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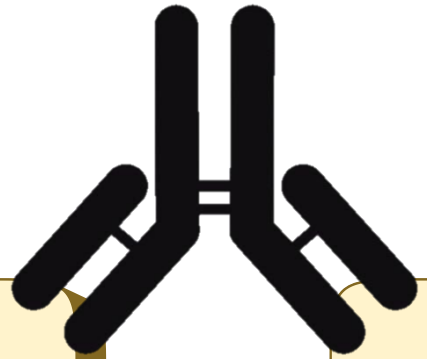
IMMUNOLOGY

FINAL | Lecture 1

Antigen Recognition in the Adaptive Immune System & Lymphocytes Development



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وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا

المعنى: الذي ينفذ ما يريد إيجاده على الصفة التي يريدها، الذي جعل خلقه على الصور التي شاءها بمقتضى حكمته.

الورود: ورد مرة واحدة في القرآن.

الشاهد: ﴿ هُوَ ٱللَّهُ ٱلْخَٰلِقُ ٱلْبَارِئُ ٱلْمُصَوِّرُ ﴾ [الحشر:٢٤].

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اضغط هنا لشرحٍ أكثر تفصيلًا

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Note: All information explained by the doctor is included in these slides, but some points were reorganized to improve clarity, coherence, and flow, without adding or removing any content.

Antigen Recognition in the Adaptive Immune System and Lymphocytes Development

By : Nader Alaridah MD,PhD

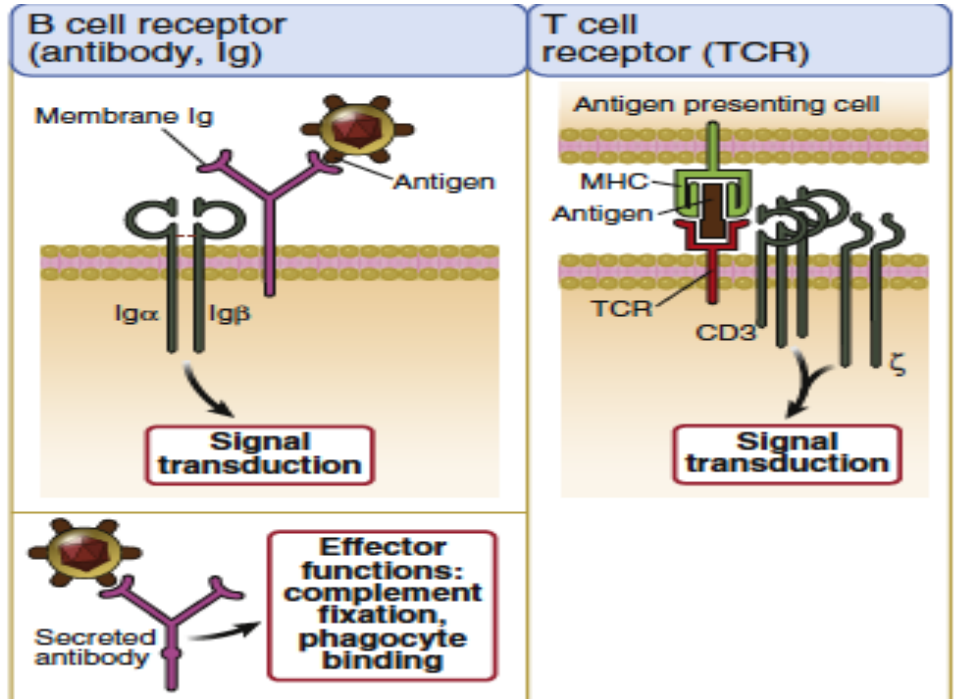
Lymphocyte Antigen Recognition: B Cells vs T Cells

➢ **B Cells:**

- The **B-cell receptor (BCR)** is an **immunoglobulin (Ig)**.
  Membrane-bound Ig = BCR
  Secreted Ig = antibody
- B-cells can recognize **unprocessed antigens (=Doesn't require MHC presentation)**
- They bind to the macromolecules **without any need for modification**, including: Proteins, lipids, polysaccharides, nucleic acids, and small chemical moieties
- Antigens may be recognized in **conformational or linear** form.

➢ **T Cells:**

- The **T-cell receptor (TCR)** is **always membrane-bound**.
- T cells recognize **processed protein antigens (peptides)** only (Peptides presented on **MHC molecules** by **APCs)**
- This requirement is called **MHC restriction**.
- **Most T cells are αβ T cells** which are MHC-restricted.



	B cell receptor (antibody, Ig)	T cell receptor (TCR)
Forms of antigens recognized	Macromolecules (proteins, polysaccharides, lipids, nucleic acids), small chemicals Conformational and linear epitopes	Mainly peptides displayed by MHC molecules on APCs Linear epitopes
Diversity	Each clone has a unique specificity; potential for $>10^9$ distinct specificities	Each clone has a unique specificity; potential for $>10^{11}$ distinct specificities
Antigen recognition is mediated by:	Variable (V) regions of heavy and light chains of membrane Ig	Variable (V) regions of α and β chains of the TCR
Signaling functions are mediated by:	Proteins (Igα and Igβ) associated with membrane Ig	Proteins (CD3 and ζ) associated with the TCR
Effector functions are mediated by:	Constant (C) regions of secreted Ig	TCR does not perform effector functions

Continued

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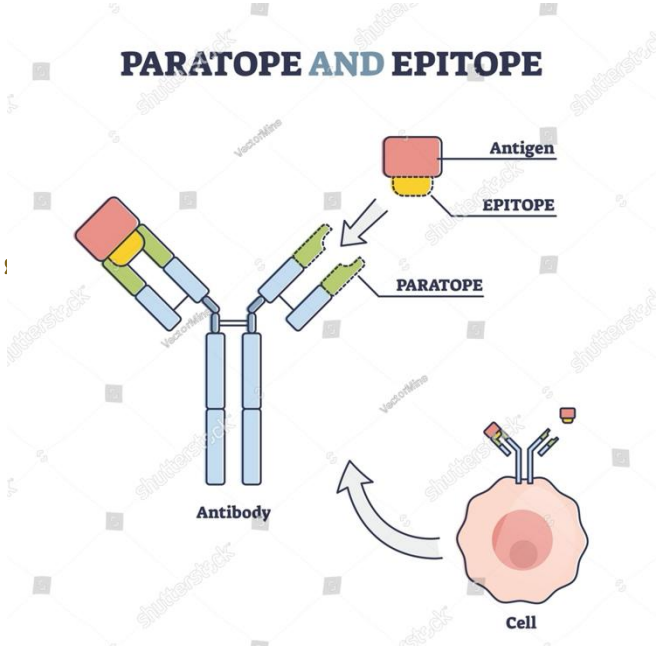
- However, unlike conventional **αβ T cells**, which are strictly MHC-restricted and recognize processed peptide antigens, **γδ T cells** and **natural killer (NK)** cells **can recognize non-MHC-presented or unprocessed ligands.**
- Each **B cell or T cell** expresses receptors with the **same idiotype and antigen-binding specificity**.
- Each lymphocyte carries approximately **10^4–10^5 identical receptors**, all recognizing the same antigen.
- The original lymphocyte and all of its progeny constitute a **clone**, sharing the same idiotype.
- Across all circulating lymphocytes, the total number of **distinct antigen specificities (clones)** can reach up to **10^{16}**.
- **All of this diversity is generated in the absence of antigen exposure.**

Antigen Recognition Site

- In **B-cell receptors (BCRs)**, the antigen-binding site is formed by the **variable domains of the heavy chain and the light chain**.
- In **T-cell receptors (TCRs)**, the antigen-binding site is formed by the **variable domains of the α (alpha) and β (beta) chains**.

