Immunology

Title : Tumor Immunology

Lec no : 11

Done By : Johainah + Nour + Ahmad + Nada

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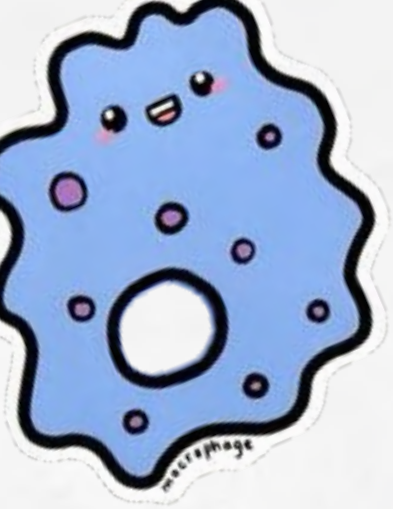
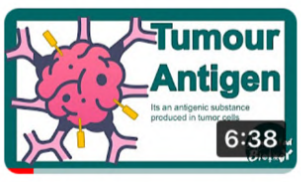


Useful Links

1. 

What are driver mutations vs passenger mutations?
HealthTree University Myeloma · 10K views

https://youtube.com/watch?v=JWPt7AUuo-w&si=bqTJ8uOA4so85Mkw

2. 

Tumour antigens | Tumour specific antigen | Tumour-associated antigen | Tumour immunity
Animated biology With arpan · 2.8K views

https://youtube.com/watch?v=iY4QxrWABcI&si=DwPZFIPdT_oFsWpg

3. 

Adoptive Cell Therapy: Turning Immune Cells into Cancer Fighters
Cancer Research Institute · 64K views

https://youtu.be/Hivji9V9i-8?si=ol--4iWrreOh6tsT

4. 

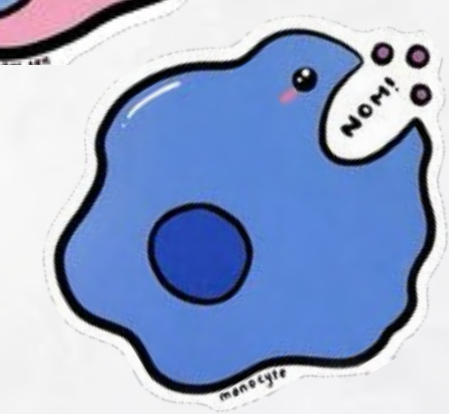
Cancer immunology (how cancer cells elude immune system)
Shomu's Biology · 45K views

https://youtu.be/h6E2Kv-OzjM?si=iGHTyYIcEjcXUvU6

5. 

How mRNA cancer vaccines work
Science in Motion · 2.8K views

https://youtu.be/zL1l8PpAJJg?si=-4vwHyEE8bSDercg



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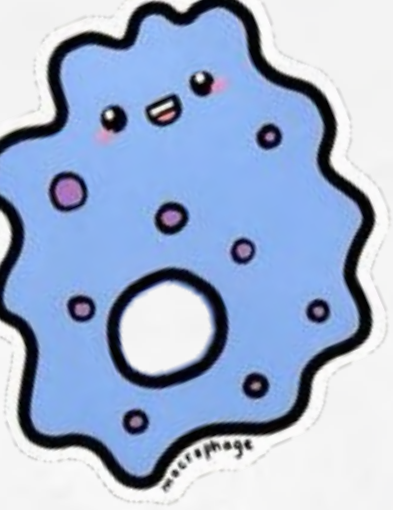


Introduction

احياناً بنسمع مثلاً حد عمره 35 و صار عنده tumor قبل هيك ما كان مريض يعني هاد immune competitive مش immune supression

في عندنا immune surveillance في جسمنا بضل مراقب الوضع اذا عندنا tumor او pathogen، ممم طيب لو عنا ال immune surveillance اذا ليش بصير عنا tumor ؟ في عنا عدة عوامل بتساهم بهاد الموضوع حنتطرق الها اليوم

و بيعلموا escape من surveillance، مثلا الخلية ما تطلع ال neoantigens او ال cells عم تعمل interfering لل presentation تبع هدول الantigens يعني انا عندي antigen بس ما في MHC لتعمل presentation

و ايضا من الامثلة على ال immune evasion ممكن ال tumor cells تعمل maniculating لل immune system فال T regulatory وظيفتها تثبط جهاز المناعة لما يصير عنا clearance طيب ممكن هاي ال T regulatory تحفزها ال T cells بحيث تثبط جهاز المناعة و ما تتعرف على ال Tumor cells

**الدكتور سأل الفرق بين passenger mutation and driver mutation ؟

Passenger mutation : changes in the sequence of DNA do not cause problems, it will give us neoantigen, mutation in normal protein in cell, immune system will recognize them

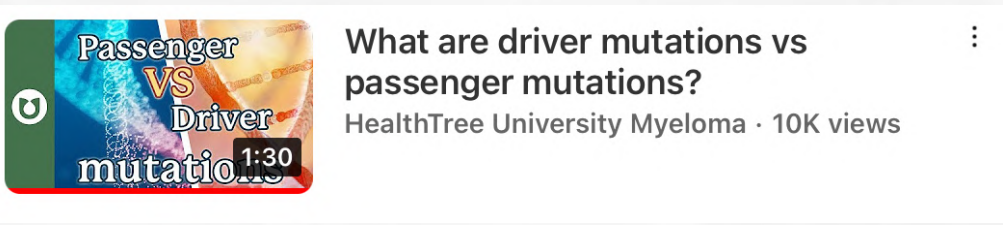
Driver mutation : allow cancer to grow and invade the human body, neoantigen not present in normal cells, it will recognise as forgiven

We are all generating mutations, we all have genes in which changes are occuring in the DNA, and we never know about ot because they are not bad changes, maybe the cell does not survive.

So if we look at all the mutations we may find that there are sequences in the DNA that may be different than normal but they do not have a problem.

We refare to the mutations as a driver mutation, they drive a trait, they drive a cell to proliferate, then they drive a cell to go to the bone marrow, they may drive the cell to not die, then they drive the cell to resist a therapy, these mutations are actionable

Passenger mutations have no particular effect on the cell



- Pathological cell masses derived by abnormal and uncontrollable clonal expansion of a single cell
- Cells that continue to replicate, fail to differentiate into specialized cells, and become immortal.

الخلايا تتكاثر بدون توقف و حتفشل بأنها تتمايز و رح تصير immortal يعني خالدة بالتالي ما رح الاقي عندهم death mechanism الي متعارف عليها يعني ما رح تموت

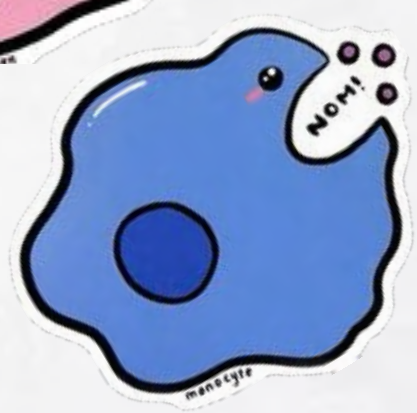
- Cells become antigenically different from normal cells

بسبب سرعة الreplication حيظهر antigen جديد على tumor cell مختلف عن الخلية الأصلية

- They are recognized and destroyed by immune system

- Tumors can be:

1. Malignant: A tumor that grows indefinitely and spreads (metastasis)--also called cancer: kills host
2. Benign: A tumor that is not capable of metastasis: does not kill host



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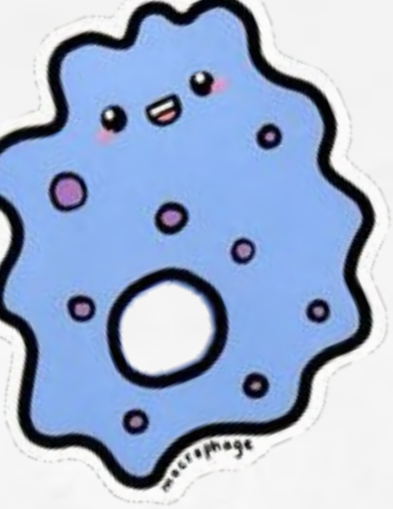

Types of Cancer

- **Carcinoma:** arising from **epithelial tissue,** such as glands, breast, skin, and linings of the urogenital, digestive, and respiratory systems **(89.3% of all cancers)**

- **Sarcoma:** solid tumors of muscles, bone, and cartilage that arise from the embryological **mesoderm** (1.9% of all cancers)

muscles, bones, cartilages <- هي الي رح تبني mesoderm ال
sacroma و لو الcancer طلع منها رح أسميه

- **Leukemia:** disease of **bone marrow** causing excessive production of **leukocytes** (3.4% of all cancers)

- **Lymphoma, Myeloma:** diseases of **the lymph nodes and spleen** that cause excessive production of **lymphocytes** (5.4% of cancers)

Etiology of Tumor

- **Inherited :**

Expression of inherited oncogene: Breast, colon, prostate cancers

- **Viral:**

- Viral genome incorporated into host gene

دمج الجينوم الفايروسي بالجين

Viruses might lead to transformation of the cell and development of cancer especially DNA viruses. As, these viruses become latent which means that they remain in the cell without replication and when they have studied the cancerous cell transformed due to these viral infections they found that the integration of the viral genome into the host cell is directly linked to the cancerous transformation.

- Human papilloma, herpes type 2, HBV, EBV (DNA) +CMV
- Human T-cell leukemia virus (RNA)

تذكير هدول الفايروسات بينهم شي مشترك و هو انهم latent viruses و بتخبوا في certain cells و مجرد ما صار supression برجعوا active

- **Chemical:**

- Poly cyclic hydrocarbons **cause** sarcomas موجود بالنفط و الفحم الخام و البنزين

- Aromatic amines **cause** mammary carcinoma Found in industrial and manufacturing plants, tobacco smoke, commercial hair dyes, and diesel exhaust

- Alkyl nitroso amines **cause** hepatoma

- **Radiological:** Ultraviolet & ionizing irradiation

- **Spontaneous:** failure in the cellular growth control

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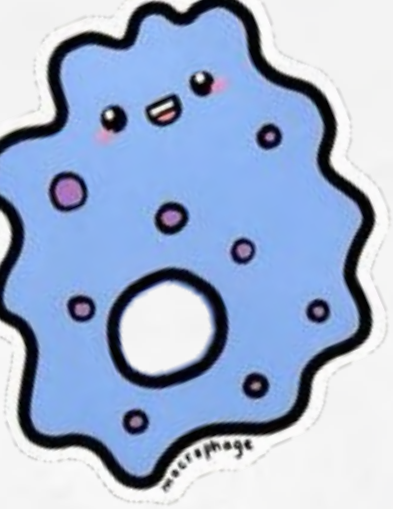
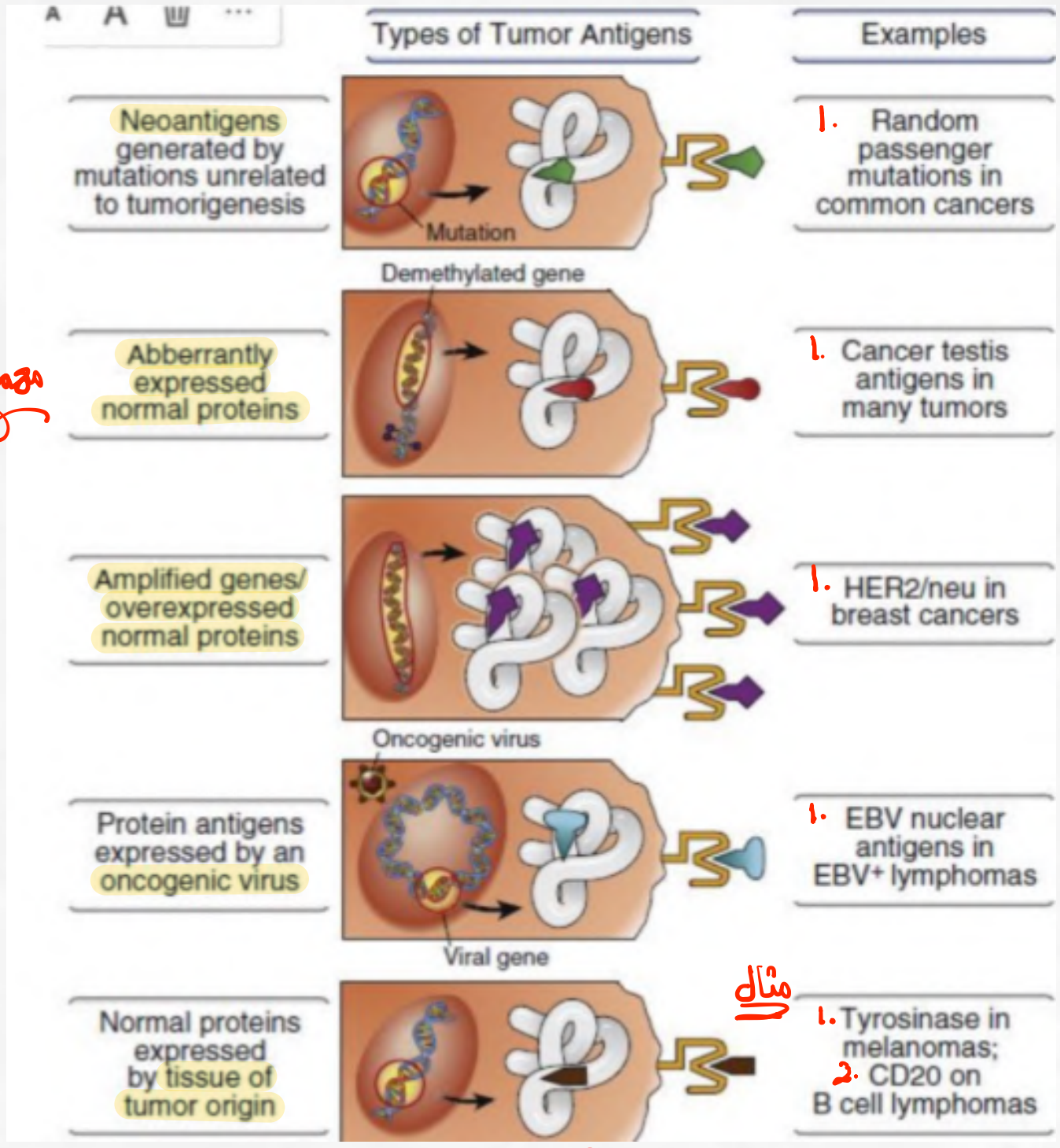


