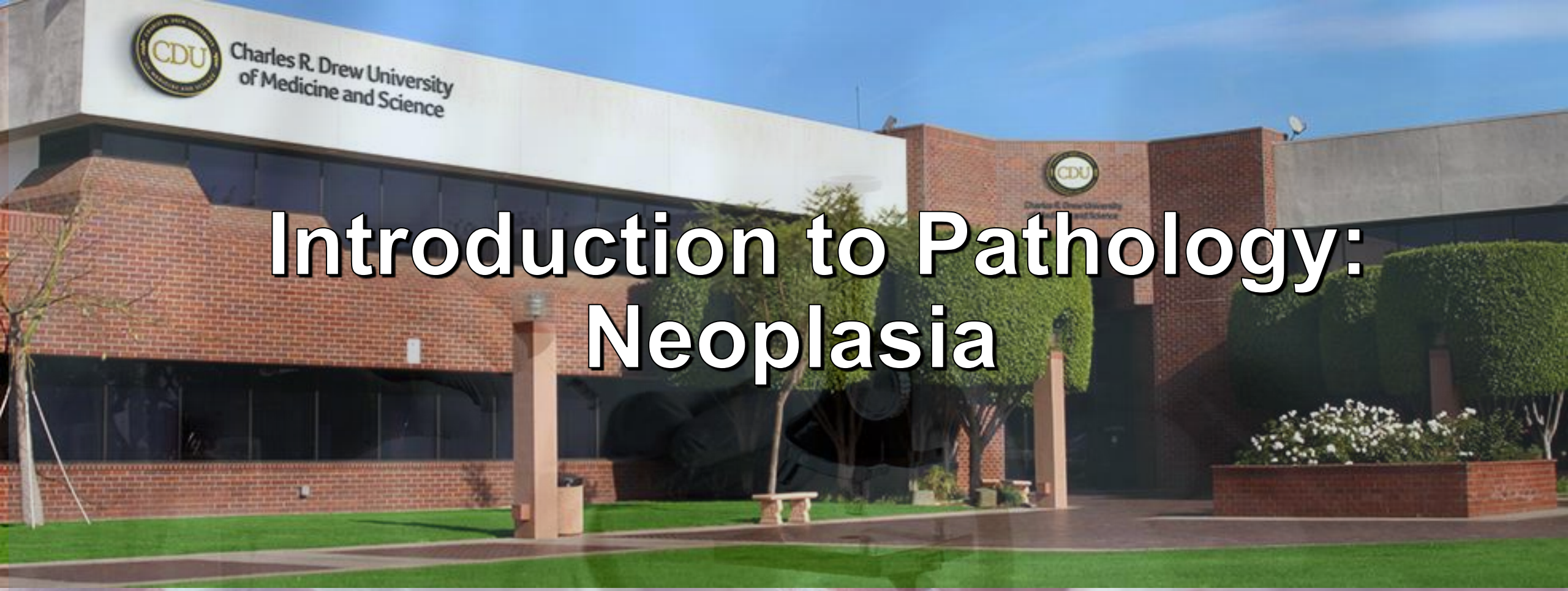


Introduction to Pathology: Neoplasia

Charles R. Drew University of Medicine and Science

A Private University with a Public Mission

FM 5 MED 718

Neoplasia

By the end of this section, you will be able to understand:

- **Epidemiology of Cancer**
- **Definition of Neoplasia & Nomenclature**
- **Inherited Cancer Syndromes and Systemic Effects of Cancer**
- **Hallmarks of Cancer: Biological & Molecular pathogenesis of Cancer**
- **Disrupted Systems in Cancer: Oncogenes; Tumor Suppressor Genes; Regulators of Apoptosis; Invasion and Metastasis**
- **Histologic Characteristics of Benign vs. Malignant Neoplasms**
- **Cancer Staging and Grading; Clinical characteristics**

Epidemiology of Cancer

Cancer is the **2nd** leading *cause of death* in adults and children.

Adults:

1) Cardiovascular disease
2) Cancer
3) Stroke

Children:

1)Accidents (preventable)
2) Cancer
3) Congenital defects

By Incidence	By Mortality
Breast (Women) Prostate (Men)	Lung (Men & Women)
Lung	Breast (Women) Prostate (Men)
Colorectal	Colorectal

Epidemiology of Cancer

- Geographic and Ethnic differences
- Esophageal cancer in Iranian women
- Gastric cancer in Japanese
- Skin cancer in northern Australia
- Types of lymphomas more common in Asian populations
- Migrant population studies: different factors influence the pathogenesis of cancer
- Hereditary Conditions Associated with an Increased Risk of Cancer

Influential factors of Cancer: Inherited vs. Acquired

- Acquired vs. Genetic predisposing conditions
- Carcinogens (damage cell DNA)
- Age
- Environment: Alcohol, Diet, Reproductive history
- Carcinogens: Chemicals; Viruses; Radiation
- Immunodeficiency
- Precursor lesions

Chemical Carcinogens

CHEMICALS		
Aflatoxins	Hepatocellular carcinoma	Derived from *Aspergillus*, which can contaminate stored grains
Alkylating agents	Leukemia/lymphoma	Side effect of chemotherapy
Alcohol	Squamous cell carcinoma of oropharynx and upper esophagus, pancreatic carcinoma, and hepatocellular carcinoma	
Arsenic	Squamous cell carcinoma of skin, lung cancer, and angiosarcoma of liver	Arsenic is present in cigarette smoke.
Asbestos	Lung carcinoma and mesothelioma	Exposure to asbestos is more likely to lead to lung cancer than mesothelioma.
Cigarette smoke	Carcinoma of oropharynx, esophagus, lung, kidney, and bladder	Most common carcinogen worldwide; polycyclic hydrocarbons are particularly carcinogenic.
Nitrosamines	Stomach carcinoma	Found in smoked foods; responsible for high rate of stomach carcinoma in Japan
Naphthylamine	Urothelial carcinoma of bladder	Derived from cigarette smoke
Vinyl chloride	Angiosarcoma of liver	Occupational exposure; used to make polyvinyl chloride (PVC) for use in pipes
Nickel, chromium, beryllium, or silica	Lung carcinoma	Occupational exposure

(Sattar, 2022, p. 25)

Infectious Agents linked to Cancer

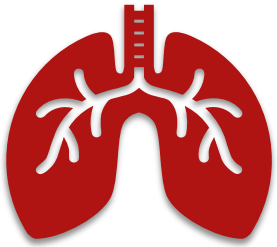
Agent	Cancers	Mechanisms
DNA viruses		
HPV	SCC of cervix, vulva, penis, tonsil (Subtypes: 16,18,31,33)	Oncoproteins that inactivate p53 &RB
EBV	B cell lymphomas; nasopharyngeal ca	Oncogenic signaling activation
HHV8	Kaposi sarcoma; B cell lymphomas	Activation of oncogenic signaling
RNA viruses		
Hepatitis C	Hepatocellular carcinoma	Causes chronic liver inflammation
Retroviruses		
HTLV1	Adult T cell leukemia	Proteins that cause expansion of infected T cells
Bacteria		
H. Pylori	Gastric ca; gastric B cell lymphoma	Chronic gastritis: repair and stimulation of chronic immune response
Parasites		
Schistosoma	Bladder ca	Chronic cystitis and repair
Liver fluke	Cholangiocarcinoma	Chronic inflammation and repair

Radiation as a Carcinogen

RADIATION		
Ionizing (nuclear reactor accidents and radiotherapy)	AML, CML, and papillary carcinoma of the thyroid	Generates hydroxyl free radicals
Nonionizing (UVB sunlight is most common source)	Basal cell carcinoma, squamous cell carcinoma, and melanoma of skin	Results in formation of pyrimidine dimers in DNA, which are normally excised by restriction endonuclease

(Sattar, 2022, p. 25)

Detection & Screening

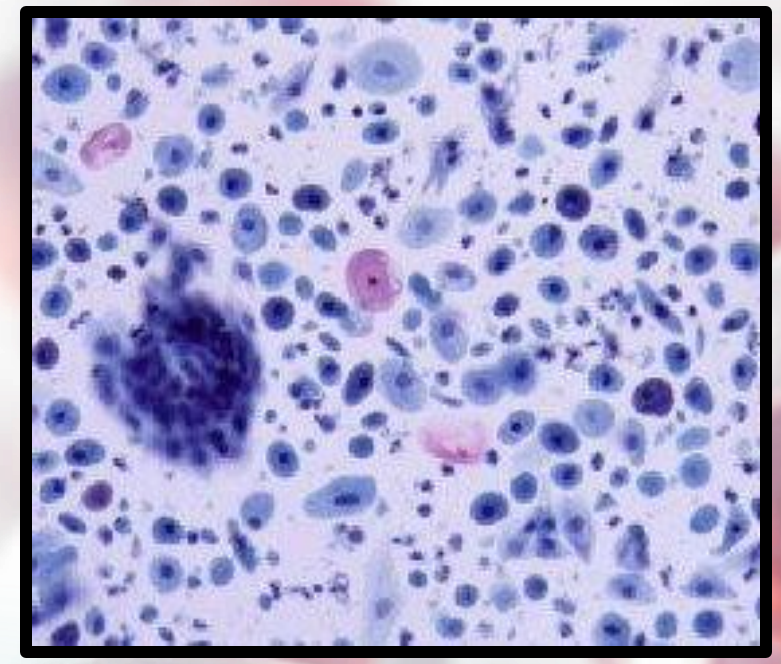


Early detection is our greatest way to serve our patients

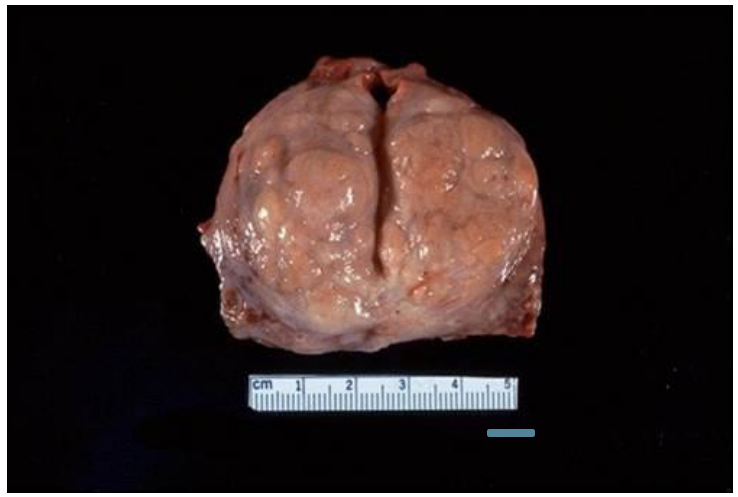
Survival rate of lung cancer has not changed despite better treatments because we don't have a good screening method for lung cancer

A readily available, relatively inexpensive tool to detect tumors and cancer early enough (before clinical symptoms) so that intervention can reduce morbidity and mortality (i.e., to catch dysplasia before it becomes malignant)

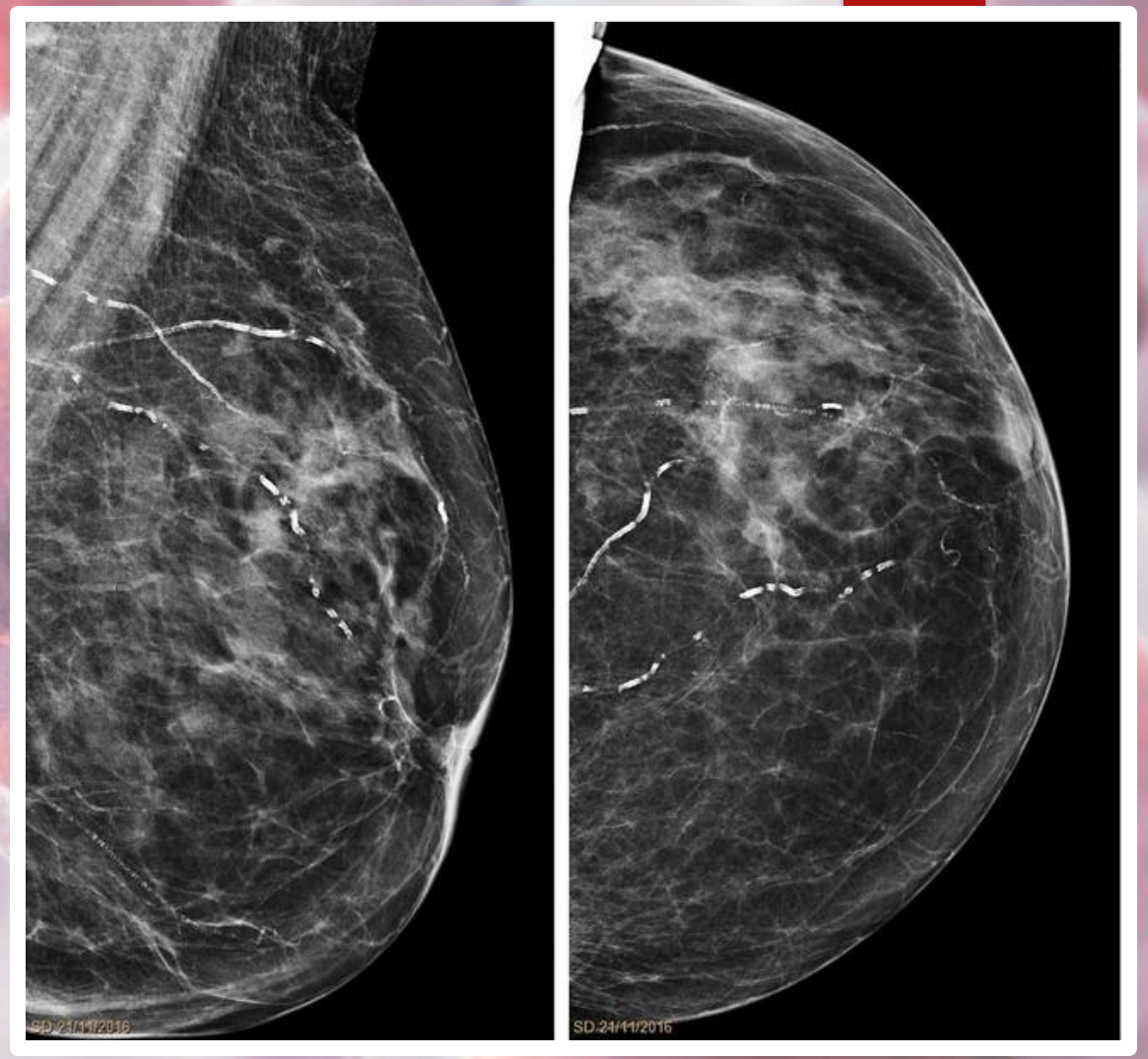
E.g. Pap smear, Mammography, PSA+DRE, Hemoccult + Colonoscopy



cervical pap smear



prostate



breast mammogram

Neoplasia

- **Neoplasia = new tissue growth**
- A neoplasm is **unregulated**, **irreversible** and **monoclonal**
- A “neoplasm” is a growth derived from cells that normally multiply, but have escaped the usual restraints on cell proliferation
- It is a disease of *cell growth* triggered by acquired or inherited *mutations* affecting a single cell and its progeny
- Distinct from hyperplasia and repair
- Neoplasms come in two flavors: *benign* and *malignant* (cancer)

