Medical Immunology - Lecture "1"

Self-tolerance and selected autoimmune diseases (SLE, Type 1 Diabetes, Graves' disease)

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1. Core concept: Self-tolerance

Type	Where it happens	Goal	Main outcomes
Central tolerance	Primary lymphoid organs (thymus for T cells; bone marrow for B cells)	Remove or fix strongly self-reactive lymphocytes before they enter circulation	Deletion (negative selection) and/or receptor editing
Peripheral tolerance	Peripheral tissues and lymphoid sites after lymphocytes mature	Prevent self-reactive cells that escaped central tolerance from causing damage	Anergy, apoptosis, and suppression by regulatory T cells (Treg)

2. Autoimmune diseases: overview

Autoimmune diseases can be classified as organ-specific (focused on one organ) or systemic (multi-organ). Risk is commonly influenced by genetic susceptibility (often involving HLA) plus environmental factors.

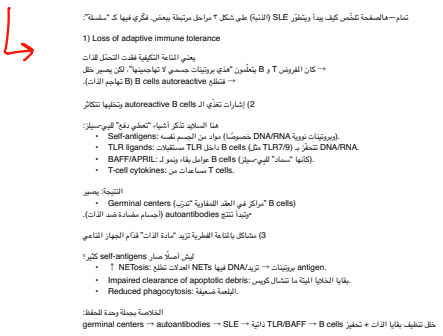
3. High-yield disease table (memorize)

Disease	Type	Target	Immune driver / hallmark	Clinical result
Systemic Lupus Erythematosus (SLE)	Systemic	Multiple organs (skin, joints, kidneys, blood, etc.)	B cells produce autoantibodies; immune complexes; innate activation (pDC/TLR → IFN-alpha, NETs)	Multi-system inflammation and tissue injury
Type 1 Diabetes (T1D)	Organ-specific	Pancreatic beta cells (islets)	T cell-driven beta-cell destruction (HLA association)	Beta-cell loss → hyperglycemia → clinical diabetes
Graves' disease	Organ-specific	Thyroid	Autoantibodies against TSH receptor mimic TSH	Hyperthyroidism + goiter

4. Mechanisms in detail

4.1 SLE: breaking immune tolerance (step-by-step)

Step	Mechanism	What it leads to
1	Loss of adaptive tolerance → increased autoreactive B cells	Start of autoantibody-prone B-cell responses
2	Amplifiers: self-antigens + TLR ligands + BAFF/APRIL + T-cell cytokines → germinal centers	More autoantibodies and immune complexes
3	Innate defects: increased NETosis + impaired apoptotic debris clearance + reduced phagocytosis	More available self-antigens → stronger feedback loop
4	Innate sensing: TLR on pDC activated by immune complexes → IFN-alpha (plus NETs)	Inflammation amplification and persistence



1) Loss of adaptive immune tolerance

يعني المناعة التكيفية فقدت التحمّل للذات
كان المفروض B و T يتعلّمون "هذي بروتينات جسمي لا تهاجمها"، لكن يصير خلل → فتطلع B cells autoreactive (تهاجم الذات).

2) إشارات تغذّي الـ autoreactive B cells وتخليها تتكاثر

هنا السلايد تذكر أشياء "تعطي دفع" للي سبق:
- Self-antigens: مواد من الجسم نفسه (خصوصًا DNA/RNA وبروتينات نووية).
- TLR ligands: مستقبلات TLR داخل B cells (مثل TLR7/9) تتحفّز بـ DNA/RNA.
- BAFF/APRIL: عوامل بقاء وتنمو لـ B cells (كانها "سماد" للي سبق).
- T-cell cytokines: سماعات من T cells.

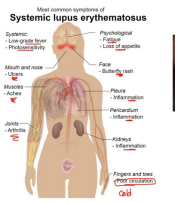
النتيجة يصير
- Germinal centers ("مراكز في العقد اللمفاوية "تتدرّب" B cells)
وبيدأ تنتج autoantibodies (أجسام مضادة ضد الذات).

3) مشاكل بالمناعة الفطرية تزيد "مادة الذات" فتأم الجهاز المناعي

ليش أصلاً صار self-antigens كثير؟
- ↑ NETosis: العدلات تطلع NETs فيها DNA/ تزيد → بروتينات antigen.
- Impaired clearance of apoptotic debris: بقايا الخلايا الميتة ما تتشال كويس.
- Reduced phagocytosis: الماصة ضعيفة.

الخلاصة بجملة وحدة للحفظ:
germinal centers → autoantibodies → SLE → ذاتية TLR/BAFF → B cells خلل تنظيف بقايا الذات + تحفيز

Associated with genes of the complement system: C_{4_1}, C_2, C_4



4.2 Type 1 Diabetes (T1D): stepwise pathogenesis

Step	Mechanism	Result
1	Reduced negative selection in thymus → escape of beta-cell specific T cells	Autoreactive T cells reach the periphery
2	Suboptimal development/function of beta-cell specific Foxp3+ Treg ← فيل بهذا	Less suppression of autoreactive T cells
3	Activation in pancreatic lymph nodes (pLN) by APC from islets → Teff differentiation	Effector T cells are generated
4	Teff infiltrate islets → chronic inflammation	Decreased beta-cell function/survival
5	Inflammation generates neoautoantigens	Epitope spreading and worsening disease
6	Sufficient beta-cell loss	Hyperglycemia → clinical diabetes ↳ ↓ insuline

يعني: مستضد "جديد" ما كان جهاز المناعة متعوّد يشوفه كهدف—يطلع أثناء الالتهاب أو تلف النسيج.