مطلوبة و الشرح بالأسفل



**هذي

What are the types of tumor antigen?

neoantigen generated by mutation unrelated to tumorgenises = passenger mutation

Driver mutation = drive the normal cell to cancer cell as result a quick replication occure, introduction of multiple mutations into other sites in gene of these cell so it will I've neoantigen + express normal proteins

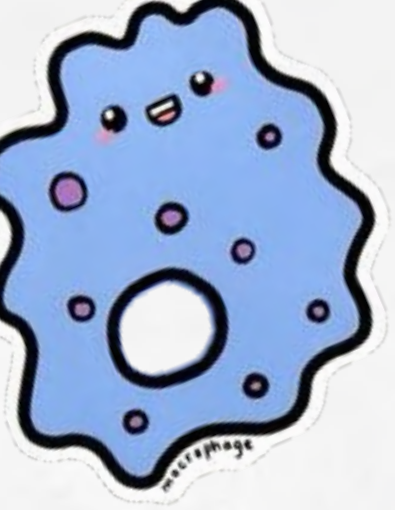
حيصير عنا زيادة في عدد normal protein بدل 10 بصيروا 30

مفهوم جداً

Tumour antigens | Tumour specific antigen | Tumour-associated antigen | Tumour immunity

Animated biology With arpan · 2.8K views

وقل رب زدني علماً



Tumor Antigens

شرح للرسمة
في الاعلى و
مهم

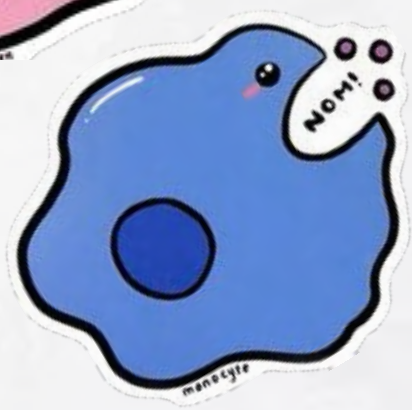
Malignant tumors express various types of molecules that may be recognized by the immune system as foreign antigens. Protein antigens that elicit CTL responses are the most relevant for protective antitumor immunity. These tumor antigens have to be present in the cytosol of tumor cells in order to be recognized by CD8 + CTLs. The tumor antigens that elicit immune responses can be classified into several groups:

• Neoantigens encoded by randomly mutated genes . Recent sequencing of tumor genomes has revealed that common human tumors harbor a large number of mutations in diverse genes, reflecting the genetic instability of malignant cells. These mutations usually play no role in tumorigenesis and are called passenger mutations. Many of these mutations result in expression of mutated proteins, called neoantigens because they are newly expressed in the tumor cells but not in the normal cells of origin of the tumor. Because T cells only recognize peptides bound to major histocompatibility complex (MHC) molecules, mutated tumor proteins can be recognized only if peptides carrying the mutated amino acid sequences can bind to the patients' MHC alleles. Tumor neoantigens may not induce tolerance because they are not present in normal cells, and are the most common targets of tumor-specific adaptive immune responses. In fact, the number of these mutations in human cancers correlates with the strength of the antitumor immune responses patients mount and the effectiveness of immunotherapies that enhance those responses. In experimental tumors induced by chemical carcinogens or radiation, the tumor antigens are also mainly random mutants of normal cellular proteins.

• Products of oncogenes or mutated tumor suppressor genes . Some tumor antigens are products of mutations, called driver mutations, in genes that are involved in the process of malignant transformation. The driver mutations that encode tumor antigens may be amino acid substitutions, deletions, or new sequences generated by gene translocations, all of which can be seen as foreign.

• Aberrantly or overexpressed expressed structurally normal proteins . In several human tumors, antigens that elicit immune responses are normal (unmutated) proteins whose expression is dysregulated in the tumors, sometimes as a consequence of epigenetic changes such as demethylation of the promoters in genes encoding these proteins, and sometimes by gene amplification. These structurally normal self antigens would not be expected to elicit immune responses, but their aberrant expression may be enough to make them immunogenic. For example, self proteins that are expressed only in embryonic tissues may not induce tolerance in adults, and the same proteins expressed in tumors may be recognized as foreign by the immune system.

• Viral antigens . In tumors caused by oncogenic viruses, the tumor antigens may be products of the viruses



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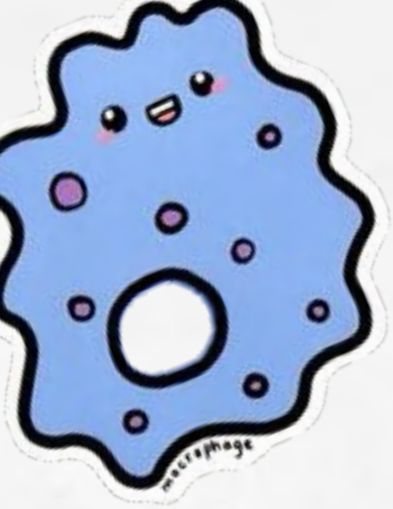


Tumor Associated Antigens

الموضوع مهم جداً

- Viral Antigen: Viral proteins and glycoproteins

New antigens produced by virally infected host cells under control of viral nucleic acid

بلاقي viral antigen موجود بالخلية متل بروتين والخلية المصابة قاعده تفرزها لان nucleic acid الموجود بالخلية هو المسيطر والي يخليها تفرز

- Tumor specific antigens: Tumor cells develop new antigen specific to their carcinogen

خلية محدده صار فيها كانسر رح تنتج antigen خاص فيها

مثل WBC اذا صار فيها lymphoma رح تصير تفرز specific antigen متل CD12

- Tumor specific transplantation antigens: Tumor cells express new MHC antigens due to alteration of normally present MHC antigens

مرات الكانسر رح يغيرلي MHC الموجود بالخلية

- Oncofetal antigens:

1. Carcino-embryonic antigens (CEA)

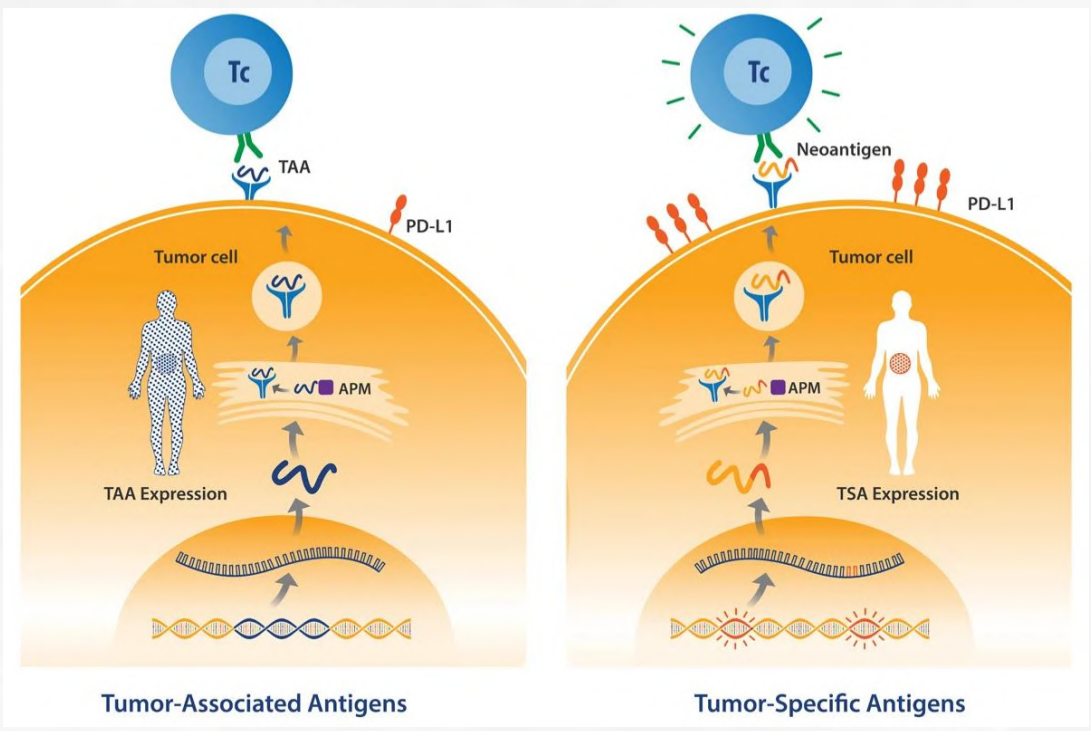
Normally expressed during fetal life on fetal gut

Reappearance in adult life: GIT, pancreas, biliary system and breast cancers

2. Alpha fetoprotein:

Normally expressed in fetal life

Reappearance in adult life; hepatoma

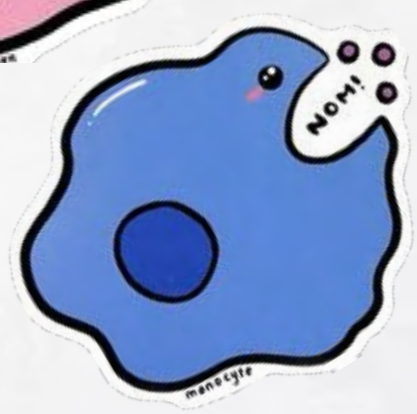


- Public shared antigens, further divided into :

a) Tumor specific antigen, founded on cancerous cells only & not on normal cells

b) Tumor associated antigens, expressed at low level in healthy cells but at high level in cancerous cells (considered self antigens).

