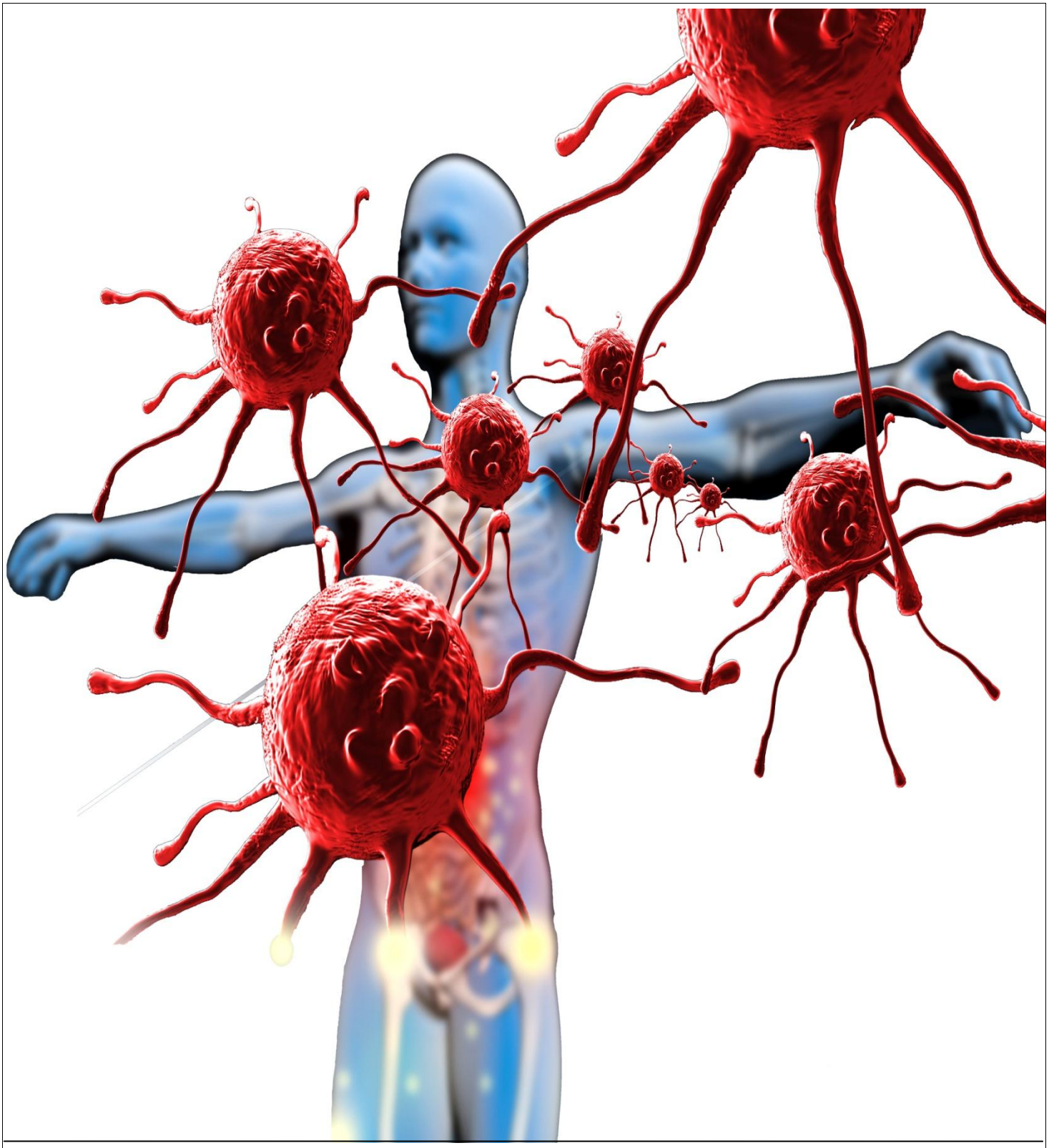

IMMUNOLOGY

Done By: Rajai Zurikat

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Dr. Hassan Abu Al-Ragheb

By Mohammed Nawasreh

Tumor Immunology

Pathologist usually deal with tumors, so they should inform us about tumor pathology& etiology which they did, so we are going to discuss tumors from an immunological point of view.

Theory of Immune surveillance:

The theory suggests that cancer cells develop in our bodies all the time ☺ , however the immune system identifies these cells and destroys them.

The doctor agrees with the theory.

Facts that support this theory

When examining a tumor you can find an infiltration of immune cells around it, like macrophages, lymphocytes.

