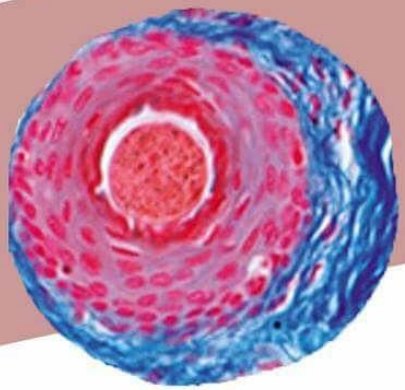
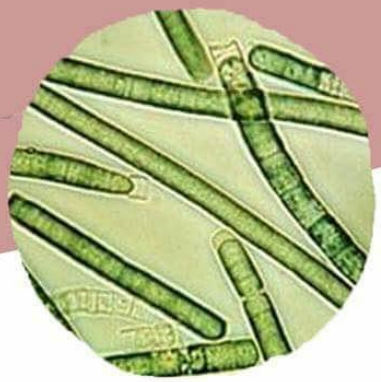
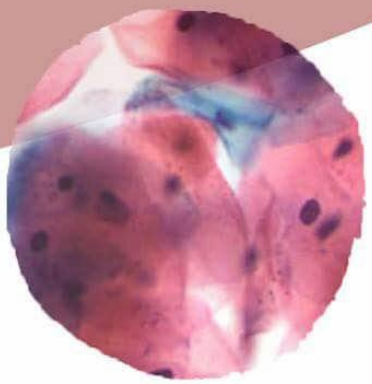
INTRODUCTION TO PATHOLOGY

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Sheet# 23

TUMOR IMMUNITY

- The original idea is that the immune system is responsible for getting rid of newly appearing tumor cells, and this prove that immune-suppress patients have a high risk of getting tumor (actually, those patients have a higher risk to get tumor than normal population by 200 folds), so once we take about transplantation, HIV patients and patients who had inherent abnormality in his immune system, we consider that they have a higher risk to get a tumor.

☒To understand tumor immunity, we are going to discuss **a short introduction to immunology.**

- Our immune system is divided into two major portions:
1) Innate immunity
2) Adaptive immunity

◊Innate immunity

- It is always found, there is no pre sensitization, and it doesn't need to see something to react.

- It based on epithelial barriers, phagocytes, complement system proteins and natural killer cells (NK).

◊Adaptive immunity

- Adaptive immunity is divided into two portions:
1) Humoral immunity: depends on B cells that produce antibodies, these antibodies haven't a major role in immune surveillance, however we are using them as a part of treatment of cancer.

2) Cell-mediated immunity: depends on T cells.
T cells can be divides into two major categories: **CD4+ T cells (helper cells) and CD8+ T cells (cytotoxic T lymphocytes)**

Antitumor Effector Mechanisms

◊ CD4+ T cells (helper cells)

- They don't directly kill the infected cells or the tumor cells, but they produce several cytokines that induce inflammation and inflammatory cells (like macrophages, neutrophils,… ect), which can cause damage to the tissues.

◊ CD8+ T cells (cytotoxic T lymphocytes)

- It will directly identify abnormal cells (cells that contain viruses and cells that produce abnormal proteins and express it on the surface of the cell), and they directly kill that cells.

- T cells (The both types) require two stimulatory events:
* Class I major histocompatibility complex MHC (also called HLA proteins) presents bits and pieces of internal proteins on the surface of the cell and other Co-stimulatory molecules,
*They need both of these two events to properly stimulate.
*This now gives you an idea that down regulating MHC-1 is not the only way to turn-off T cells; because stimulatory molecules could be also mutated and down regulated.

◊NK cells (natural killer)

- Whenever your NK cells recognize an MHC molecule with a self protein on it, this will turn NK down off.

- Whenever the cells are under stress, they will up-regulate certain proteins (like NKG2D) that stimulate NK cells.

- There is a balance between inhibitory function of MHC and stress proteins, so if a cell is not stress and down regulates MHC molecules, stimulatory singles will remain at the surface of the cell and turn on NK, so even though tumor cells down regulate MHC molecules, they may be recognized by NK cells.

- If a cell is stressed even in the presence of MHC molecules, the stress respond can over out the inhibitory effect of MHC molecules and turn on NK cells.

