ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

HSeT
Health Sciences
e-Training
Foundation

7. The B cell response

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Outline

Introduction

7.1 Antibody response to T-independent antigens

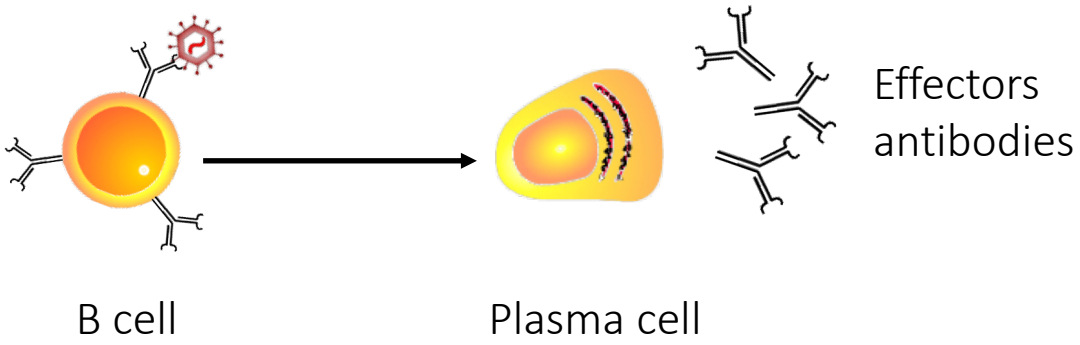
7.2 Antibody response to T-dependent antigen

