Immunology

Title : Adaptive Immunity
(humoral Immunity)

Lec no : 9

Done By : Johainah Taha

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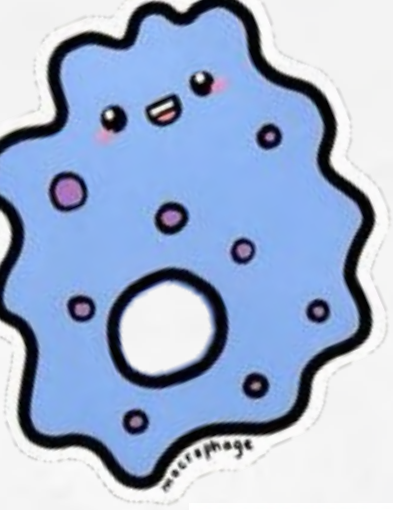

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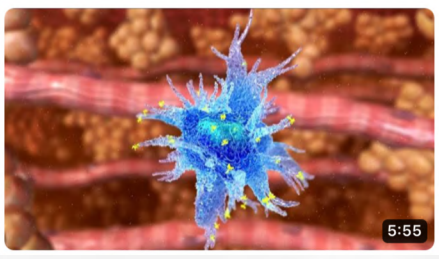
1. 

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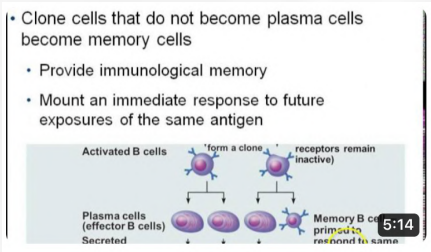
2. 

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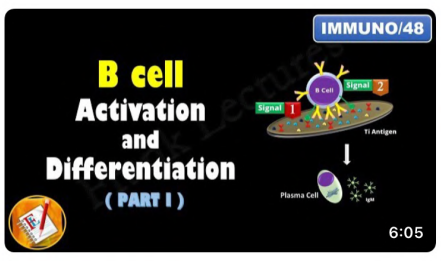
3. 

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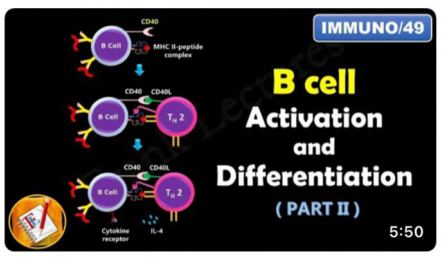
4. 

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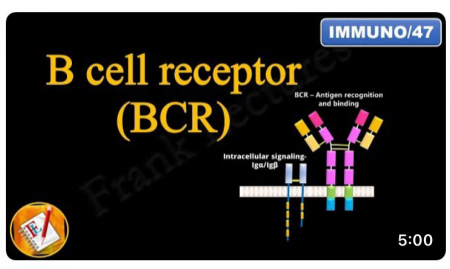
5. 

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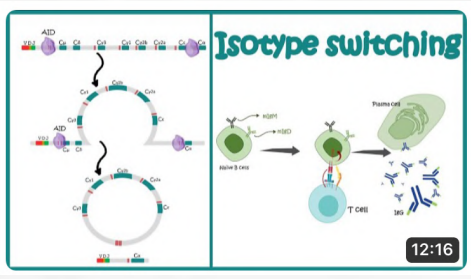
6. 

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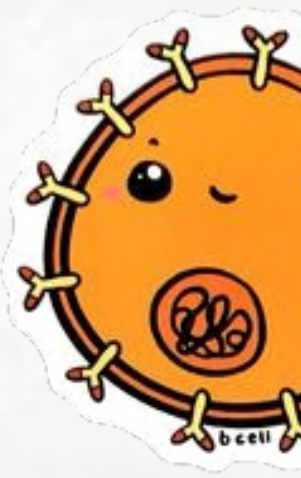
رسالة اليوم



يجب أن يكوُن احساسك ايجابياً مهما كانت الظّروف
ومهما كانت التّحديات و مهما كان المؤثّر الخارجِي 🌸

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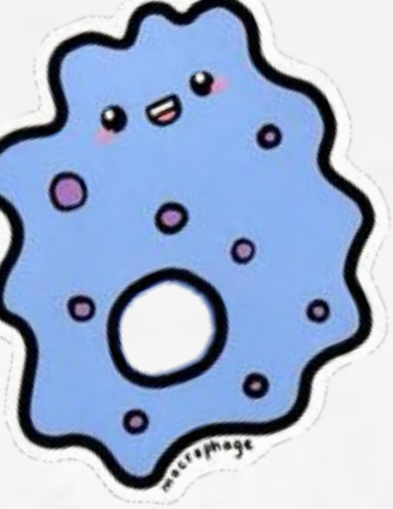

Why are HIV patients more susceptible for viral infections and tumor?

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 .

الدكتور رجع ذكرنا بال B7 و انها مهمة و تعتبر rate limitting step لنحول ال T cell الى active cell اذا ناسيينها راجعوا محاضرة 8 الان 🙂 ،و سألنا سؤال كواجب

شو علاقة ال B7 الي هي costimulatory بال vaccine adjuvants و شو دورها

Protein antigens, such as those used in vaccines, fail to elicit T cell–dependent immune responses unless these antigens are administered with substances that activate APCs, especially dendritic cells. Such substances are called adjuvants, and they function mainly by inducing the expression of costimulators on APCs and by stimulating the APCs to secrete cytokines that activate T cells.

الفكرة من الفقرة الي فوق نعرف شو يعني adjuvants الي هي عبارة عن مواد بتنحط باللقاح لحتى تثير الاستجابة المناعية و تحديداً ال T cells

Most adjuvants used in experimental immunology are products of microbes (e.g., killed mycobacteria, which is often used in experimental studies) or substances that mimic microbes, and they bind to pattern recognition receptors of the innate immune system, such as Toll-like receptors and NOD-like receptors).

بهاي الفقرة حكالنا من وين بجيب هدول الadjuvants

Adjuvants used in human vaccines are mainly aluminum salts that induce local inflammation, which secondarily leads to dendritic cell costimulator expression. Thus, adjuvants trick the immune system into responding to purified protein antigens in a vaccine as if these proteins were parts of infectious microbes.

هي بتخدع جهاز المناعة لحتى يستجيب لبروتينات مش pathogen اصلا، بتخليه بالاول يعمل التهاب موضعي و الي يؤدي لبعدين الى تحفيز ال dendritic cells

* إذاً هي بتحفز خروج B7 ليرتبط بـ CD28

The increasing understanding of costimulators has led to new strategies for inhibiting harmful immune responses. Agents that block B7:CD28 interactions are used in the treatment of disorders in which T cell activation causes organ dysfunction, such as certain autoimmune diseases and graft rejection, and antibodies that block CD40:CD40L interactions are being tested in these diseases.

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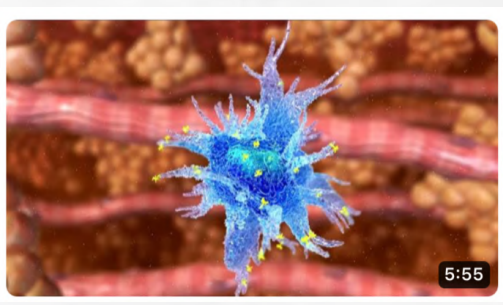

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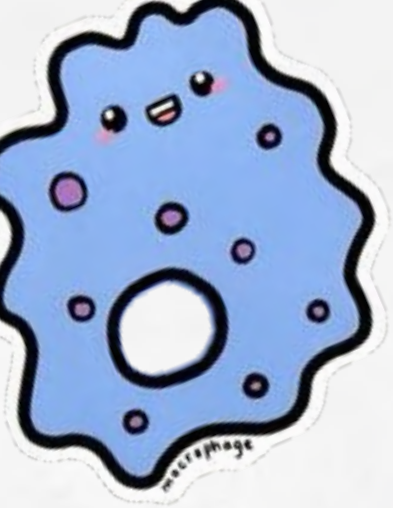


Introduction - Humoral immunity

- Arise and mature in the red bone marrow

- Found primarily in the spleen, lymph nodes, and (The mucosa-associated lymphoid tissue (MALT), also called mucosa-associated lymphatic tissue, is a diffuse system of small concentrations of lymphoid tissue found in various submucosal membrane sites of the body, such as the gastrointestinal tract, thyroid, breast, lung, salivary glands, eye, and skin).

- Small percentage of B cells circulates in the blood

- Major function is the secretion of antibodies

<u>Importance:</u>

•Humoral immunity helps cellular immunity to perform action through interaction of T helper cells with B cells

- Is the arm of adaptive immunity in killing extracellular microbes and microbial toxins

•Important in defending against microbes with capsule

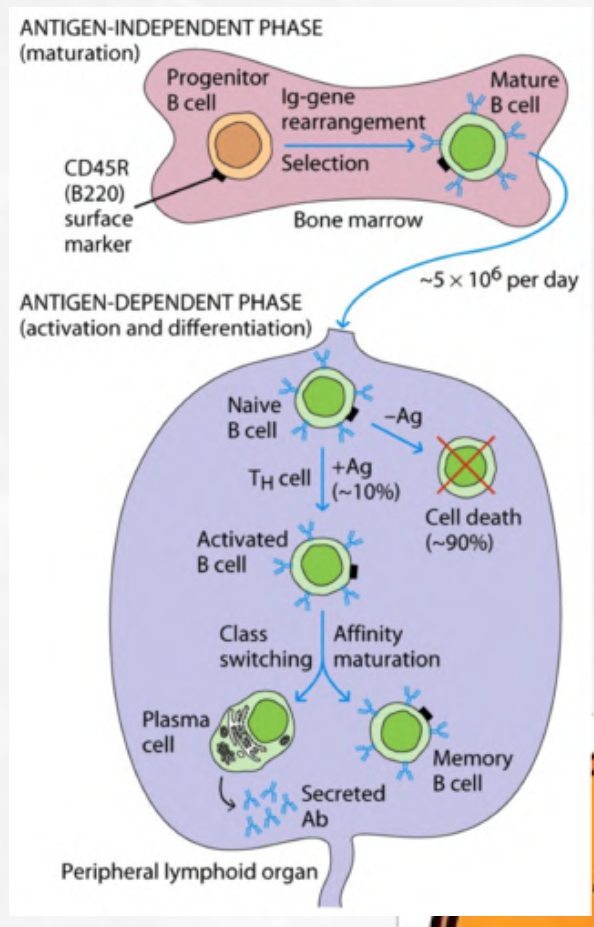
When taling about the Capsule, we are talking about the Bacteria which is usually compsed of polysaccarides, so this is a T-independant activation of B -cells

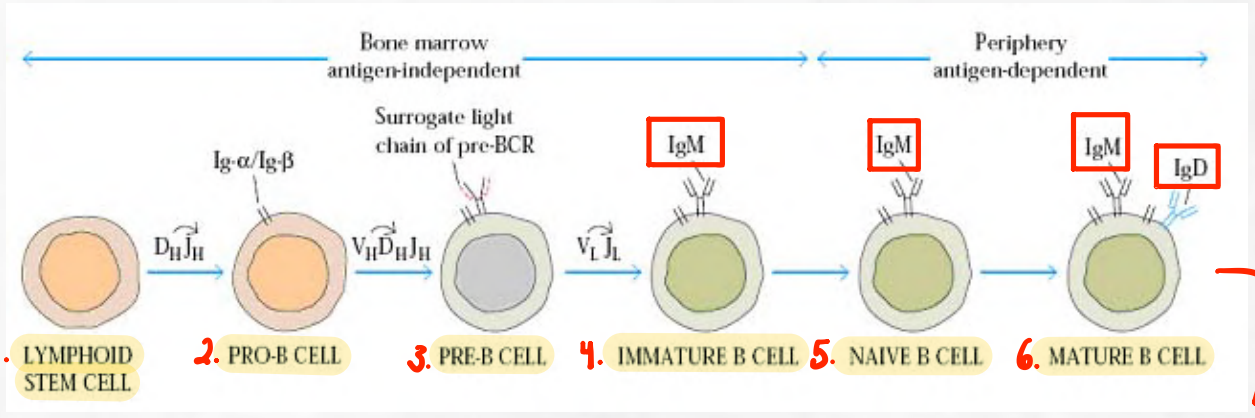
لو كانت بروتينات لكانت T-dependant

B Cells Maturation

- B cells matures in bone marrow independent of antigen, then continue to maturate in peripheral lymphoid organs with the presence of antigen

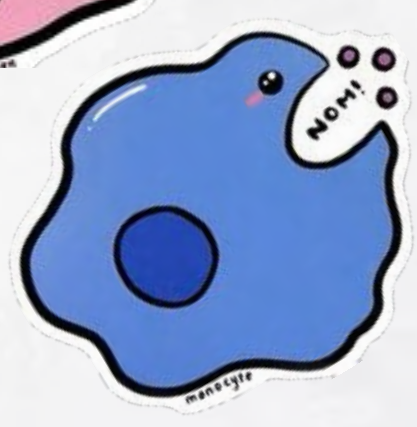
- Three main steps of maturation: حط الدكتور ماركن عليهم
1. Progenitor- Ig alpha and beta- for signal transduction (long tails)
2. Pre-B cell- IgM heavy chain, and light chain
3. "mature"- IgD





بس هاي الرسمة الدكتور ركز عليها، احفظوا الترتيب و اعرفوا كل نوع خلية شو نوع الantibody الي بكون presented عليها

Most pre-B cells synthesize mu heavy chains but, without light-chain partners, these undergo rapid cytoplasmic degradation



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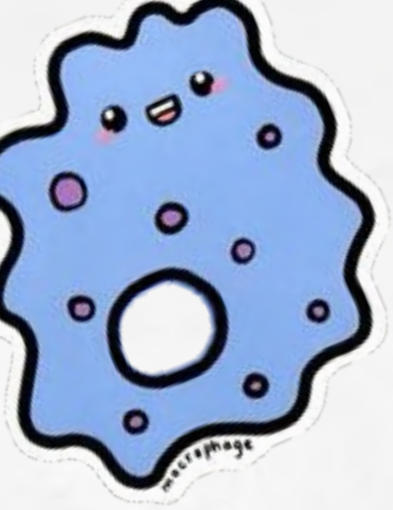
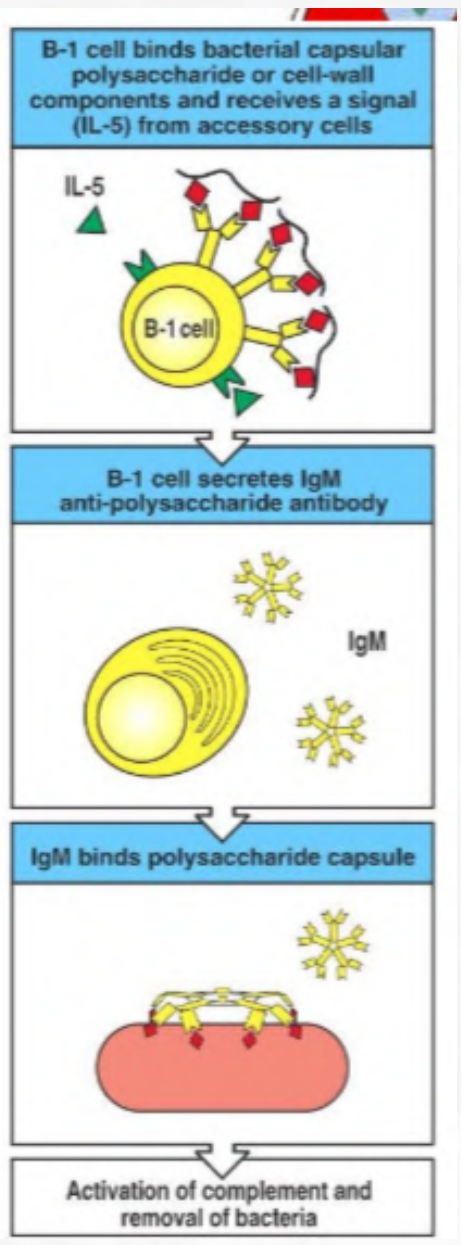


B-1 B cells



- "Innate-like" subset of B cells.