- So if you think about this, there are multiple ways for cancer cells to get rid of effect of NK cells. Not only can they avoid MHC molecule to avoid cytotoxic T cells, they also can get rid of these stress molecules (mutate them or no longer express them on the surface)to prevent NK cells from identifying them.

- Stress molecules are expressed in tumor cells and especially when there is DNA damage, so your NK should be able to detect a whole host of mutated events.

- When T cells and NK are activated, they produce interferon-γ , and INF-γ will activate macrophages in the classical pathway.

◊ M1 microphages

- They can produce nitric oxide, reactive oxygen species and lysozymes that can be used to kill microbes, as well as microphages use the same mechanism to kill tumor cells.

Tumor antigens

- Tumor antigens: the part of the tumor cells that activates the immune system.

- In the past, tumor antigens were subdivided into two categories: **Tumor specific antigens and Tumor associated antigens.**

-Tumor specific antigens are particular antigenic material that is expressed only on tumor cells; therefore we could use it for diagnoses and as a therapeutic target.
-Tumor associated antigens are associated with tumors more than they are with normal cells. They could be used for therapeutic targeting, but the collateral damage will be more.

- Unfortunately, a lot of the antigens that thought to be tumor specific antigens in the past turned out to be just tumor associated antigens; that is because we did not have the techniques that detect them in the

normal cells. So that old system of classification is defunct. The modern classification of tumor antigens is based on their origin.

☒We will take about different antigens that we have:

◊ Products of Oncogenes and Mutated Tumor Suppressor Genes

- In oncogene (that originally was proto-oncogene), the product was not expressed a lot, and it was rarely (if ever) introduced on MHC molecules, so T cells never learned it to be a self protein. Now, tumor cells are over-expressing this protein (the product of the oncogene), therefore that protein is going to be presented on MHC molecules. Immune tolerance to that protein was never built up, and it was never recognized as a self-protein, so CD8+ cells (we will focus on CD8+ cells, because we don't fully understand the role of other cells in tumor immunity) will recognize it as a foreign-protein (not recognized as a self-protein), that they never seen it before on MHC molecules, then they will target the cell and kill it.

- A mutated Tumor suppressor genes even if they had been included on MHC molecules and recognized as self in the past (before mutation), now (after mutation) the genetic code has been mutated; therefore the protein consequence has been changed, so it will not be recognized as self and the CTL (cytotoxic T lymphocytes) can potentially attack and kill the tumor cell.

*****Examples of oncogenic products: mutated RAS, and BCR-ABL fusion proteins.
*****Examples of TSG products: mutated P53

◊ *Products of Other Mutated Genes*

- Mutated self-protein does not necessarily have to be an oncogene or TSG or a DNA repairing enzyme ((Any other gene that is not related to carcinogenesis at all)), so we take about cells that had been radiated or cells that have resaved carcinogenesis from chemicals or viruses or cells that have P53 or DNA repair enzyme mutation that induce a mutator phenotype that will mutate many things (Not necessarily related to the

cancer). Any of these genes that have products which are now over-expressed on the outside of the cell, can be recognized by CTL, and be killed.
- Through that, another layer of protection is added, in addition to DNA repair systems and cell-cycle check points, to protect the body from mutations. If a mutation occurred and had not been corrected, and then was allowed to exist, then it would be detected by CTL through the abnormal proteins, and then it would be eliminated by killing the cell.

- Examples: several proteins that can rise from chemicals, carcinogen or radiation that induce tumors and melanomas that seem to be the favorite type of tumor, where CTL can detect other proteins that are not responsible of the caner.

◊ Over Expressed or Aberrantly Expressed Cellular Proteins (Self-proteins)

- We mentioned that these proteins volume was very low, there expression level was very low as well as they were not normally present on the MHC molecules, but now they are over-expressed, so the chance for them being put on MHC molecules increases massively, and therefore the chance to be recognized by CTL as supposed-to-be-self-proteins that they have never seen before increases.

- Now, there are other proteins that are normal, but not expressed in adult tissues so called oncofetal proteins (alpha fetoprotein and carcinoembryonic antigen (CEA)). These are normally expressed in the fetus but not in normal adult tissues. As tumor cells gain a variety of mutations which can turn on some dormant areas of human genome, so they express these fetal proteins, and they can be recognized as Non-self-protein and therefore will be attacked. If you look at these proteins from the old classification you will find them as an example for tumor specific antigens.