- The tumor-specific antigen arise mostly from oncogenic driver mutations that generate novel peptide sequences. So, when cancerous transformation takes place, synthesis of new proteins which are specific to this cell will follow. Forming what is called “Neoantigen.
- In the case of tumor-associated antigens, it arises mostly from either genetic amplification (increase in translations so that the amount of protein expressed from this cell increases) or due to post-translation and modification after a translation of the protein, a slight modification occur as a result of this cancer's transformation which is going to lead to a change in the folding of the protein to be recognized as a cancerous protein.
- the tumor-specific antigens can also be generated by a oncoviruses while for the tumor associated antigens, the tendency for expression that is higher and preferential for tumor cells.
- An example of a tumor specific antigen is the alpha fetal protein and the carcino-embryonic antigens (CEA) which are normally expressed in the fetal life and they appear upon cancerous transformation in the adult life



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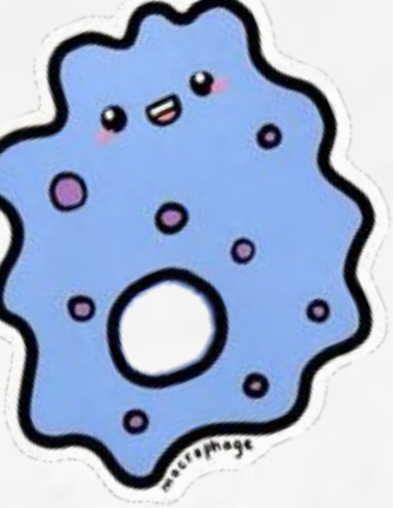


Tumor-Associated Antigens			Tumor-Specific Antigens		
Overexpressed proteins, differentiation antigens	Cancer testis antigens	Target types	Oncoviral antigens	Shared Neoantigens	Private Neoantigens

Fetal antigen

Virus that can cause cancer

Present in other normal cell
more display on tumor cell بس يصير

Neoantigen which are more specific to the type of cancer cell,differ from person to person

VARIABLE	GOOD	Tumor specificity	IDEAL

Good displaying ✅

HIGH	LOW	Central tolerance	NONE

Already in the cell

Because it is foreign

100% foreign

HIGH	Prevalence in multiple patients	HIGH	LOW

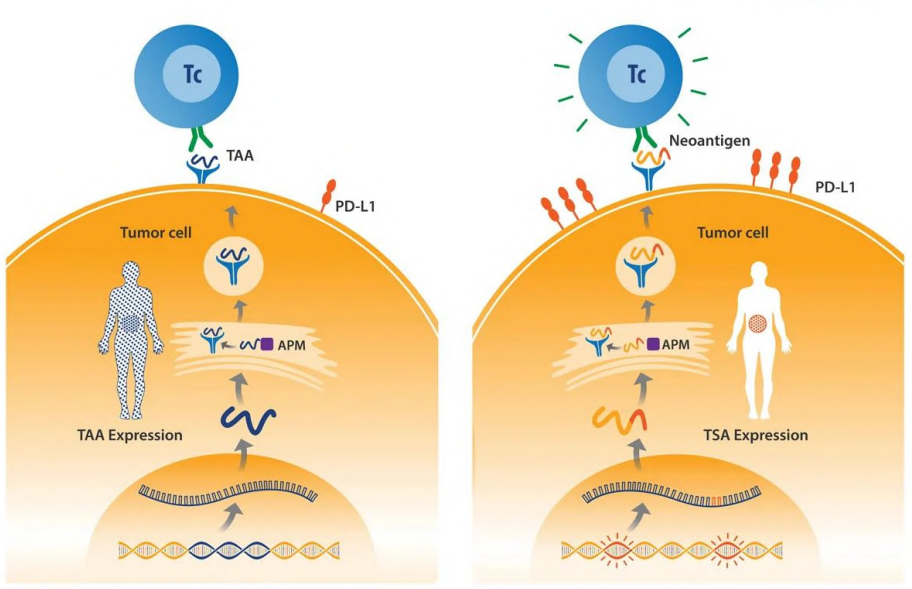
لو جبت 100 شخص كلهم مصابين بال cervical cancer بسبب HPV معناته معظمهم يعني اكثر من 90 % منهم بكون عندهم displayed antigen

كل مريض ممكن يختلف عن الاخر

جزء من العلاج الي عم يشتغلوا عليه هو انهم يجيبوا كل مريض و يعملوا اله sequence و نشوف شو الmutation الموجودة عنده على الgenes بعدين نستخدم الAI و تشوف شو هي الmutation الموجودة و تربطها مع ال HLA أو ال MHC و نشوف الاكثر قابلية للارتباط مع HLA و بالتالي احنا بنعمل vaccine ضد هدول ال specific antigens و بالتالي بتختلف من شخص لآخر

Targeting TSA and TAA

CrownBio
CONNECTING SCIENCE TO PATIENTS



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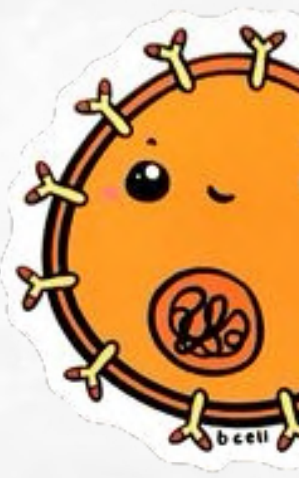

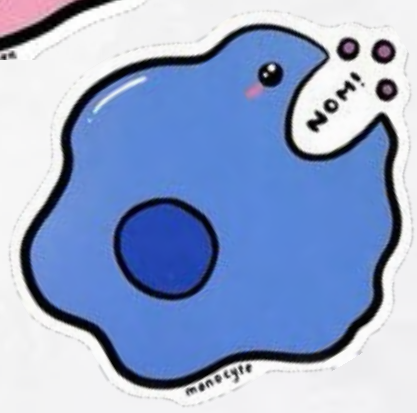

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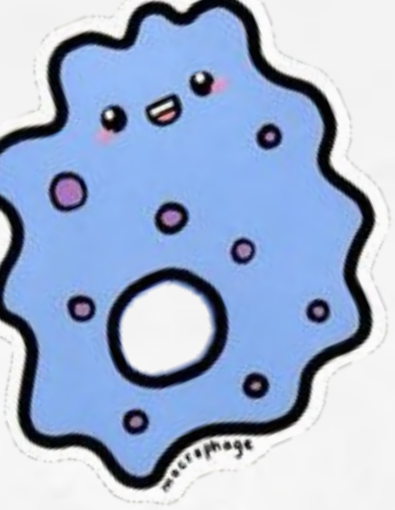


Evidence for Immune Reactivity to tumors

• Tumors that have severe lympho-reticular infiltration have a better prognosis than those that do not.

الي يكون فيهم واضح انه عندك immune response وبلاقي infliltration في lymphocytes و ال immune cells
هاد معناته عندهم better prognosis
ليش لان lymph node هي مكان وجود B,T cell واستقرارها، ف اذا تكون ال tumor هناك رح يكون سهل الالتقاء والتعرف عليه

• Certain tumors regress spontaneously ← Spontaneous Shrinkage.

• There is an increased incidence of primary and secondary malignancies (particularly lympho-reticular tumors) in immunodeficient patients

ضعف immune system رح يودي الى زيادة فرصة التعرض لل cancer
الدكتور ذكرنا بتوضيح سابق من محاضرة 8 حأحط الكم سكرين التفريغ

Why are HIV patients more susceptible for viral infections and tumor?

حكينا المرة الماضية عن الcross priming او الcross presentation، بكون عنا ال antigen extracellular و جزء منه بروح عالendocytic vessicle و بصير اله destruction و fusion مع ال MHC II و جزء منه بروح على cytoplasm و بصير اله destruction عبر الproteosomes بعدين بصير الها displaying على MHC I لهيك ال antigen presenting cell بتكون رابطة CD4+ و ال CD8+
و بنفس الوقت الCD4 حيفرز cytokines لتنشط و تفعل الCD8، و لما يصير هاد الحكي ال CD8 بتكون activated
هسا مرضى الHIV بكون عندهم ال CD4 قليل و بالتالي ال activation تبع cd8 حيتأثر .

• Antibodies and immune T lymphocytes have been detected in patients with tumors.

لنفرض عند المريض tumor محدده رح الاقي في هديك المنطقة خلايا T lymphocytes او antibodies خصوصا ضد هاد ال tumor

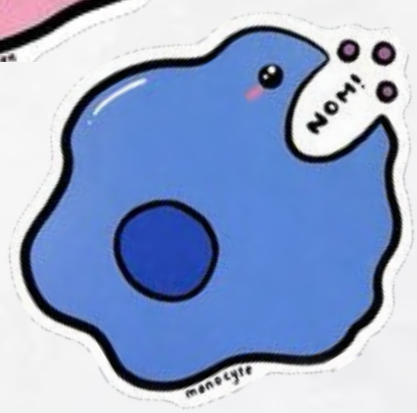
• The young and the very old have an increased occurrence of tumors.

• Finally, animals can be specifically immunized against various types of tumors

cancerous cells can produce neoantigens (antigens which are specific for this cancerous cell) if we take if we take these specific antigens and inject them into the animals the immune system in the animals is going to form antibodies against these antigens. So, on second encounter of those antigens we can see that animals are protected due to the preformed antibodies.

خلينا نشرح بالعربي ،اجيت اخذت tumor cell وبضاعفها واعطيها لحيوان ورح يبلش يتعرف عليها شوي شوي بواسطة ال adaptive system ويكون الها memory,وبعد فتره لو تعرض الحيوان لنفس ال tumor ما رح يصير فيه كانسر

نفس الطريقة ما نجحت عن الانسان مع الاسف



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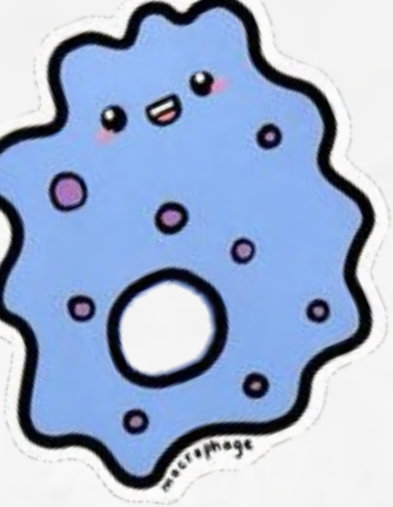

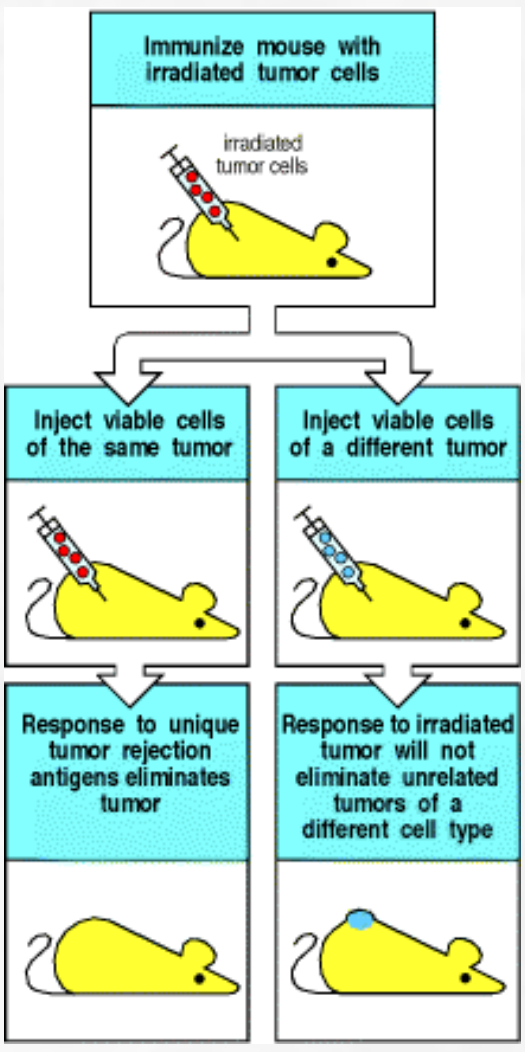

Animal models showed that pre-treatment of mice with killed tumour material could protect against a subsequent challenge.

T cell ablation or T-cell deficient mice removed this protection.

Transfer of T cells from an immunized mouse could protect a naïve mouse from tumour challenge. (Adoptive immunotherapy)

جابوا فار وحقنوا فيه irradiated tumor cells
وبعد فتره بلش يصير Tcell adaptive immune response لهاي ال tumor

حقنوه نوع مختلف من tumor صار عنده كانسر

رجعوا حقنوه بنفس tumor لقوا انه
الفار ما صار فيه tumor

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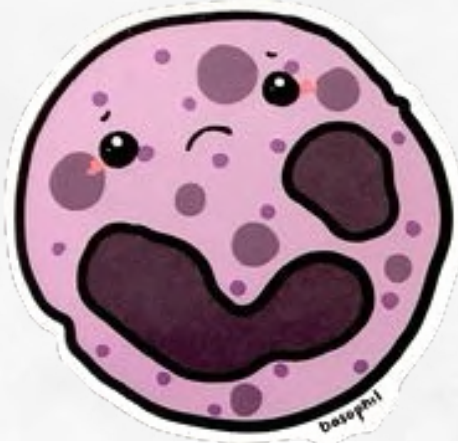
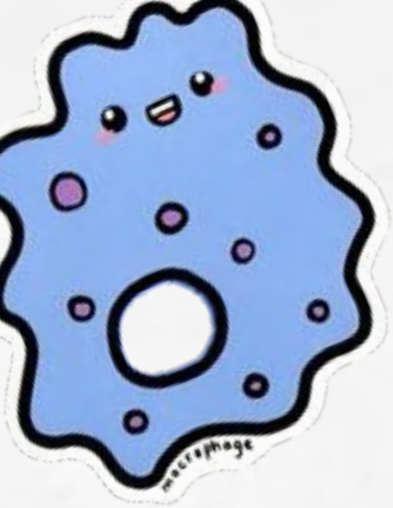




Immune Surveillance System

- During neoplastic transformation, new antigen develop
- The host recognize them as non-self antigens
- Cell mediated immune reactions attack these non-self tumor cells
- Immune response act as surveillance system to detect and eliminate newly arising neoplastic cells

Immune surveillance systems

يعمل متل المراقب ،يعني خلايا السرطانية نتجت ،بس جهاز المناعة الي مصحصح وعارف شغله منيح رح يلقطها بسرعة بمرحلة متقدمة وينتهي الموضوع

This system include :

1) Natural killer (NK) cells : They kill directly tumor cells, helped by interferon, and IL-2

مهمة 2) Cytotoxic T-cells : They also kill directly tumor cell

التوضيح الصفحة التالية ت

One of the modalities to treat cancers is to block the inhibitory signals (the binding between CTLA4 and B7-2 + the binding between PD-l and PD1) to promote more B7 - CD28 binding and therefore killing of the tumor cell.