You can find reactive changes in nearby draining lymph nodes, usually enlargement, not necessarily due to metastasis but to the actual tumor (reacts to it)

It is believed that When a tumor is surrounded by immune cells its prognosis is better again (usually).

These observations suggest that the immune system might have an important role in fighting cancer cells.

Most tumors are found in elderly people (the immune system is weaker and not functioning at the level it used to), and the very young people (like leukemia) probably because their immune system is not fully developed yet, so cancer cell escape the immune cells and become tumors.

For a tumor to be identified it must have some sort of antigens that are different from the body cells.

Written by Rajai Zurikat.

Data collected from experiments:

Done on animals

A sarcoma can be induced by injecting the mice with a carcinogen.

Next the tumor is resected and then some cells of the tumor are taken and implanted into a syngeneic mouse, (which is a mouse that is identical, genetically speaking, this is done by excessive interbreeding generations of mice, meaning having the offspring mate with each other up to 20 generations) so they are like identical twins, we find out that when these cancer cells are planted in the syngeneic mouse a tumor actually grows because they have the same genes so the tumor is allowed to grow.

The cells from the original tumor are injected into the old mouse again (the one that originally had the tumor) we find out that the tumor doesn't grow, meaning that the mouse has developed some sort of immunity against the tumor and is actually recovered.

Finally, another syngeneic mouse is used here this one is given T-cells from the recovered mouse (with the developed immunity) then the cancer cells are injected into it, the result is no tumor will grow.

RECAP: so what we did is we caused cancer in a mouse (original) then we resected the tumor, took some cells and planted them in a syngeneic mouse (let's call him S1) and found out that the cells formed a tumor. Next we went back to the original mouse (that had the tumor) and injected him with the cancerous cells but this time the cells didn't grow thus suggesting a developed immunity by the original mouse. Finally we bought another syngeneic mouse (S2) and injected this mouse(S2) with T-cells that were extracted from the original(immune)mouse , then introduced the cancerous cells to the mouse(S2) the result was no tumor developed(rejected) thus an acquired immunity.

So all this information tells us that

Some sort of immunity is developed against cancer cells and is transferred by T-cells.

The tumors (or cancer cells in general) have some sort of antigen that are recognized as foreign by the animal and are attacked. These antigens are known as **TSTA** or **tumor specific transplantation antigens**, these antigens are specific to the tumor and transplantation referees to the experiments we discussed.

We don't know what these TSTA antigens are, we know that the tumors have them but it's very difficult to isolate and recognize them.

So tumors have specific antigens that may be recognized as foreign and be attacked or the tumors might not be recognized and develop cancer.

Another Varity, is **tumor associated antigens** i.e.; they are found or can be found on normal cells in certain stages in their development but are **heavily produced** by cancer cells.

So 2 antigen types: specific (belong to tumors) and associated (can be found on normal cell during development and/or differentiation, in low amounts but in cancer cells they are presented in high amounts).

So TSTAs are very difficult to identify and recognize because they have many variations, but the tumor associated antigens can be used as **cancer markers.**

Examples:

I. **CEA** or **carcinoembryonic antigen**, it is present in the fetus normally during differentiation in low amounts. But is expressed by cancer cells in chronic cases like in colon cancer or other cases like stomach cancer we find a rise in the amount of this antigen.

So if you find a rise in CEA its probably linked to colon cancer or other GIT cancers, however this is not specific as the antigen can be over expressed in other conditions like inflammatory bowel disease, which means it's not a diagnostic tool but it helps like if someone is known to have colon cancer CEA levels can be used in follow ups to check the patients' status.

When you resect the tumor (colon cancer) CEA decreases, if not then the tumor has grown again or metastases has occurred.

II. **Alpha fetoprotein**, again present in the fetus and its amount is low but can be associated with cancer of the liver, again it is not specific because it can be associated with other inflammatory diseases which means it's not a diagnostic tool but it helps in the follow ups and treatment of the patient.

III. **PSA (prostate specific antigen**) associated with prostate cancer.

IV. **Prostatic acid phosphatase** also used for prostate cancer but less useful.

V. **Carbohydrate antigens** , **CA** or known as **cancer antigens** like

- **CA-125** associated with ovarian cancers
- **CA19** is associated with pancreatic cancer
- **CA15** is associated with breast cancer

  These are most linked to these cancers but can be found with other types of cancers.

  Again all these antigens CA, PSA, PAP alpha fetoprotein…. Are used to aid the diagnosis not confirm it, and they are usually used to check the patient's condition after therapy (follow ups).

What causes cancers?