Monoclonal

Neoplastic cells are derived from a single mother cell (a single progenitor cell)

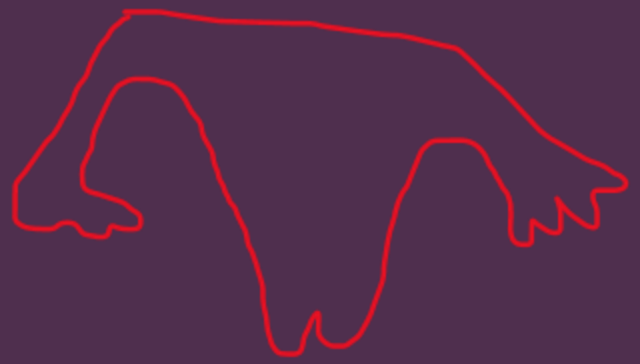
Clonality can be determined by G6PD isoforms (or androgen receptor isoforms

Clonality of B cells

uterus

cells

uterus

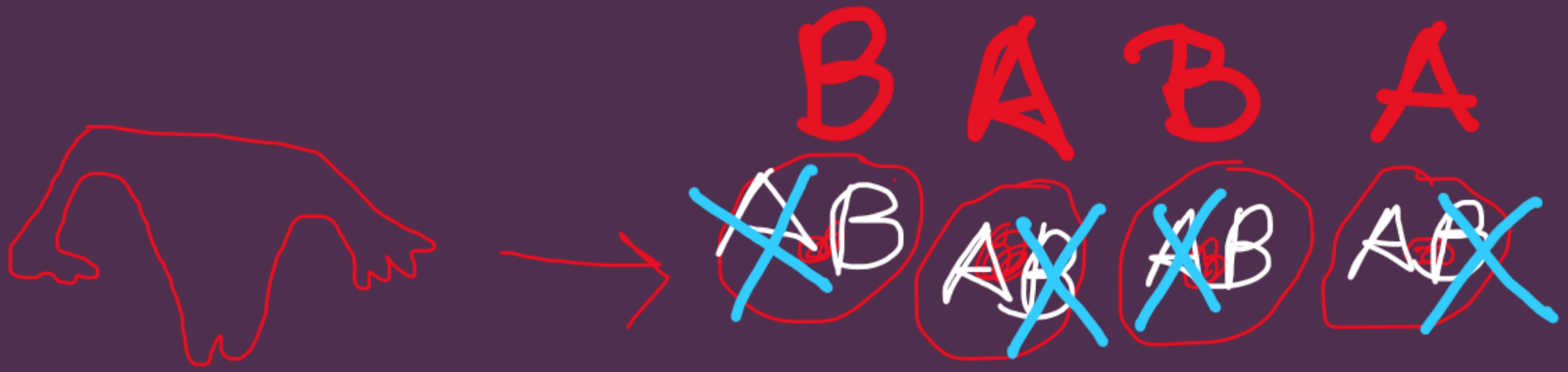


cells

G6PD

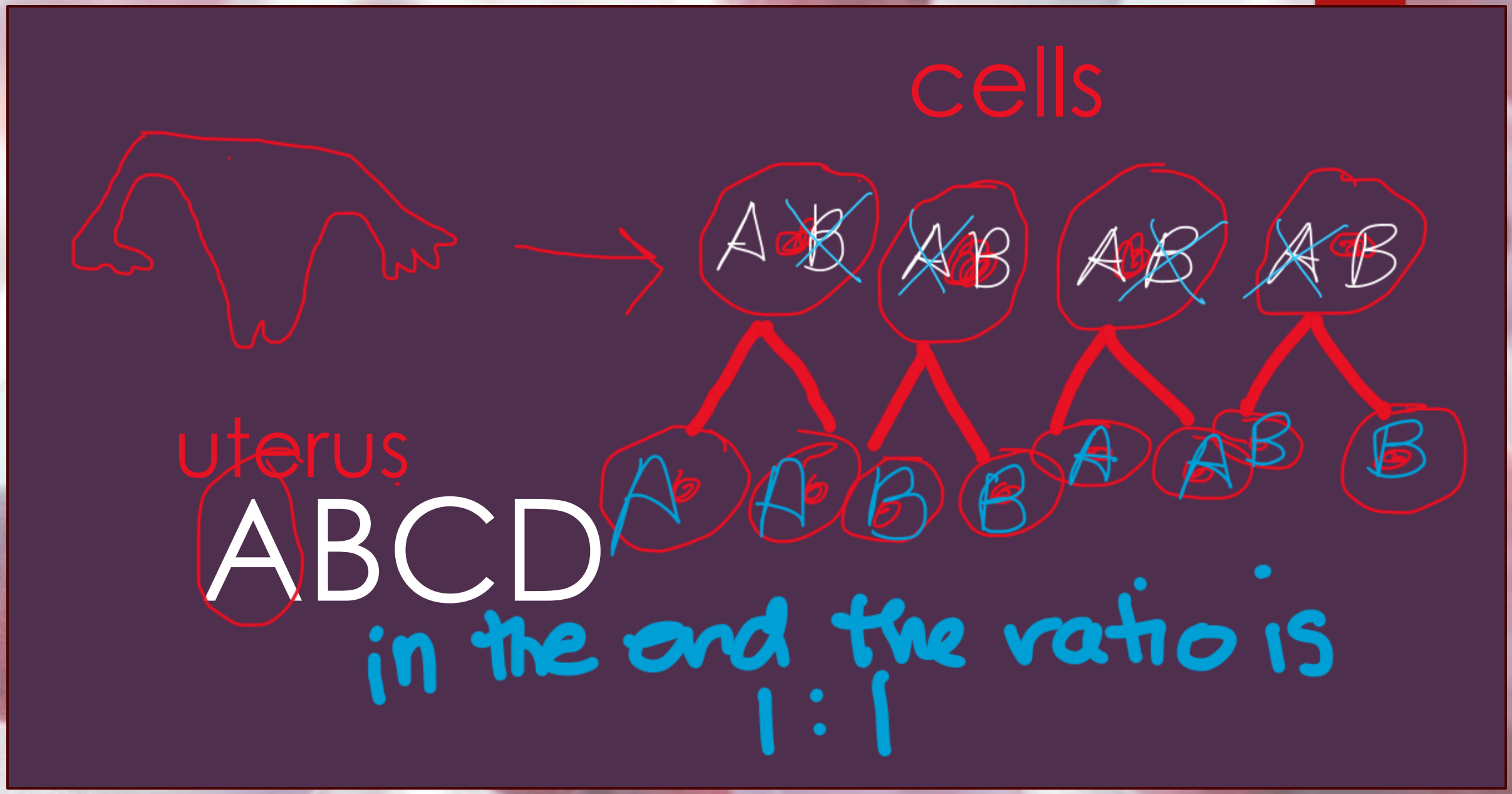
isoforms ABCD

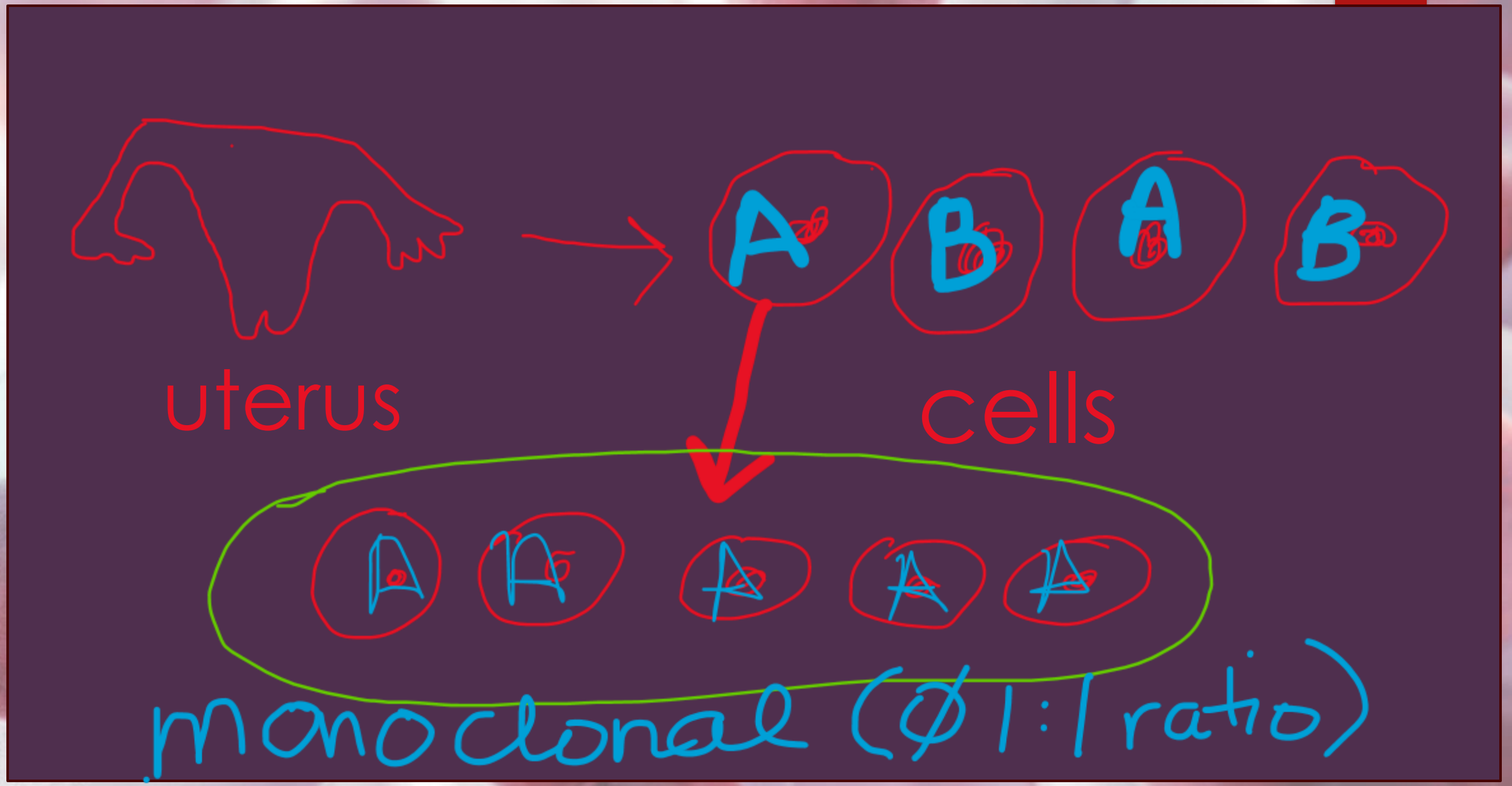
X-chromo inactivation is RANDOM



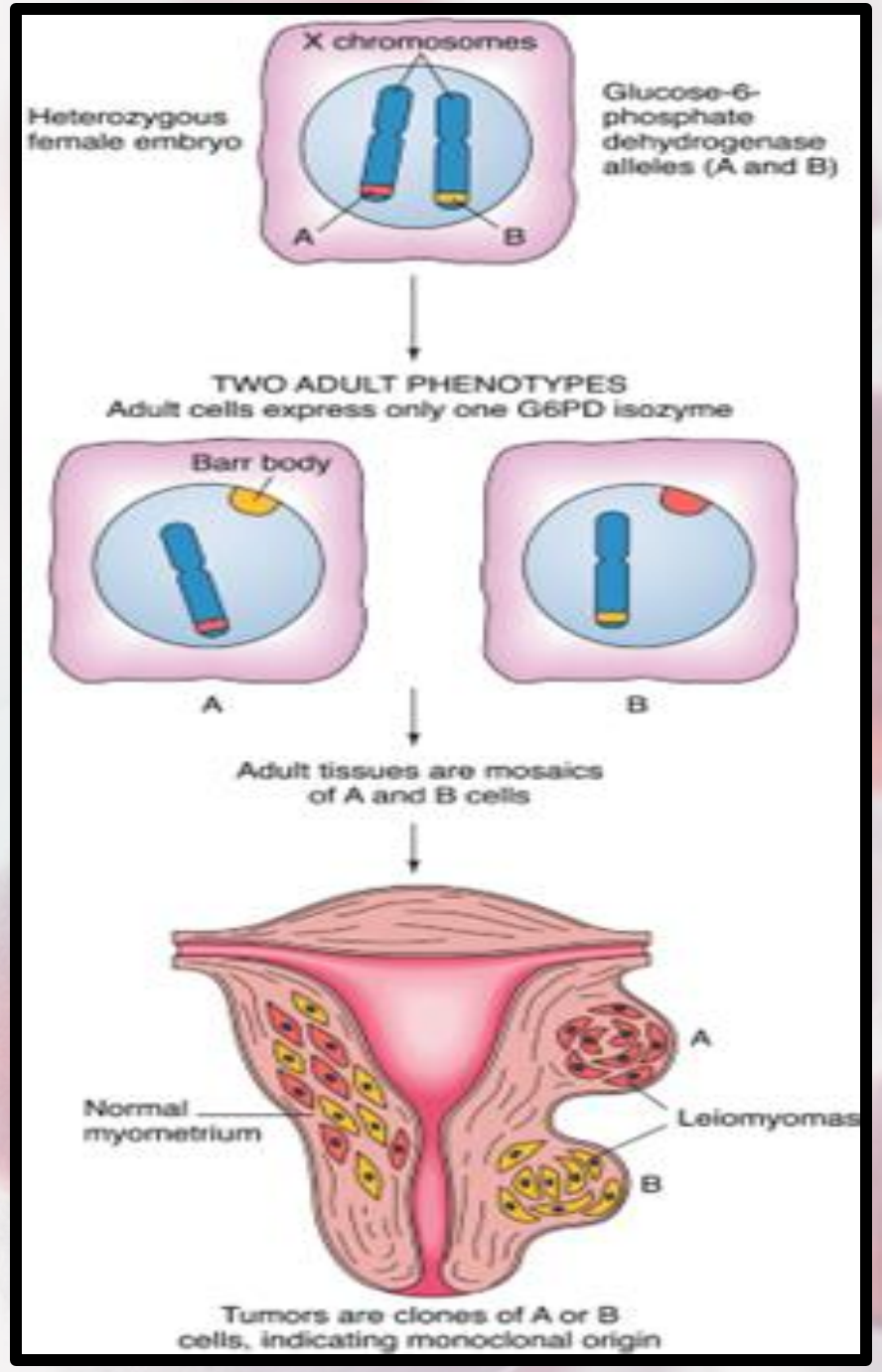
uterus cells

in the end, the ratio of G6PDA : G6PDB = 1 : 1 A:B


cells
uterus
ABCD
in the end the ratio is
1 : 1


A
B
A
B
uterus
cells
monoclonal (∅1:1 ratio)

Clonality



Growth from one mother cell to create "identical" daughter cells

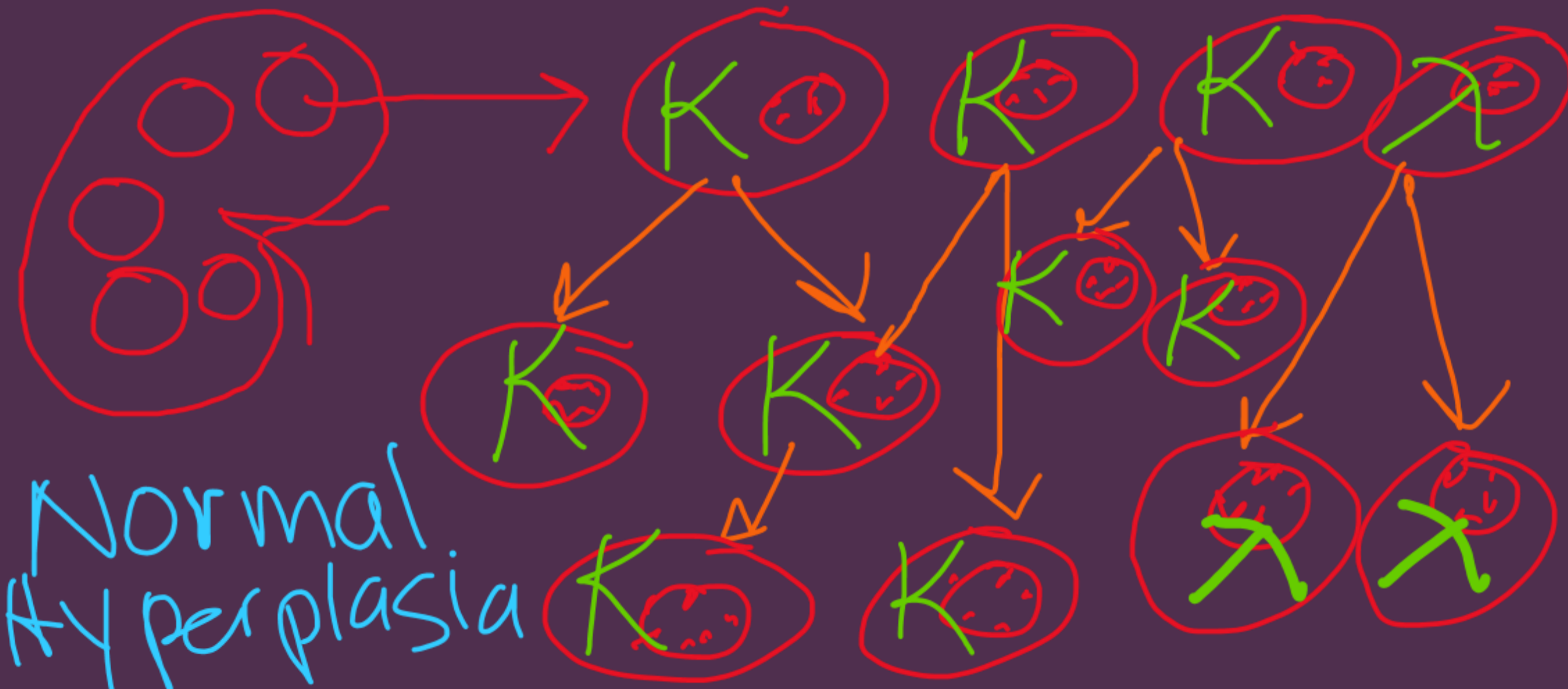
- Examples:
  - G6PD Isoforms: X-linked
