Neoplasia 2023/24 lectures 10

Dr Heyam Awad

MD, FRCPath

ILOS

- 1. understand the concept of immune surveillance.
- 2. list the most common tumor antigens and understand their origins.
- 3. understand the mechanisms through which tumor cells evade the immune system.
- 5. understand the role of inflammation as an enabler of malignancy.
- 6 list the most important DNA repair genes and understand their role in carcinogenesis.

8th hallmark of cancer

- Evading the immune system is an important tumor hallmark.
- Our immune system can destroy tumor cells, because tumor cells express antigens that can be recognized by the immune system as foreign.
- Once antigens are recognized the immune system can destroy the malignant cells.. This is called immune surveillance
- One of the promising treatments of cancer is immunotherapy: drugs that stimulate the immune system to attack cancer cells.

TUMOR IMMUNITY

- Tumor cells are recognized by the host (the body) as non self.
- Once recognized, immunologic reactions are activated to destroy the tumor cells.
- This process is called immune surveillance
- However, immune surveillance is imperfect and that's why tumors still occur i:e many of the tumor cells escape destruction by the immune system.

- Immune system recognizes cells by their antigens.(مولد الضد) مستضد)

- If cells express antigens that are perceived by the immune cells as non self , the immunologic reaction starts
- So: what are the antigens present on the cancer cells?

Classification of tumor antigens

based on their molecular structure and source

1. Products of Mutated Oncogenes and Tumor Suppressor Genes
2. Products of other Mutated Genes
3. Over expressed or Aberrantly Expressed Cellular Proteins
4. Tumor Antigens Produced by Oncogenic Viruses
5. Oncofetal antigens
6. Altered glycolipids and glycoproteins
7. Cell type-specific differentiation antigens

Oncofetal antigens

- These are proteins expressed only in embryos
- In some tumors (mainly colon and liver) they are re-expressed

- examples: CEA= carcino-embryonic antigen and alpha fetoprotein
- These are important serum markers of cancer

Anti-tumor mechanisms

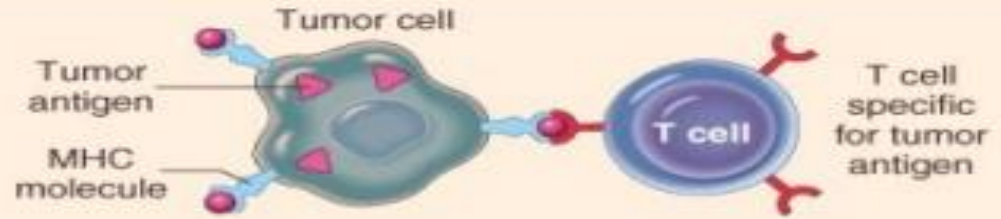
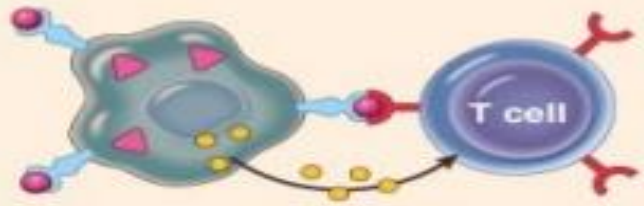
- The cells responsible for immune surveillance are:
- 1. cytotoxic T lymphocytes
- 2. Natural killer cells
- 3. macrophages

Mechanisms of evasion of the immune system

- 1. Selective growth of antigen negative variants (subclones). The highly antigenic subclones are deleted from the tumor mass
- 2. Loss or reduced expression of histocompatibility molecules.
- 3.Downregulation of co-stimulatory molecules
- 4. Antigen masking by producing a thick coat of external glycocalyx molecules
- 5.Immunosuppression (see next slide)

Immunosupression

- Tumor cells can suppress host immunity by:
- A. TGF beta production by tumor cells.
- B. Expression of fas ligand that binds to fas receptor on host lymphocytes causing apoptosis of these lymphocytes
- C. Some oncogenic agents suppress host immunity, especially chemicals and ionizing radiation.

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

Enablers of malignancy

- We said that there are 8 cancer hallmarks and 2 enablers.
- We discussed all hallmarks; let’s talk about the 2 enablers:
- 1. inflammation.
- 2. genomic instability.

