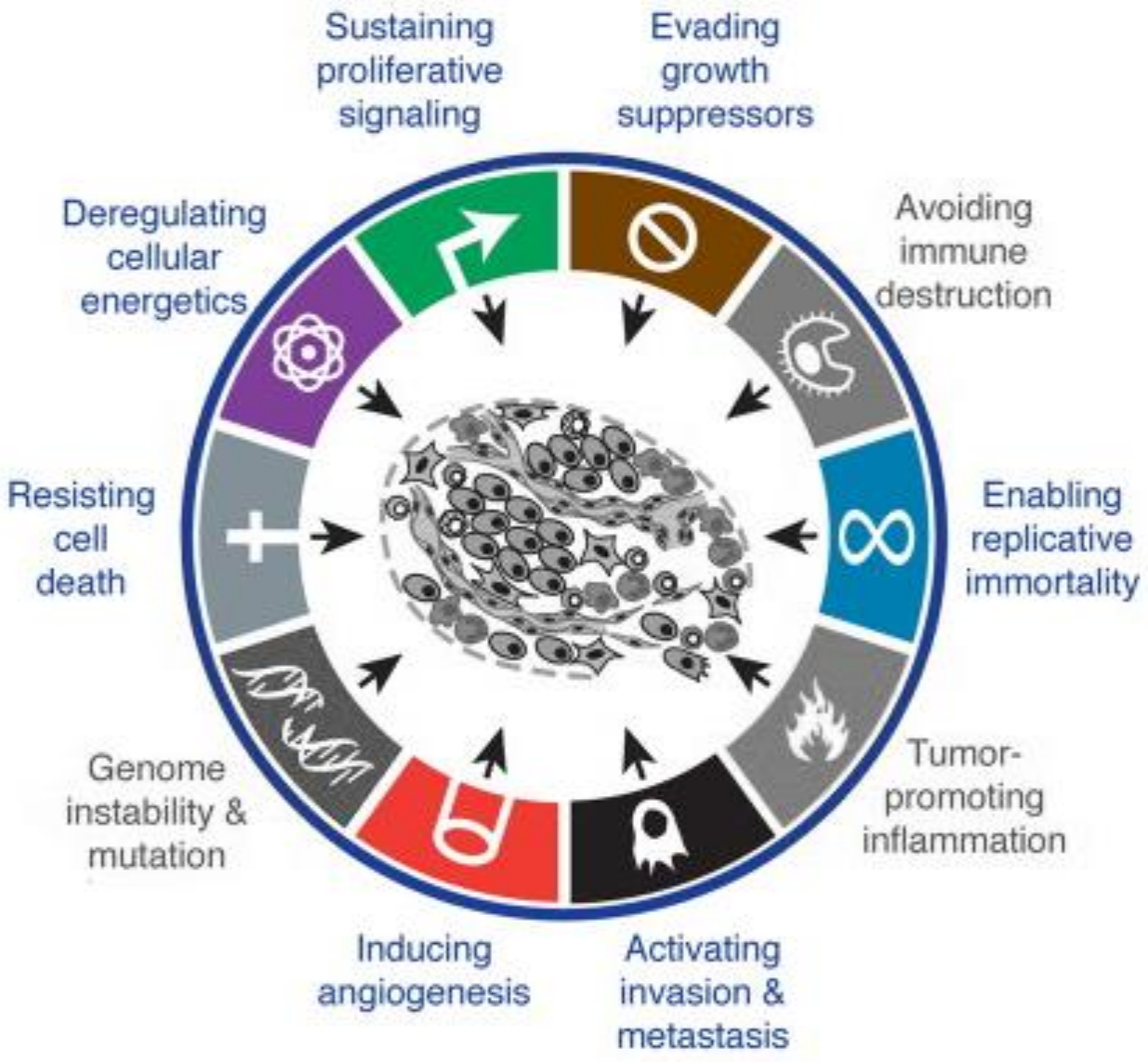
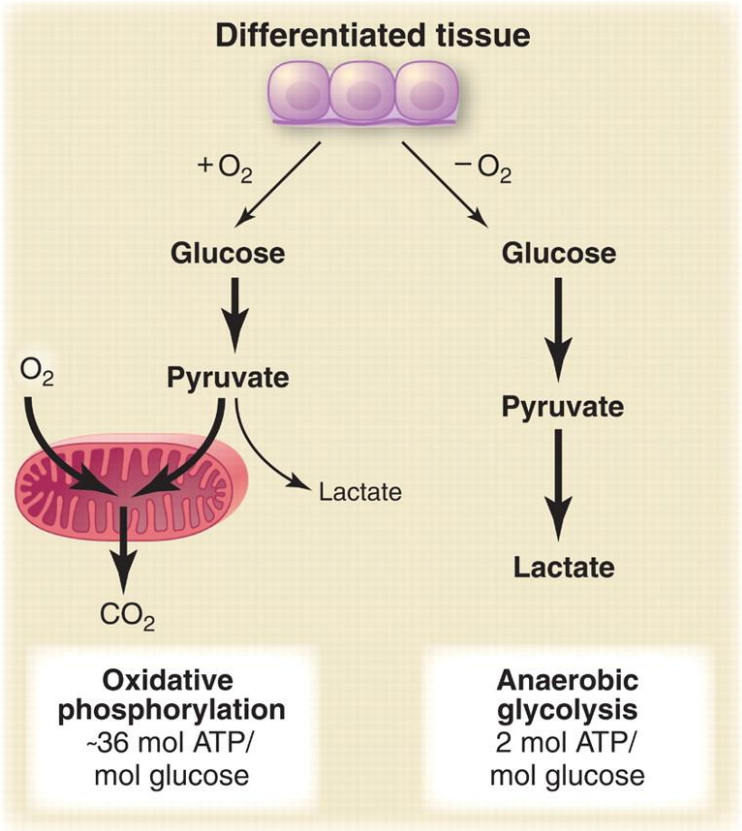
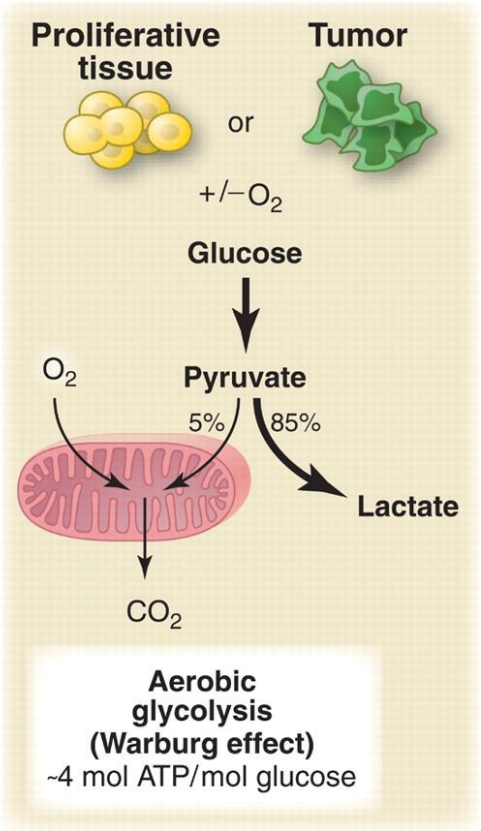
Hallmarks of Cancer
Reprogramming Energy Metabolism


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

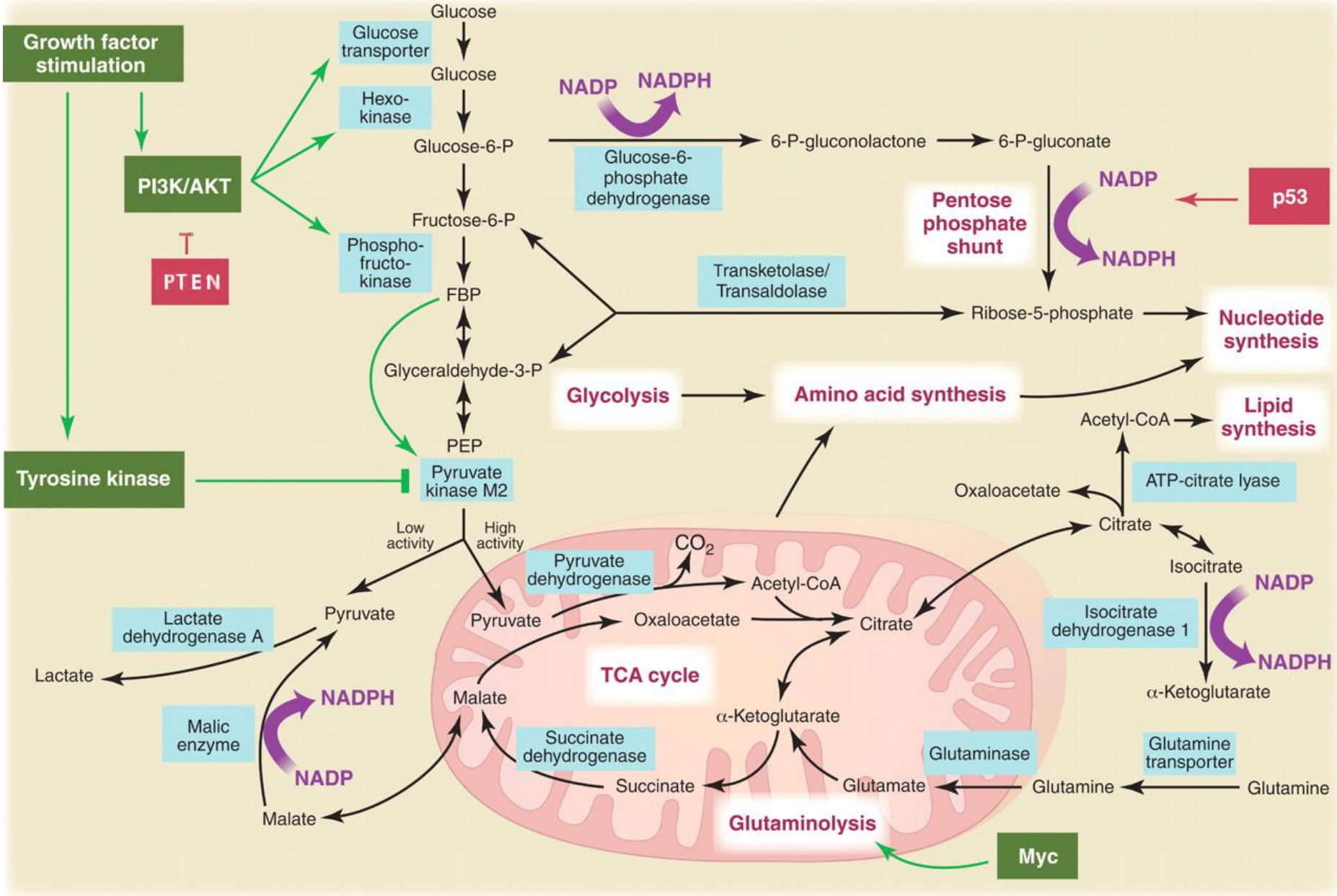
aka aerobic glycolysis



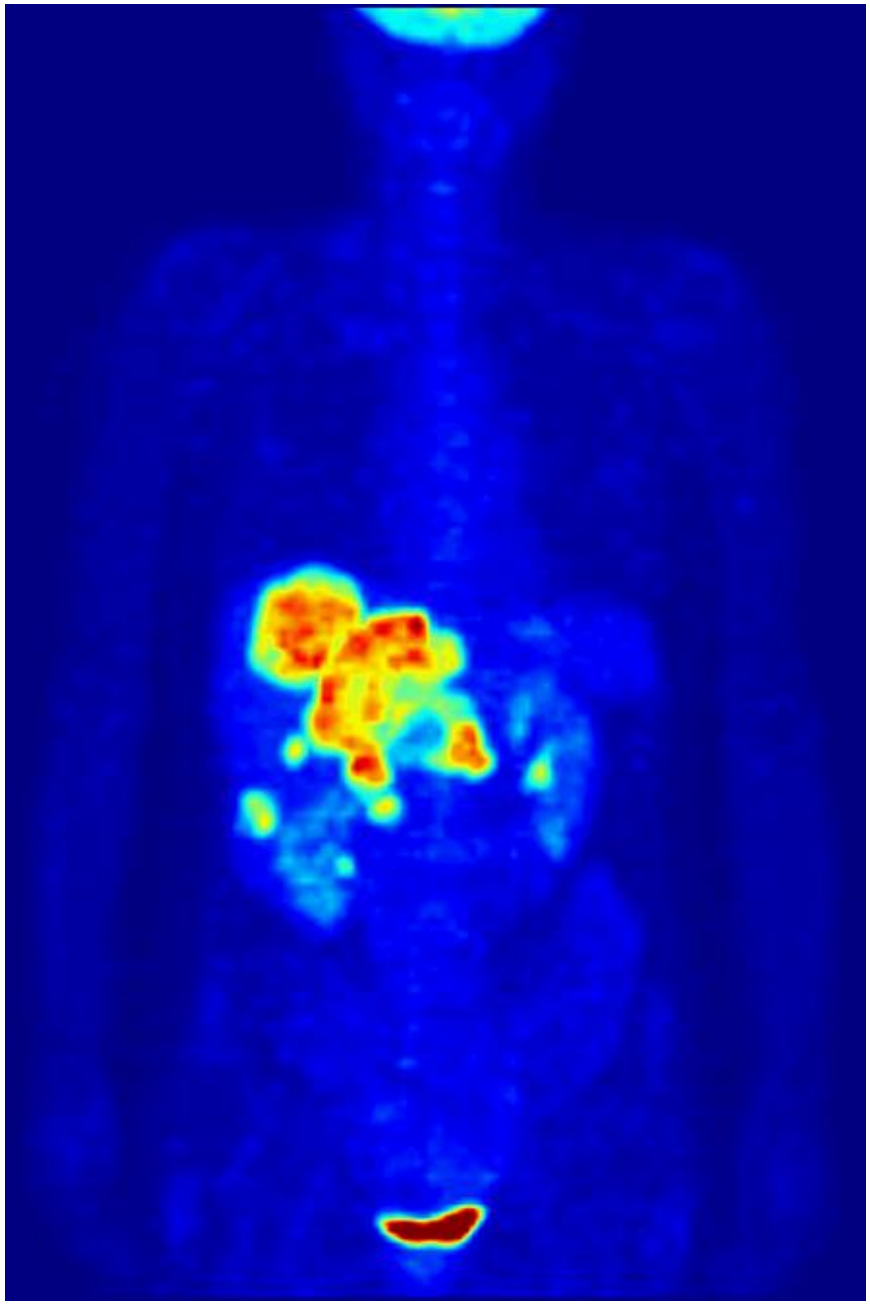


Otto Warburg

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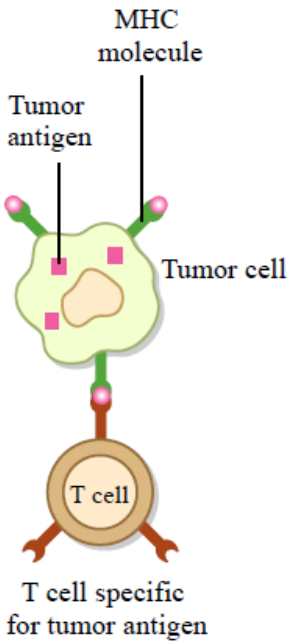
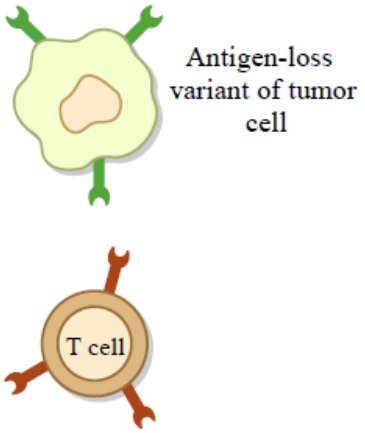
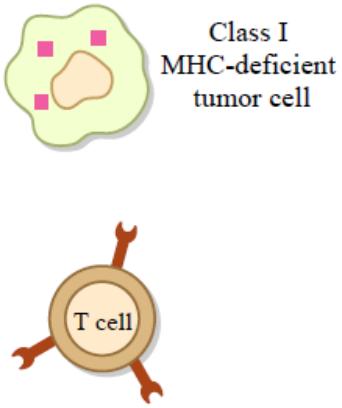
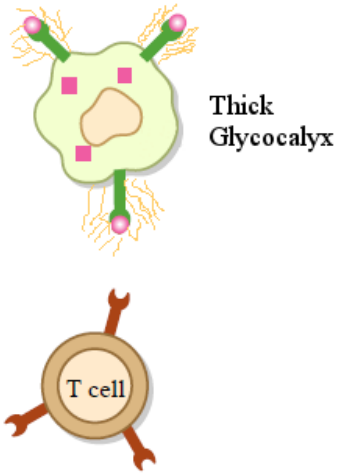
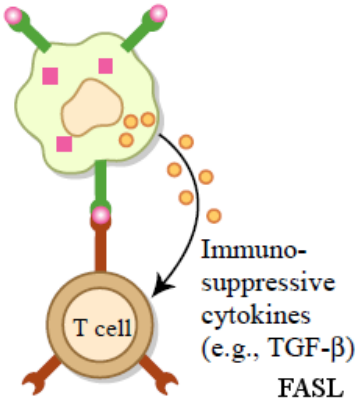
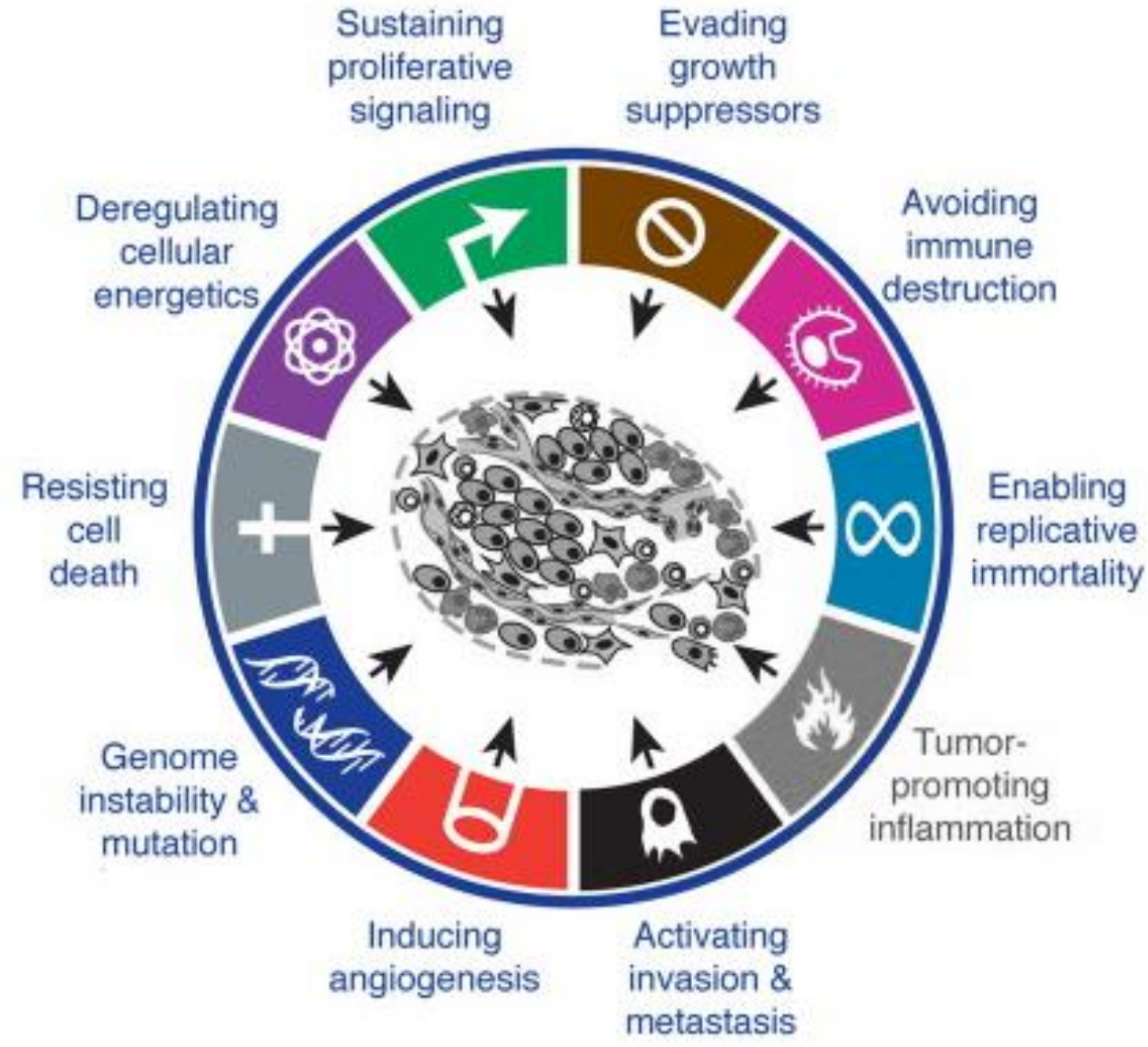
Anti-tumor immunity	Immune evasion by tumors			
	**Failure to produce tumor antigen** 	**Mutations in MHC genes or genes needed for antigen processing** 	**Antigen masking** 	**Production of immuno-suppressive protein** 
T cell recognition of tumor antigen leading to T cell activation	Lack of T cell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

