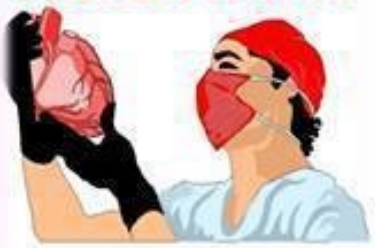
PATHOLOGY



Medical Committee
The University of Jordan

☐ SHEET

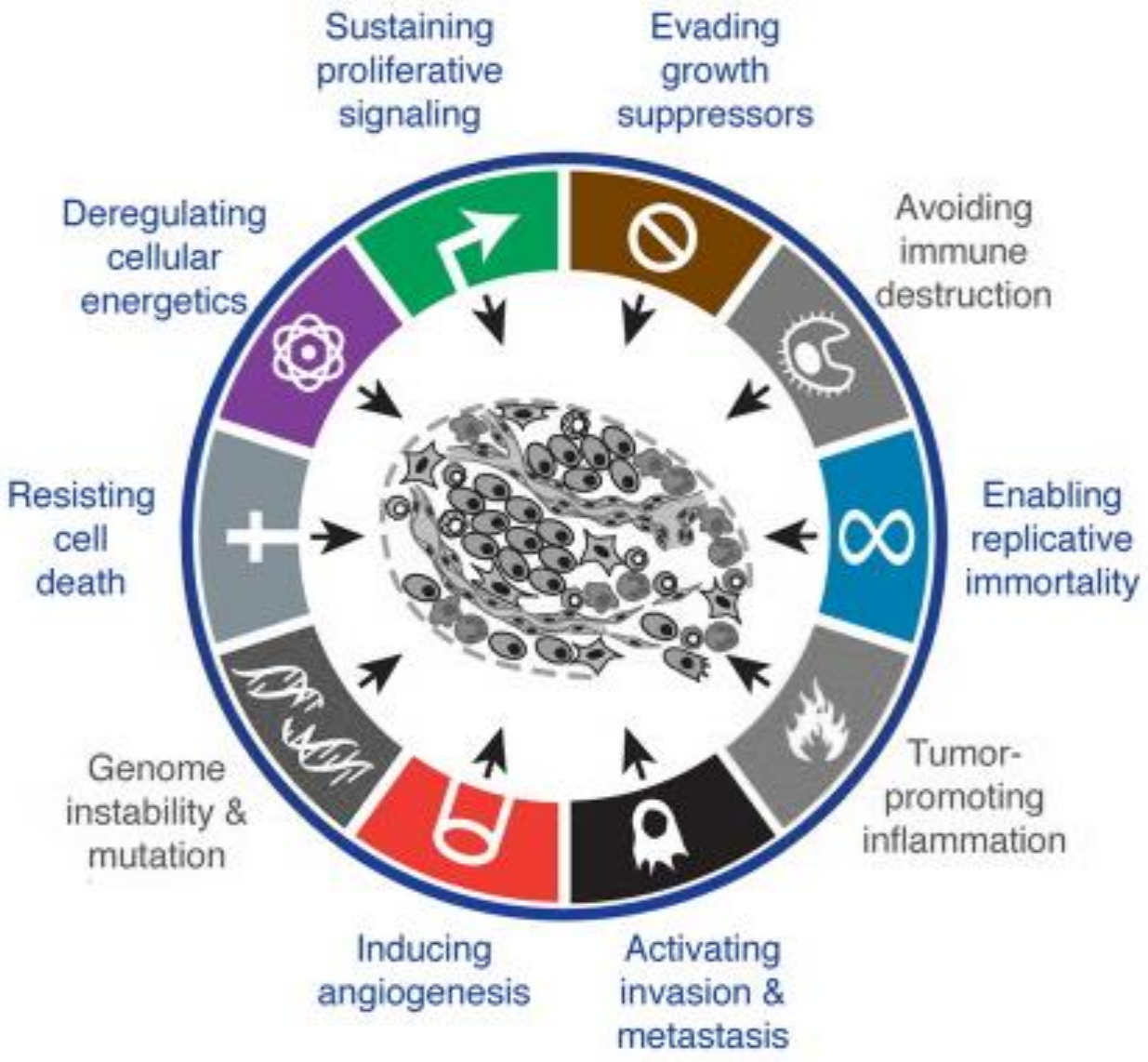
■ SIIDE

Slide : 19- Reprogramming Energy Metabolism

Doctor: Dr. Mazen

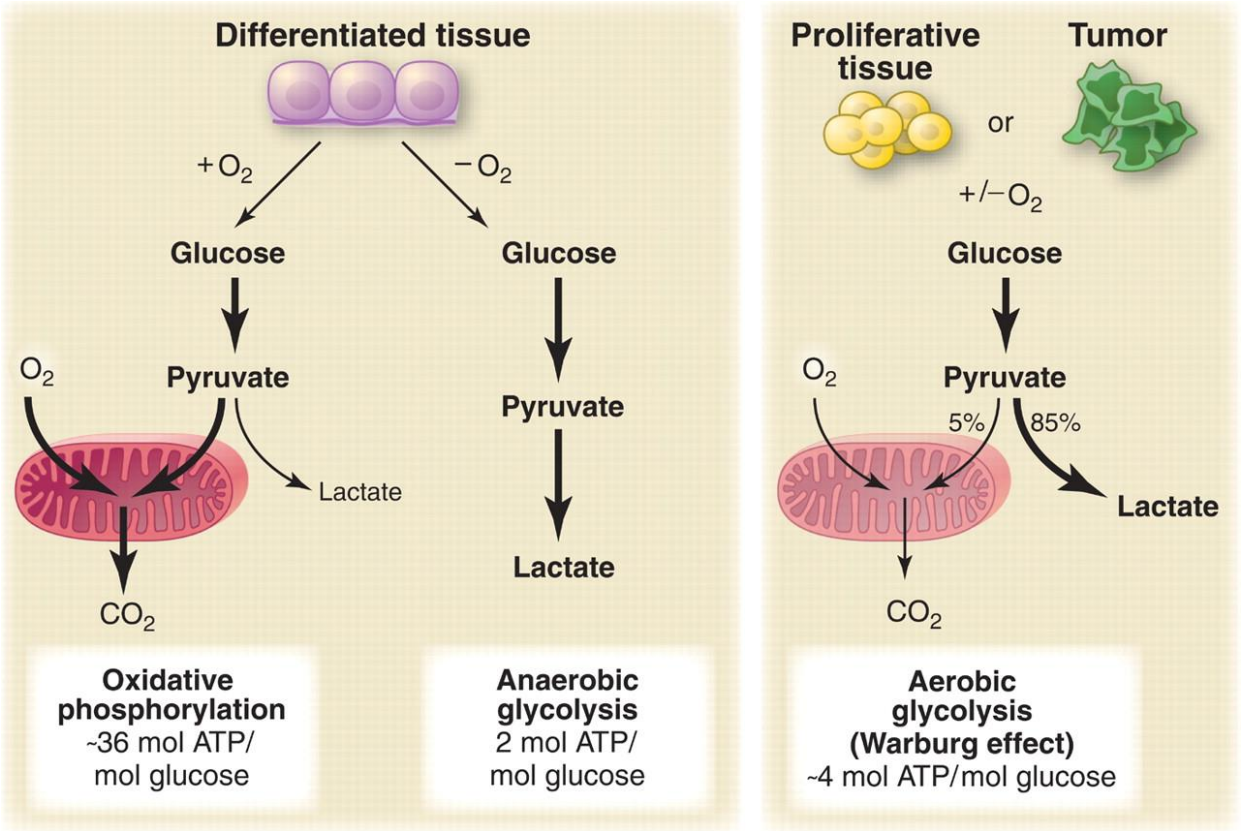
Designed by: Majida Al-Foqara'

Hallmarks of Cancer
Reprogramming Energy Metabolism


Sustaining proliferative signaling
Evading growth suppressors
Avoiding immune destruction
Enabling replicative immortality
Tumor-promoting inflammation
Activating invasion & metastasis
Inducing angiogenesis
Genome instability & mutation
Resisting cell death
Deregulating cellular energetics