- Appear during fetal life and express IgM but little IgD and display CD5. Are also found in peritoneum and pleural space.

- Originates from stem cell in bone marrow, but also from proliferation of B- 1 cells outside the BM.

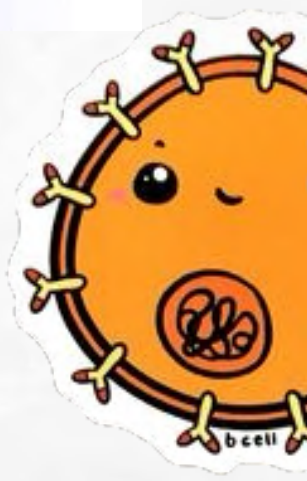
- Responds poorly to protein antigen, but strongly to carbohydrate antigens.

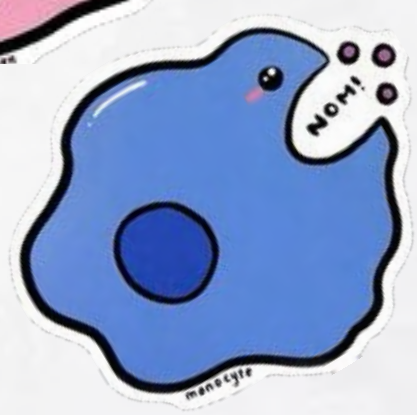
- Antibodies produced are of low affinity.

- No memory produced

Attribute	Conventional B cells (B-2 B cells)	B-1 B cells
Major sites	Secondary lymphoid organs	Peritoneal and pleural cavities
Source of new B cells	From precursors in bone marrow	Self-renewing (division of existing B-1 cells)
V-region diversity	Highly diverse	Restricted diversity
Somatic hypermutation	Yes	No
Requirements for T-cell help	Yes	No
Isotypes produced	High levels of IgG	High levels of IgM
Response to carbohydrate antigens	Possibly	Definitely
Response to protein antigens	Definitely	Possibly
Memory	Yes	Very little or none
Surface IgD on mature B cells	Present on naive B cells	Little or none

Somatic hypermutation involves a programmed process of mutation affecting the variable regions of immunoglobulin genes





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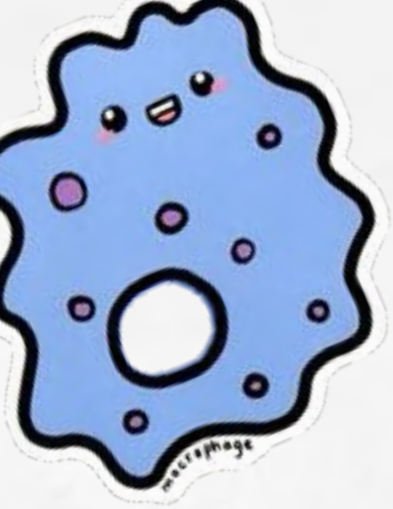

B cells Clonal Selection

- Self-reactive B cells are eliminated in bone marrow (BM).

The self antigens are presented on the surface of B cells and if they recognize these self antigens and bind to them, these B cells won't be maturated and they will be deleted in the bone marrow

- BM produces 5 x 10^7 B cells/day, but only 5 x 10^6 B cells/day or 10% actually enter the circulation.

احنا بننتج اعداد كبيرة و لكن نسبة صغيرة جداً بتدخل الcirculation ليصيروا mature و function في ال immune system

- Some of this loss is due to negative selection and elimination or clonal deletion of immature B cells expressing auto antibodies to self-antigens.

الnegative selection يعني اذا الantigen كان non harmful زي self antigen معناته ال Bcell ما بتكمل عنا maturation و بصير الها deletion و ما بتوصل الcirculation

- "Cross-linking" of mIgM by self Ag may lead to cell death or anergy

لو انعرض ال self antigen و صار عنا cross linking يعني binding of multiple epitopes على اكثر من immunoglobulin molecule الي موجودين على الsurface تبع B-CELL لو تعرف عليهم ك self antigen معناته رح يصير الها deletion (كله اعادة نفس الفكرة)

- The clones of lymphocytes that can be interacted with corresponding Ag will be selected and lead to activation, proliferation, produce Ab and specific memory cells.

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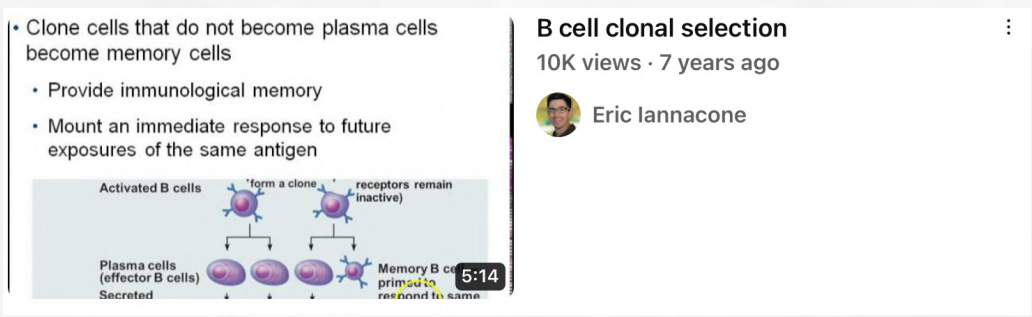


Stages of B cells Activation

• <u>B cells development involve three main stages:</u>

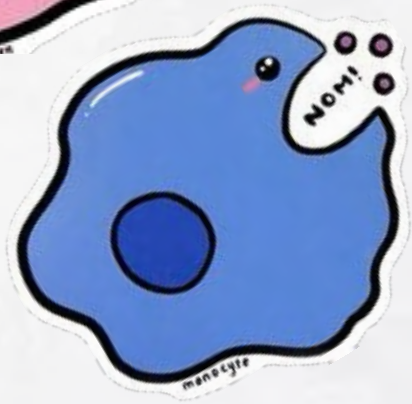
1. B cells recognition and binding

2. B cells undergo Ag-induced activation, proliferation and differentiation in the periphery

3. Activated B cells give rise to Ab-secreting plasma cells and memory cells

4. Effector B cells start to function

5. Shut down of immune response



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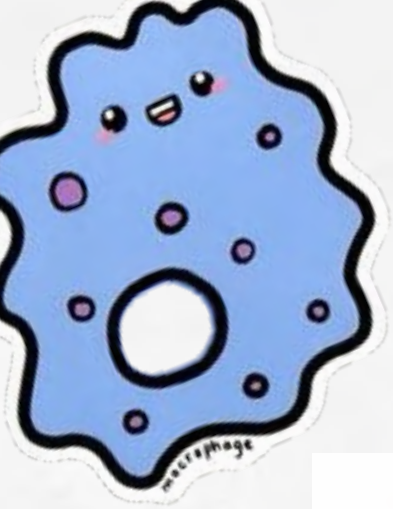


حنشرحها بالتفصيل

عنا naive B cell عاملة displaying لل IgM و ال IgD، حتتعرض لAntigen و تتعرف عليه، بالتالي بصير عنا activation لل B cell اما بمساعدة الT cell و هاد بنحكيله T cell dependent B cell activation او بدون مساعدة T cell و هاد بنحكيله T cell independant B cell activation
نوع الantigen بال T independent هو protein, polysaccharides, lipid

بعدين بصير عنا proliferation و differentiation لل cells بعدين بصير عنا antibody secretion

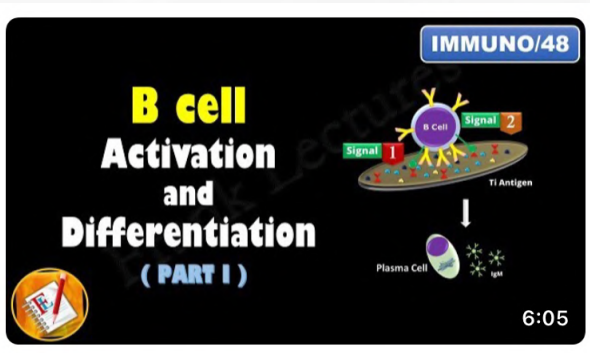
ال IgM اول واحد بصير اله secretion و الي هو جزء من الIg الي موجودة على سطح الB cell هي و الIgD لهيك ما بصير الهم isotype switching

هسا لو بدنا نحول للIgA او ال IgE او IgG حنحتاج شي اسمه isotype switching
ال بيعمل reorganisation في ال constant region تبعت الheavy chain و بالتالي بتحول من IgM الى IgA او IgG او IgE

عملية اختيار الspecefic antibodies بنسميها الaffinity maturation

بالاضافة الى انتاج memory B cells

هدول الفيديوهين حلوين كمقدمة على الي حنشرحه



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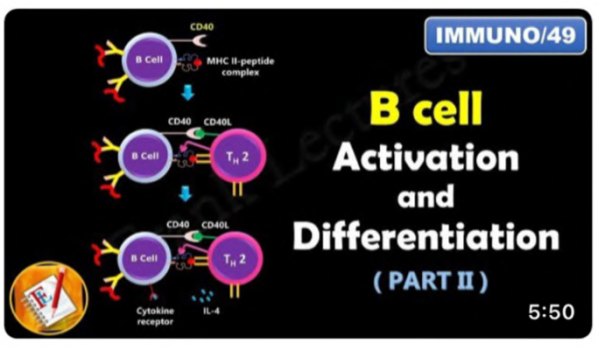

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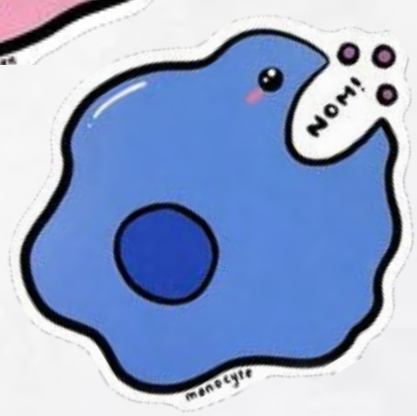

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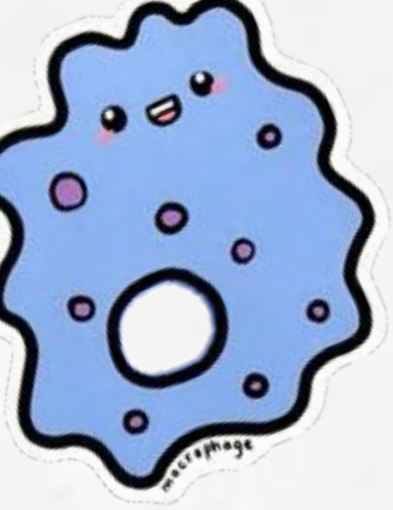
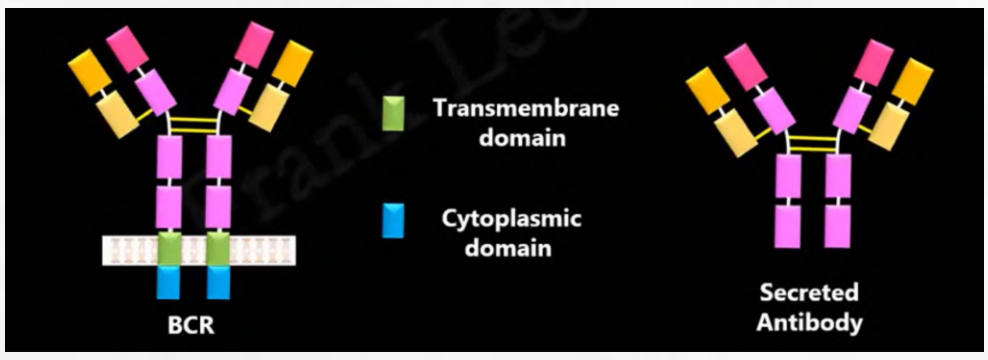