اذا ال teatement بكون انه نعطي anti-CTLA4 او anti-PD1

3) Cell mediated T-cells (effector T-cells) : They produce and release a variety of lymphokines :

a-Macrophage activation factor that activate macrophages

b-Gamma interferon and interleukin-2 that activate NK

c-Tumor necrosis factor (cachectine): apoptosis, necrosis, immune cell activation, differentiation, and cell migration.

مهم 4) B-cells :

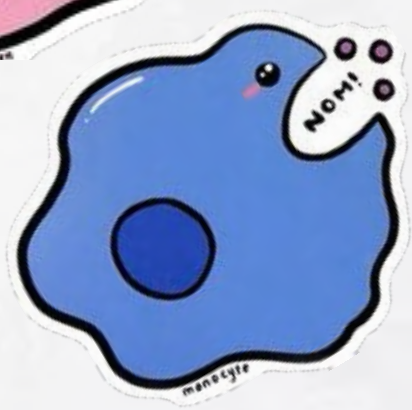
* Tumor associated antigens stimulate production of specific antibodies by host B-cells

* These specific antibodies bind together on tumor cell surface leading to destruction of tumor through:

1. Antibody mediated-cytotoxicity : Cytotoxic T-cells kill IgG-coated tumor cells

2. Activation of macrophages: Sensitized T-cells release macrophage activating factor which activate macrophages

3. Activation of classical pathway of complement leading to Lysis of tumor cells



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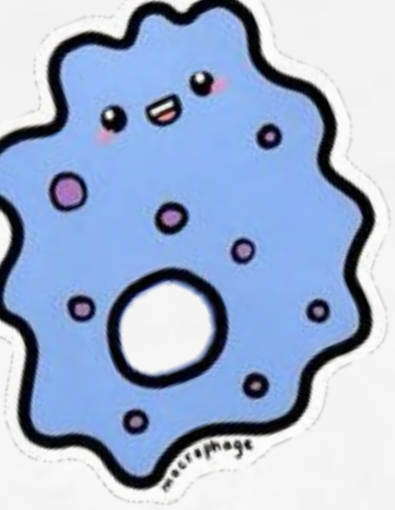


Immune Mechanisms of Tumor Rejection

مهم جدًا من الكتاب

CTL responses against tumors are initiated by recognition of tumor antigens on host antigen-presenting cells (APCs). The APCs ingest tumor cells or their antigens and present the antigens to naive CD8+ T cells in draining lymph nodes.

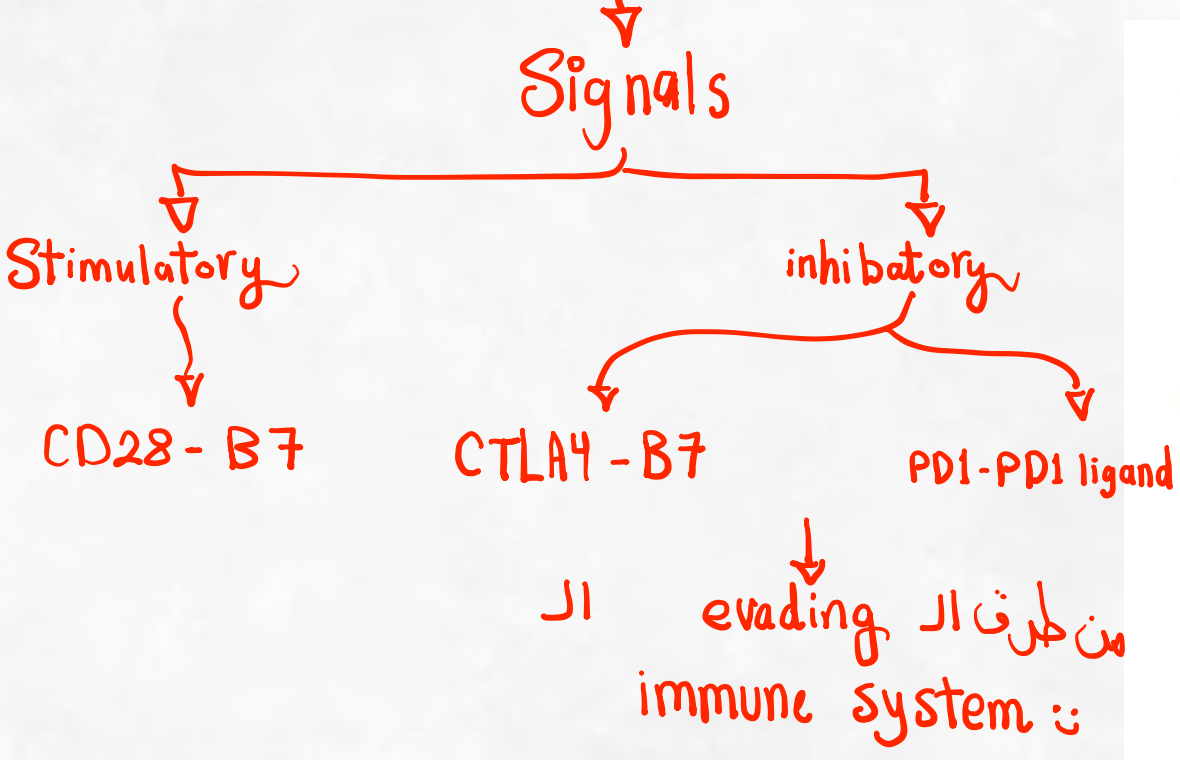
Tumors may arise from virtually any nucleated cell type in any tissue, and, like all nucleated cells, they usually express class I MHC molecules, but often they do not express costimulators or class II MHC molecules. We know, however, that the activation of naive CD8+ T cells to proliferate and differentiate into active CTLs requires recognition of antigen (class I MHC–associated peptide) on dendritic cells in secondary lymphoid organs and also costimulation and/or help from class II MHC–restricted CD4+ T cells .

How, then, can tumors of different cell types stimulate CTL responses? The likely answer is that

1. tumor cells or their proteins are ingested by the host's dendritic cells, transported to lymph nodes draining the site of the tumor, and the protein antigens of the tumor cells are processed and displayed by class I MHC molecules on the host dendritic cells. This process, called cross-presentation or cross-priming. Dendritic cells can also present peptides derived from ingested tumor antigens on class II MHC molecules. Thus, tumor antigens may be recognized by CD8+ T cells and by CD4+ T cells.
2. At the same time that dendritic cells are presenting tumor antigens, they may express costimulators that provide signals for the activation of the T cells. It is not known how tumors induce the expression of costimulators on APCs because, the physiologic stimuli for the induction of costimulators are usually microbes, and tumors are generally sterile. A likely possibility is that tumor cells die if their growth outstrips their blood and nutrient supply, and adjacent normal tissue cells may be injured and die due to the invasive tumor. These dying cells release products (damage-associated molecular patterns (DAMPS) that stimulate innate responses. The activation of APCs to express costimulators is part of these responses.

Once naive CD8+ T cells have differentiated into effector CTLs, they are able to migrate back to any site where the tumor is growing, and kill tumor cells expressing the relevant antigens without a requirement for costimulation or T cell help.

Immune mechanisms in addition to CTLs may play a role in tumor rejection. Antitumor CD4+ T cell responses have been detected in patients, and increased numbers of CD4+ effector T cells, especially Th1 cells, in tumor infiltrates are associated with good prognosis.



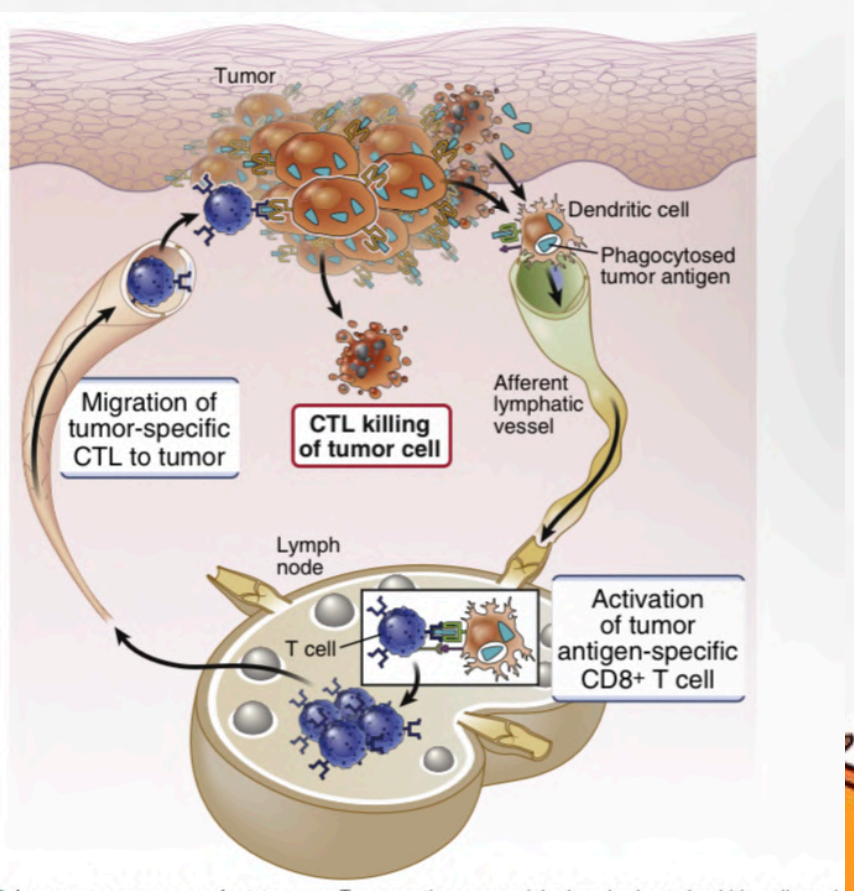


Fig. 10.3 Immune response against tumors. Tumor antigens are picked up by host dendritic cells and responses are initiated in peripheral (secondary) lymphoid organs. Tumor-specific CTLs migrate back to the tumor and kill tumor cells. Other mechanisms of tumor immunity are not shown. *CTL*, Cytotoxic T lymphocyte.

Antitumor antibodies are also detectable in some cancer patients, but whether these antibodies protect individuals against tumor growth has not been established. Experimental studies have shown that activated macrophages and natural killer (NK) cells are capable of killing tumor cells, and Th1 responses work largely by activating macrophages, but the protective role of these effector mechanisms in tumor-bearing patients is not clearly established.

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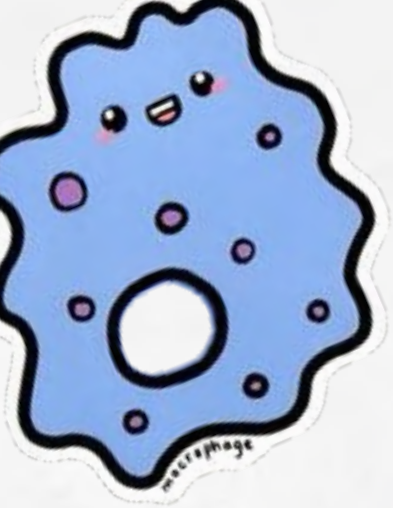


Tumor Escape

Mechanisms by which tumor escape immune defenses:

1) Reduced levels or absence of MHCI molecule on tumor cells so that they can not be recognized by CTLs

اول ما يدخل tumor رح يعمل inhibition لل MHC1 او بغير شكله ف CTLs ما رح تقدر تتعرف عليه وما رح تقدر انها تقتل هاي الخليه ،فهي كانها هربت من جهاز المناعة

2) Some tumors stop expressing the antigens (not essential for tumor growth) These tumors are called "antigen loss variants"

لما يطلع tumors يبلش يفرز antigens وتتعرف عليه immune system وتقتله، تجي خلية كانسر تعمل حركة ذكيه تتعرف على هاد antigen وتخفف من انتاجه لغاية ما تفقده تماما ويختفي هاد antigen وتبطل خلايا immune system قادره انها تتعرف عليه

3) Production of immunosuppressive factors by tumor e.g. transforming growth factor (TGF-β): the early stages it inhibits cellular transformation and prevents cancer progression. In later stages TGF-β plays a key role in promoting tumor progression through mainly 3 mechanisms: facilitating epithelial to mesenchymal transition, stimulating angiogenesis and inducing immunosuppression

خلايا tumor cell تبلش تفرز TGF عشان تعمل immunosuppressive مثل :
IL8, Vascular enduthelum growth factor, IL10

4) Tumor antigens may induce specific immunological tolerance: state of unresponsiveness of the immune system to substances or tissue that have the capacity to elicit an immune response in a given organism.