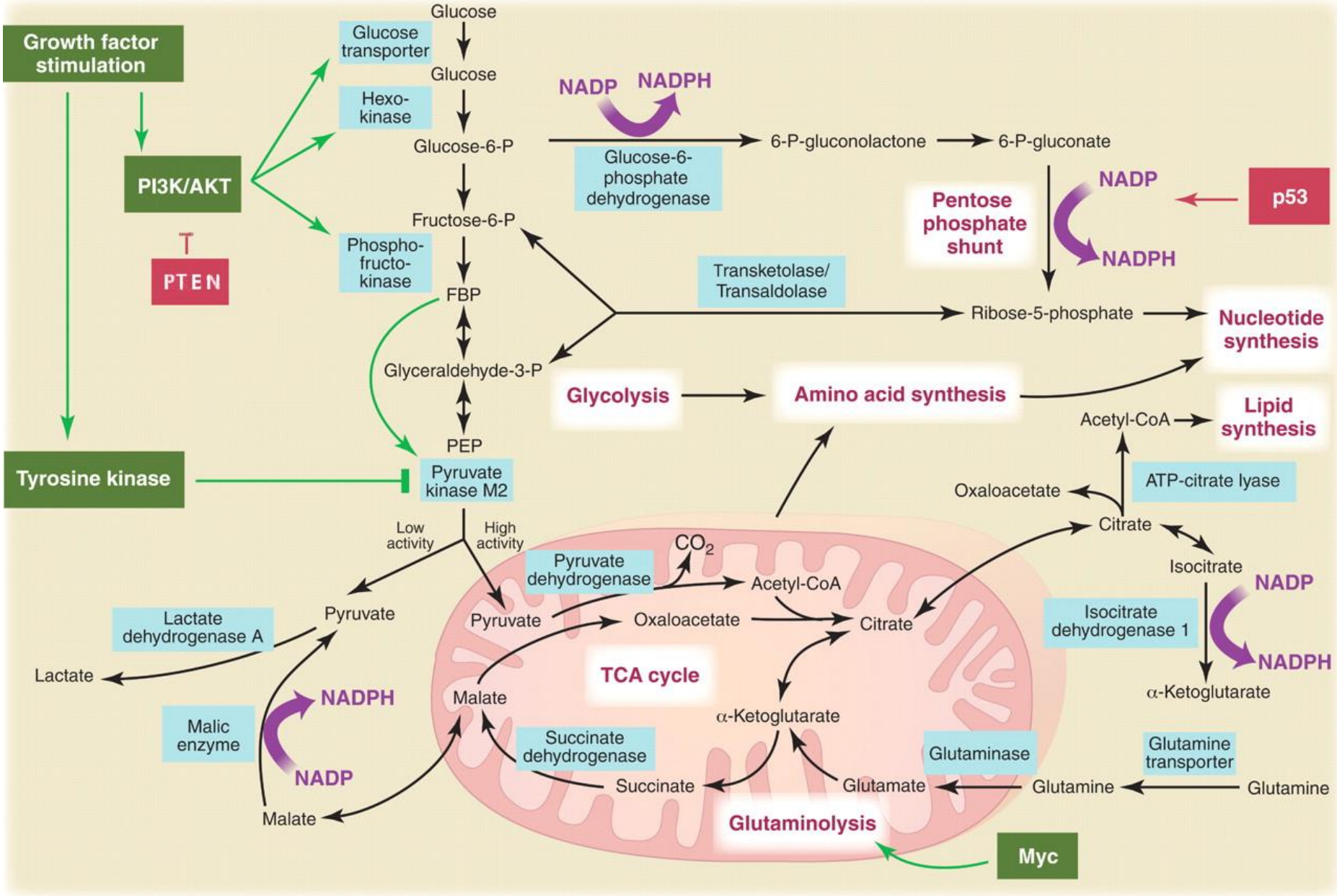
The Warburg effect

aka aerobic glycolysis

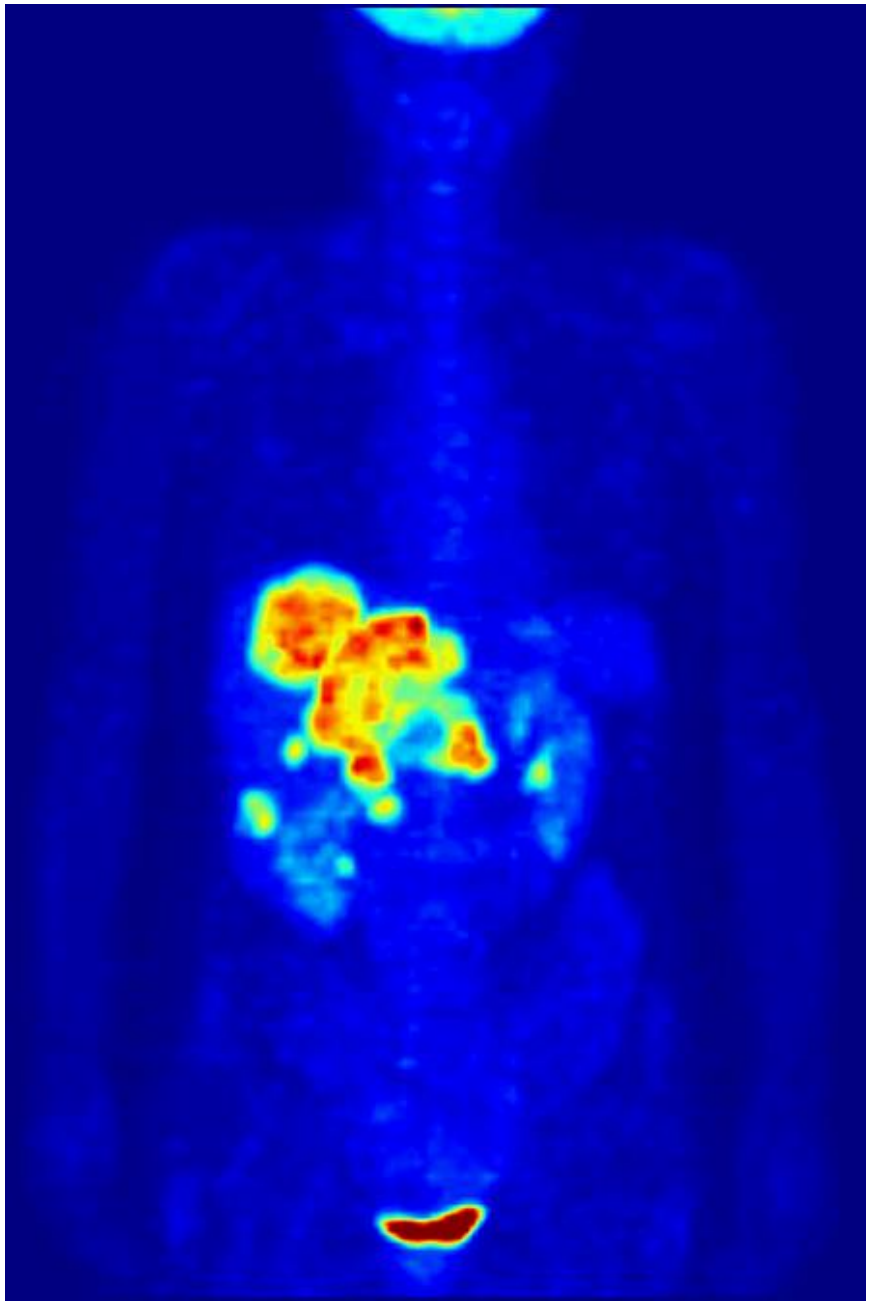


Otto Warburg

- *Vander Heiden et al.: Understanding the Warburg effect. Science 324:1029, 2009.*



Modified *Vander Heiden et al.: Understanding the Warburg effect. Science 324:1029, 2009.*



Positron Emission Tomography (PET) scanning

"Glucose Hunger"

^{18}F-fluorodeoxyglucose (non-metabolizable derivative)