    - Endometrial myocytes develop G6PD isoforms from both parents (A&B). When dividing normally, there is a mixture of isoforms in the ensuing daughter cells. If it is a neoplasm (eg. a fibroid, "myoma"), the daughter cells only have one isoform and is "homozygous" for that isoform.

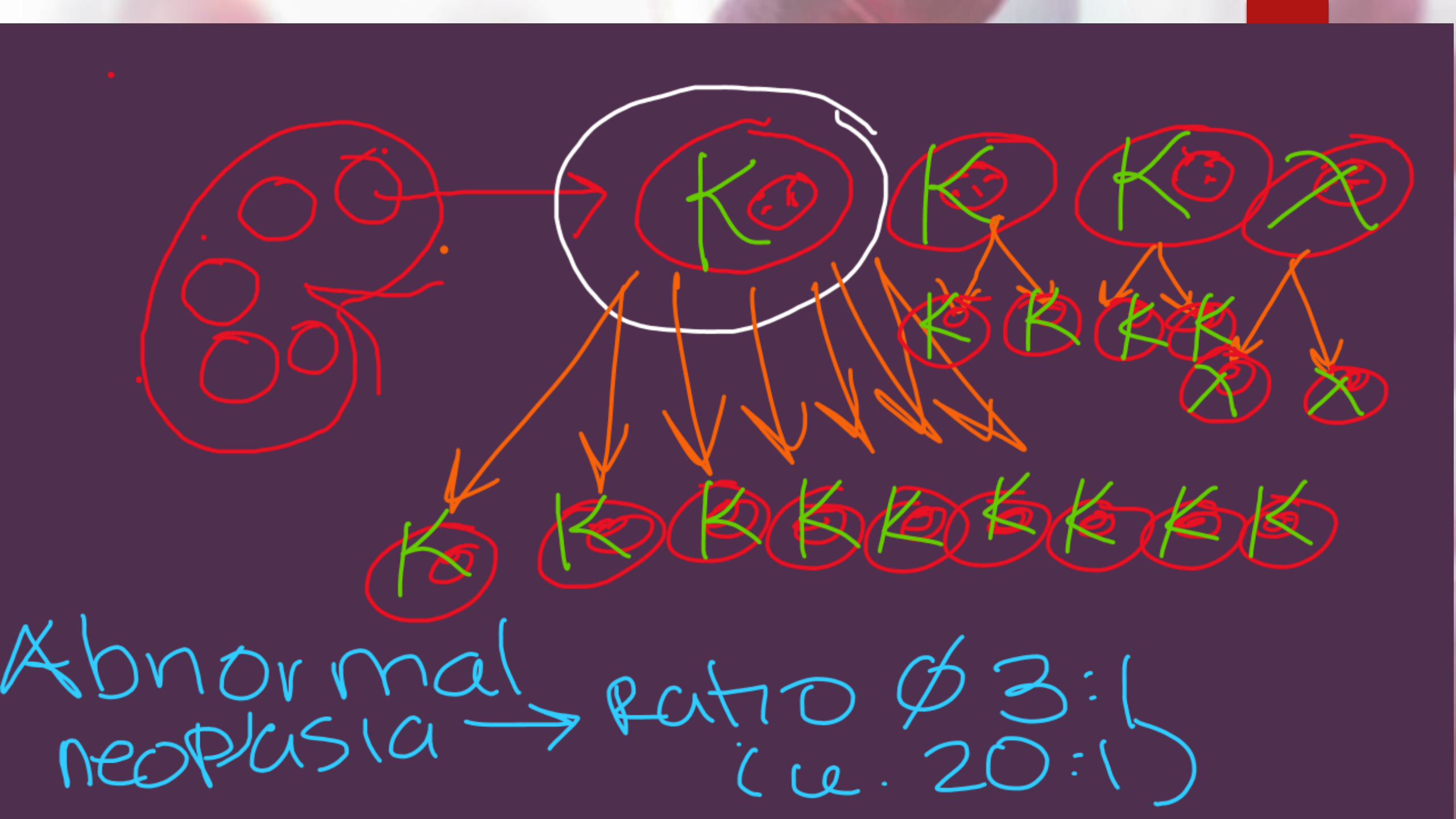
Clonality Of B Cells is determined by Immunoglobulin Light Chain Phenotype

Enlarged lymph nodes:

- Proliferation of lymphocytes: reactive hyperplasia (infection/inflammation); Kappa: Lambda ratio = 3:1
- Proliferation of lymphocytes: monoclonal proliferation of lymphocytes which will show a proliferation of one light chain over the other (i.e. a light chain ratio of 20:1)= lymphoma
- Metastatic cancer

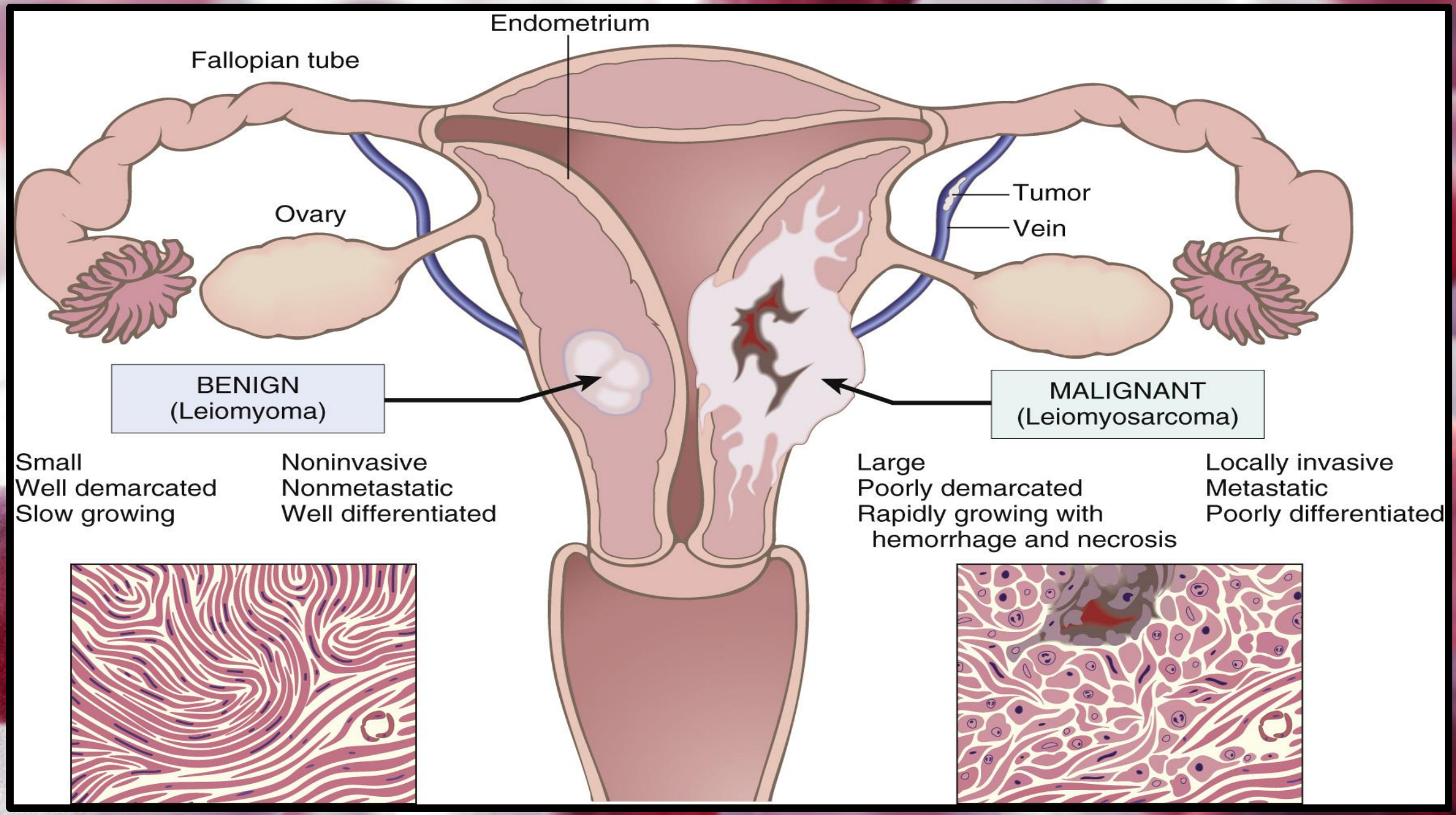
Normal → K : λ = 3 : 1


Normal
Hyperplasia
Ratio→
6:2 = 3:1


Abnormal
neoplasia → ratio ♀ 3:1
(i.e. 20:1)