7.3 Effector phase

7.4 Contraction phase

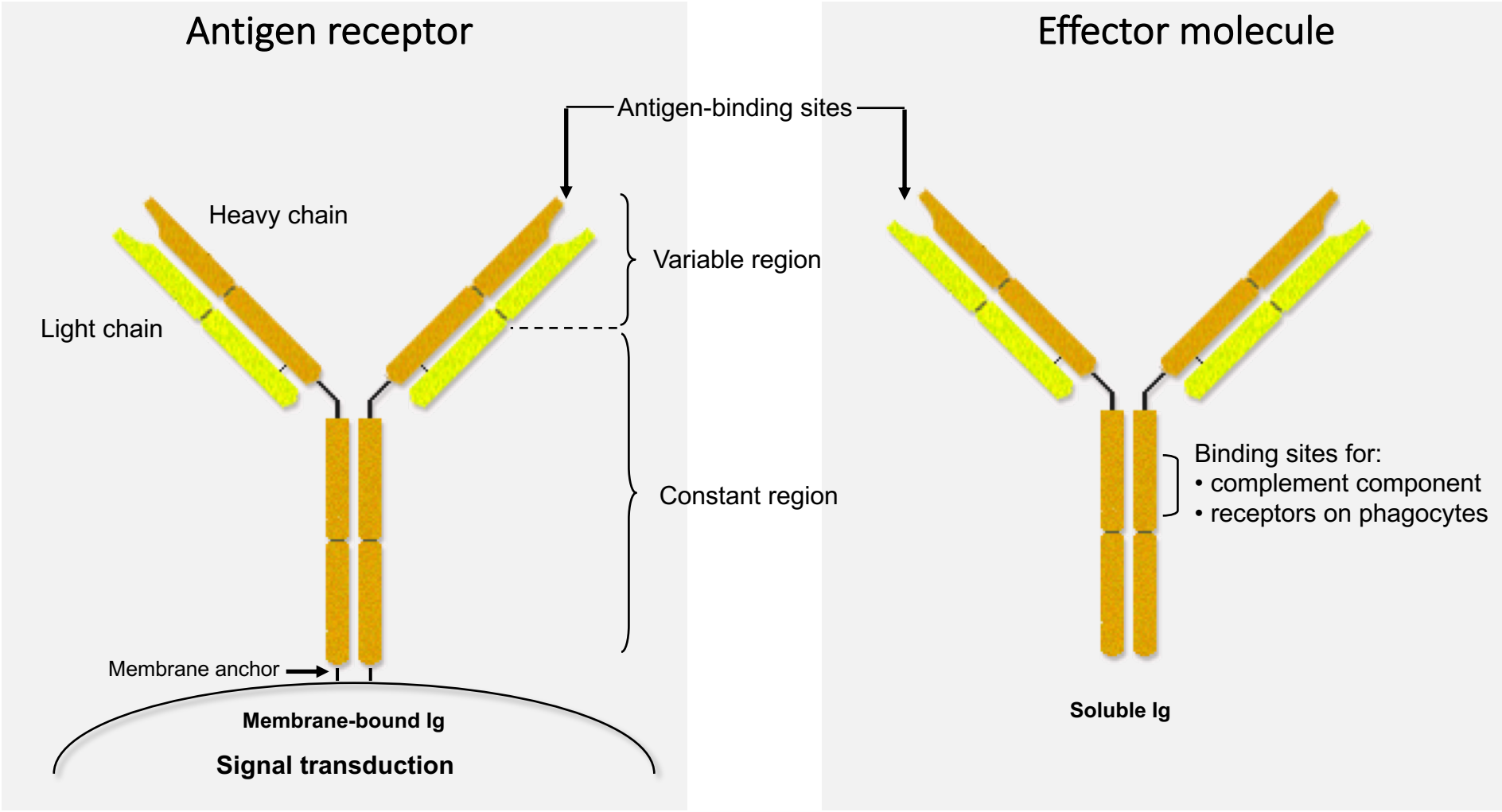
The B cell response: Introduction

- The humoral response is mediated by B cells and is important for protecting the body against:
  - Extracellular microbes (bacteria, parasites) and their toxins.
  - Intracellular pathogens (bacteria, viruses, parasites) as they move to their target cells
- B cells recognize antigens via their receptors, cell surface membrane-bound immunoglobulins (Ig)
- B cells defend the body from invading pathogens by secreting a soluble form of their Igs (antibodies)
- Antibody secretion occurs only in response to antigen recognition. Plasma cells can secrete 100-2000 Ig molecules/sec