Hallmarks of Cancer
Evasion of the Immune System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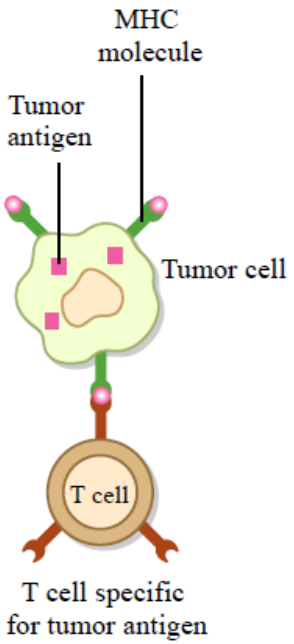
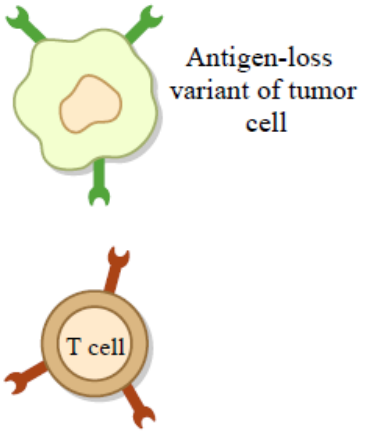
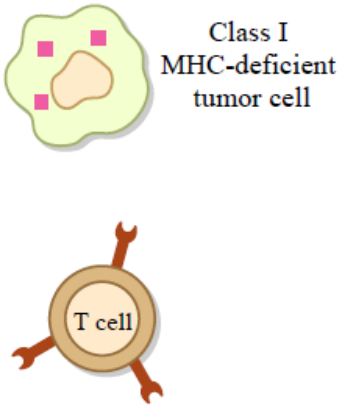
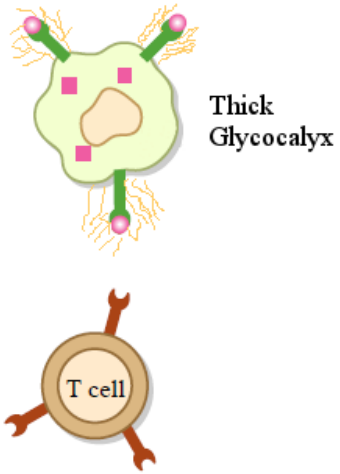
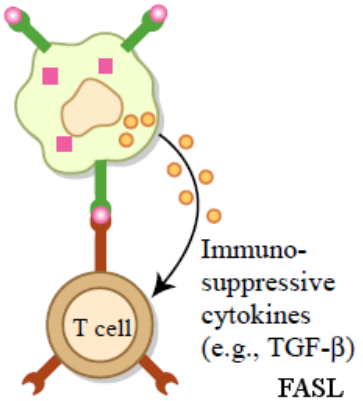
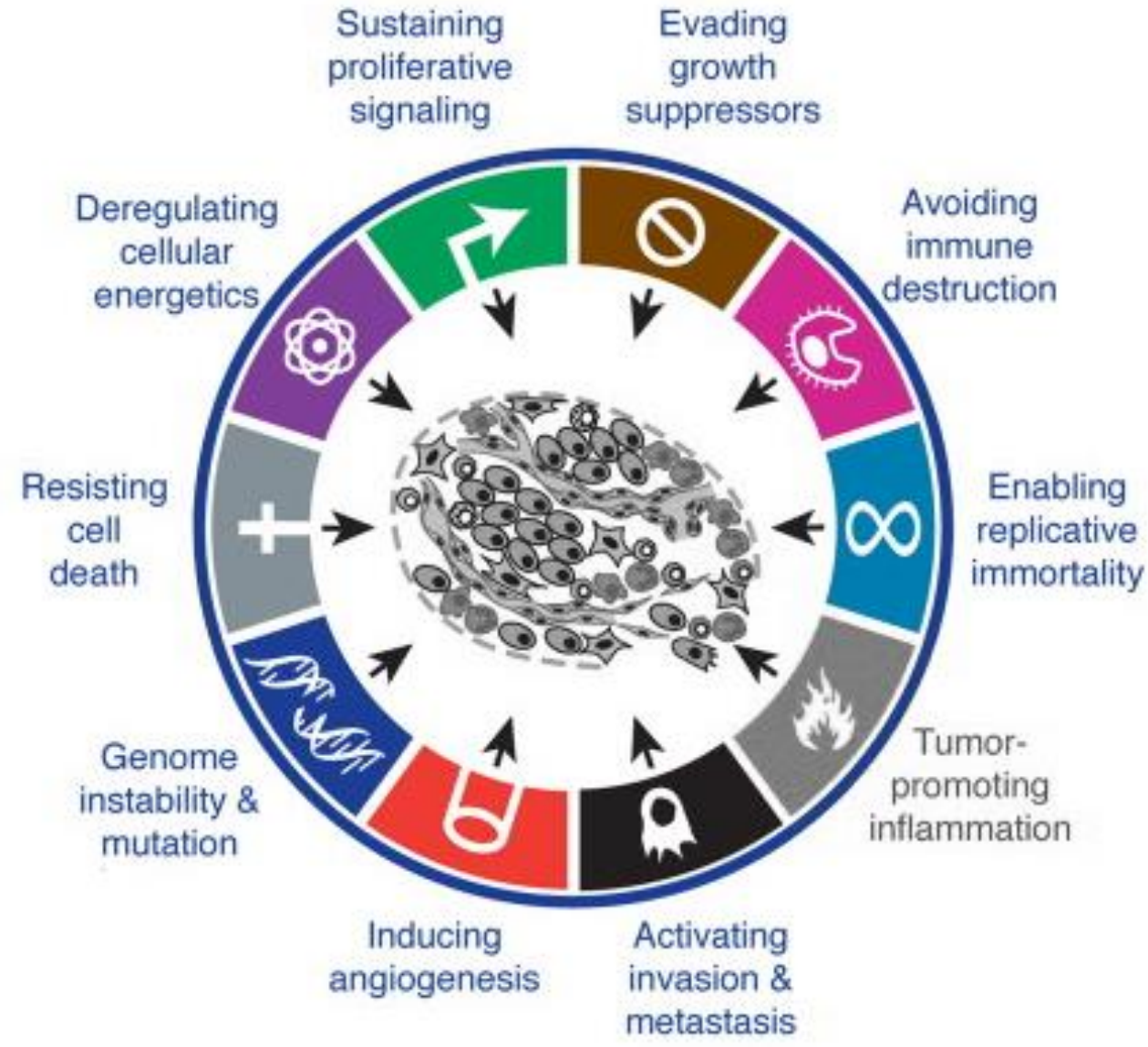
Anti-tumor immunity	Immune evasion by tumors			
	**Failure to produce tumor antigen** 	**Mutations in MHC genes or genes needed for antigen processing** 	**Antigen masking** 	**Production of immuno-suppressive protein** 
T cell recognition of tumor antigen leading to T cell activation	Lack of T cell recognition of tumor	Lack of T cell recognition of tumor	Lack of T cell recognition of tumor	Inhibition of T cell activation

- Modified from MIT OCW

Hallmarks of Cancer
Genomic Instability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DNA damage and repair

