CARCINOGENESIS:
THE MOLECULAR BASIS OF CANCER

Department of Pathology

Group B & A 1st year- Oct 2020

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أولا تحية من القلب لكم يامن يعجز اللسان عن وصفهم
وأحيي بصفة خاصة قروب B
الذين سيسجل التأريخ اسمهم ويرسمون مستقبلا لم يفكر أحد في رسمه من قبل

تنويه:هذا اللي ركز عليه الدكتور ولايعني أنه فقط اللي تذاكرونه ،فلذلك أخلي مسؤوليتي من أي شي خارج عن هذا الملخص البسيط

Note:

Red line (important)

طالب العلا

Red marker (very very important)

Important → Mean it will come in exam

 → Dr said it's for explanation only and will not ask in exam

Objectives

1. **Genetic aberrations**

2. **Cancer genes classes**

3. **Genetic lesions in cancer**

4. **Eight cancer hallmarks**

Genetic Aberrations

CYTOGENETICS VERSUS MOLECULAR GENETICS

CYTOGENETICS	MOLECULAR GENETICS
The study of inheritance in relation to the structure and function of chromosomes	A branch of genetics dealing with the structure and activity of genetic material at the molecular level
The study of the influence of chromosomes on cell behavior during mitosis and meiosis	The study of the structure and function of genes at the molecular level
Techniques: Karyotyping, chromosome staining, FISH, CGH, etc.	Techniques: PCR, molecular cloning, DNA and RNA isolation, cell cultures, etc.
Studies the diseases due to the abnormal number and structure of chromosomes	Studies hereditary, genetic variation, and mutations by means of chromosomes and gene expression

Genetic Aberrations

- Molecular Vs. Cytogenetics.

- Not all mutation results in loss of gene functionality. Some may lead to gain and overexpression.

- Loss of gene functionality not necessarily leads to cell death. It might have a proliferation impact on the cell.

Cancer Genes

- Researchers and students alike can easily get lost in the growing forest of information.
- It has become eminently clear that cancer is a disease caused by mutations that alter the function of a finite subset of the 20,000 or so human genes.
- For simplicity, we will refer to these genes as cancer genes and usually they fall into one of **four major functional classes (*Oncogenes*, *Tumor suppressor genes*, *Genes that regulate apoptosis*, *Genes that regulate interactions between tumor cells and host cells*).**

1) Oncogenes

- ***Oncogenes*** are genes that induce a transformed phenotype when expressed in cells by promoting increased cell growth.
- A major discovery in cancer was the realization that oncogenes are mutated or overexpressed versions of normal cellular genes, which are called ***proto-oncogenes***.
- Most oncogenes encode **transcription factors**, factors that participate in **pro-growth signaling pathways**, or **factors that enhance cell survival.**
- They are considered **dominant genes** because a mutation involving a single allele is sufficient to produce a pro-oncogenic effect.

2) Tumor Suppressor Genes

- ***Tumor suppressor genes*** are genes that normally prevent uncontrolled growth and, when mutated or lost from a cell, allow the transformed phenotype to develop.
- Often both normal alleles of tumor suppressor genes must be damaged for transformation to occur (not a case in TP53).
- Tumor suppressor genes can be placed into two general groups,

1. ***"governors"*** that act as important brakes on cellular proliferation.
2. ***"guardians"*** that are responsible for sensing genomic damage.

3) Apoptosis Regulatory Genes

- *Genes that regulate apoptosis* primarily act by enhancing cell survival, rather than stimulating proliferation.

- Understandably, genes of this class that protect against apoptosis are often overexpressed in cancer cells, whereas those that promote apoptosis tend to be underexpressed or functionally inactivated by mutations.

4) Interaction Regulatory Genes

- Genes *that regulate interactions between tumor cells and host cells,* as these genes are also recurrently mutated or functionally altered in certain cancers.

- Particularly important are genes that enhance or inhibit recognition of tumors cells by the host immune system.