*we can use the presence of CEA and alpha fetoprotein in the serum as diagnoses for tumor. Also, they can be used to evaluate and follow up the patient's therapy.

- There are other proteins such as GAGE, BAGE, and RAGE that are specific for testis (they are called testis-cancer antigens.) The reason for calling them testis-cancer antigens is that these proteins are only expressed in the testis, and although the protein is present in the testis, it is not expressed on the cell surface in an antigenic form, because sperms do not express MHC class I molecules, therefore these proteins are never detected by T cells. So, Testis is an immune privilege tissue. Same thing for the breast tissue; there are antigens that are only expressed on the apex (apical side of the ductular epithelial of the breast (especially during lactation)).

- So those tissues are immune privilege (they are never seen by the immune system), and there should be abnormality that case testis antigens or breast tissue to be expressed in a non-immune privilege location such as in melanoma, or, in ductular carcinoma of the breast, where these cells lose their polarity, and by losing their polarity , they no longer know on which side to express those particular proteins, and now they are no longer in privilege side; they are in the side that faces ECM and therefore the immune system. So they could be detected as abnormal proteins. Again, we can use these proteins as therapeutic target especially if they are specific to certain area, as well as they can be used for diagnosis.

◊ *Tumor Antigens Produced by Oncogenic Viruses*

- When there is a protein produced by viruses, it is definitely not a self-protein. MHC molecules will present it outside the cell, and this will tell the CTL that there is something definitely abnormal here, and this is how immune system gets rid of viruses. For example EBNA proteins produced by EBV (that induce lymphoma), and (E6 and E7) produced by HBV can be detected by immune system, and this explains why viruses (for example in EBV) have to avoid the immune system in order to induce tumor formation, otherwise, if viruses did not avoid the immune system, they will be killed by CTL.

◊ *Altered Cell Surface Glycolipids and Glycoproteins*

- Some cancer cells can produce a very thick outer-coating glycoprotein-polysaccharide (glycocalyx) that masks the MHC molecules with the proteins that present on them. These can be detected in the blood stream.

-Several mucins could be used for diagnostic and therapeutic studies. These include CA-125 and CA-19-9 that are expressed in ovarian carcinomas, and MUC-1 expressed on Breast carcinomas. These have diagnostic and therapeutic significances. Once they are present in the serum, there will be a risk of having a cancer. We are not sure that the patient has a cancer until we take a biopsy.

☒The reason for mentioning all of these tumor antigens is that almost all of them are being used to induce immune system to react to tumors. So, presenting tumor antigens to the immune system is a way of vaccination. There are a lot of programs on vaccination against cancers. We can use these vaccination techniques to stimulate immune system in cancer patients to kill the tumor (a way to reactivate dormant immune system.)

☒There are many ways that tumor cells use in order to avoid the immune system by producing TGF-b, FASL and being in a location that is privilege as well as we will take about some of them:

-losing the antigens:

Tumor cells lose their antigens to avoid immune system by natural selection. The immune pressure that causes natural selection makes the tumor lose the antigens; because the other tumor cells that had this antigen will be killed by the immune system (*Selective outgrowth of antigen-negative variants.*) This brings us to the fact that such natural selection occurs only in immunocompetent patients; since the driving force of such natural selection is the presence of competent immune system.

-Mutation in MHC genes (Loss or reduced expression of histo-compatibility molecules)

This will result in turning on NK cells unless tumor gets rid of stress molecules

-Antigen masking

Produces a thicker coat of external glycocalyx molecules that will mask the antigens.

-Immunosuppression

Produces immunosuppressive proteins like TGF-b and FASL.

-Downregulation of co-stimulatory molecules

Co-stimulatory molecules are required to initiate strong T cell responses with the presence of MHC molecules. If you produce an inhibitory molecule even in the presence of MHC molecules you will end up with unresponsive or apoptotic T cells, as well as if you completely get rid of stimulatory molecule even in the presence of MHC molecules *no* stimulation will occur.

*Remember: cancer cells do not have to evade immune system in immunosuppressed patients; so immunosuppressed patients have an increased risk for development of cancer.

"IF you are doing your best you will not have time to think about failure"

Good luck