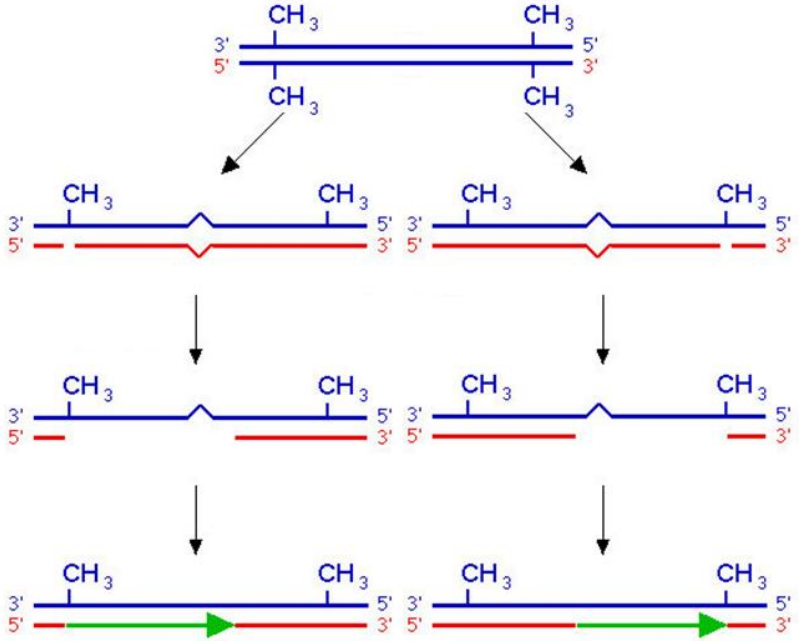
Damaging agents

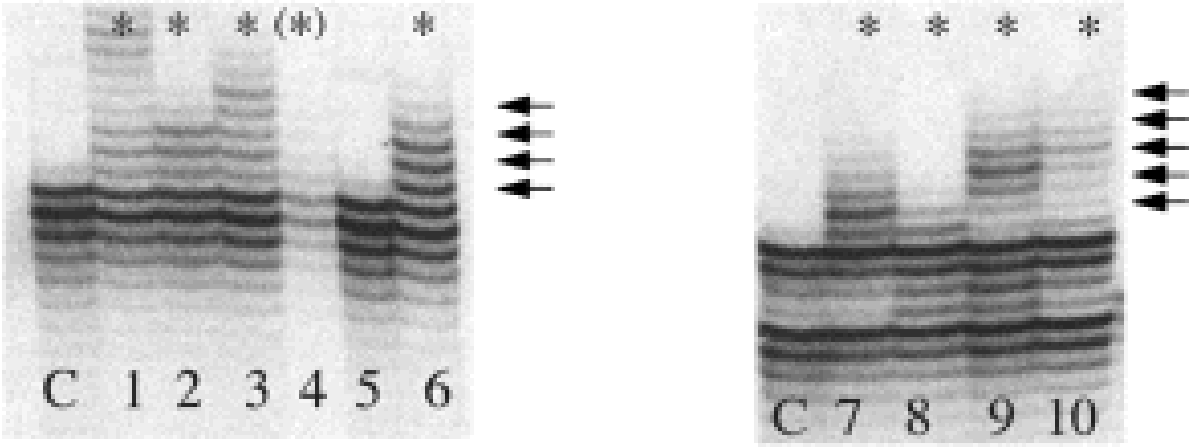
X-rays alkylating agents hydrolysis O_2 radicals	UV irradiation chemical mutagens	X-rays anti-tumor agent	replication errors

abnormal bases base adducts single-strand break abasic site	bulky adducts thymidine dimers	double-strand break interstrand crosslink	A-G mismatch T-C mismatch base insertion base deletion

Repair processes

base-excision repair (BER)	nucleotide-excision repair (NER)	recombination repair (HR, EJ)	mismatch repair





Mismatch repair

HNPCC

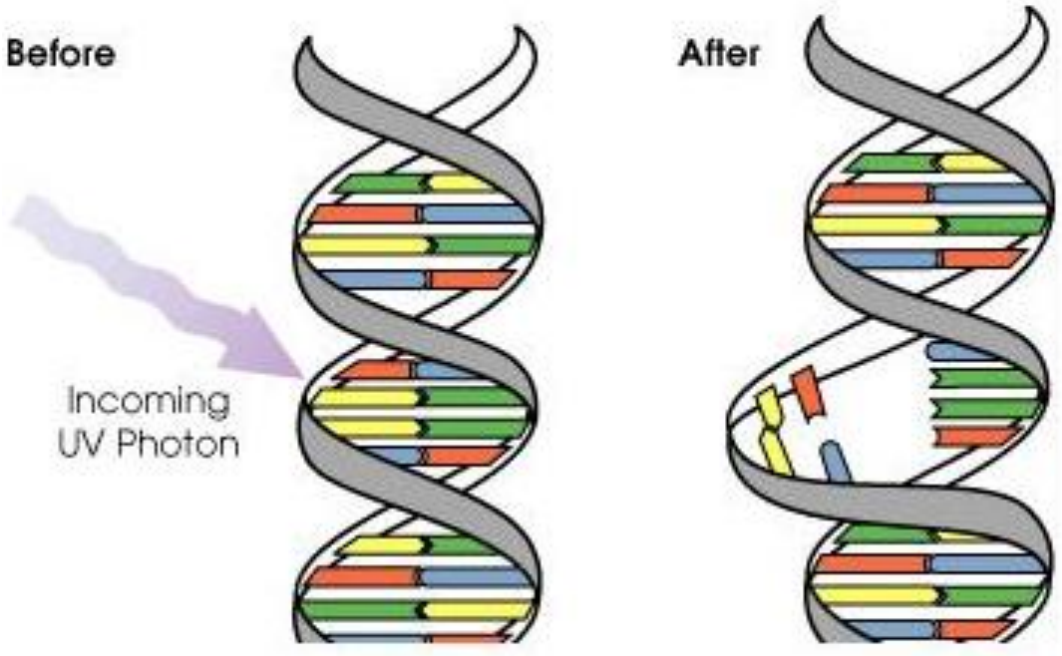
AD

DNA mismatch repair gene defects

Mutator phenotype (e.g. TGFβ type II receptors, BAX)

Microsatellite instability

Right Colon predisposition



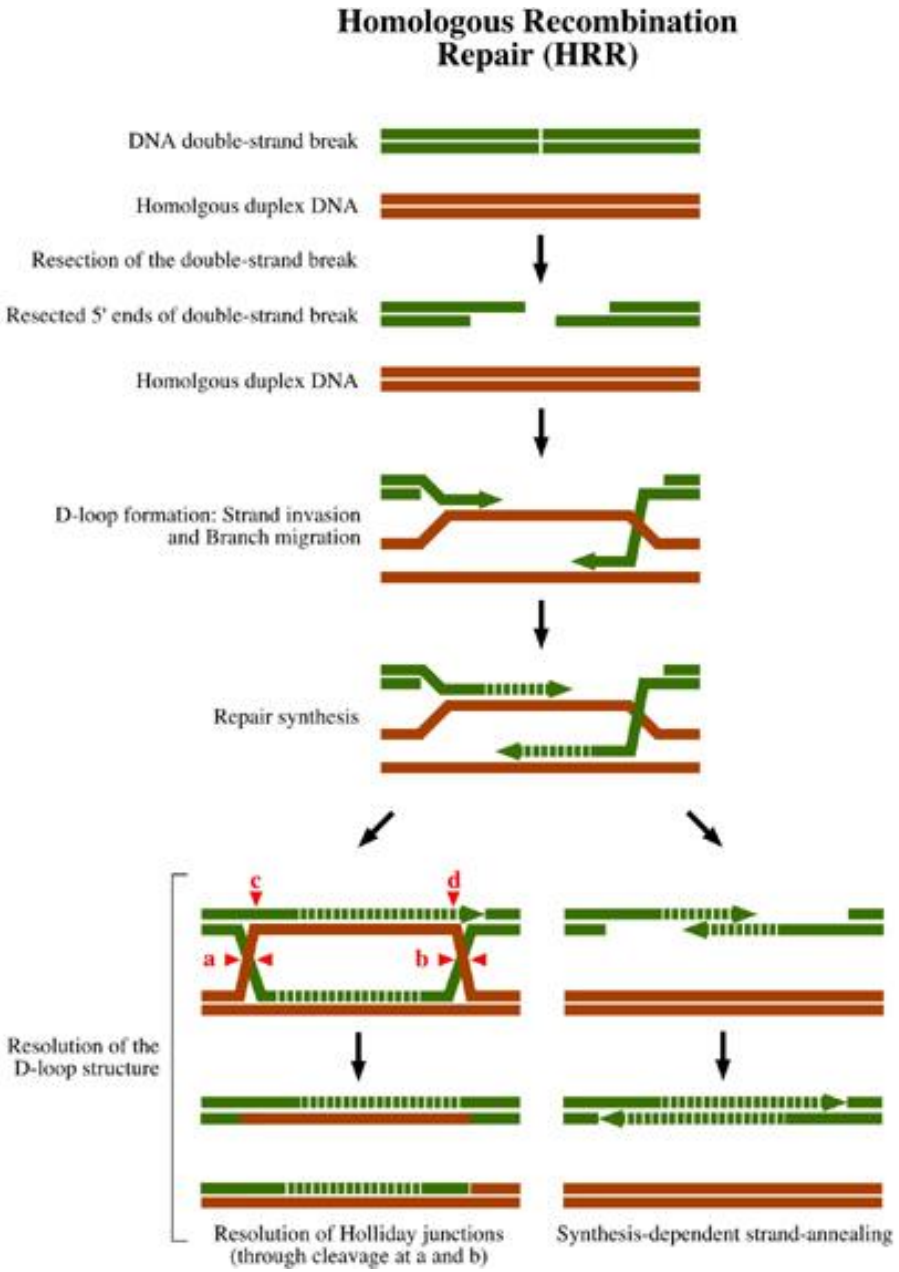
Nucleotide Excision Repair

Xeroderma Pigmentosum

AR

UV sensitivity (pryimidine dimer/cross-links)