Neoplastic tumors can be either benign or malignant

- **Benign** tumors remain localized and do not metastasize
- **Malignant** tumors (cancers) invade locally and have the *potential* to metastasize
- Classifying a tumor as benign or malignant is a prediction of its eventual biological behavior and clinical outcome
- ***Remember both benign and malignant tumors are MONOCLONAL***


Endometrium
Fallopian tube
Ovary
Tumor
Vein
BENIGN
(Leiomyoma)
MALIGNANT
(Leiomyosarcoma)
Small
Well demarcated
Slow growing
Noninvasive
Nonmetastatic
Well differentiated
Large
Poorly demarcated
Rapidly growing with
hemorrhage and necrosis
Locally invasive
Metastatic
Poorly differentiated

Clinical Behavior Exceptions

not all “malignant” tumors metastasize (e.g., basal cell carcinoma of the skin)

a benign tumor does not mean it is not lethal: tumors of the brain, regardless of classification, can be just as life-threatening, as they can locally invade and cause death by compromising adjacent vital structures

Tumor Nomenclature

Tissue Lineage		
Epithelium	Lines surfaces	Skin, urogenital tract, gastrointestinal tract
Mesenchyme	Soft tissue	Fat, bone, connective tissue, blood vessels
Lymphoid	Lymph nodes	Immune cells: B cells, T cells
Melanocytic	Neural crest origin	Melanocytes

"-oma"

- The primary descriptor of tumors is its cell of origin followed by"**-oma**" suffix
- Based mostly on lineages of differentiation:
  - *Carcinoma*: malignant *epithelial* tumors (e.g. squamous cell carcinoma)
  - *Sarcoma*: malignant *mesenchymal* tumors (e.g. liposarcoma)
  - *Lymphoma*: malignant tumors of lymph nodes (e.g. follicular lymphoma)
  - *Melanoma*: malignant proliferation of melanocytes
- Poorly understood histogenesis may be given eponyms, (e.g. Ewing Sarcoma)

Tumor Nomenclature

Tissue Lineage	Benign	Malignant
Epithelium	Adenoma Papilloma	Adenocarcinoma Papillary carcinoma
Mesenchyme	Lipoma	Liposarcoma
Lymphocyte		Lymphoma/ Leukemia
Melanocyte	Nevus (mole)	Melanoma

Progression to Malignancy

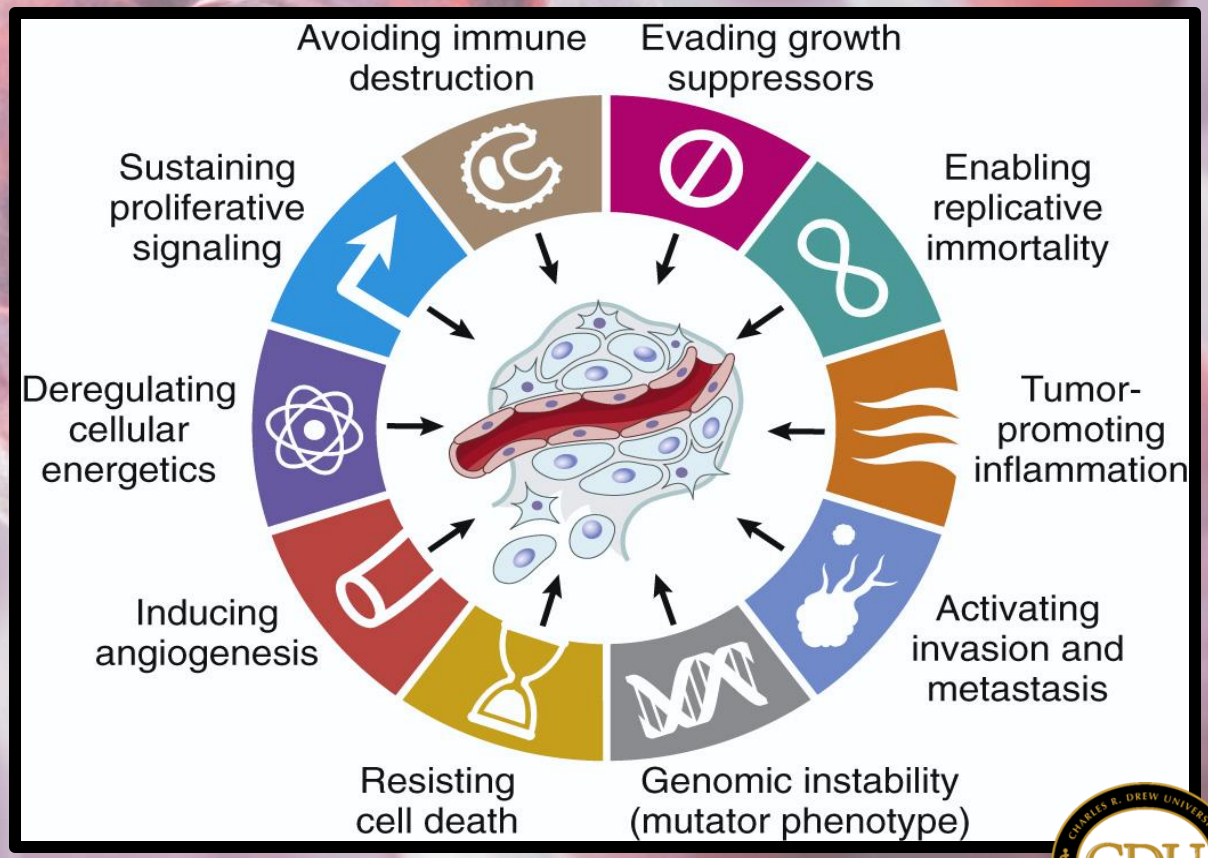
- Cancer starts with a *single* mutated cell
- Cells mutate due to genetic changes that affect cell cycle regulation, DNA repair, apoptosis, etc
- There is clonal expansion of a single precursor cell (genetic damage is passed on: the tumor shares the same set of mutations)
- From minute atypical appearances, to dysplasia, to carcinoma-in-situ (when early cancers do not yet penetrate the basement membrane)
- Approximately **30 divisions** occur before the earliest clinical symptoms arise

Cell Divisions: More Mutations

- Overtime, more mutations happen allowing for unregulated growth and higher likelihood of invasion and metastatic ability: Darwinian process (survival of the fittest)
- Lifetime risk of developing cancer depends on organ specific stem cell divisions for maintenance of that particular organ
- Only 35% of cancer is due to environment and hereditary factors; 65% is random, due to chance
- Cancers that do not produce symptoms until late in the disease will have undergone additional divisions and mutations
- Cancers that are detected late tend to have poor prognosis (Eg. Ovarian, Pancreatic, Lung)

Hallmarks of Cancer: Distinguishing Factors

- Unregulated Cellular Proliferation
- Cellular Immortalization
- Evasion of Programmed Cell Death
- Angiogenesis
- Inactivation of Tumor Suppressors
- Invasion and Metastasis



Etiology of Cancer: DNA Mutations

The incidence of cancer increases with age. Why? Because most cancers develop due to multiple mutations that accumulate in dividing cells.

- DNA mutations disrupt key regulatory systems: allowing tumor promotion (growth) and progression (spread)
- These genetic changes that affect cell-cycle regulation also affect DNA repair and telomerase activity which are critical to tumor development and disrupt apoptosis

Familial cancer syndromes

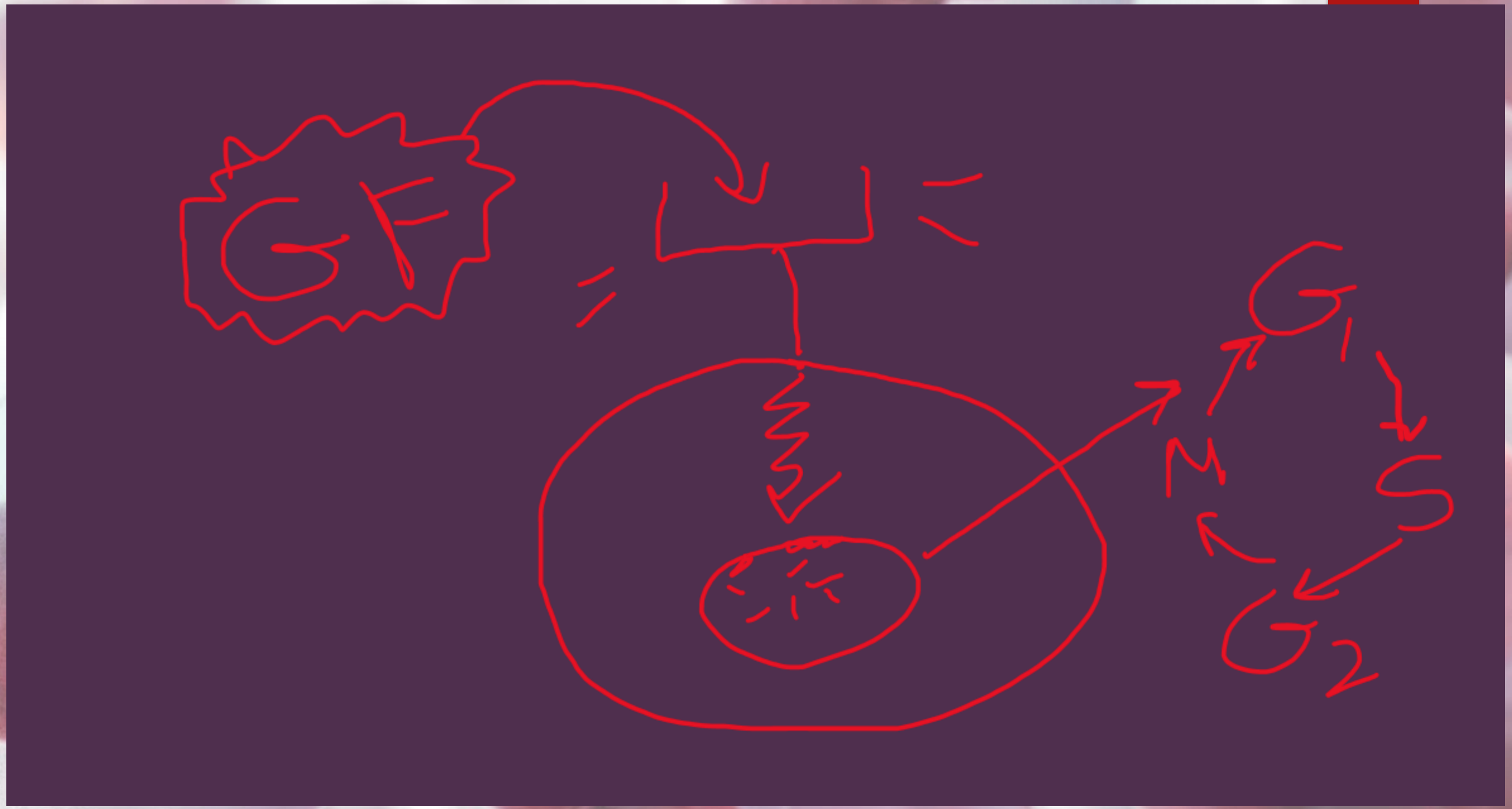
INHERITED DISORDER	*GENE*	*FUNCTIONAL DEFECT*
Retinoblastoma	RB	Loss of cell cycle control
Li-Fraumeni syndrome	TP53	Increased genomic instability
Melanoma	P16-INK4A	Loss of cell cycle control
Familial adenomatous polyposis/ colon cancer	APC	Increased *Wnt* pathway signaling
Breast & ovary tumors	BRCA 1 & 2	Increased genomic instability
Hereditary nonpolyposis colon cancer	MSH2, MLH1, MSH6	Increased genomic instability
Nevoid basal cell carcinoma syndrome	PTCH1	Increased *Hedgehog* pathway signaling

Disrupted Systems: Gain of Function vs. Loss of Function

Proto-oncogenes*→*Oncogenes*:** activate specific mutations that ***stimulate passage through the cell cycle (GOF)

