Graves's disease	Hashimotos thyroiditis
1. Hyperactivity	1. Fatigue, lethergy
2. Weight loss with increase of Appetite	2. Weight again
3. Heat intolerance	3. Cold intolerance
4. Thirst/polyuria	4. Dry coarse skin
5. Diffuse goiter	5. Rubbery, nodular goiter
6. Ophthalamopathy, eyelid Retraction, exophthalmous, peri-orbital odema	6. Facial edema (myxodema)
7. Tachycardia	7. Mostly bradycardia
8. Free T3 ↑ Free T4 ↑ Total T3 ↑ Total T4 ↑ Anti-Tg N(rarely ↑ in few cases) Anti-TPO N (slightly in 50% of cases) Anti-TSH-R ↑ TSH ↓	8. Free T3 N- ↓ Free T4 ↓ Total T3 N- ↓ Total T4 ↓ Anti-Tg ↑ Anti-TPO ↑ Anti-TSH-R N TSH ↑
9. Treatment Anti-thyroid drugs Radioactive iodine Thyroidectomy	9. thyroxine
10. TH2	10. TH1

Lecture No. 27-28

Tumor

Tumor is an overgrowth (uncontrolled growth) of tissues and cells in certain organs in the body which result in a mass of tissue that has result in destruction of normal architecture of the tissue and lost the normal function of the healthy original tissue.

Tumor can be generally classified into

1. **Benign tumor:** cluster of tumor cells that are localized in a restricted area in the body without the ability to move to other areas in the body.
2. **Malignant tumor:** cluster of tumor cells that can move and invade (**metastasis**) other adjacent and far away tissues.

Metastasis means spreading of the invasion tumor cells from the primary focus of tumor to other parts of the body via blood or lymph circulation to form a secondary focus of tumor.

Tumor classifications

A. According to the involved tissue:
   1. **Carcinoma:** Tumor of epithelial cells.
   2. **Sarcoma:** Tumor of muscle and connective tissues.
   3. **Adenoma:** Tumor of the glandular tissue which is benign.
   4. **Adenocarcinoma:** Tumor of the glandular tissue which is malignant.

B. According to the system or organ:
   1. **Lymphoma:** Tumor of lymph nodes.
   2. **Leukemia:** Tumor of the blood, bone marrow and immune system.
   3. **Hepatocarcinoma:** Tumor of the liver.
   4. **Astrocytoma, gilioma, retinoblastoma, neuroblastoma:** Tumor of the central nervous system.

Causes

1. **Environmental:** there are so many environmental carcinogenic factor including:
   A. Chemical carcinogens: including wide range of food preservatives, dyes, smokes and many others.
   B. Physiological carcinogens: including UV light, X ray, nuclear radiation and many others.
   C. Biological carcinogens: including mostly viruses and some bacteria:
      1. Hepatitis B virus (HBV) and (HCV) can cause hepatocellular carcinoma in chronically infected persons.
      2. Epstein Barr virus (EBV) can cause Burkitt's lymphoma.
      3. Human T lymphocyte virus-1 (HTLV-1) can cause T cell leukemia.
      4. Human papilloma virus (HPV) can cause cervical carcinoma in women.
      5. Helicobacter pylori can cause gastric carcinoma.
      6. Human herpes virus-8 (HHV-8) can cause Kaposi sarcoma in AIDS patients.
2. **Genetic:** many of the people with tumors have certain genetic constitutions which indicate a familial association of tumors like breast cancer and ovarian cancer.
3. **Hormonal:** hormonal changes (mainly in women) may trigger certain types of tumors. The best example of that is the breast cancer which occurs more commonly in women with
   1. Pregnancy at old ages (>35 years).
   2. Early age of menstruation.
   3. Late onset of menopause.
   4. Post menopausal hormone replacement therapy.

Tumor antigens

In tumor, there are many antigens (which they are not found normally or found in different forms or quantities) are expressed on the tumor cells surface or generalized inside the tumor cell. The earliest classification of tumor antigens was based on their patterns of expression.