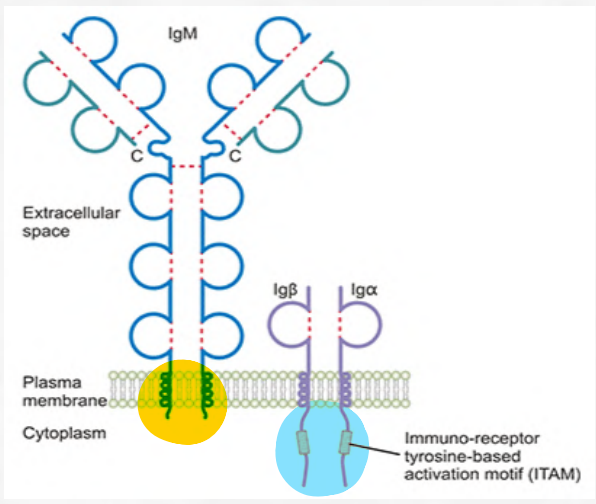
1. Antigen Recognition

• Naive B lymphocyte too express membrane bound antibodies IgM and IgD that function as antigen receptors (B cells receptors – BCR)

حكينا انه بالT cell عنا T cell receptor ، بال B cell عنا immunoglobulins زي IgM و IgD
These immunoglobulins by themselfes are not called a B cell receptor, they are immunoglobulins and are responsible for the binding of the antigen in the variable region in the antigen binding site
الي بميزهم عن ال free Ig هو وجود transmembrane domain و cytosolic domain



ال cytosolic part من الimmunoglobulins ما بيوصل للdeep (اللون الاصفر)
و بالتالي B cell بحاجة الى Ig alpha و Ig beta الي بكون مربوط ب covalent bond مع ال Ig على الsurface
تبع الB cells (اللون الازرق)
هسا هاد ال cytosolic part بكون اطول من الIg و بكون مسؤول عن signaling cascades الي بتصير نتيجة للantigen recognition بال B cell
و بالتالي الcombination of both ممكن نسميه B cell receptor



• Protein antigen only processed by APCs and recognized by helper T cells that play important role in B cells activation this is referred to as T dependent B cell activation

• Non protein antigen including lipids and polysaccharides activate B cells directly without involvement of helper T cells (T-independent activation). B cells in return can activate T helper cells

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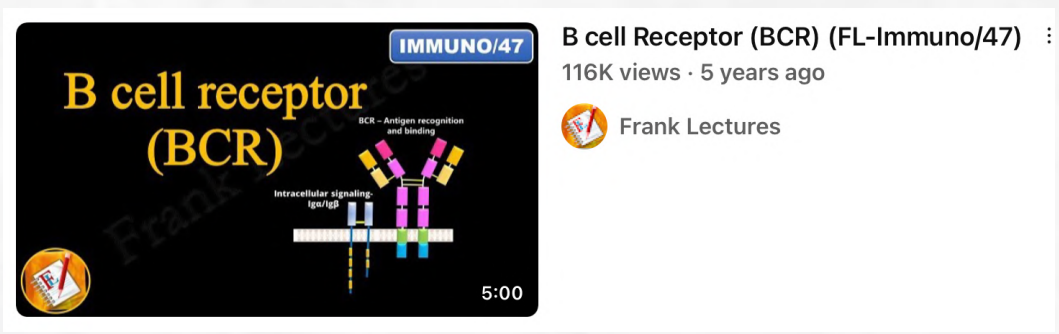

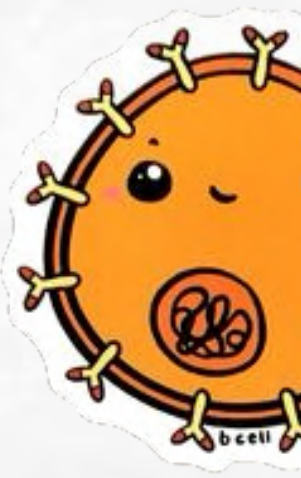

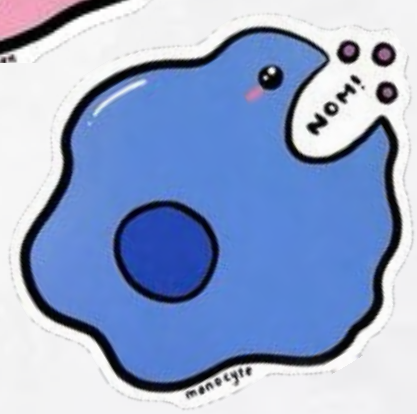

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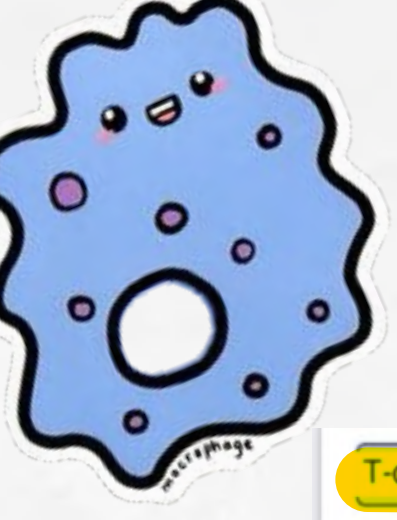
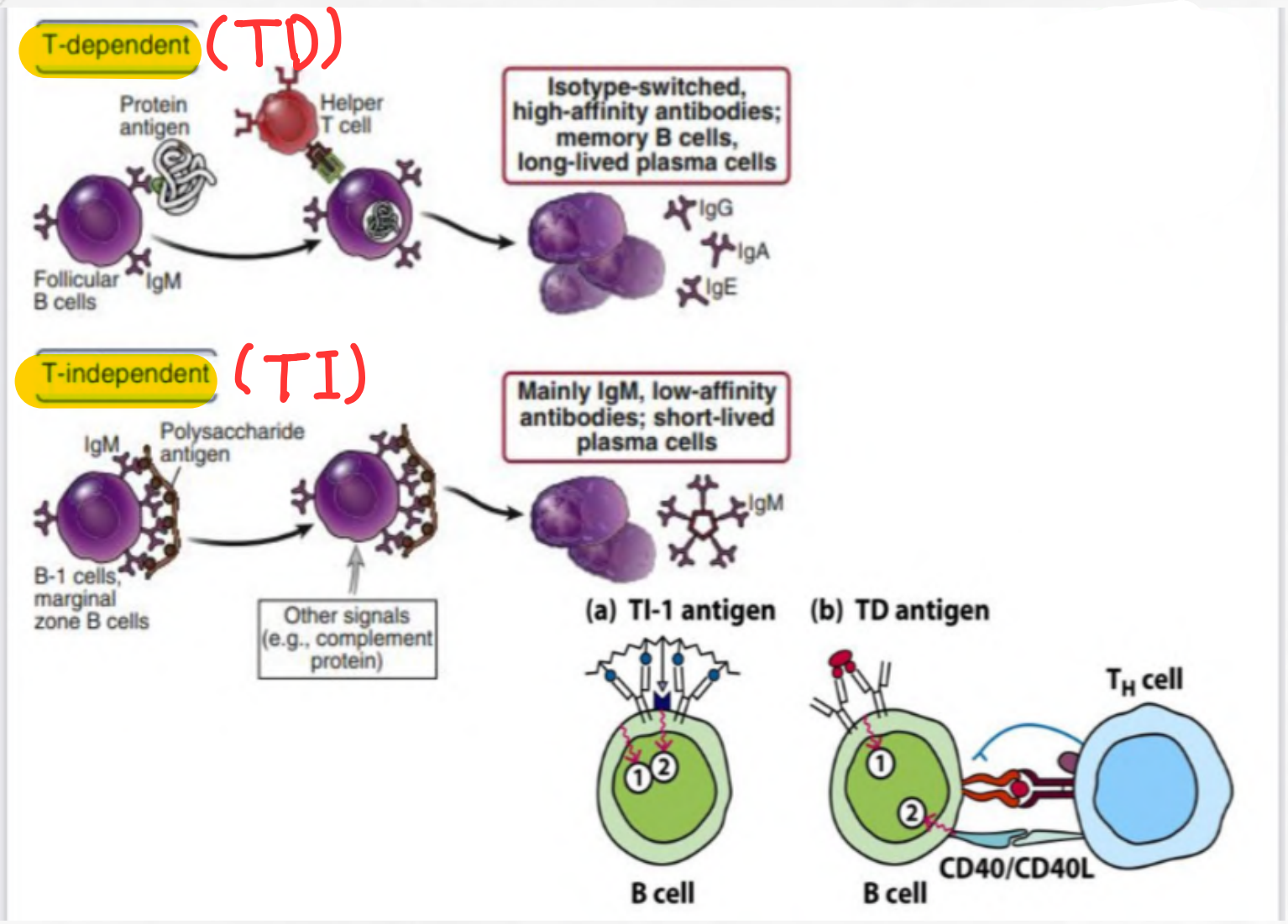




بال TD عنا الprotein antigen بصير اله recognition من T cell بعدين ال helper T cell بتعمل اله displaying عال MHC و بصير عنا هاد الحكي بالlymph node

ال B cell موجودة في الprimary follicle و ال T cell بال center of lymph node بعدين بصير عنا attraction فال T cell بتنتقل من منطقتها الى منطقة الB cell و ال B cell بنتقل من منطقته الى منطقة ال T cell

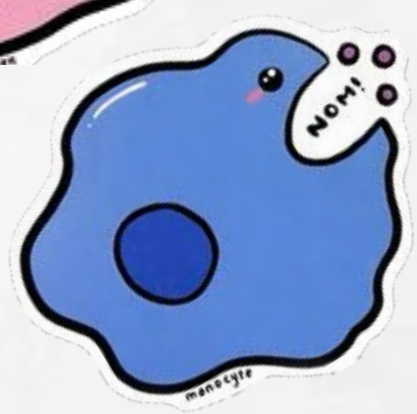
بال TI بصير عنا cross linking يعني الpolysccaride antigen ال structure تبعه في عليه epitopes بتكون repeative يعني الpolysaccaride الموجود قد يكون عليه عدة epitopes

ولكن a epitope عشرين ثليثين بروح يرتبط مع عدة ig

يعني ارتباط الepitope تبع الantigen مع عدة antibodies

مطلوب تدابل

	TD Antigens	TI Antigens
Chemical nature	Proteins	Polymeric antigens, especially polysaccharides; also glycolipids, nucleic acids
Features of Response		
Primary B cell subset	Follicular B (B2) cells	MZ(/B1) B cells
Germinal center formation	Yes	No
Secondary isotypes (isotype switching)	Yes; IgG, IgE, and IgA	Little; some IgG and IgA
High affinity Ab's (affinity maturation)	Yes	No
Secondary response and memory B cells	Yes	Limited, only for some antigens
Long-lasting serum antibody titers (long-lived PCs)	Yes	No/limited



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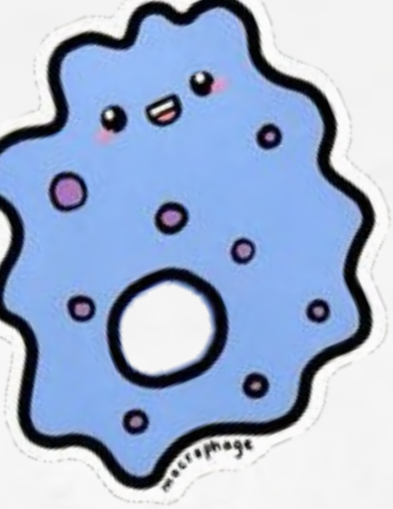


2. B Cell Activation and Signaling

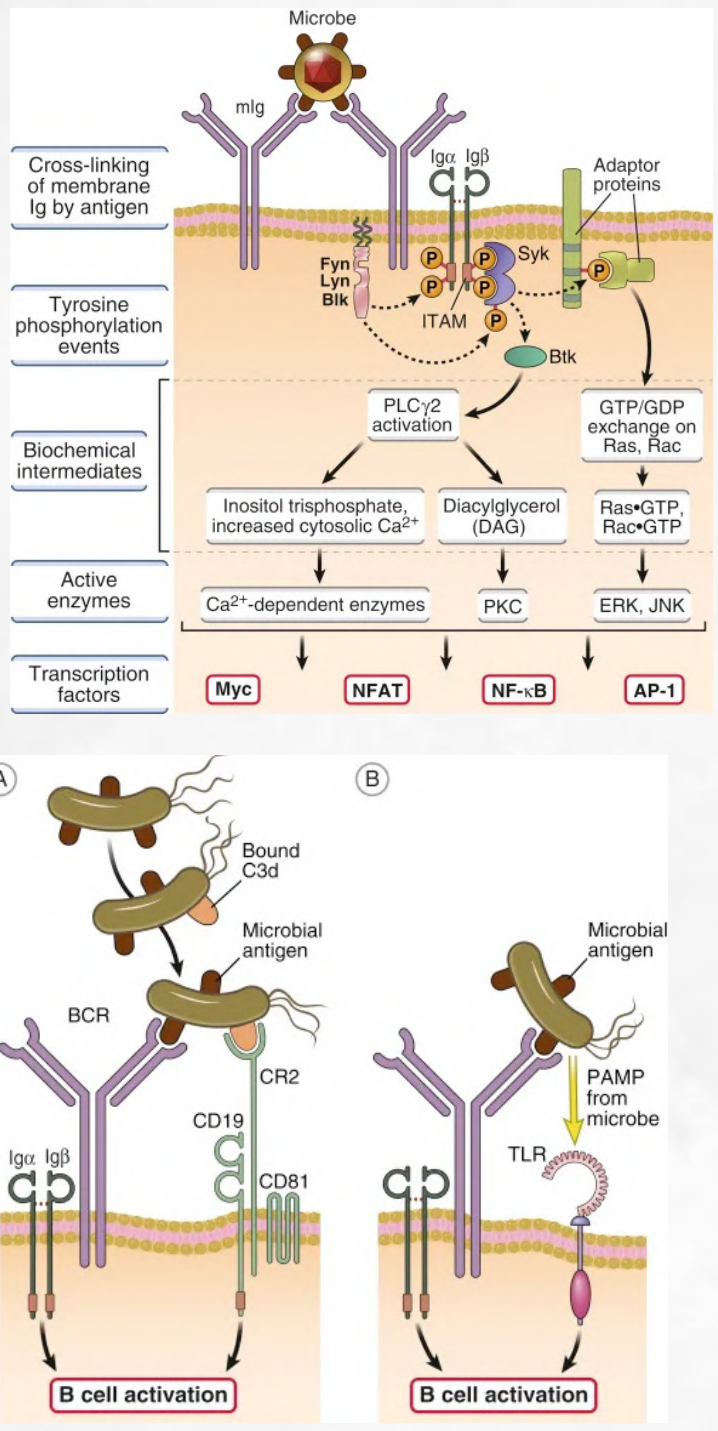
• Antigen induce clustering (cross linking- or bring together) of membrane Ig receptors. Ig clustering occurs when antigen molecules forms aggregates, or antigen have repeated epitopes molecules