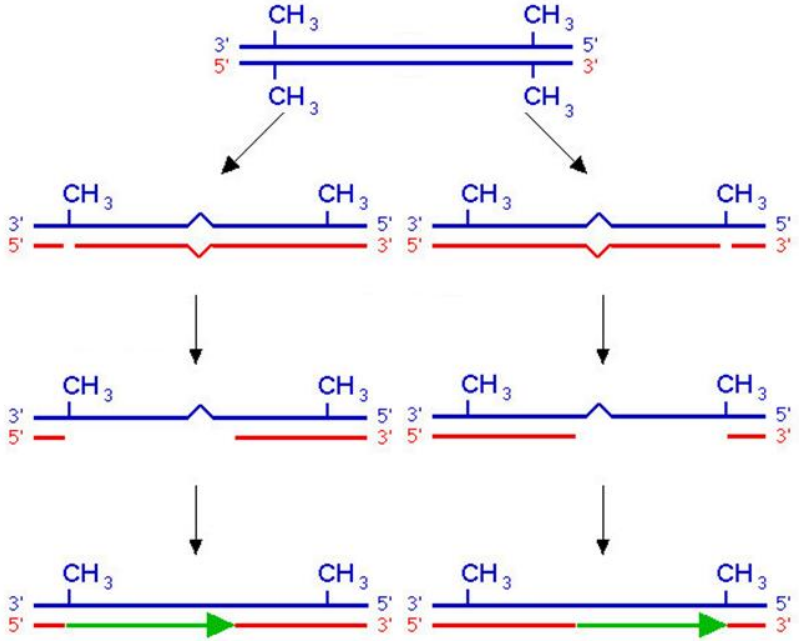
Damaging agents

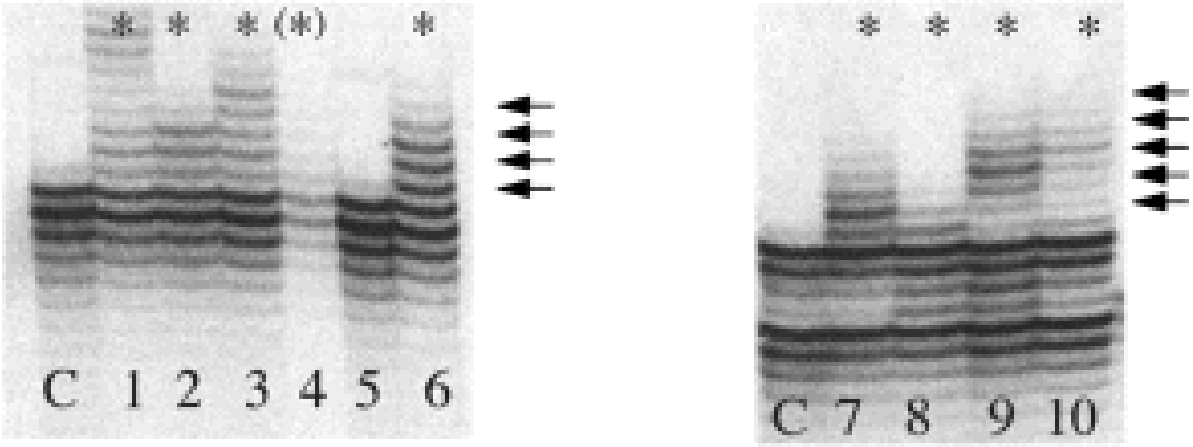
X-rays alkylating agents hydrolysis O_2 radicals	UV irradiation chemical mutagens	X-rays anti-tumor agent	replication errors

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

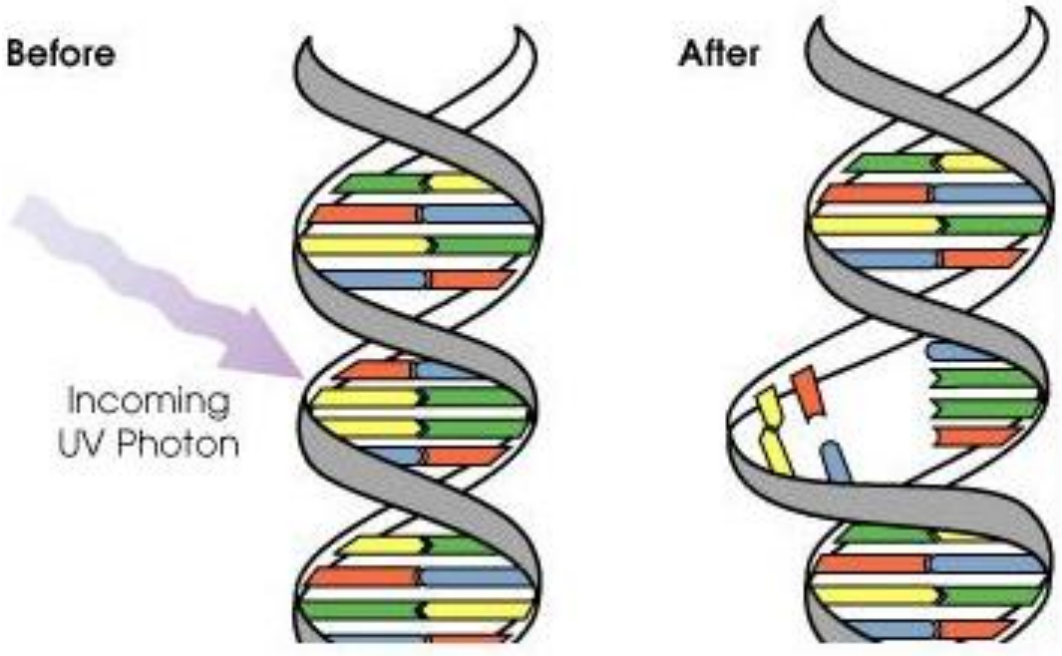
AD

DNA mismatch repair gene defects

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

Microsatellite instability

Right Colon predisposition



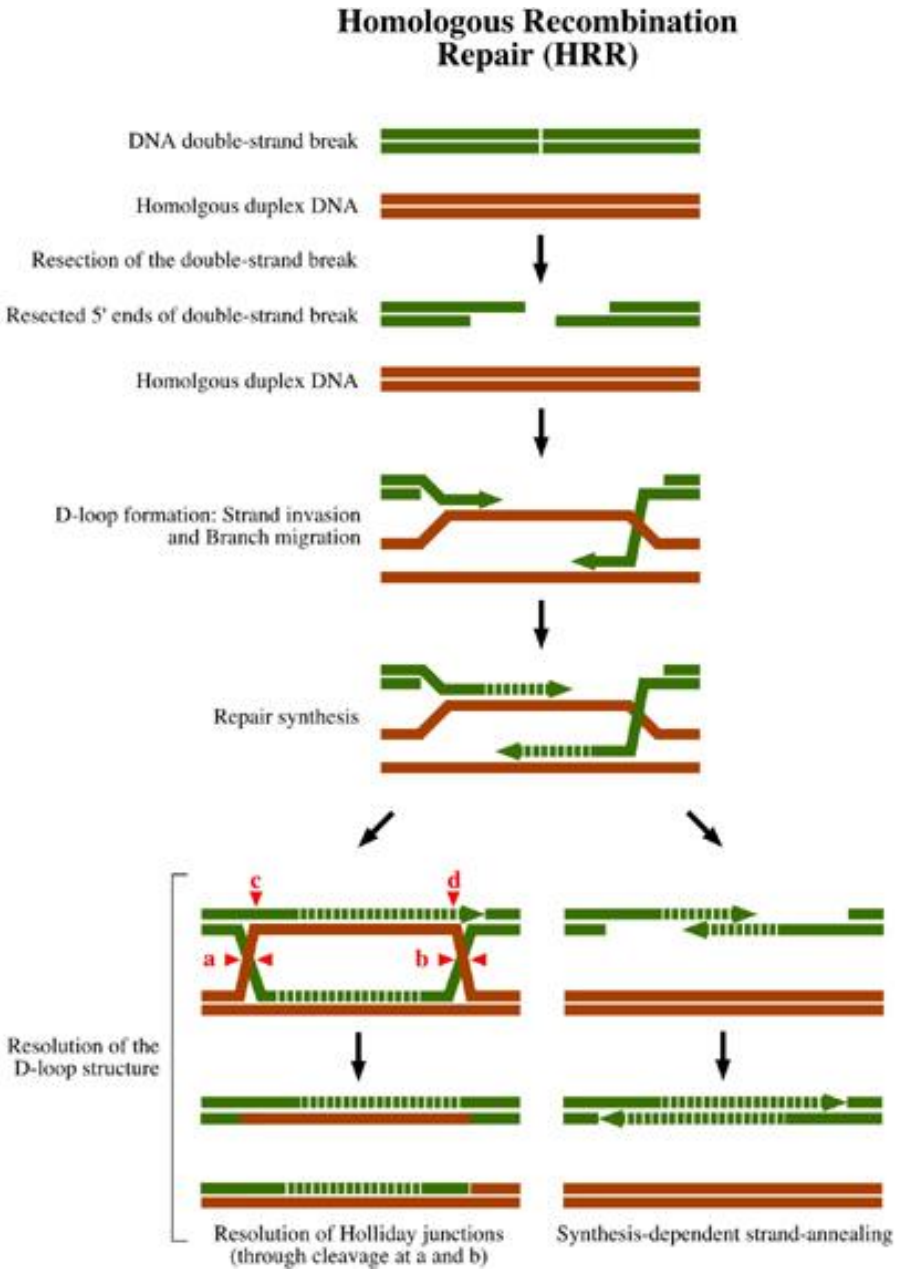
Nucleotide Excision Repair

Xeroderma Pigmentosum

AR

UV sensitivity (pryimidine dimer/cross-links)

Skin cancer (sun exposure)



Homologous Recombination Repair

AR

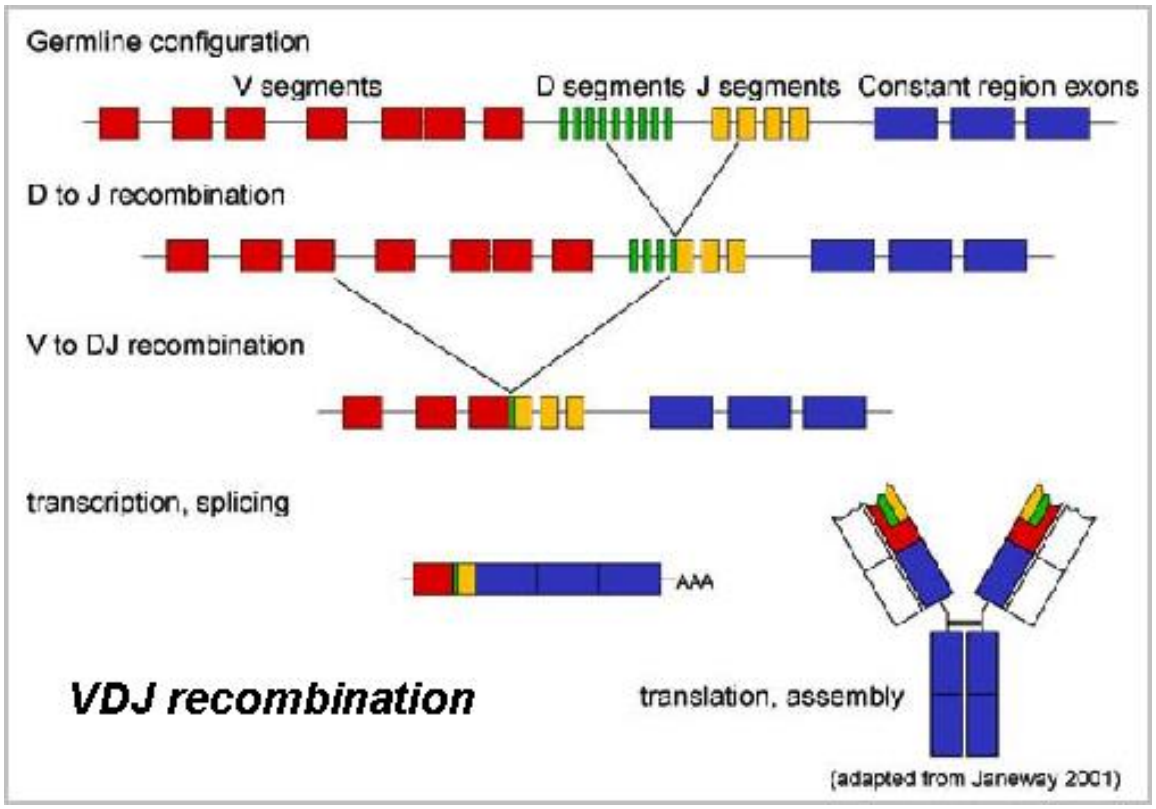
Bloom syndrome
Ataxia-telangiectasia

Ionizing radiation sensitivity

Fanconi Anemia

DNA cross-linking agent sensitivity

Regulated Genomic Instability

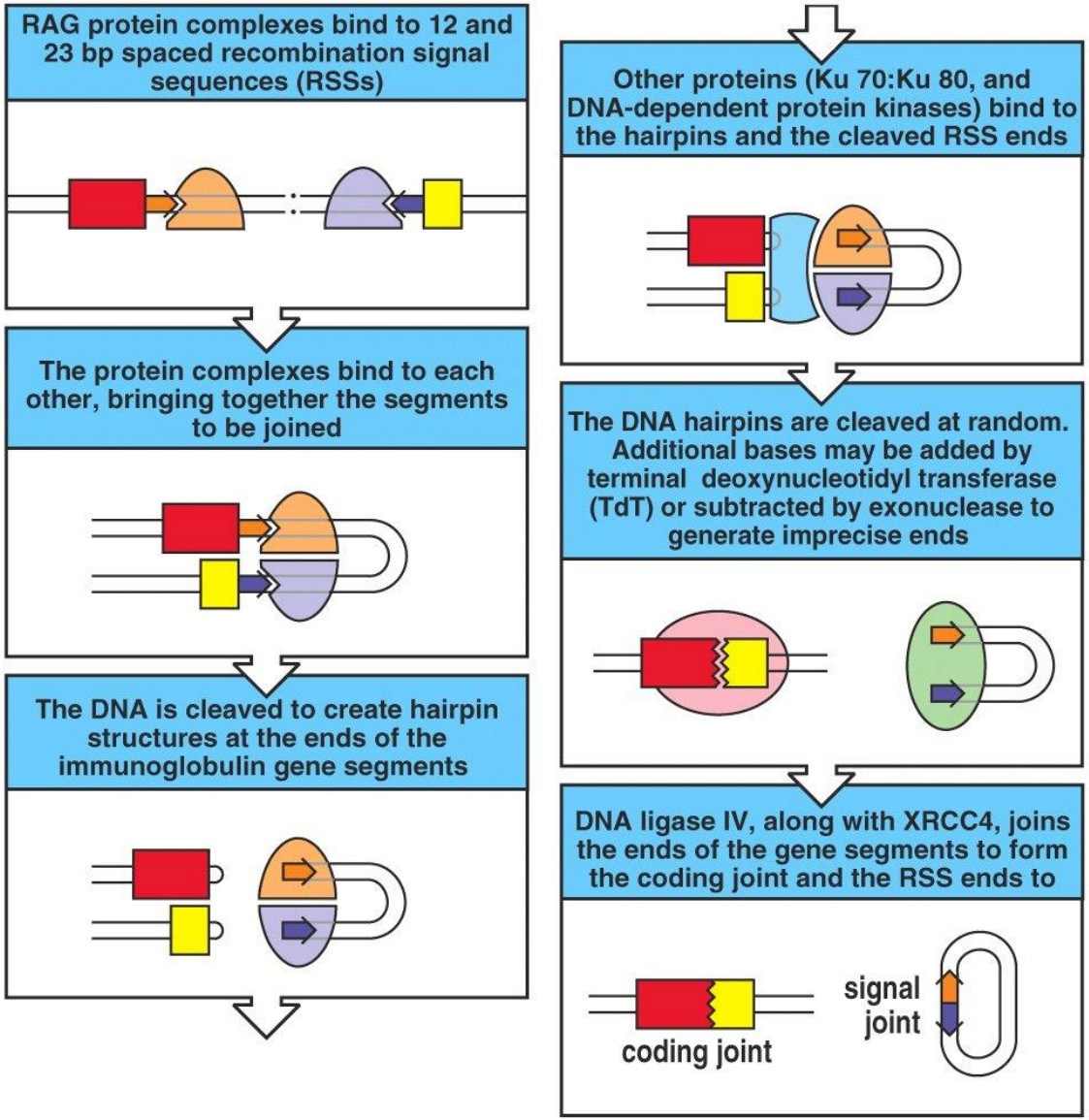


or how do 84 genes produce ~10^{16} antibodies!

Variable

Diversity

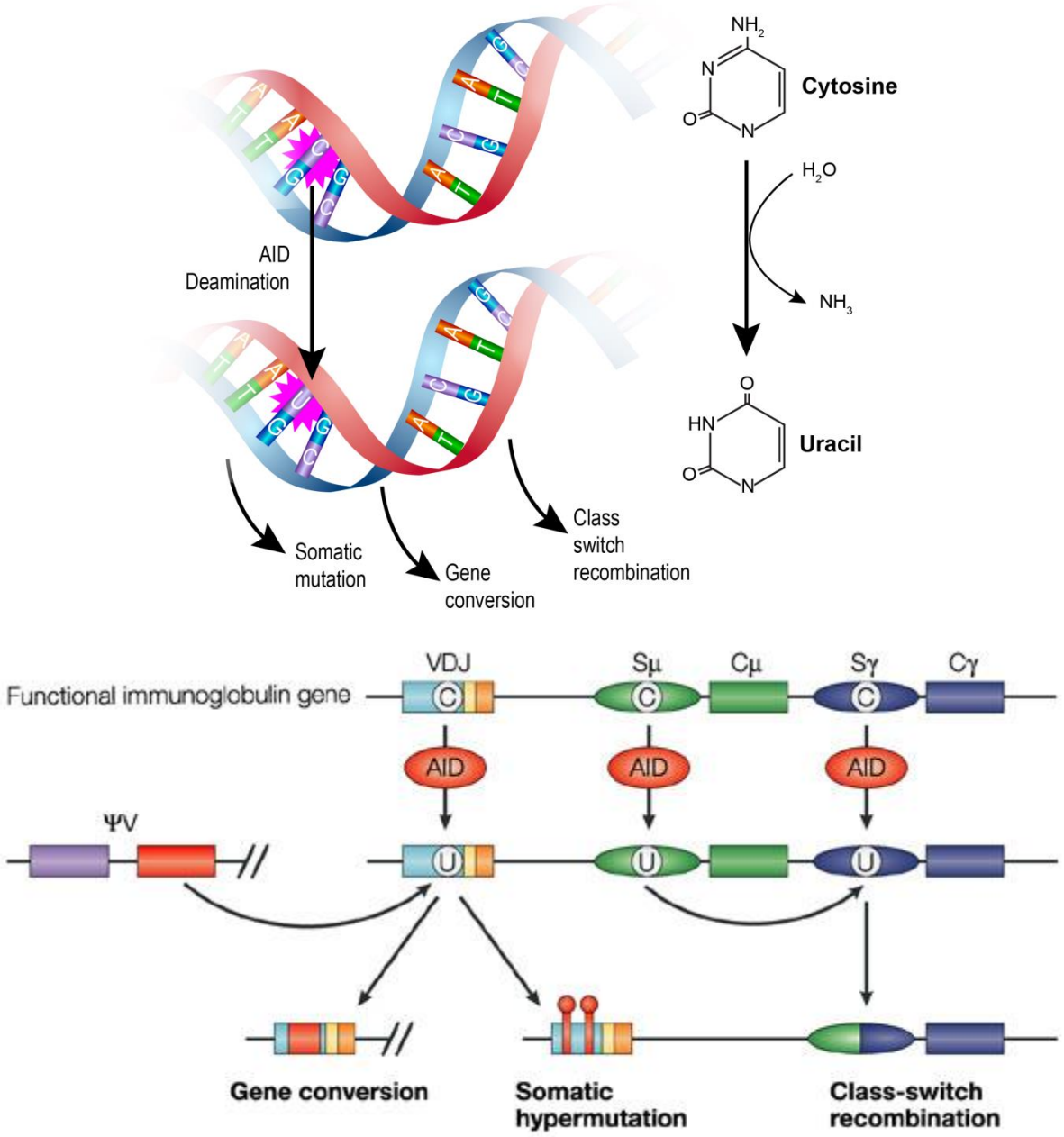
Joining



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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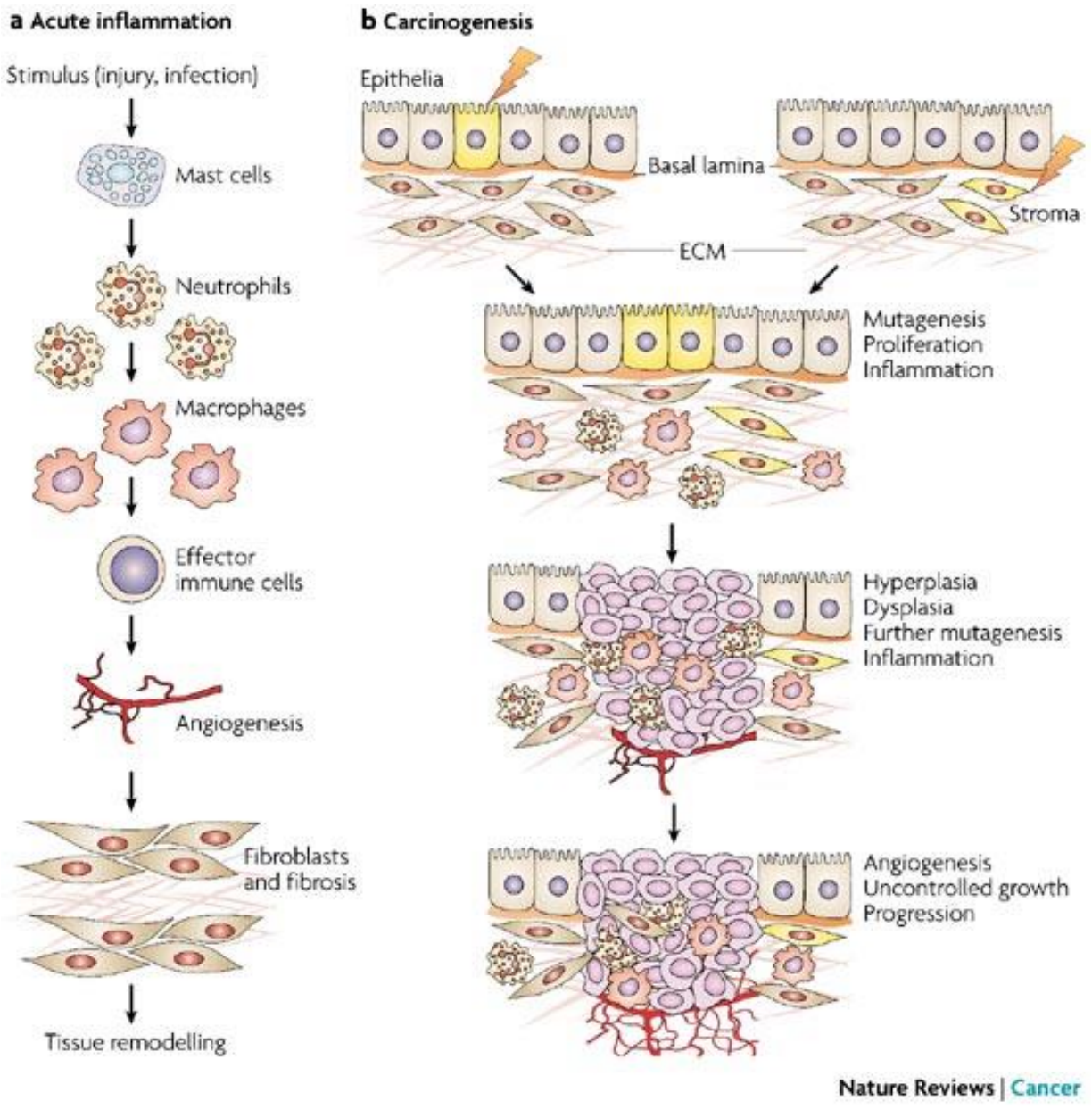