1. **Tumor-specific antigens:** Antigens that are expressed on tumor cells but not on normal cells were called tumor-specific antigens; some of these antigens are **unique** to individual tumors **(chemical carcinogens)**, whereas others are **common**, shared among tumors of the same type **(viral carcinogens)**.
2. **Tumor-associated antigens:** Many of tumor antigens that expressed in case of tumor could also expressed in normal cells but either with low level or at different development stage. For examples
   A. **Alpha-feto protein (αFP):** is a protein that secreted by the liver of embryo, but it should be disappear after birth. When it appears again in adult serum it may indicate liver and gonadal (testes) cancer.
   B. **Carcino-embryonic antigen(CEA):** this types of antigens is expressed in certain tumors of the gastrointestinal tract (as colonic cancer),however it can also expressed in the patient serum with inflammation of pancreas (pancreatitis) or inflammation of colon (colitis). The presence of CEA is not specific to the tumor only and not diagnostic. However it can used to monitor the response to therapy against colonic cancer by measuring its level in the patient serum.
   C. **Cancer testes antigens:** these antigens are expressed normally in the tissue of the testes, but when expressed in other tissue as lung or breast it indicates tumors of these organs.
   D. **Mutated antigen:** certain antigens are found normally in the body, but when they mutated they change into tumor antigens example: protein 53 (P53) this protein normally inhibit cellular proliferation.
   E. **Melanoma-melanocyte differentiation antigens:** certain enzymes like tyrosinase enzyme is found normally in skin cells (melanocytes) in small amount, but it also found in skin tumor cells (melanoma) in large amount (quantitative difference). **Example (tyrosinase enzyme, melanoma antigen recognized by T cells)**

Immune responses to tumors

Innate immunity

The role of **macrophages** in anti-tumor immunity is largely inferred from the demonstration that invitro, activated macrophages can kill many tumor cells more efficiently than they can kill normal cells.

NK cells kill many types of tumor cells, especially cells that have reduced class I MHC expression and can escape killing by CTLs. Invitro, NK cells can kill virally infected cells and certain tumor cell lines, especially hematopoietic tumors.

Adaptive immunity

The effector mechanisms of both cell-mediatedimmunity and humoral immunity have been shown to kill tumor cells in vitro.

Cell-mediated immunity

The principal mechanism of tumor immunity is killing of tumor cells by CD8 CTLs.