Important

TABLE 6.4 Inherited Predisposition to Cancer

Inherited Predisposition	Gene(s)
Autosomal Dominant Cancer Syndromes	
Retinoblastoma	*RB*
Li-Fraumeni syndrome (various tumors)	*TP53*
Melanoma	*CDKN2A*
Familial adenomatous polyposis/colon cancer	*APC*
Neurofibromatosis 1 and 2	*NF1, NF2*
Breast and ovarian tumors	*BRCA1, BRCA2*
Multiple endocrine neoplasia 1 and 2	*MEN1, RET*
Hereditary nonpolyposis colon cancer	*MSH2, MLH1, MSH6*
Nevoid basal cell carcinoma syndrome	*PTCH1*
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum	Diverse genes involved in nucleotide excision repair
Ataxia-telangiectasia	*ATM*
Bloom syndrome	*BLM*
Fanconi anemia	Diverse genes involved in repair of DNA cross-links

Genetic Lesions in Cancer

- The genetic changes found in cancers vary from **point mutations (Molecular lab)** involving single nucleotides **to abnormalities large** enough to produce gross changes **in chromosome structure (Cytogenetics lab).**
- **Driver mutations** are mutations that alter the function of cancer genes and thereby directly contribute to the development or progression of a given cancer.
- **Passenger mutations** are acquired mutations that are neutral and do not affect cellular behavior but proven to be important in cancer.
- Passenger mutations greatly outnumber driver mutations.

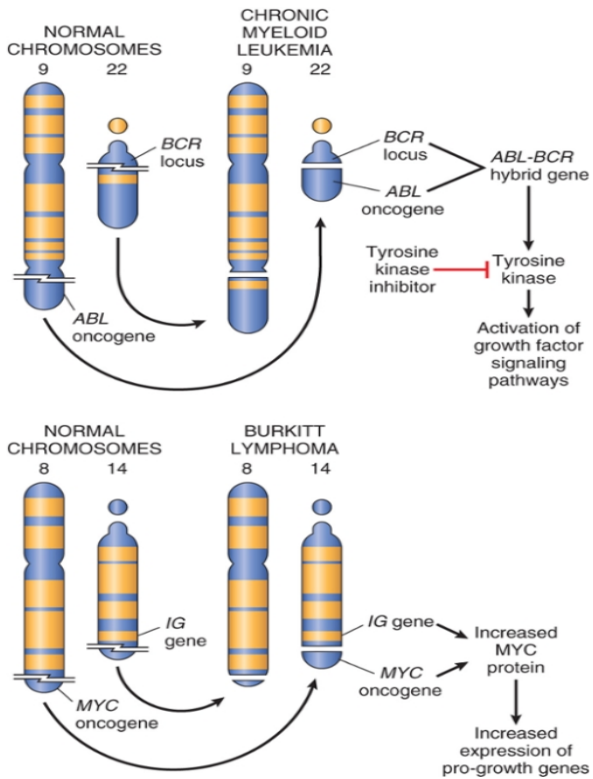
Point Mutations

- Point mutations can either **activate or inactivate** the protein products of the affected genes **depending on their precise position and consequence.**
- Point mutations that convert **proto-oncogenes** into oncogenes (class 1) generally produce a **gain-of-function**, like ***RAS* gene** into a cancer gene, one of the most comment events in human cancers.
- By contrast, point mutations (as well as larger aberrations, such as insertions and deletions) in **tumor suppressor genes** (class 2) reduce or **disable the function** of the encoded protein, like ***TP53***, a prototypical "guardian" type tumor suppressor gene.

Gene Rearrangements

- Gene rearrangements may be produced by **chromosomal translocations or inversions**.
- Specific chromosomal translocations and inversions are highly associated with certain malignancies, particularly neoplasms derived from **hematopoietic cells** and other kinds of **mesenchymal cells.**
- Some gene rearrangements result in **overexpression** of proto-oncogenes leading to highly active promoter or enhancer like in >90% cases of ***Burkitt lymphoma; t(8;14), CMYC-IHG.***
- Other oncogenic gene rearrangements create **fusion genes** encoding novel chimeric proteins. Most notable is the Philadelphia (Ph) chromosome in ***chronic myeloid leukemia (CML), t(9;22), BCR-ABL1.*** Important