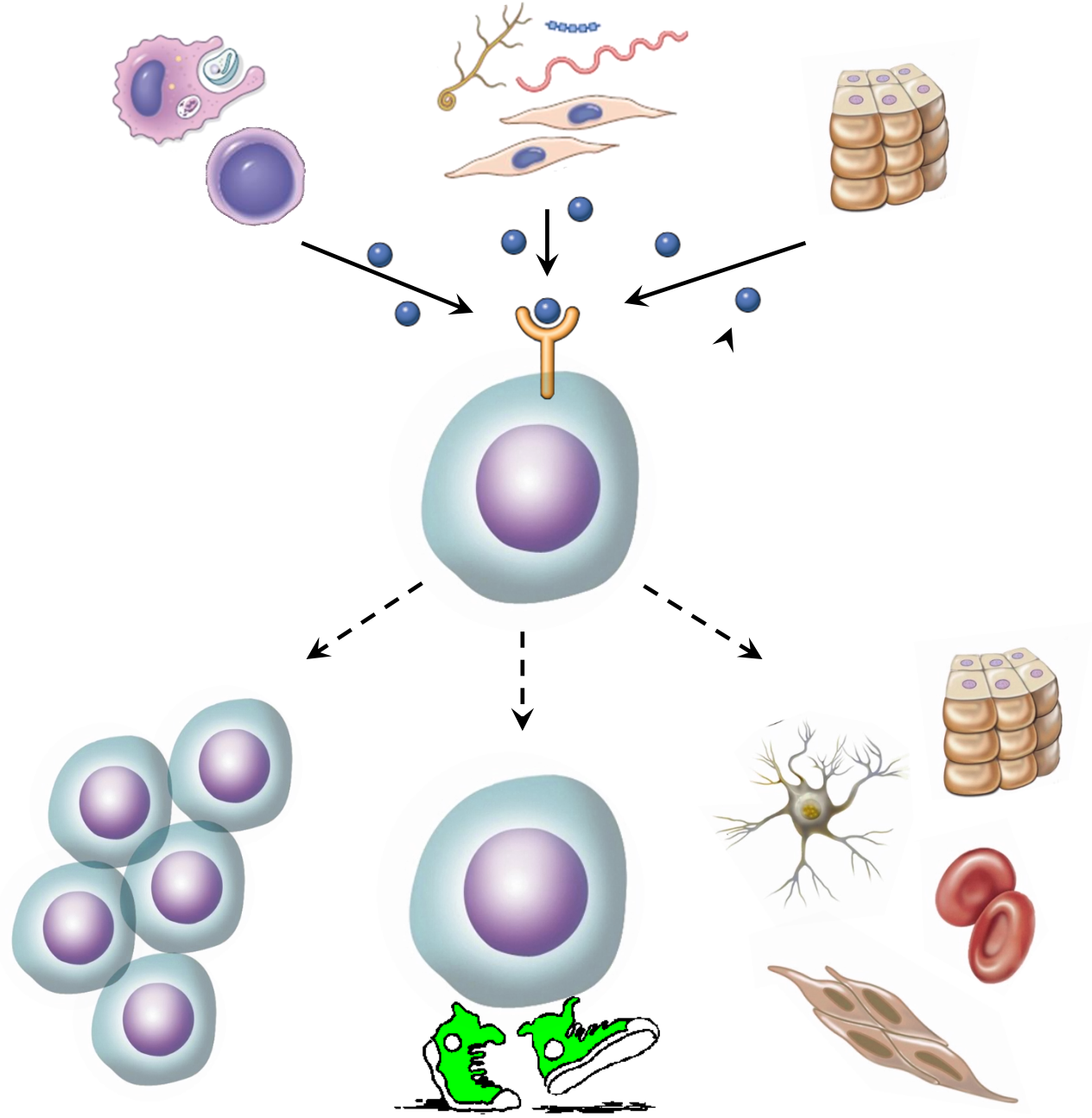
Chicken & Egg

Persistent chronic inflammation

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

Inflammation in response to tumors

COX-2 induction



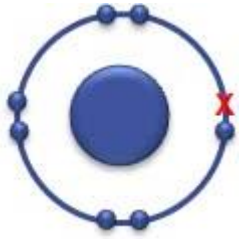
Growth factors

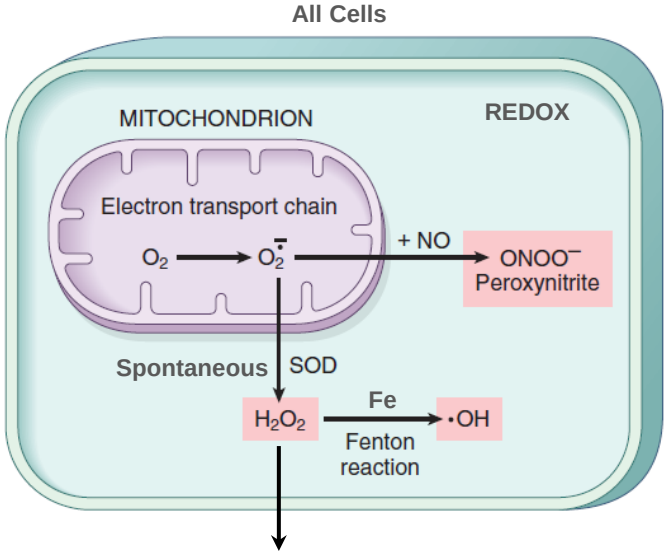
Mostly proteins from:
- Lymphocytes
- Macrophage
- Stromal cells
- Parenchymal cells

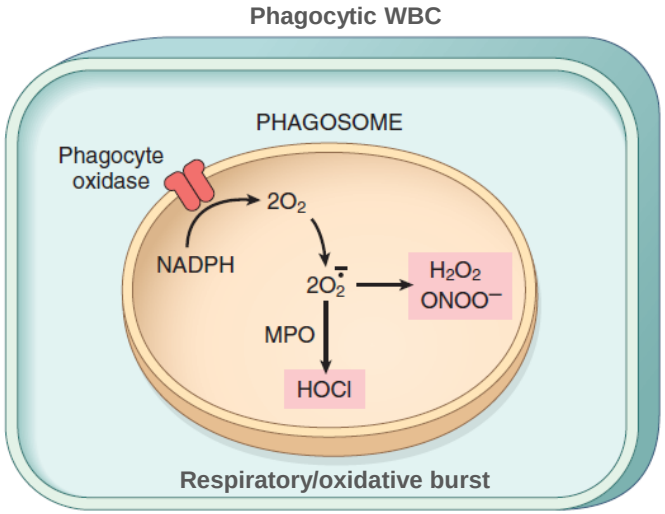
Induce cells to:
- Survive/Proliferate
- Migrate
- Differentiate

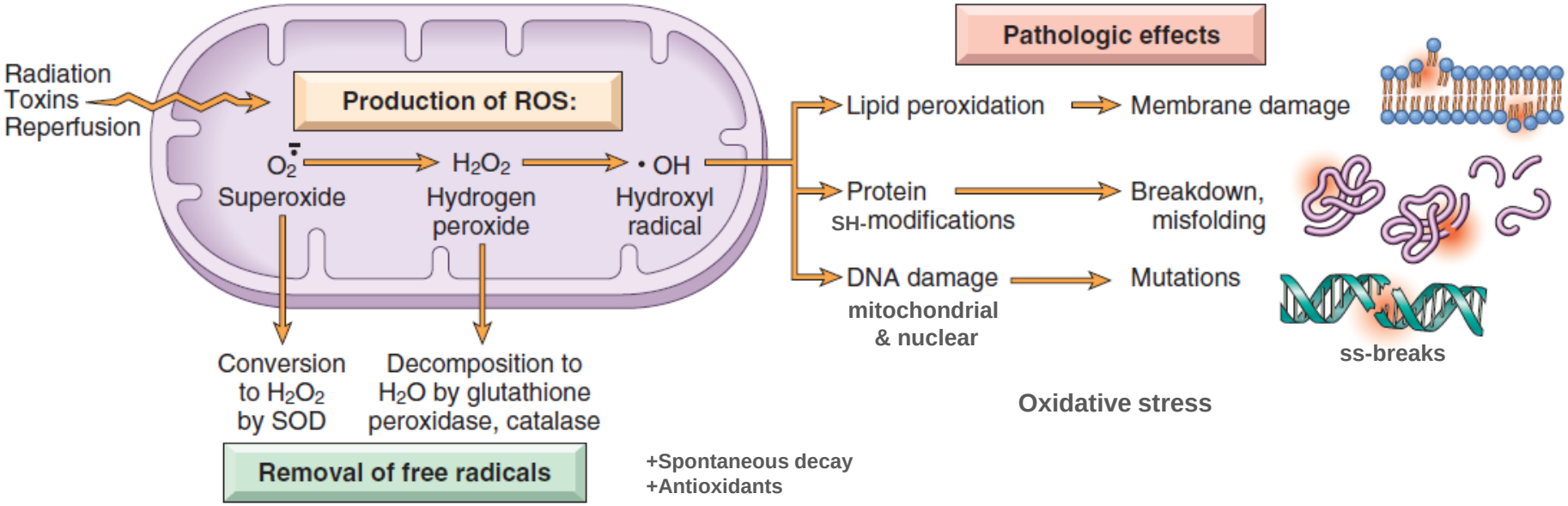
Induce proliferation through gene expression:
- Promote cell cycle entry
- Relieve cell cycle blocks
- Inhibit apoptosis
- Protein production ↑

Free radicals & ROS



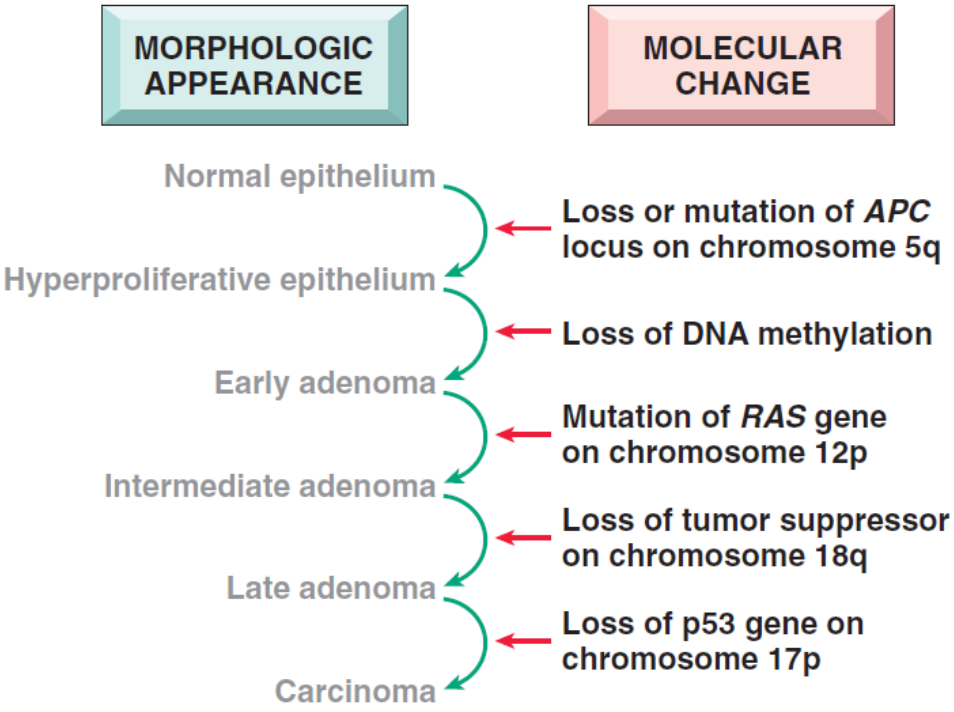


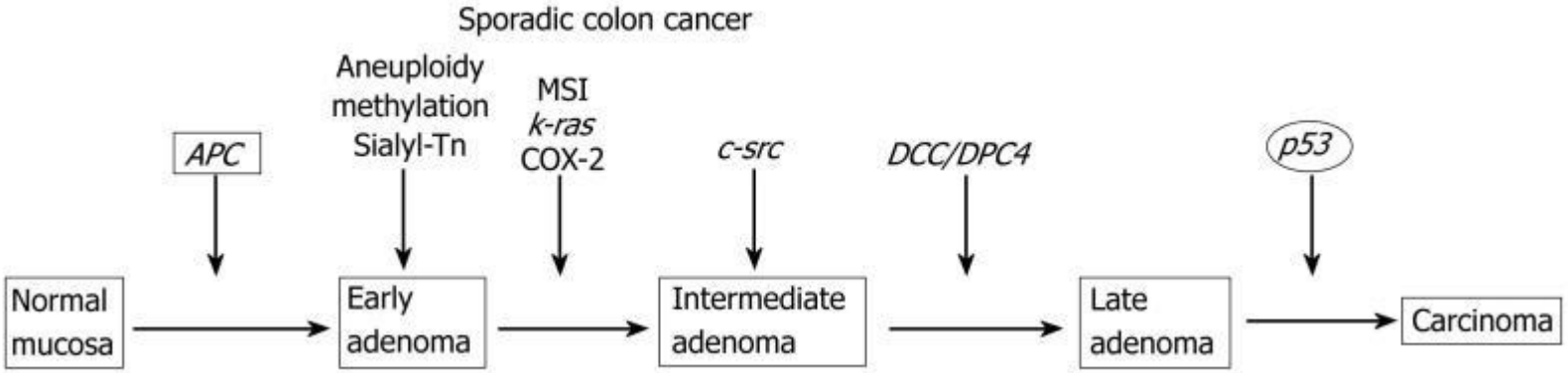




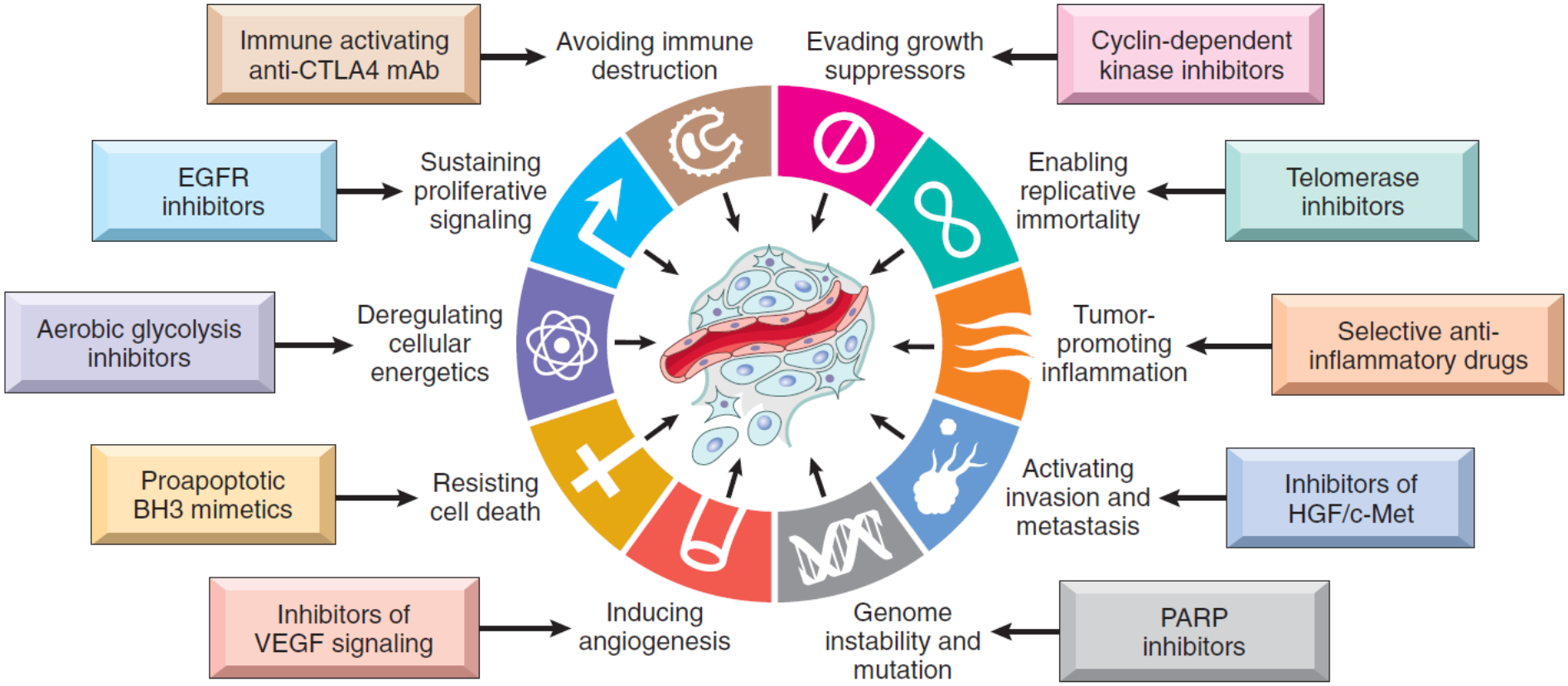
Carcinogenesis is a multistep process

Carcinogenesis is a multistep process



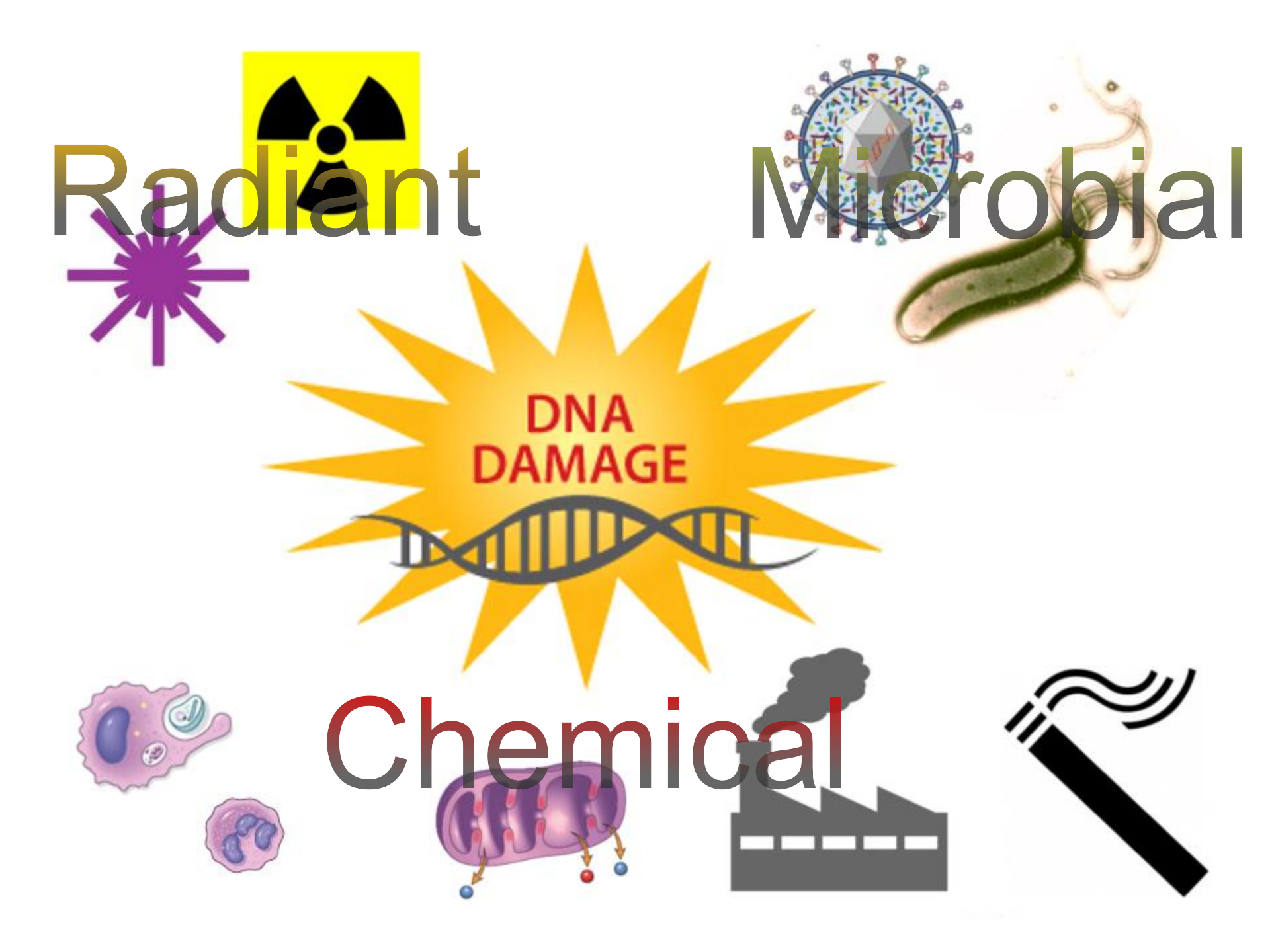


Hallmarks Concluded!



