Tumor immunology

Tried to make things a simple as they can get ,,, hope that u enjoy it !
لا تخافوا بس أربع صفحات وشوي ☺

- ✓ Tumors can occur, they can be considered as something foreign that should be dealt with by the immune system.
- ✓ Immune surveillance theory: The immune system continuously inspects body cells for signs of neoplasia and recognizes and kills the neoplastic cell, it can happen at anytime to anyone but will be controlled by immunity.
- ✓ How strong is this theory?

  It's not proven for sure but what supports this theory is that:

  1- If you examine a tumor (histologically) you can always find infiltration of mononuclear cells (macrophages-NK cells-T lymphocytes) cuz probably that tumor is foreign, and the more the infiltration is, the better the prognosis.

  2- Swelling of regional lymph nodes draining a tumor area(Hyperplasia not metastasis) but may be caused by rxn of immune response.

  3- Immunodeficient people are more susceptible to have tumor (if u consider them as a hole) , since function is reduced. That's why most common in young/elderly.

- old ppl : immune system as the person ages will not do very well .

- Young ppl: there immune system is not mature enough to do the job.

- ✓ To mount an Immune response, a tumor <u>must</u> have foreign Ag's, they can be of 2 kinds :

  - TSTA (tumor specific transplantation Ag) :
    tumor specific : because it is peculiar to that tumor, transplantation: because they actually discovered them after transplantation of tumors in animals
    Found in most tumors (<u>most common</u>)
    Has novel Ag <u>specific/peculiar</u> to that tumor.

  - Tumor associated Ag's: <u>not specific</u> to that tumor.
    those Ag's can normally be found on cells but in v. low amount or at some stage of development / differentiation, but they can be found elevated abnormally in association with tumor production .
    They are <u>not diagnostic</u>, diagnostic of tumors usually done by histopathology.

- ✓ Examples on tumor associated ag's :
  - **Oncofetal Ag's** : (alpha-feto protein in HCC , & CEA in GIT Ca's especially colon carcinoma but can be in inflammatory processes of clarge intestines , like colitis).

    Oncofetal Ag's can normally be found on cells but in v. low amount . OR on cells at some stage of development / differentiation , in some cancers they can be found elevated abnormally . Again : they are not specific to that Ca.
    In case of those 2 aforementioned, they are expressed at fetal life and almost don't Exist at adult life. In certain cancers they can rise.

    They are helpful in Dx but not used for real Dx (not diagnostic) as they may also increase in infections / other tumors / other conditions. For real Dx u would need to do pathological examination (histoimmunology).
    They are also helpful to monitor treatment and progress: if there is an increase all of a sudden→ indicates recurrence of the tumor. ,, if decrease → pt. is being cured.

  - Prostate specific Ag: related to prostate Ca.

    In the past they used the marker acid phosphatase for Dx (increase then associated with cancer) but not used anymore cuz PSA is more liable.
    Again they are not 100% diagnostic as they may increase in other condition such as benign prostatic hyperplasia (which affects most men after the age of 50)→ in this case Ag can be really high. → that's why need histological examination.

  - CA-125 (CA = carb Ag): associated with ovarian tumors → most of them have this Ag BUT once again not diagnostic alone cuz can be associated with other tumors / other conditions.
  - CA 19-9 : pancreatic cancer.
  - CA 15-3 : breast cancer.
  - High HCG : germ cell tumors / gonadal usually have raised HCG (ovarian , testicular)

- ✓ Experiement done on mice to prove immune surveillance theory:

  - Scientists injected a mouse with carcinogen → it developed tumor → they resected it so they cured the mouse→ took cells again and re-injected them in the same mouse → x Growth of the Tumor (rejected)
    Why ? some sort of immunity developed during tumor growth (T-cells or other cells of immune system→ cell mediated immunity)that prevented growth when re-injected.
    While if they took those resected tumor cells and transplant them into a **sergenic** mouse (another identical mouse) → tumor grows .

- These scientist took the T-lymphocytes (presumably CD8) from the 1st mouse after excision then injected them to control mouse that's not subjected to carcinogens → inject tumor cells → x Growth (i.e. he was protected from tumor development → immune).
- Control experiment : taking T-cells from control mouse and inject them to other mouse that's not exposed to carcinogen → transplant tumor cells → Tumor grows.

These experiments indicate that Adoptive transfer of T lymphocytes into another animal leading to the protection against growth of tumor.

✓ In human beings , u can do tumor resection but u need to stage the Ca and make sure there is no metastasis for the resection to be 100% effective as it did in mice .

✓ what can go wrong in tumors ? (variety of things).