Skin cancer (sun exposure)



Homologous Recombination Repair

AR

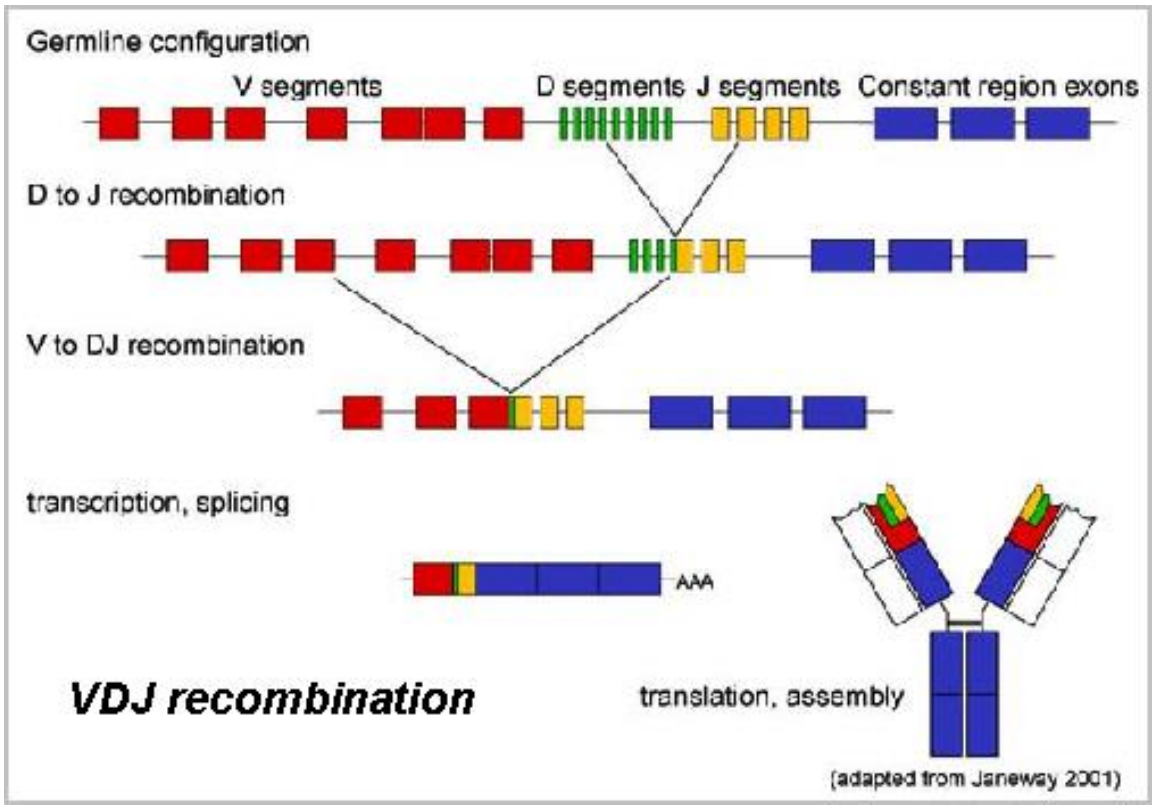
Bloom syndrome
Ataxia-telangiectasia

Ionizing radiation sensitivity

Fanconi Anemia

DNA cross-linking agent sensitivity

Regulated Genomic Instability

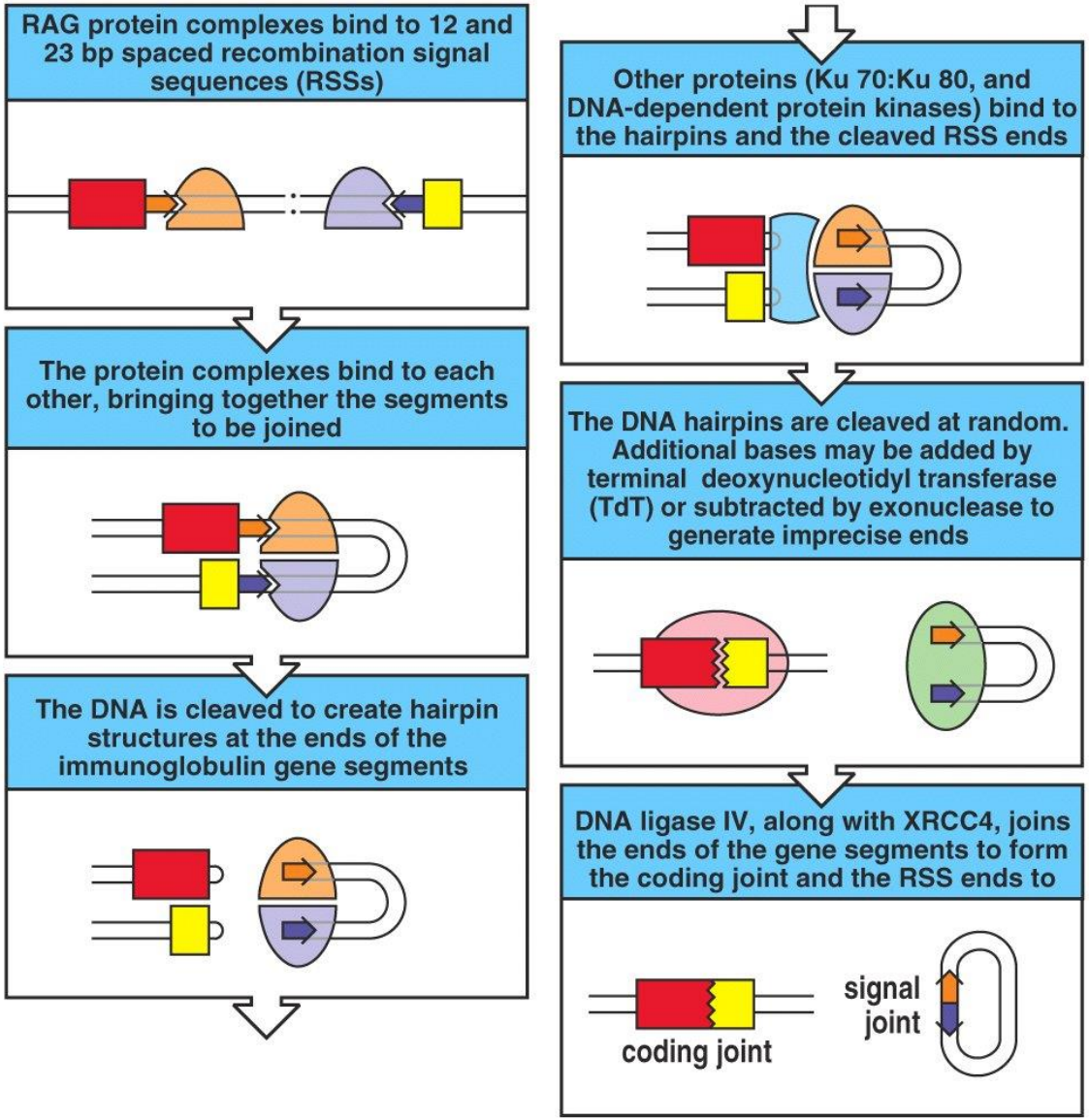


or how do 84 genes produce ~10^{16} antibodies!