• Ig clustering induce signaling through Igα and Igβ proteins in the B cell receptor complex

Cross linking : 2 epitopes bound to 2 different types of antibodies on B cells

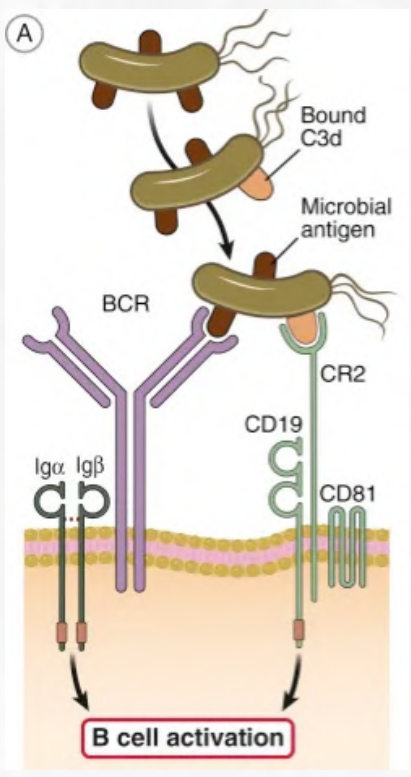
Notice that Ig alpha and Ig beta are uncovalently bound to the Ig

و بعدها بنبدأ بالsignaling pathway الي تفاصيلها مو مطلوبة
في عنا cd3 و zeta chain protein الي بشكلوا الITAM و بعدها بتبدأ signaling pathwayال لتعمل activation لل NF-KB

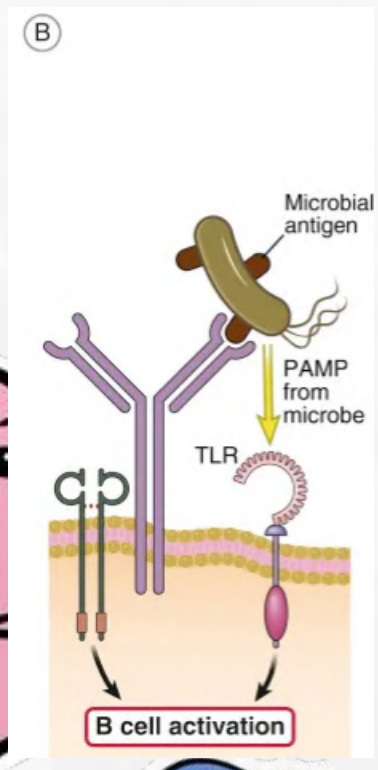


• Furthermore, microbes can activates complement system including C3 to form C3d. C3d can directly bind to B cells through CR2 and other receptors which enhance B cells activation (second signal)

• Later on signal from Ig and CR2 activates many biochemical's and enzymes that ends by formation of different transcription factors



ال innate immunity الها دور بال activation تبع الB-cells ، و ممكن تحصل عبر شغلتين :
الاولى ، complement system
فبالalternative pathway بصير عنا autolysis لل C3 و بتعطينا مكونات من ضمنهم ال C3d الي بتلتصق في microbe ليصير الها selection من ال B cell فبرتبط مع الEpitope تبع الmicrobe و بنفس الوقت مع الB cell عبر complement receptor 2
C3d برتبط مع CR2 الموجودة على B cell و بيعمل النا Further activation لل CD 19 و CD81
و الantigen برتبط مع B cell receptor complex ، و بعدها بتبدأ ال signaling pathway من ال Ig alpha و Ig beta بيعمل cell activation
اذا صار عنا activation للB cell من طرفين



الثانية ، عن طريق ال PAMPs
حكينا في مناطق على الmicrobe بكونوا unique لل pathogen بالتالي برتبط ال epitope تبع الpathogen مع الIg على surface of B cell و نفس الوقت ال PAMPS بترتبط بال-toll like receptor
بالتالي الsignals بتيجي من ال toll like receptor و من B cell receptor

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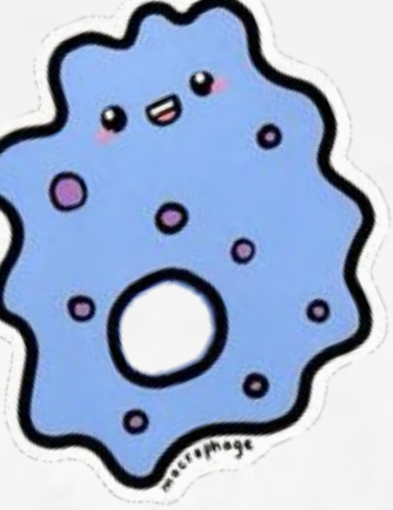
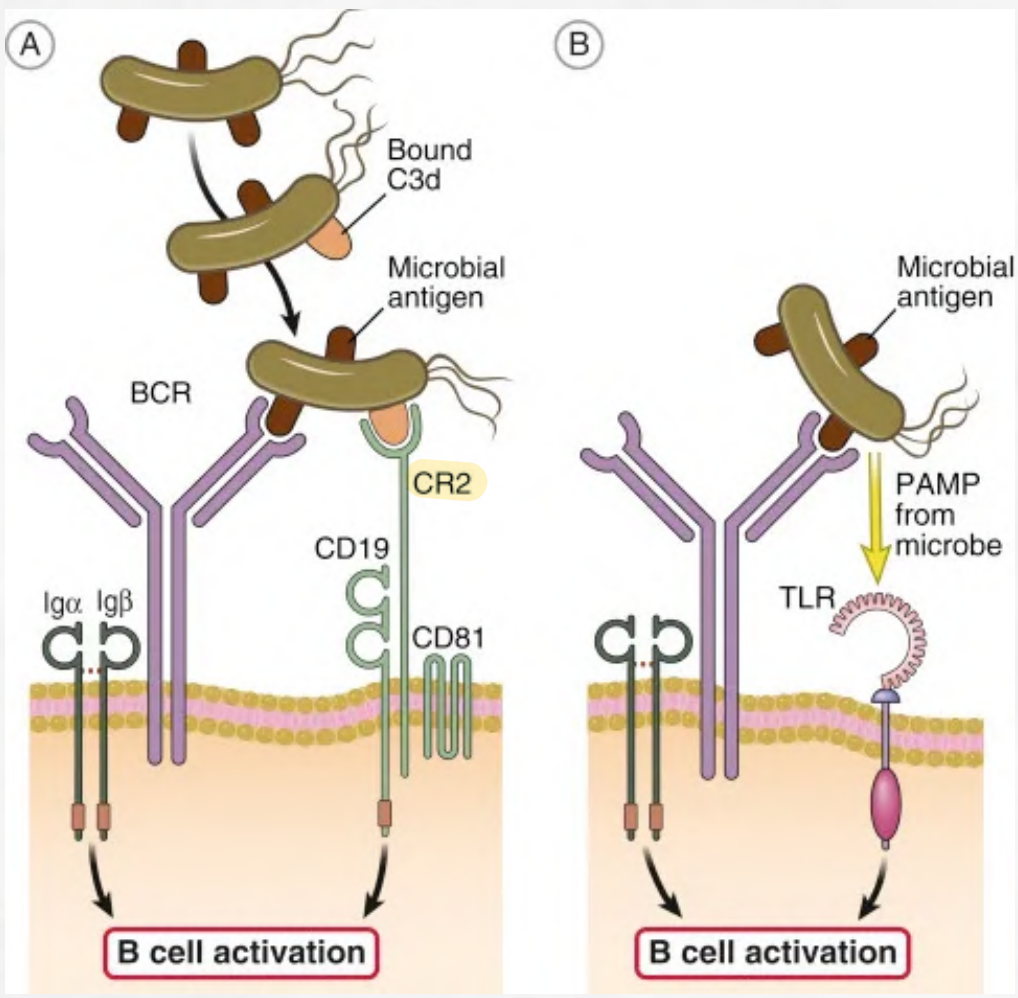


Role of Innate Immune Signals in B Cell Activation



B lymphocytes express a receptor for a complement system protein that provides second signals for the activation of these cells. The complement system, is a collection of plasma proteins that are activated by microbes and by antibodies attached to microbes and function as effector mechanisms of host defense. When the complement system is activated by a microbe as part of the innate immune response, the microbe becomes coated with proteolytic fragments of the most abundant complement protein, C3. One of these fragments is called C3d. B lymphocytes express a receptor for C3d called complement receptor type 2 (CR2, or CD21). B cells that are specific for a microbe's antigens recognize the antigens by their BCRs and simultaneously recognize the bound C3d via the CR2 receptor. Engagement of CR2 greatly enhances antigen-dependent activation responses of B cells by enhancing tyrosine phosphorylation of ITAMs. This role of complement in humoral immune responses illustrates the fundamental tenet of the two-signal hypothesis, that microbes or innate immune responses to microbes provide signals in addition to antigen that are necessary for lymphocyte activation. In humoral immunity, complement activation represents one way in which innate immunity facilitates B lymphocyte activation.

Microbial products also directly activate B cells by engaging innate pattern recognition receptors. B lymphocytes, similar to dendritic cells and other leukocytes, express numerous Toll-like receptors. Pathogen-associated molecular patterns (PAMPs) bind to TLRs on the B cells, which triggers activating signals that work in concert with signals from the antigen receptor. This combination of signals stimulates B cell proliferation, differentiation, and Ig secretion, thus promoting antibody responses against microbes.

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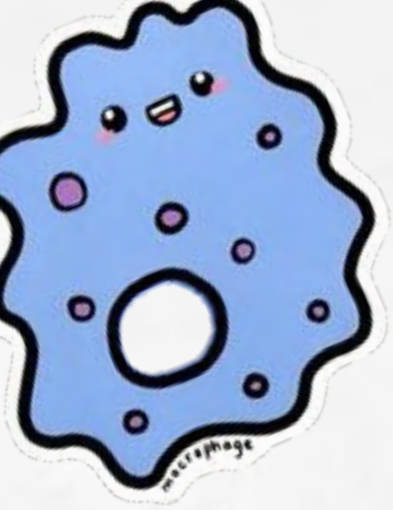
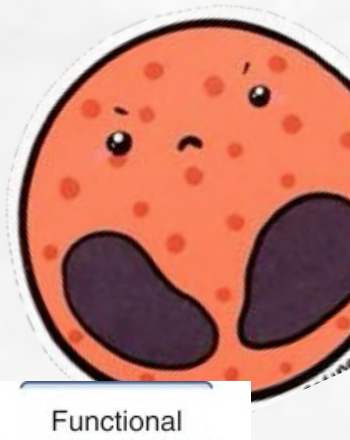
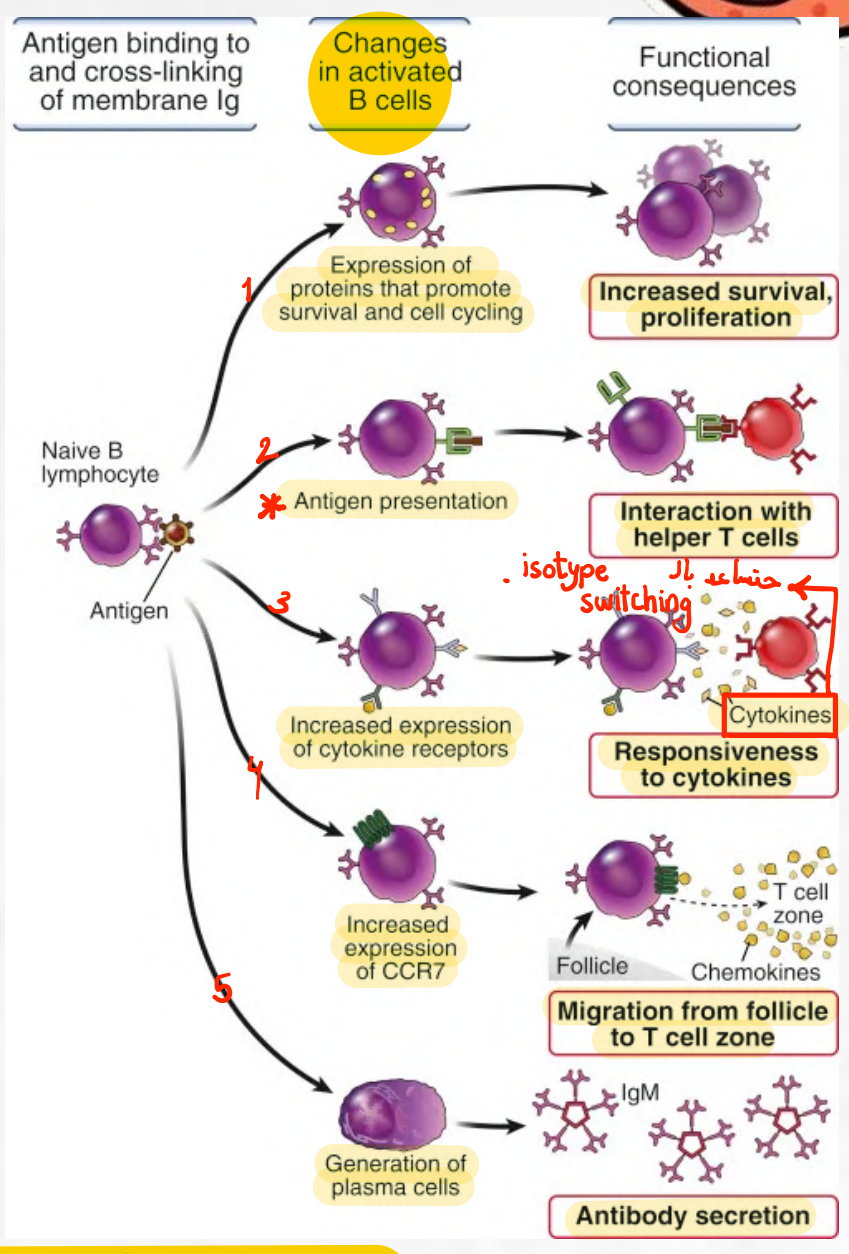