Immunological tolerance: is a state of unresponsiveness of the immune system to substance or tissue that has the capacity to elicit an immune response in a given organism.
*meaning that if there is a foreign Ag, Once it is recognized by the immune system, activation of the adaptive immune system will take place leading to the killing of this Ag. But if it was Self- antigen, No Activation of the adaptive immunity will follow the antigen recognition in which it is called (self tolerance)
*cancerous cell antigens can undergo the Self tolerance in which after recognition No activation of the adaptive immunity occurs and the cancerous cell continue growing.

5) Tumor cells have an inherent defect in antigen processing and presentation

As known before, cancerous antigens must attach to MHC to appear on the surface of the cell, and with the ability of tumor cells to modify the MHC and change their antigens; this will create a defect in the process of antigen presentation upon the cell surface, preventing the recognition of the tumor cells by immune system

6) Blocking of receptors on T-cells by specific antigen antibodies complex (after shedding of tumor Ag) prevents them from recognizing and attacking tumor cells

tumor cells antigens after being shedded or being soluble, it can bind to the TCR (T cell receptors) and neutralize it so that T- cells cant bind to or recognize the antigens on the surface of tumor cells and attack them

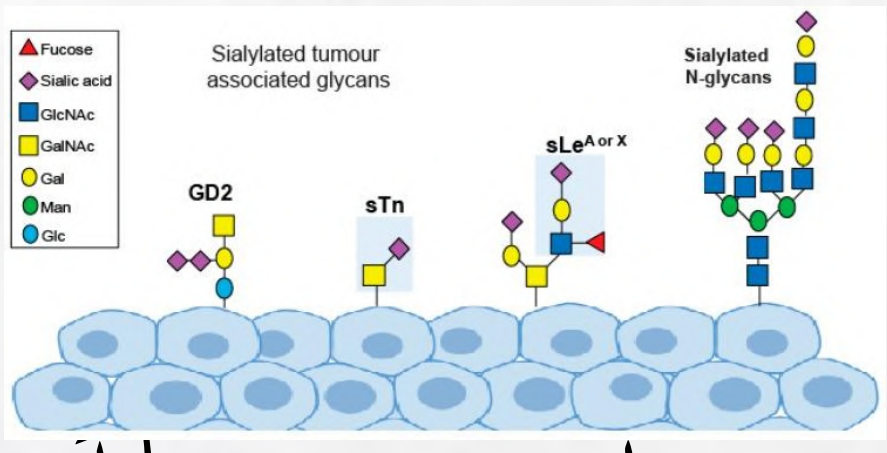
7) Antigens on the surface of tumors may be masked by sialic acid-containing mucopolysaccharides

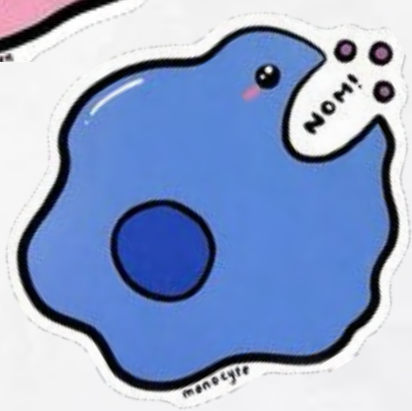
هون رح تغطي ال antigen بماده متل sialic acid عشان ما يتعرف عليه ال immune system

8) Immune suppression of the host as in transplant patients who show a higher incidence of malignancy

immune-suppression which is used in cases of transplantation can increase the possibility of cancer transformation.

لما بدي اجي اعمل عملية زراعة ،بثبط جهاز المناعة وهاد الاشي بخلي المريض اكتر عرضه انه يصير عنده كانسر لان في خلايا تكون منتظره لحظه الضعف هاي عشان تتحول وتهجم





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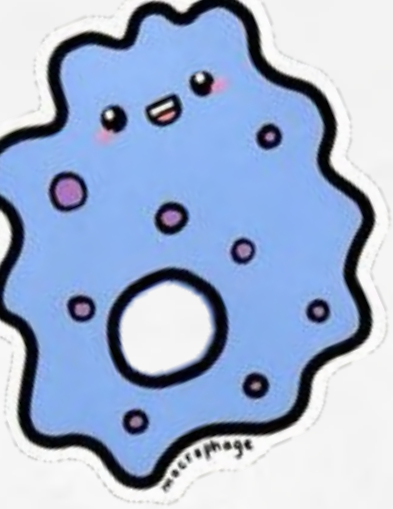

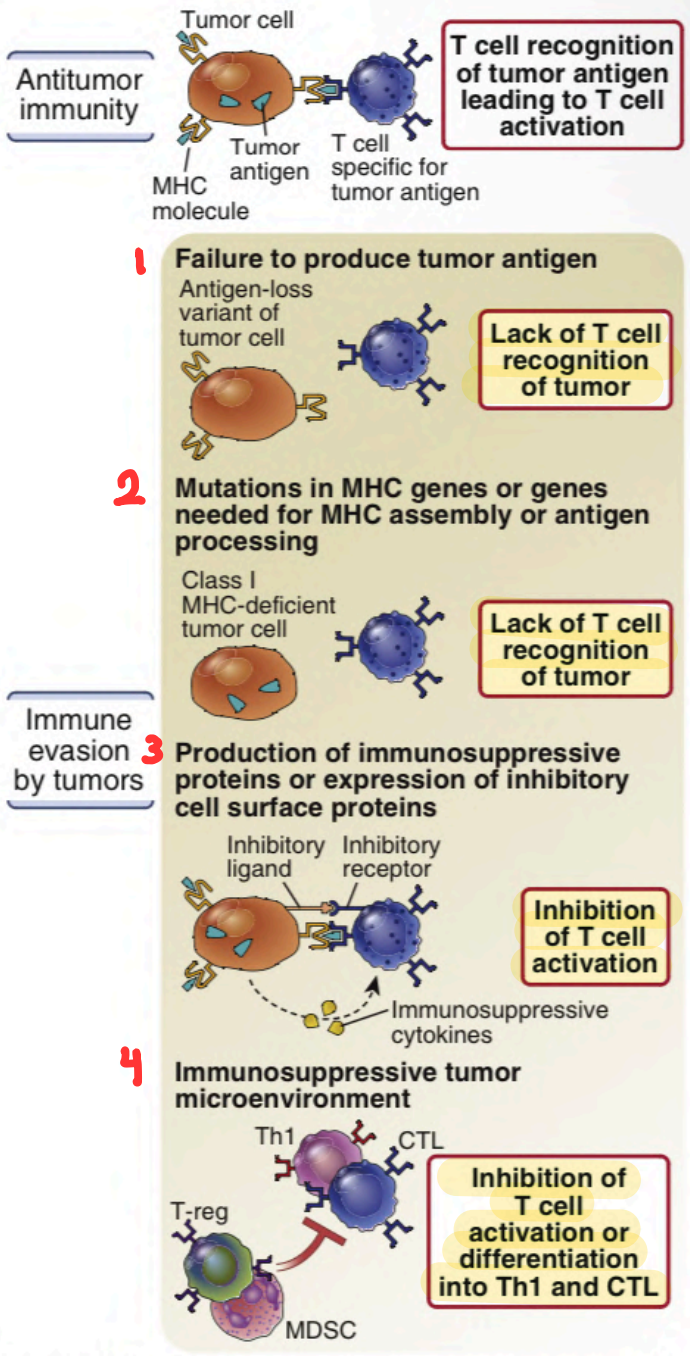

Fig. 10.4 How tumors evade immune responses. Antitumor immunity develops when T cells recognize tumor antigens and are activated. Tumor cells may evade immune responses by losing expression of antigens or major histocompatibility complex *(MHC)* molecules or by producing immunosuppressive cytokines or ligands such as PD-L1 for inhibitory receptors on T cells. Tumors may also create an immunosuppressive microenvironment with regulatory T cells and antiinflammatory myeloid cells. *CTL*, Cytotoxic T lymphocyte, *MDSC*, myeloid derived suppressor cell.

Tumor Markers

• Anything present in or produced by cancer cells or other cells of the body in response to cancer or certain benign (noncancerous) conditions that provides information about a cancer

أي شيء موجود في الخلايا السرطانية أو تنتجها أو خلايا الجسم الأخرى استجابًة للسرطان أو بعض الحالات الحميدة)غير السرطانية(التي توفر معلومات حول السرطان

- Tumor markers : They are either

1. Tumor antigens

• diagnose, stage, and/or classify cancer
• estimate prognosis
• select an appropriate treatment

2. Tumor products (enzymes and hormones)

• found in the blood, urine, stool, or other bodily fluids of some patients with cancer

• USED TO:

• Estimate prognosis
• Determine the stage of cancer
• Detect cancer that remains after treatment (residual disease) or that has returned after treatment
• Assess how well a treatment is working
• Monitor whether the treatment has stopped working

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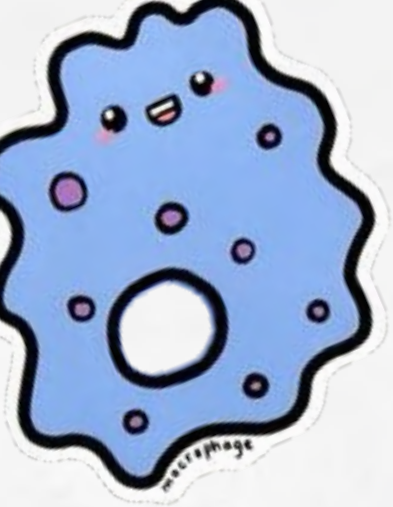


1 Tumor Antigens

1) Alpha fetoprotein antigen (AFP) in cases of hepatoma

2) Carcinoembryoinic antigen (CEA) in gastrointestinal tumors, tumors of biliary system and cancer breast

3) Cancer antigen 125 (CA 125) in ovarian carcinoma

4) Cancer antigen 15-3 (CA15-3) in breast cancer

5) Cancer antigen 19-9 in colon and pancreatic tumor

**6) Prostatic specific antigen (PSA) in prostatic tumors

ال PSA بستخدمه لاعمل diagnose للprostatic cancer و كمان لما ابدأ علاج بساعدني اشوف وضع انتشار السرطان

2 Tumor Products

a) Hormones:

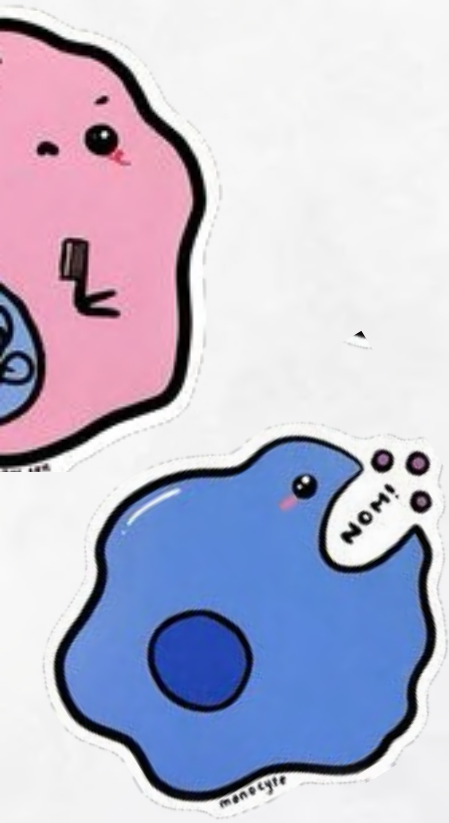
-Human chorionic gonadotrophins (HCG) are secreted in cases of choriocarcinoma

-Thyroxin (T3 & T4) is secreted in cases of cancer of thyroid gland

b) Enzymes:

Acid phosphatase enzymes in cases of cancer prostate

Alkaline phosphatase, lipase and amylase enzymes in cases of pancreatic cancer



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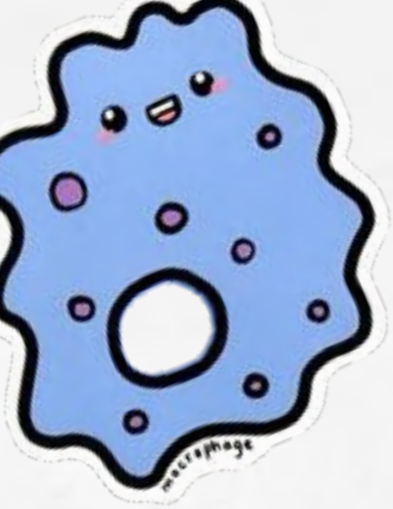


Applications of Tumor Immunology

• Diagnosis:

Immunodiagnostics is a diagnostic methodology that uses an antigen-antibody reaction as their primary means of detection.

– Monoclonal antibodies labeled with radioisotope have been used for in vivo detection of relatively small tumor foci. → theraputic + diagnostic.

– Antibodies have also been used in vitro to identify the cell origin of undifferentiated tumors, particularly of lymphocytic origin.

