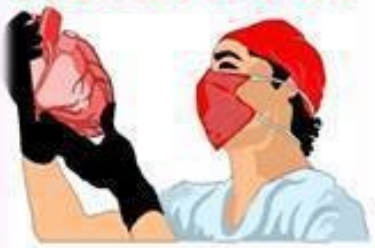
PATHOLOGY



Medical Committee
The University of Jordan

SHEET

SIIDE

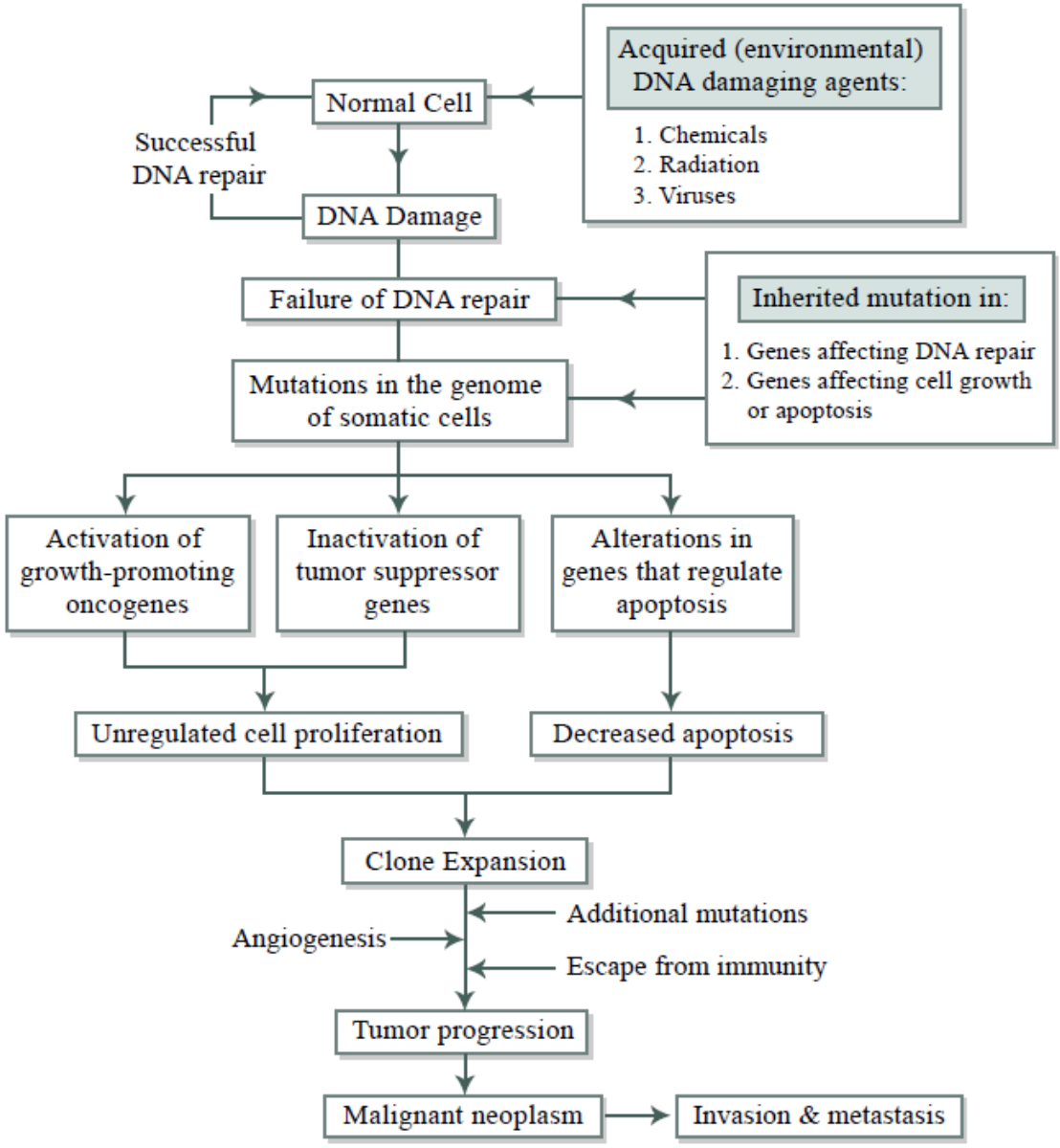
Slide :16-genetics epigenetics

Doctor: Dr. Mazen

Designed by: Majida Al-Foqara'

Molecular Biology of Cancer

Introduction



Carcinogenesis

Nonlethal genetic damage + Clonal expansion

Involved gene classes
- Oncogenes
- Tumor suppressors
- Genes regulating apoptosis
- DNA repair genes