Functional Consequences of B Cell Activation by Antigen

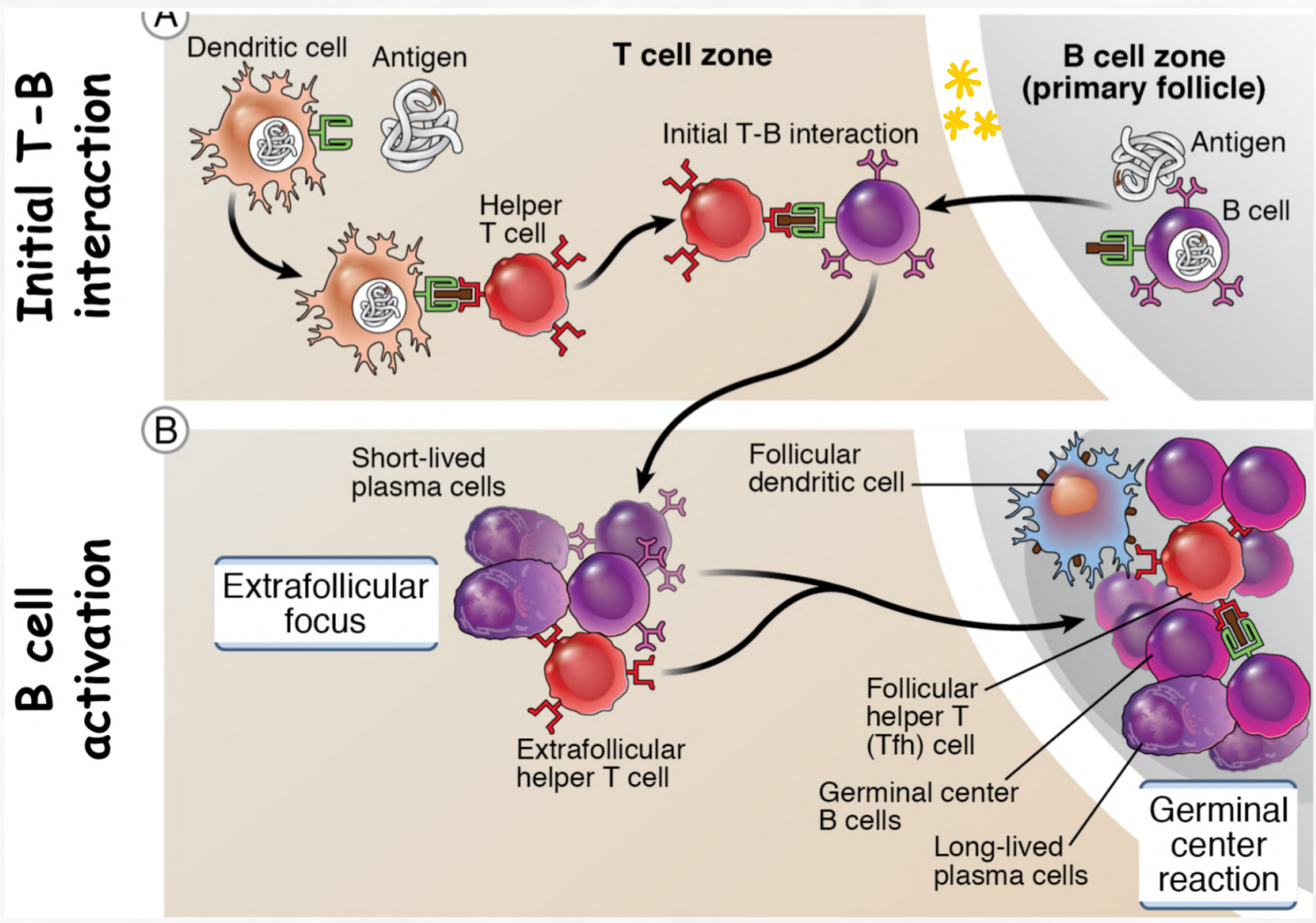


بالنسبة لنقطة 3 , افراز ال cytokines حترتبط بال cytokine
الي isotype switching و تعمل على B cell الموجود receptor
حنشرح عنه لبعدين
فلو صار عنا افراز للIF-gamma كمان و ارتبطت مع الreceptors هاد
حيعمل isotyping switching لل class تبع IgG

بالنسبة لنقطة 4، ال CCR7 حيصير الها display على B cell و T cell
الي كل وحدة منهم الها موقع بال lymph node، ال CCR7 الها علاقة
بالchemotaxis و ال movement لل B cells



Activation and migration of helper T cells and B cells



Sequence of events in helper T cell–dependent antibody responses.

A) T and B lymphocytes independently recognize the antigen in different regions of peripheral lymphoid organs and are activated. The activated cells migrate toward one another and interact at the edges of lymphoid follicles.

B) Antibody- secreting plasma cells are initially produced in the extrafollicular focus where the antigen-activated T and B cells interact. Some of the activated B and T cells migrate back into the follicle to form the germinal center, where the antibody response develops fully.

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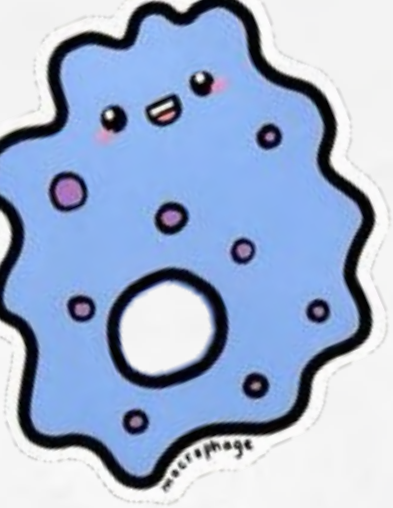
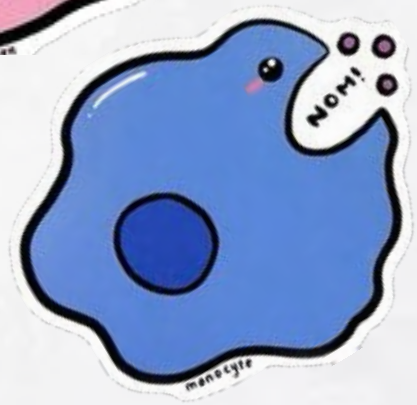


Activation and Migration of Helper T Cells and B cells

- Helper T cells that have been activated by dendritic cells migrate toward the B cell zone and interact with antigen-stimulated B lymphocytes in parafollicular areas of the peripheral lymphoid organs.

- The initial activation of T cells requires antigen recognition and costimulation. The antigens that stimulate CD4+ helper T cells are proteins derived from microbes that are internalized, processed in late endosomes and lysosomes, and displayed as peptides bound to class II MHC molecules of antigen-presenting cells (APCs) in the T cell–rich zones of peripheral lymphoid tissues. T cell activation is induced best by microbial protein antigens and, in the case of vaccines, by protein antigens that are administered with adjuvants, which stimulate the expression of costimulators on APCs. The CD4+ T cells differentiate into effector cells capable of producing various cytokines and CD40 ligand, and some of these T lymphocytes migrate toward the edges of lymphoid follicles.

- B lymphocytes are activated by antigen in the follicles, as described above, and the activated B cells begin to move out of the follicles toward the T cells. The directed migration of activated B and T cells toward one another depends on changes in the expression of certain chemokine receptors on the activated lymphocytes. Activated T cells reduce expression of the chemokine receptor CCR7, which recognizes chemokines produced in T cell zones, and increase expression of the chemokine receptor CXCR5, which binds a chemokine produced in B cell follicles. Activated B cells undergo precisely the opposite changes, decreasing CXCR5 and increasing CCR7 expression. As a result, antigen-stimulated B and T cells migrate toward one another and meet at the edges of lymphoid follicles or in inter- follicular areas. The next step in their interaction occurs here. Because antigen recognition is required for these changes, the cells that move towards one another are the ones that have been stimulated by antigen. This regulated migration is one mechanism for ensuring that rare antigen-specific lymphocytes can locate one another and interact productively during immune responses to the antigen.



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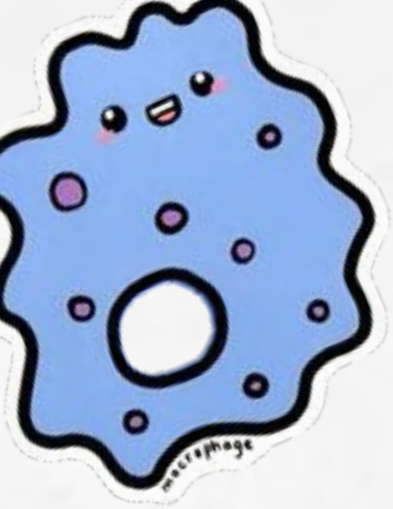
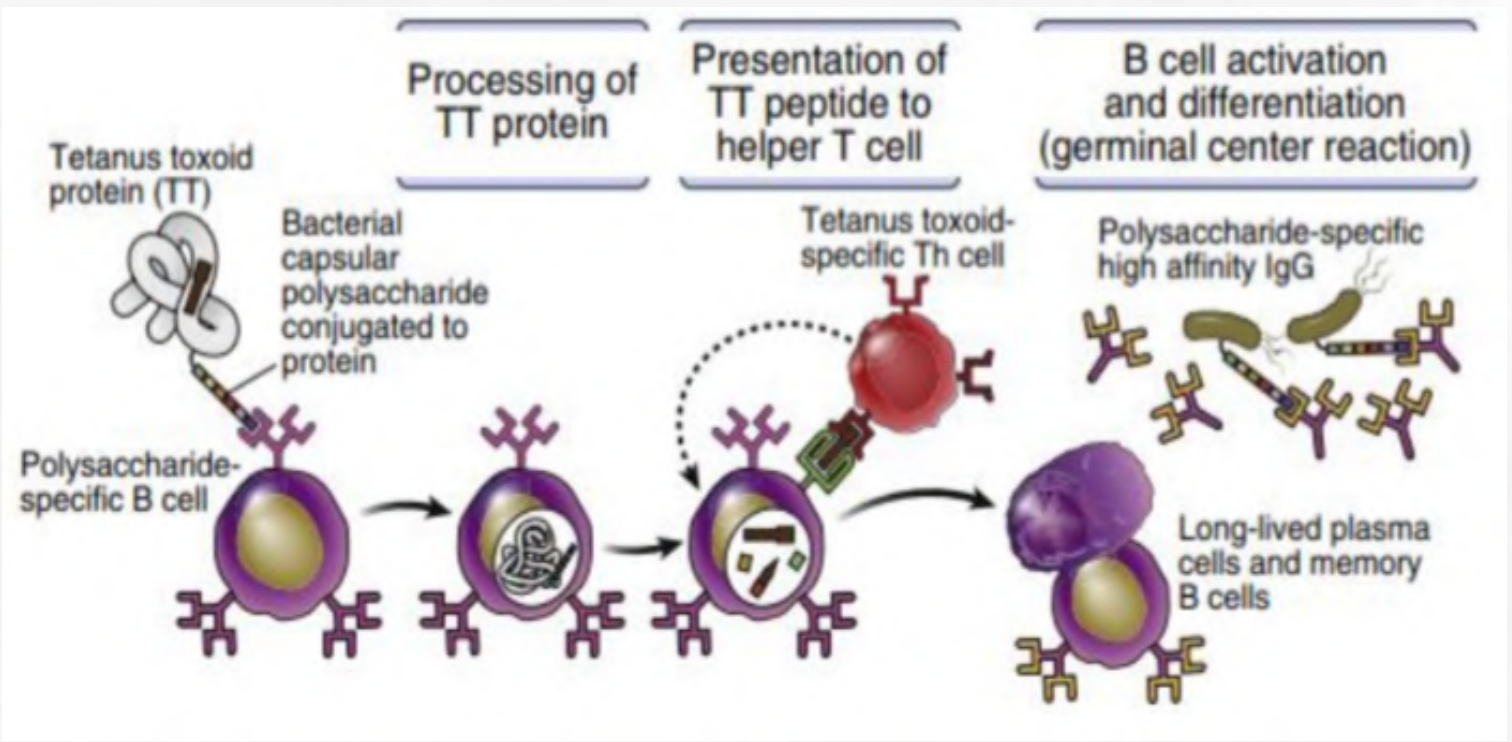


Conjugate vaccine

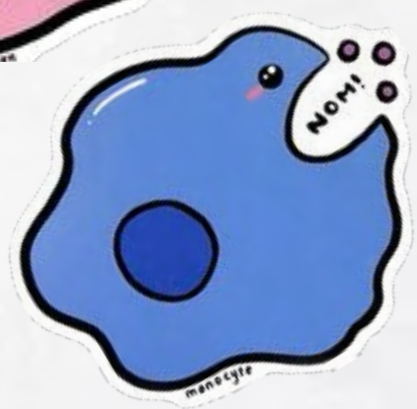
-The idea that a B cell recognizes one epitope of an intact antigen and displays different epitopes (peptides) for recognition by helper T cells was first demonstrated by studies using hapten-carrier conjugates. A hapten is a small chemical that is recognized by B cells but stimulates strong antibody responses only if it is attached to a carrier protein.

-In this situation, the B cell binds the hapten portion, ingests the conjugate, and displays peptides derived from the carrier to helper T cells. The antibody response is, of course, specific for the epitope that the B cell recognized (the hapten in this example), and the peptides derived from the carrier protein simply bring helper T cells into the reaction. This concept has been exploited to develop effective vaccines against microbial polysaccharides.

-Some bacteria have polysaccharide-rich capsules, and the polysaccharides themselves stimulate T-independent antibody responses,which are weak in infants and young children. If the polysaccharide is coupled to a carrier protein, however, effective T-dependent responses are induced against the polysaccharide because helper T cells specific for the carrier are engaged in the response.
In this situation, the B cell recognizes the polysaccharide (equivalent to the hapten) and the T cell recognizes peptides from the attached protein (the carrier); the antibody response is specific for the polysaccharide, but it is much stronger than conventional T-independent responses because helper T cells are "forced" to participate. Such conjugate vaccines have been very useful for inducing protective immunity against bacteria such as Haemophilus influenzae, especially in infants, and current vaccines against pneumococcus are also conjugate vaccines.