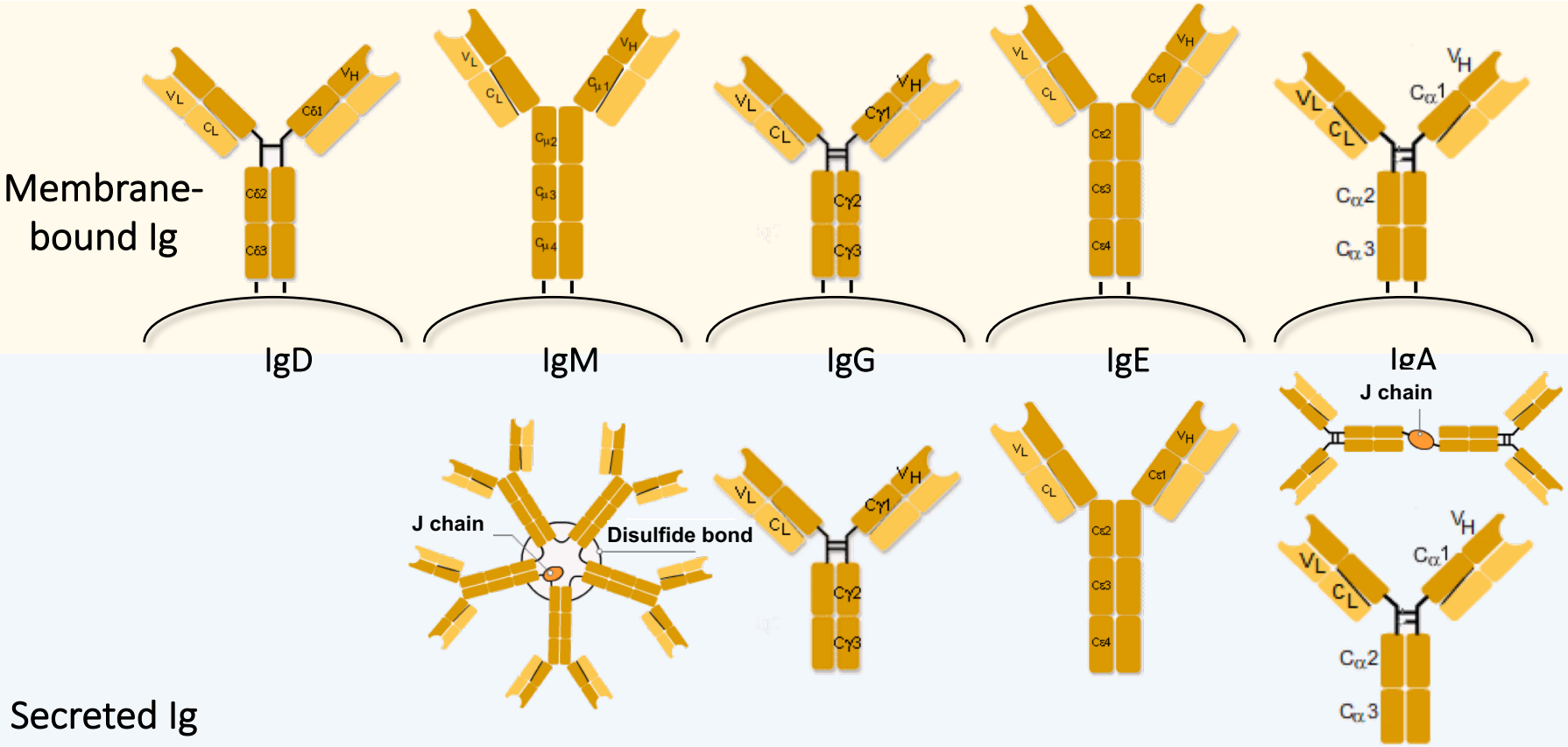
Immunoglobulins (Igs) = antibodies

- Igs are produced by B cells in one of two forms: **membrane-bound Ig** (antigen receptor) and **soluble Ig** (antibody)
- These two Ig forms serve distinct functions.
- Igs are composed of **2 heavy chains (50kDa)** and **2 light chains (25kDa).**



5 classes (isotypes) of Immunoglobulins

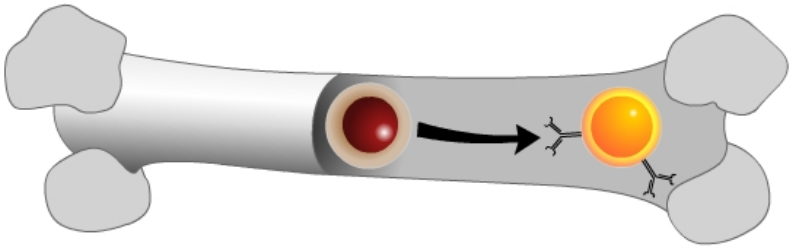
- 5 types of **heavy chains: μ, δ, γ, ε and α**
- Heavy chain determines **isotype: IgM, IgD, IgG, IgE or IgA**
- The different heavy chains differ in their constant region.
- Antibodies combine one type of heavy chain with one type of **light chain (κ and λ)**