Variable

Diversity

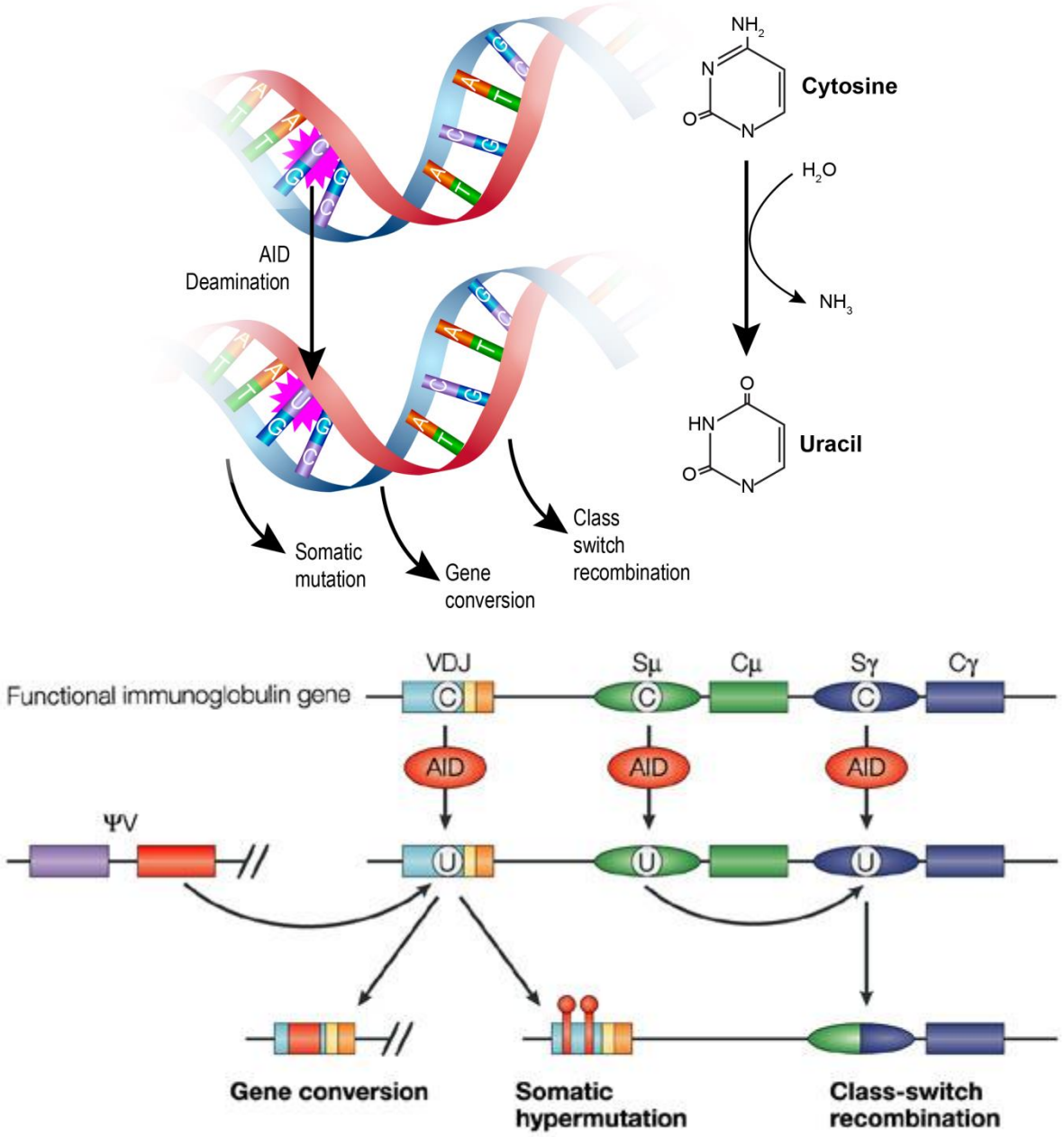
Joining



Regulated Genomic Instability

or how do 84 genes produce ~10^{16} antibodies!

RAG 1 & 2



Regulated Genomic Instability

or how do 84 genes produce ~10^{16} antibodies!

Activation induced cytosine deaminase (AID)

Hallmarks of Cancer
Tumor-Promoting Inflammation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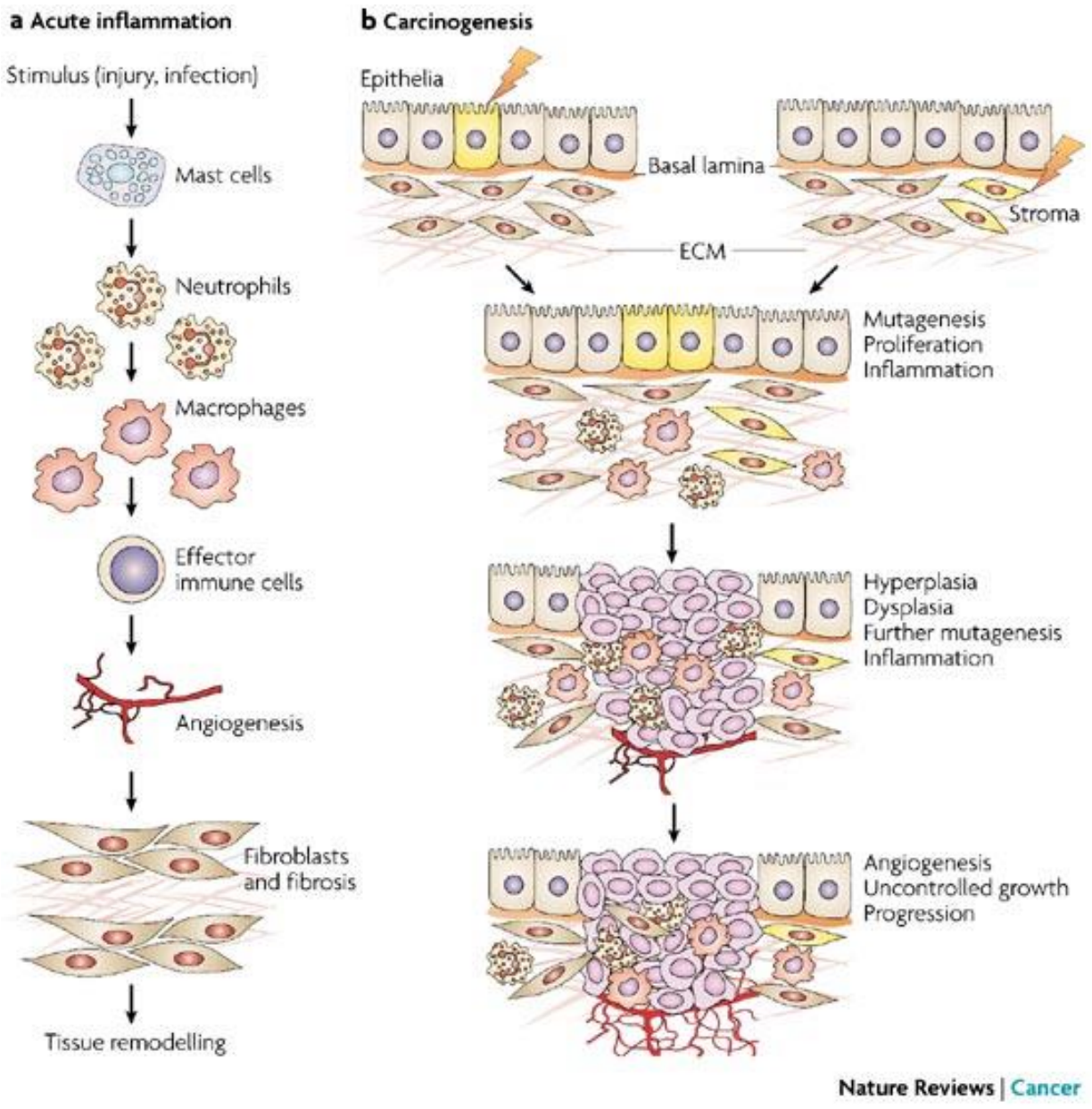