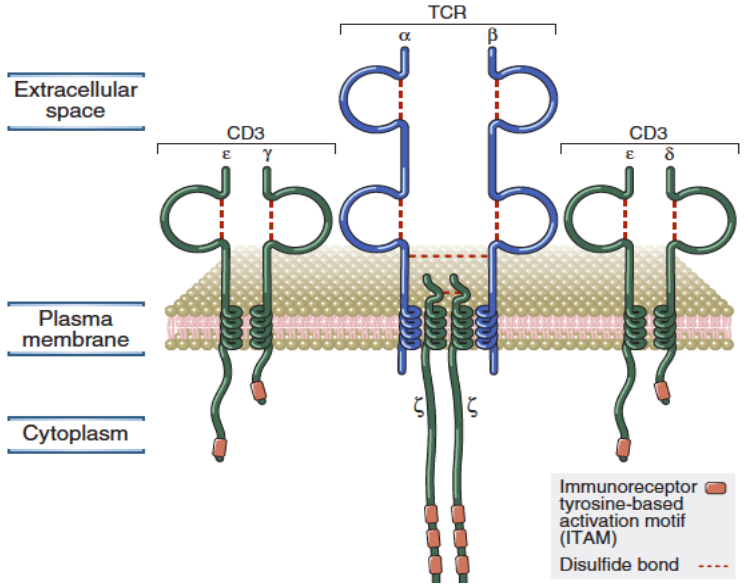
- Within each variable domain, there are **three hypervariable regions** known as **complementarity-determining regions (CDRs)**. Thus:
  Each receptor (/Immunoglobulin) has 4 variable regions (= 1 V-region per chain), making a total of **12 CDRs per receptor** (/Immunoglobulin).

- The combined neighboring CDRs form a **paratope** (the antigen-binding site of the receptor), which specifically binds to the **epitope** on the antigen. (= 2 Paratopes per receptor/immunoglobulin)



Effector Function vs Signaling

- **B-cell receptors (BCRs)** have **effector functions:**
- ✓ The **constant region of the heavy chain** determines the **isotype (class)** of the immunoglobulin
- ✓ The isotype dictates the antibody's **effector function** (e.g., complement activation, Fc receptor binding)
- **T-cell receptors (TCRs)** have **no effector function:**
- ✓ Their role is limited to **signal transduction**
- ✓ They transmit activation signals **intracellularly** only



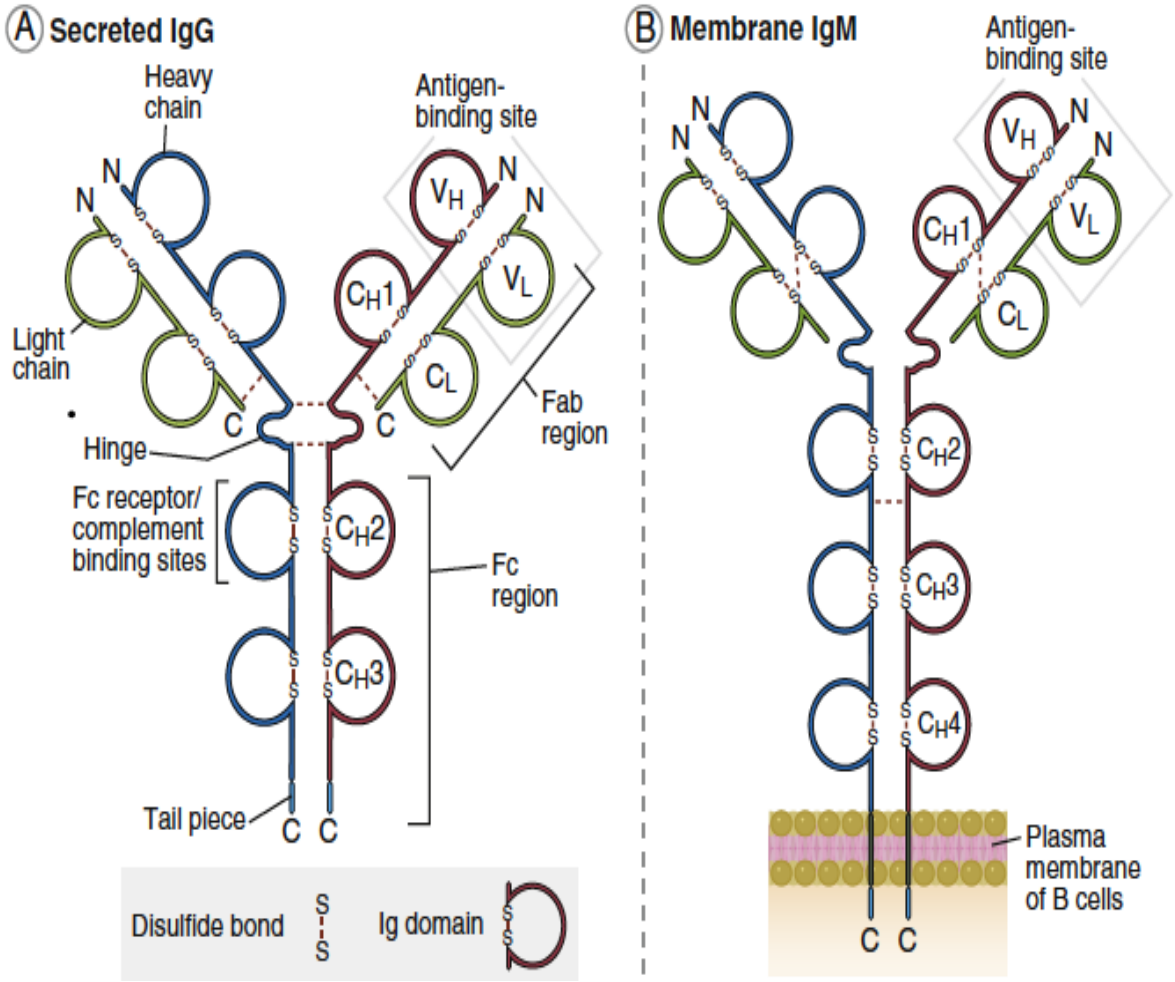
- **Exam Note: Receptor vs Receptor Complex**
- ✓ When referring to the **receptor itself:**
  BCR = heavy + light chains
  TCR = α (alpha) + β (beta) chains
- ✓ When referring to the **receptor complex:** (The receptor is **accompanied by the "Associated signaling molecules", which the BCR and TCR signaling activities can't function without)**
  BCR → Igα & Igβ
  TCR → CD3 & ζ (zeta) chains

Differences between BCR and TCR:

Feature	BCR (B-cell receptor)	TCR (T-cell receptor)
Alternative form	Can exist **membrane-bound** *and* **secreted** as an **immunoglobulin (antibody)**	**Only membrane-bound** (never secreted)
Antigen processing required?	❌ **No processing required**	✅ **Requires antigen processing**
Mode of antigen recognition	Recognizes **native antigens**	Recognizes **processed antigens presented on MHC**
Type of epitope recognized	**3D conformational (linear + discontinuous)** epitopes	**Linear epitopes only**
Constant (C) region function	Has **effector functions**	**No effector function**
Heavy chain constant region	Determines **immunoglobulin class** (IgM, IgG, IgA, IgE, IgD)	❌ No class switching
Role of constant region	Effector function **+ signaling**	**Signal transduction only**
Affinity maturation	✅ **Occurs** (somatic hypermutation)	❌ **Does NOT occur**
Class switching	✅ **Occurs**	❌ **Does NOT occur**
Associated signaling molecules	**Igα (CD79a) & Igβ (CD79b)**	**CD3 complex & ζ (zeta) chains**

Antibodies

- An antibody molecule is composed of four polypeptide chains—two identical heavy (H) chains and two identical light (L) chains—with each chain containing a variable region and a constant region.
- The antigen-binding site of an antibody is composed of the V regions of both the heavy chain and the light chain, and the core antibody structure contains two identical antigen binding sites .
- In each Ig molecule, there are two identical Fab regions that bind antigen and one Fc region that is responsible for most of the biologic activity and effector functions of the antibodies.



Antibodies Structure

- Between the Fab and Fc regions of most antibody molecules is a flexible portion called the **hinge region**. The hinge allows the two antigen-binding Fab regions of each antibody molecule to move independent of each other.

- There are five types of heavy chains, called μ, δ, γ, ε, and α, which differ in their C regions. Antibodies that contain different heavy chains belong to different **classes,** or **isotypes,** and are named according to their heavy chains (IgM, IgD, IgG, IgE, and IgA) .

- The antigen receptors of naive B lymphocytes, which are mature B cells that have not encountered antigen, are membrane-bound IgM and IgD.

- After stimulation by antigen and helper T lymphocytes, the antigen-specific B lymphocyte clone may expand and differentiate into progeny that secrete antibodies.