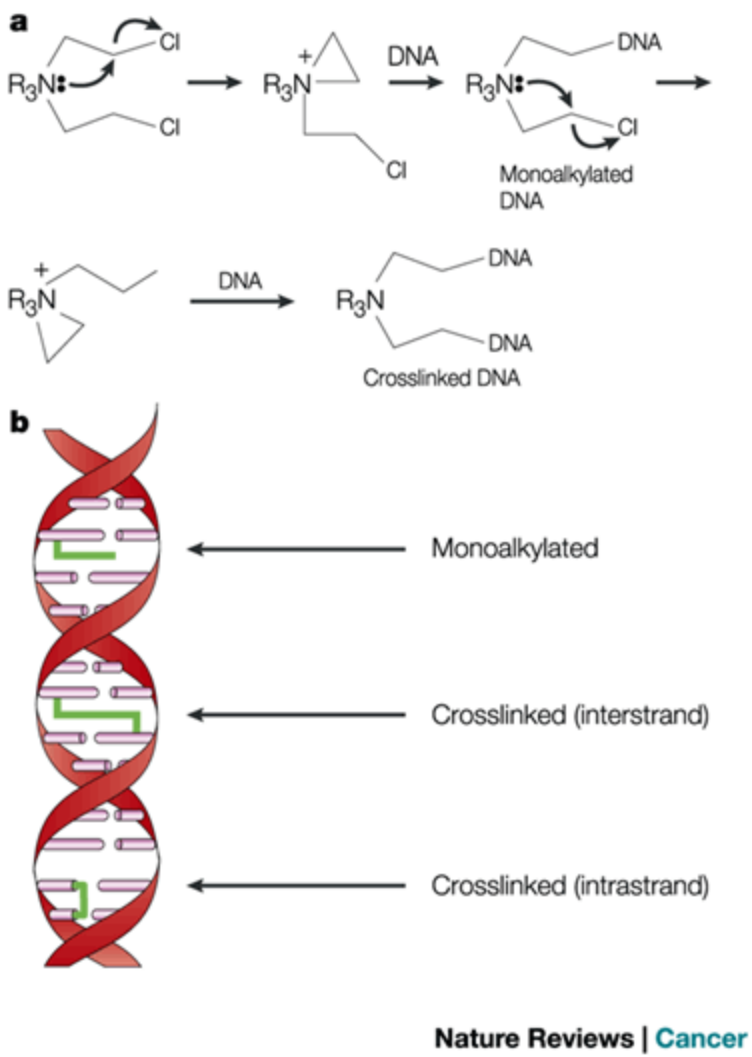
- *Hanahan D, Weinberg RA: The hallmarks of cancer: the next generation. Cell 144:646, 2011.*

Etiology of cancer
Carcinogenic agents


Radiant
Microbial
DNA
DAMAGE
Chemical

Chemical

Chimney sweeps & scrotal cancer



Chemical

Direct acting

Generally weak

No metabolic conversion required

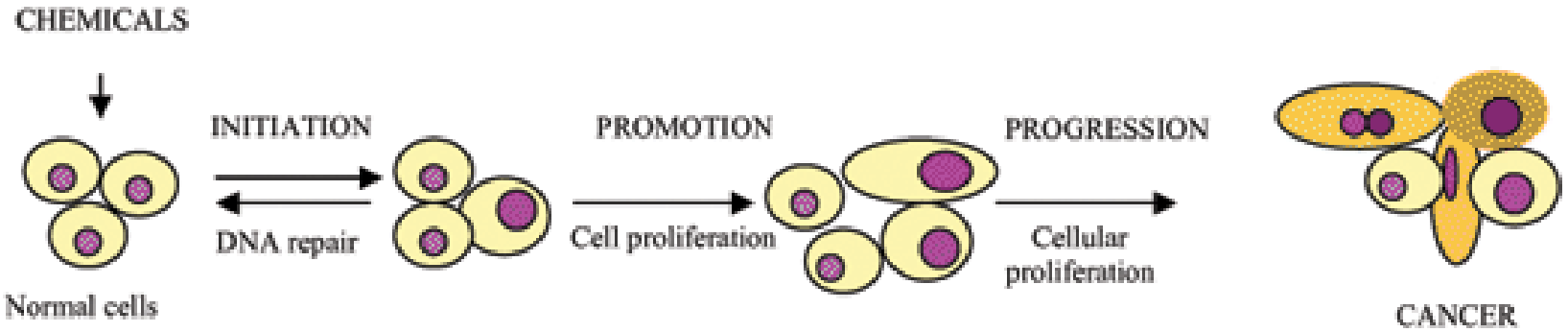
e.g. Alkylating agents

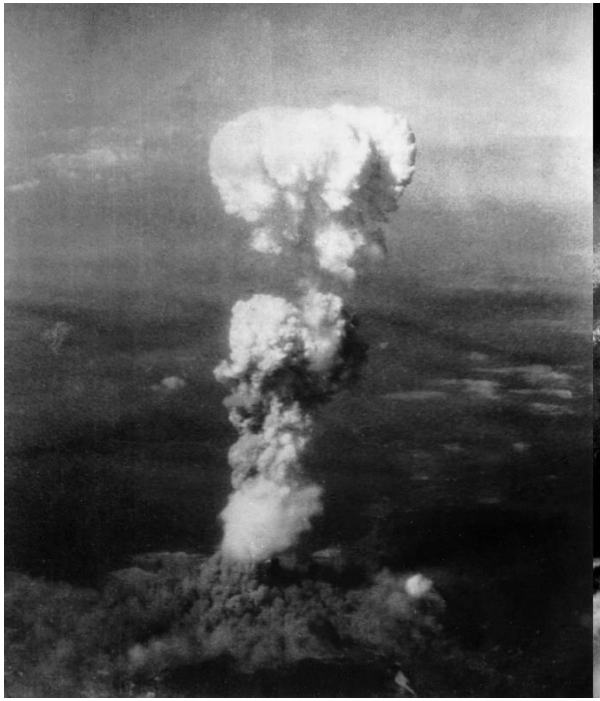
Indirect acting

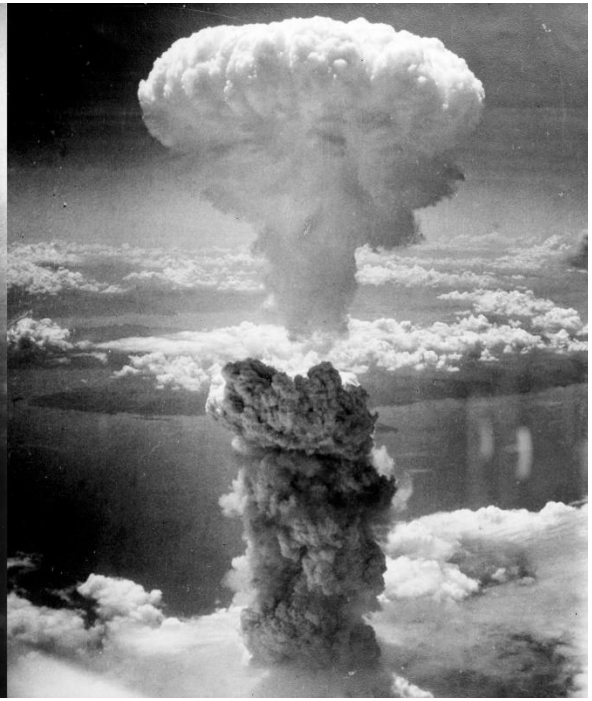
Require metabolic conversion (e.g. P450)

e.g. Polycyclic hydrocarbons (fossil fuel /cigarettes)

Initiation Promotion Progression



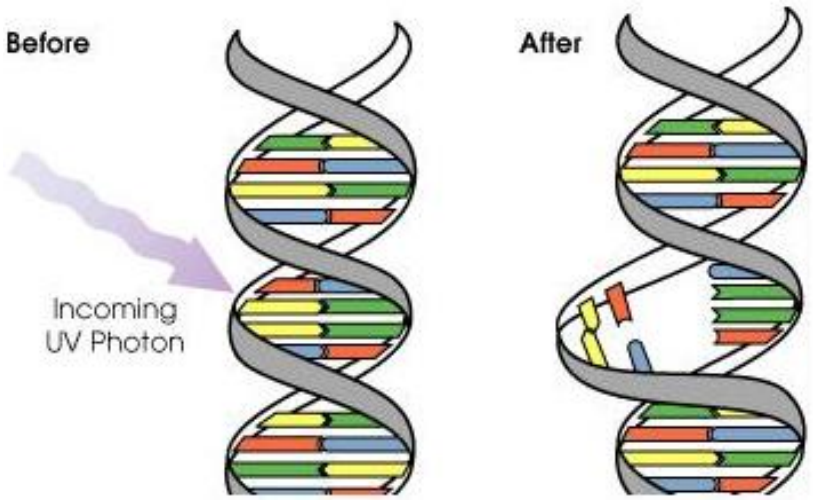


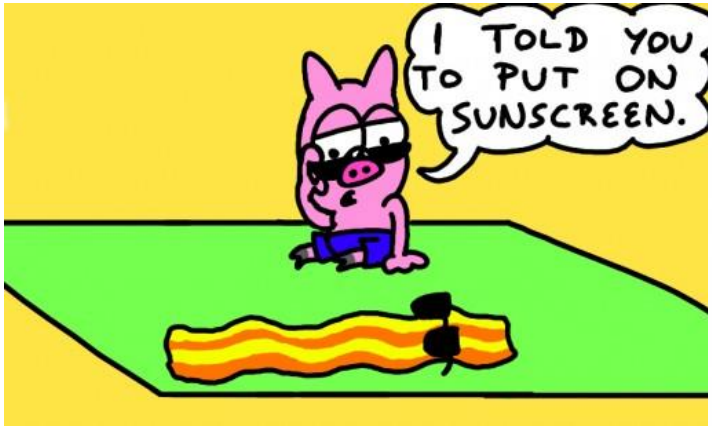


Radiation

UV, X-rays, nuclear

- Chromosome breakage
- Translocations
- Point mutations





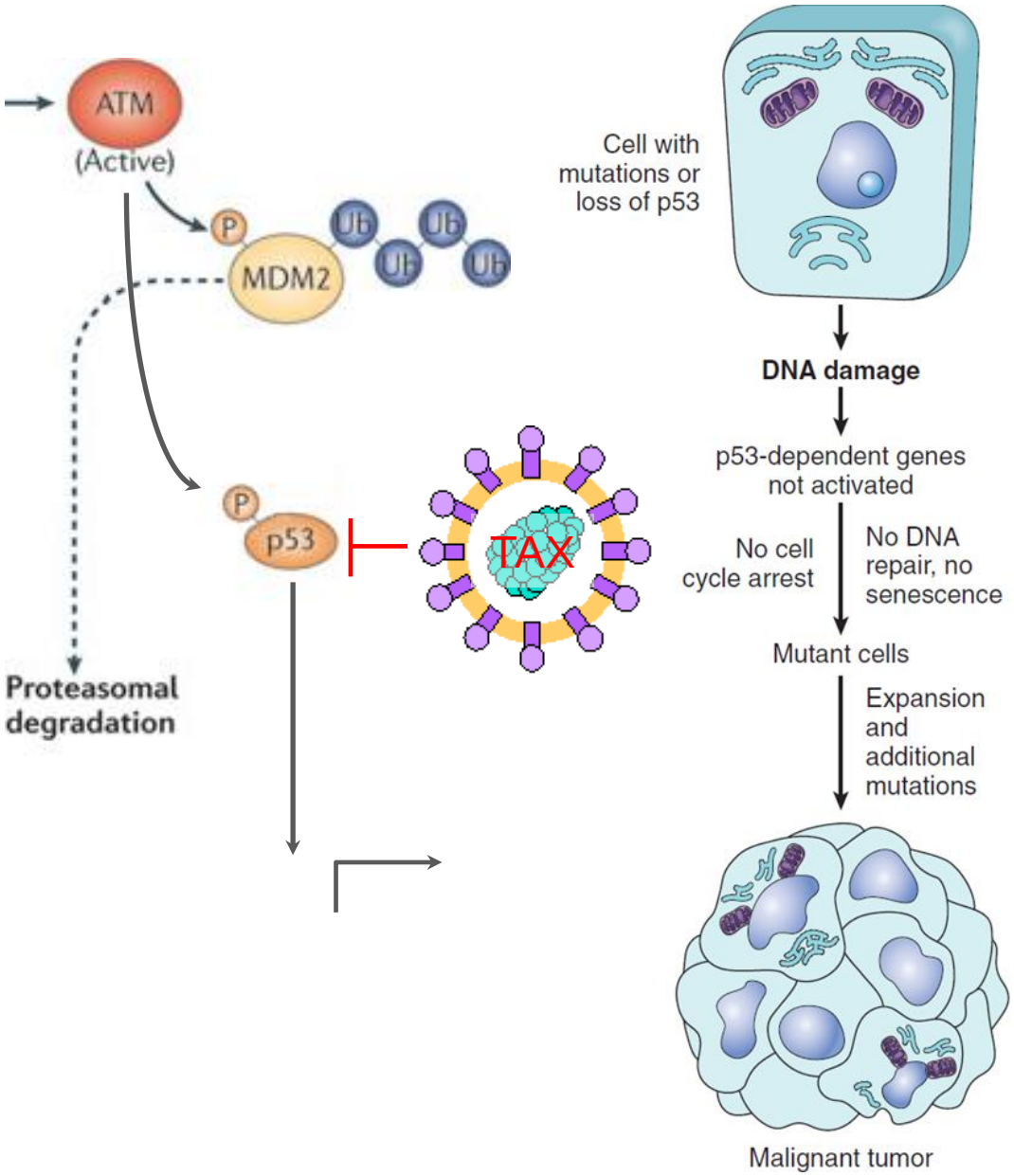
Skin Cancer & UV

Non-melanoma - Accumulative exposure

Melanoma - Intense intermittent exposure

Risks:

- Fair skin
- Geography
- Personal habits



Microbial

HTLV-1 (retrovirus)

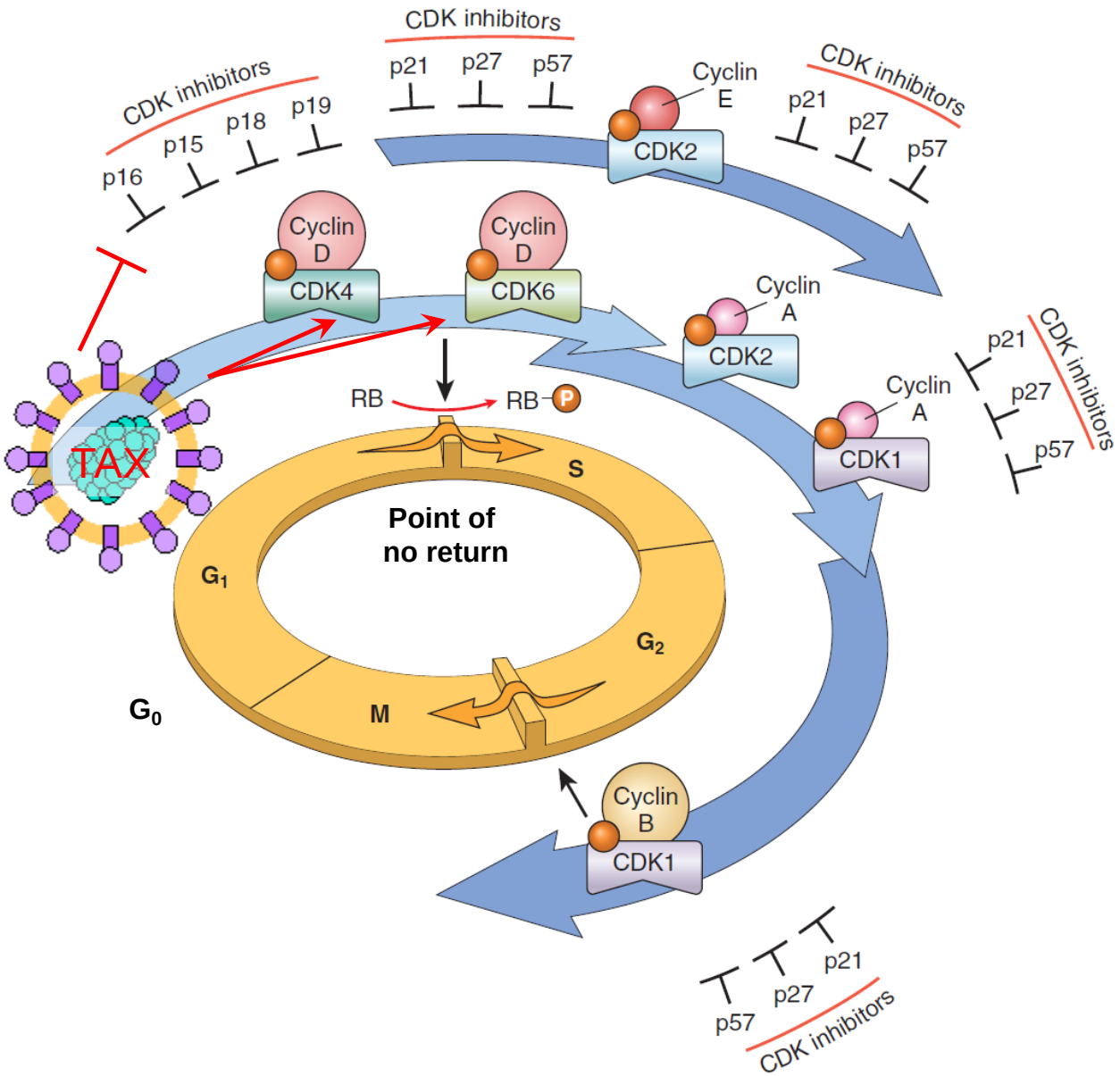
T cell leukemia/ lymphoma 3-5% (Japan Caribbean)

Sex/Blood/Breastfeeding

Long latency 20-50yrs

CD4+ T cell transformation

No viral oncogene/oncogene integration site



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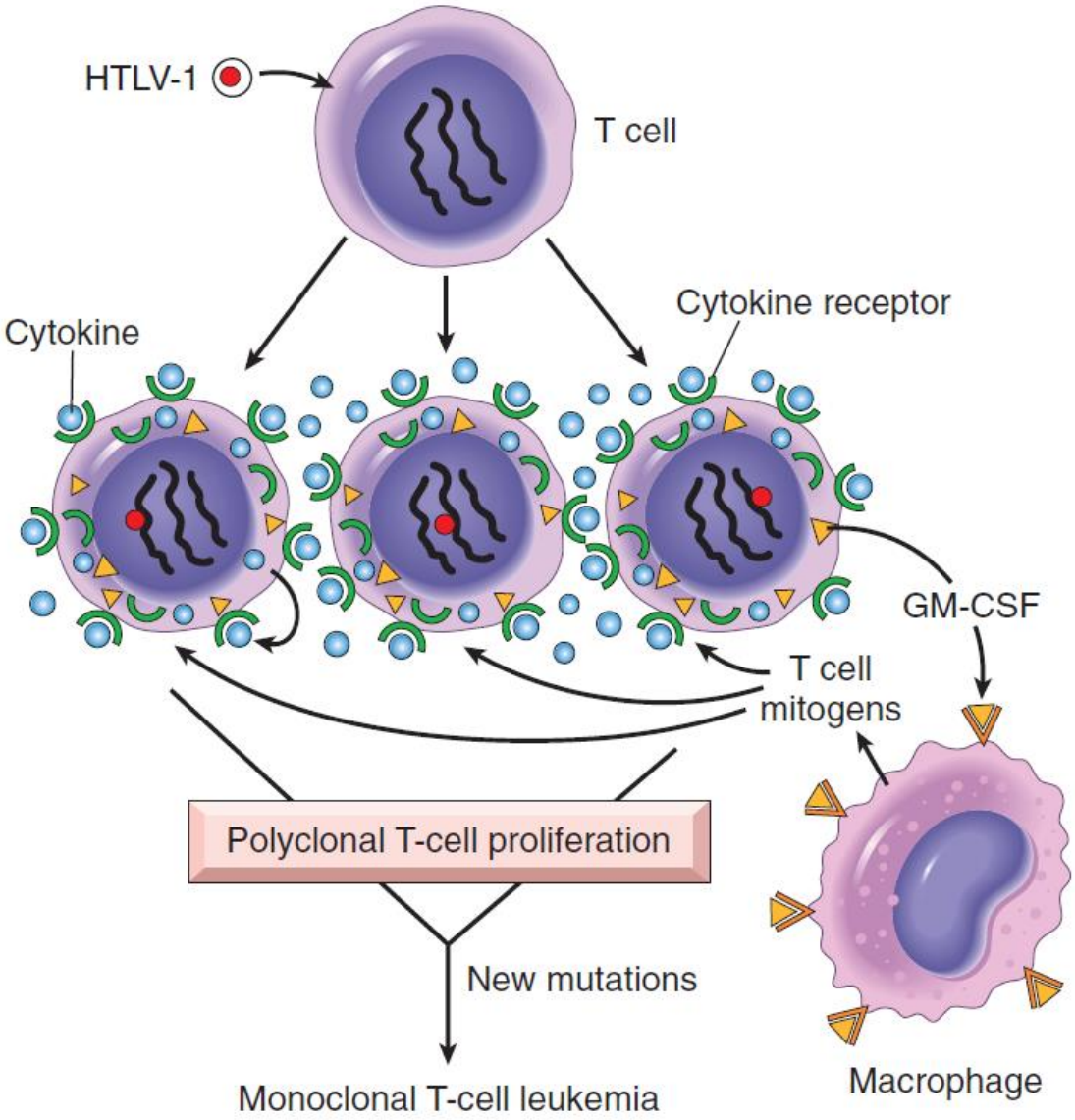