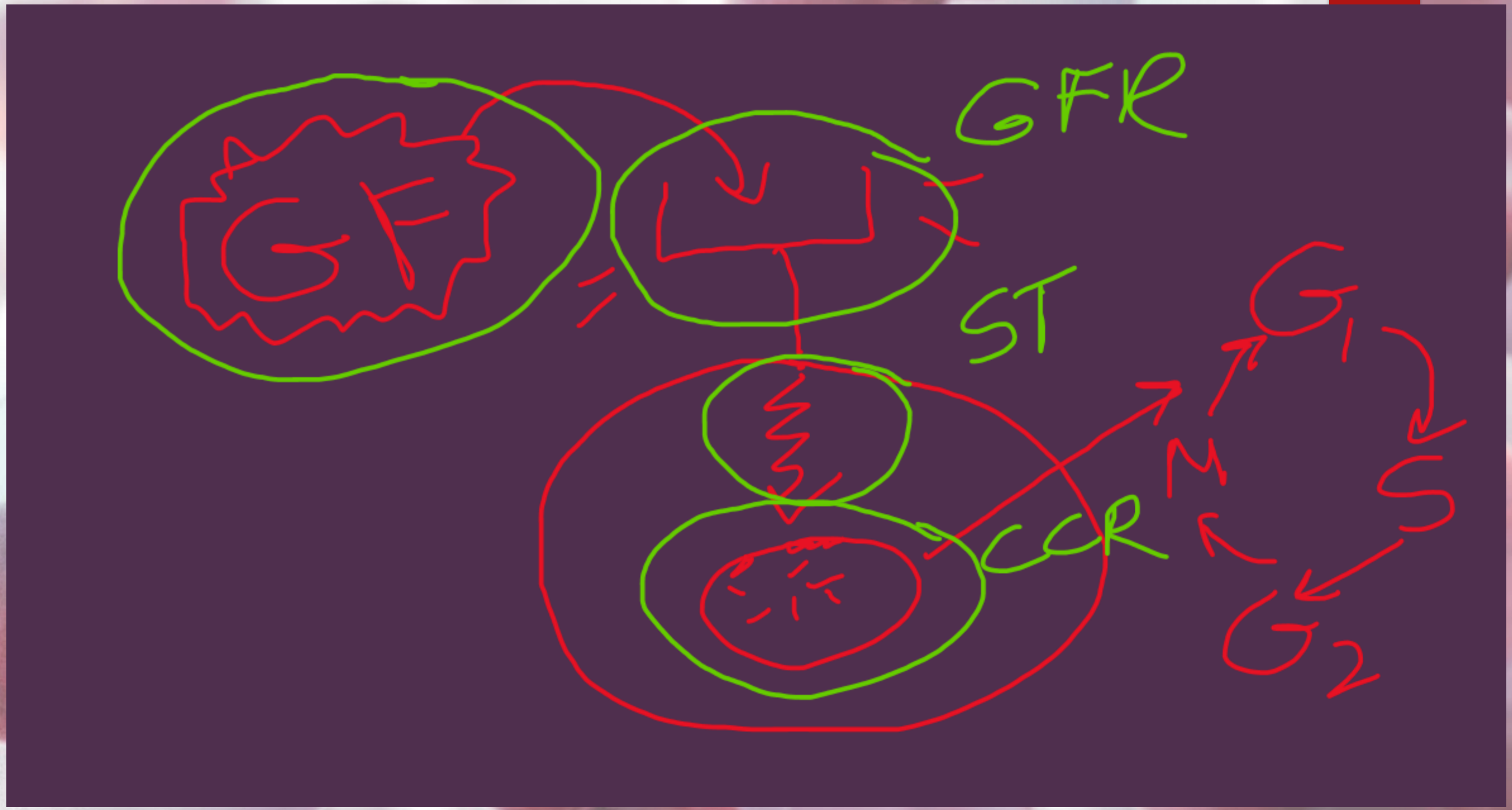
Tumor suppressor genes*: *prevent tumors from forming (LOF)

Regulators of *apoptosis*: *prevent* programmed cell death (LOF)


GF
G1
S
G2
M

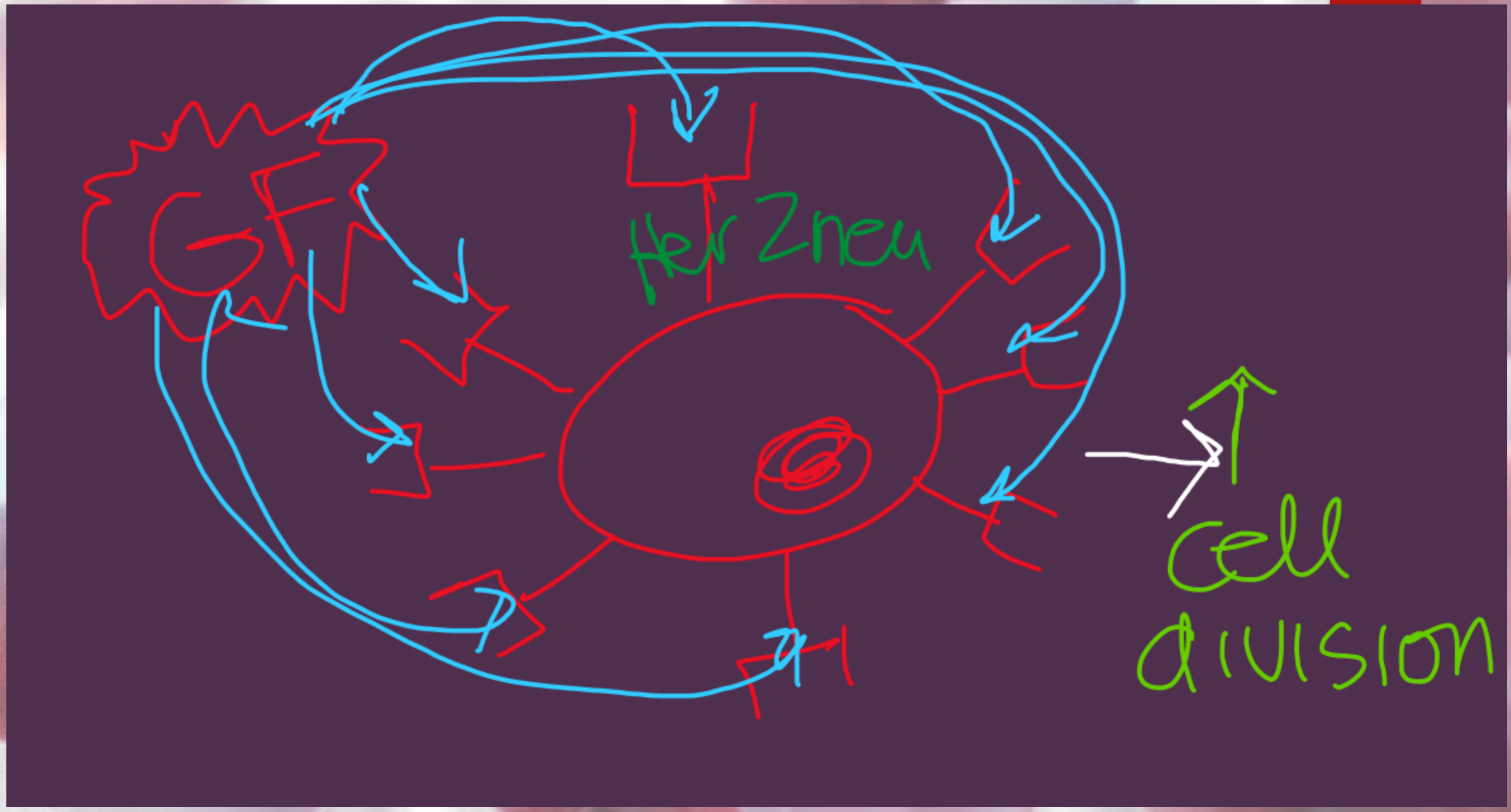
Proto-Oncogenes

- Growth Factors (GF)
- Growth Factors Receptors (GFR)
- Signal Transducers (SD)
- Cell Cycle Regulators (CCR)


GFR
GF
ST
CCR
M
G1
S
G2

GROWTH FACTOR			
PDGFB	Platelet-derived growth factor	Overexpression, autocrine loop	Astrocytoma
GROWTH FACTOR RECEPTORS			
ERBB2 [HER2/neu]	Epidermal growth factor receptor	Amplification	Subset of breast carcinomas
RET	Neural growth factor receptor	Point mutation	MEN 2A, MEN 2B and sporadic medullary carcinoma of thyroid
KIT	Stem cell growth factor receptor	Point mutation	Gastrointestinal stromal tumor
SIGNAL TRANSDUCERS			
RAS gene family	GTP-binding protein	Point mutation	Carcinomas, melanoma, and lymphoma
ABL	Tyrosine kinase	t(9;22) with BCR	CML and some types of ALL
NUCLEAR REGULATORS			
c-MYC	Transcription factor	t(8;14) involving IgH	Burkitt lymphoma
N-MYC	Transcription factor	Amplification	Neuroblastoma
L-MYC	Transcription factor	Amplification	Lung carcinoma (small cell)
CELL CYCLE REGULATORS			
CCND1 (cyclin D1)	Cyclin	t(11;14) involving IgH	Mantle cell lymphoma
CDK4	Cyclin-dependent kinase	Amplification	Melanoma

(Sattar, 2022, p. 26)


GF
Her2neu
cell
division

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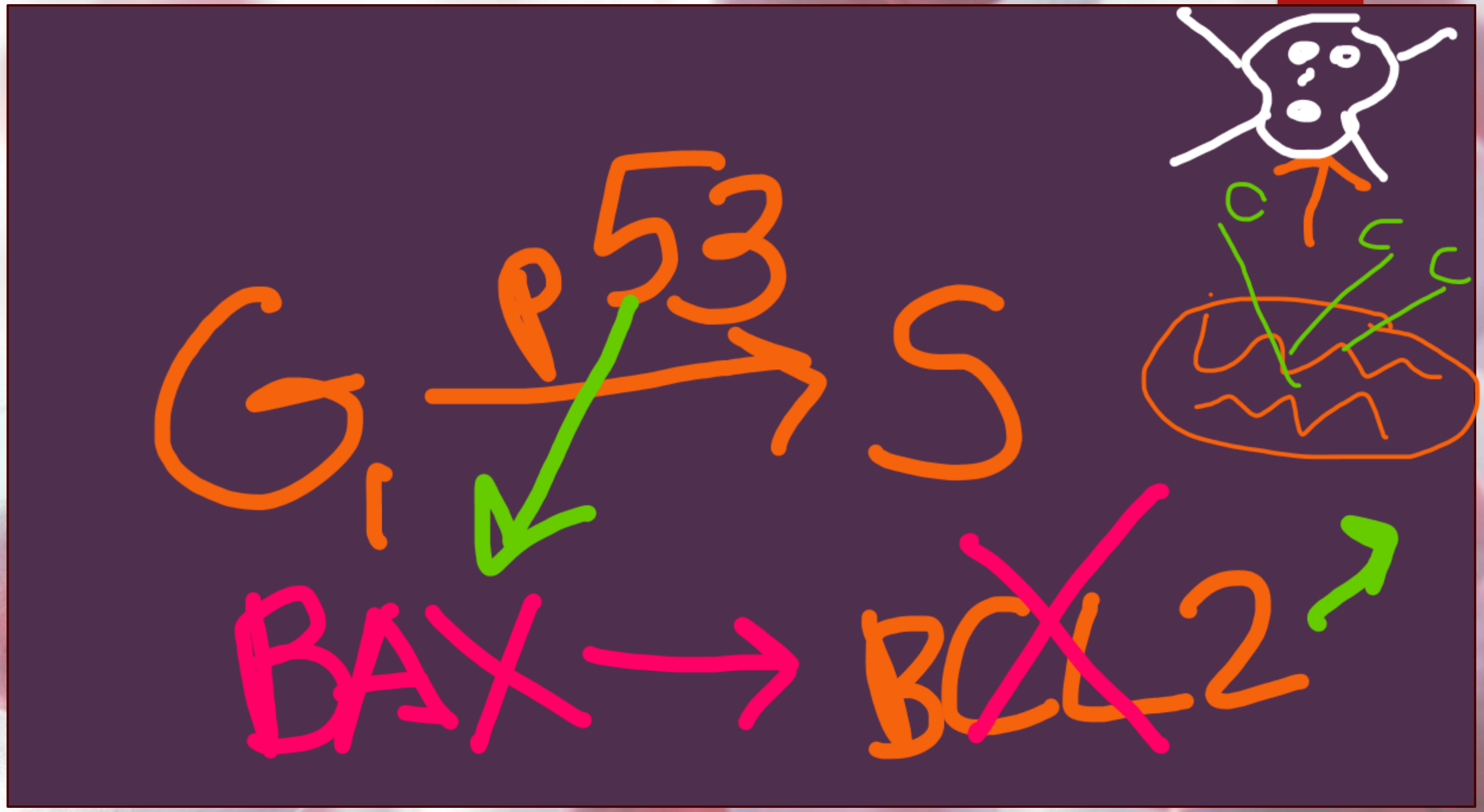
(Sattar, 2022, p. 26)