- The same B cells may produce antibodies of other heavy-chain classes .This change in Ig isotype production is called **heavy-chain class** (or **isotype**) **switching**

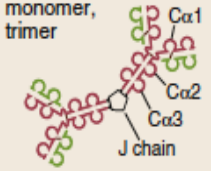
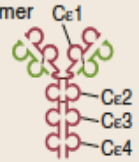
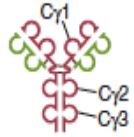
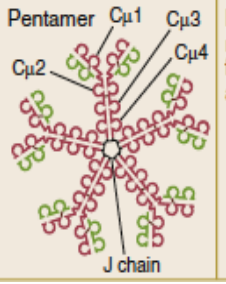
Antibody Structure and Isotype Notes

➢ **Important notes regrading this table:**

- When antibodies consist of **more than one monomer**, the monomers are linked by a **J (joining) chain**.
- **IgA** has a **secretory component** (secretory tail), which facilitates **trans-epithelial transport** across mucosal surfaces.
- **IgD** is expressed on the surface of **mature naïve B cells** via **alternative RNA splicing for the initially expressed IgM** –To be discussed later in the slides–
- **IgG** is the **only antibody class that crosses the placenta**
- Provides **passive neonatal immunity** lasting up to **~6 months**
- **IgM:**
- Exists as a **monomer when membrane-bound** on mature naïve B cells
- Is secreted mainly as a **pentamer**

➢ **Primary vs Secondary Immune Response :**

- **Primary exposure to an antigen**: The first antibody secreted is **IgM**
- **Secondary (re-exposure) to the same antigen**: Predominantly **IgG,** also includes **IgA and IgE**

Isotype of antibody	Subtypes (H chain)	Serum concentration (mg/ml)	Serum half-life (days)	Secreted form	Functions
IgA	IgA1,2 (α1 or α2)	3.5	6	Mainly dimer, also monomer, trimer 	Mucosal immunity
IgD	None (δ)	Trace	3	Monomer	Naive B cell antigen receptor
IgE	None (ε)	0.05	2	Monomer 	Defense against helminthic parasites, immediate hypersensitivity
IgG	IgG1-4 (γ1, γ2, γ3 or γ4)	13.5	23	Monomer 	Opsonization, complement activation, antibody-dependent cell-mediated cytotoxicity, neonatal immunity, feedback inhibition of B cells
IgM	None (μ)	1.5	5	Pentamer 	Naive B cell antigen receptor (monomeric form), complement activation

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Binding of Antigens by Antibodies

- The parts of antigens that are recognized by antibodies are called **epitopes** or **determinants.**
- The strength with which one antigen-binding surface of an antibody binds to one epitope of an antigen is called the **affinity** of the interaction. (single strength of binding)
- The total strength of binding is much greater than the affinity of a single antigen-antibody bond and is called the **avidity** of the interaction. (Total binding strength)
- Antibodies produced against one antigen may bind other, structurally similar antigens. Such binding to similar epitopes is called a **cross-reaction.**

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About the previous slide (Cross-Reactivity)

- **Streptococcus pyogenes** (Group A β-hemolytic streptococci) commonly infects children, causing **streptococcal pharyngitis**.
- After about **one week**, the infection resolves and the patient produces **antibodies against the M protein** in the bacterial cell wall.
- Within **1–2 weeks**, these antibodies may **cross-react with host tissues**, particularly **cardiac myosin**, due to **structural similarity**, leading to **rheumatic fever**.
- This immune **cross-reactivity** is known as **molecular mimicry** and can also involve the kidneys, resulting in **post-streptococcal glomerulonephritis**.
- These immune-mediated complications are collectively referred to as **post-streptococcal infection sequelae**.

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Monoclonal Antibodies

- The realization that one clone of B cells makes an antibody of only one specificity has been exploited to produce **monoclonal antibodies.**
- To produce monoclonal antibodies, B cells, which have a short life span in vitro, are obtained from an animal immunized with an antigen and fused with myeloma cells (tumors of plasma cells), which can be propagated indefinitely in tissue culture
- by fusing the two cell populations and culturing them, it is possible to grow out fused cells derived from the B cells and the myeloma, which are called **hybridomas.**

One of the major advancements in immunology is monoclonal antibodies used in diagnosis and therapeutics

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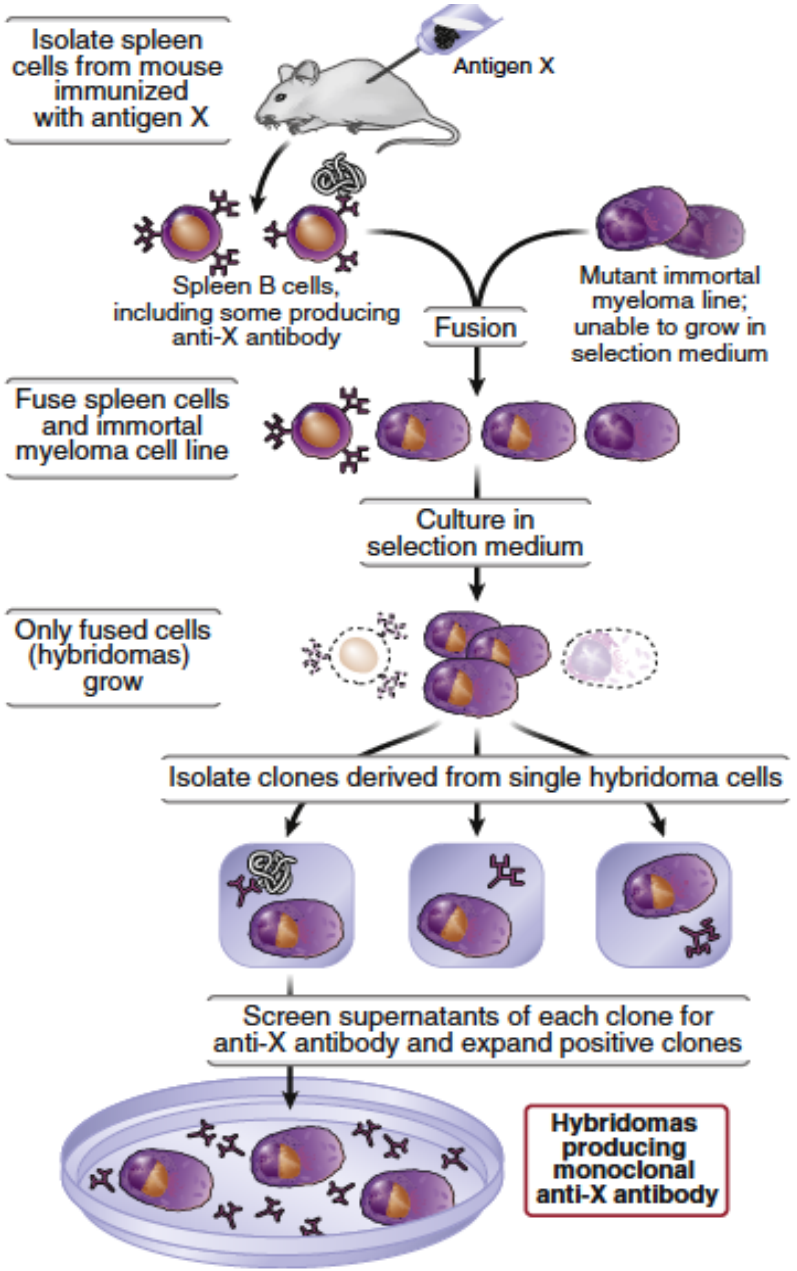


Monoclonal Antibody Production process is to be discussed thoroughly in the upcoming slides .

Monoclonal Antibody Production

➢ **Specific Ab Production:**

- **A mouse is injected with antigen X → Antigen-specific B cells are activated** → production of **antibodies against antigen X.**

➢ **Limitation of the B cells**

- Antigen-specific B cells are **short-lived and have limited proliferative capacity**.
- Therefore, they **cannot produce large or sustained quantities of antibodies**.