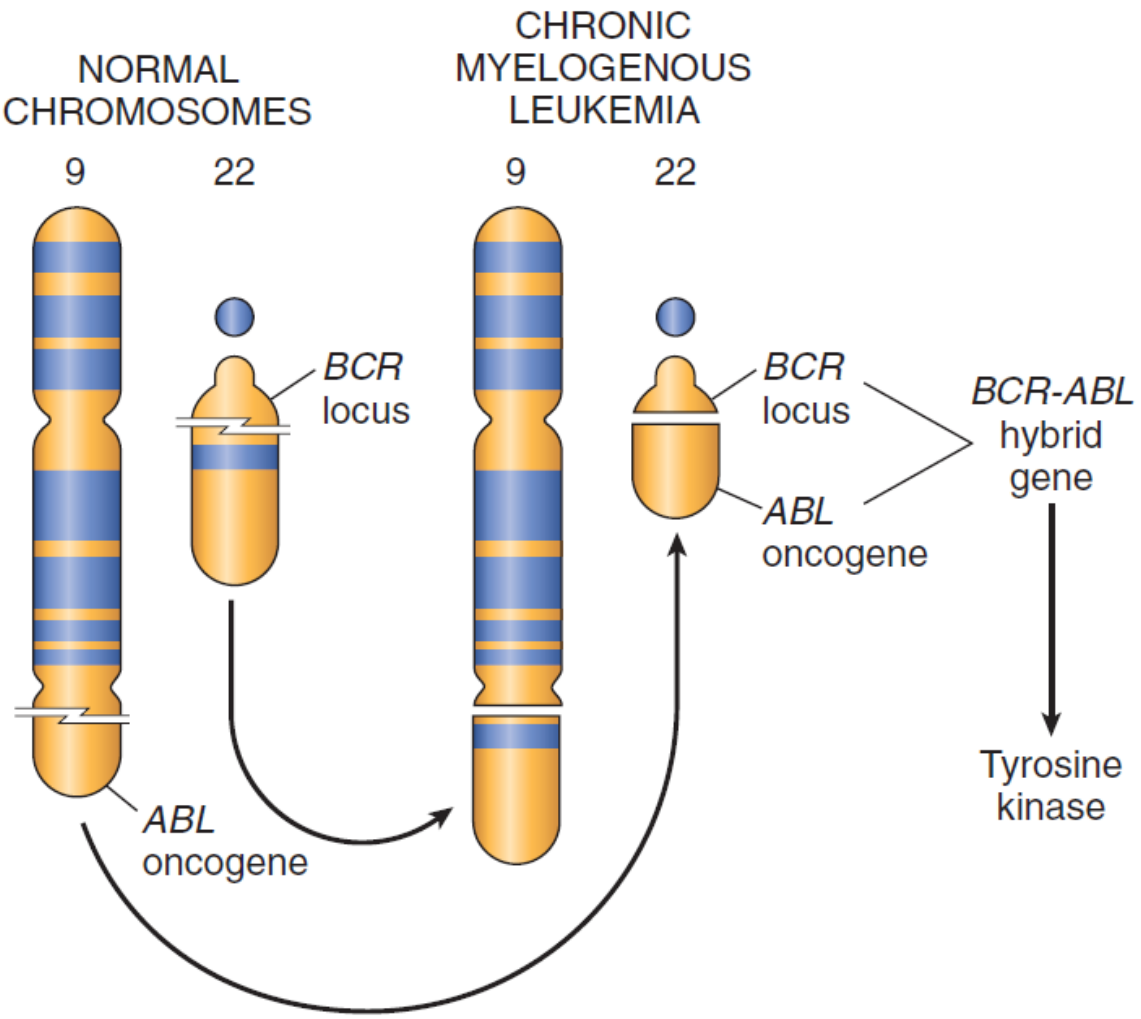
Carcinogenesis is a multistep process

Definitions

- Oncogene
  - Mutation/over-expression of a proto-oncogene
    - Transcription factors
    - Growth regulation
    - Cell survival
    - Cell-cell-matrix interactions
  - Cellular transformation
  - Dominant (one damaged allele enough)

- Tumor suppressor gene
  - Mutation = uncontrolled growth/transformation
  - Both alleles/LOH/haploinsufficiency
  - Governors (growth control e.g. *RB*)
  - Guardians (sensing DNA damage e.g. *TP53) – mutator phenotype*

Genetic Lesions in Cancer



Karyotypic changes

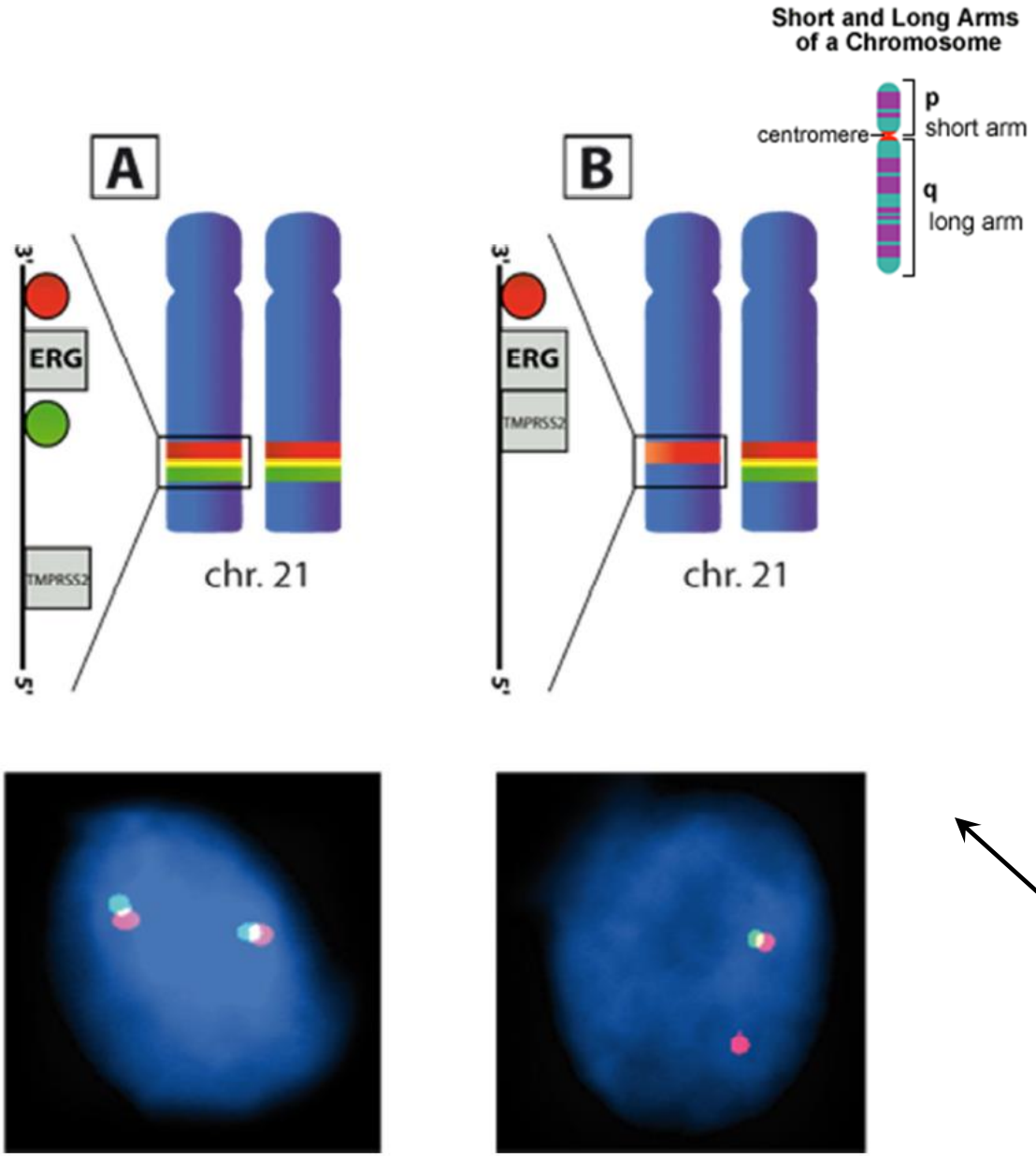
Balanced Translocations

Proto-oncogene activation by:

1. Over-expression
   - t(8;14) *MYC*
   - t(14;18) *BCL2*

2. Fusion products
   - t(9;22) *BCR-ABL*
   - t(11;22) *EWS-Fli-1*
   - *TMPRSS-ETS**

from deletion on chr. 21 or translocation



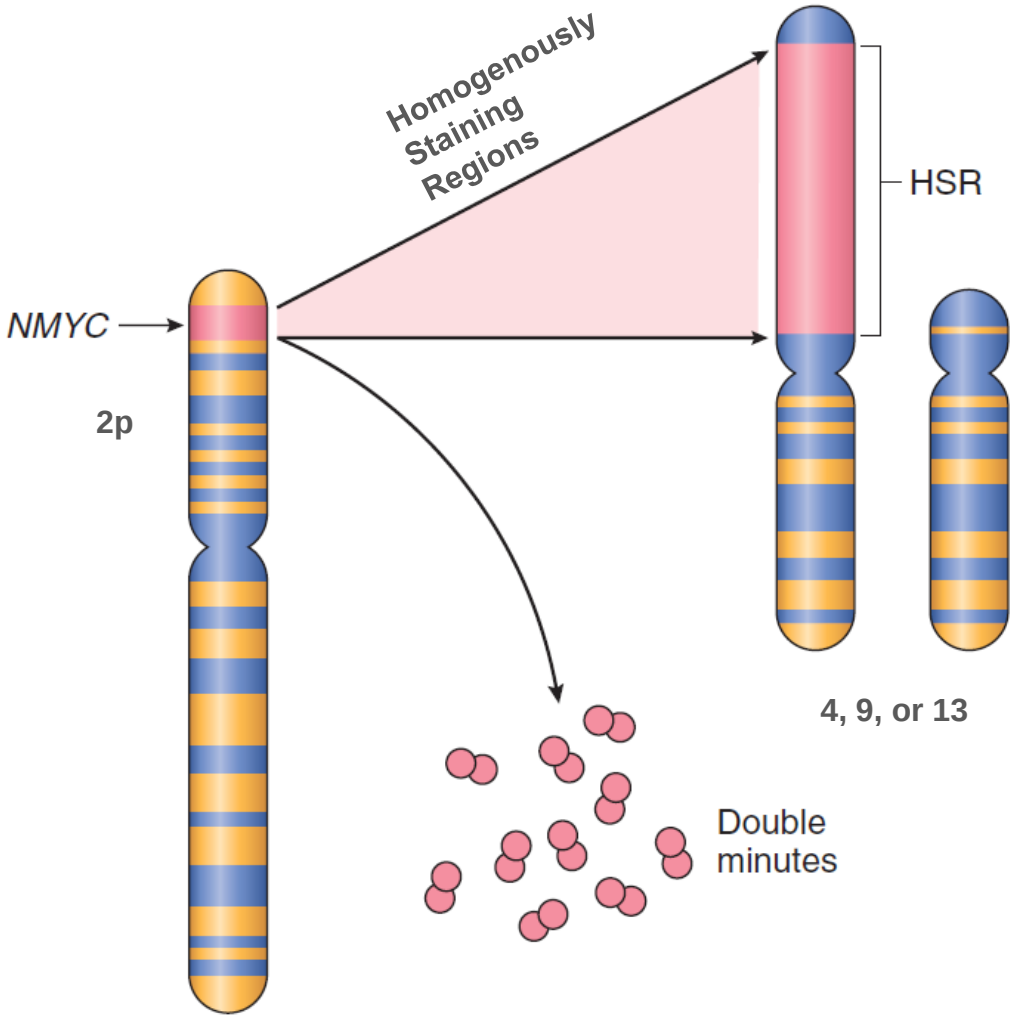
Karyotypic changes

Deletions

2nd most prevalent karyotypic abnormality

Karyotypic deletions are more common in nonhematopoietic solid tumors

- 13q14 deletions *(RB)*
- 17p deletions *(TP53)*
- 21q deletions



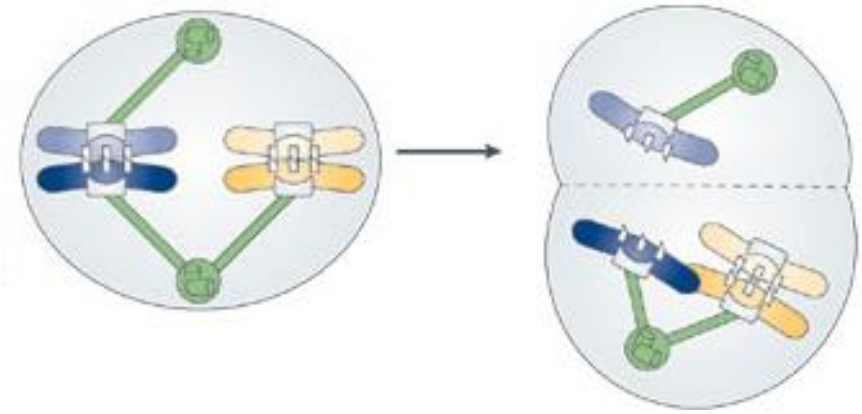