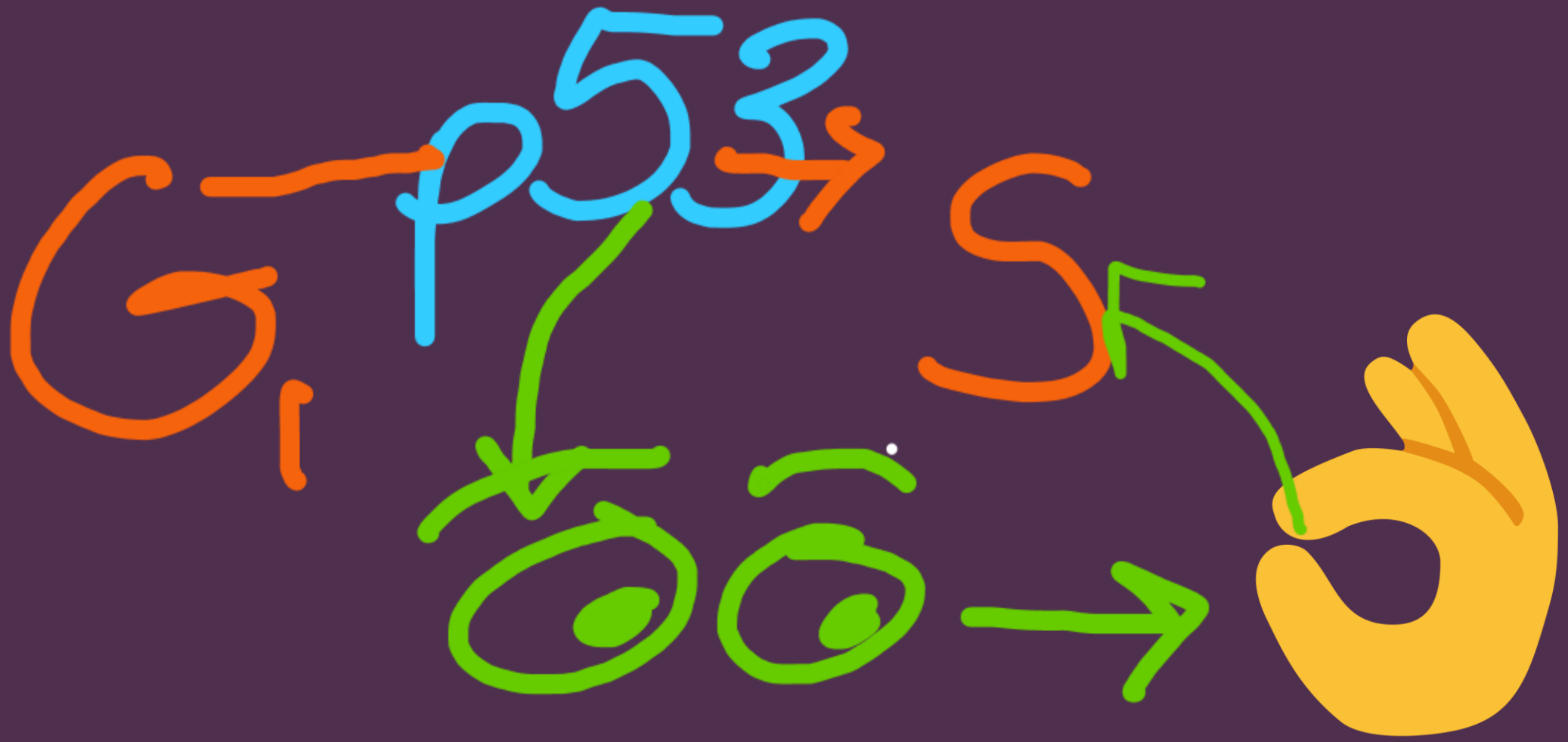
Tumor Suppressor Genes

- Regulators of cell growth
- Mutations in them cause "*loss of function*" (LOF)
- No brakes…tumors grow
- **p53 & Rb**

P53: "Guardian of the Genome"

- Found in >50% of cancers
- Thwarts neoplastic transformation
- Growth arrest (& repair), senescence, apoptosis
- In response to DNA damage, p53 *slows* the cell cycle and upregulates DNA repair enzymes (giving it time to repair the damage)
- If repair is not possible, then p53 induces *apoptosis*
- Both copies of tumor suppressor genes must be knocked out for tumor formation (Knudson's 2 Hit Hypothesis)
- Germline mutations in p53→Li-Fraumeni Syndrome (increased risk of multiple carcinomas and sarcomas)


G1
P53
S
BAX
BCL-2

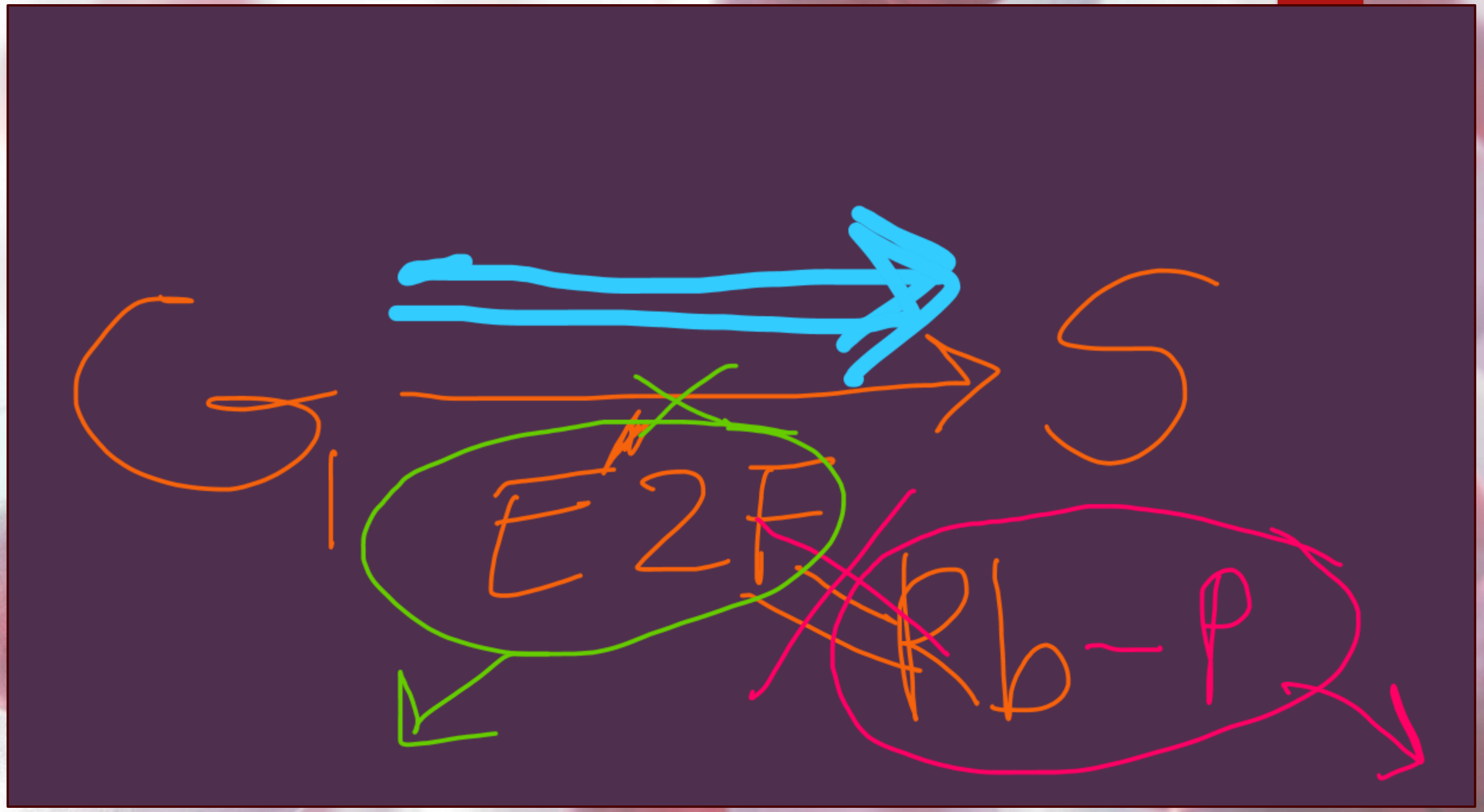

G1
p53
S
G2
M

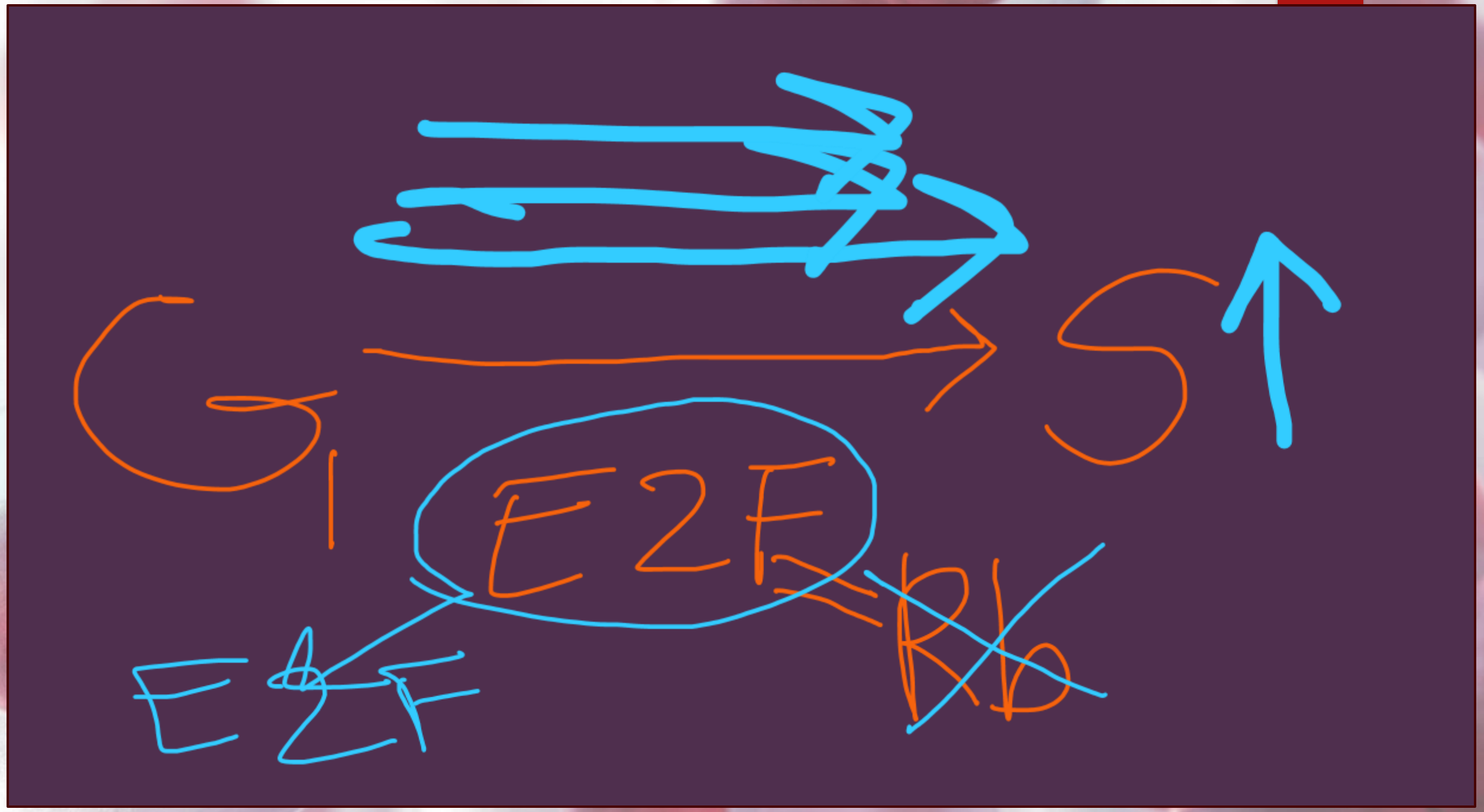
Tumor Suppressor Genes: RB

- Loss of Rb normal function
- Rb regulates progression from G1 to S phase
- A mutation in Rb, will allow the cell cycle to go from G1 to S phase easily, resulting in the formation of a tumor

P53 Regulates Cell Cycle Progression (G1->S)

- In response to DNA damage, p53 slows the cell cycle and upregulates DNA repair enzymes
- If repair is not possible, p53 induces apoptosis
- Both copies of p53 must be knocked out for tumor formation (Knudsen's Hypothesis)
- Germline mutations result in Li-Faumeni syndrome, Increased risk of carcinomas and sarcomas


G1
S
E2F
Rb-P


G1
S1
E2F
E2F
Rb

Retinoblastoma gene (Rb)

- Rb *inhibits* progression of the cell cycle from ***G1 to S***
- Rb binds E2F: It "holds" E2F transcription factor, which is necessary for the transition from G1 to S
- E2F is released when Rb is phosphorylated by CyclinD / CDK4 complex (protein phosphorylator)
- If there is a mutation in Rb, then E2F is "free", which allows for G1→S, and cell can divide = **uncontrolled progression through the cell cycle**

Rb Gene

- Both copies of Rb must be knocked out for tumor (Knudsen's 2 Hit Hypothesis)
- Sporadic mutation: unilateral retinoblastoma (very rare)
- Germline mutation: (familial retinoblastoma): bilateral retinoblastoma; osteosarcoma (more likely)

Regulators of Apoptosis

- Programmed cell death
- Cancer evades cell death (apoptosis)
- Apoptosis is highly regulated
- Apoptosis is usually prevented in a normal cell but promoted in a mutated cell
- How cancer avoids apoptosis:
  - Incapacitates the apoptotic intrinsic pathway via BCL 2
  - Loss of TP53 function (via MDM2)

Regulators of Apoptosis: BCL 2

- Normally, it stabilizes the mitochondrial membrane, so that cytochrome C cannot be released
- If BCL2 gets disrupted, cytochrome c leaks out of the mitochondria, which then activates caspases, which then results in apoptosis

Regulators of Apoptosis: BCL2

BCL2 protects transformed lymphocytes from *apoptosis*

How? It stabilizes the mitochondrial membrane, blocking release of cytochrome c.