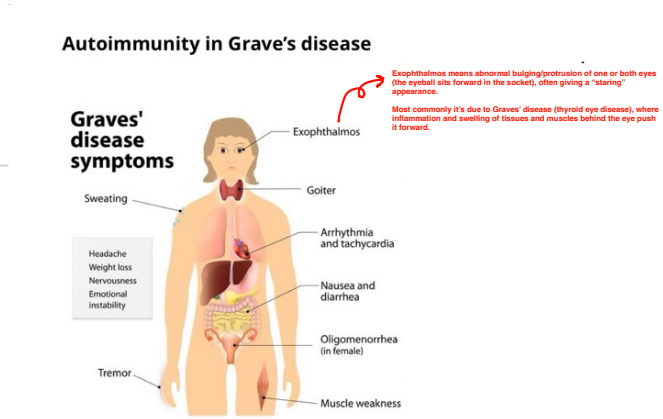
في سياق Type 1 Diabetes بالمحاضرة:
- لا يصير التهاب مزمن في جزر البنكرياس. هذا الالتهاب ممكن يسبب تغيّرات/تكسير/تعديل في بروتينات خلايا β فتتكوّن neoautoantigens (أهداف جديدة)
- وبهذا يصير الهجوم المناعي "يتوسع" ويزيد تدهور خلايا β.

↳ Genetic association with: HLA
↳ remember:

وظيفته الأساسية: HLA (خصوصًا HLA-DR) عرض البيبتيدات (antigens) على خلايا T المساعدة CD4+.
يعني في APCs (dendritic cells, macrophages, B cells) موجود على MHC class II.
لهيك مهم بالمناعة الذاتية.
بحالة أمراض المناعة الذاتية: HLA تعرض self-peptides → خلايا T cells CD4+ تفعّل → B cells تصير autoantibodies.

4.3 Graves' disease: key mechanism

Autoantigen/target	Autoantibody action	Outcome
TSH receptor	Autoantibodies mimic TSH (stimulating the receptor)	Hyperthyroidism and goiter



Medical Immunology - Lecture "2"

Main theme: How mature B cells capture antigen, become activated (T-dependent vs T-independent), and differentiate into plasma cells and memory B cells; plus a key effector function of antibodies (ADCC).

1) Where mature B cells live and how they find antigen

Mature B lymphocytes continuously **recirculate** through secondary lymphoid organs in search of antigen.

Most B cells enter **follicles** guided by **CXCL13** (from follicular dendritic cells) binding **CXCR5** on naive follicular B cells.

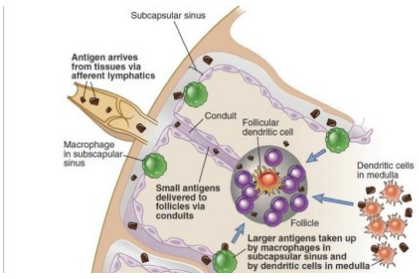
Naive follicular B cells survive only for limited periods unless supported by signals from the **BCR** and **BAFF (BLyS)** via the BAFF receptor.

↳ B cell receptor

Antigen capture and delivery to B cells (overview)

	Antigen type / location	Main "delivery" route to follicle	Key idea
1	Small soluble antigens (< ~70 kD)	Travel through conduits from subcapsular sinus to follicle	Can contact specific B cells directly
2	Large microbes & immune complexes	Captured by subcapsular sinus macrophages and delivered to follicles	Antigen kept *intact/native* IMP !
3	Medium-sized antigens	Captured by resident dendritic cells (medulla) and transported into follicles	Facilitates B cell activation
4	Immune complexes + complement	Bind complement receptors (esp. **CR2**) on marginal zone B cells; transferred to follicular B cells	Efficient "hand-off" to follicular B cells

receptor جاءك من C3d



1. Initiation
- التنشيط يبدأ لما الأنتيجين يرتبط بـ membrane Ig (جزء من BCR) مع Igα/Igβ.

2.نتيجتين فوريتين لارتباط الأنتيجين:
- (أ) Signals: إشارات كيميائية حيوية تدخل الخلية وتبدأ تفعيلها.
- (ب) Internalization: الأنتيجين ينشفط للداخل في endosomes.

3.لو الأنتيجين Protein
- يتقصقص إلى peptides
- ثم تُعرض على سطح MHC II على B cell
- عشان تتعرف عليها Helper T cells (هذا أساس الـ T-dependent responses).

4. Full response: مثل BCR يحتاج مؤثرات إضافية مع
- complement proteins
- pattern recognition receptors (مثل TLRs)
- وفي البروتينات خصوصًا: مساعدة T helper

C3d of its receptor CR2

CDL 40 → CD40 on B cell

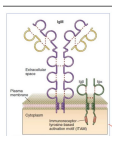
How it works?

2) B cell receptor (BCR) basics and immediate activation changes

Naive B cells express membrane **IgM** and **IgD** with very short cytoplasmic tails; signaling is transmitted by associated **Igα** and **Igβ**.

Antigen binding to the BCR triggers signaling *and* internalizes antigen for endosomal processing (protein antigens) so peptides can be presented on **MHC class II** to helper T cells.

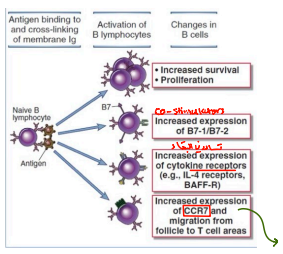
After BCR cross-linking, resting B cells enter **G1**, increase in size/RNA/organelles, upregulate survival proteins (notably **Bcl-2**), may proliferate and secrete some antibody, and increase cytokine receptor expression.