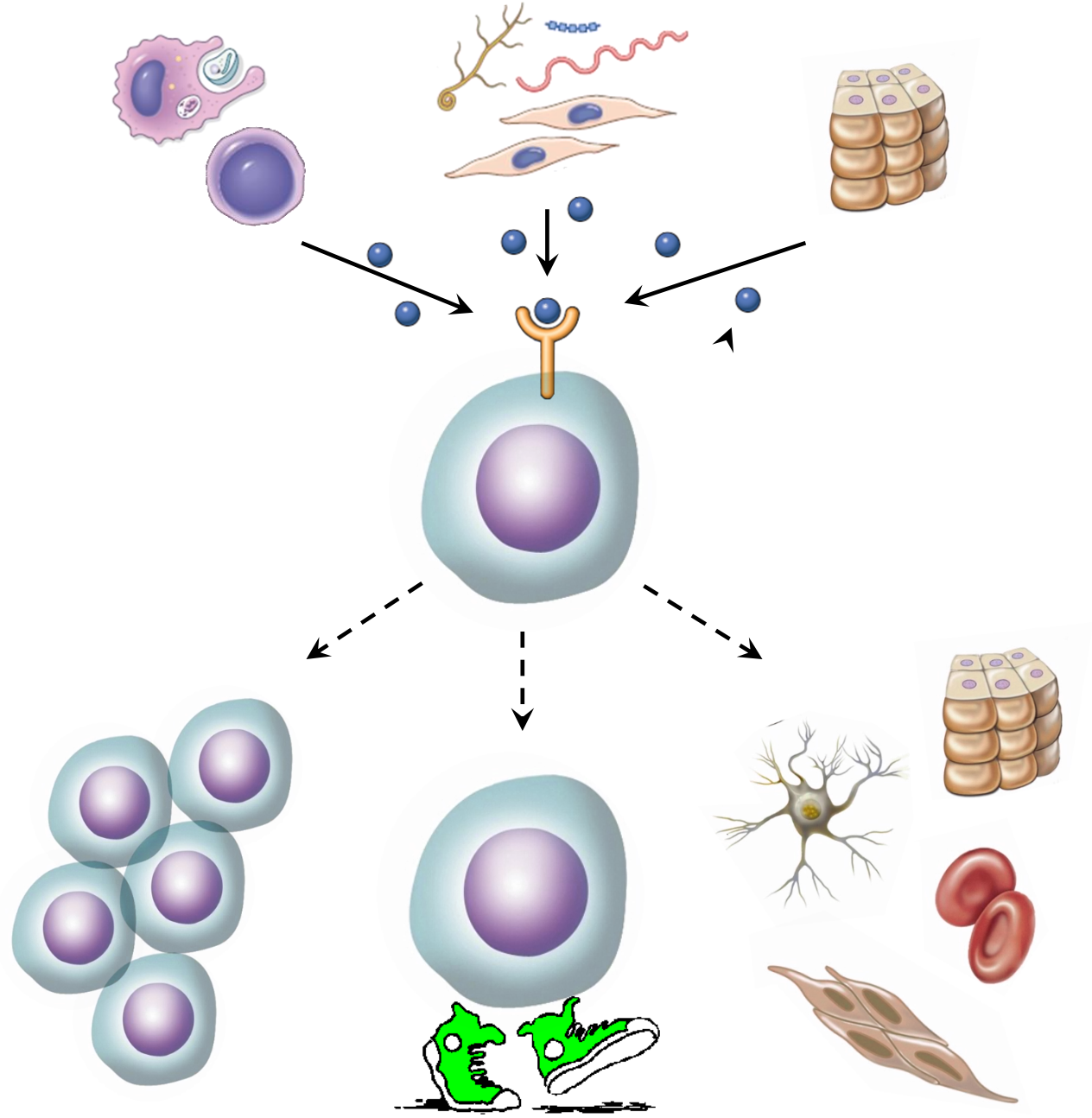
Chicken & Egg

Persistent chronic inflammation

Barrett esophagus, ulcerative colitis, H. pylori gastritis, HBV/HCV, & chronic pancreatitis

Inflammation in response to tumors

COX-2 induction



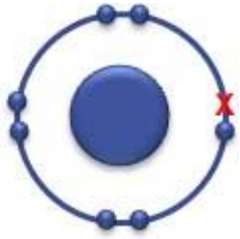
Growth factors

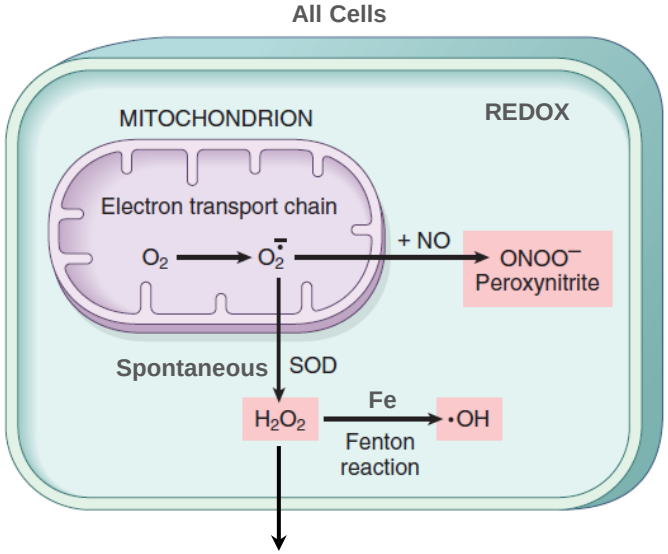
Mostly proteins from:
- Lymphocytes
- Macrophage
- Stromal cells
- Parenchymal cells

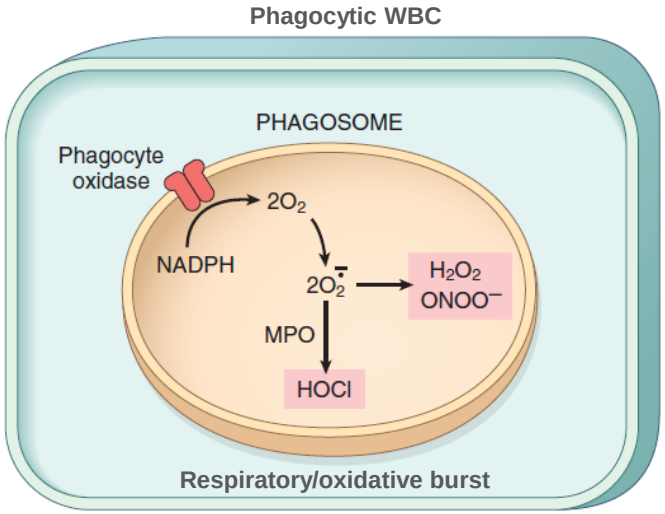
Induce cells to:
- Survive/Proliferate
- Migrate
- Differentiate

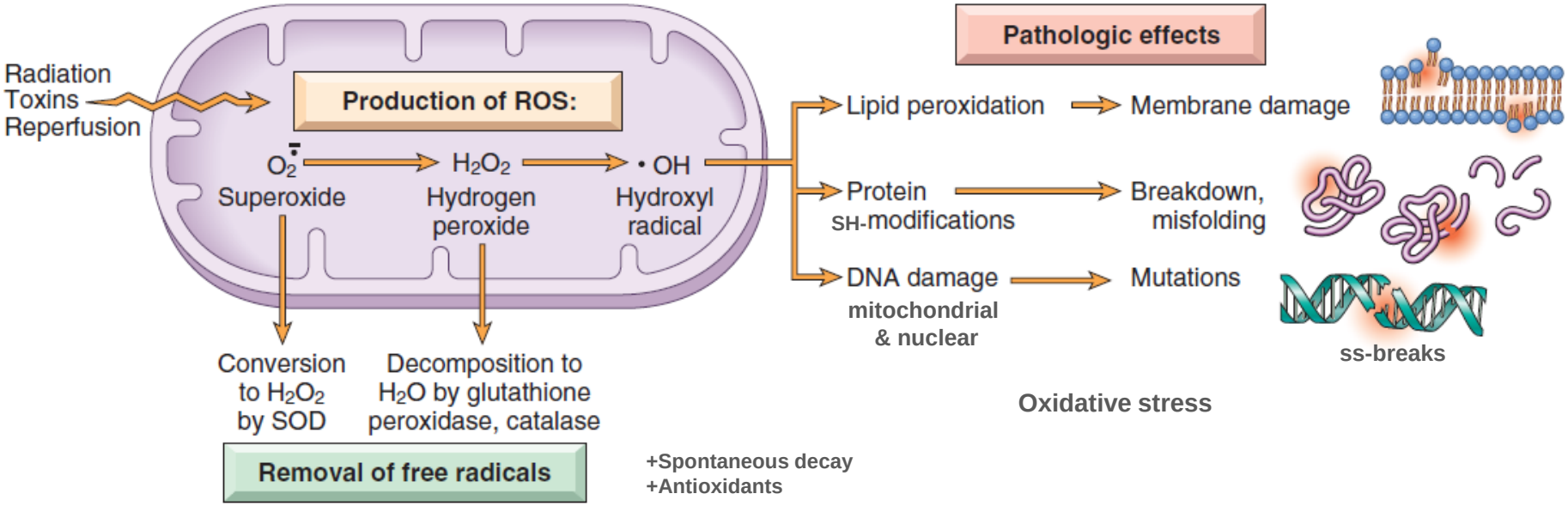
Induce proliferation through gene expression:
- Promote cell cycle entry
- Relieve cell cycle blocks
- Inhibit apoptosis
- Protein production ↑