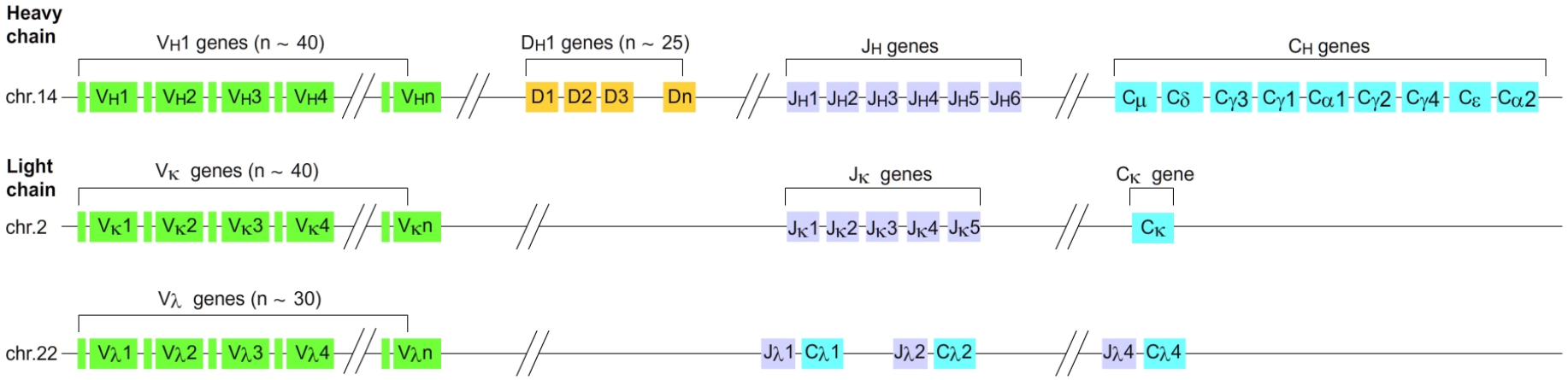


B cell development

B cells originate and develop in the bone marrow in a process called **B lymphopoiesis.**

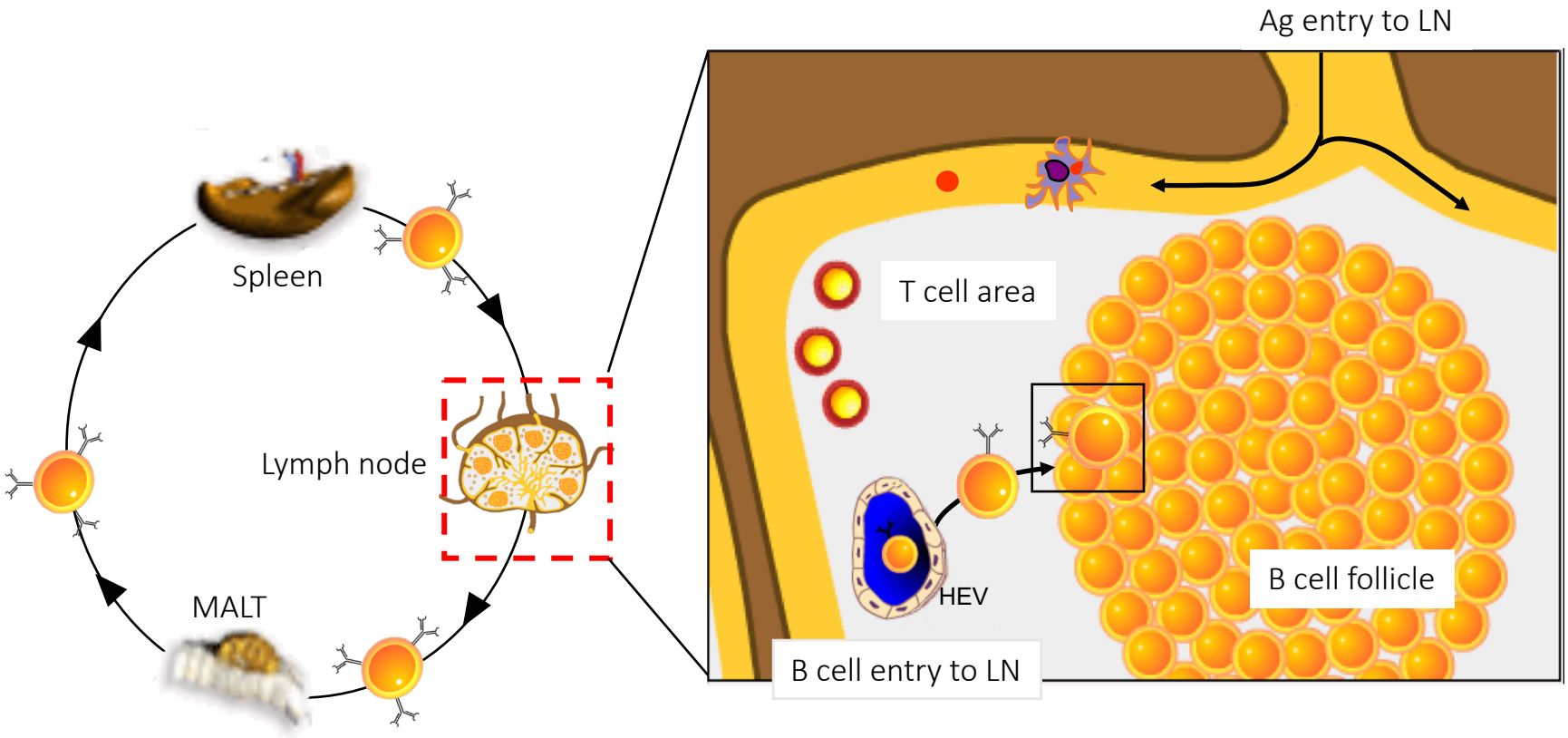
During lymphopoiesis, B cells acquire surface receptors to detect antigens.