بعد الـ class switching لـ BCR فيه الـ B cells تحوّلت من IgG أو IgA أو IgE إلى switch memory b cells

Signals that cooperate with BCR engagement

Signal type	Examples from the lecture	Why it matters
BCR engagement (core signal)	Antigen binding + receptor cross-linking	Initiates activation + antigen internalization
Innate / "extra" signals	Complement, pattern-recognition receptors (e.g., TLRs)	Amplifies response; supports full activation
T cell help (protein antigens)	CD40L-CD40 + helper T cytokines	Drives strong responses: isotype switching, affinity maturation, memory



هاي الرسمة بتشرح شو بصير للـ naïve B cell أول ما يمسك الـ antigen (خصوصًا لما يعمل binding + cross-linking للـ membrane Ig/BCR). بعدها بتطلع "تغييرات" تخليها جاهزة تستجيب

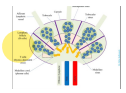
T-independent antigens (often polysaccharides with repetitive epitopes) can strongly cross-link many BCRs and induce responses without helper T cell; they mainly induce **IgM** with little isotype switching.

على سطح الـ B cell فيه كتير BCRs (مو واحد).
الـ polysaccharide غالبًا: multivalent يكون فيه نفس الـ epitope مكرر (repeating units)، مو شرط "أنواع مختلفة" من epitopes.
فبالتالي جزيء polysaccharide واحد يقدر يمسك BCR #1 و BCR #2 و BCR #3... بنفس الوقت → هذا هو cross-linking → يعطي إشارة قوية.

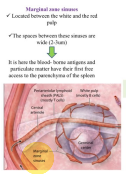
مثال حفظة: capsular polysaccharide للبكتيريا يعمل cross-linking قوي → T-independent response (غالبًا IgM)

3) Major B cell subsets (high-yield)

Subset	Where found / origin	Typical role
Follicular (recirculating) B cells	Most mature B cells; live in B cell follicles; express IgM and IgD	Dominant population for T-dependent responses
B-1 B cells	Develop from fetal liver-derived HSCs; enriched in peritoneum; contribute at mucosal sites	Spontaneously secrete "natural" IgM; rapid responses to microbial polysaccharides/lipids
Marginal zone B cells	Primarily spleen marginal zone	Limited diversity; respond to polysaccharides; generate natural antibodies



At mucosal sites, as many as half the IgA-secreting cells in the lamina propria may be derived from B-1 cells



اغلب الـ B cells respond بصيرلها polysaccharides هنا خصوصًا polysaccharides اللي تكون من بكتيريا مغلّفة (capsular polysaccharides) وتوصل للدم

4) Helper T cell-dependent antibody responses to protein antigens

Protein antigens require: (1) B cell recognition + internal processing, (2) peptide presentation to helper T cells, and (3) physical B-T collaboration.

Precursor frequencies are low (as rare as 1 in 10^5-10^6 lymphocytes), so activated B and T cells must migrate and find each other.

داخل جسمك فيه ملايين الفطريات، لكن الخلايا اللي "مناسبة" لهيك epitope تحديدًا جدًا:
يمكن 1 من كل 100,000 إلى 1 من كل 1,000,000 من الـ B cells أو T cells تكون قادرة تتعرف على نفس epitope
هاد يسمّى strong antibody response (خصوصًا T-dependent مثل IgG + memory)
1. لازم تتنشط أول B cell الخاصة بهيك antigen
2. ولازم تتنشط الـ CD4 T helper اللي يتعرف على نفس peptide من MHC II
3. ويصير لازم يتفاعل مع بعض (غالبًا بنفس الوقت) في العقدة الليمفاوية: عند حدود T-B ويصير بينهم: physical interaction وبعدين B: CD40L + cytokines
وبعدين فالمساعدة ما بتصير class switching/affinity maturation بشكل قوي

DC primes naive CD4 T cells in the T cell zone. Activated Tfh then meets antigen-specific B cells at the T–B border; both present the same peptide–MHC II, and T cells deliver help (CD40L + cytokines).

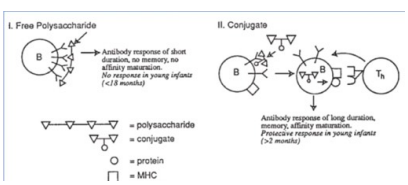
How B and T cells meet at the T-B interface

Cell type	Chemokine receptor change after activation	Resulting movement
Activated CD4+ helper T cells	↓CCR7, ↑CXCR5 → هاد بيرتبط بالـ CXCL13 اللي على الـ FDC و Follicular dendritic cell	Leave T cell zone and move toward follicle (CXCL13 gradient)
Activated B cells	↓CXCR5, ↑CCR7 → CCL19, CCL21 are ligands for CCR7	Move toward T cell zone (CCL19/CCL21 gradient)

A T-dependent response typically uses **two epitopes**: a native (often conformational) epitope ① recognized by the BCR, and a linear peptide epitope ② presented on MHC II to helper T cells. The antibodies produced are usually specific for the native antigen structure.

النقطة المهمة:
الـ T cell تساعد الـ B cell لأنها شافت peptide خطي من نفس البروتين،
لكن الـ الأجسام المضادة اللي تنتجها B cell لاحقًا راح تكون ضد الـ native = antigen determinants ضد الشكل الطبيعي ثلاثي الإبعاد للـ antigen (اللي كانت B cell ماسكته أصلًا).
مو لازم ضد نفس الـ peptide اللي عرضته على MHC II

Hapten-carrier effect: haptens are not immunogenic alone but become immunogenic when coupled to proteins; this principle is used in **conjugate vaccines** (polysaccharide + protein carrier).



Activated helper T cells provide **CD40L** (binds CD40 on B cells) and cytokines; early proliferation occurs in **extrafollicular foci**, and later specialized reactions occur in **germinal centers**.

5) Germinal center reactions: switching, affinity maturation, memory

Germinal centers form a few days after activation and are the main site for: **isotype switching**, **affinity maturation**, **memory B cell generation**, and **long-lived plasma cell differentiation**.