So The principle of conjugate vaccines: the hapten-carrier concept.
In order to generate strong antibody responses against a microbial polysaccharide, the polysaccharide is coupled to a protein (in this case, tetanus toxoid). B cells that recognize the polysaccharide ingest it and present peptides from the protein to helper T cells, which stimulate the polysaccharide-specific B cells. Thus isotype switching, affinity maturation, and long-lived plasma cells and memory cells (all features of responses to proteins) are induced in a response to polysaccharides. (Note that some B cells will also recognize the tetanus toxoid and antibodies will be produced against the carrier protein, but this has no bearing on the antipolysaccharide response.) Ig, Immunoglobulin.



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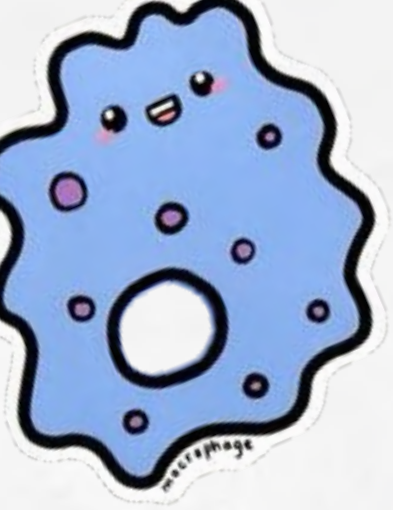
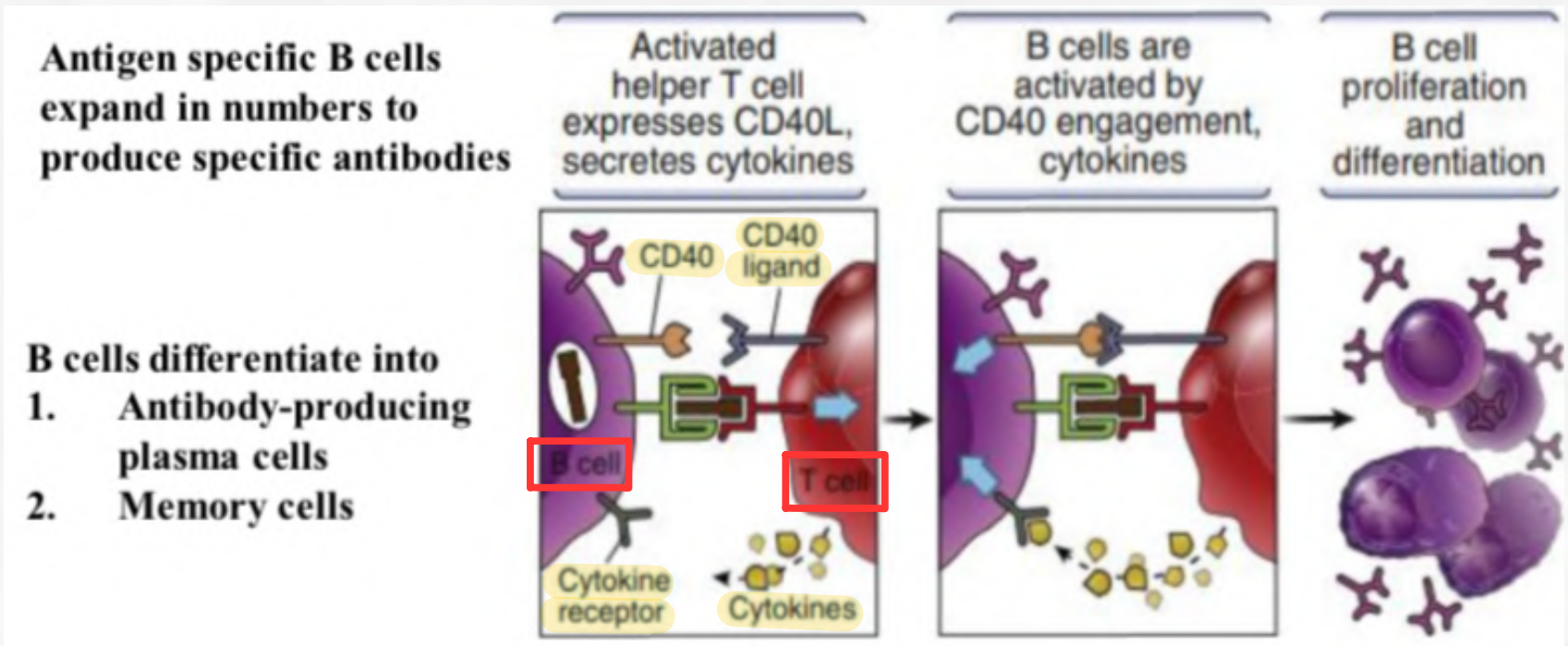


3. Clonal Expansion, proliferation and differentiation.



Mechanisms of Helper T Cell–Mediated Activation of B Lymphocytes:

- Activated helper T lymphocytes that recognize antigen presented by B cells use CD40 ligand (CD40L) and secreted cytokines to activate the antigen-specific B cells.

- The process of helper T cell–mediated B lymphocyte activation is analogous to the process of T cell–mediated macrophage activation in cell-mediated immunity.

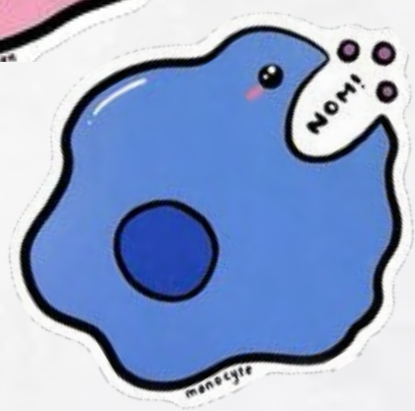
- CD40L expressed on activated helper T cells binds to CD40 on B lymphocytes. Engagement of CD40 generates signals in the B cells that stimulate proliferation and the synthesis and secretion of antibodies. At the same time, cytokines produced by the helper T cells bind to cytokine receptors on B lymphocytes and stimulate more B cell proliferation and Ig production.

- The requirement for the CD40L-CD40 interaction ensures that only T and B lymphocytes in physical contact engage in productive interactions. As described previously, the antigen-specific lymphocytes are the cells that physically interact, thus ensuring that the antigen-specific B cells are the cells that receive T cell help and are activated.

← حنشرح عنهم كمان شوي

- The CD40L-CD40 interaction also stimulates heavy-chain isotype switching and affinity maturation, which explains why these changes typically are seen in antibody responses to T-dependent protein antigens.

* Cytoleines are responsible for isotype switching.
* The first Ig to be released is IgM



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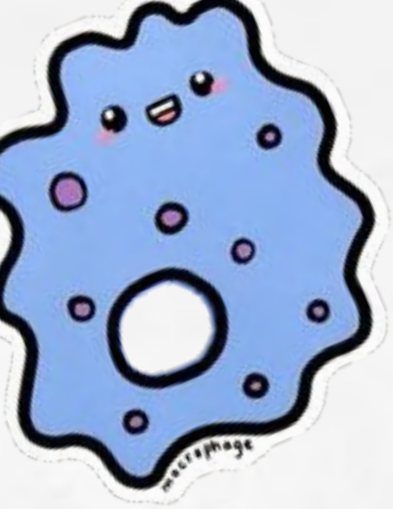


4. Antibodies Production (isotype switching)

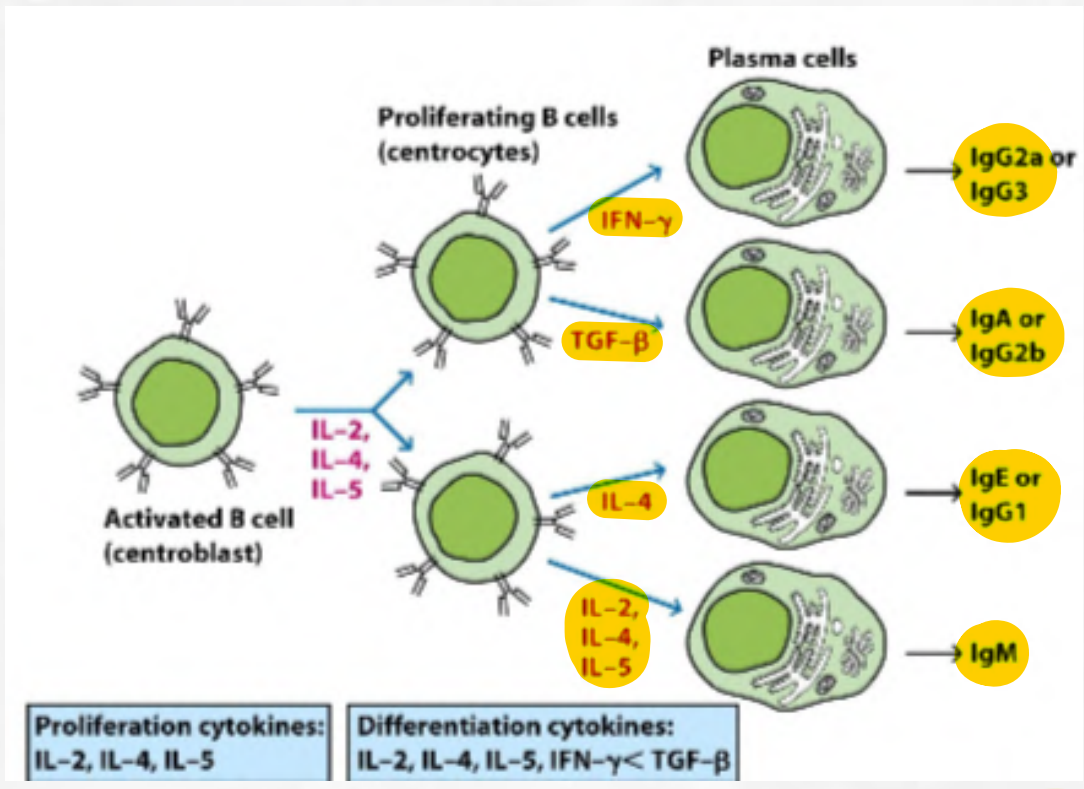
- Activated B cells start to produce different classes of antibodies in large amount to eliminate infection

- Antigen stimulated B cells may differentiate into IgM producing antibodies, however, later on, under the influence of CD40L and cyokines B cells can differentiates into cells producing other classes of heavy chain antibodies (antibody switching)

This step is the rate limitting step for isotype switching.

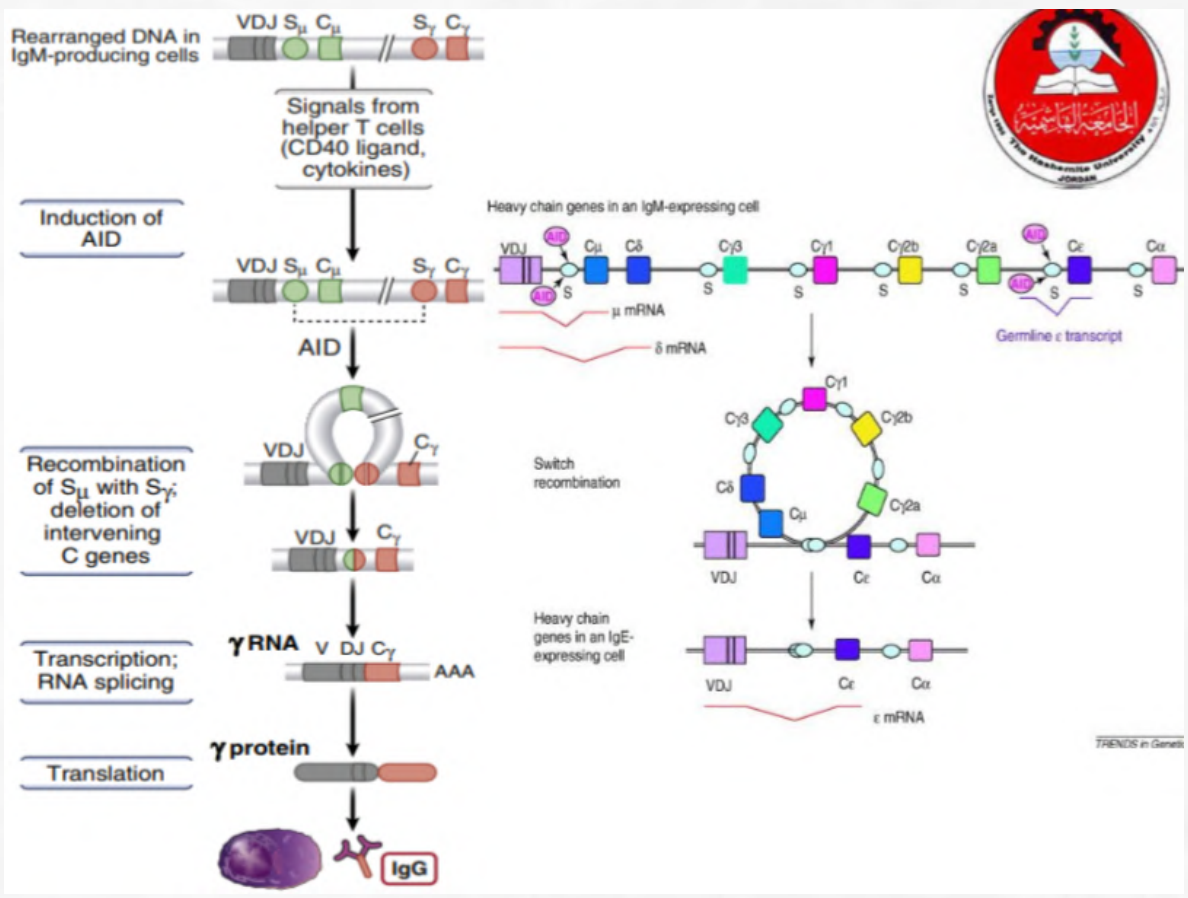
And if there is a mutation is CD40L as in x-linked hyper IgM syndrome, it will not bind to CD40 on B cells -> cytokines will no be released -> isotype switching will not occure -> the produced Ig are only IgM.