Gene Rearrangements

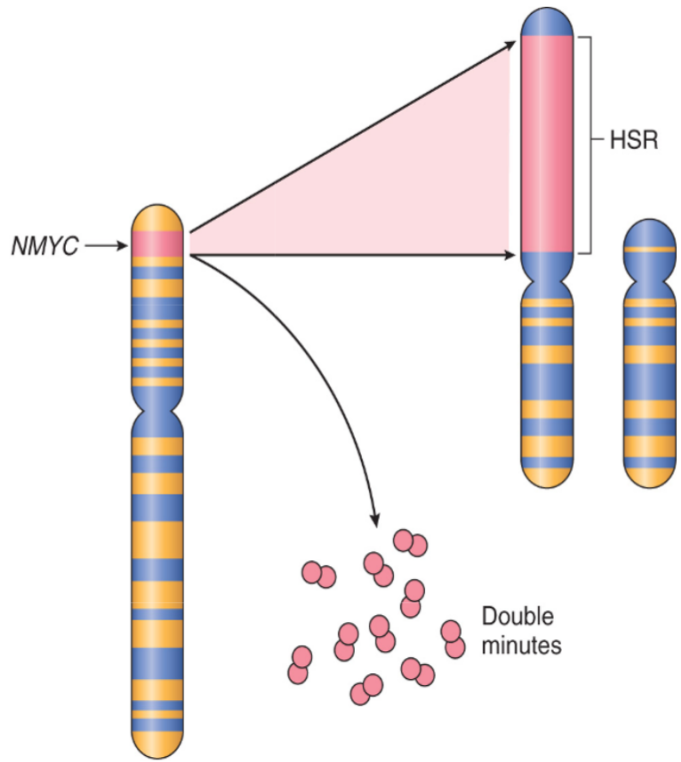


Gene Amplifications

- Proto-oncogenes may be converted to oncogenes by **gene amplification**, with consequent overexpression and hyperactivity of otherwise normal proteins **by** producing **several hundred copies of the gene**, a change in copy number that can be readily detected by **molecular hybridization (FISH or CGH-array)** with appropriate DNA probes.
- Two mutually exclusive patterns are seen:

1. Multiple small, extra-chromosomal structures called ***double minutes***.
2. ***Homogeneously staining regions (HSR)*** derives from the insertion of the amplified genes into new chromosomal locations (might be detected by G-banded karyotype).

Gene Amplifications



Aneuploidy

- ***Aneuploidy*** is defined as a number of chromosomes that is not a multiple of the haploid state; for humans, that is a chromosome number that is not a multiple of 23.
- Aneuploidy is remarkably common in cancers.
- Mechanistic data establishing aneuploidy **as a cause of carcinogenesis, rather than a consequence.**
- However, **tumor development and progression** may be molded by changes in chromosome numbers that enhance the dosage of oncogenes while restricting the activity of tumor suppressor genes.

MicroRNAs and Cancer

- **MicroRNAs (miRNAs)** are noncoding, single-stranded RNAs, approximately 22 nucleotides in length, that function **as negative regulators of genes**.
- They inhibit gene expression post-transcriptionally by **repressing translation** or, in some cases, by **messenger RNA (mRNA).**
- Specifically, if the target of a miRNA is a **tumor suppressor gene**, then overactivity of the miRNA **can reduce** the tumor suppressor protein.
- Downregulation or deletion of certain miRNAs in some leukemias and lymphomas results in increased **expression of *BCL2***, an anti-apoptotic gene (also in *RAS* and *MYC* oncogenes).

Epigenetic Modifications and Cancer

- **Epigenetics** refers to reversible, heritable changes in gene expression that occur without mutation. Such changes involve **posttranslational modifications of histones and DNA methylation**.