Follicular dendritic cells (FDCs) in follicles display antigen using complement receptors (CR1/CR2/CR3) and Fc receptors, enabling selection of high-affinity B cells.

Affinity maturation (somatic hypermutation + selection)

Affinity maturation = increased antibody affinity over time due to somatic mutation of Ig genes followed by selective survival of the highest-affinity clones.

Requires helper T cells and CD40:CD40L signaling; therefore mainly seen in T-dependent protein antigen responses.

Mutation rate is about **1 per 1000** V-region base pairs per cell division (roughly 1000x higher than typical genes), concentrated in complementarity-determining regions (CDRs).

In the light zone, **IL-21** from TFH cells promotes apoptosis unless B cells are rescued by antigen recognition; high-affinity BCRs bind limited antigen best, so these clones survive preferentially.

IMP NOTE:

المعنى:
إذا الـ B cell ما لقت rescue (إنها ما التقطت antigen كويس) → تموت.
فالسلايد صاغها كأن IL-21 "يدفع للموت" إلا إذا في recognition/rescue.

الخلاصة بجملة وحدة للحفظ:

light zone: High affinity → في الـ more antigen → more Tfh help (IL-21/CD40L) → survive
Low affinity → no help → apoptosis.

فعليًا الخطوة الأولى في الـ light zone تكون مع FDC:
1. B cell تروح للـ FDC وتجرّب تمسك الـ antigen (المعروض كـ native antigen).
2. إذا قدرت تمسكه كويس ← تلتقطه وتعرض peptide على MHC II.
3. بعدها تروح لـ Tfh عشان تاخذ help (CD40L + IL-21...) وتنجو وتكمل.

Isotype switching (cytokine-directed)

Typical trigger	Dominant helper T subset / cytokine	Common isotype outcome (as emphasized)
Polysaccharide antigens (T-independent)	No T cell help	Mostly IgM; minimal switching
Viruses & many bacteria	TH1 → IFN-γ	Switching to IgG subclasses
Helminths	TH2 → IL-4	Switching to IgE
Mucosal tissues	Local site-specific signals	Switching to IgA (best transported across epithelia)

6) Plasma cells and long-term antibody production

Plasma cells are terminally differentiated B cells specialized for massive antibody secretion; generated after B cell activation via signals from the BCR, CD40, TLRs, and cytokine receptors.

Plasma cell type	When generated	Where found / maintained	Key feature
Short-lived plasma cells	T-independent responses; early T-dependent responses (extragenic/extrafollicular foci)	Secondary lymphoid organs and peripheral nonlymphoid tissues (Spleen, LNs, MALT)	Rapid burst of antibody; limited lifespan
Long-lived plasma cells	T-dependent germinal center responses to protein antigens	Home to bone marrow; maintained by BAFF-family cytokines	Sustain antibody secretion for months to years

IMPORTANT!

1

Comparison of B-cell Responses

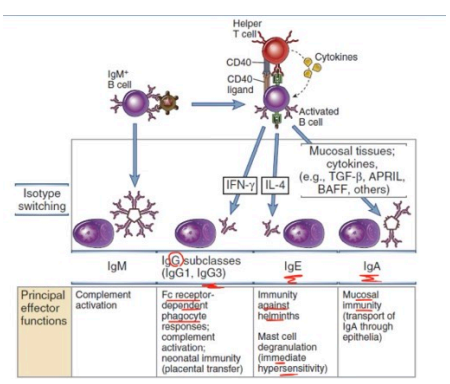
Feature	Extrafollicular foci	Germinal center (GC)
Location	Outside follicles (T–B border, medullary cords)	Inside B-cell follicles
Speed	Rapid (days)	Slower (~1 week or more)
Main purpose	Rapid antibody production	Quality improvement & immune memory
Main output cells	Short-lived plasmablasts	Memory B cells & long-lived plasma cells
Antibody isotype	Mostly IgM (limited switching)	IgG / IgA / IgE
Affinity	Low to moderate	High (affinity maturation)
Somatic hypermutation	Minimal or absent	Extensive
Selection process	Limited selection	Strong selection via FDCs & Tfh
Immune memory	Poor	Strong and long-lasting

2

شو الفرق بينها وبين الـ dendritic cell العادية (DC)؟

	DC العادية (classical DC)	FDC
نقطة		
المكان	T-cell zone	B follicle / germinal center
مين تستهدف؟	T cells (naïve)	B cells
كيف تعرض antigen؟	تبلع antigen → تقطعه → تعرض على MHC II + تعطي co-stimulation (B7)	ما تقطع: تعرض native antigen على سطحها (3D)
الهدف	تفعيل T cells لأول مرة (priming)	اختيار B cells الأعلى affinity + دعم GC

3



About 2-3 weeks after immunization with a T-dependent antigen, the **bone marrow** becomes a major site of antibody production.

Long-lived plasma cells can keep secreting antibodies long after antigen disappears; almost **half of circulating antibody** in healthy adults may come from long-lived plasma cells specific for past antigens.

Secreted antibodies enter the circulation and mucosal secretions, but mature plasma cells do not recirculate

7) Memory B cells and secondary humoral responses

Some germinal center-derived B cells become **memory B cells** by expressing high levels of anti-apoptotic proteins (notably **Bcl-2**) and can survive long-term without ongoing antigen stimulation.

Memory B cells may remain in the original lymphoid organ or recirculate; they are produced in T-dependent responses and often emerge in parallel with memory helper T cells.

On re-exposure, memory B cells respond faster and generate large quantities of **isotype-switched, high-affinity** antibodies; they rapidly form plasma cells and can re-enter germinal centers to further improve affinity.

8) Antibody feedback (negative regulation of B cells)

Secreted antibodies can **inhibit ongoing B cell activation** by forming antigen-antibody complexes that bind both the BCR (via antigen) and inhibitory **FcγRIIB** (via the antibody Fc).