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Microbial

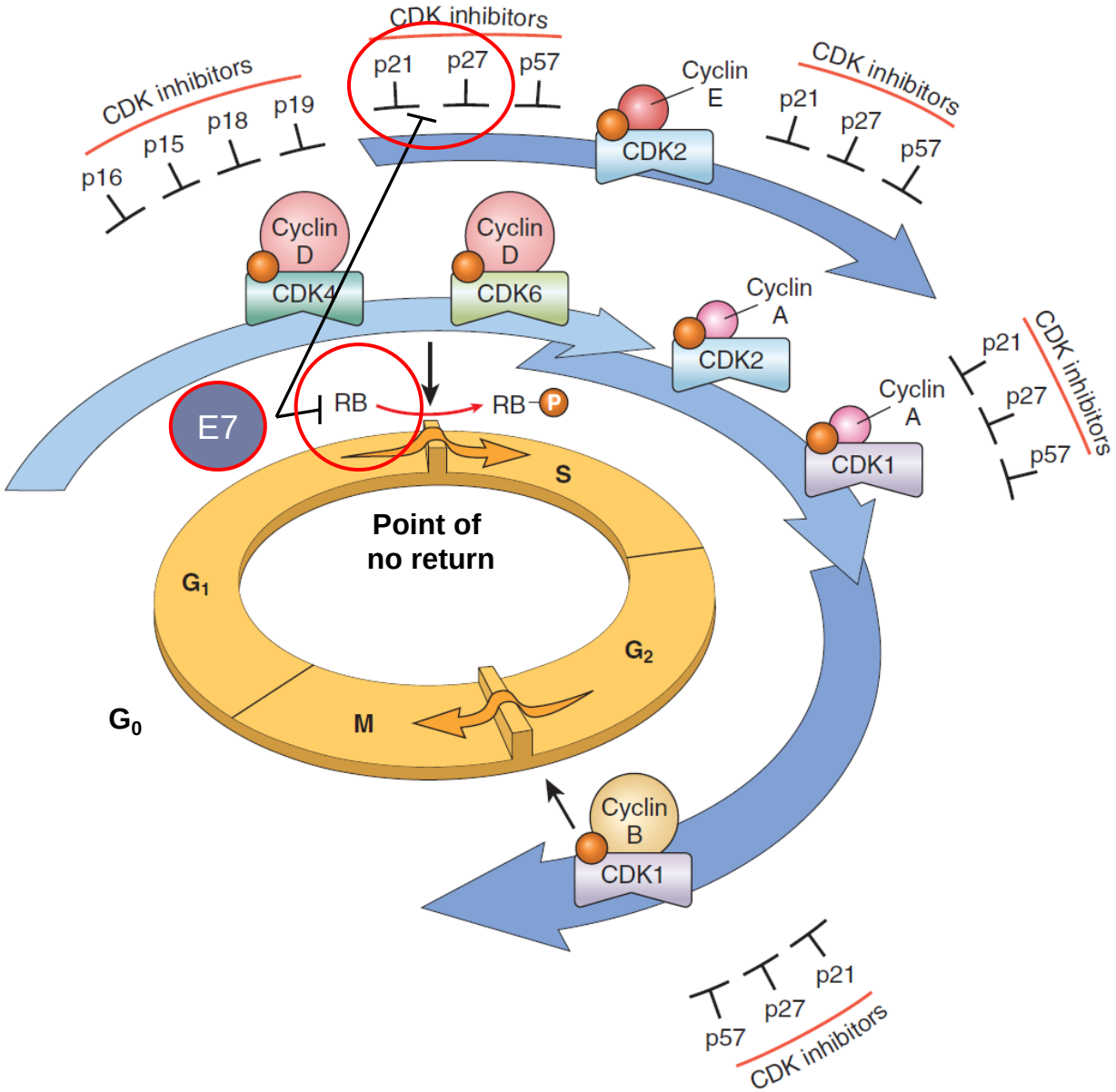
HPV (DNA)

Several types

- 1,2,4,7 Warts
- 6,11 Genital warts
- 16,18 SCC (cervix & anogenital)

Viral proteins responsible

- E6
- E7



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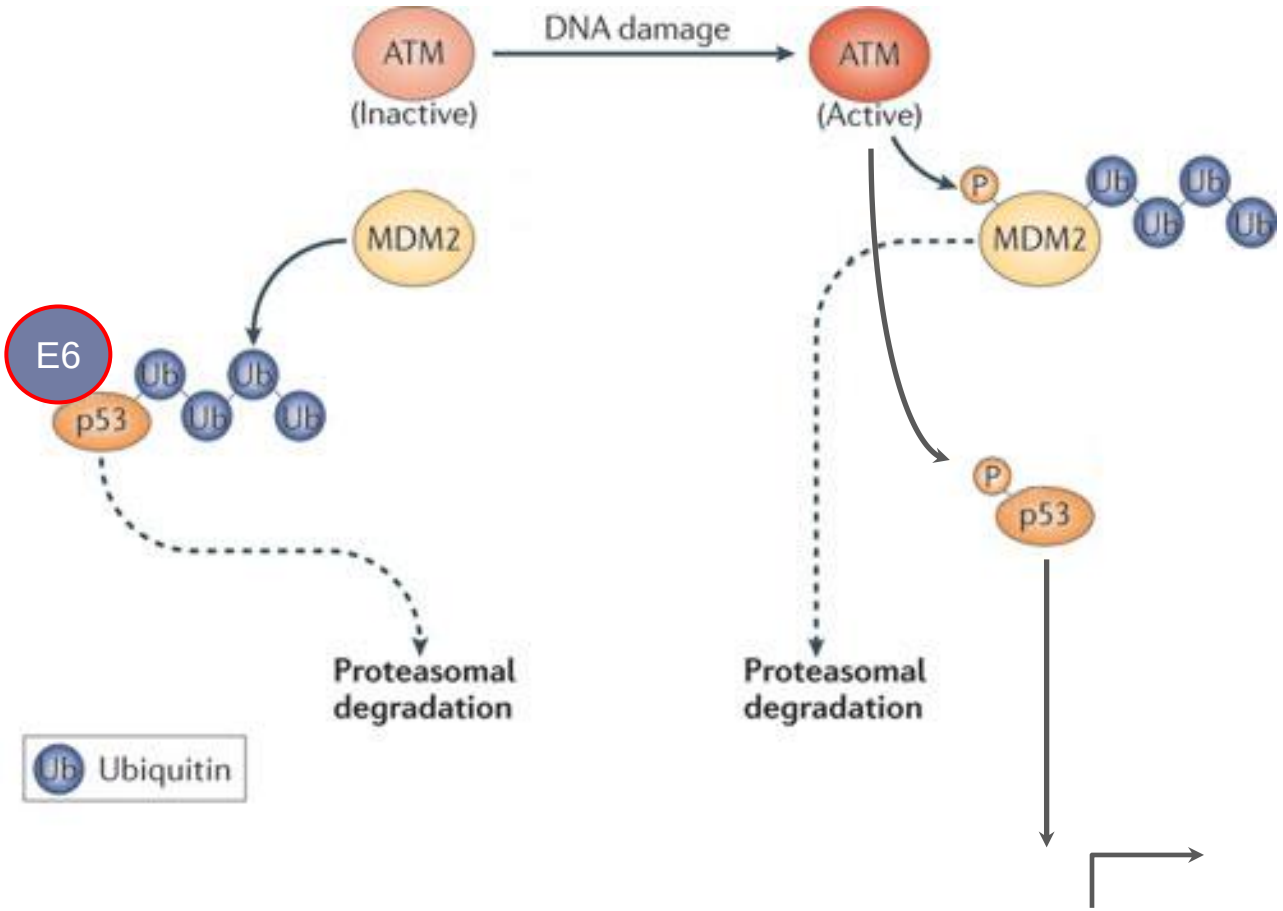

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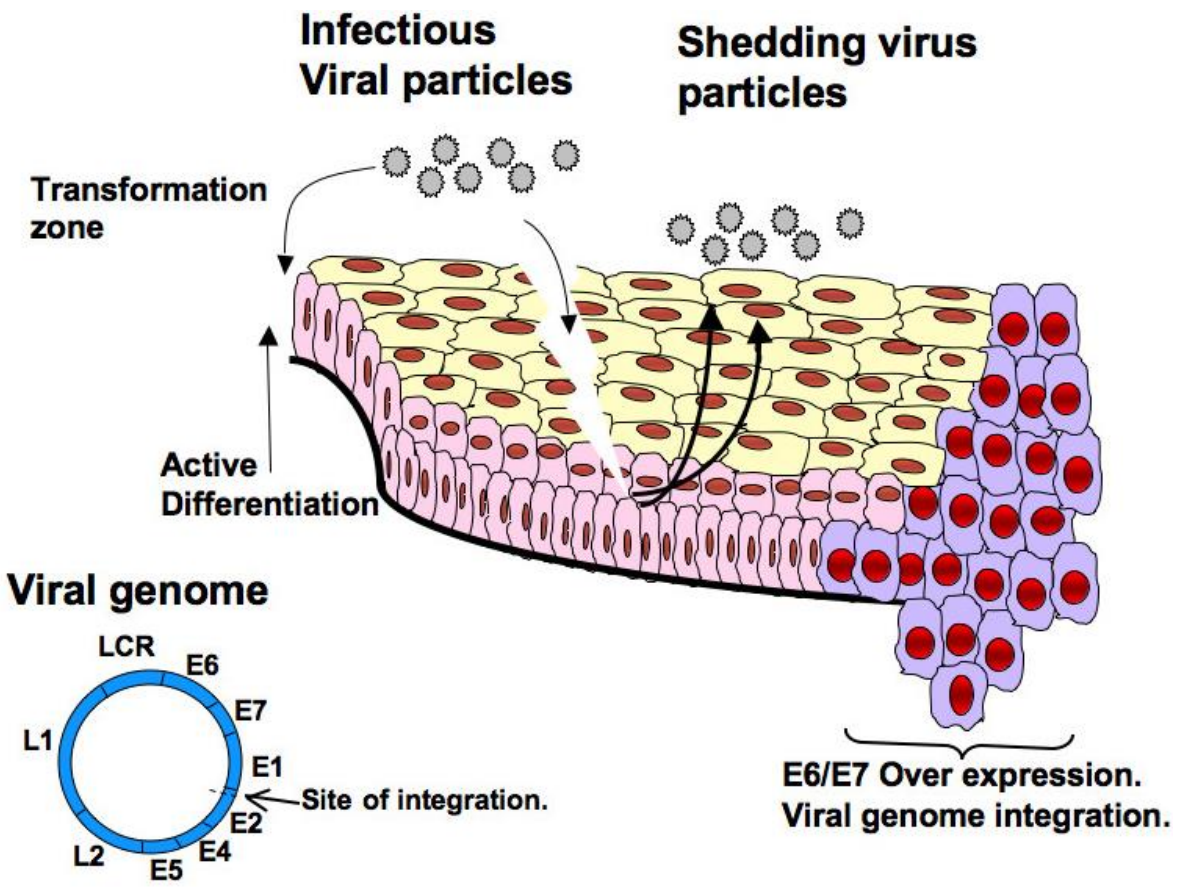

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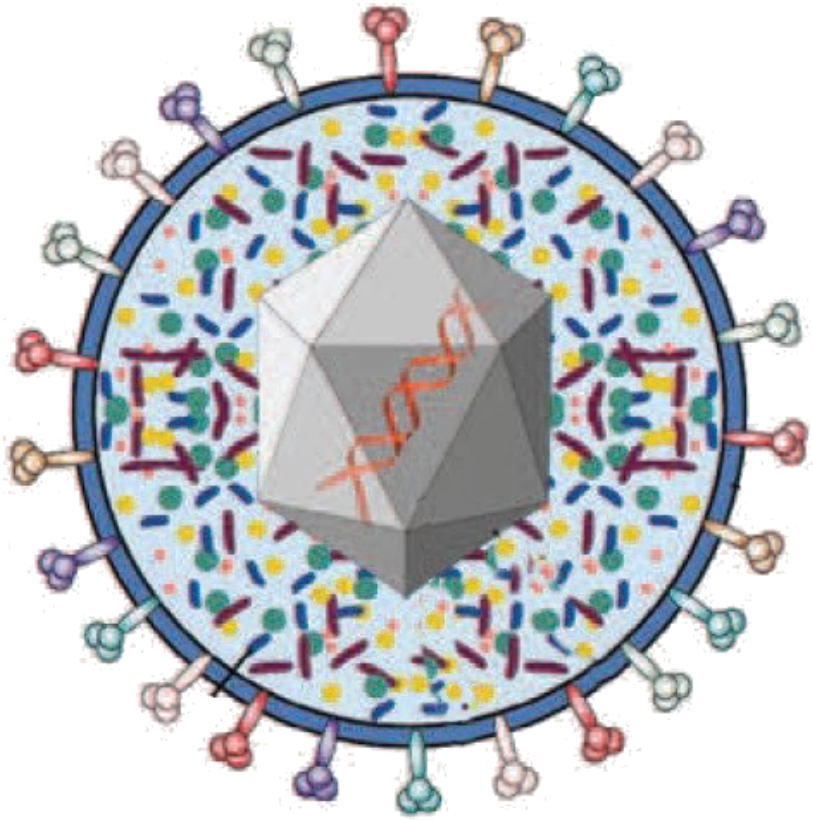
Necessity & Sufficiency

Oxygen is necessary for human life. However, Oxygen alone is not sufficient.

Pouring freezing water on your “friend” is sufficient to wake him/her up, but not necessary. There are other ways.



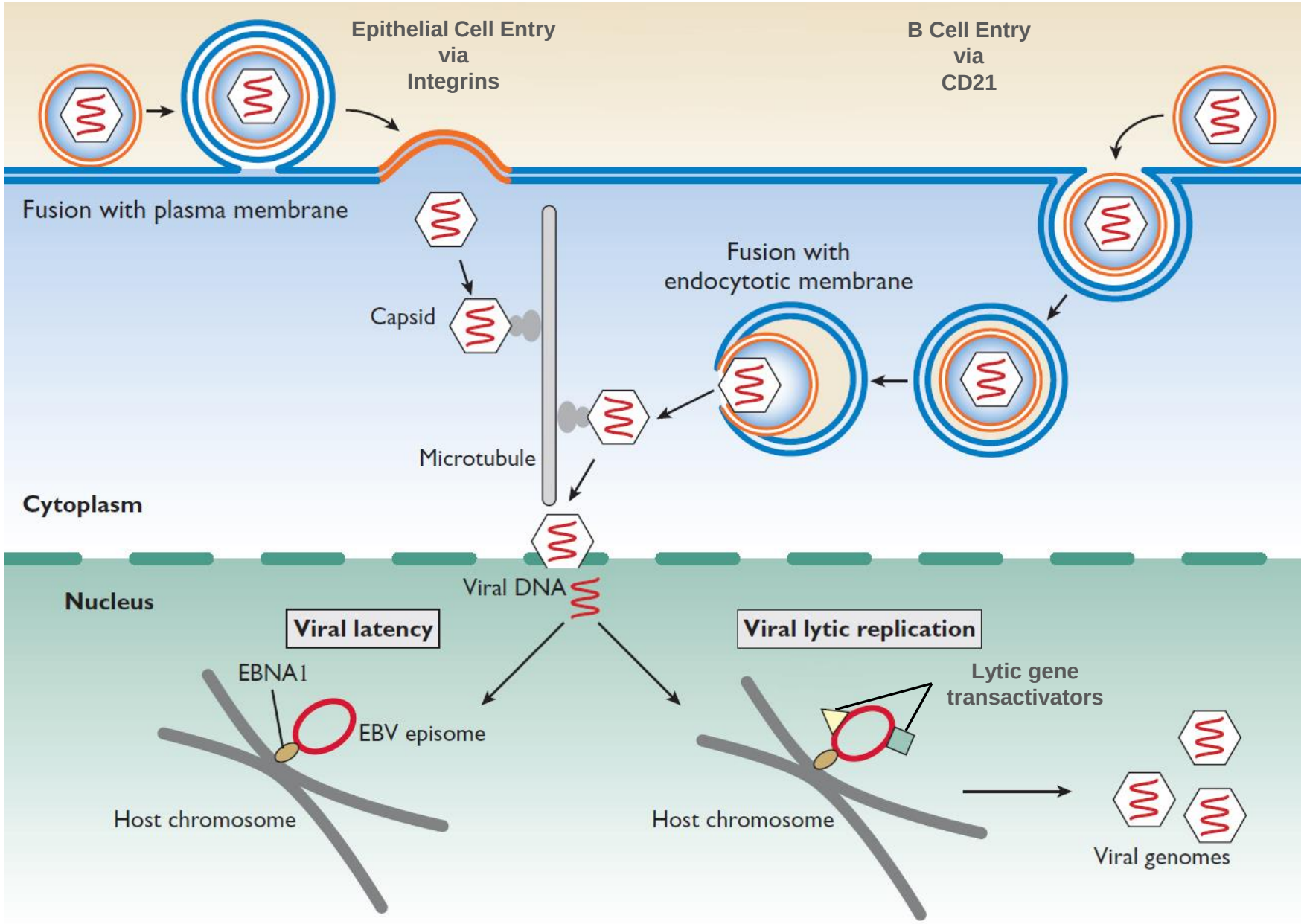
Microbial

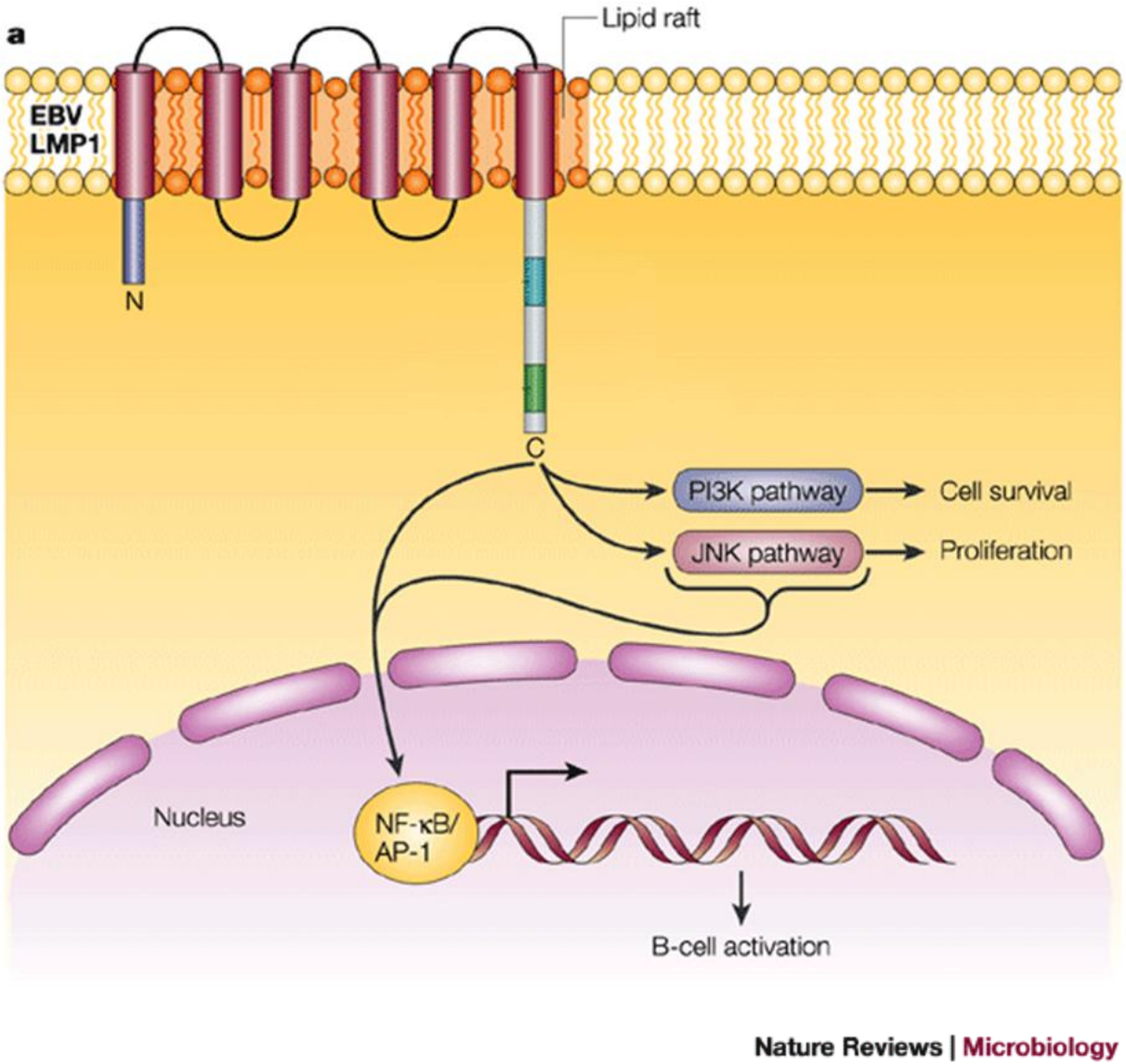
EBV (DNA)