Cytochrome c activates caspases, which would then activate apoptosis

Increase in BCL2 = **No** apoptosis

Disrupt BCL2 = cytochrome c to leak out =>

CELL DEATH

Follicular Lymphoma t(14;18): Inhibition of apoptosis

BCL 2 is on Chromosome 18

When BCL 2 (c18) moves to Ig Heavy chain locus (c14), increased BCL 2 results

The cells cannot undergo apoptosis→ accumulation of B cells→ Follicular lymphoma

Take home: BCL 2 is overexpressed in Follicular Lymphoma

Recap: Oncogenes & Tumor Suppressor Genes

https://www.osmosis.org/learn/Oncogenes_and_tumor_suppressor_genes?from=/md/foundational-sciences/pathology/introduction-to-pathology/neoplasia

Telomerase: The Key to Cell Immortality

- Normally, telomeres shorten with serial cell divisions, resulting in senescence
- Cancers have upregulated telomerase: preserving telomeres

Angiogenesis

- Requires O2 and blood supply
- *Neogenesis →new abnormal vessels*
- *FGF & VEGF*
- Hypoxia triggers angiogenesis through increased transcription of proangiogenic factors, such as VEGF
- Other factors: driver mutations increase VEGF (Increase in RAS, MYC, MAPK) and inhibition of p53 (which inhibits angiogenesis)

Evasion of Immune Surveillance

- Ways cancer can evade immune surveillance:
  - Tumor cells evade immune surveillance by downregulating expression of MHC I
  - Mutations in CD8+ cells, whereby neoantigens are not “seen” by CD8+ cells
  - Selective growth of tumor cell clones without neoantigens (therefore can’t be recognized)
- Immunodeficiency increases the risk of cancer

Cancer Stem Cells (CSC)

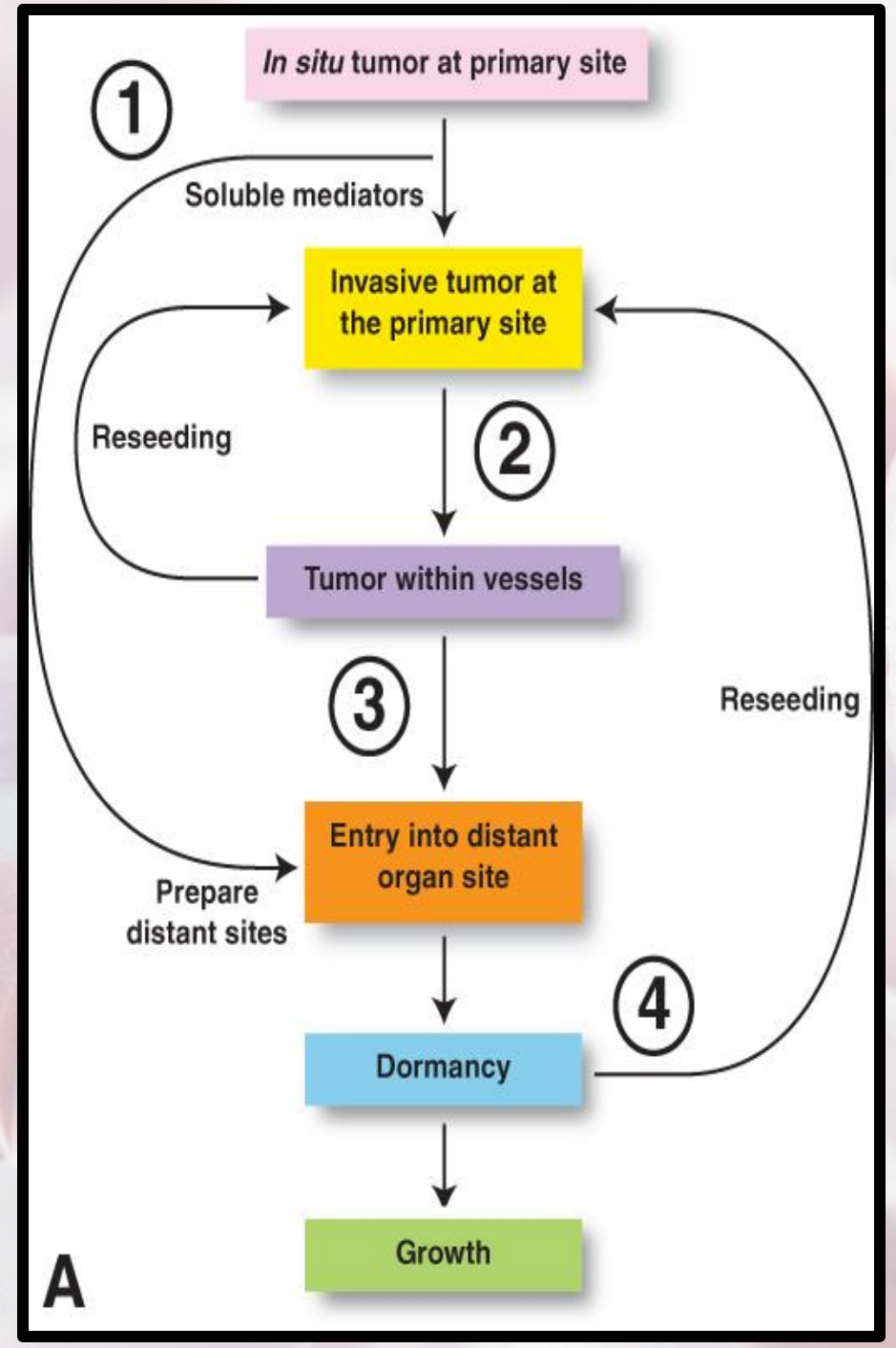
- Cancer cells must have some sort of self-renewal → "cancer stem cells"
- These cells are immortal and have limitless replicative potential
- CSC evade senescence and mitotic crisis (telomerase)
- CSCs are thought to arise in 2 most likely ways:
  - Directly from transformed tissue stem cells with intrinsic "stemness"
  - A proliferating cell that acquires "stemness"
- They evade the body's defenses because they do not divide frequently (therefore, difficult to treat with chemotherapy)

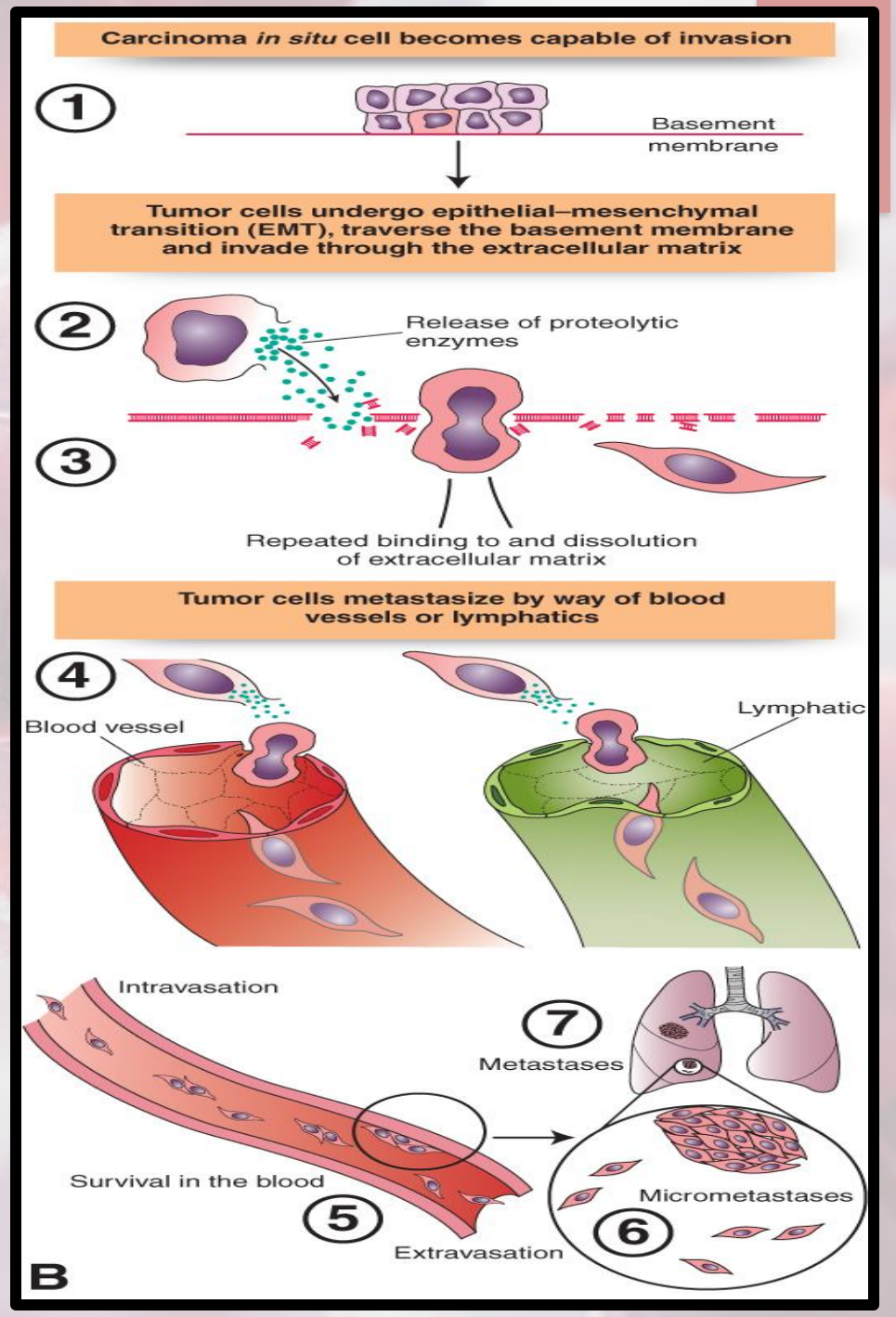
Hallmark of Cancer: Tumor Invasion and Metastasis

- Accumulation of mutations allow for tumor progression, local invasion and spread
- Multistep process
- Invasion of the basement membrane via downregulation of E-cadherin (MMPs, Integrins)
- Movement through the ECM (laminin & fibronectin)
- Penetration of vascular or lymphatic channels
- Survival within circulation
- Homing to a new site and exiting circulation
- Colonization
- Establishment of micro metastasis

Mechanism of Invasion & Spread

- Downregulation of E-Cadherin
- Attachment to laminin
- Destruction of basement membrane (collagenase type IV)
- Attachment to fibronectin in the ECM and spread locally
- Entrance into vascular and lymphatic spaces, allowing for metastasis


1
In situ tumor at primary site
Soluble mediators
Invasive tumor at the primary site
Reseeding
2
Tumor within vessels
3
Reseeding
Entry into distant organ site
Prepare distant sites
4
Dormancy
Growth
A


Carcinoma in situ cell becomes capable of invasion
1
Basement membrane
Tumor cells undergo epithelial–mesenchymal transition (EMT), traverse the basement membrane and invade through the extracellular matrix
2
Release of proteolytic enzymes
3
Repeated binding to and dissolution of extracellular matrix
Tumor cells metastasize by way of blood vessels or lymphatics
4
Blood vessel
Lymphatic
Intravasation
7
Metastases
Survival in the blood
5
Extravasation
Micrometastases
6
B

Spread of Cancers

- Bloodstream
- Lymphatic channels
- Seeding of body cavities: omental caking, malignant ascites
- Usually, **CARCINOMAS** spread via the LYMPHATICS to regional lymph nodes
- **SARCOMAS** spread HEMATOGENOUSLY
- *Organotropism*: how tumors metastasize have prognostic significance (e.g. to brain vs. to bone)
- Brain: Lung, Breast, Colon, Melanoma, Kidney
- Bone: Prostate, Breast, Lung, Kidney, Melanoma, Ovary, Follicular thyroid, Lymphoma

Spread of Cancers: *Exceptions*

Carcinomas that spread hematogenously

- Renal cell carcinoma via renal vein
- Hepatocellular carcinoma (hepatic vein)
- Follicular carcinoma of the thyroid
- Choriocarcinoma

Clinical Characteristics of Tumors

BENIGN	MALIGNANT
slow growing	rapidly growing
well-circumscribed	poorly circumscribed
mobile	fixed
does not invading locally	infiltrative

Biopsy Or Excision

Tissue is required before a tumor can be identified and classified as either benign or malignant with certainty.

Grading & Staging

- Grading and Staging are important in understanding tumors as it relates to treatment and outcomes- how to better treat our patients
- They are used to estimate the probable clinical aggressiveness of a given neoplasm and to provide a standard that is used when comparing outcomes of different treatments.