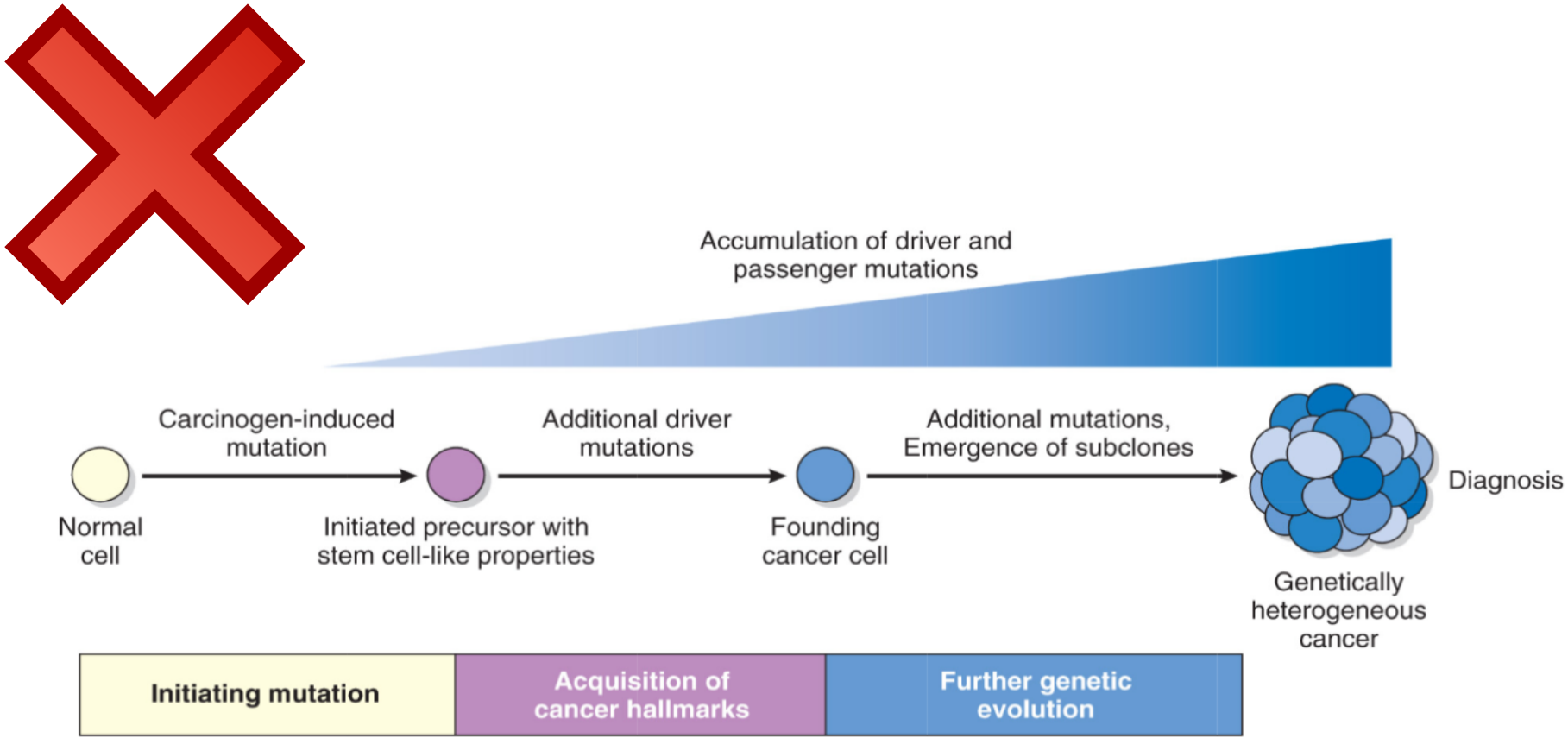
- The epigenetic state of particular cell **types dictates their response to signals that control growth and differentiation**. For example, the ***NOTCH1* gene** has an oncogenic role in **T-cell leukemia**, yet acts as a **tumor suppressor in squamous cell carcinomas**. As would be expected, this dichotomy exists because activated *NOTCH1* turns on pro-growth genes in T-cell progenitors and tumor suppressor genes in keratinocytes.

- Mutations in cancer cells fall into two major classes,
  - **driver (pathogenic) mutations and**
  - **passenger (neutral) mutations**.

- Passenger mutations may become driver mutations if selective pressure on the tumor changes, for example, in the setting of treatment with an effective therapeutic drug.

- Tumor cells acquire driver mutations through several means, including point mutations and nonrandom chromosomal abnormalities that contribute to malignancy; these include gene rearrangements, deletions, and amplifications.