Co-ligation brings inhibitory phosphatases close to the antigen receptor signaling machinery, dampening BCR signaling.

9) Effector mechanism highlighted: ADCC

Antibody-dependent cellular cytotoxicity (ADCC): NK cells (and some other leukocytes) bind antibody-coated cells through Fc receptors and kill them.

Engagement of **FcγRIII** on NK cells by antibody-coated targets triggers cytokine production (e.g., **IFN-γ**) and granule release that mediates killing.

TABLE 12–3 Fc Receptors

FcR	Affinity for Immunoglobulin	Cell Distribution	Function
FcγRI (CD64)	High ($K_d < 10^{-9}$ M); binds IgG1 and IgG3, can bind monomeric IgG	Macrophages, neutrophils; also eosinophils	Phagocytosis; activation of phagocytes
FcγRIIA (CD32)	Low ($K_d > 10^{-7}$ M)	Macrophages, neutrophils; eosinophils, platelets	Phagocytosis; cell activation (inefficient)
FcγRIIB (CD32)	Low ($K_d > 10^{-7}$ M)	B lymphocytes	Feedback inhibition of B cells
FcγRIIC (CD32)	Low ($K_d > 10^{-7}$ M)	Macrophages, neutrophils, NK cells	Phagocytosis, cell activation
FcγRIIIA (CD16)	Low ($K_d > 10^{-6}$ M)	NK cells	Antibody-dependent cell-mediated cytotoxicity
FcγRIIIB (CD16)	Low ($K_d > 10^{-6}$ M); GPI-linked protein	Neutrophils	Phagocytosis (inefficient)
FcεRI	High ($K_d > 10^{-10}$ M); binds monomeric IgE	Mast cells, basophils, eosinophils	Cell activation (degranulation)
FcεRII (CD23)	Low ($K_d > 10^{-7}$ M)	B lymphocytes, eosinophils, Langerhans cells	Unknown
FcαR (CD89)	Low ($K_d > 10^{-6}$ M)	Neutrophils, eosinophils, monocytes	Cell activation?

GPI, glycophosphatidylinositol; NK, natural killer.

Medical Immunology - Lecture "3"

Focus: immunization concepts, vaccine platforms, key examples, herd immunity, and adjuvants.

1) Immunization: core concepts

Goal: induce protective immunity (neutralizing antibodies, cellular responses, and immune memory) without causing disease.

1) Naturally through infection with a certain pathogen.

2) Artificially through administration of vaccines containing weekend or inactive pathogen

Feature	Active immunization (vaccination)	Passive immunization
What you receive	Antigen (live attenuated, inactivated, subunit, toxoid, etc.) to trigger your own immune response	Pre-formed antibodies (IgG) or antibody-containing products
Onset	Slower (days-weeks)	Immediate
Duration	Long-lasting (memory B/T cells; may need boosters)	Short-term (weeks-months)
Immune memory?	Yes	No
Typical uses	Prevention at population level	Post-exposure prophylaxis; immunodeficiency; maternal IgG (natural passive)

Passive immunization refers to the transfer of "ready-made" antibodies, from one individual to another. It can occur:
1) naturally by transplacental transfer of maternal antibodies to the developing fetus, or through colostrum and breast milk rich in IgA.

2) it can be induced artificially by injecting a recipient with exogenous antibodies targeted to a specific pathogen or toxin.

2) Vaccine platforms

	Platform	What it contains / mechanism	Main strengths	Main limitations	Examples
1	Live attenuated	Weakened pathogen replicates to a limited extent; closely mimics natural infection.	Strong humoral + cellular immunity; often long-term protection with 1-2 doses.	Contraindicated in immunocompromised; rare reversion/complications (e.g., OPV).	MMR; varicella; OPV; BCG.
2	Inactivated (killed)	Whole pathogen inactivated by heat/radiation/chemicals; cannot replicate.	Safer; stable; can be used in immunocompromised.	Weaker/shorter immunity than live; usually needs boosters/adjuvant.	IPV; whole-cell pertussis; rabies; hepatitis A.
3	Subunit / split / recombinant protein	Selected antigens (proteins/polysaccharides) or purified fragments; may include VLPs.	Fewer adverse reactions; focused immune response.	Lower immunogenicity; often requires adjuvant and multiple doses.	Tetanus toxoid, inactivated split & subunit seasonal influenza, acellular pertussis and pneumococcal polysaccharide vaccines
4	Viral vector / nucleic acid (DNA/mRNA)	Delivers antigen-encoding genetic material; host cells produce antigen.	Strong cellular immunity; rapid design; can be highly effective.	Cold chain/technology considerations; reactogenicity varies.	COVID-19: viral vector and mRNA platforms.
5	Reassortant live	Genetic reassortment between strains/species to create vaccine virus.	Can broaden protection while maintaining replication-based immunity.	Platform-specific constraints; still a live vaccine approach.	Reassortant rotavirus vaccines.

Both fall under: Non live vaccines

Prime-boost principle: many non-live vaccines require repeated doses and/or adjuvants to build strong, long-term immunity.