- Mutated gene : altered (novel) protein / product. → In TSTA tumors.
  Some says that these are products of Reactivation of silent gene by the tumor → Ag's will be displayed on the cell.
- Influence of chemical or physical carcinogens.
- Differentiation Ag's to help u identify origin of tumor / it's site : found at specific stage of differentiation ,like :
  IF : CD10 / Ig's → markers for B-cells ,,, CD10 is an early marker -- > if there is Cancer of unknown origion and these markers were found , then probably it origionated from B-cells.
  IF : CD4 → T-cells.
- Oncogenes : normally oncogenes (el doc. 7ka oncogenes bs akeed a9do proto-oncogenes) control cell division and growth , but if mutated → produce different product concentration .
- (virally associated) Some viruses are oncogenic / tumergenic: the Ag's don't necessarly have to be on the virus but associated with viral infection.
  #EBV → Burkitt's lymphoma
  # HPV → cervical Ca.
  # HLTV (human lymphotropic virus)→ T-cell leukemia.
  # HBV →Hepatoma .

✓ Immunity agaist Tumors (Anti-tumor immunity):

- NK cells (1st line of defense since many tumors lack MHCI) : by granzyme injection & sometimes ADCC / or thrombosis.
- T-lymphocytes : CD8 produce (perforins + granzymes) and are helped by CD4 TH cells.
- Macrophages: can be by ADCC but most likely they do their job by cytokine production: especially TNF (discover ed because of it's actions on tumors)→ can attach to certain receptors on cells and produce toxic effect.
  can cause thrombosis of B.vessels of tumor cells → tumor becomes necrotic.

- Ab → their role is debatable but they may play a role by ADCC + complement activation (Lysis).

✓ Immunomodulation mechanism of tumors / how do they evade the action of I.system ?
Since they can multiply + survive this means that they must have a way to evade I. system :

- Down regulation/lack of MHC calss I molecules: many tumors don't have OR they lose MHCI molecules so CD8 cells can't do their job if these have abnormal antigen . NOTE THAT : here the job is taken by NK cells which kill cells that don't have MHCI (yet , tumor may have ways to dodge these too !).
- Lack of MHCII molecules (most tumors) : no Ag presentation for Immune response.
- Lack of co-stimulation (since they don't have B7)
- X Express stress molecules (MIC A + MIC B).
- Production of large amounts of glycocalyx (thick layer or mucin / mucous / GP) that covers all Ag's → Ab's or immune cells won't be able to recognize these tumor cells.
- Some produce suppressive cytokines (some produce lots of TGF-beta)→ suppress B +T cells → evades killing by I.system .
- Immunomodulation of Ag's (foreign Ag's) by endocytosis (so not detected by Ab's / CD8/NK) OR shedding if binds to Ab (thus will go away and won't do it's job).--> Ag modulation !
- Some proposed that tumor Ag's presented in a way that will produce tolerance rather than I. Response (may be by cells like T reg = suppressor cells).
- Sneaking through (تسلل): if you inject small amount of tumor cells into an animal: mouse / human it won't be noticed and will grow (may be caused by Low dose tolerance: tolerance rather than activation) , while if inject large amount , it will be rejected.

✓ Therapy :

- Standards: chemotherapy + resection + radiation .
- V.limited: Immuno therapy: still most experiemental and results not that successful.

✓ Examples for immunotherapy :

- Stimulation of immune response by vaccination (immunize) . Eg: BCG vaccine (against TB) → if injected at site of tumor → stimulate arrival of B + T cells to kill the tumor.
- Give low doses of anti-CD3 (that's what he said in the lecture but I'm not sure how accurate that is!): transmits signal to the inside of T –cell to activate it + mimics the result of binding of TCR to Ag. BUT don't give too much or else the cell will kill the cell.(this is experimental).
- If u take NK / CD8 cells around the tumor (most probably they have specifity o that tumor or else what are they doing there!) :

Take the cells → treat with cytokines in vitro (expose to large amounts of IL-2)
→stimulates activation and growth and proliferation + expand to get LAK (lymphokine

activated killer cells) → re-inject them ➔ THIS IS KNOWN AS : (adoptive cell therapy). → usednot just experimental.

- Active immunization → take tumor cells + re-inject them into the pt. to try to treat him by increasing immunity against it (this Is experimental and not affective cuz we don't know which exact Ag to use).
- Ab against tumor Ag (magic bullet): direct Ab's very specific toward the tumor's Ag and combine that with → to concentrate cytotoxic drugs (chemotherapy) or radiotherapy's effect on cells , while if not given : this therapy will affect not just tumor cells but also normal cells.
- Cytokines may be used but only in hopeless cases / terminal cases because of their many side effects.
  eg: IL -1 / IL -2 / TNF (v.toxic, should be avoided) / IFN-gamma ➔ U CAN GET VARIABLE RESULTS.

where there is a will …… there is a way!

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