Karyotypic changes

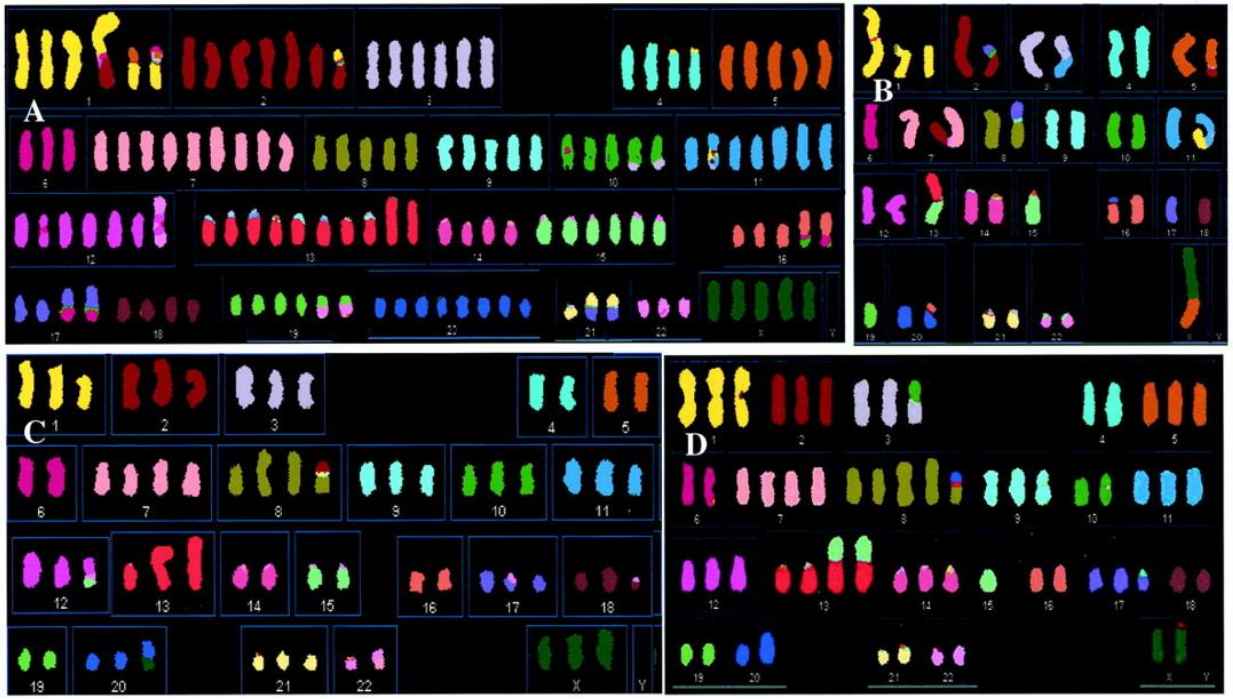
Gene amplifications

Proto-oncogene activation by over-expression

- *NMYC*
  neuroblastomas
  25-30%
  poor prognosis

- *ERBB2 (HER2/NEU)*
  breast cancer
  20%
  α-ERBB2 antibody Tx





Karyotypic changes

Aneuploidy

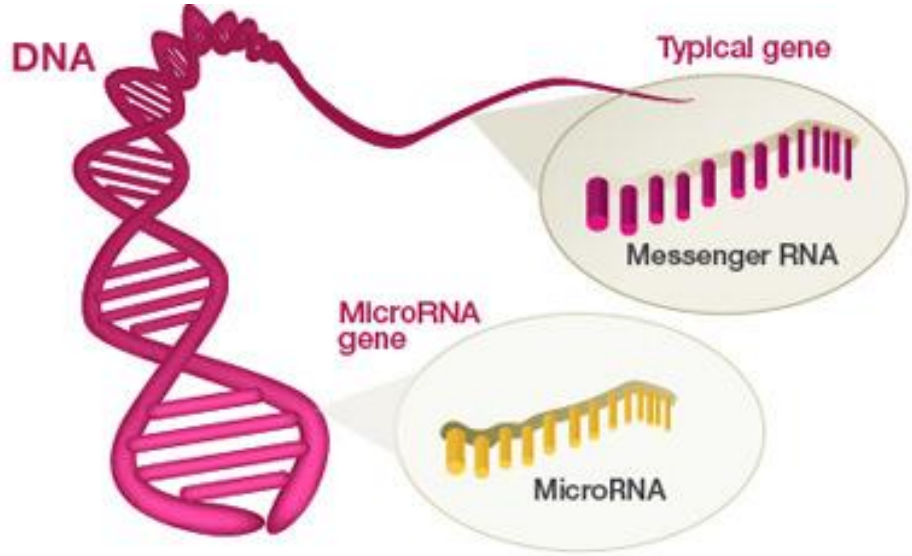
Chromosomal number not a multiple of the haploid state

Human haploid number 23

Frequently due to abnormal mitotic checkpoint

Cause vs consequence?