Grading & Staging

- Staging is the most important prognostic indicator
- Grading looks at whether the tumor resembles the parent tissue?
- Well Differentiated: resembles tissue of origin
- Poorly differentiated: does not resemble parent tissue

Language of Malignancy

- Differentiation
- Pleomorphism
- Anisonucleosis
- Loss of Polarity
- Desmoplasia
- (Dysplasia & Metaplasia)
- Carcinoma-in situ

Grading: Histologic Features

Benign Tumors

- Organized growth
- Uniform nuclei
- Low nuclear to cytoplasmic ratio
- Low mitotic activity
- Lack of Invasion
- No metastatic potential

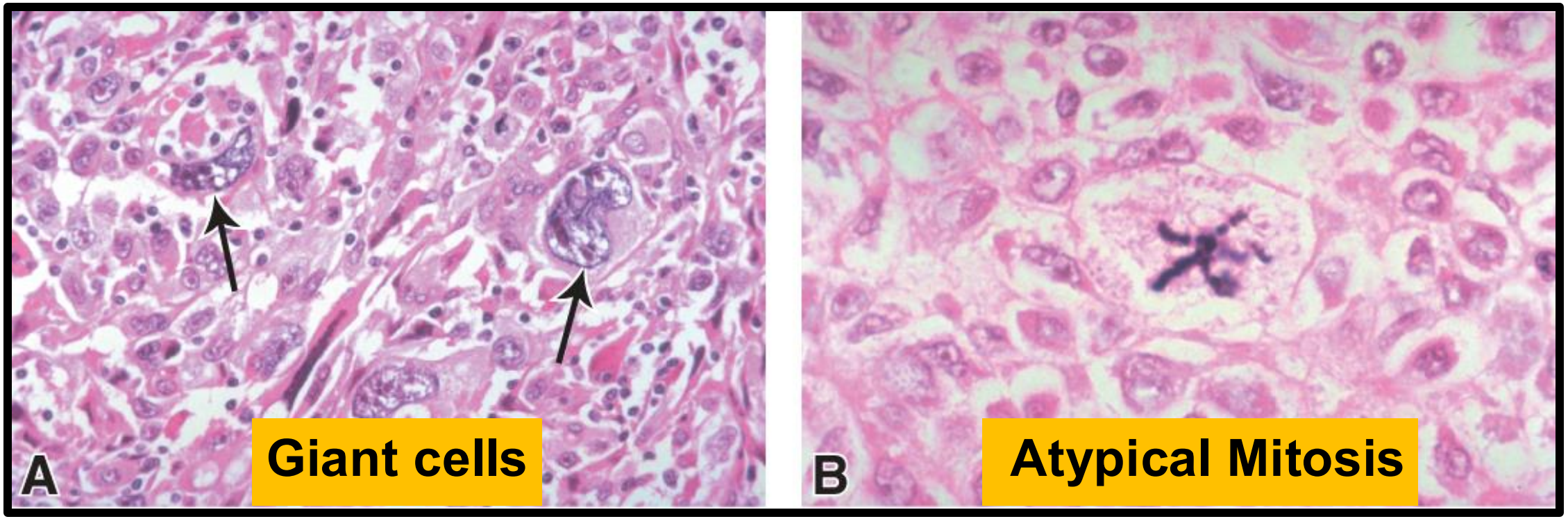
Malignant Tumors

- Disorganized growth
- Pleomorphic nuclei
- High nuclear to cytoplasmic ratio
- High mitotic activity
- Invasion
- Metastatic potential

Cancer Grading: Nucleus & Architecture

- *Nuclear features*: mitoses, shape, size Mitoses: How many? Are they atypical?
- What is the *ratio* of nucleus to cytoplasm? (high N/C ratio)
- *Architecture*: Is the tumor made up of its "normal" arrangements or groupings? (i.e., poorly differentiated tumors lose their normal functions, such as regular gland formation and instead present as sheets of abnormal cells)

Cytological atypia



Immunohistochemistry

Sometimes metastatic tumors are identified before a primary site of the cancer is found

IHC is used to characterize tumors that are difficult to classify on histology

Determination of cell lineage is important as it helps determine what kind of therapy a patient may get

The cells can be stained by an antibody that correlates to a tissue of origin (immunohistochemical stains)

Immunohistochemistry: Binding

Intermediate filaments

- **Keratin:** Epithelium (carcinoma)
- **Vimentin:** Mesenchyme (sarcoma)
- **Desmin:** Muscle
- **GFAP:** Neuroglia (brain)
- **Neurofilament:** Neurons

Others

- **PSA:** Prostatic epithelium
- **ER:** Breast Epithelium
- **Thyroglobulin**: Thyroid follicular cells
- **Chromogranin:**
- Neuroendocrine cells (small cell tumor; carcinoid)
- **S-100:** melanoma; glial cells
- **Calcitonin:** Medullary
- Thyroid Ca

Tumor Markers

A. A poorly differentiated metastatic bladder cancer

B. Bladder tumor highlighted by immunohistochemical stain.

C. Metastatic malignancy to the colon

D. S100 immuno-stain is positive in the tumor

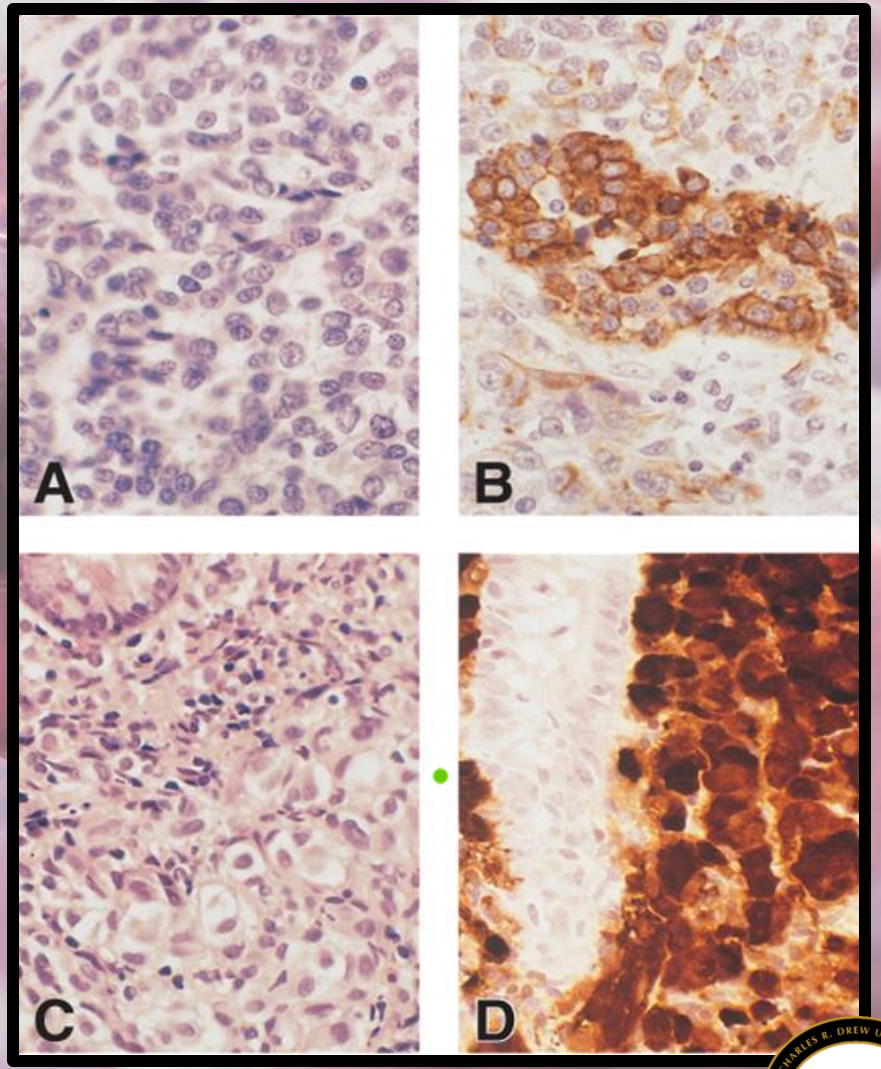


TABLE 5-1
FREQUENTLY USED MARKERS TO IDENTIFY TUMORS

Marker	Target Cells
Epithelial Cells	
Cytokeratins (CKs)	Carcinomas, mesothelioma
CK7	Many nongastrointestinal adenocarcinomas
CK20	Gastrointestinal and ovarian carcinomas, urothelial carcinomas, Merkel cell tumor
Epithelial membrane antigen (EMA)	Carcinomas, mesothelioma, some large cell lymphomas
Ber-Ep4	Most carcinomas, but not in mesothelioma
B72.3 (tumor associated)	Many adenocarcinomas, but not in mesothelioma
Carcinoembryonic antigen (CEA)	Many adenocarcinomas of endodermal origin but not in others (e.g., renal, mesothelioma)
Mesothelial Cells	
Cytokeratins CK5/6	Mesothelioma
Vimentin	Mesothelioma
HBME	Mesothelioma, thyroid tumors
Calretinin	Mesothelioma
Melanocytes	
HMB-45	Malignant melanoma
S-100 protein	Malignant melanoma, glial cells
Mel A	Malignant melanoma
Neuroendocrine and Neural Cells	
Chromogranins, particularly chromogranin A	Neuroendocrine tumors
Synaptophysin	Neuroendocrine tumors
CD57	Neuroendocrine tumors, T and NK cells, Schwann cells
Glial Cells	
Glial fibrillary acidic protein (GFAP)	Astrocytoma and other glial tumors
Mesenchymal Cells	
Vimentin	Most sarcomas
Desmin	All types of muscle tumors
Muscle-specific actin	Muscle tumors, myofibroblast tumors
CD99	Ewing sarcoma, peripheral neuroectodermal tumors (PNETs), acute lymphoid and myeloid leukemias

Marker	Target Cells
Specific Organs	
Prostate-specific antigen (PSA)	Prostatic cancer
Prostate-specific alkaline phosphatase (PSAP)	Prostate cancer
Thyroglobulin	Thyroid cancer
α-Fetoprotein (AFP)	Hepatocellular carcinoma, yolk sac tumor
HepPar1	Hepatocellular carcinoma
WT1	Wilms tumor, some mesotheliomas
Placental alkaline phosphatase (PLAP)	Seminoma, embryonal carcinoma
Human chorionic gonadotropin (hCG)	Trophoblastic tumors
CA19-9	Pancreatic and gastrointestinal carcinomas
CA125	Ovarian carcinoma, endometrial carcinoma, some other nongynecologic tumors (pancreas, mesothelioma)
Calcitonin	Medullary carcinoma of the thyroid
CD Markers	
CD1	Some T-cell leukemias, Langerhans cell proliferations
CD2	T cells, T-cell malignancies
CD3	T cells, T-cell malignancies
CD4	T cells, T-cell malignancies, monocytes, monocytic malignancies
CD5	T cells, some B-cell malignancies
CD8	Suppressor T cells, some T-cell malignancies
CD10 (common ALL antigen, CALLA)	Acute lymphoblastic leukemia, some B-cell lymphomas, renal cell carcinomas
CD15	Reed-Sternberg cells, some T cells, some myeloid leukemias, many adenocarcinomas, but not in mesothelioma
CD19	B cells, B-cell malignancies
CD20	B cells, B-cell malignancies
CD30	Hodgkin disease, anaplastic large cell lymphoma
CD33	Myeloid leukemias

(Rubin & Strayer, 2019, p. 174)

Cancer Staging: Size & Spread

- #1 key prognostic factor (stage is more important than grade)
- Helps predict clinical behavior and inform doctors which therapy is best
- Criteria used for staging vary with different organs
- Commonly used criteria:
  - Size & Spread:
    - tumor *size*; *extent* of local *growth*; presence of *lymph node* metastasis; presence of *distant* metastasis
- TNM cancer staging system:
  - T= tumor size or depth of invasion; N= Lymph node metastasis; M=distant metastasis
- Final stage is determined after the resection of the tumor

Clinical Systemic Effects of Cancer

Symptoms of cancer are usually due to local effects of the primary tumor or its metastasis

Fever

Anorexia

Weight loss

Paraneoplastic Syndromes: symptoms that are not directly caused by the primary tumor

Hypercalcemia, Migratory Superficial; Cushing's; SIADH; Thrombophlebitis (Trousseau’s syndrome); DIC

Table 5.7 Paraneoplastic Syndromes

Clinical Syndrome	Associated Neoplasms	Causal Mechanism(s)/Agent(s)
Endocrinopathies		
Cushing syndrome	Small cell lung carcinoma Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Small cell lung carcinoma Intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell lung carcinoma Breast carcinoma Renal cell carcinoma Adult T-cell leukemia/lymphoma	Parathyroid hormone–related protein, TGF-α, TNF, IL-1
Hypoglycemia	Fibrosarcoma Other mesenchymal sarcomas Ovarian carcinoma	Insulin or insulin-like substances
Nerve and Muscle Syndromes		
Myasthenia	Lung carcinoma Thymoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma Teratoma	Immunologic
Dermatologic Disorders		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunologic; secretion of epidermal growth factor
Dermatomyositis	Lung carcinoma Breast carcinoma	Immunologic
Osseous, Articular, and Soft Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Lung carcinoma	Unknown
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Lung carcinoma Other cancers	Hypercoagulability due to secreted tumor products (e.g., mucins) that activate clotting factors
Red cell aplasia	Thymoma	Immunologic
Polycythemia	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin secretion by tumor cells
Renal Dysfunction		
Nephrotic syndrome	Various cancers	Immune complexes

ACTH, Adrenocorticotropic hormone; IL-1, interleukin-1; TGF-α, transforming growth factor-α; TNF, tumor necrosis factor.

(Kumar, A. et al., 2021, p. 85).

Serum Tumor Markers: Proteins Released by Tumor

- Useful for monitoring response to treatment, and monitoring recurrence
- If used for screening, elevated levels require a tissue biopsy for diagnosis of carcinoma

Circulating tumor markers

Marker	Tumor	Use
PSA	Prostate carcinoma	Screening; Following response to therapy
HCG	Choriocarcinoma, Mixed germ cell tumors	Following response to therapy
AFP	Germ cell tumors; Hepatocellular carcinoma	Following response to therapy
CEA	Colon carcinoma	Following response to therapy
CA-125	Ovarian carcinoma	Following response to therapy

Summary

- Benign and malignant tumors can be distinguished from one another based on the degree of differentiation, local invasiveness, and distant spread.
- Benign tumors resemble the tissue of origin and are well differentiated; malignant tumors are less well differentiated or completely undifferentiated (anaplastic).
- Benign tumors are more likely to retain functions of their cells of origin, whereas malignant tumors sometimes acquire unexpected functions due to derangements in differentiation.
- Benign tumors are slow growing, while malignant tumors generally grow faster.
- Benign tumors are circumscribed and have a capsule; malignant tumors are poorly circumscribed and invade surrounding normal tissues.
- Benign tumors remain localized at the site of origin; malignant tumors metastasize to distant sites. Carcinomas tend to spread via lymphatics, whereas sarcomas prefer the hematogenous route.

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