– Immuno-histological staining is used to confirm suspected metastatic foci, especially in bone marrow

• Treatment (immune therapy):

Immunotherapy is a type of cancer treatment that helps your immune system fight cancer.

- T-cell transfer therapy, which is a treatment that boosts the natural ability of your T cells to fight cancer. In this treatment, immune cells are taken from your tumor. Those that are most active against your cancer are selected or changed in the lab to better attack your cancer cells, grown in large batches, and put back into your body through a needle in a vein.T-cell transfer therapy may also be called adoptive cell therapy, adoptive immunotherapy, or immune cell therapy.

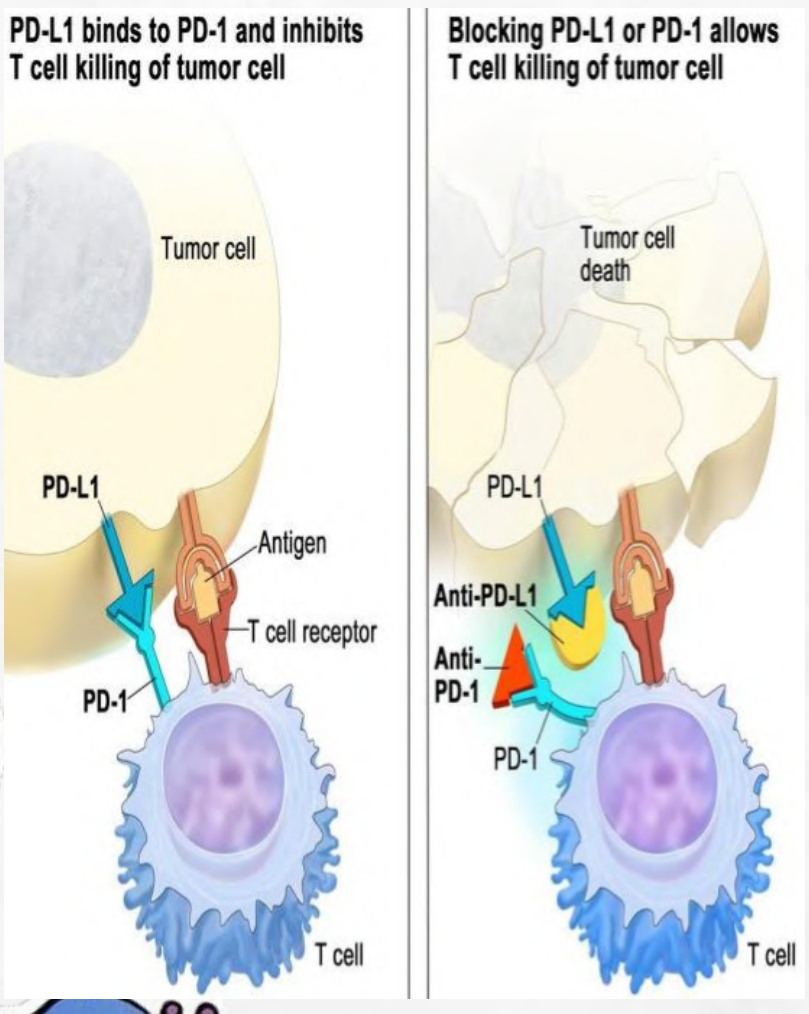
- Monoclonal antibodies, which are immune system proteins created in the lab that are designed to bind to specific targets on cancer cells. Some monoclonal antibodies mark cancer cells so that they will be better seen and destroyed by the immune system. Such monoclonal antibodies are a type of immunotherapy.Monoclonal antibodies may also be called therapeutic antibodies.

- Treatment vaccines, which work against cancer by boosting your immune system's response to cancer cells. Treatment vaccines are different from the ones that help prevent disease.

They are theraputic not prophylatic as infections

- Immune system modulators, which enhance the body's immune response against cancer. INF, ILs, EPO, GM-CSF, and BCG.

- Immune checkpoint inhibitors, which are drugs that block immune checkpoints. → PD1, CTLA4



Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep immune responsesin check. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body (left panel). Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 oranti-PD-1) allows the T cells to kill tumor cells (right panel)

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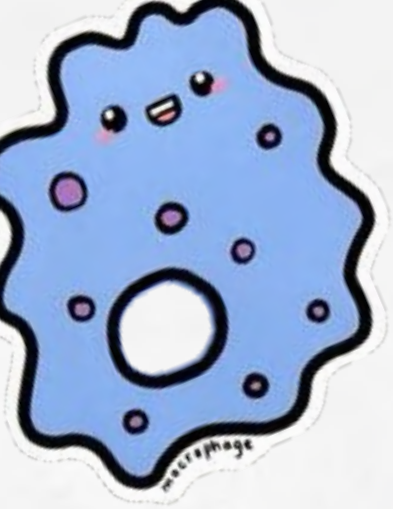

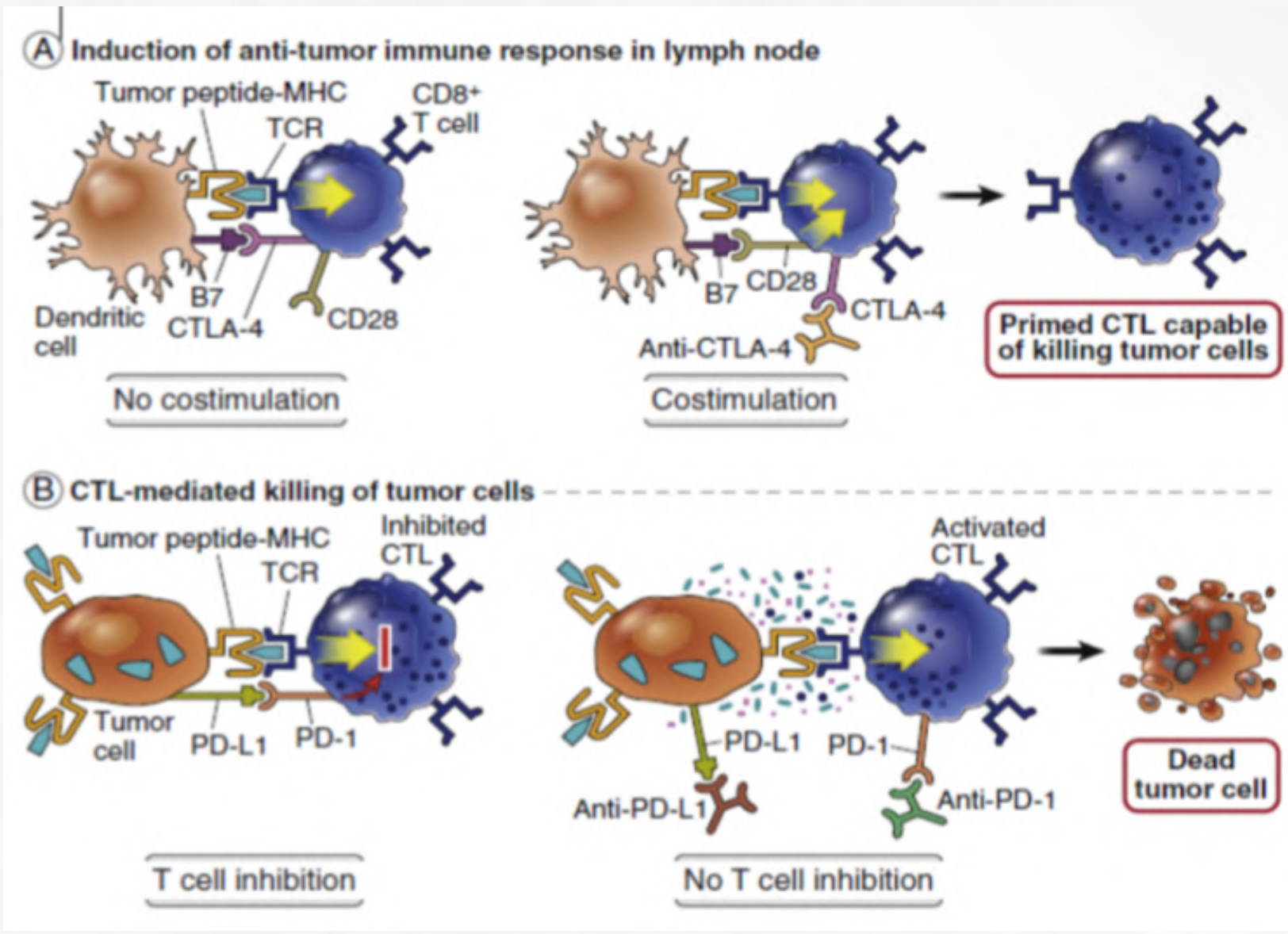

Tumor immunotherapy by immune checkpoint blockade.

Tumor patients often mount ineffective T cell responses to their tumors because of the upregulation of inhibitory receptors such as CTLA-4 and PD-1 on the tumor specific T cells, and expression of the ligand PD-L1 on the tumor cells. Blocking anti-CTLA4 antibodies (A) or anti-PD-1 or anti-PD-L1 antibodies (B) are highly effective in treating several types of advanced tumors by releasing the inhibition of tumor-specific T cells by these molecules. Anti-CTLA-4 may work by blocking CTLA-4 on responding T cells (shown) or on Treg. CTL, Cytotoxic T lymphocyte; CTLA-4, cytotoxic T lymphocyte-as- sociated antigen 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; TCR, T cell receptors.

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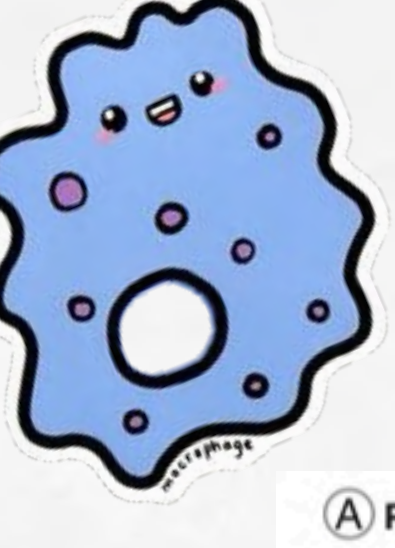


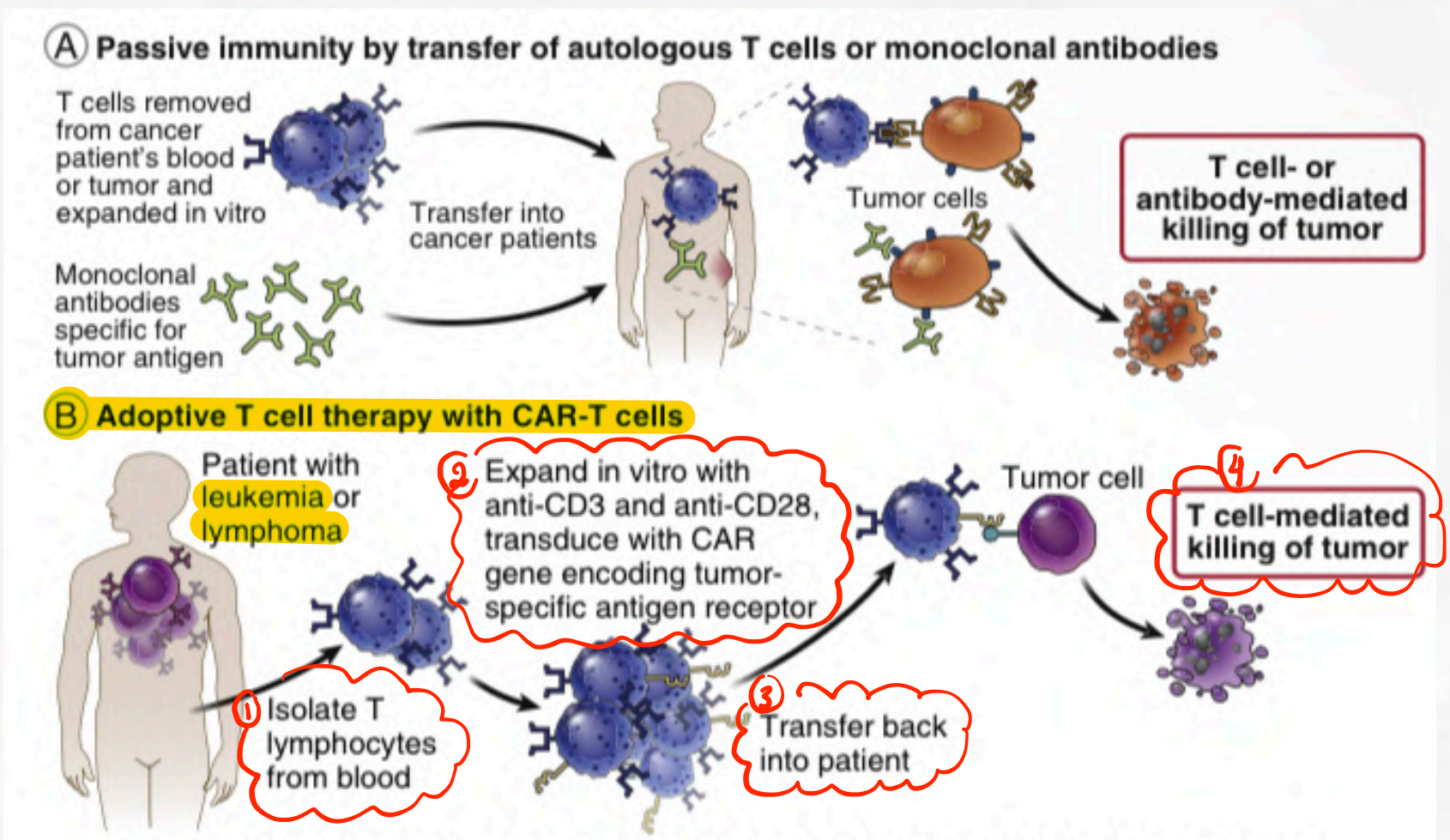
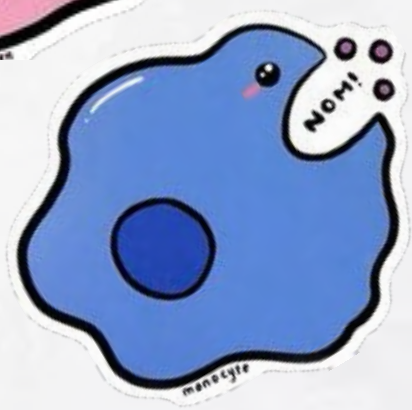