1st virus linked to a human tumor (Burkitt lymphoma)

Wide range of B, T & NK lymphomas as well as some carcinomas & sarcomas

Endemic in Africa (BL)
Endemic in SEA (NPC)


Epithelial Cell Entry
via
Integrins
B Cell Entry
via
CD21
Fusion with plasma membrane
Capsid
Fusion with
endocytotic membrane
Microtubule
Cytoplasm
Viral DNA
Nucleus
Viral latency
Viral lytic replication
EBNA1
EBV episome
Lytic gene
transactivators
Host chromosome
Host chromosome
Viral genomes



Microbial

EBV (DNA)

LMP1 - viral oncogene

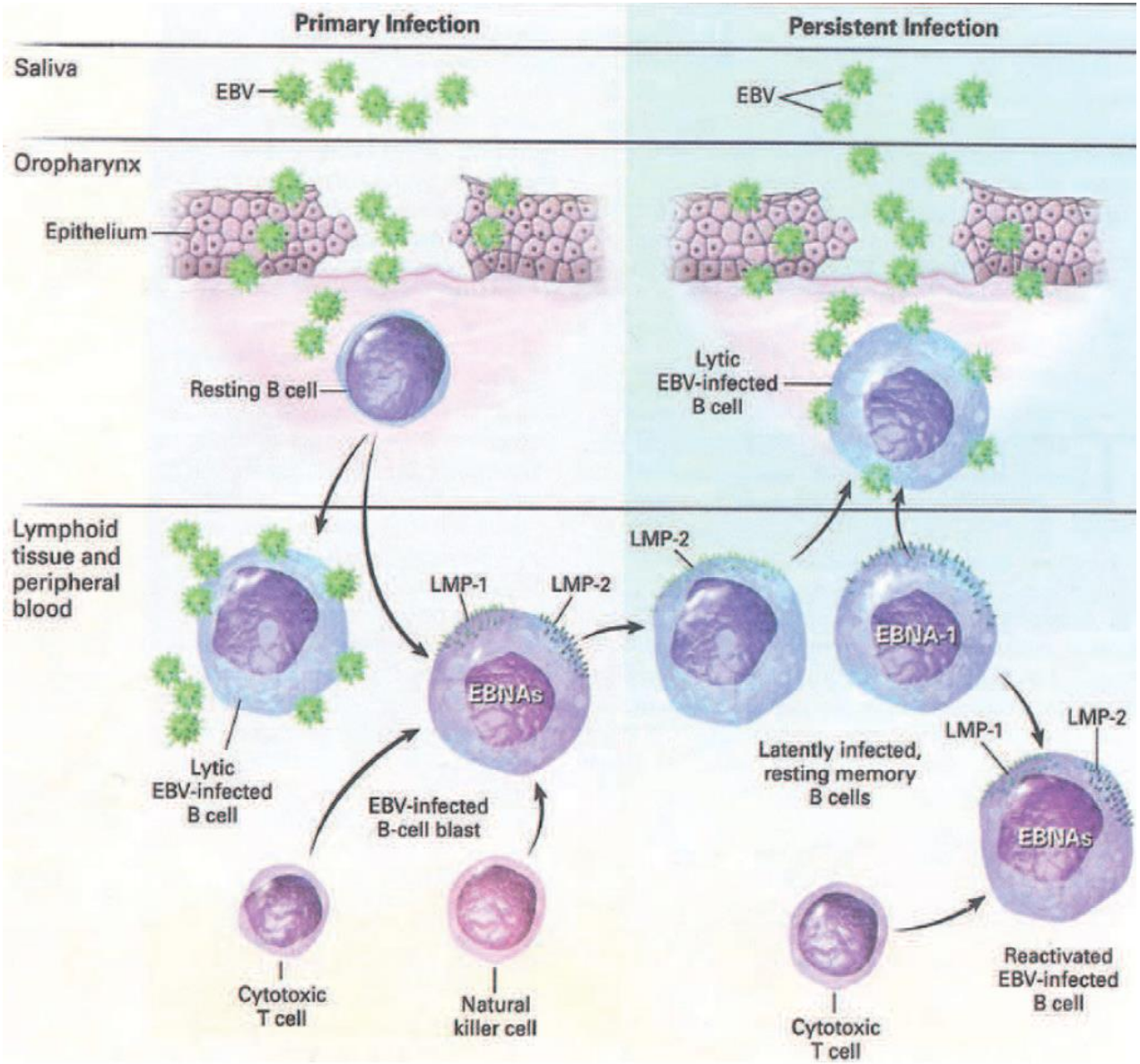
Mimics CD40 signalling (TNF receptor)

- JAK/STAT
- NF- κB

Inhibits apoptosis by activating Bcl-2

EBNA2

- ↑ CyclinD
- ↑ src proto-oncogene



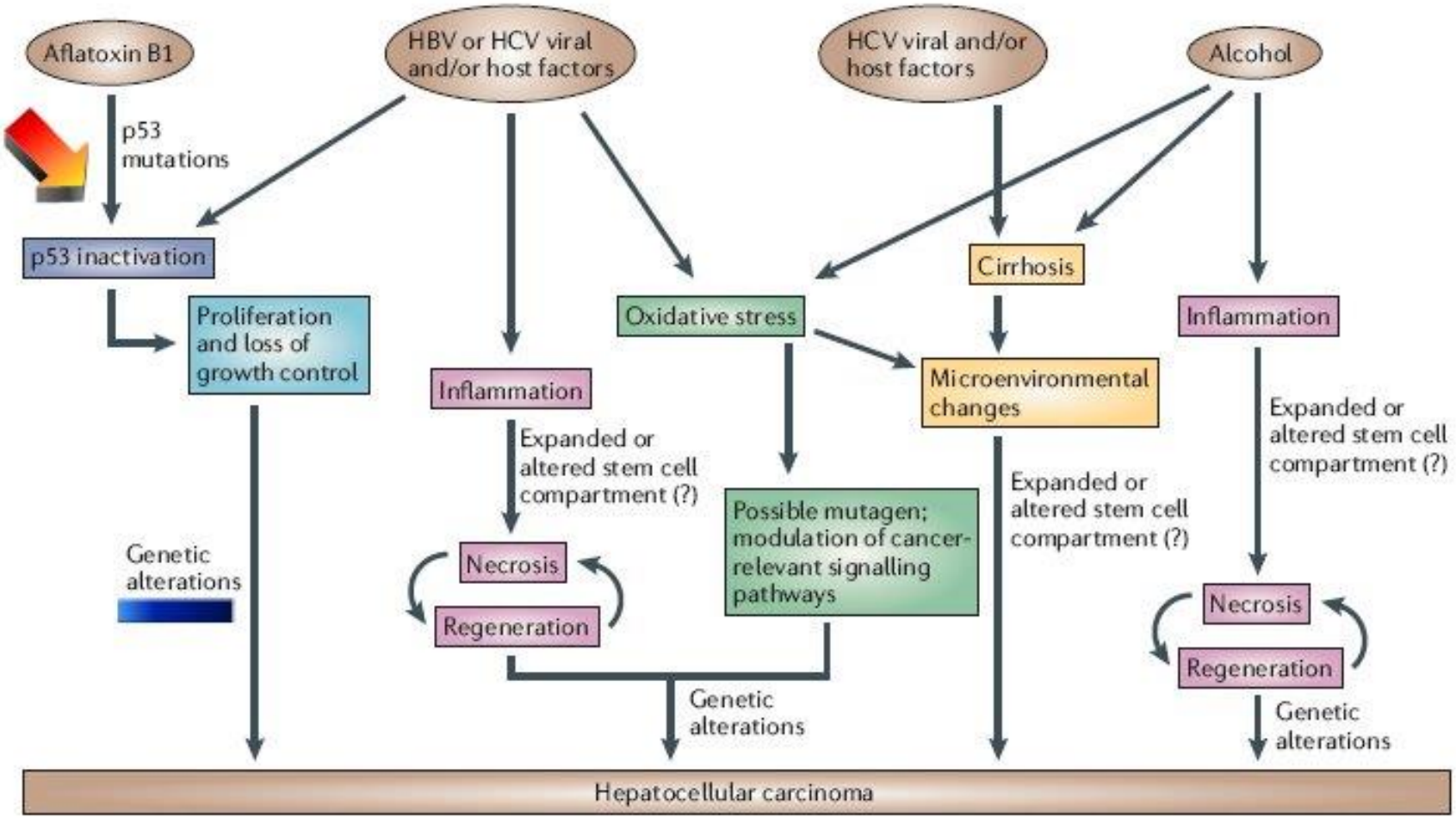
Microbial

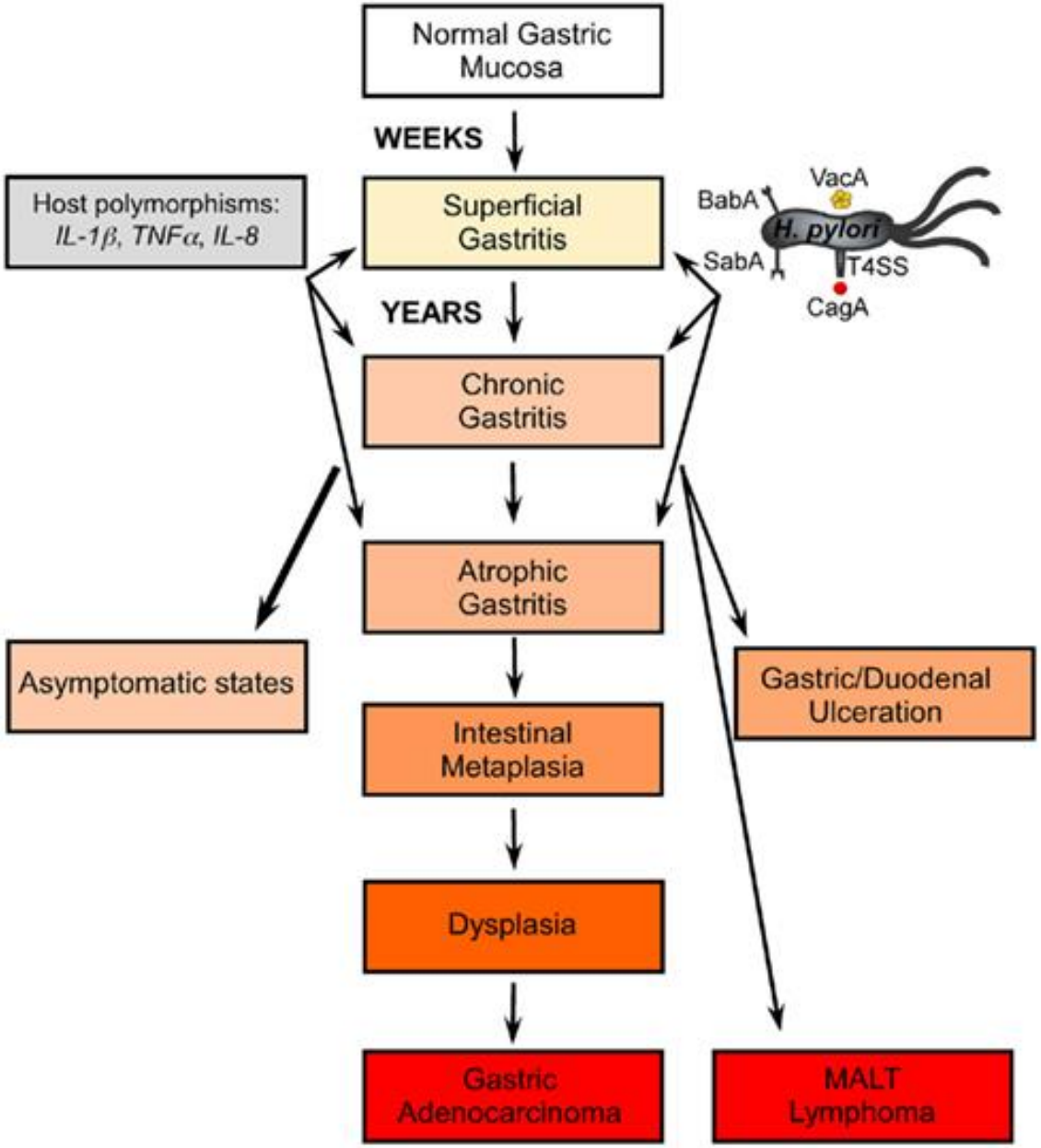
EBV (DNA)

vIL10 - viral cytokine

- Pirated (evolution)
- Inhibits M/M T cell activation

Microbial **HBV/HCV** (DNA/RNA)





Microbial

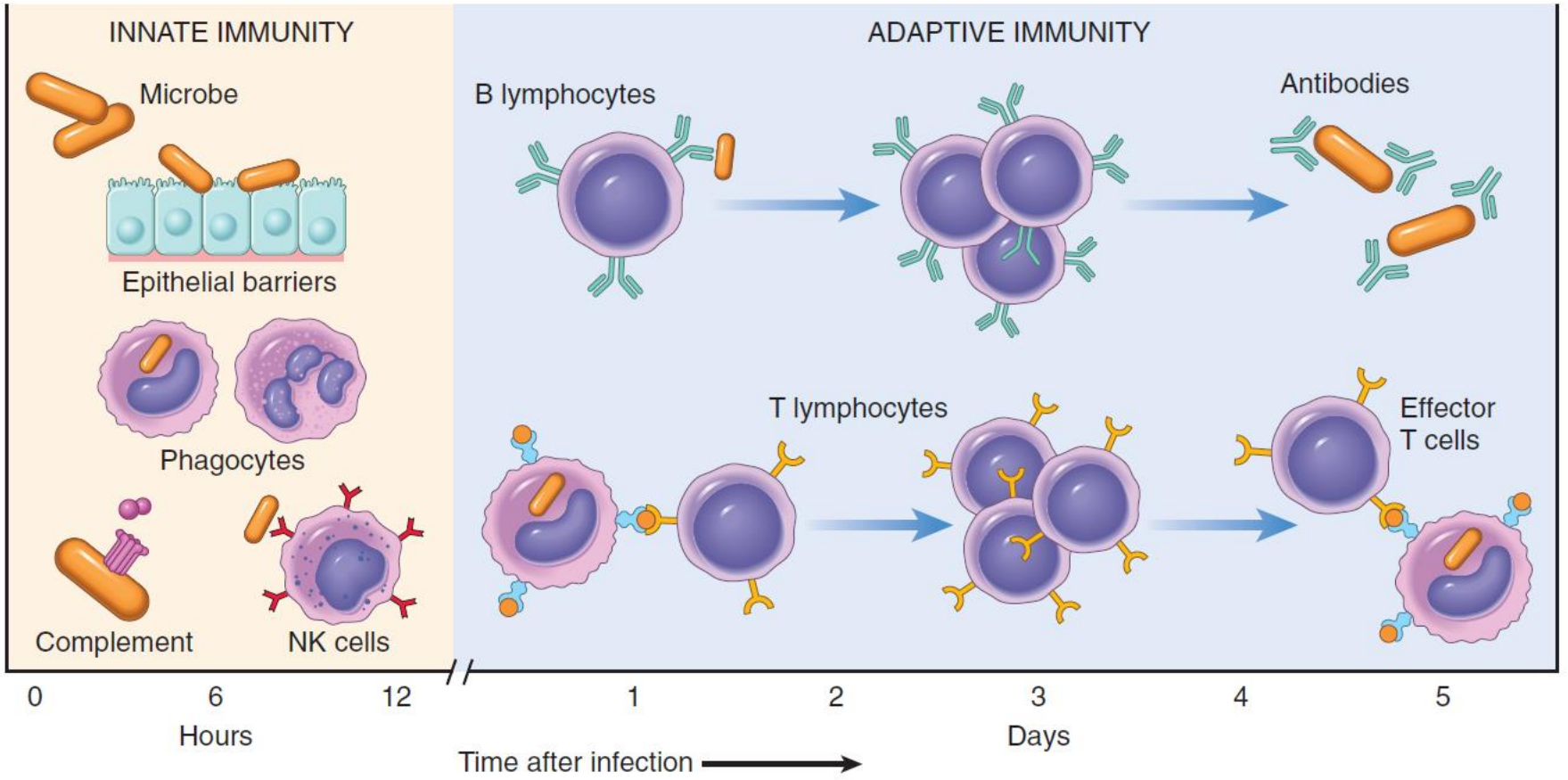
Helicobacter pylori

Gastric adenocarcinomas & MALT lymphomas

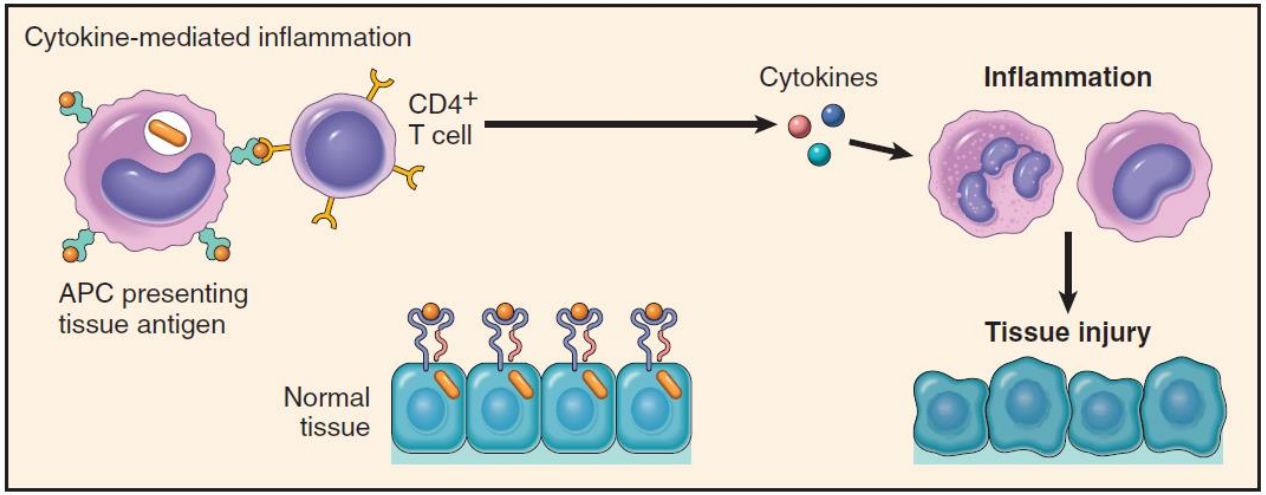
Similar scenario to HBV (chr. inflammation/ROS)