- Repeated exposure to antigen leads to increase the binding abilities of antibodies through affinity maturation, where high affinity B cells are selected to produce antibodies



الرسمة
حفظ

The molecular mechanism of isotype switching



بتصير على ال heavy chain على كروموسوم رقم 14 من ال Ig و في عليه ال gamma و ال epsilon.
ال gamma هي الي بتعطينا ال IgG و ال epsilon هي الي بتعطينا الIgE و ال alpha بعطينا الIgA

ارتباط ال CD40L على ال T cells مع CD40 على B cells بيعمل activation لـ NF kB و لما يصير عنا cytokine production و ارتباطه على الreceptors على B cells حيصيرَ عنا 2 molecules
الي هم NF kB و STAT 1

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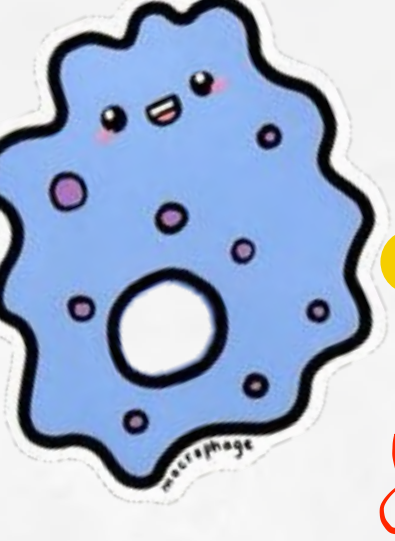
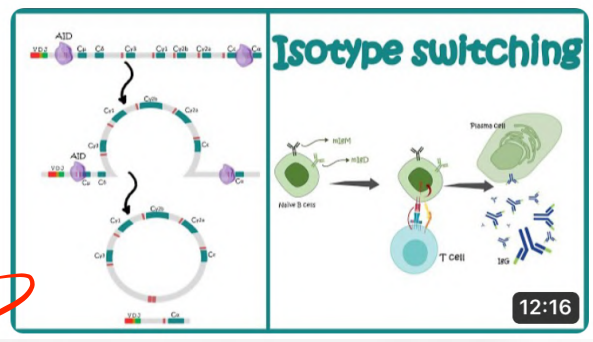


The molecular mechanism of isotype switching

you must watch this Video!



Isotype switching | class switching recombination | Antibody class switc...
61K views · 3 years ago
Animated biology With arpan

الموضوع هاد شوي معقد و نصيحة احضروا الفيديو، اجباري تحضروه لانو صعب حتى تفهموا شرح الكتاب اله ،
كل شي عليه هايلايت فالدكتور بكون ذكره بالمحاضرة

The molecular mechanism of isotype switching, called switch recombination, takes the previously formed VDJ exon encoding the Variable domain of an Ig μ heavy chain and moves it adjacent to a downstream Constant region. IgM-producing B cells, which have not undergone switching, contain in their Ig heavy- chain locus a rearranged VDJ exon adjacent to the first constant region cluster, which is Cμ.

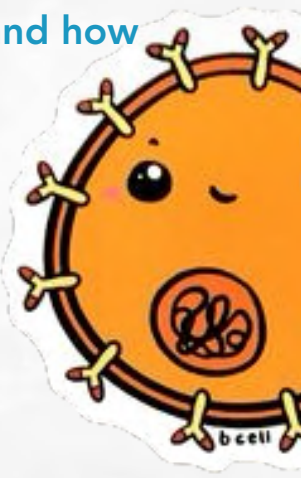
The heavy-chain mRNA is produced by splicing a VDJ exon to Cμ exons in the initially transcribed RNA, and this mRNA is translated to produce a μ heavy chain, which combines with a light chain to give rise to an IgM antibody. Thus, the first antibody produced by B cells is IgM.

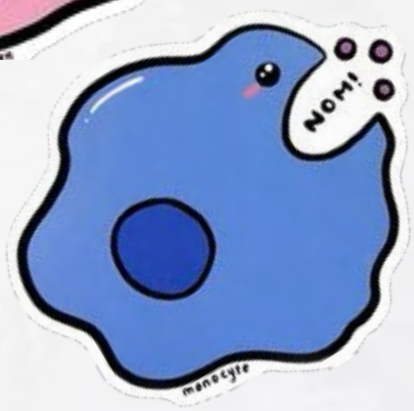
In the intron 5′ of each constant region is a guanine-cytosine (GC) rich sequence called the switch region. Signals from CD40 and cytokine receptors stimulate transcription through one of the constant regions that is downstream of Cμ. During switch recombination, the switch region upstream of Cμ recombines with the switch region adjacent to the transcriptionally active downstream constant region, and the intervening DNA is deleted.

An enzyme called activation-induced deaminase (AID), which is induced by CD40 signals, plays a key role in this process. AID converts cytosines in the transcribed switch region DNA to uracil (U). The sequential action of other enzymes results in the removal of the U's and the creation of nicks in the DNA. Such a process on both strands leads to double-stranded DNA breaks. When double-stranded DNA breaks in two switch regions are brought together and repaired, the intervening DNA is removed, and the rearranged VDJ exon that was originally close to Cμ may now be brought immediately upstream of the constant region of a different isotype (e.g., IgG, IgA, IgE).

The result is that the B cell begins to produce a new heavy-chain isotype (determined by the C region of the antibody) with the same specificity as that of the original B cell, because specificity is determined by the sequence of the VDJ exon, which is not altered.

Cytokines produced by follicular helper T cells determine which heavy-chain isotype is produced. The production of opsonizing IgG antibodies, which bind to phagocyte Fc receptors, is stimulated by IL-10 and other cytokines in humans and mainly by IFN-γ in mice Thus, the nature of the helper T cell response to a microbe guides the subsequent antibody response, making it optimal for combatting that microbe. These are excellent examples of how different components of the immune system are regulated coordinately and function together in defense against different types of microbes and how helper T cells may function as the master controllers of immune responses.
The antibody isotype produced is also influenced by the site of immune responses.





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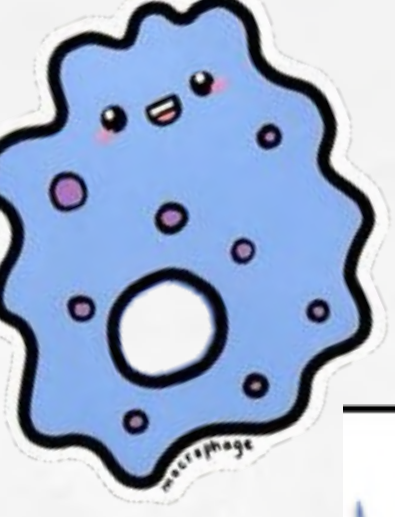
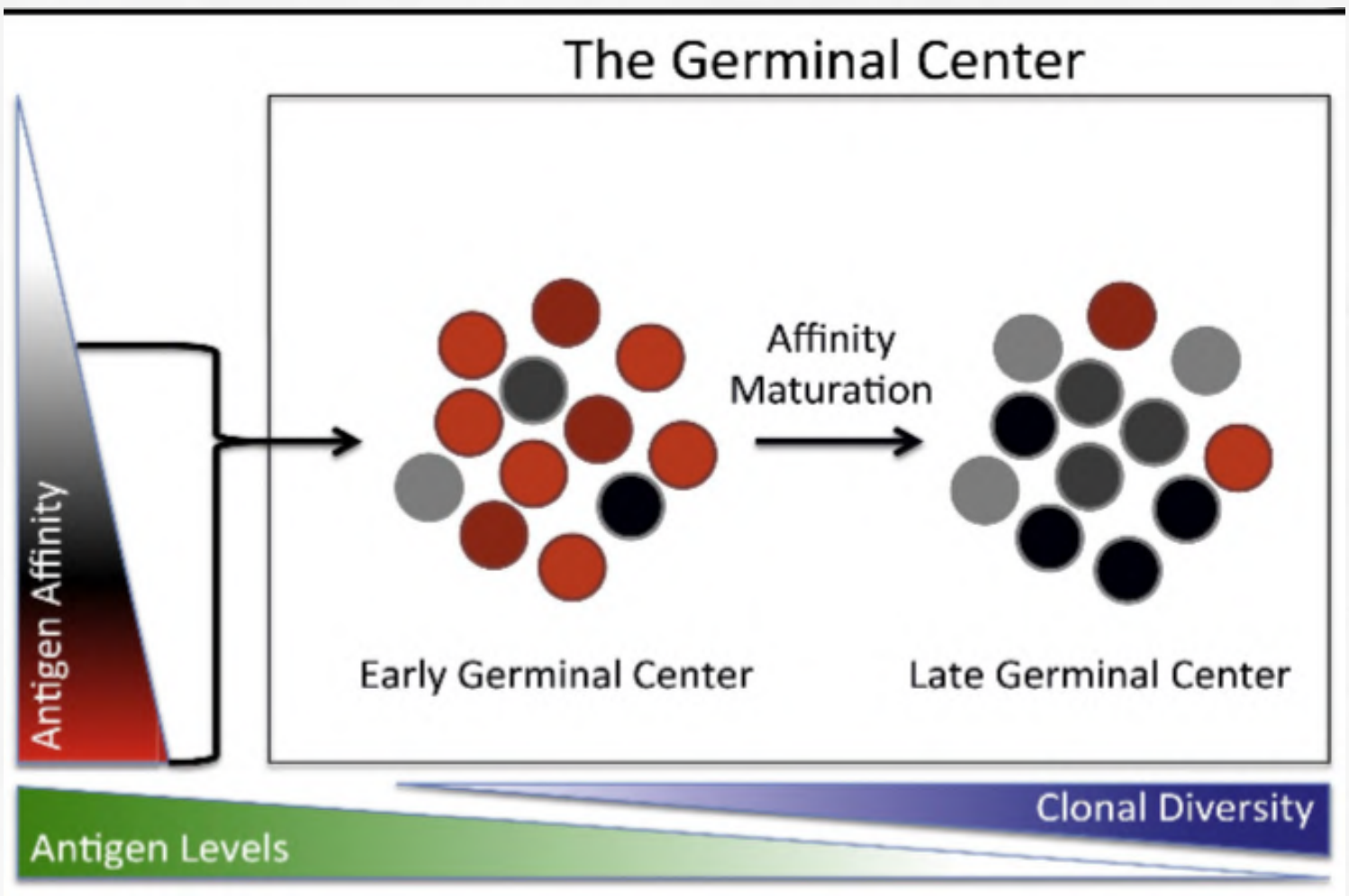


Affinity maturation



Affinity maturation is the process by which the affinity of antibodies produced in response to a protein antigen increases with prolonged or repeated exposure to that antigen.

هي عملية انتاج plasma cells و antibodies بكونوا the best fit for the antigen

عنا اول شي الخط الاخضر الي هو بمثل ال antigen level: تركيز ال Ag اول ما يدخل على ال lymph node اول شي بكون تركيزه عالي بعدين بقل مع الوقت

ال clonal diversity : اول ما يدخل ال antigen بكون التنوع قليل بعدين ببدأ يزيد

ال antigen affinity : اول ما يتم تصنيع الantibodies بتكون ال affinity بالاول broad و بعديم بتبدأ تزيد ال specifity مع الوقت

بنلاحظ من الرسمة انه مع الوقت بتصير ال affinity اقوى من ال antigen

كيف بتصير ؟ نحكي مثلا بال first cycle انتجنا antibody 1000 هدول الالف في جزء منهم برتبط مع الantigen فبضل عايش و في جزء ما برتبط مع ال Ag و بصير اله apoptosis

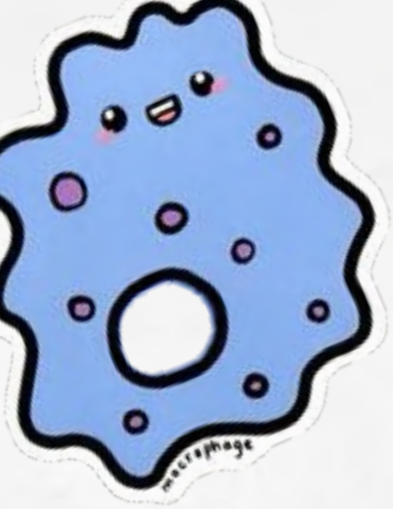
على فرض بكل cycle انتجنا antibody 1000 بضل منهم بكل دورة بس 100 الهدف بكون احصل ال Ab الي عندهم افضل affinity لاعمل الهم release على circulation

اذا ضلينا نعمل mutation لحتى نحصل على افضل affinity

هسا بالرسمة اللون الاحمر بمثل ال affinity القليلة و الاسود affinity عالية، بنلاحظ انه مع الوقت و بعد مرور عدة cycles ضل عنا الAb الي عندهم افضل affinity

حكينا فوق انه ال antibody مع الوقت بتنعرض على concentration اقل من ال Ag و لكن ال response تبعها قوي

وَقُل رَّبِّ زِدْنِي عِلْمًا



Affinity Mutation

Because of affinity maturation, the ability of antibodies to bind to a microbe or microbial antigen increases if the infection is persistent or recurrent. This increase in affinity is caused by point mutations in the V regions, and particularly in the antigen-binding hypervariable regions, of the genes encoding the antibodies produced.

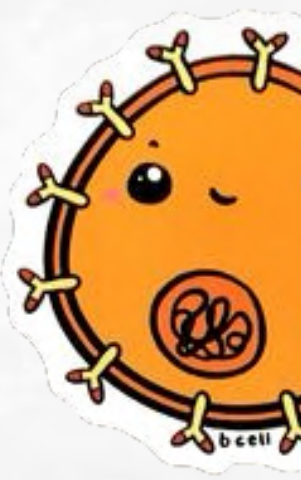
Affinity maturation is seen only in responses to helper T cell–dependent protein antigens, indicating that helper cells are critical in the process. These findings raise two intriguing questions: how are mutations in Ig genes induced in B cells, and how are the highest affinity (i.e., most useful) B cells selected to become progressively more numerous?

Affinity maturation occurs in the germinal centers of lymphoid follicles and is the result of somatic hypermutation of Ig genes in dividing B cells, followed by the selection of high-affinity B cells byantigen. In the dark zones of germinal centers (where the proliferating B cells are concentrated), numerous point mutations are introduced into the Ig genes of the rapidly dividing B cells.