Fig. 10.6 Tumor immunotherapy by adoptive transfer of antibodies and T cells. **A,** Passive immunotherapy with tumor specific T cells or monoclonal antibodies. **B,** Adoptive T cell therapy with CAR-T cells: T cells isolated from the blood of a patient are expanded by culture with anti-CD3 and anti-CD28, genetically modified to express recombinant chimeric antigen receptors *(CARs)* (see Fig. 10-7), and transferred back into the patient.

الدكتور شرح B كالتالي، الها شرح مفصل بالكتاب حأحطه الكم السلايد الجاي لو حابين تشوفوه:
اول شي لحتى يزيدوا الresponse بيعطوا الvaccine ك adjuvant
ثاني شي بالنسبة ل B طريقة(Adoptive T therapy with CAR-T cell)استخدموها لمرضى الleukemia و الlymphoma، الي بكون الaccess فيهم اسهل من الsolid tumors
تابعوا الثلاث خطوات الي عالرسمة
الي بصير انه ال T cellالجديدة عاملة displaying لل CAR الي هي زي MHC و شكلها مثل المفتاح، و حتيجي ترتبط مع الantigen الي عالtumor cell و بتكون اصلا مربوطة مع الsignaling pathway تبعت الT cell من جهة
و هاد بخلي الBinding يصير more specific و بالتالي بيعمل activation لل CD8 و killing the tumor



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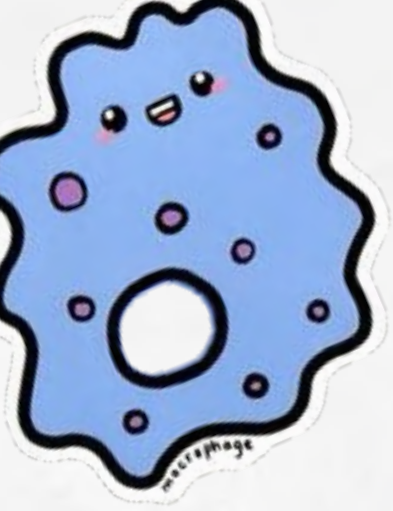


Adoptive T Cell Therapy

من الكتاب ♡

Tumor immunologists have attempted to enhance antitumor immunity by removing T cells from cancer patients, activating the cells ex vivo so there are more of them and they are more potent effector cells, and transferring the cells back into the patient. Many variations of this approach, called adoptive T cell therapy, have been tried.

• Adoptive therapy with autologous tumor-specific T cells. T cells specific for tumor antigens can be detected in the circulation and among tumor- infiltrating lymphocytes of cancer patients. T cells can be isolated from the blood or tumor biopsies of a patient, expanded by culture with growth factors, and injected back into the same patient. Presumably, this expanded T cell population contains activated tumor-specific CTLs, which migrate into the tumor and destroy it. This approach, which has been combined with administration of T cell-stimulating cytokines such as interleukin-2 (IL-2) and traditional chemotherapy, has shown inconsistent results among different patients and tumors. One likely reason is that the frequency of tumor-specific T cells is too low to be effective in these lymphocyte populations.

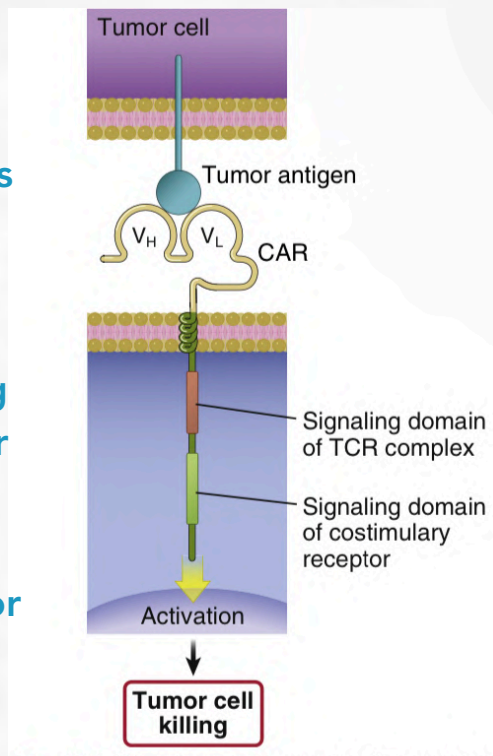
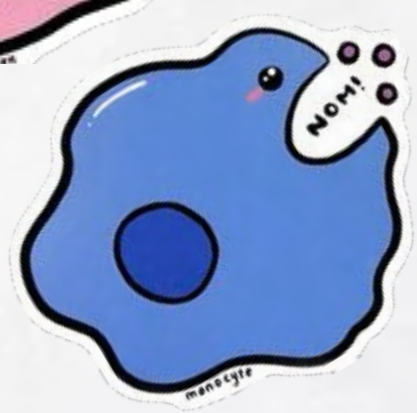


Fig. 10.7 Chimeric antigen receptor. The receptor that is expressed in T cells consists of an extracellular Ig part that recognizes a surface antigen on tumor cells and intracellular signaling domains from the TCR complex and costimulatory receptors that provide the signals that activate the killing function of the T cells.

• Chimeric antigen receptor (CAR) expressing T cells. In a more recent modification of adoptive T cell therapy, blood T cells from cancer patients are transduced with viral vectors that express a chimeric antigen receptor (CAR), which recognizes a tumor antigen and provides potent signals to activate the T cells. The CARs currently in use have a single chain antibody-like extracellular portion with both heavy- and light-chain variable domains, which together form the binding site for a tumor antigen. The specificity of the endogenous T cell receptors (TCRs) of the transduced T cells is irrele- vant to the effectiveness of this approach. The use of this antibody-based antigen recognition structure avoids the limitations of MHC restriction of TCRs and permits the use of the same CAR in many differ- ent patients, regardless of the human leukocyte anti- gen (HLA) alleles they express. Furthermore, tumors cannot evade CAR-T cells by downregulating MHC expression. In order to work in T cells, the CARs have intracellular signaling domains of both TCR complex proteins, for example the ITAMs of the TCR complex ζ protein, and the signaling domains of costimulatory receptors such as CD28 and CD137. Therefore, upon antigen binding, these receptors provide both antigen recognition (via the extracellular immunoglobulin [Ig] domain) and activating signals (via the intro- duced cytoplasmic domains). CAR-expressing T cells are expanded ex vivo and transferred back into the patient, where they recognize the antigen on the tumor cells and become activated to kill the cells. CAR-T cell therapy targeting the B cell protein CD19, and more recently CD20, has shown remarkable efficacy in treating and even curing B cell-derived leukemias and lymphomas that are refractory to other therapies. CARs with other specificities for different tumors are in development and clinical trials. The most serious toxicity associated with CAR-T cell therapy is a cyto- kine release syndrome, mediated by massive amounts of inflammatory cytokines, including IL-6, interfer- on-γ, and others, that are released because all of the injected T cells recognize and are activated by the patients' tumor cells. These cytokines cause high fever, hypotension, tissue edema, neurologic derangements, and multi-organ failure. The severity of the syndrome can be mitigated by treatment with anticytokine anti- bodies. CAR-T cell therapy may also be complicated by on-target, off-tumor toxicities, if the CAR-T cells are specific for an antigen present on normal cells as well as tumors. In the case of CD19- or CD20-specific CARs, the therapy results in depletion of normal B cells, requiring antibody replacement therapy to pre- vent immunodeficiency. Such replacement may not be feasible for other tissues that are destroyed because of the reactivity of the CAR. Although CAR-T cell ther- apy is effective against leukemias and tumors in the blood (to which the injected T cells have ready access), it has so far not been successful in solid tumors because of difficulties in getting T cells into the tumor sites and the challenge of selecting optimal tumor antigens to target without injuring normal tissues.



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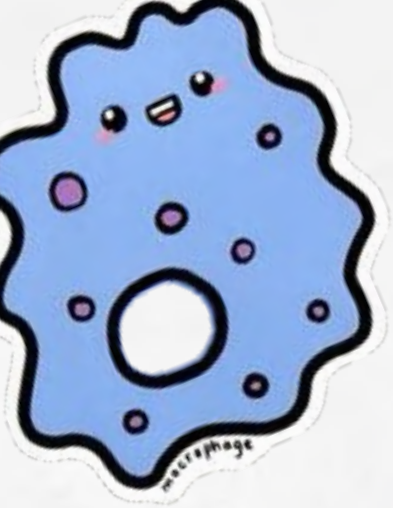
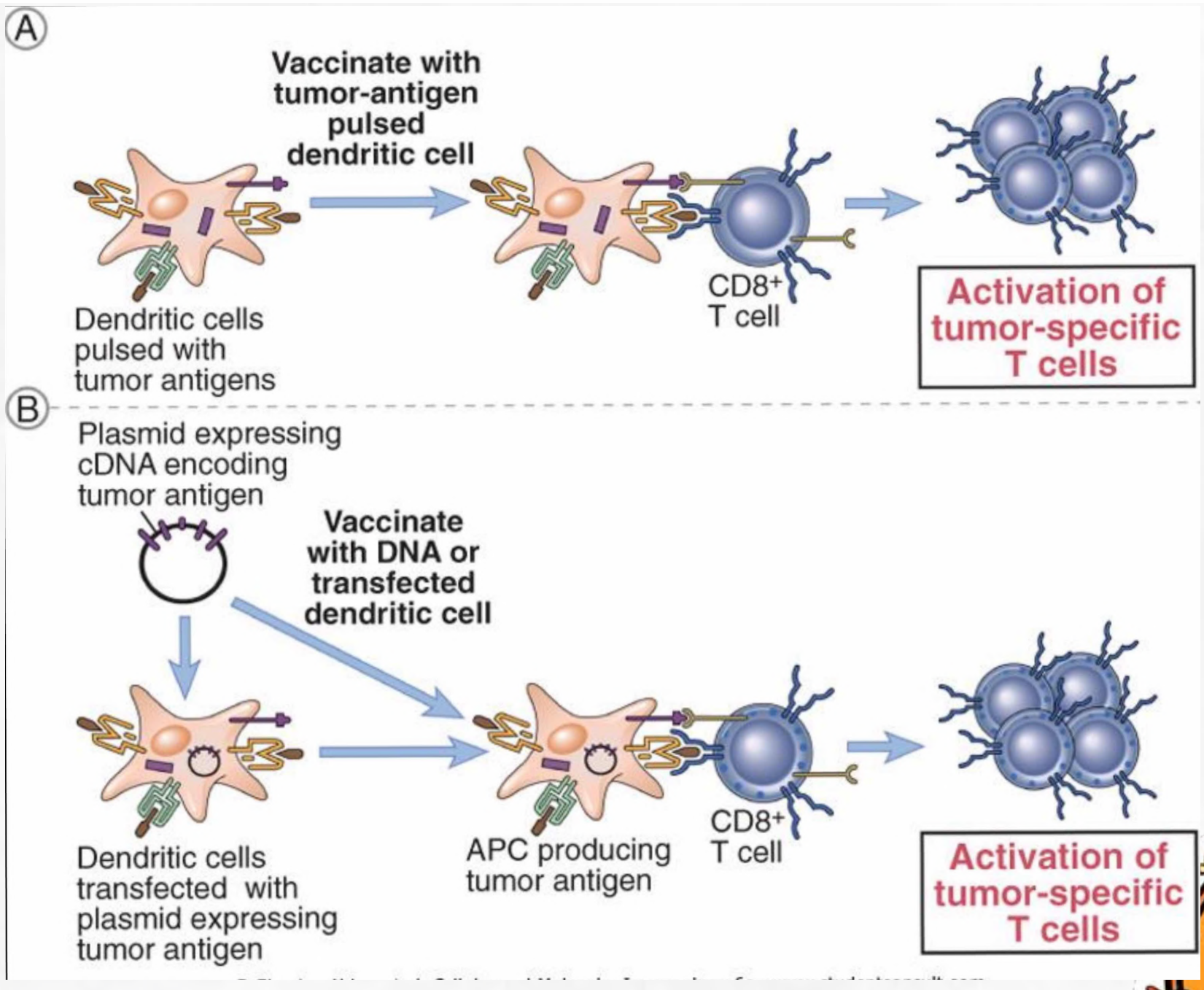
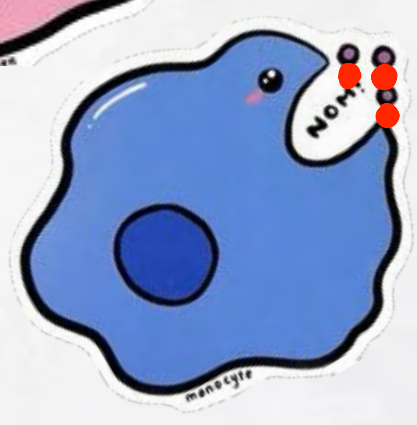