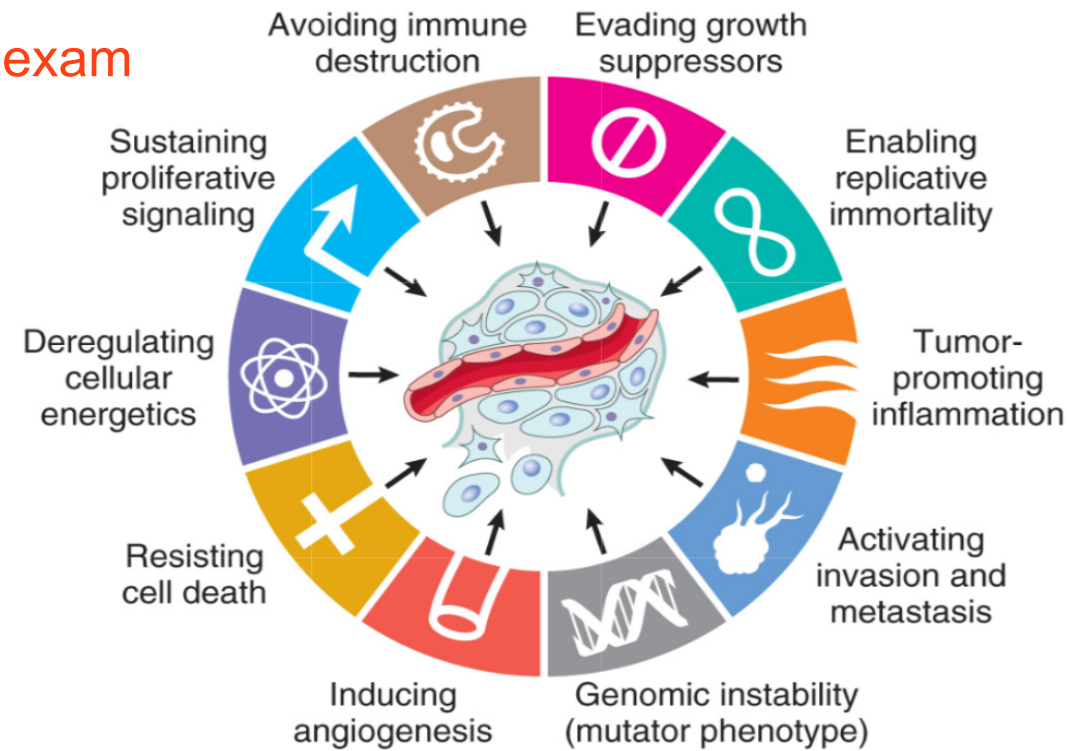
- **Gene rearrangements** (usually caused by translocations, but sometimes by inversions of other more complex events) contribute to carcinogenesis by **overexpression** of oncogenes or generation of novel fusion proteins with altered signaling capacity. **Deletions** frequently affect tumor suppressor genes, whereas gene **amplification** increases the expression of oncogenes.
- **Overexpression of miRNAs** can contribute to carcinogenesis by reducing the expression of tumor suppressors, while **deletion or loss of expression of miRNAs** can lead to overexpression of proto-oncogenes.
- **Tumor suppressor genes and DNA repair genes also may be silenced by epigenetic changes**, which involve reversible, heritable changes in gene expression that occur not by mutation but by methylation of the promoter.


Accumulation of driver and passenger mutations
Carcinogen-induced mutation
Additional driver mutations
Additional mutations, Emergence of subclones
Normal cell
Initiated precursor with stem cell-like properties
Founding cancer cell
Genetically heterogeneous cancer
Diagnosis
Initiating mutation
Acquisition of cancer hallmarks
Further genetic evolution