Inflammation as an enabler of malignancy

- inflammatory cells modify the tumor microenvironment to enable many of the hallmarks of cancer.
- These effects may occur from direct interactions between inflammatory cells and tumor cells, or through indirect effects of inflammatory cells on other resident stromal cells.

Inflammation in response to tumors

- With any tumor there is associated inflammatory response, the aim of which is to protect tissue against cancer cells. However, inflammatory cells can enable malignant transformation.

- How do inflammatory cells help cancer cells to proliferate? By the variable chemical mediators and cytokines that are released from inflammatory cells.
- These mediators have several effects that enable growth, increase angiogenesis and even metastasis.. See next slide.

How do inflammatory cells affect tumor microenvironment??

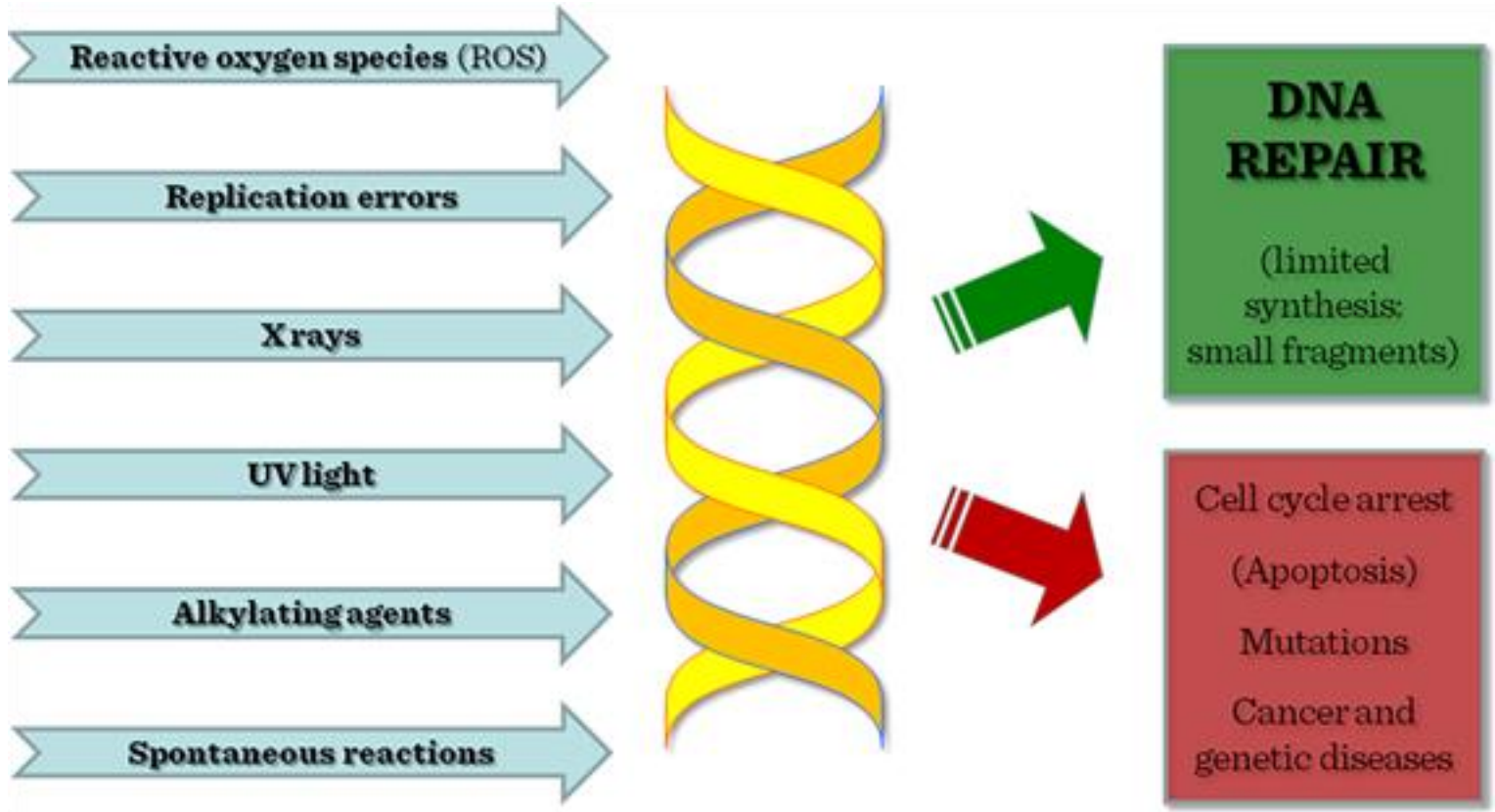
- 1. They secrete growth factors, such as EGF, and proteases that can liberate growth factors from the extracellular matrix (ECM).
- *2.* Removal of growth suppressors*.* growth of epithelial cells is suppressed by cell–cell and cell–ECM interactions. Proteases released by inflammatory cells can degrade the adhesion molecules that mediate these interactions, removing a barrier to growth.
- 3. Angiogenesis*.* Inflammatory cells release VEGF, that stimulate angiogenesis.
- *4.* Invasion and metastasis*.* Proteases released from macrophages foster tissue invasion by remodeling the ECM, while factors such as TNF and EGF may directly stimulate tumor cell motility.
- *5.*Evasion of immune destruction*.* TGF-β and other factors favor the recruitment of immunosuppressive T regulatory cells or suppress the function of CD8+ cytotoxic T cells.