Tumor vaccines

	Type of vaccine	Vaccine preparation	Clinical trials
1.	Killed tumor to give the antigen itself.	killed tumor cells + adjuvants tumor cell lysates + adjuvants	Melanoma, colon cancer Melanoma
2.	Purified tumor antigens specific antigen.	Melanoma antigens Heat shock proteins	Melanoma Melanoma, renal cancer, sarcoma
3.	APC based grow dendritic cell → mix with tumor antigen	DC pulsed with TAA DC transfected with TAA	Various
4.	Cytokine and costimulator-enhanced	Cytokine or B7 gene transfected tumor cells APC transfected with cytokines and pulsed with TAA	Various
5.	DNA	plasmids encoding TAA	Melanoma
6.	Viral vectors as covid vaccine.	Adenovirus, vaccinia virus encoding TAA +/- cytokines	Melanoma





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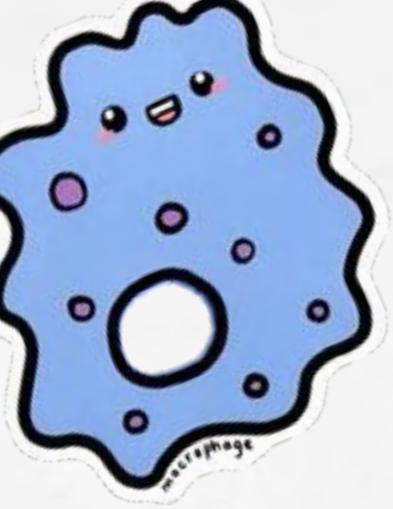
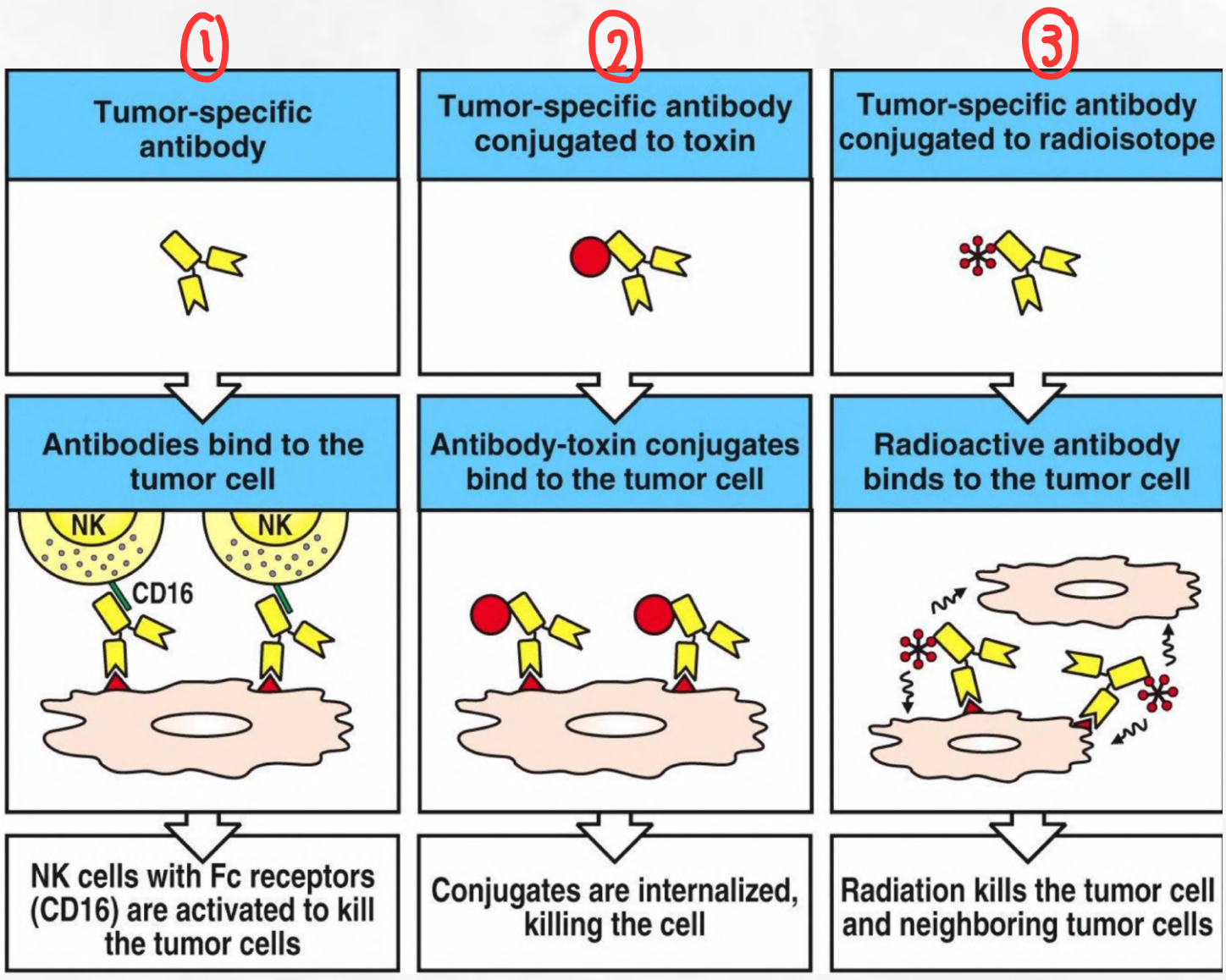


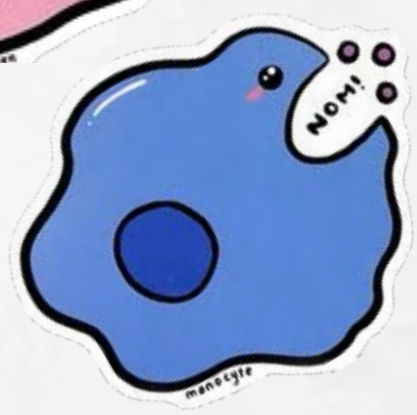
موحفظ نت

Monoclonal antibodies

Antibody name generic/trade	Antibody format	Target antigen	Therapeutic area	Approved year
Rituximab/Rituxan	Chimeric IgG1	CD20	B-cell lymphoma, NHL	1997
			Chronic lymphocytic leukemia	2010
Trastuzumab/Herceptin	Humanized IgG1	HER-2	Metastatic breast cancer	1998
			Early stage breast cancer	2006
			Metastatic stomach cancer	2010
Gentuzumab Ozogamicin/Mylotarg	Humanized IgG1	CD33	Acute myeloid leukaemia	2000
Alezumtumab/ Campath	Humanized IgG1	CD52	Chronic myeloid leukaemia	2001
Ibritumomab Tiuxetan/ Zevalin	Mouse IgG1 conjugated to ^{90}Y)	CD20	NHL	2002
Tositumomab/Bexxar	Mouse IgG1 conjugated to ^{131}I	CD20	NHL	2003
Bevacizumab/Avastin	Humanized IgG1	VEGF	Metastatic colorectal cancer	2004
			Non-small-cell lung cancer	2006
			Metastatic renal cancer	2009
			GBM	2009
			Ovarian cancer (in Europe only)	2011
Cetuximab/Erbitux	Chimeric IgG1	EGFR	Metastatic colorectal cancer	2004
			Head and neck cancer	2006
			Metastatic colorectal cancer (first-line treatment)	2012
Panitumumab/Vectibix	Human IgG2	EGFR	Metastatic colorectal cancer	2006
Ofatumumab/Arezera	Human IgG1	CD20	Chronic lymphocytic leukaemia	2009
Removab®	Bi-sepecific mouse/ rat Hrbrid IgG	EpCAM X CD3	Patients with malignant ascites (in Europe)	2009
Ipilimumab/Yervoy	Human IgG1	CTLA-4	Metastatic melanoma	2011
Brentuximab/Adcetris	Chimeric IgG1	CD30	ALCL and Hodgkin lymphoma	2011
Pertuzumab/Perjecta	Humanized IgG1	HER2	Metastatic breast cancer	2012

monoclonal





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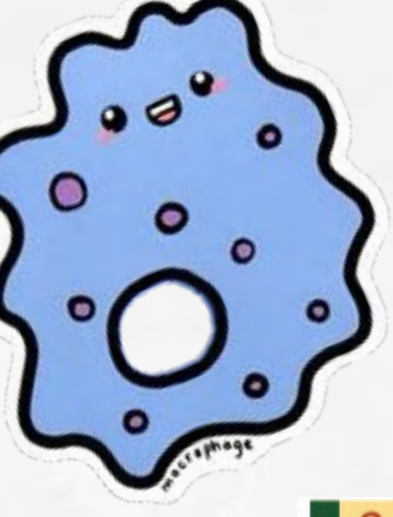
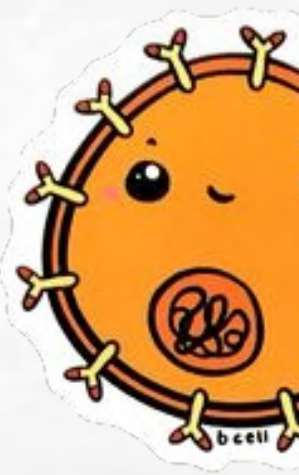


ملخص جيل من الكتاب ♡

SUMMARY

- The adaptive immune system is able to eradicate or prevent the growth of tumors.
- Tumors may induce antibody, $CD4^+$ T cell, and $CD8^+$ T cell responses, but $CD8^+$ CTL killing of tumor cells appears to be the most important antitumor effector mechanism.
- Most cancer antigens that induce T cell responses are neoantigens encoded by randomly mutated genes (passenger mutations), which do not contribute to the malignant phenotype of the cancer cells. Other tumor antigens include products of oncogenes and tumor suppressor genes, overexpressed or aberrantly expressed structurally normal molecules, and products of oncogenic viruses.
- CTLs recognize mutant peptides derived from tumor antigens displayed by class I MHC molecules. The induction of CTL responses against tumor antigens involves ingestion of tumor cells or their antigens by dendritic cells, cross-presentation of the antigens to naïve $CD8^+$ T cells, activation of the T cells and differentiation into CTLs, CTL migration from the blood into tumors, CTL recognition of the tumor antigens on the tumor cells, and killing of the tumor cells.
- Tumors may evade immune responses by losing expression of their antigens, shutting off expression of MHC molecules or molecules involved in antigen processing, expressing ligands for T cell inhibitory receptors, and inducing regulatory T cells or secreting cytokines that suppress immune responses.
- CAR-T cell immunotherapy is another breakthrough approach now in clinical practice. CAR-T cells are generated in vitro by transducing a cancer patient's T cells to express a recombinant receptor with an antibody-like binding site for a tumor antigen and a cytoplasmic tail with potent signaling functions. Adoptive transfer of CAR-T cells back into patients has been successful in treating B-cell–derived leukemias and lymphomas.
- Immune checkpoint blockade is the major cancer immunotherapy strategy in current practice. Monoclonal antibodies that block the function of T cell inhibitory molecules, such as CTLA-4 and PD-1, are injected into the patient, which enhances the activation of tumor-specific T cells by tumor antigens. This approach has been highly successful in treating patients with many kinds of advanced cancers, but more than 50% of patients do not respond, and many patients develop autoimmune side effects.
- Personalized neoantigen vaccines are now in clinical trials. The creation of these vaccines relies on cancer genome sequencing to identify neoantigen peptides unique to an individual patient's tumor, which bind to that patient's MHC molecules.



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