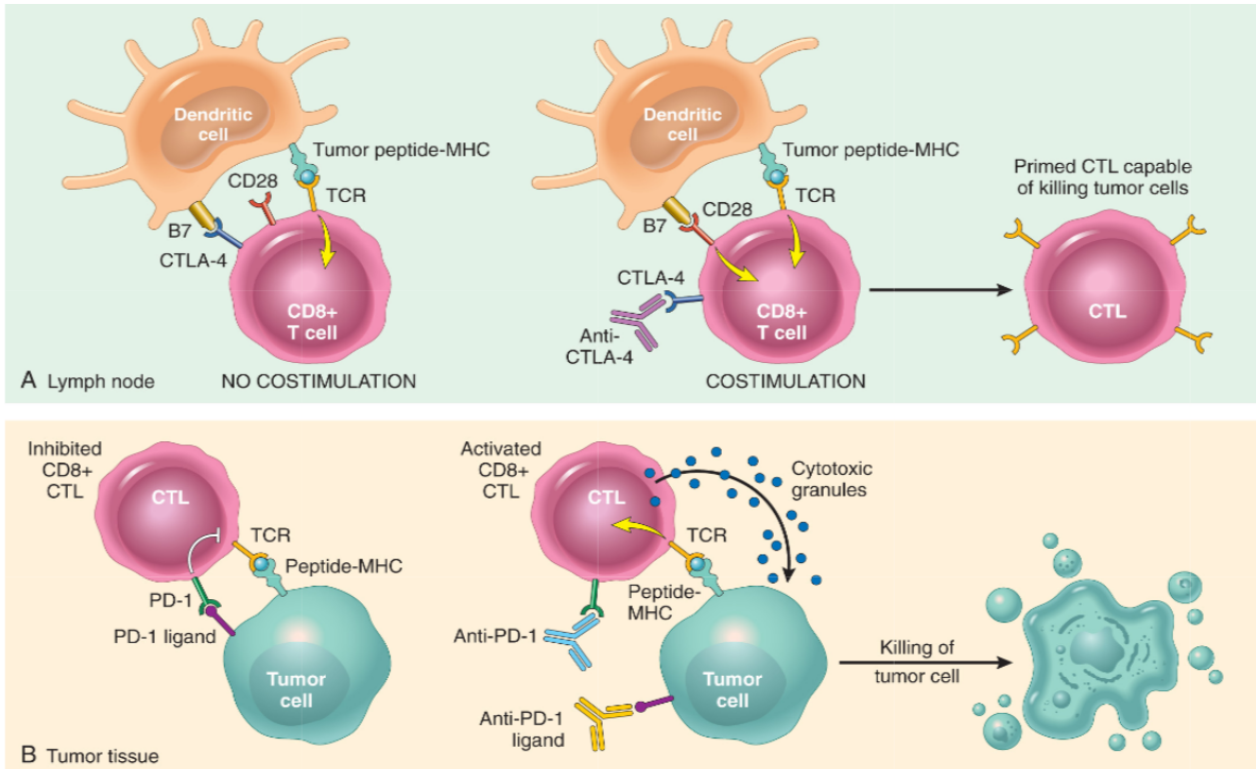
Important

Eight cancer hallmarks and two enabling factors (genomic instability and tumor-promoting inflammation). Most cancer cells acquire these properties during their development, typically due to mutations in critical genes.

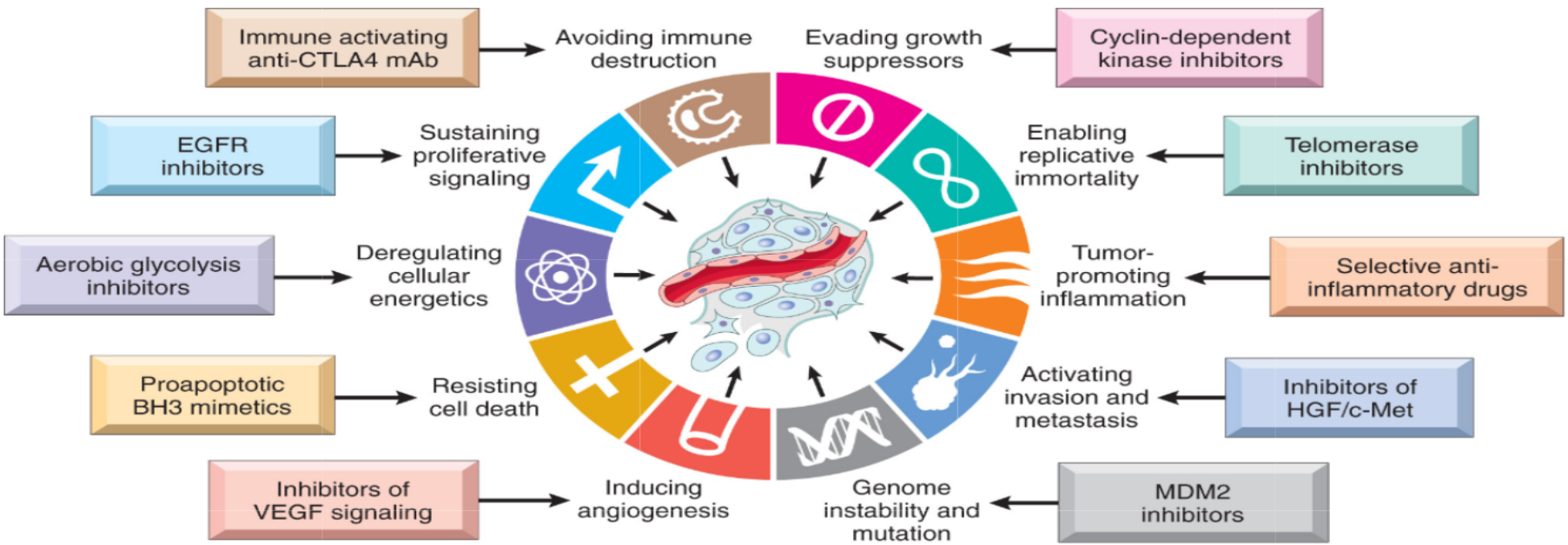
Question in exam



Example: Avoiding Immune Destruction



Therapeutic Targeting of the Hallmarks of Cancer



THANK YOU