Measles, mumps, rubella

The only live attenuated bacterial vaccine

oral polio vaccine

can make: vaccine-associated paralytic poliomyelitis

inactivated polio vaccine

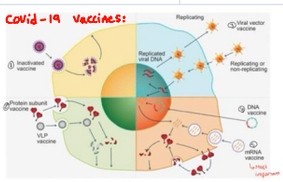
Toxoid type

recombinant type

purified protein type

polysaccharide or conjugate

virus-like particles



Some malaria vaccines are recombinant subunit (VLP-based) vaccines because they present parts of the Plasmodium falciparum circumsporozoite protein (CSP) on an HBsAg VLP scaffol

made by combining gene segments from a human virus and an animal virus

Types of Subunit Vaccines: 5 types, first two are: → Protein subunit (purified protein); → Recombinant protein subuni

Platform	What it contains / mechanism	Main strengths	Main limitations	Examples
Toxoid	Inactivated bacterial toxin (→ by formaldehyde); induces neutralizing anti-toxin antibodies.	Prevents toxin-mediated disease (pathogenesis).	Does not prevent infection/transmission; boosters needed.	Diphtheria and tetanus toxoids. ϕ C. difficile toxoid
Polysaccharide	Purified capsular polysaccharide; tends to be T-cell independent.	Can provide short-term protection in some settings.	Poorly immunogenic (esp. infants); weak memory; shorter protection.	Streptococcus pneumoniae, Haemophilus influenzae type b and N. meningitidis
Conjugate polysaccharide	Polysaccharide coupled to a protein carrier -> becomes T-cell dependent.	High-affinity antibodies + immune memory; effective in infants.	More complex/expensive manufacturing.	Streptococcus pneumoniae, Haemophilus influenzae type b and N. meningitidis "Conjugate"

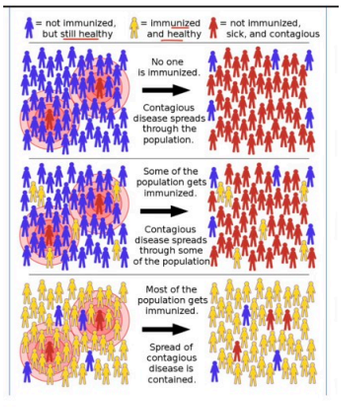
4) Polysaccharide vs conjugate: why conjugation matters

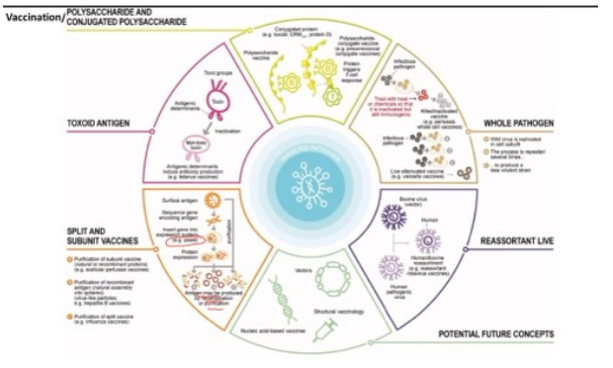
Point	Polysaccharide vaccine	Conjugate vaccine
T-cell help	Mostly no (T-independent)	Yes (T-dependent)
Antibody quality	Lower affinity; limited class switching	Higher affinity; better class switching
Memory	Weak/limited	Strong immune memory
Best age group	Less effective in infants	Effective in infants

3) Herd immunity

Definition: indirect protection that occurs when a large percentage of the population is immune, reducing transmission and protecting non-immune individuals.

Key idea: higher vaccine coverage -> fewer infectious contacts -> outbreaks are contained.





4) Adjuvants (why they are used)

Adjuvants are substances that **enhance and modulate** the immunogenicity of an antigen. They are often unnecessary for live attenuated vaccines because replication self-amplifies the response.

They work mainly by **activating innate immunity** and improving antigen presentation, which can broaden/extend responses and improve memory.

Medical Immunology — Lecture "4"

Immunodeficiencies

Ex: asthma

Immune malfunction can present as hypersensitivity, autoimmunity, or immunodeficiency. Immunodeficiency reflects a failure/absence of immune elements (lymphocytes, phagocytes, complement) and may be **primary (congenital/genetic)** or **secondary (acquired)**.

↳ more common, & caused by environmental factor

Primary vs Secondary Immunodeficiency

Feature	Primary (Congenital)	Secondary (Acquired)
Cause	Genetic defects in immune development/function	Environmental/clinical factors that compromise immunity
Typical onset	Often infancy/childhood (may be detected later)	Any age; depends on exposure/condition
Frequency	Less common	Far more common
Clinical clues	Recurrent infections, infections with rare organisms, opportunistic infections	History suggests an underlying condition (infection, malnutrition, drugs, cancer, etc.)
Other risks	Certain cancers (often related to oncogenic viruses e.g., EBV)	Depends on cause (e.g., HIV, immunosuppression)

Congenital (Primary) Immunodeficiencies: "Innate"

Primary defects can affect **innate immunity** (phagocytes, complement, NK cells, pattern recognition) and/or **adaptive immunity** (T cells, B cells, combined defects). Clinical presentation and prognosis are heterogeneous and depend on defect severity.

1) Defects in Innate Immunity

Innate immunity is the first line of defense. Two key mediators are **phagocytes** and **complement**; congenital defects commonly cause **recurrent infections**.

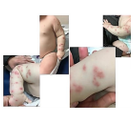
Disorder	Key mechanism/defect	Classic clinical points	Management pearls
Chronic Granulomatous Disease (CGD)	Mutation in phagocyte oxidase (phox) complex → ↓ reactive oxygen species (superoxide)	Failure to kill phagocytosed microbes, esp. **catalase-positive**; granuloma formation	Antibiotics/antifungals; **IFN-γ** often used (X-linked CGD)

$H_2O_2 \rightarrow H_2O$ فالبكتيريا "تمسح" الـ H2O2 تبعها ، فاليعميات بتقدرش تستعمله وتحضير اليتعميات اللي فيها CGD ما عندها ROS من اي جهة. فيفلت الميكروب

Because the infections are not controlled by phagocytes, they stimulate chronic cell-mediated immune responses, resulting in T cell–mediated macrophage activation and the formation of granulomas composed of activated macrophages.

The disease is often fatal, even with aggressive antibiotic therapy.

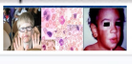
IFN-γ therapy is now commonly used for the treatment of X-linked CGD.