Role of M2 macrophages

- There is abundant evidence in cancer models and emerging evidence in human disease that advanced cancers contain mainly alternatively activated (M2) macrophages .
- M2 macrophages produce cytokines that promote angiogenesis, fibroblast proliferation, and collagen deposition.

Genomic instability as an enabler of malignancy

- Many mutations occur in normal individuals.. But are repaired by DNA repair genes
- If the DNA repair genes are inactivated… mutations can accumulate leading to cancer
- DNA repair genes are recessive.
- A cell with DNA repair gene mutated is not neoplastic yet but has the capacity to accumulate carcinogenic mutations. At this stage it is a “mutator phenotype”


Reactive oxygen species (ROS)
Replication errors
X rays
UV light
Alkylating agents
Spontaneous reactions
DNA REPAIR
(limited synthesis: small fragments)
Cell cycle arrest
(Apoptosis)
Mutations
Cancer and genetic diseases

- DNA repair genes can be inactivated by mutations or deletions in sporadic cancers and in some inherited diseases

DNA repair genes

- 1. **mismatch repair gene**… repairs nucleotide mismatch.. i:e makes sure that each A is paired with T and each C is paired with G (not A or T) for example
- 2. **nucleotide excision repair genes**, repair nucleotide cross linking that results from UV exposure
- 3. **recombination repair**

Mismatch repair gene

- Mismatch repair gene is mutated in HNPCC = hereditary non-polyposis colorectal cancer syndrome
- People with the syndrome inherit one abnormal copy of the mismatch repair gene, and acquire the other mutation
- The syndrome causes familial colon cancer at a relatively young age, and mainly affecting the right side of the colon, mainly cecum.

Nucleotide excision repair gene

- This gene is mutated in xeroderma pigmentosum
- The nucleotide excision repair gene repairs nucleotide cross-linking occurring upon exposure to UV light
- People with the syndrome are predisposed to skin cancers

Recombination repair genes

- Certain DNA repair genes are important for repairing recombination errors
- Mutations in these genes occurs in several autosomal recessive diseases like
- 1. Fanconi anemia: there is predisposition to cancer and to anemia
- 2. Bloom’s syndrome : there is predisposition to cancer and developmental defects
- 3. Ataxia telangiectasia: cancer and gait imbalance