➢ **Role of Myeloma Cells**

- **Myeloma cells** are **malignant B-cell-line cells,** that are: **Immortal** and **Deficient in antibody secretion** (Can't produce their own immunoglobulins)

➢ **Hybridoma Formation**

- **Antibody-producing B cells (specific for antigen X)** are fused with **myeloma cells.**
- This fusion creates a **hybridoma**, which combines: **Immortality** (from myeloma cells) + **Specific antibody secretion** (from B cells)

➢ **Selection and Screening**

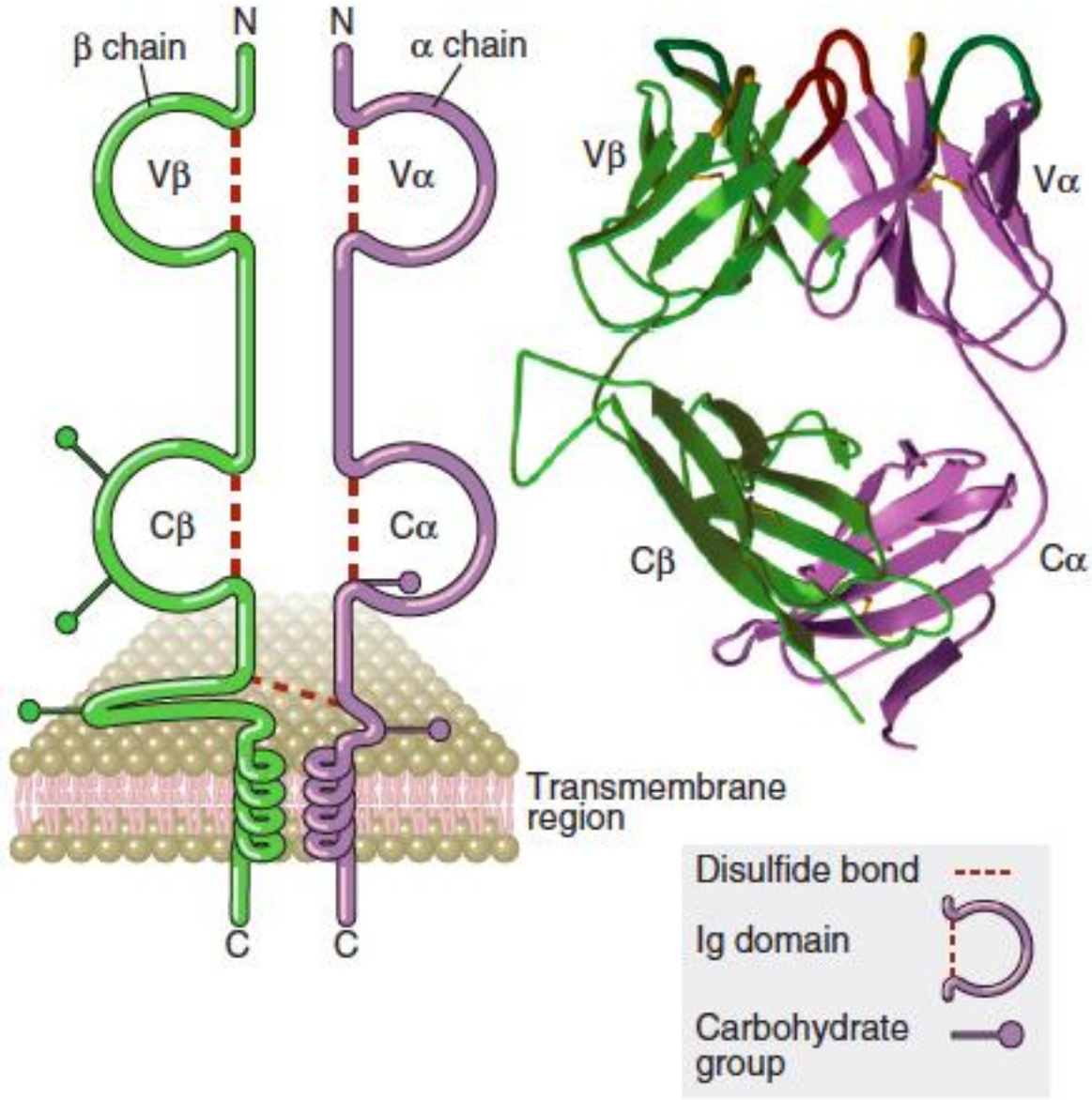
- **Screening and selection** are performed to identify the **hybridoma clone** that secretes antibodies **specific for antigen X**
- The final result is **one stable clone** producing a **single (monoclonal) antibody** against antigen X.

➢ **Antibody Humanization**

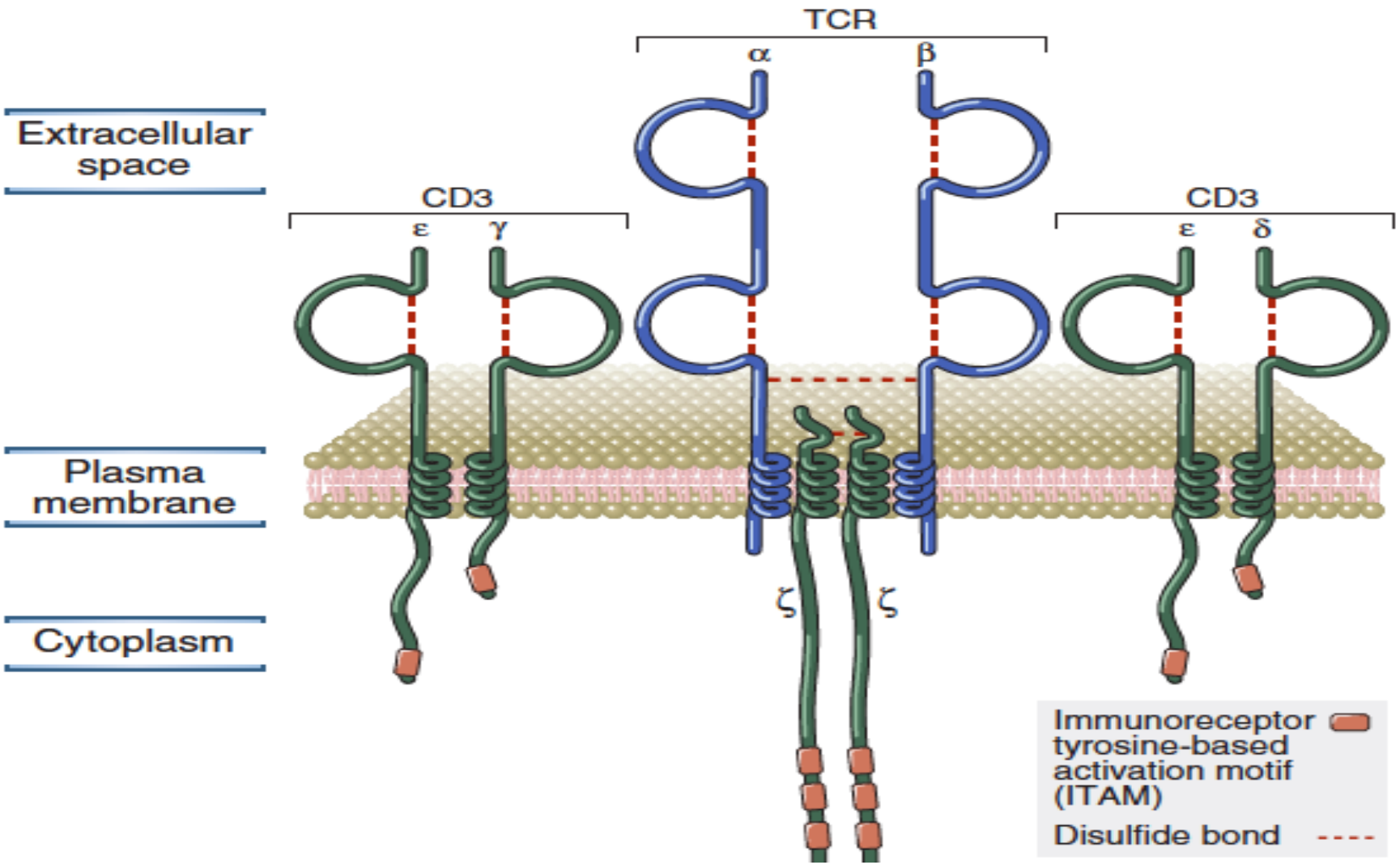
- **Recombinant DNA engineering** is used to **humanize the Fc region** of mouse antibodies
- This reduces **immune reactions** when the antibody is used in humans

The Structure of the T Cell Receptor for Antigen

- The antigen receptor of MHC-restricted CD4+ helper T cells and CD8+ cytotoxic T lymphocytes (CTLs) is a **heterodimer consisting of two transmembrane polypeptide chains**, designated **TCR α** and **β**, covalently linked to each other by a disulfide bridge between extracellular cysteine residues.
- Notice that the intra-membrane domain in the TCR (Constant domain) has only signaling functions, while in the BCR it has both signaling and effector functions (Ag neutralization, opsonization …) .



Components of the TCR complex.



The T Cell Receptor Complex and T Cell Signaling

- **T lymphocytes express different receptors that recognize antigens: T cell receptors (TCRs) on T lymphocytes.**
- The antigen receptors of lymphocytes must be able to bind to and distinguish between many, often closely related, chemical structures.
- **each lymphocyte clone is specific for a distinct antigen and has a unique receptor, different from the receptors of all other clones.**
- The total number of distinct lymphocyte clones is very large, and this entire collection makes up the immune **repertoire**.
- Although each clone of T lymphocytes recognizes a different antigen, the antigen receptors transmit biochemical signals that are fundamentally the same in all lymphocytes and are unrelated to specificity.