Leukocyte Adhesion Deficiency (LAD)	Defects in adhesion molecules → impaired neutrophil recruitment	Recurrent infections/periodontitis starting early; **no pus**	Supportive care: manage infections aggressively

There are different types of LAD such as LAD 1 (The molecular basis of the defect is absent or deficient expression of the β2 integrins) and LAD 2 (results from an absence of sialyl Lewis X, the tetrasaccharide carbohydrate ligand on neutrophils and other leukocytes that is required for binding to E-selectin and P-selectin.

Complement deficiencies	Classical components (C1q/C4/C2/C3) or terminal C5-9; **C2 most common**	**C3 deficiency** → severe pyogenic infections; terminal C5-9 → **Neisseria** infections	Vaccination/prophylaxis; consider terminal complement risk (meningococcal)
Chédiak-Higashi syndrome	LYST mutation → defective phagolysosome fusion; abnormal lysosomal trafficking	Recurrent pyogenic infections; albinism; neurologic & platelet defects (bleeding)	Supportive/anti-infective care; manage bleeding risk
TLR signaling defects	Defects affecting TLR/IL-1R or NF-κB pathways → impaired innate activation	Recurrent infections due to impaired inflammatory responses	Supportive; tailored prophylaxis based on defect



هذا موجود بالجدول التالي، فاحفظوه:

TABLE 20–2 Congenital Disorders of Innate Immunity

Disease	Functional Deficiencies	Mechanism of Defect
Chronic granulomatous disease	Defective production of reactive oxygen species by phagocytes; recurrent intracellular bacterial and fungal infections	Mutation in genes of phagocyte oxidase complex; phox-91 (cytochrome b_{588} α subunit) is mutated in X-linked form
Leukocyte adhesion deficiency type 1	Defective leukocyte adhesion and migration linked to decreased or absent expression of β_2 integrins; recurrent bacterial and fungal infections	Mutations in gene encoding the β chain (CD18) of β_2 integrins
Leukocyte adhesion deficiency type 2	Defective leukocyte rolling and migration linked to decreased or absent expression of leukocyte ligands for endothelial E- and P- selectins, causing failure of leukocyte migration into tissues; recurrent bacterial and fungal infections	Mutations in gene encoding a GDP-fucose transporter required for the synthesis of the sialyl Lewis X component of E- and P- selectin ligands
Leukocyte adhesion deficiency type 3	Defective leukocyte adhesion and migration linked to defective inside-out signaling and therefore defective integrin activation	Mutations in gene encoding KINDLIN-3
Chédiak-Higashi syndrome	Defective vesicle fusion and lysosomal function in neutrophils, macrophages, dendritic cells, natural killer cells, cytotoxic T cells, and many other cell types; recurrent infections by pyogenic bacteria	Mutation in LYST leading to defect in secretory granule exocytosis and lysosomal function
Toll-like receptor signaling defects	Recurrent infections because of defects in TLR and CD40 signaling and defective type I interferon production	Mutations in NEMO, UNC93B, MyD88, IκBα, and IRAK-4 compromise NF-κB activation downstream of Toll-like receptors

2) Combined Immunodeficiencies "Adaptive"

Combined immunodeficiencies affect both humoral and cell-mediated immunity. A subset with missing/defective peripheral T cells (IMP) are **Severe Combined Immunodeficiencies (SCIDs)**. SCID results from impaired T-lymphocyte development with or without B-cell maturation defects; ~50% are autosomal recessive and the rest are X-linked.

يعني الـ T cells متأثرة (وبالتالي cell-mediated immunity ضعيفة) وغالبا كمان تتأثر الـ humoral immunity.

لكن "humoral immunity" مو شرط يكون الخلل الأساسي داخل B cell نفسها؛ احيانا B cell تكون موجودة بس ما تشتغل لانها محتاجة T help

DiGeorge Syndrome (T-cell Deficiency)

DiGeorge syndrome is due to congenital malformation affecting structures derived from the third and fourth pharyngeal pouches → defective thymus and parathyroid development. Correction may be achieved with fetal thymic transplantation or bone marrow transplantation; often not necessary because T-cell function improves with age in a large fraction of patients.

Remember: thymic hypoplasia → T-cell deficiency and parathyroid hypoplasia → hypocalcemia.

↳ symptomes : CATCH-22

Cardiac abnormalities
Abnormal facies
Thymic absence/abnormality, **T** cell abnormality
Cleft palate
Hypocalcemia
Chromosome **22**

Severe Combined Immunodeficiencies:

Category	Example disorders	Key mechanism	Functional result
Cytokine signaling defects	X-linked SCID; autosomal recessive forms	Mutations affecting cytokine receptor signaling (e.g., IL-2Rγ chain / JAK pathways)	↓ T cells; variable B/NK effects; ↓ serum Ig
Nucleotide salvage pathway defects	ADA deficiency; PNP deficiency	Toxic metabolite accumulation in lymphocytes	Progressive loss of T, B, and/or NK cells; ↓ serum Ig
V(D)J recombination / DNA repair defects	RAG1/2 deficiency; Artemis; DNA-PKcs, etc.	Failed antigen receptor gene rearrangement / repair	Markedly reduced T and B cells; ↓ serum Ig
Thymus development defects	DiGeorge syndrome	Defective thymic development (3rd/4th pharyngeal pouches)	T-cell deficiency (often improves with age in many patients)