Gene mutations: any gene mutation can cause cancer

Physical or chemical agents can react with cells, damage them and cause cancer. (Carcinogens)

Viruses: some viruses are (can be) oncogenic/tumorgenic like

- **Epstein-Barr virus(EBV**), is a herpes virus , it has complement receptor2, which is also present on b-cells and can be present on nasopharyngeal cells and cervical cells too

So the virus can infect these cells and cause cancers like Burkitt's lymphoma, B-cell lymphoma, and nasopharyngeal carcinoma can be associated with EBV.

EBV causes glandular fever.

- **HTLV1 (human T- lymphotropic virus)** it's a retro virus associated with T-cell leukemia.

- **Hepatitis B virus** associated with liver cancer (hepatic carcinoma)
- **Human papillomavirus** associated with cervical cancer.

Immunity against tumors:

We talked about immune surveillance; here are some elements of that:

I. **NK-Cells**: can non-specifically attack tumor cells (one of the first elements to attack tumors.) why because cancer cells start to express less MHC molecules on their surface (less MHC1 molecules) the cancer cells do that to escape cytotoxic CD8 T cells but this allows NK-cells to destroy them.
II. **CD8 cells** can have a roll in eradicating cancer cells if MHC1 molecules are present.
III. **CD4 cells** as they help all the other cells of the immune system(CD8,NK-cells)
IV. **Macrophages:** can attack tumors, by several ways like ADCC (antibody dependent cell mediated cytotoxicity) which is killing cells that are identified by the antibodies that bind with receptors on the cells, so NK-cells can recognize the antibodies and kill the cancer cells, other way macrophages use is by injecting perforins and granenzymes into tumor cells, so macrophages can phagocytose cells by ADCC.
Macrophages are an important source of TNF (tumor necrosis factor), TNF binds to its receptors (can be found on tumors) and cause apoptosis, and can cause thrombosis of blood vessels of tumor killing them.
Antibodies don't play a big role in immunity against tumors unless through ADCC.

Complement system doesn't play a role because cells have protective molecules on their surface like, RCD59 which protect the cells from lyses by complement system activation.

Written by Rajai Zurikat.

Treatment

"From an immunologic approach".

- We take cells from around the tumor , grow them in vitro supply them with IL2 ,supposedly this process can active the cells and expanding them more , then we take the cells and place them back around the tumor and they will attack it .the doctor says these are probably **NK-cells** as when they are exposed to IL2 they get activated.

These cells are called **lymphokine activated killer cells**. (Kill the tumor)

- You can also use **TNF** and **interferons** but this is rather toxic as TNF can cause toxic shock, thus **cytokine** treatment can be used but can be dangerous so it's used as a last resort if the patient is going to die.
- **Antibodies** can be used, these are referred to as **magic bullets**:

These antibodies are made against a certain tumor then a toxic substance (like arisen, cytotoxic drugs) is added, what happens is these antibodies seek tumor cells and destroy them as they provide a route for the cytotoxic drug, disposing large amounts on the tumors, by this way not the whole body is affected only the cells that bind to the antibody unlike the traditional way were the drug is given systemically thus eliminating many unwanted side effect (like bone marrow damage).

This is limited and not that successful because your body will produce antibodies against the magic bullets antibodies destroying them.

How can tumors avoid the immune system if the surveillance theory does exist?

- Stop expressing MHC molecules thus preventing CD8 from killing them yet this can help NK-cells in finding them.

- To avoid NK-cells cancer cells can surround themselves by a mucus capsule hiding its antigens.
- The bigger the tumor, the less affect the immune system has on it as a whole, because many cells will be hidden inside and those won't be exposed to the immune cells.
- Aseil told the doctor about another mechanism we took before about how cells cluster together to hide their antigens (marker) to metastasize to other tissues, the doctor isn't sure but it's the same concept as the previous point.

So many camouflages by not expressing MHC or forming a capsule.

- **Immunomodulation**: clustering of the antigen and antibody on the cell surface, leading to endocytosis into the cell or shedding of the complexes other way the tumor protects itself.
- Some tumors can produce Faz-ligand and destroy NK-cells with Faz on them.
- Some tumors can produce TGF-beta (cytokine) suppressing immune cells so they won't attack the tumor.
- Tumors don't have MHC2 so they won't present antigens to cells and won't be attacked by that mechanism.
- Some say that T-regulator cells (suppresser cells) might play a role in tumor immunity against our body's immune system.

The end

Buon natale& felice capodanno a tutti

Merry Christmas, happy eid el mawoled el naboui and happy New Year.

Happy Chanukah rami. ☺

Find what you love the most ….. and let it kill you . GB