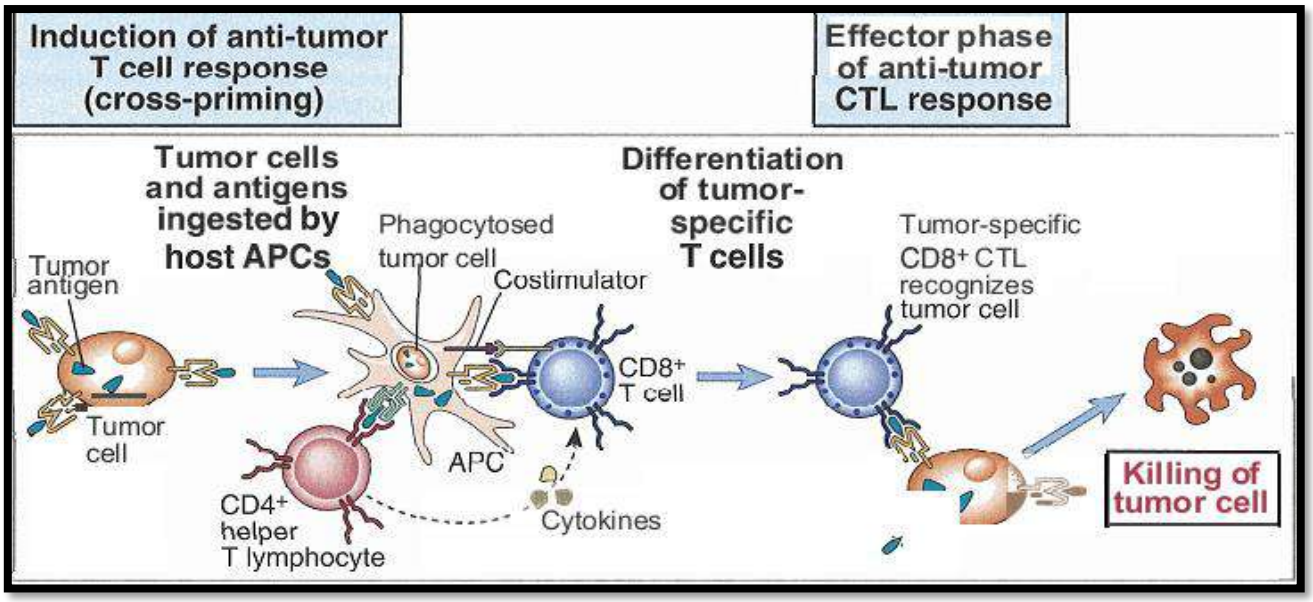


Figure: lnduction of T cell responses to tumors. antigens.

Humoral immunity

Tumor-bearing hosts may produce antibodies against various tumor antigens. For example, patients with serum antibodies against EBV encoded antigens expressed on the surface of the lymphoma cells. Antibodies may kill tumor cells by activating complement or by antibody-dependent cell-mediated cytotoxicity, in which Fc receptor-bearing macrophages or NK cells mediate the killing. However, the ability of antibodies to eliminate tumor cells has been demonstrated largely invitro, and there is little evidence for effective humoral immunity against tumors.

Evasion of immune responses by tumors

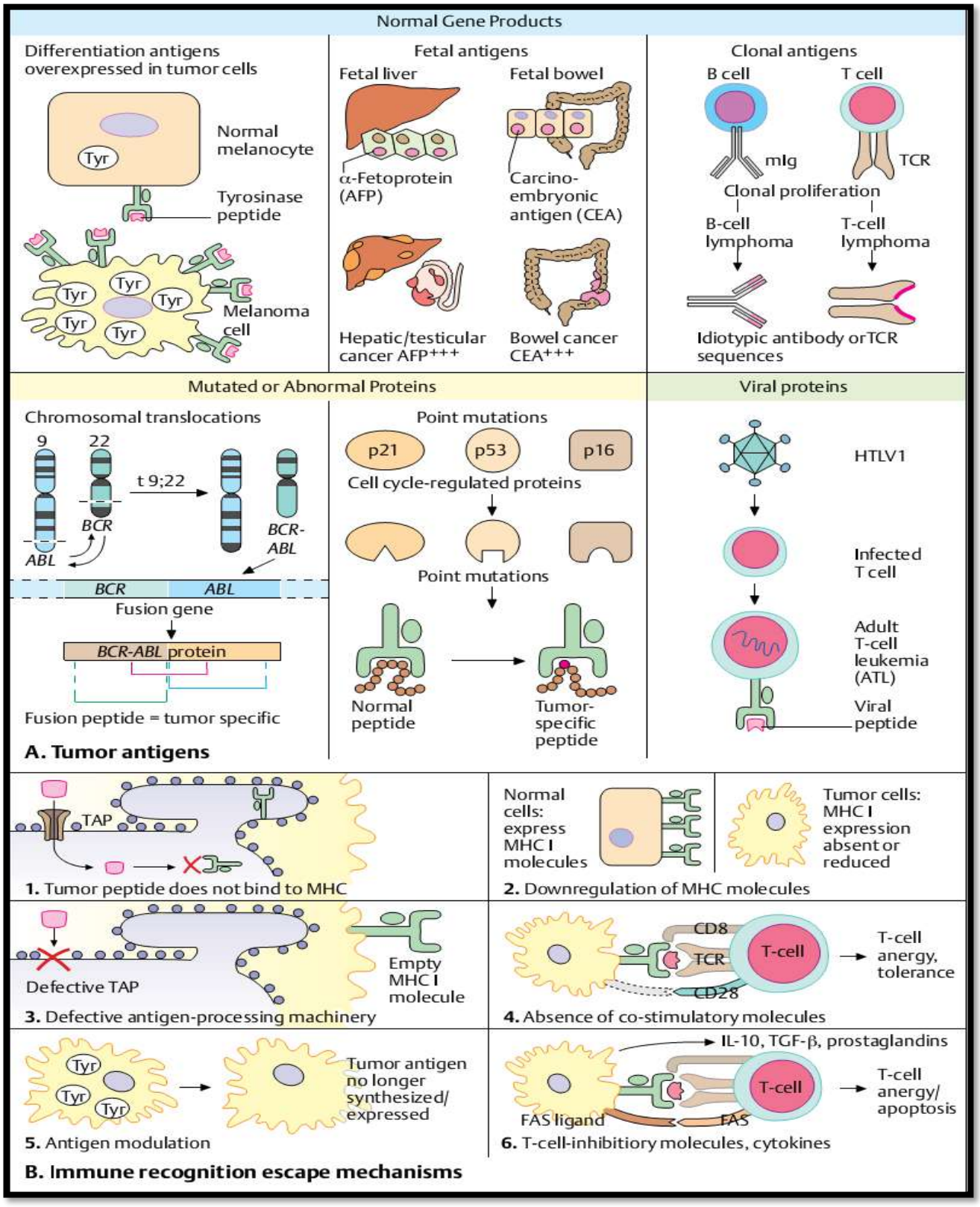
Many malignant tumors possess mechanisms that enable them to evade or resist host immune responses:

1. Class I MHC expression may be down-regulated on tumor cells so that they cannot be recognized by CTLs.
2. Tumors lose expression of antigens that elicit immune responses.
3. Tumors may fail to induce CTLs because most tumor cells do not express costimulators or class II MHC molecules.
4. The products of tumor cells may suppress anti-tumor immune responses.
5. Tumor antigens may induce specific immunologic tolerance.

Diagnosis

1. **Histopathology:** by taking a biopsy of the tumor mass and recognize the transforming cells.
2. **Enzymatic:** measuring certain enzymes that may change during the course of the disease.
3. **Clinical presentation.**
4. **Immunodiagnosis:** in many occasions immunodiagnosis is more sensitive and can diagnosis tumor more early than other diagnostic methods. This method depends basically on the detection of tumor antigens (markers) in the patient serum or tissue biopsy. Generally, there are two method for that:
    1. **In vivo method** which means injecting of radiolabelled mAb against suspected tumor marker in the body then to follow any binding reaction between the Ab and the Ag inside the body by a device called immune-scintigraphy. This method is used to monitor the level of CEA in people with colonic cancer.
    2. **In vitro method** which means taking sample (blood or tissue) from the patient and reacting it with the specific Ab for the expected tumor marker. This method is used to detect α-feto protein in the serum of patients with suspected liver tumors.

Other application for this method is to use an anti-MHC-class I Ab with breast biopsy to detect the presence or absence of MHC-class I molecules on breast cells. Breast cells with tumor are usually lack the presence of these molecules on their surfaces (IFAT method).


Normal Gene Products
Differentiation antigens overexpressed in tumor cells
Tyr
Normal melanocyte
Tyrosinase peptide
Melanoma cell
Fetal antigens
Fetal liver
Fetal bowel
α-Fetoprotein (AFP)
Carcino-embryonic antigen (CEA)
Hepatic/testicular cancer AFP+++
Bowel cancer CEA+++
Clonal antigens
B cell
T cell
mIg
TCR
Clonal proliferation
B-cell lymphoma
T-cell lymphoma
Idiotypic antibody or TCR sequences
Mutated or Abnormal Proteins
Chromosomal translocations
9
22
t 9;22
BCR
ABL
BCR-ABL
Fusion gene
BCR-ABL protein
Fusion peptide = tumor specific
Point mutations
p21
p53
p16
Cell cycle-regulated proteins
Point mutations
Normal peptide
Tumor-specific peptide
Viral proteins
HTLV1
Infected T cell
Adult T-cell leukemia (ATL)
Viral peptide
A. Tumor antigens
TAP
1. Tumor peptide does not bind to MHC
Normal cells: express MHC I molecules
Tumor cells: MHC I expression absent or reduced
2. Downregulation of MHC molecules
Defective TAP
Empty MHC I molecule
3. Defective antigen-processing machinery
CD8
TCR
T-cell
CD28
T-cell anergy, tolerance
4. Absence of co-stimulatory molecules
Tumor antigen no longer synthesized/ expressed
5. Antigen modulation
IL-10, TGF-β, prostaglandins
T-cell
FAS ligand
FAS
T-cell anergy/ apoptosis
6. T-cell-inhibitory molecules, cytokines
B. Immune recognition escape mechanisms