TABLE 20–3 Severe Combined Immunodeficiencies

Disease	Functional Deficiencies	Mechanism of Defect
Defects in cytokine signaling		
X-linked SCID	Marked decrease in T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common γ chain mutations; defective T cell development in the absence of IL-7–derived signals
Autosomal recessive forms	Marked decrease in T cells; normal or increased B cells; reduced serum Ig	Mutations in *IL2RA, IL7RA, JAK3*
Defects in nucleotide salvage pathways		
ADA deficiency	Progressive decrease in T, B, and NK cells; reduced serum Ig	ADA deficiency caused by mutations in the gene, leading to accumulation of toxic metabolites in lymphocytes
PNP deficiency	Progressive decrease in T, B, and NK cells; reduced serum Ig	PNP deficiency caused by mutations in the gene, leading to accumulation of toxic metabolites in lymphocytes
Defects in V(D)J recombination		
RAG1 or RAG2 deficiency recombination*	Decreased T and B cells; reduced serum Ig; absence or deficiency of T and B cells	Cleavage defect during V(D)J recombination; mutations in *RAG1* or *RAG2*
Double-stranded break repair and checkpoint	Decreased T and B cells; reduced serum Ig; absence or deficiency of T and B cells	Failure to resolve hairpins during V(D)J recombination; mutations in *ARTEMIS*, DNA-PKcs, *CERNUNNOS, LIG4, NBS1, MRE11, ATM*
Defective thymus development		
Defective pre-TCR checkpoint	Decreased T cells; normal or reduced B cells; reduced serum Ig	Mutations in *CD45, CD3D, CD3E, ORAI1* (CRAC channel component), *STIM1*
DiGeorge syndrome	Decreased T cells; normal B cells; normal or reduced serum Ig	22q1 1 deletion; T-box 1 (*TBX1*) transcription factor mutations
FoxN1 deficiency	Thymic aplasia with defective thymic cell development	Recessive mutation in *FOXN1*

3) Antibody Deficiencies (B-cell Development/Activation)

When the primary abnormality is in antibody synthesis (with relatively preserved T-cell development), the phenotype is dominated by recurrent infections due to impaired humoral immunity.

Disorder	Typical lab/immune finding	Mechanism (high-yield)	Clinical notes
Selective IgA deficiency	↓ IgA (often isolated)	Defects in TACI in some patients (heterogeneous)	Most common primary immunodeficiency (~1/700 Caucasians); variable: asymptomatic to recurrent respiratory infections/diarrhea
X-linked agammaglobulinemia (Bruton)	Very low/absent serum Ig; absent B cells; no germinal centers/plasma cells	BTK mutation → failed B-cell maturation	T cells normal; treated with periodic pooled Ig (gamma globulin) injections
Common variable immunodeficiency (CVID)	↓ serum Ig; poor antibody responses	Heterogeneous; mutations in ICOS/TACI in some	Increased infections; variable B-cell numbers
Hyper-IgM syndrome (X-linked)	High/normal IgM with low other isotypes	CD40L (CD154) mutation → no class switching & impaired germinal centers	Defects in T helper-mediated B-cell activation; also affects macrophage/DC activation

TABLE 20–4 Antibody Deficiencies

Disease	Functional Deficiencies	Mechanism of Defect
Agammaglobulinemias		
X-linked	Decrease in all serum Ig isotypes; reduced B cell numbers	Pre-B receptor checkpoint defect; Btk mutation
Autosomal recessive forms	Decrease in all serum Ig isotypes; reduced B cell numbers	Pre-B receptor checkpoint defect; mutations in IgM heavy chain (μ), surrogate light chains (λ5), Igα, BLNK
Hypogammaglobulinemias/isotype defects		
Selective IgA deficiency	Decreased IgA; may be associated with increased susceptibility to bacterial infections and protozoa such as *Giardia lamblia*	Mutations in *TACI* in some patients
Selective IgG2 deficiency	Increased susceptibility to bacterial infections	Small subset have deletion in IgH γ2 locus
Common variable immunodeficiency	Hypogammaglobulinemia; normal or decreased B cell numbers	Mutations in *ICOS* and *TACI* in some patients
ICF syndrome	Hypogammaglobulinemia, occasional mild T cell defects	Mutations in *DNMT3B*

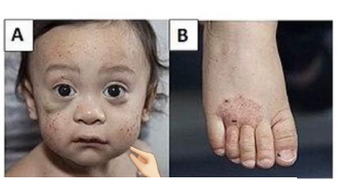
Hyper-IgM syndromes

X-linked	Defects in T helper cell–mediated B cell, macrophage, and dendritic cell activation; defects in somatic mutation, class switching, and germinal center formation; defective cell-mediated immunity	Mutation in *CD40L*
Autosomal recessive with cell-mediated immune defects	Defects in T helper cell–mediated B cell, macrophage, and dendritic cell activation; defects in somatic mutation, class switching, and germinal center formation; defective cell-mediated immunity	Mutations in *CD40, NEMO*
Autosomal recessive with antibody defect only	Defects in somatic mutation and isotype switching	Mutations in *AID, UNG*

AID, activation-induced cytidine deaminase; DNMT3B, DNA methyltransferase 3B; ICF, immunodeficiencies-centromeric instability-facial anomalies; ICOS, inducible costimulator; NEMO, NF-κB essential modulator; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; UNG, uracil N-glycosylase.

Defects in T-cell Activation & Multisystem Syndromes

Variable degrees of T and B cell immunodeficiency occur in congenital diseases with multisystem abnormalities. A classic example is **Wiskott-Aldrich syndrome** (X-linked): eczema, thrombocytopenia (low platelets), and susceptibility to bacterial infection.



Clinical Recognition & Assessment

Think immunodeficiency when there is a history of: **recurrent infections**, infections with **unusual/rare organisms**, or **opportunistic infections**. Patients may also be susceptible to certain cancers, many linked to oncogenic viruses (e.g., EBV).

Suggested investigation (from the lecture):

- Immunoglobulins: quantitative serum Ig levels
- B and T lymphocyte counts
- Lymphocyte stimulation assays (functional testing)
- Complement components quantification
- Phagocytic activity assessment
- Microbiological studies to evaluate pathogens and guide management