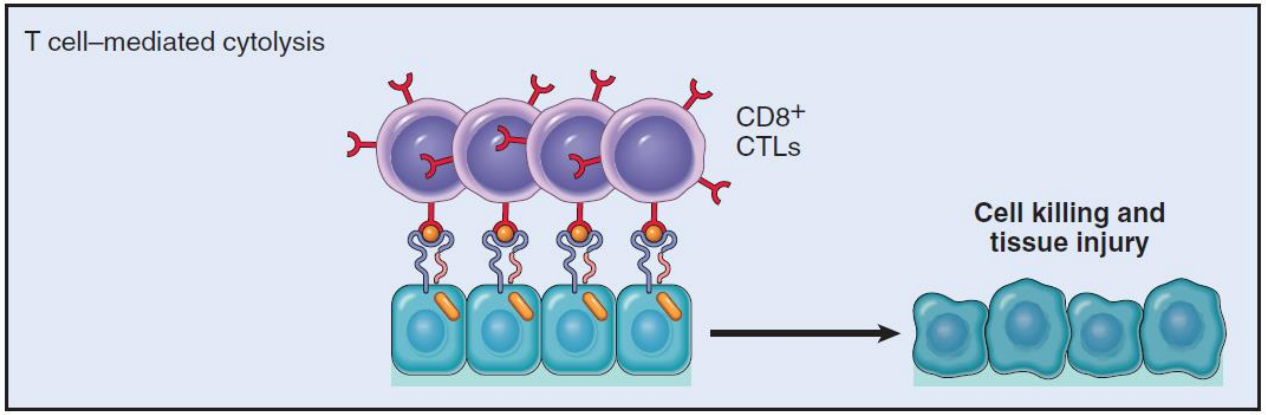
Tumor Immunity

Innate/Adaptive-Humoral/Cell-mediated



CD4+/CD8+ T cells





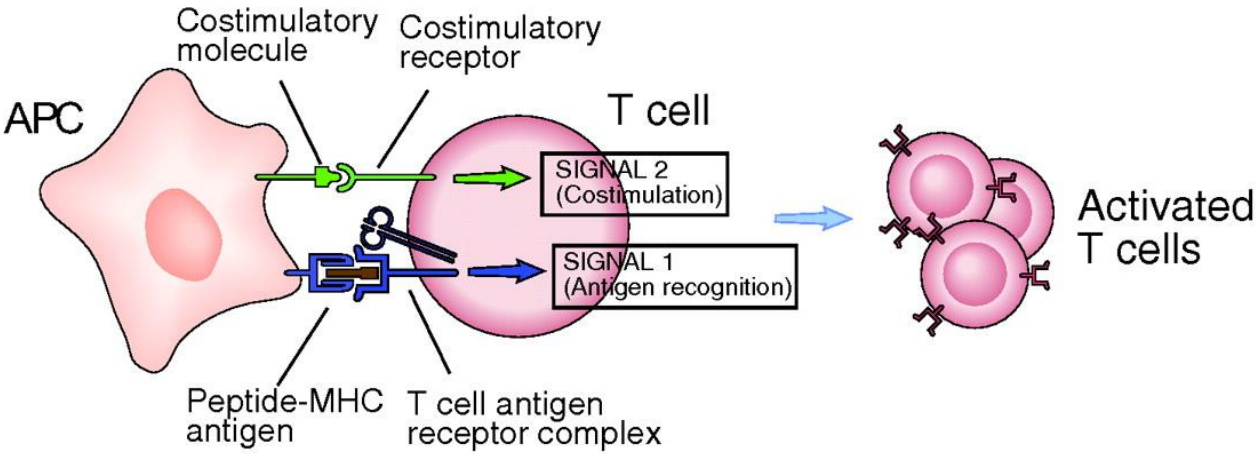
CD4+ T cells: cytokine production

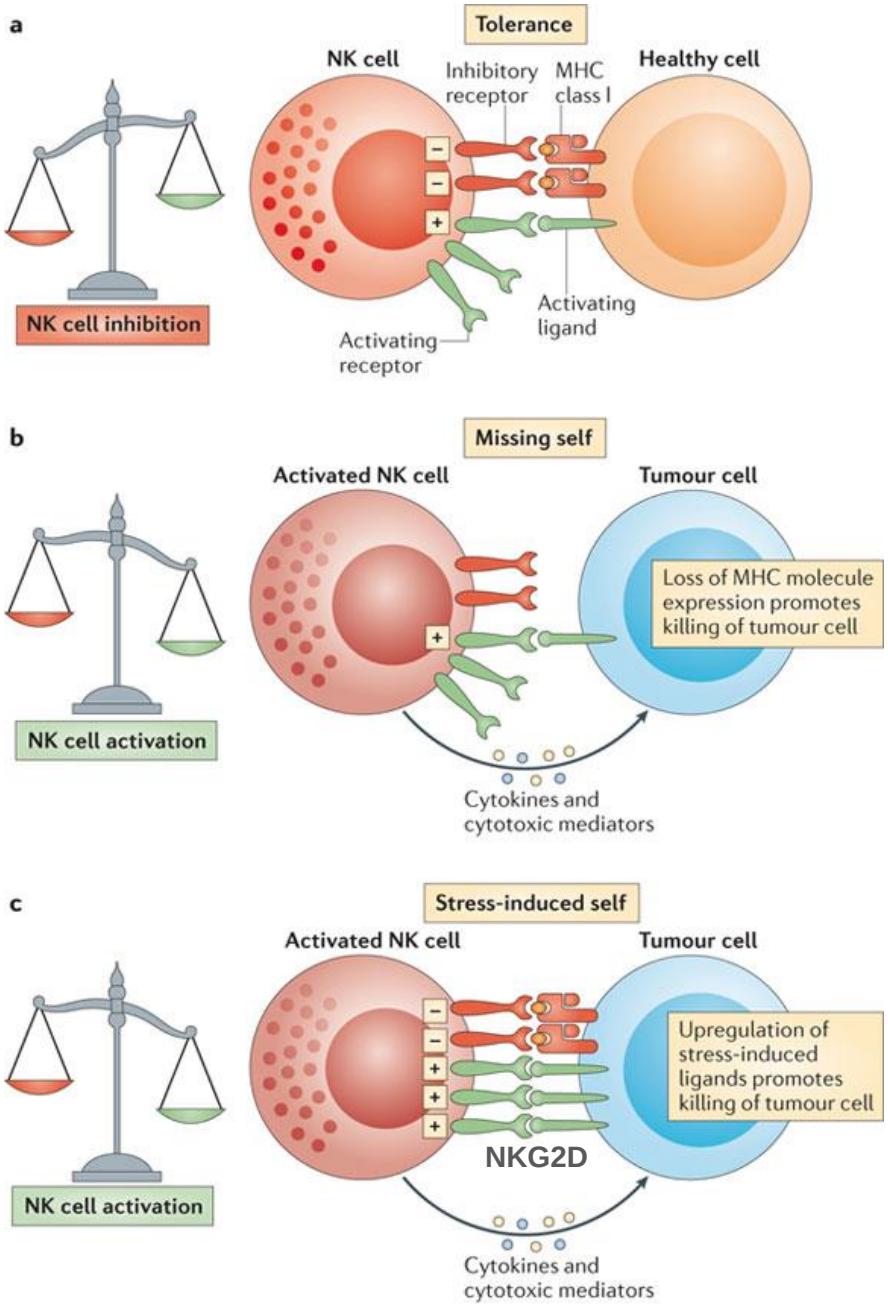
CD8+ T cells: direct killing

CD4+/CD8+ T cells

CD4+ T cells: cytokine production

CD8+ T cells: direct killing





NK cells

No Prior sensitization

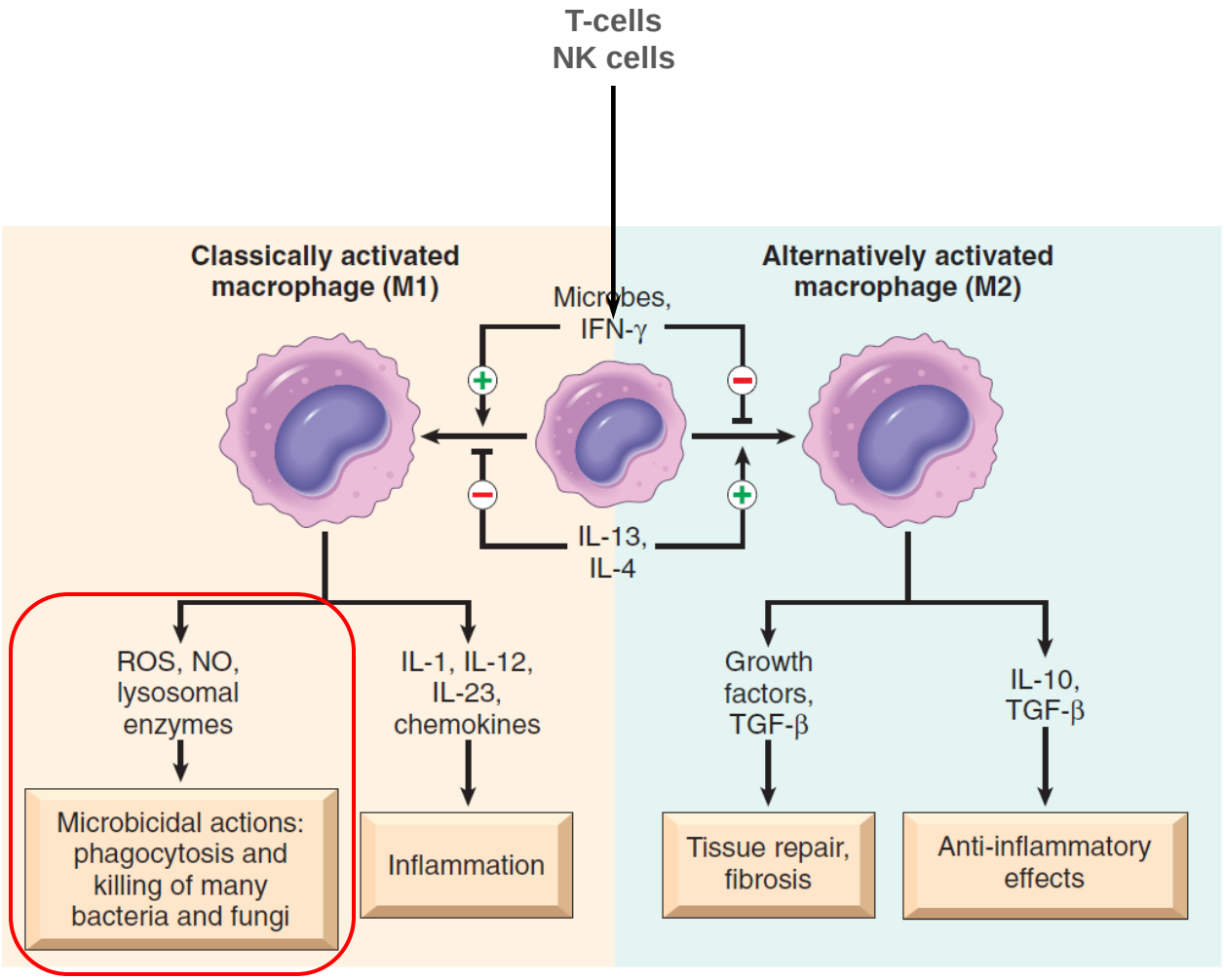
IL-2 induced activation

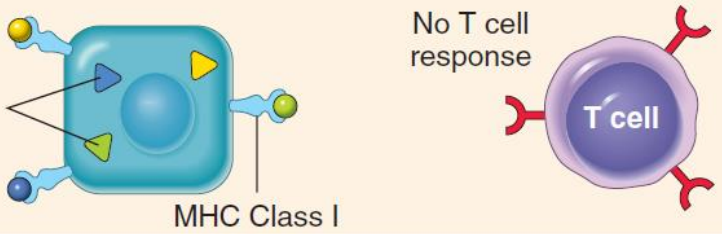
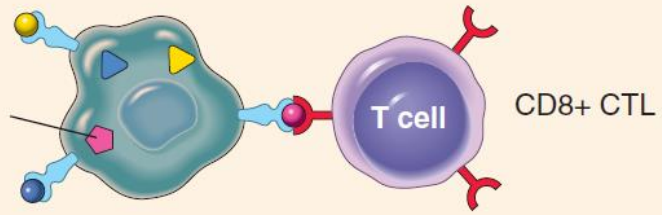
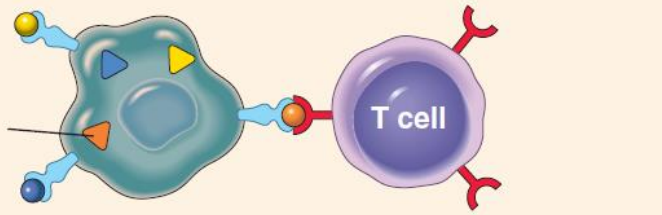
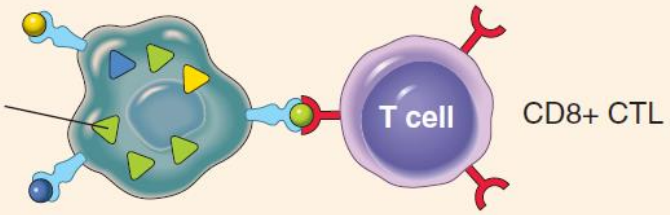
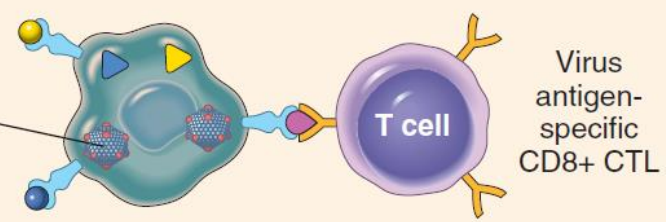
Stress induced ligands (e.g. NKG2D ligands) expressed:

- Tumor cells
- DNA damage

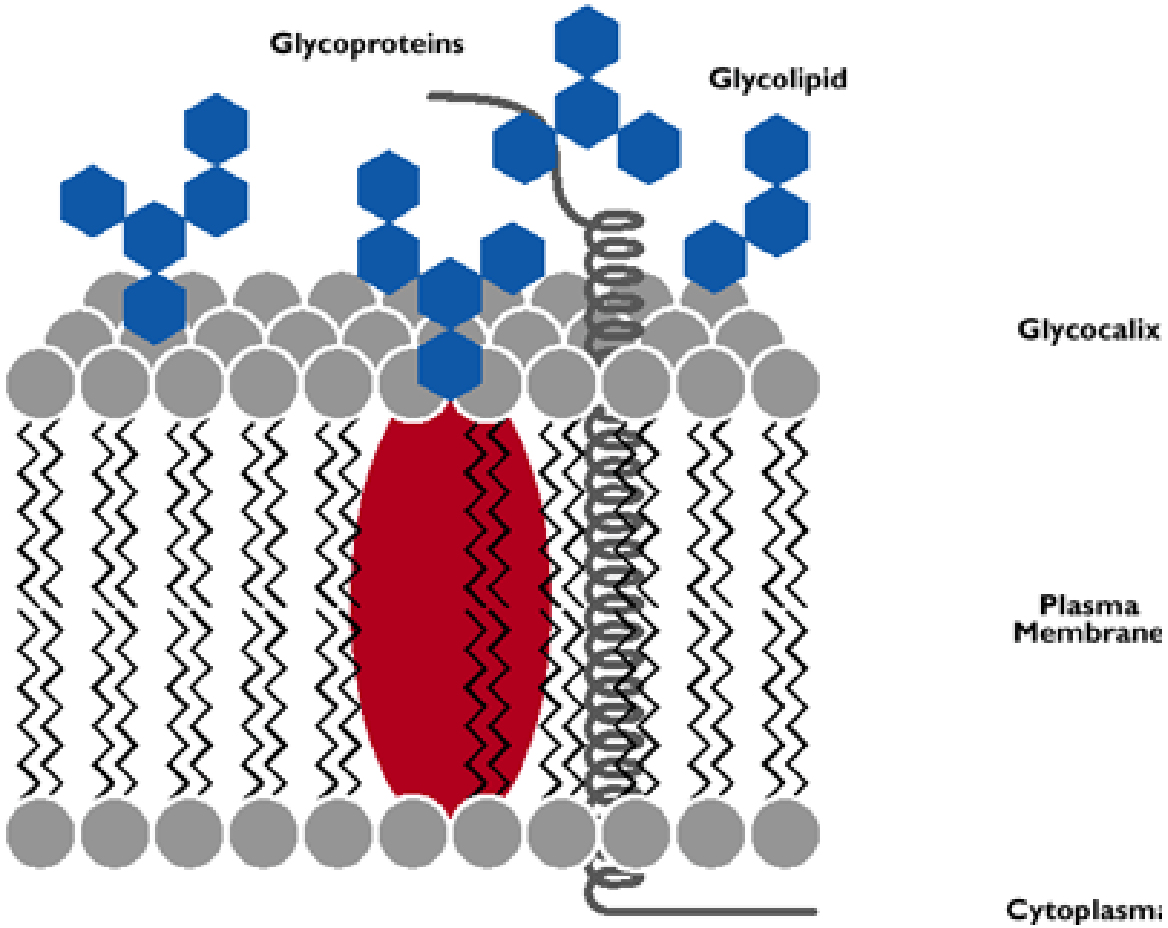
M1 macrophages

Kill tumor cells by similar mechanisms as used on microbes.



Normal host cell displaying multiple MHC-associated self antigens		EXAMPLES
Tumor cells expressing different types of tumor antigens		Oncogene products: mutated RAS, BCR/ABL fusion proteins Tumor suppressor gene products: mutated p53 protein
		Various mutant proteins in carcinogen- or radiation-induced animal tumors; various mutated proteins in melanomas
		Overexpressed: tyrosinase, gp100, MART in melanomas **Oncofetal antigens (CEA)** Aberrantly expressed: cancer-testis antigens (MAGE, BAGE) **Differentiation antigens (CD20)**
		Human papilloma virus E6, E7 proteins in cervical carcinoma; EBNA proteins in EBV-induced lymphoma

Glycolipids and Glycoproteins

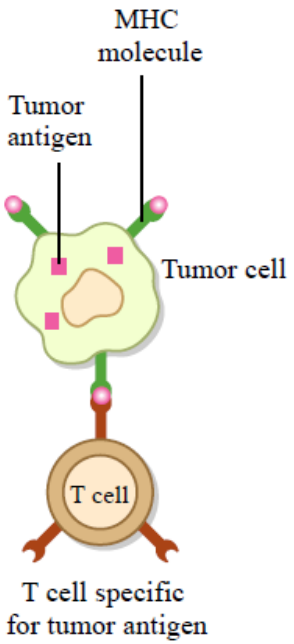
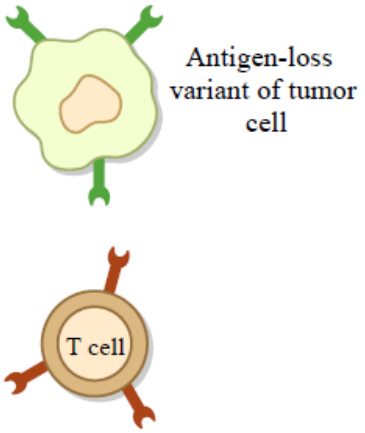
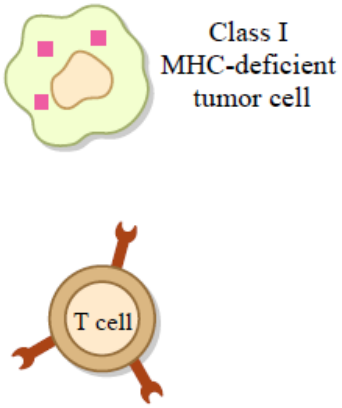
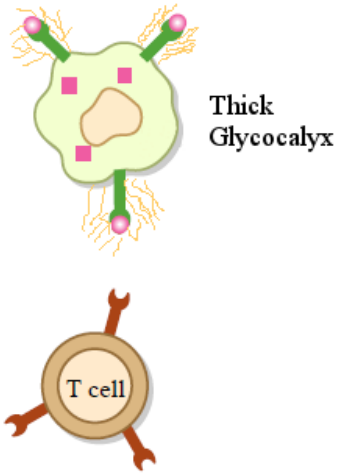
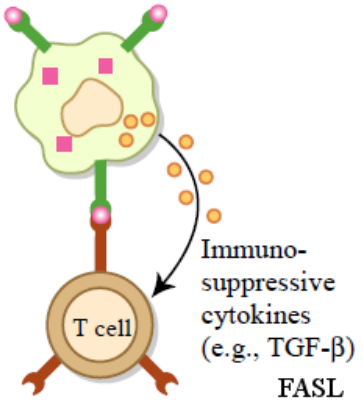