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DEVELOPMENT OF IMMUNE REPERTOIRES

- As the clonal selection hypothesis predicted, there are many clones of lymphocytes with distinct specificities, perhaps as many as 109, and these clones arise before an encounter with antigen.
- **The process of lymphocyte maturation first generates a very large number of cells each with a different antigen receptor and then preserves the cells with useful receptors.**
- receptors are expressed on developing lymphocytes, selection processes come into play that promote the survival of cells with receptors that can recognize antigens, such as microbial antigens, and eliminate cells that cannot recognize antigens in the individual or that have the potential to cause harm.
- BCR and TCR diversity is generated by **random antigen-receptor rearrangement**, producing a potential repertoire of up to 10^{16} specificities even before antigen exposure.

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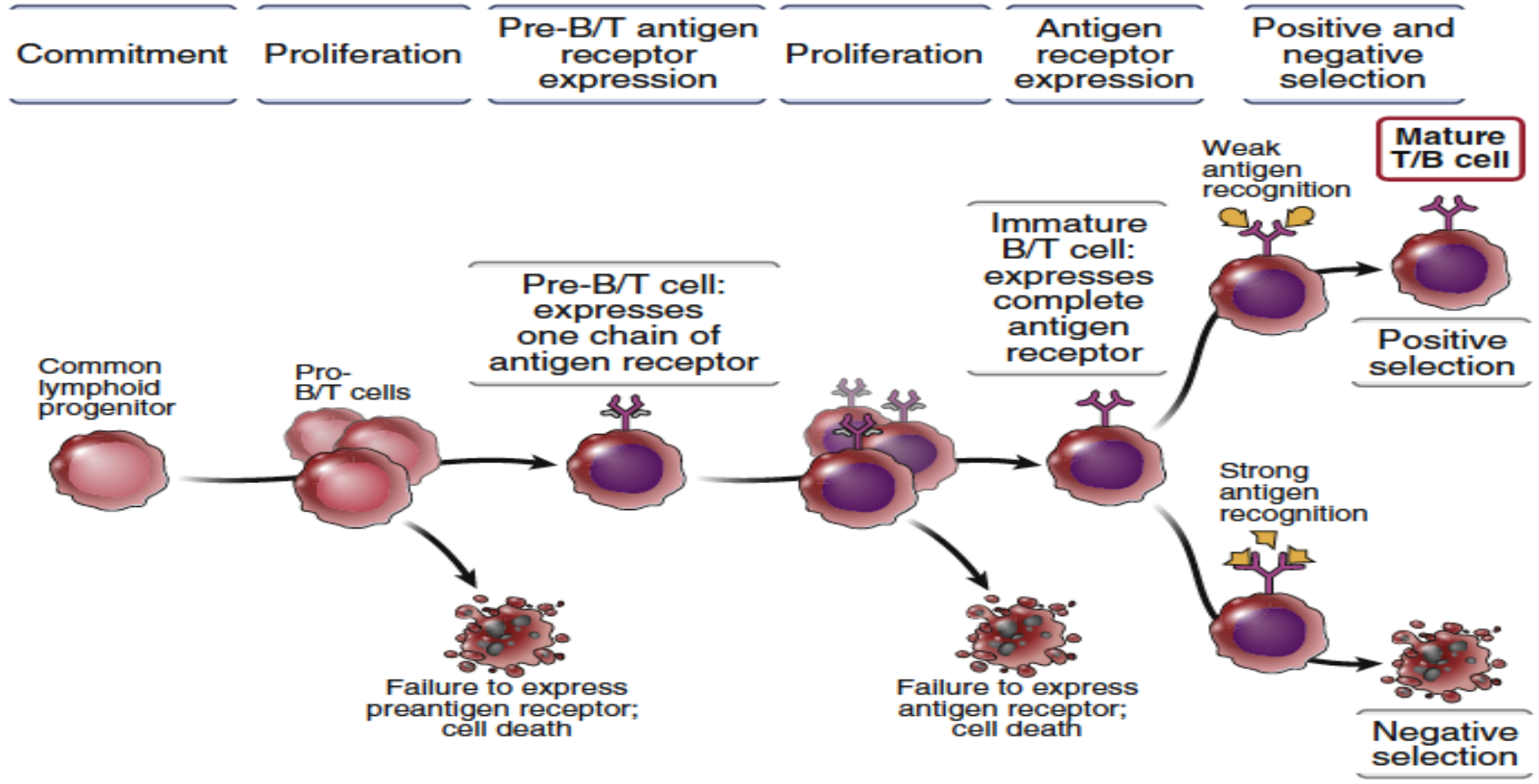
Lymphocyte Development



Lymphocyte Development process is to be discussed thoroughly in the upcoming slides .

➢ Lymphocyte Development (B cells & T cells):

- Both **B cells and T cells** originate from a single **common lymphoid progenitor (CLP)**.
- Lineage commitment depends on the **signals and transcription factors** the CLP receives:
  - ✓ **Pax5 signaling → B-cell lineage**
  - ✓ **Notch + GATA-3 signaling → T-cell lineage**
  - ✓ **IL-7 is required for survival and proliferation of both lineages**

➢ Pro-B cell / Pro-T cell stage:

- After lineage commitment, cells enter the **pro-stage**, where **RAG enzymes** initiate antigen-receptor gene rearrangement **(Somatic Recombination):**
  - ✓ **B cells** rearrange the **immunoglobulin heavy chain**
  - ✓ **T cells** rearrange the **TCR β chain** (functionally equivalent to the Ig heavy chain)

- At this stage, the rearranged chains remain **inside the cytoplasm** and are **not expressed on the cell surface**, so the cells are still **functionally considered Double Negative.**
- **Only cells that can produce the heavy chain (or the β-chain in T-cell) are selected to survive and become pre-B or T cells**

➢ Pre-B cell / Pre-T cell stage:

- **Light chain rearrangement (B cells)** and **α chain rearrangement (T cells)** occur **here**.

- **Until the rearrangement of the light chain (or α-chain) finishes , the pre-cells** express a **pre-receptor,** where the heavy chain pairs with a **surrogate (temporary) light chain forming a Pre-BCR**, while the **pre-T cells** express a **pre-TCR.** These pre-receptors stay expressed on the surface of the pre-cell until the rearrangement of the light chain (or α-chain) finishes. Once the cell can fully produce the light (or α) chain, it starts to express a full antigen receptor on its surface, marking the start of the immature state

- These pre-receptors are **not fully functional antigen receptors**; their role is **quality control**, ensuring that the rearranged heavy chain can signal and allowing the cell to survive and proliferate, so the Pre-cell is still considered **double negative cell.**

➢ Immature lymphocyte stage:

- A **complete antigen receptor** is now expressed on the surface.

- **Immature B cells** initially express **IgM only**. After undergoing **selection** (negative selection for self-reactivity), the same heavy-chain transcript then undergoes **alternative splicing**, leading to co-expression of **IgM and IgD** as the cell becomes a mature naïve B cell.