miRNA



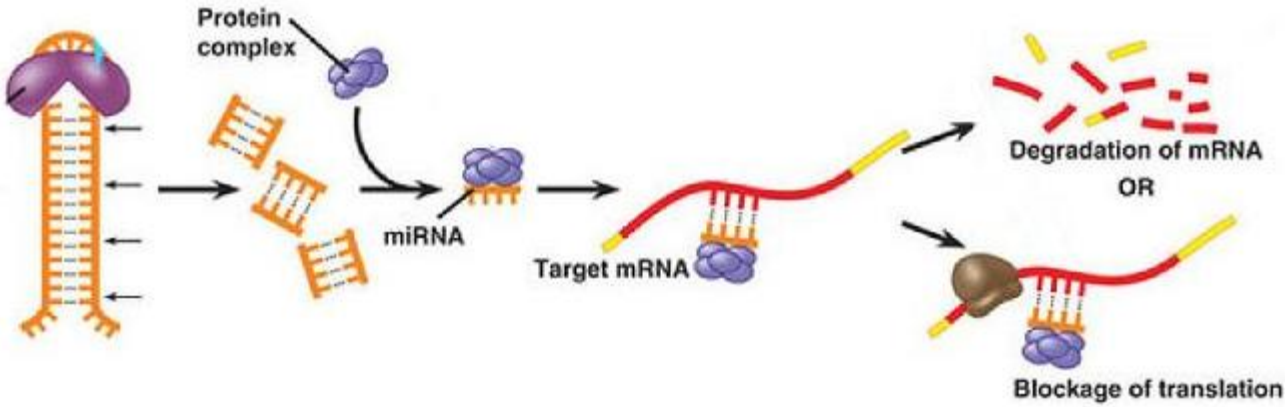
miRNA

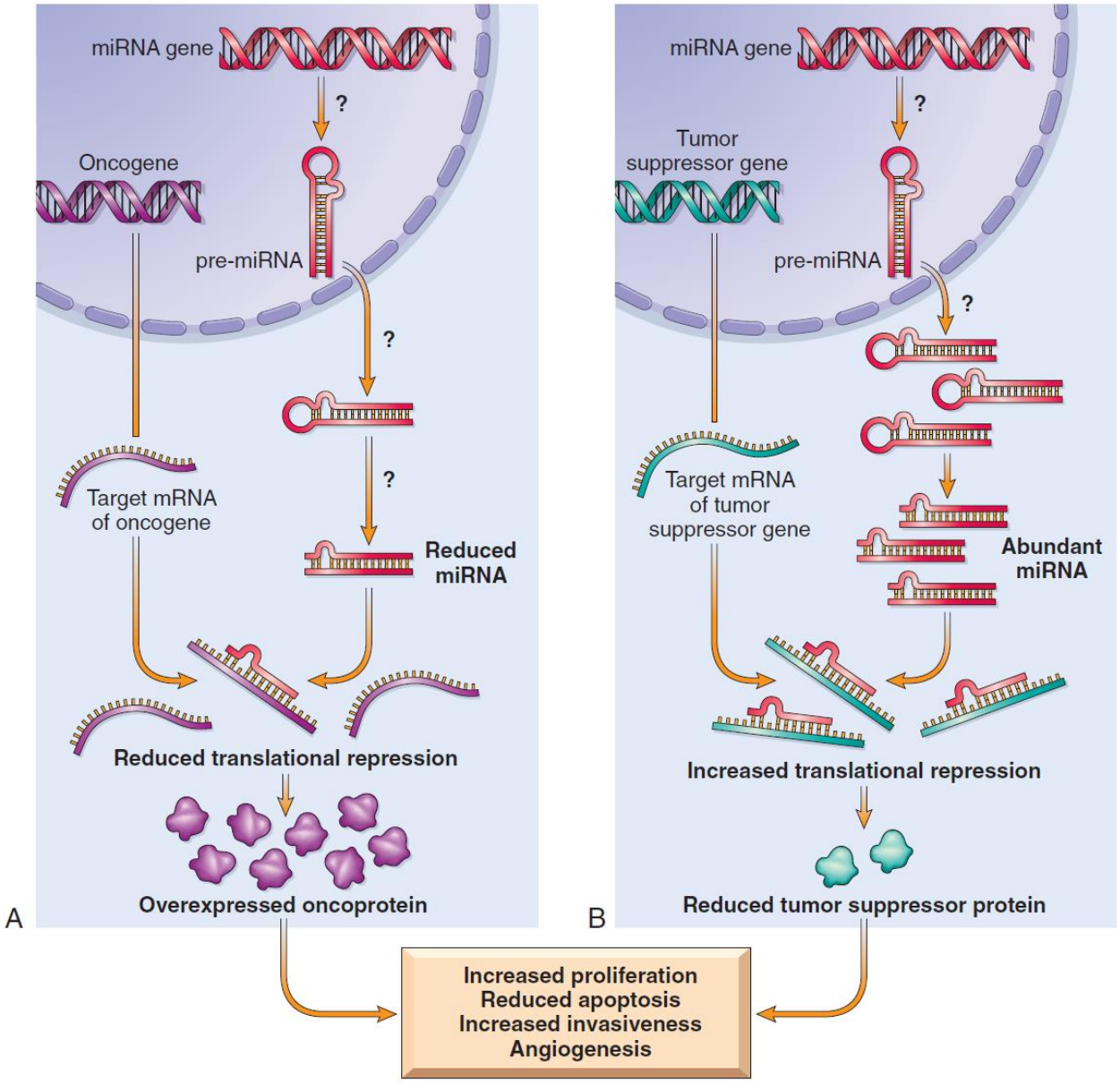
ssRNA

~22 nucleotides long

Repression of translation

mRNA cleavage





miRNA

In cancer:

↑ oncogene expression
↓ tumor suppressor

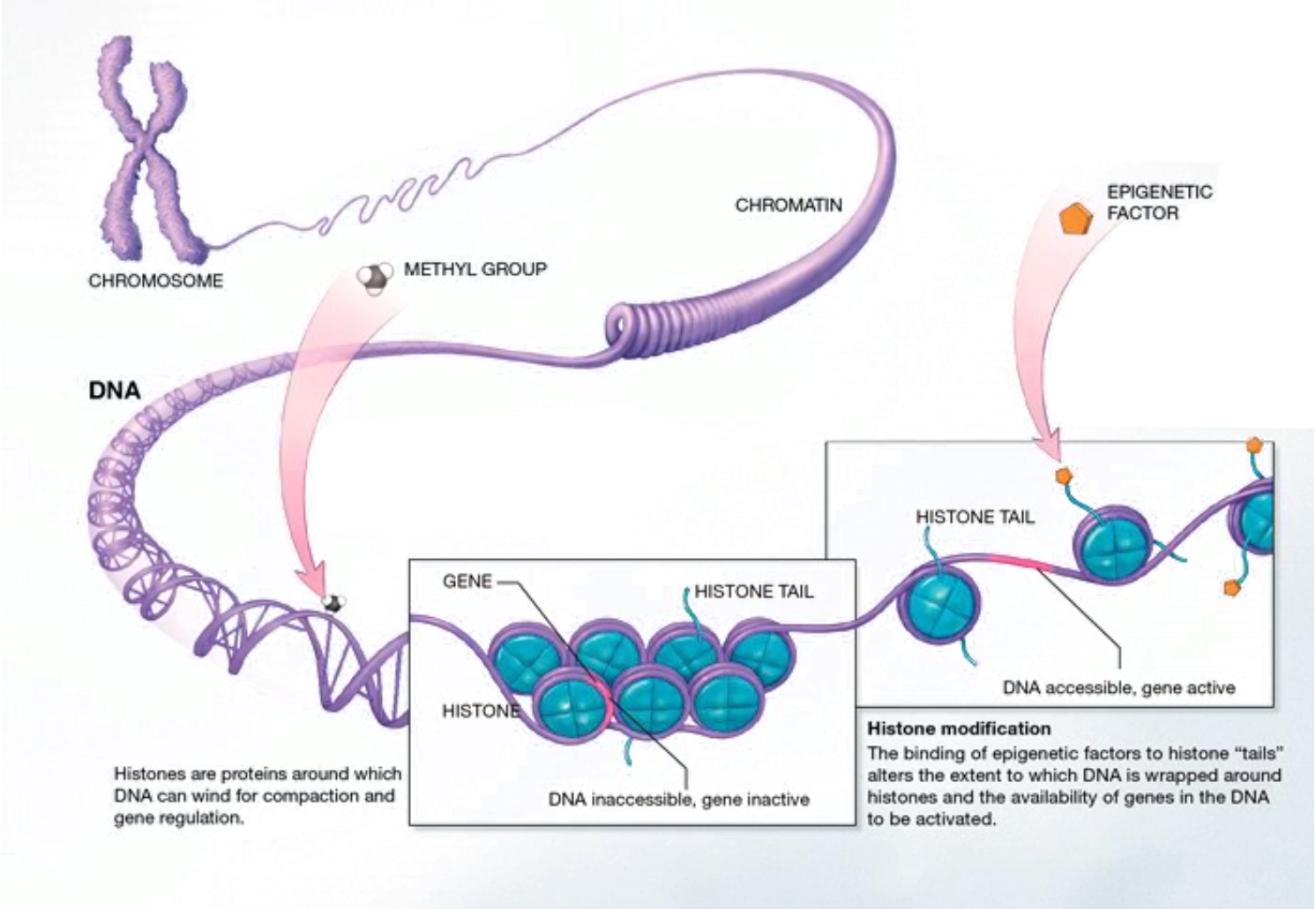
BCL2: Leukemia/Lymphoma

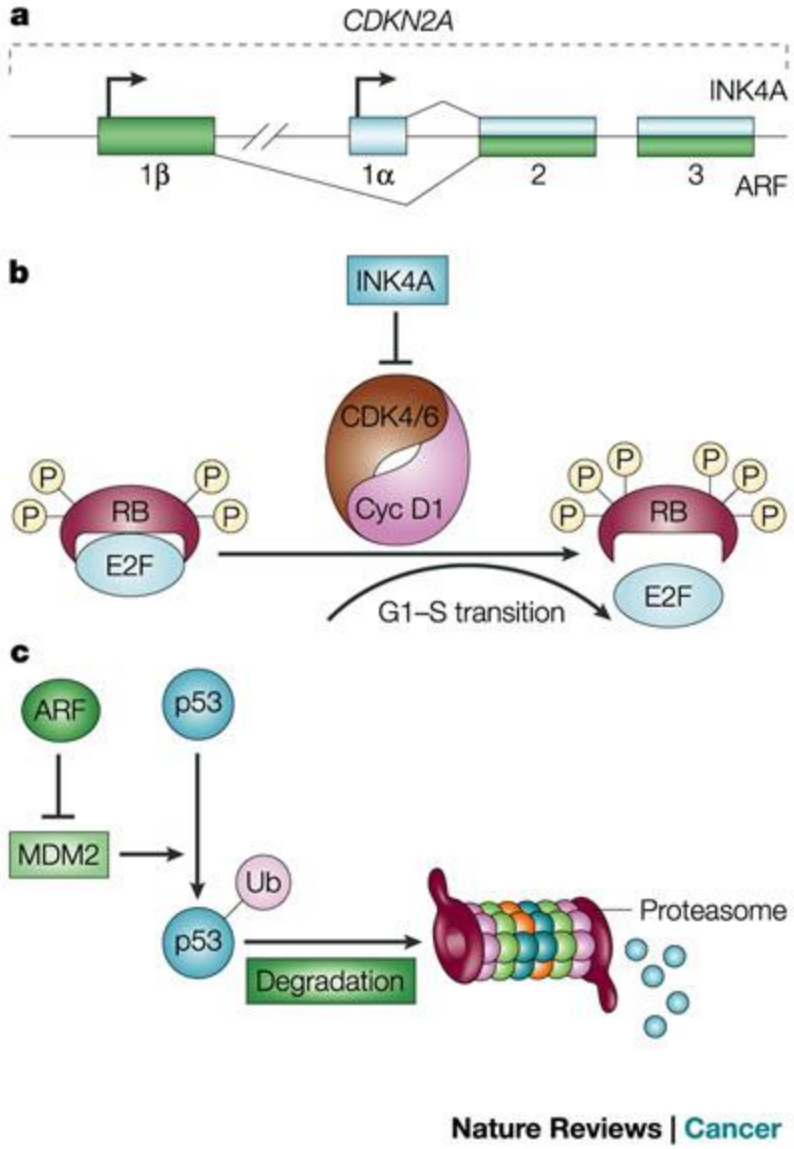
RAS: Lung

MYC: B cell leukemia

Epigenetic Changes in Cancer

Epigenetics

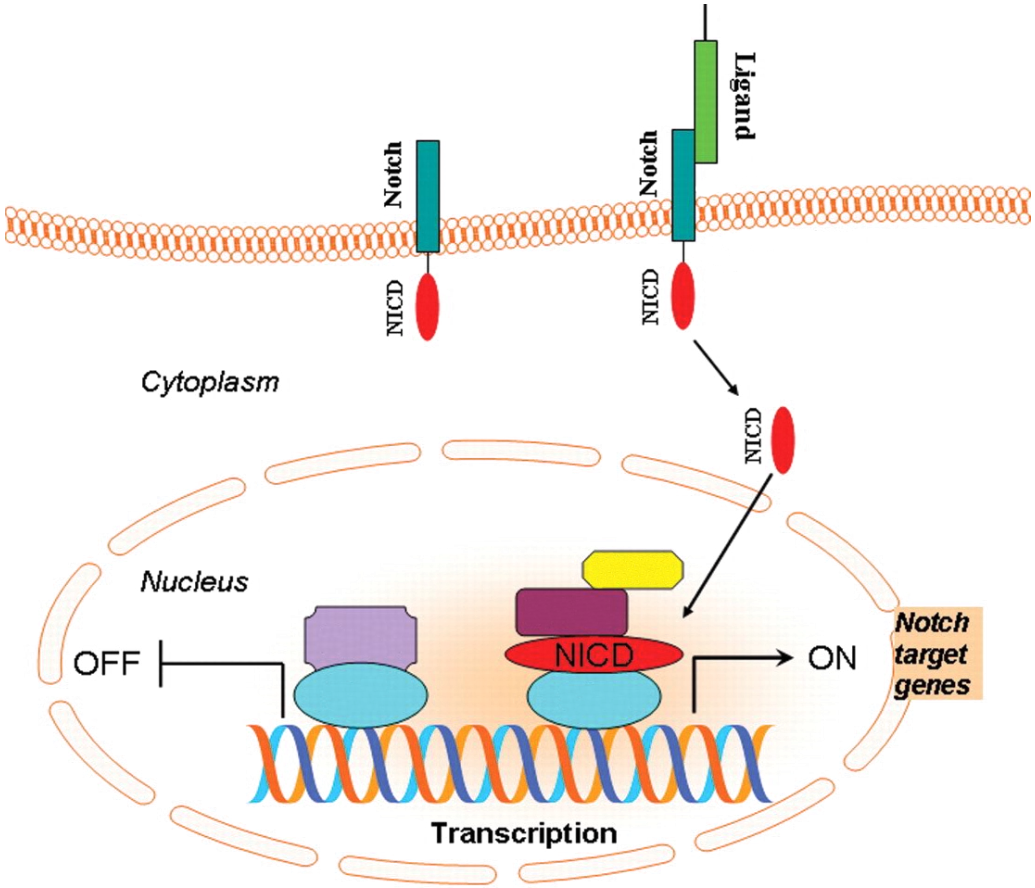




Cancer epigenetics

Global DNA hypomethylation