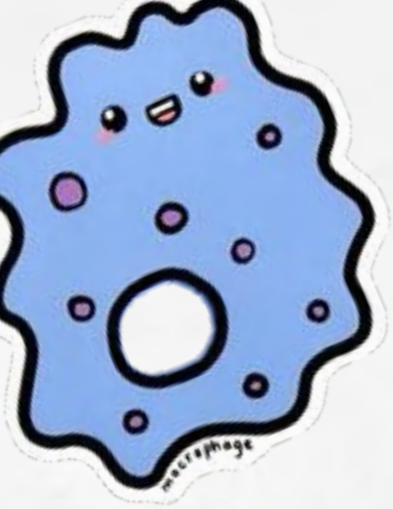
The enzyme AID,which is required for isotype switching, also plays a critical role in somatic mutation. This enzyme, as stated above, converts C into U. The uracils that are produced in Ig V-region DNA are frequently replaced bythymidines during DNA replication, creating C-to-T mutations, or they are removed and repaired by errorprone mechanisms that often lead to introduction of nucleotides other than the original mutated cytosine. The frequency of Ig gene mutations is estimated to be one in 103 base pairs per cell division, which is much greater than the mutation rate in most other genes. For this reason, Ig mutation in germinal center B cells is called somatic hypermutation. This extensive mutation results in the generation of different B cell clones whose Ig molecules may bind with widely varying affinities to the antigen that initiated the response. The next step in the process is the selection of B cells with the most useful antigen receptors.

Germinal center B cells undergo apoptosis unless rescued by antigen recognition and T cell help. While somatic hypermutation of Ig genes is taking place in germinal centers, the antibody secreted earlier during the immune response binds residual antigen. The antigen-antibody complexes that are formed may activate complement. These complexes are displayed by follicular dendritic cells (FDCs), which reside in the light zone of the germinal center and express receptors for the Fc portions of antibodies and for complement products, both of which help to display the antigen-antibody complexes. B cells that have undergone somatic hyper-mutation are given a chance to bind antigen either on FDCs or free in the germinal center. These B cells can internalize the antigen, process it, and present peptides to germinal center Tfh cells, which then provide critical survival signals. High-affinity B cells more effectively compete for the antigen and thus are more likely to survive than B cells with Igs that have lower affinities for the antigen, akin to a process of Darwinian survival of the fittest.

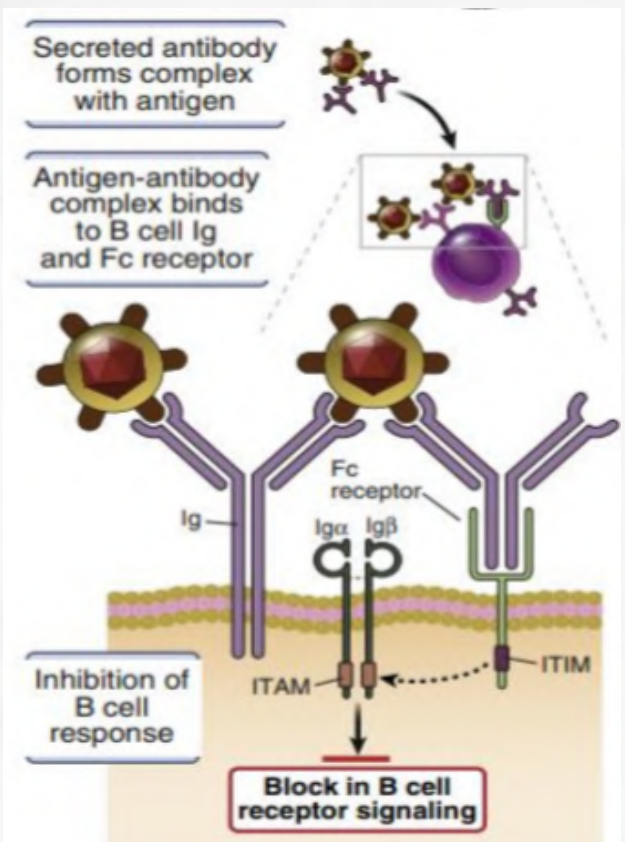
As the immune response to a protein antigen develops, and also with repeated antigen exposure, the amount of antibody produced increases. As a result, the amount of antigen available in the germinal center decreases. The B cells that are selected to survive must be able to bind antigen at lower and lower concentrations, and therefore these are cells whose antigen receptors are of higher and higher affinity.



وَقُل رَّبِّ زِدْنِي عِلْمًا



6. Humoral immunity shut down and formation of memory B cells



- After antibodies are capable of killing invading microorganisms, most of activated B cells die by programmed cell death

- Furthermore, circulating IgG antibodies that binds to antigen in periphery induce negative feedback mechanism to inhibit further antibody production

لما نعمل elimination لل Pathogen بصير دور نعمل inhibition لل immune response و هون في عنا طريقتين :
الاولى : قل عدد ال antigen = قل عدد ال signals = بصير عنا apoptosis لل B cells
الثانية : برتبط ال free antibody مع ال antigen الي كمان مرتبط مع B cell و هاد بيعمل تغذية راجعة ليصير عنا shut down

- Memory B cells are formed and stay for long time to facilitate faster antibodies production when the body is exposed to same antigen next time

TABLE 11-6 Comparison of naive and memory B cells

Property	Naive B cell	Memory B cell
Membrane markers		
Immunoglobulin	IgM, IgD	IgM, IgD(?), IgG, IgA, IgE
Complement receptor	Low	High
Anatomic location	Spleen	Bone marrow, lymph node, spleen
Life span	Short-lived	May be long-lived
Recirculation	Yes	Yes
Receptor affinity	Lower average affinity	Higher average affinity due to affinity maturation*
Adhesion molecules	Low ICAM-1	High ICAM-1

*Affinity maturation results from somatic mutation during proliferation of centroblasts and subsequent antigen selection of centrocytes bearing high-affinity mIg.

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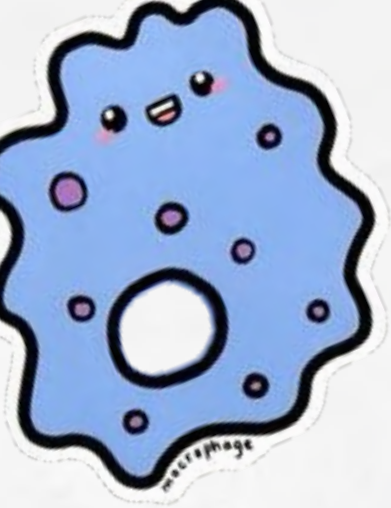
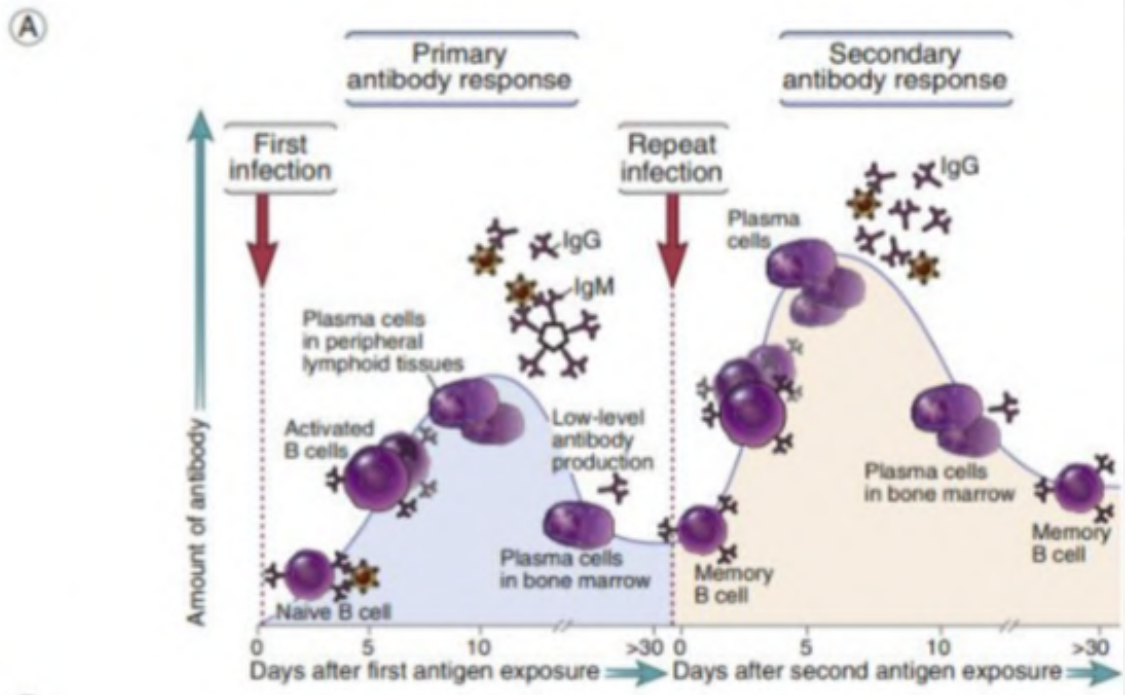


Primary and secondary humoral immunity



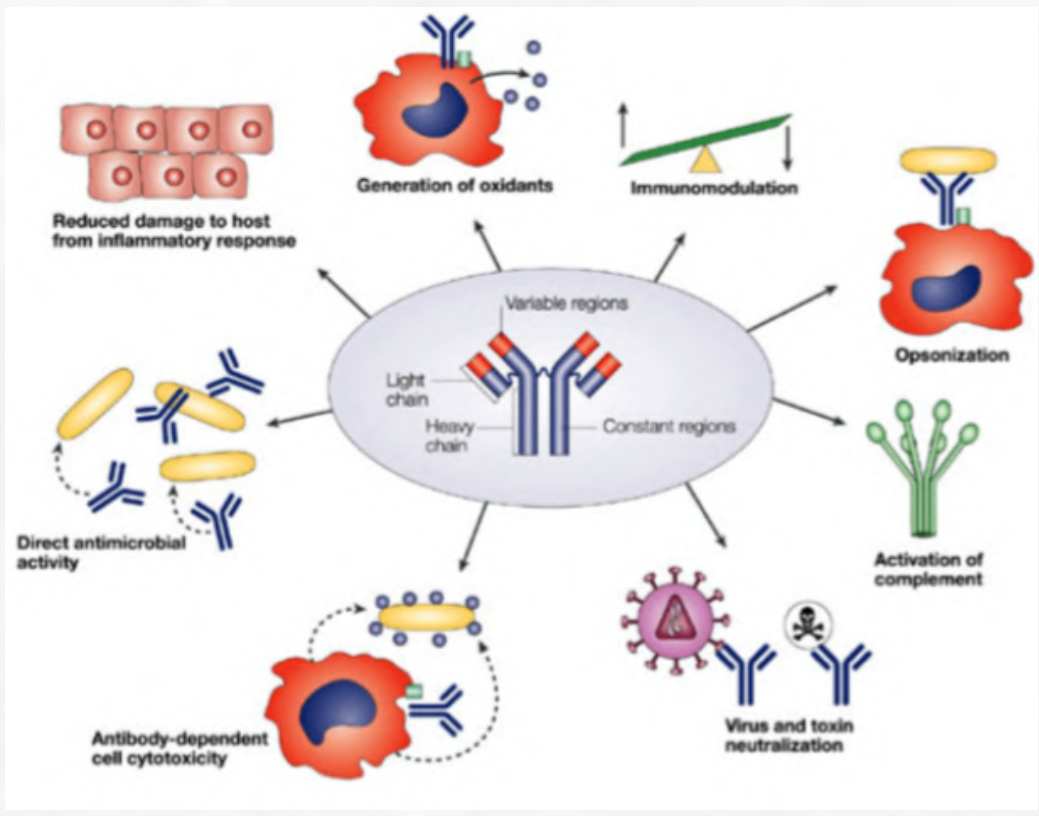
B

	Primary response	Secondary response
Lag after immunization	Usually 5–10 days	Usually 1–3 days
Peak response	Smaller	Larger
Antibody isotype	Usually IgM>IgG	Relative increase in IgG and, under certain situations, in IgA or IgE (heavy-chain isotype switching)
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)

Primary and secondary antibody responses differ in several respects.
In a primary response, naive B cells in peripheral lymphoid tissues are activated to proliferate and differentiate into anti- body-secreting plasma cells and memory cells. Some plasma cells may migrate to and survive in the bone marrow for long periods.
In a secondary response, memory B cells are activated to produce larger amounts of antibodies, often with more heavy-chain class switching and affinity maturation. These features of secondary responses are seen mainly in responses to protein antigens, because these changes in B cells are stimulated by helper T cells, and only proteins activate T cells (not shown). The kinetics of the responses may vary with different antigens and types of immunization. Ig, Immunoglobulin

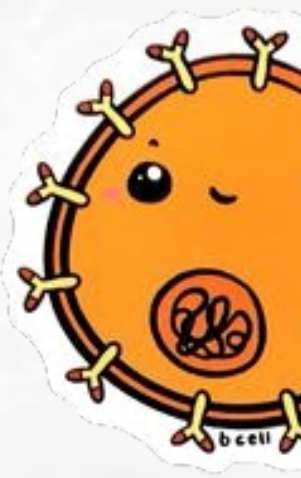
5. Effector Mechanisms

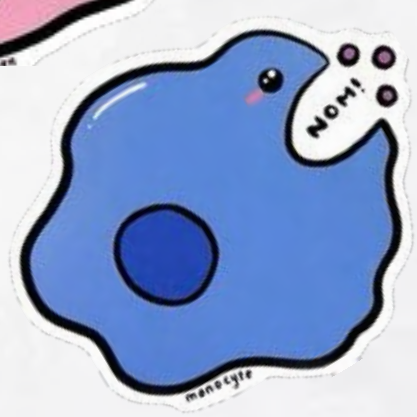
- Neutralization
- Opsonization
- Complement activation
- Antibody dependent cell mediated toxicity (ADCC)
- Transcytosis- movement across epithelial cells



﴿ فَمَا ظَنُّكُم بِرَبِّ ٱلْعَٰلَمِينَ ﴾.

الثقة بالله شقّت لِموسى البحر، وبردت النار على إبراهيم، ألا تثق بأنه سيغيّر أحوالك لِلأفضل ❤️





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