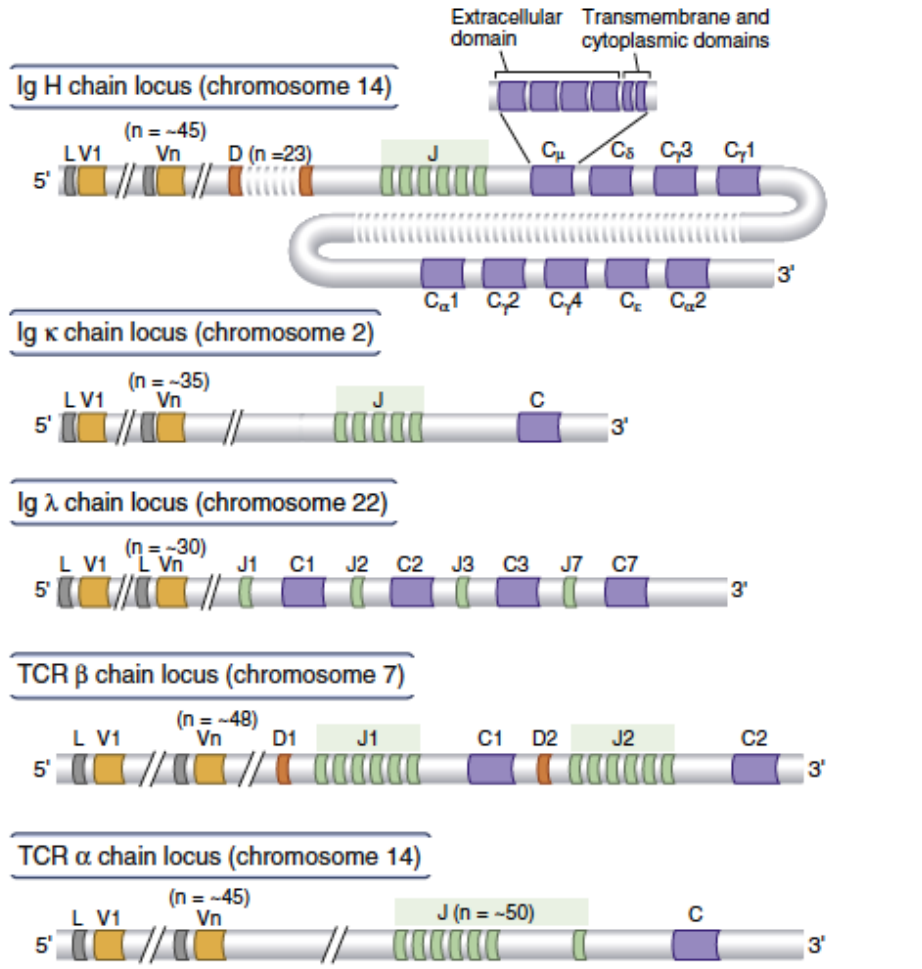
- **Immature T cells on the other hand** express a complete TCR and simultaneously express **both CD4 and CD8**, making them **double-positive ($CD4^+$ $CD8^+$)**. After selection (both positive and negative selections), they eventually differentiate into **single-positive $CD4^+$ or $CD8^+$ T cells**.
  Cells that Interact with MHC class I → $CD8^+$ T cell
  Cells that Interact with MHC class II → $CD4^+$ T cell

➢ Differences in Maturation Pathway between B cells vs T cells:

- **B cells** complete their **entire maturation within the bone marrow**. Once selection is finished, the **mature naïve B cell** exits the bone marrow and migrates to the **peripheral lymphoid organs** (e.g., lymph nodes, spleen).

- **T cells**, in contrast, **do not mature fully in the bone marrow**. Only **T-cell progenitors** leave the bone marrow and migrate to the **thymus**, where **full maturation and selection** occur. After this, **mature naïve T cells** exit the thymus and populate the **peripheral lymphoid tissues**.

Germline organization of antigen receptor gene loci



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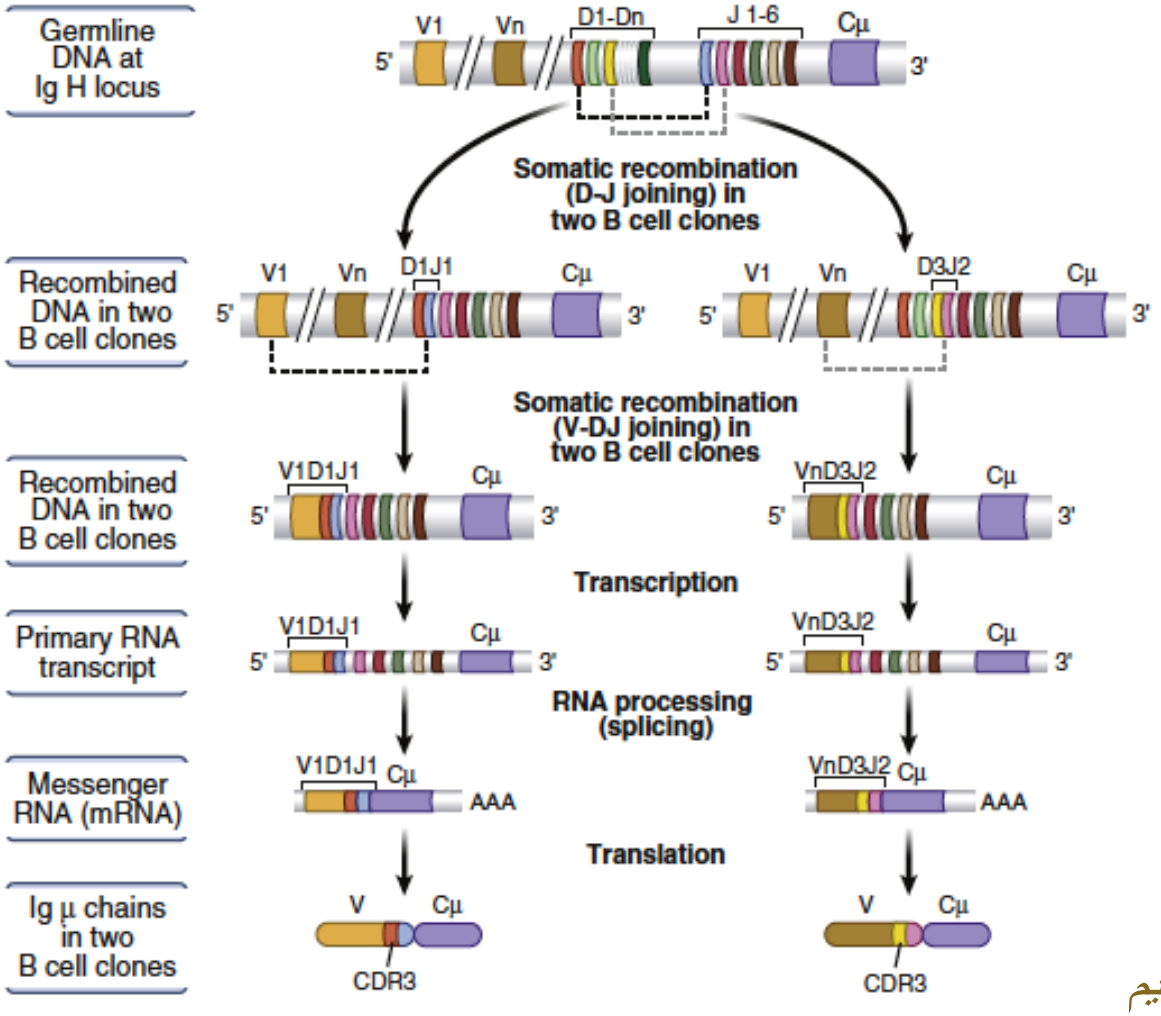
Somatic Recombination process is to be discussed thoroughly in the upcoming slides .

Recombination and expression of immunoglobulin (Ig) genes.



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Somatic Recombination process is to be discussed thoroughly in the upcoming slides .

V(D)J Rearrangement & Junctional Diversity:

Two processes contribute to the diversity of the BCRs and TCRs, these are the **V(D)J recombination** and **Junctional diversity.**

➢ V(D)J recombination (Combinatorial diversity)

- Receptor genes are assembled from **V (variable), D (diversity), and J (joining)** segments.
- The **D segment** is present **only** in:
  Immunoglobulin heavy chains (B cells)
  TCR β chains (T cells)
  (D + J recombination → V + DJ recombination)
- **Light chains (B cells)** and **TCR α chains (T cells)** use **V and J only.**
- This rearrangement is mediated by **RAG-1 and RAG-2 enzymes**.
- Produces a **recombinatorial diversity ≈ 10^6**.

➢ Junctional diversity

- After segment joining, **random nucleotides are added or removed at the junctions in both B and T-cells** mediated by an enzyme called **TdT (terminal deoxynucleotidyl transferase)**. This step greatly increases variability of the receptors.
- Results in a **total potential receptor diversity up to ≈ 10^{16}**.

Additional Differences in B-cell vs T-cell Receptor Development:

➢B cells:

- Can undergo **two proceses that doesn't happen in the T-Cells:**

1. **Receptor editing:** which is **re-stimulation of RAG** in **immature B cells** leading to **new V-J light-chain rearrangement.**
2. **Affinity maturation:** a **post-activation process** in which B cells, via **somatic hypermutation**, produce antibodies with progressively **higher affinity for the same antigen.**

- **RAG enzymes + TdT activity:**
  High in pro-B stage
  Greatly reduced / near absent in pre-B stage
- Result: **Less junctional and overall diversity** compared to T cells

➢T cells:

- **No receptor editing**
- **RAG enzymes + TdT activity:**
  Highly active during both pro-T and pre-T stages
- **Result:** Continuous rearrangement + nucleotide addition leading to **greater junctional diversity**
- **Overall: TCR diversity > BCR diversity**

Production of Diverse Antigen Receptors

- **The formation of functional genes that encode B and T lymphocyte antigen receptors is initiated by somatic recombination of gene segments that code for the variable regions of the receptors, and diversity is generated during this process.**
- Early lymphoid progenitors contain Ig and TCR genes in their **inherited, or germline, configuration**. In this configuration, Ig heavy-chain and light-chain loci and the TCR α-chain and β-chain loci each contain multiple variable region (V) gene segments, numbering about 30-45, and one or a few constant region (C) genes.
- Between the V and C genes are groups of several short coding sequences called diversity (D) and joining (J) gene segments. (All antigen receptor gene loci contain V, J, and C genes, but only the Ig heavy-chain and TCR β-chain loci also contain D gene segments.