Selective promoter hypermethylation (e.g. tumor suppressor genes)



Tumor suppressor
Keratinocytes
↓
p21

Oncogene
T-cell progenitors
↓
MYC

Epigenetic context

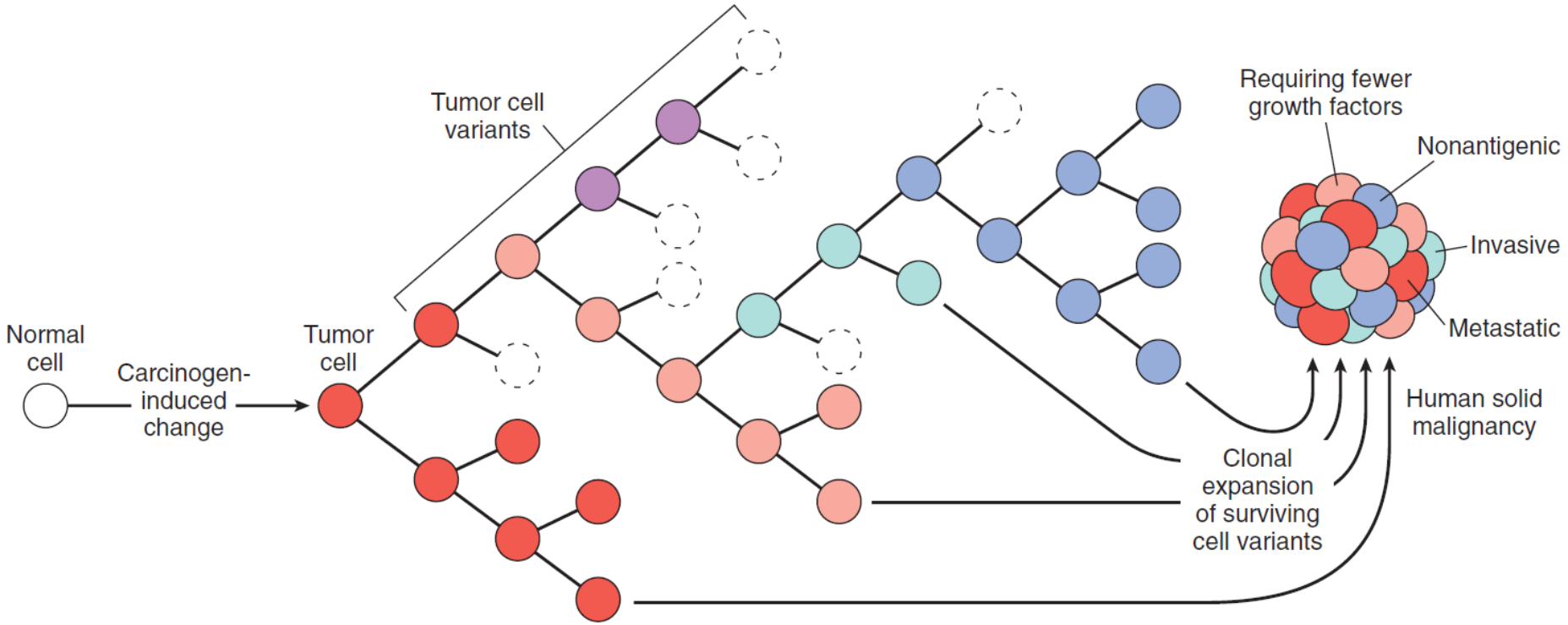
Same genetic material - wildly different cell types

Cellular epigenetic context (e.g. *NOTCH1*)