Increased/abnormal

CA-125/CA-19-9 Ovarian carcinomas

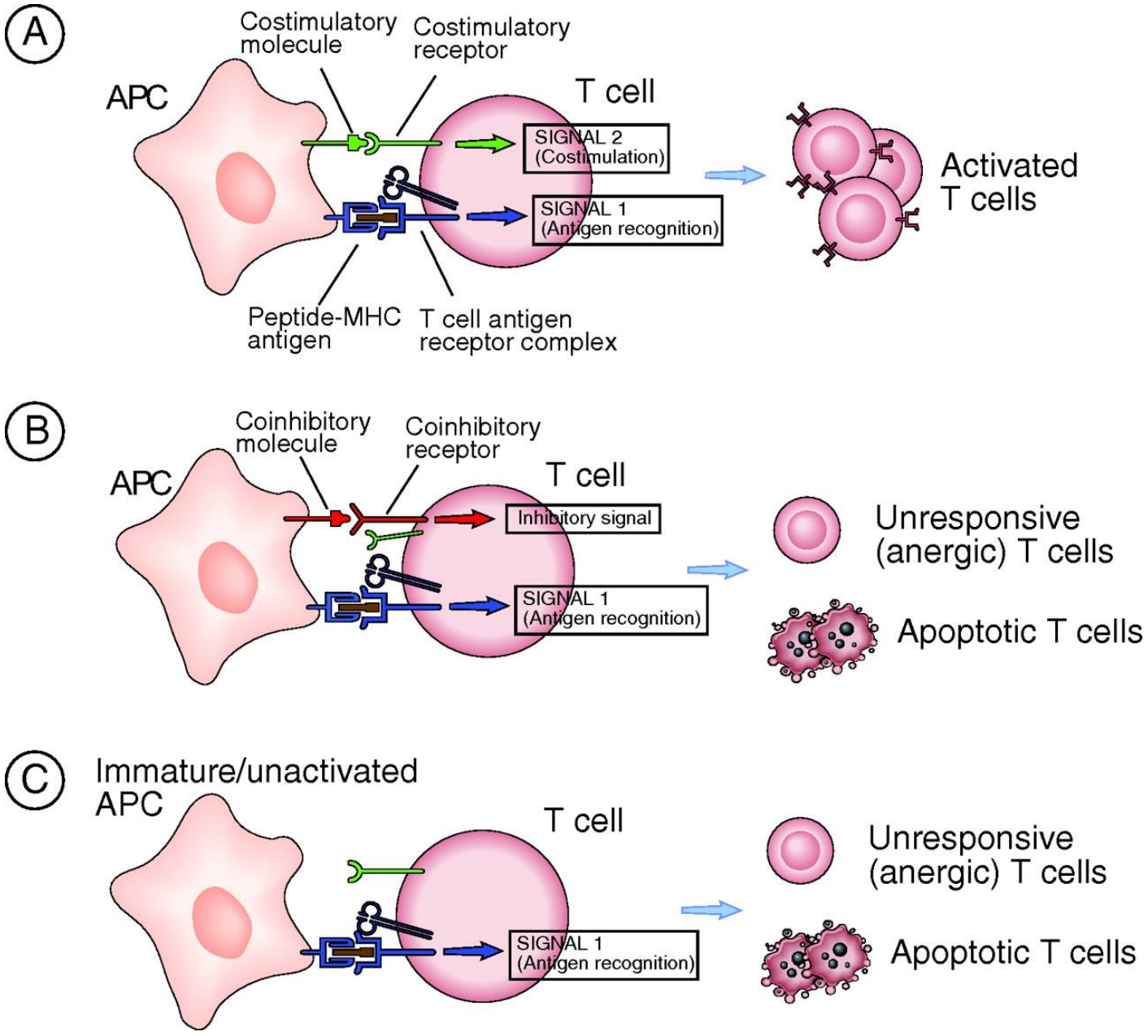
MUC-1 Breast carcinomas

Diagnostic/therapeutic targets

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

Downregulation of co-stimulatory molecules

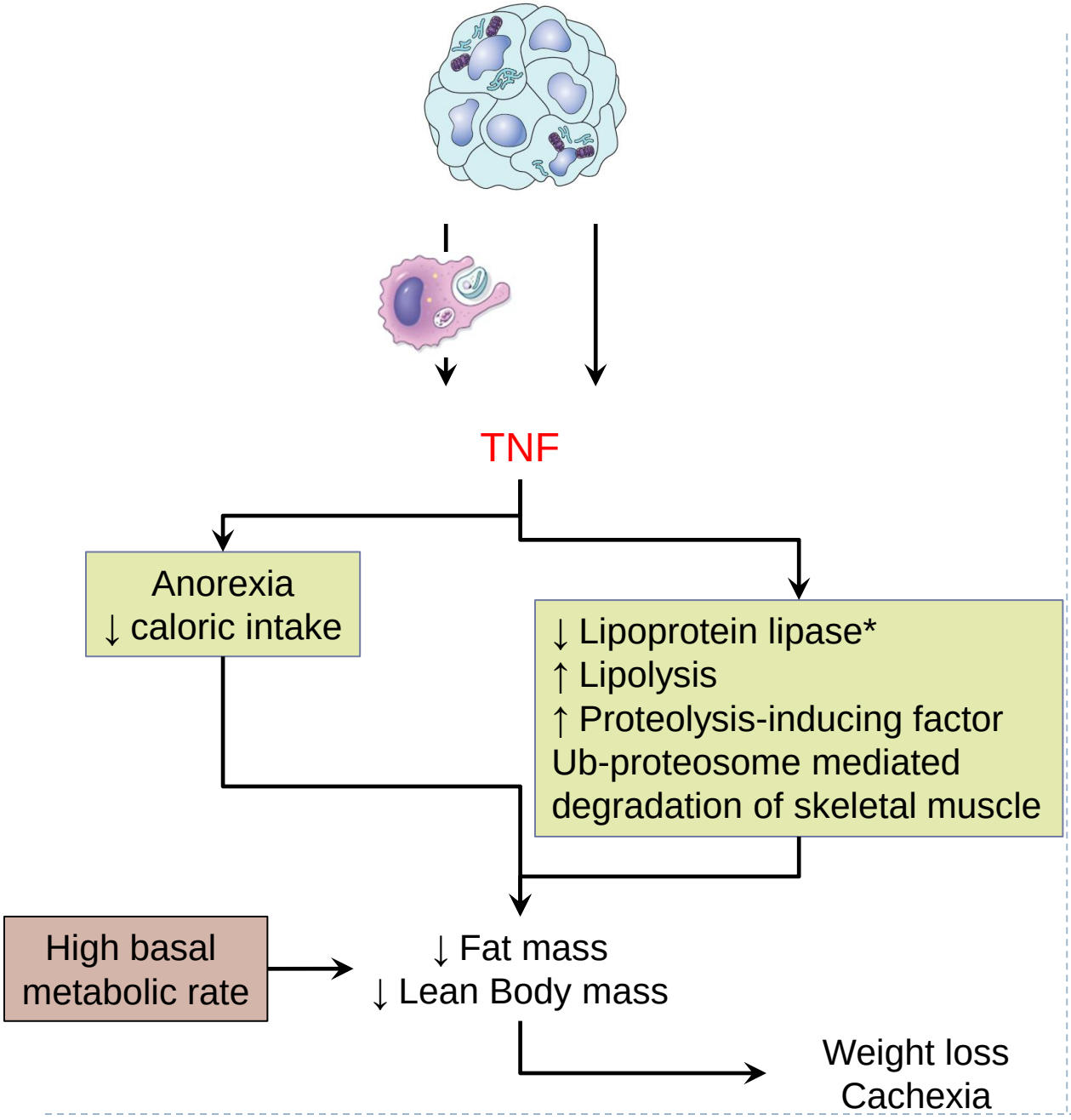


Clinical Aspects of Neoplasia

Tumor effects on host QUIZ

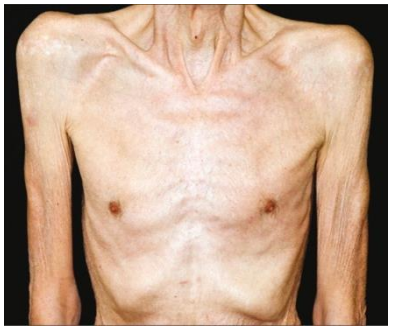
- Location
- Function
- Ulceration/bleeding/infection/rupture/infarction
- Cachexia

Cancer Cachexia



Correlation between size/spread and cachexia severity

Cachexia is **not** caused by tumor nutritional demands



Clinical Syndrome	Major Forms of Neoplasia	Causal Mechanism(s)/Agent(s)
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone secretion	Small cell carcinoma of lung; intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T cell leukemia/lymphoma Ovarian carcinoma	Parathyroid hormone–related protein, TGF-α, TNF, IL-1
Hypoglycemia	Fibrosarcoma Other mesenchymal sarcomas Hepatocellular carcinoma	Insulin or insulin-like substance
Carcinoid syndrome	Bronchial adenoma (carcinoid) Pancreatic carcinoma Gastric carcinoma	Serotonin, bradykinin
Polycythemia	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin
Nerve and Muscle Syndrome		
Myasthenia	Bronchogenic carcinoma, thymoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma, teratoma	
Dermatologic Disorders		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunologic; secretion of epidermal growth factor
Dermatomyositis	Bronchogenic and breast carcinoma	Immunologic
Osseous, Articular, and Soft Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma Other cancers	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Anemia	Thymoma	Immunologic
Others		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

Paraneoplastic syndromes

Not explained by primary tumor or metastasis

Hormones produced are not indigenous to the diseased tissue

Important in:

- Diagnosis
- Pathology
- Treatment strategy

Grading & Staging

- Based on differentiation
- Cytological
- I-IV
- Varies with cancer type

- Based on size & spread
- Clinical/radiographic/surgical assessment
- TNM: Tumor T1-T4
  Node N0-N3
  Metastasis M0-M1
- AJC combines all of the above into stages I-IV

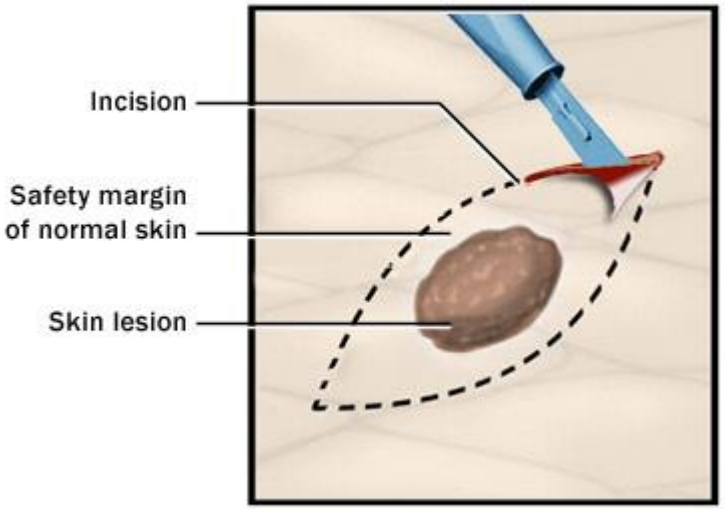
Grading & Staging (colorectal cancer)

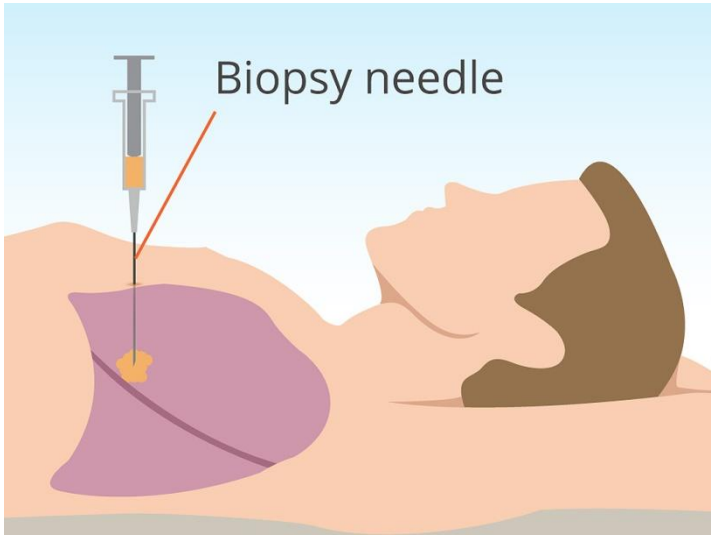
Designation	Description
Tumor	
Tis	In situ dysplasia or intramucosal carcinoma
T1	Tumor invades submucosa
T2	Tumor invades into, but not through, muscularis propria
T3	Tumor invades through muscularis propria
T4	Tumor invades adjacent organs or visceral peritoneum
Regional Lymph Nodes	
NX	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis or seeding of abdominal organs

Stage*	Tumor-Node-Metastasis (TNM) Criteria			5-Year Survival (%)
	T	N	M	
I	T1, T2	N0	M0	74
II				
IIA	T3	N0	M0	67
IIB	T4	N0	M0	59
III				
IIIA	T1, T2	N1	M0	73
IIIB	T3, T4	N1	M0	46
IIIC	Any T	N2	M0	28
IV	Any T	Any N	M1	6

Lab diagnosis

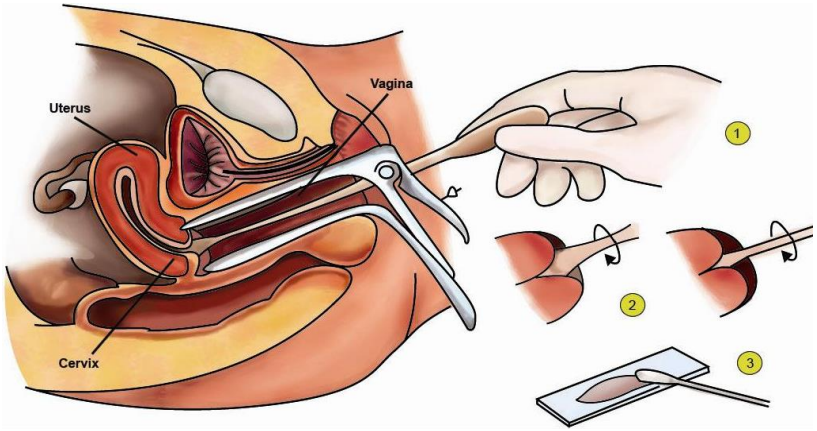
Biopsies

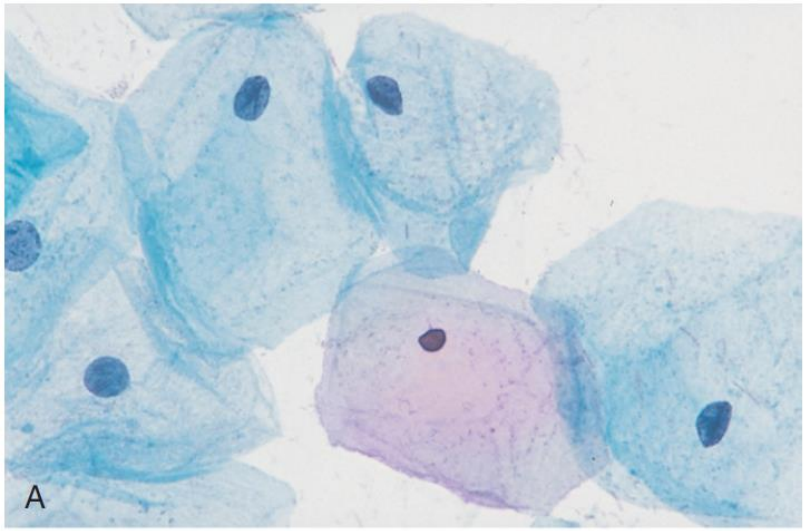


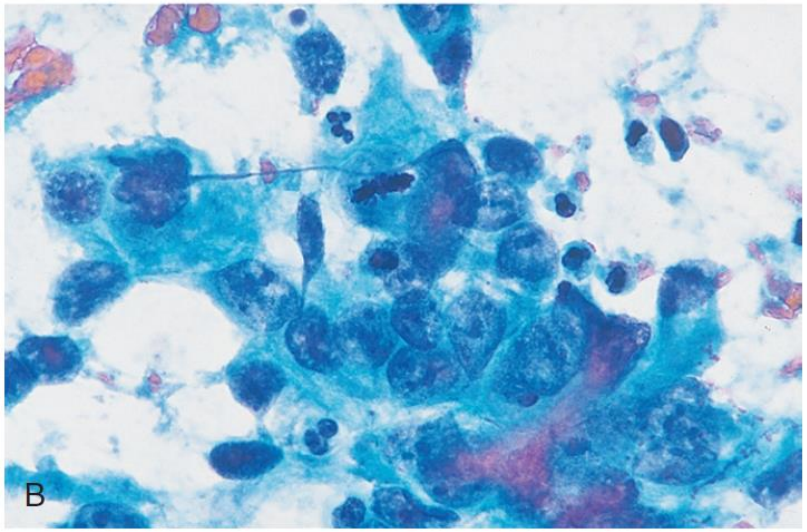


Excisional vs selective

Biopsies

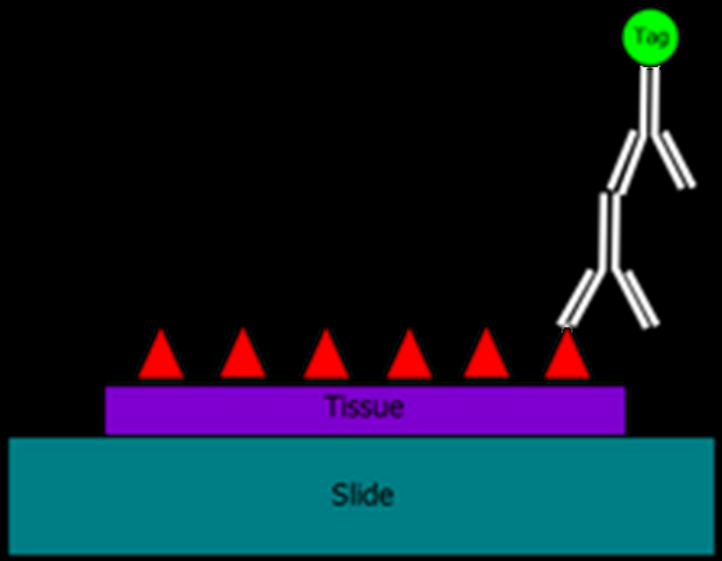




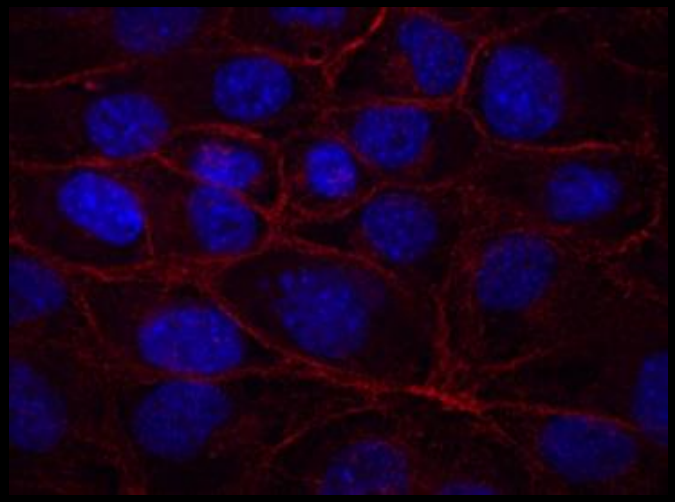


Neoplastic cells are less cohesive than other cells

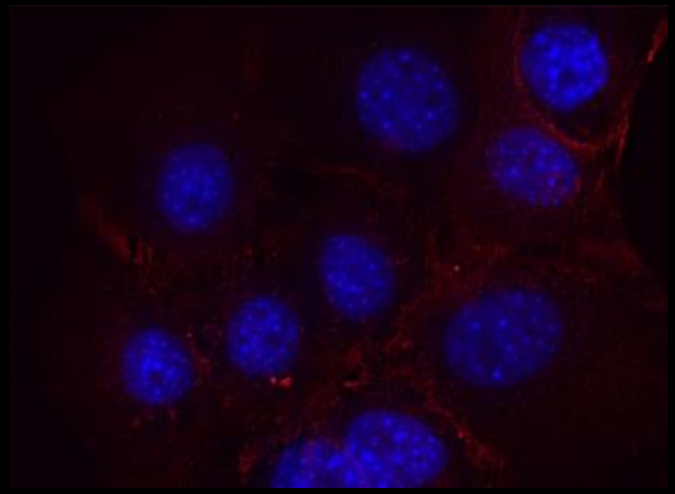
Immunocytochemistry/Immunohistochemistry

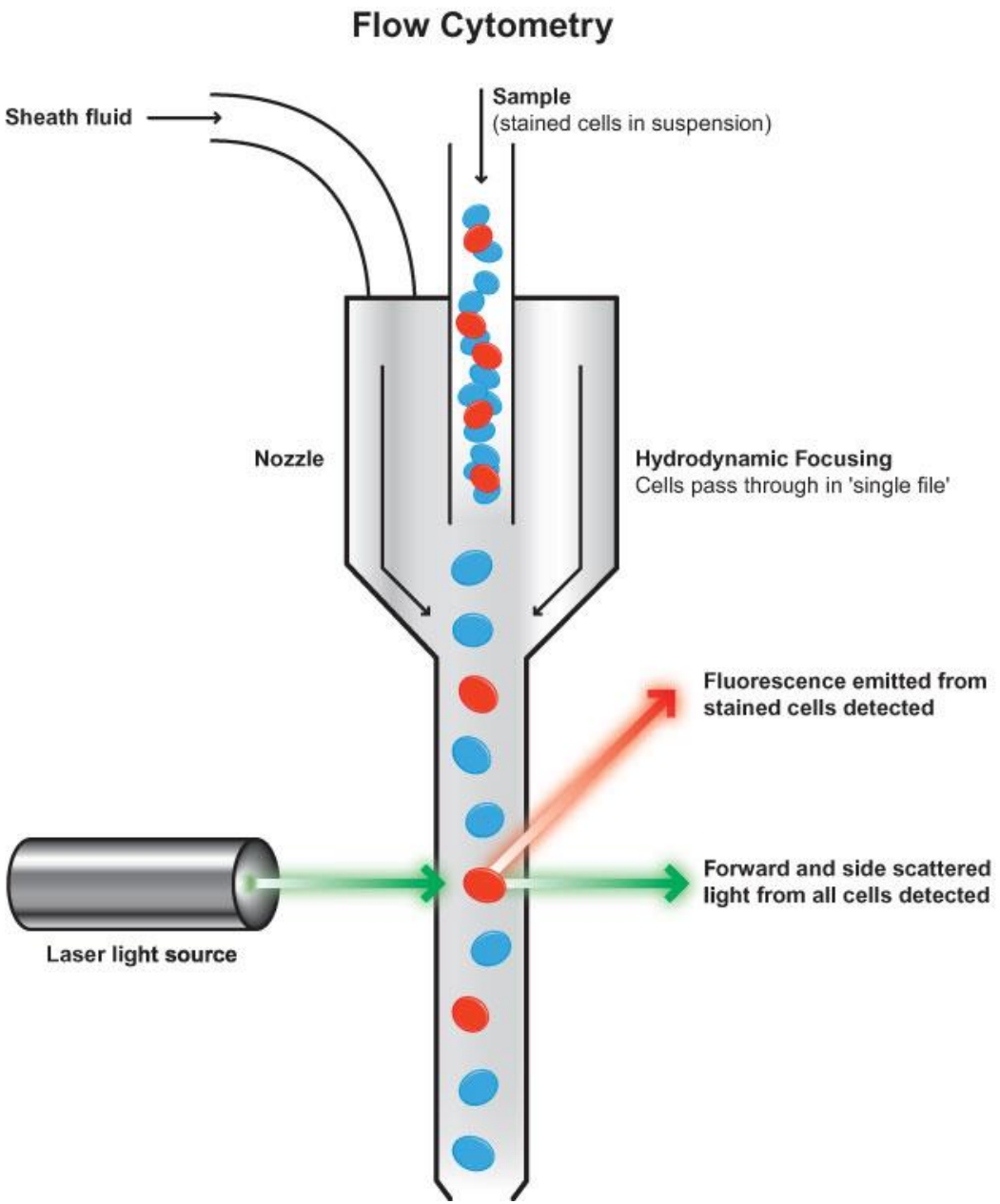


Control



TGFβ





Flow cytometry

Classification of leukemias and lymphomas

Molecular Techniques

- Diagnosis
- Genetic testing
- Prognosis
- Treatment decisions
- Response