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Mechanisms of V(D)J Recombination and Generation of Ig and TCR Diversity

- **The somatic recombination of V and J, or of V, D, and J, gene segments is mediated by a lymphoid-specific enzyme, the VDJ recombinase** (RAG-1 and RAG-2) proteins**, and additional enzymes, most of which are not lymphocyte specific and are involved in repair of double-stranded DNA breaks introduced by the recombinase.**

- **Diversity of antigen receptors is produced by the use of different combinations of V, D, and J gene segments in different clones of lymphocytes (called combinatorial diversity) and even more by changes in nucleotide sequences introduced at the junctions of the recombining V, D, and J gene segments (called junctional diversity)**

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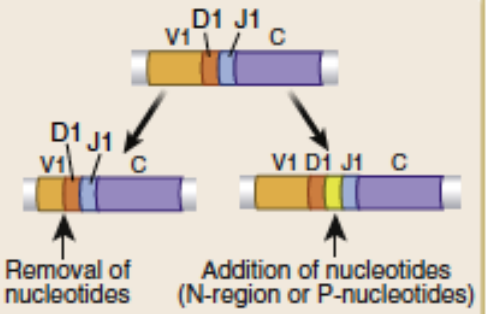
	Immunoglobulin			T cell receptor	
	Heavy chain	κ	λ	α	β
Number of variable (V) gene segments	~45	35	30	45	48
Number of diversity (D) gene segments	23	0	0	0	2
Number of joining (J) gene segments	6	5	4	50	12
Mechanism					
Combinatorial diversity:					
Number of possible V(D)J combinations	Ig: ~3×10^6			TCR: ~6×10^6	
Junctional diversity:					
Total potential repertoire with junctional diversity	Ig: ~10^{11}			TCR: ~10^{16}	

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Maturation and Selection of B Lymphocytes

- Bone marrow progenitors committed to the B cell lineage proliferate, giving rise to a large number of precursors of B cells, called **pro-B cells.**

- **The Ig heavy-chain locus rearranges first, and only cells that are able to make an Ig μ heavy-chain protein are selected to survive and become pre-B cells.**

- **The assembled pre-BCR serves essential functions in the maturation of B cells.**

Completion of B Cell Maturation.

- The IgM-expressing B lymphocyte is the **immature B cell.**
- The IgM+ IgD+ cell is the **mature B cell,** able to respond to antigen in peripheral lymphoid tissues.
- Developing B cells are **positively selected** based mainly on **expression of complete antigen receptors**, and not on the recognition specificity of these cells.
- The B cell repertoire is further shaped by **negative selection against strong recognition of self antigens.**

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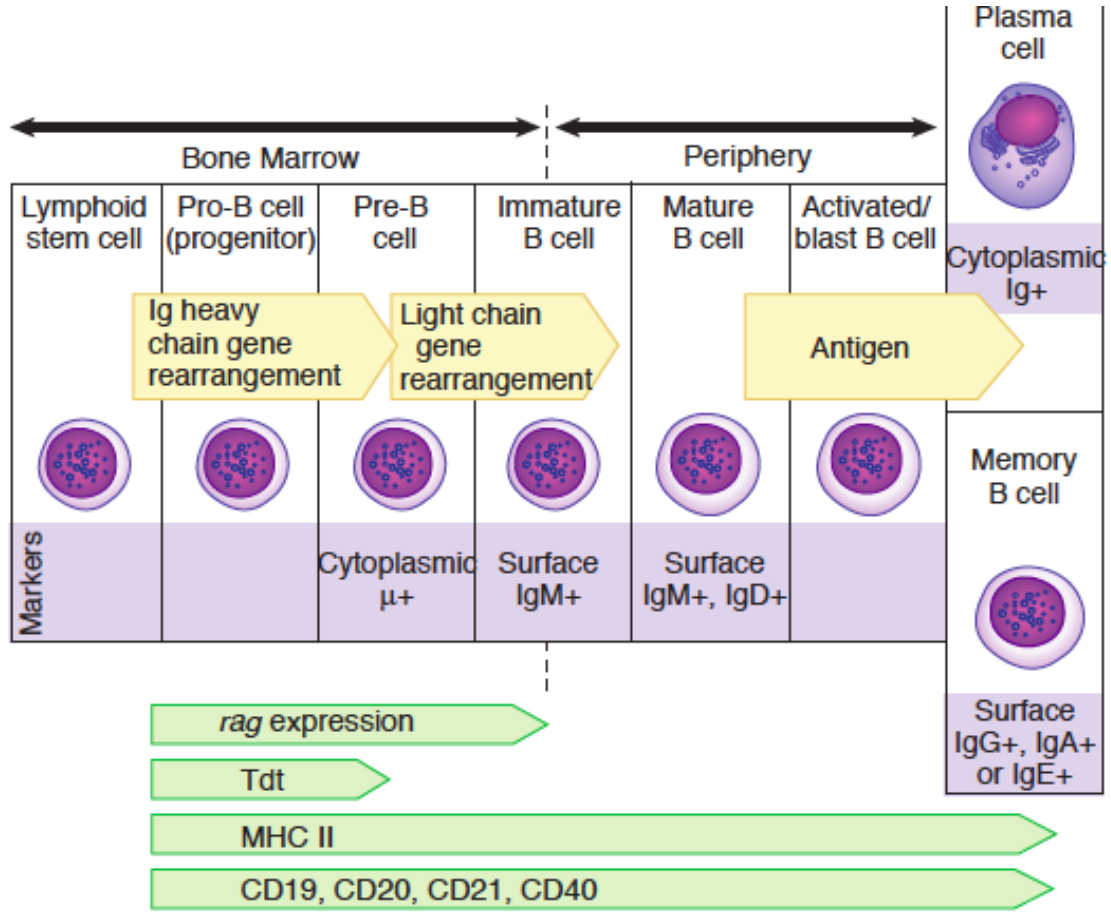
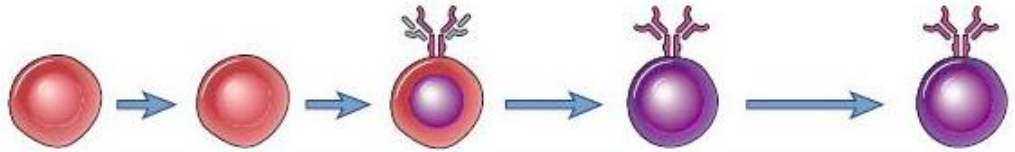

Plasma cell
Bone Marrow
Periphery
Lymphoid stem cell
Pro-B cell (progenitor)
Pre-B cell
Immature B cell
Mature B cell
Activated/ blast B cell
Cytoplasmic Ig+
Ig heavy chain gene rearrangement
Light chain gene rearrangement
Antigen
Memory B cell
Markers
Cytoplasmic μ+
Surface IgM+
Surface IgM+, IgD+
Surface IgG+, IgA+ or IgE+
rag expression
Tdt
MHC II
CD19, CD20, CD21, CD40



Stage of maturation	Stem cell	Pro-B	Pre-B	Immature B	Mature B
Proliferation					
RAG expression					
TdT expression					
Ig DNA, RNA	Unrecombined (germline) DNA	Unrecombined (germline) DNA	Recombined H chain gene (VDJ); μ mRNA	Recombined H chain gene (VDJ), κ or λ genes (VJ); μ or κ or λ mRNA	Alternative splicing of VDJ-C RNA (primary transcript), to form C_μ and C_δ mRNA
Ig expression	None	None	Cytoplasmic μ and pre-B receptor–associated μ	Membrane IgM (μ+ κ or λ light chain)	Membrane IgM and IgD
Surface markers	$CD43^+$	$CD43^+$ $CD19^+$ $CD10^+$	$B220^{lo}$ $CD43^+$	IgM^{lo} $CD43^-$	IgM^{hi}
Anatomic site	Bone marrow			Periphery	
Response to antigen	None	None	None	Negative selection (deletion), receptor editing	Activation (proliferation and differentiation)

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Maturation and Selection of T Lymphocytes

- **T cell progenitors migrate from the bone marrow to the thymus, where the entire process of maturation occurs.**
- The least developed progenitors in the thymus are called **pro-T cells** or **double-negative T cells** (or double-negative thymocytes) because they do not express CD4 or CD8.
- TCR β gene recombination, mediated by the VDJ recombinase, occurs in some of these double-negative cells.
- If VDJ recombination is successful in one of the two inherited loci and a TCR β-chain protein is synthesized, it is expressed on the cell surface in association with an invariant protein called pre-Tα, to form the pre-TCR complex of **pre-T cells.**
- If the recombination in one of the two inherited loci is not successful, recombination will take place on the other locus. If that too fails and a complete TCR β chain is not produced in a pro-T cell, the cell dies.