Molecular Biology of Cancer

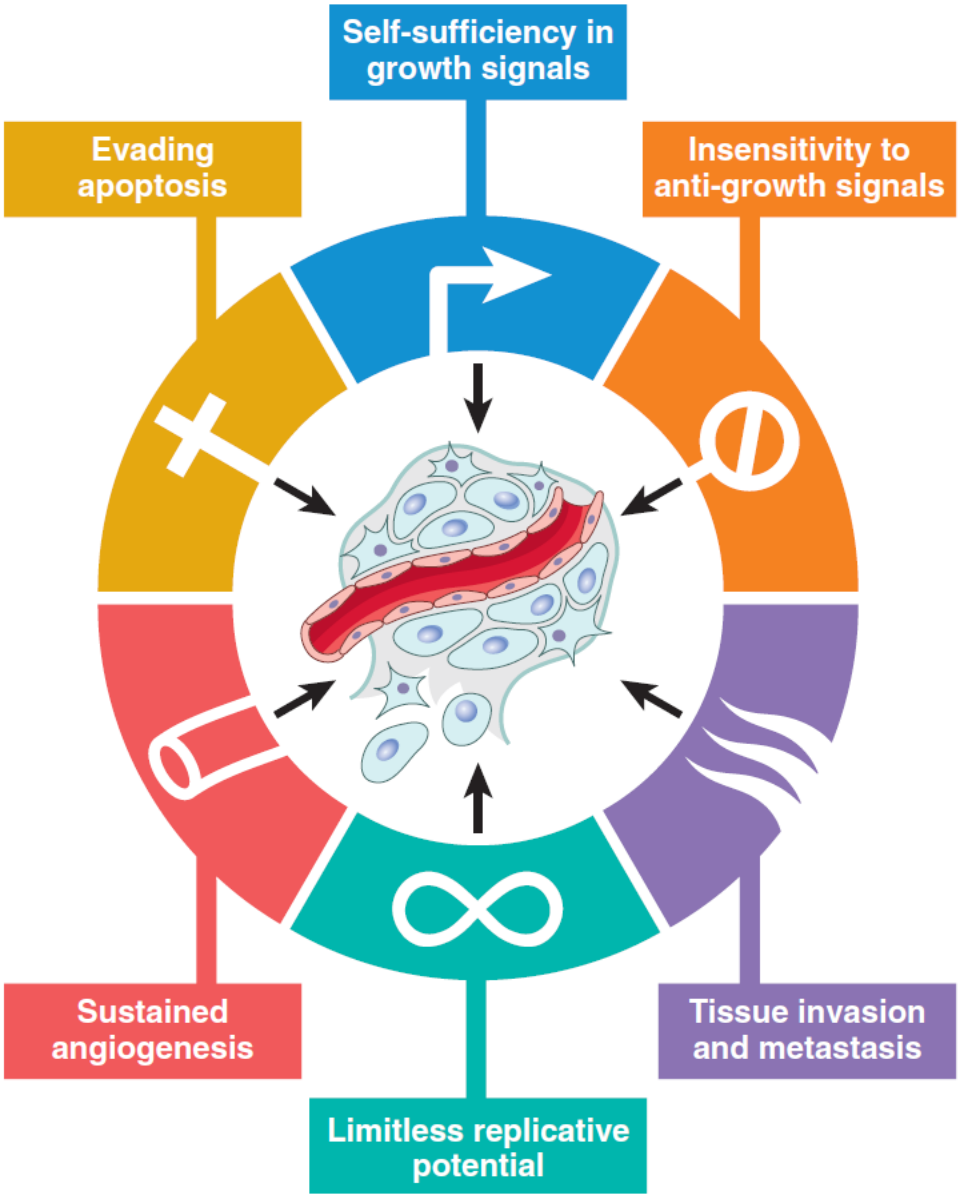
Initiation & Progression

Carcinogenesis is a multistep process



TRANSFORMATION	PROGRESSION	PROLIFERATION OF GENETICALLY UNSTABLE CELLS →	TUMOR CELL VARIANTS: HETEROGENEITY

Hallmarks of Cancer



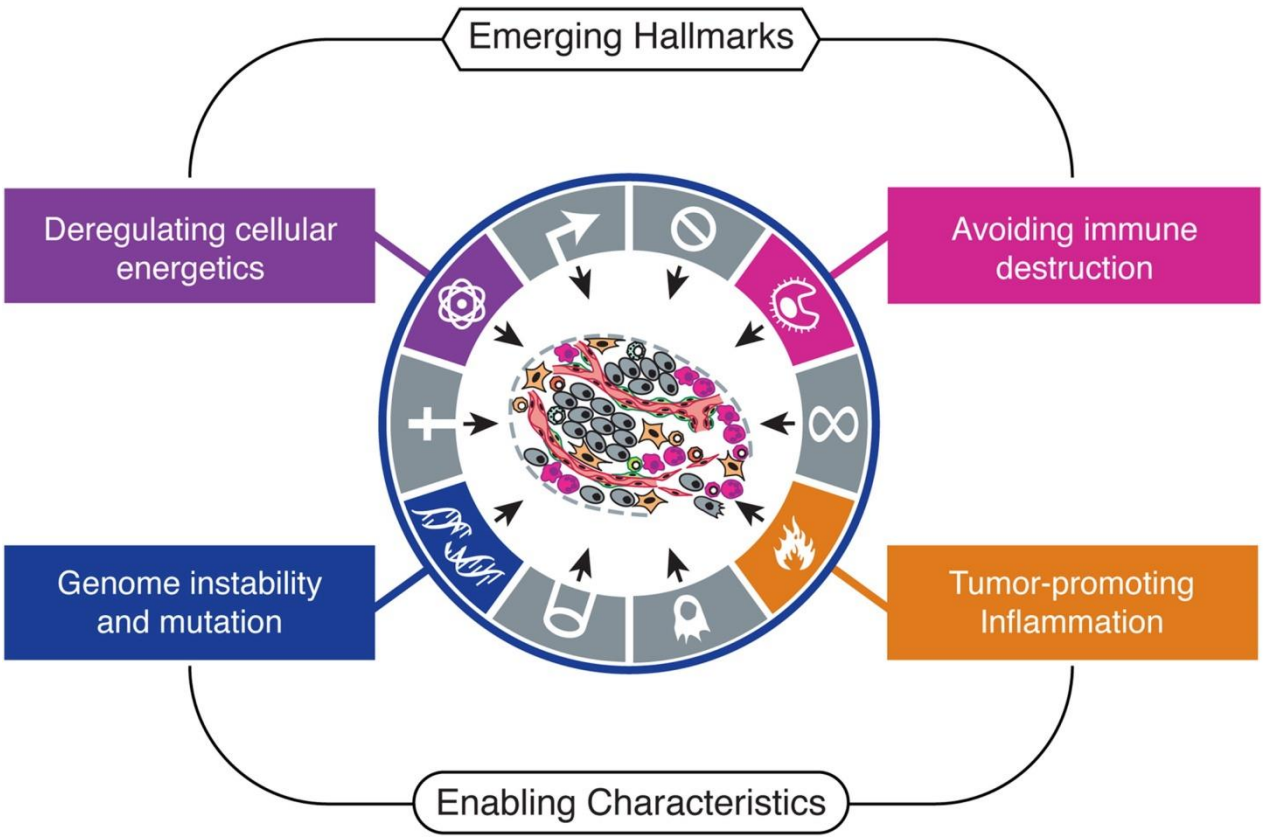
Original Hallmarks

Fundamental changes in cellular physiology compared to non-cancerous cells

Based in a large part on the SMT although some stromal interaction for angiogenesis

Hanahan D, Weinberg RA: The hallmarks of cancer. Cell 100:57, 2000.

New Hallmarks



A better understanding that there is a two way conversation between the tumor parenchymal cells and the surrounding stroma

Hanahan D, Weinberg RA: The hallmarks of cancer: the next generation. Cell 144:646, 2011.