Free radicals & ROS



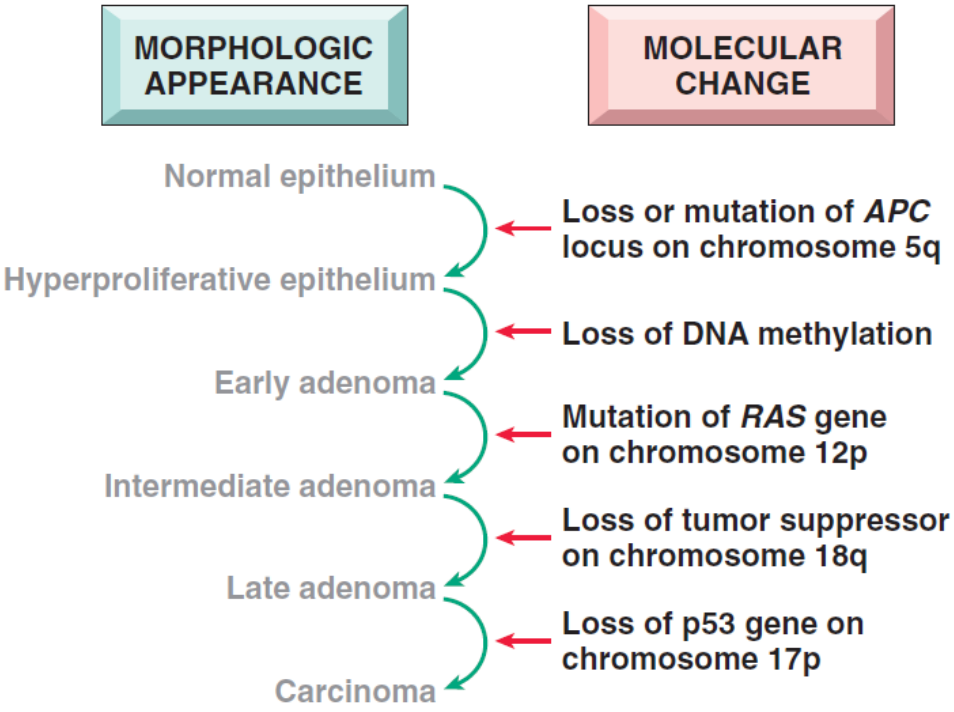


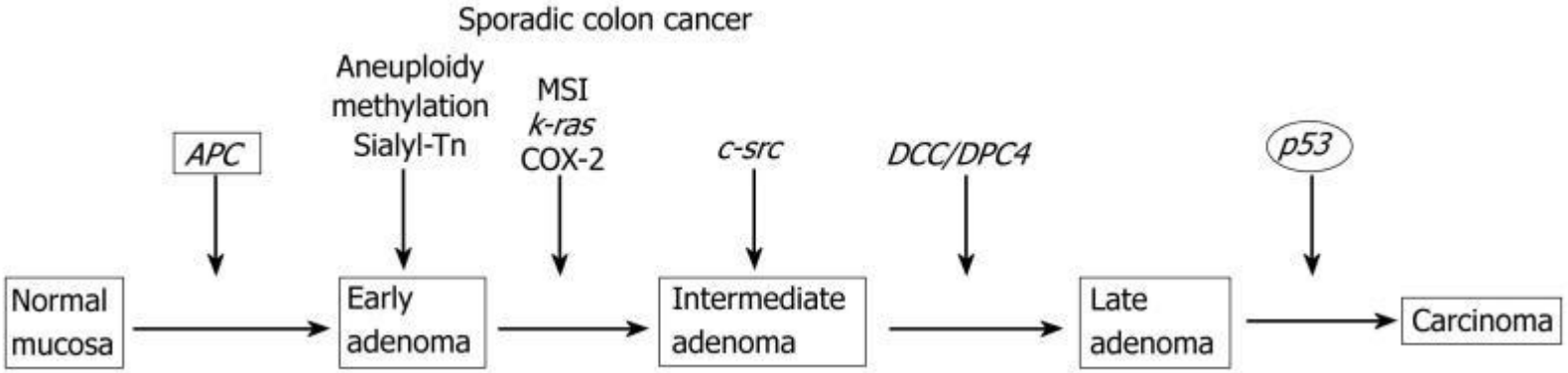




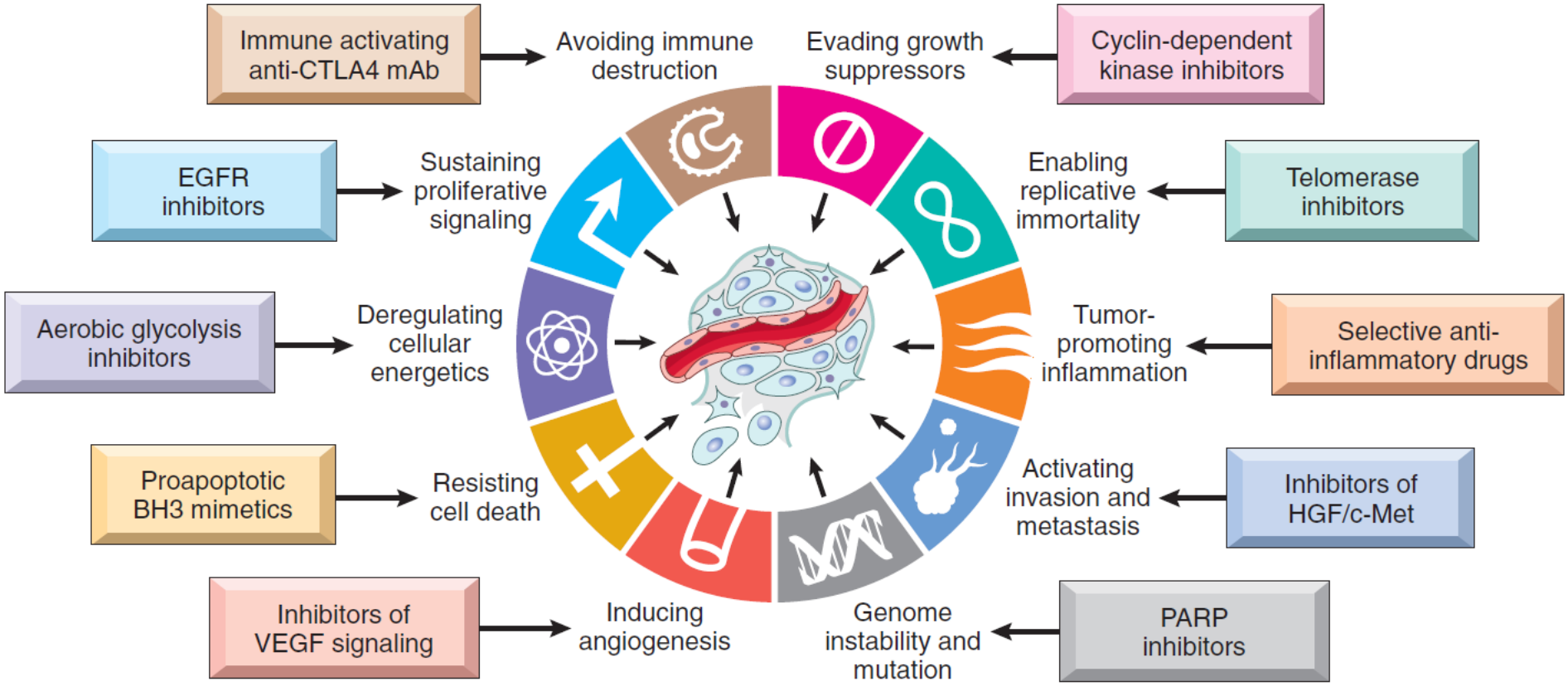
Carcinogenesis is a multistep process

Carcinogenesis is a multistep process





Hallmarks Concluded!



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