- The pre-TCR complex delivers intracellular signals once it is assembled, similar to the signals from the pre-BCR complex in developing B cells.
- These signals promote survival, proliferation, and TCR α gene recombination and inhibit VDJ recombination at the second TCR β-chain locus (allelic exclusion).
- Failure to express the α chain and the complete TCR again results in death of the cell.
- The surviving cells express the complete αβ TCR and both the CD4 and CD8 coreceptors; these cells are called **double-positive T cells** (or double-positive thymocytes).

Selection of Mature T Cells.

- If the TCR of a T cell recognizes an MHC molecule in the thymus, which must be a self MHC molecule displaying a self peptide, and if the interaction is of low or moderate affinity, this T cell is selected to survive (**positive selection).**
- During this process, T cells whose TCRs recognize class I MHC–peptide complexes preserve the expression of CD8, the coreceptor that binds to class I MHC, and lose expression of CD4, the coreceptor specific for class II MHC molecules and the other way around. **single-positive T cells .**
- Immature, double-positive T cells whose receptors strongly recognize MHC-peptide complexes in the thymus undergo apoptosis. This is the process of **negative selection.**

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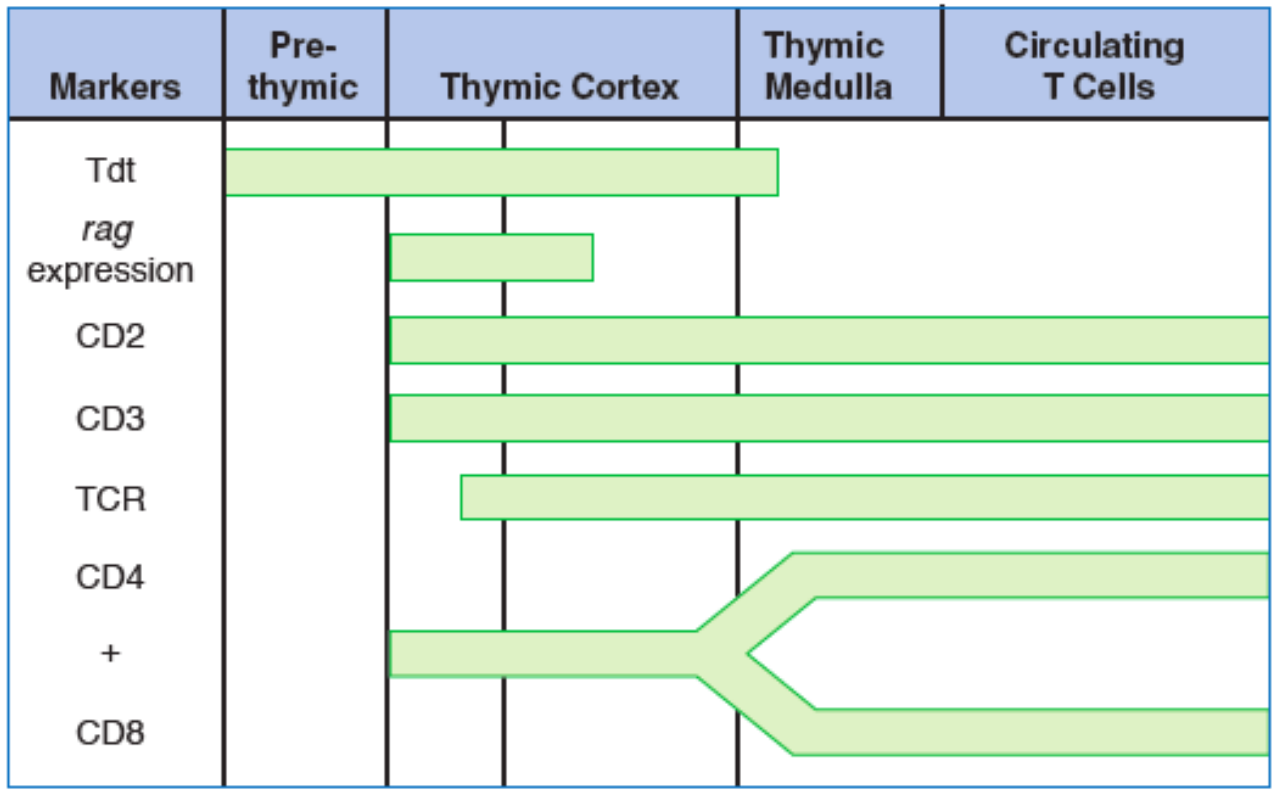
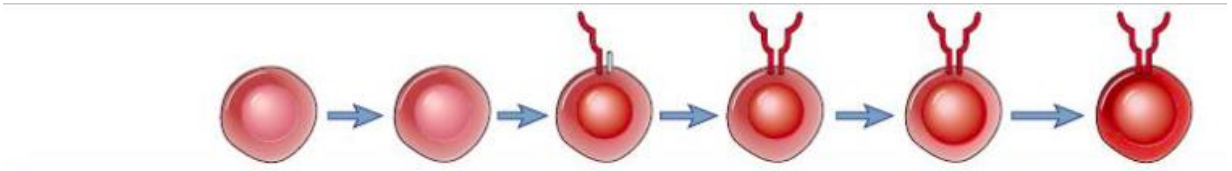


Figure I-3-13. Human T-Cell Differentiation



Stage of maturation	Stem cell	Pro-T	Pre-T	Double positive	Single positive (immature T cell)	Naive mature T cell
Proliferation						
RAG expression						
TdT expression						
TCR DNA, RNA	Unrecombined (germline) DNA	Unrecombined (germline) DNA	Recombined β chain gene [V(D)J-C]; β chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA
TCR expression	None	None	Pre-T receptor (β chain/pre-T α)	Membrane αβ TCR	Membrane αβ TCR	Membrane αβ TCR
Surface markers	c-*kit*$^+$ CD44$^+$ CD25$^-$	c-*kit*$^+$ CD44$^+$ CD25$^+$	c-*kit*$^+$ CD44$^-$ CD25$^+$	CD4$^+$CD8$^+$ TCR/CD3^{lo}	CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ TCR/CD3^{hi}	CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ TCR/CD3^{hi}
Anatomic site	Bone marrow	Thymus				Periphery
Response to antigen	None	None	None	Positive and negative selection		Activation (proliferation and differentiation)

FIGURE 8–19 Stages of T cell maturation. Events corresponding to each stage of T cell maturation from a bone marrow stem cell to

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The End

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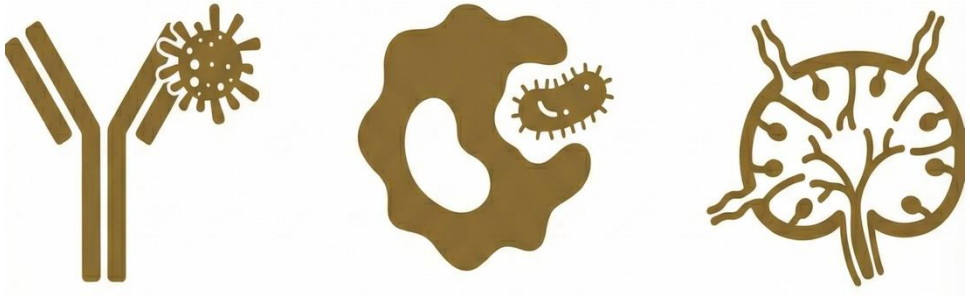

IMMUNOLOGY QUIZ LECTURE 1

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	7	6 CDRs per receptor	12 CDRs per receptor (with further explanation)
V1 → V2			