Other DNA repair genes

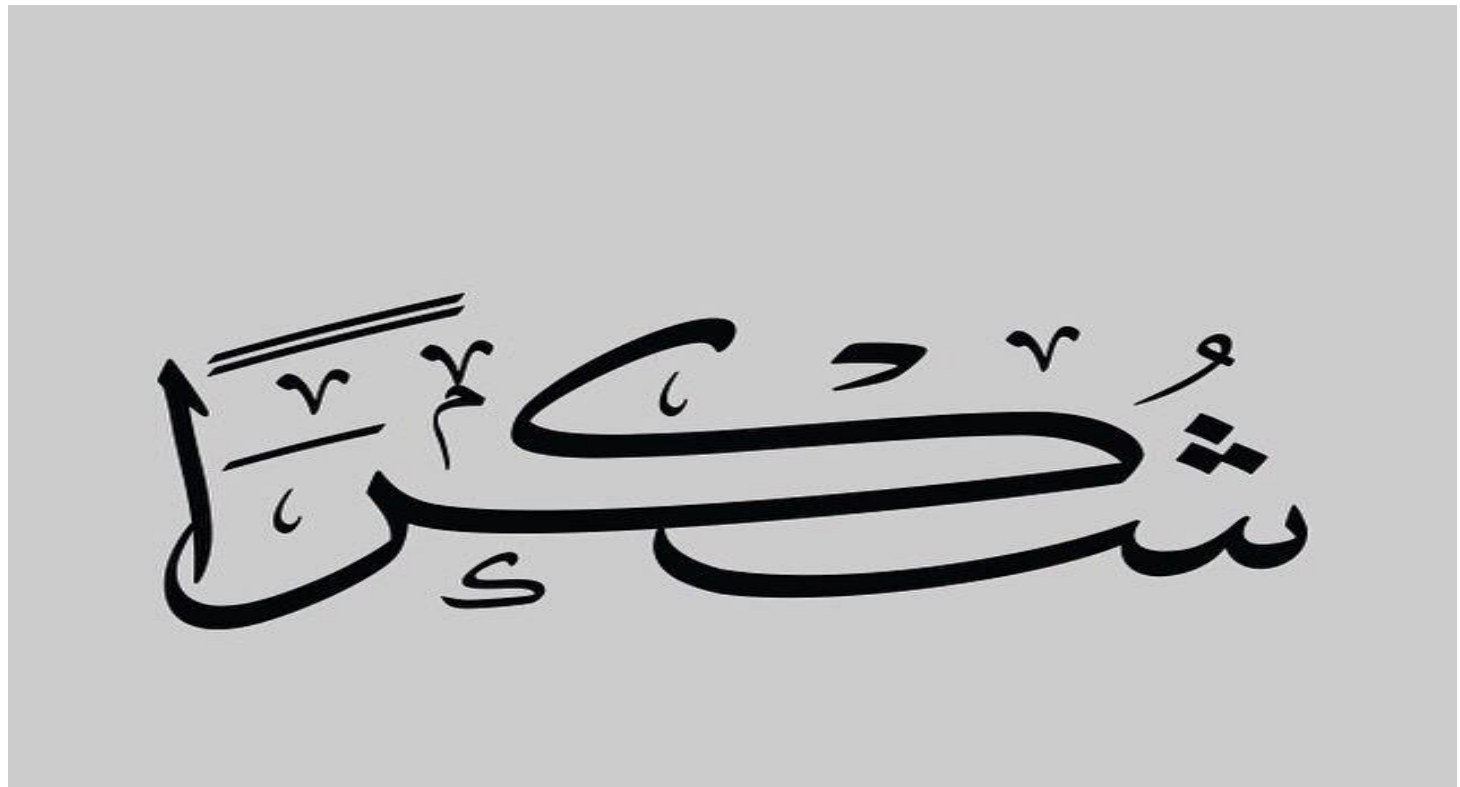
- BRCA 1 and BRCA 2 also are important genes involved in DNA repair
- They are mutated in 50% of familial breast cancer… but rarely involved in sporadic breast cancer.
- BRCA 1 important for DNA repair and is linked to ATM protein
- BRCA 2 is one of the genes mutated in Fanconi anemia

Summary 1/2

- Tumor cells express antigens, which makes them vulnerable to be recognized and destroyed by the immune system.
- These antigens can be protein products of the mutated or overexpressed genes. Antigens can also originate from oncoviral proteins, oncofetal (CEA) or abnormal mucins (CA125)
- Cellular immunity plays a role in immune surveillance whereas humoral immunity does not.

Summary 2/2

- Tumors can evade this immunologic destruction through selective growth of antigen negative subclones, loss or reduced expression of histocompatibility molecules, downregulation of co-stimulatory molecules, antigen masking by producing a thick coat of external glycocalyx molecules or immunosuppression through production of TGF beta , expression of fas ligand or as an effect of the oncogenic agent.
- Inflammation enables malignancy because inflammatory cells produce mediators and cytokines that increase growth, decrease growth inhibition, increase angiogenesis and help in metastatic spread.
- Mutation in DNA repair genes (including mismatch repair, BRCA genes and others) cause genomic instability that allows accumulation of mutations which enables transformation.


شكرا