Naïve B cells migrate to lymph nodes and spleen

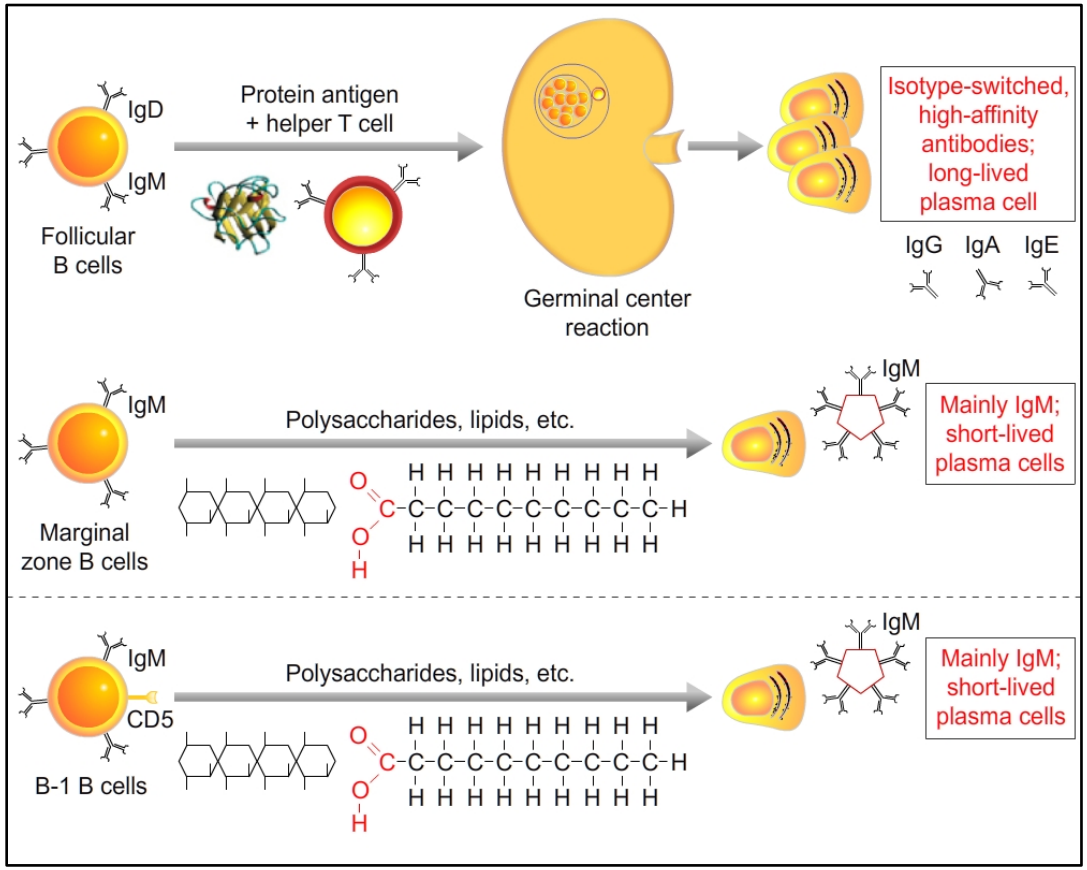
B cells enter lymph nodes from the blood through high endothelial venules (HEVs) and migrate to the B cell follicles.



Different subtypes of B cells

- **Follicular B cells (B2):** major type of B cells, reside in the follicles of lymphoid organs. They contribute to T-dependent B cell responses to protein antigens and give rise to long-lived plasma cells.
- **Marginal zone B cells**, located in the marginal zones of the splenic white pulp. They respond to blood-borne polysaccharide antigens.
- **B-1 B cells** respond to non-protein antigens in the mucosal tissues.

Marginal zone and B-1 B cells express antigen receptors of limited diversity and make predominantly IgM responses.

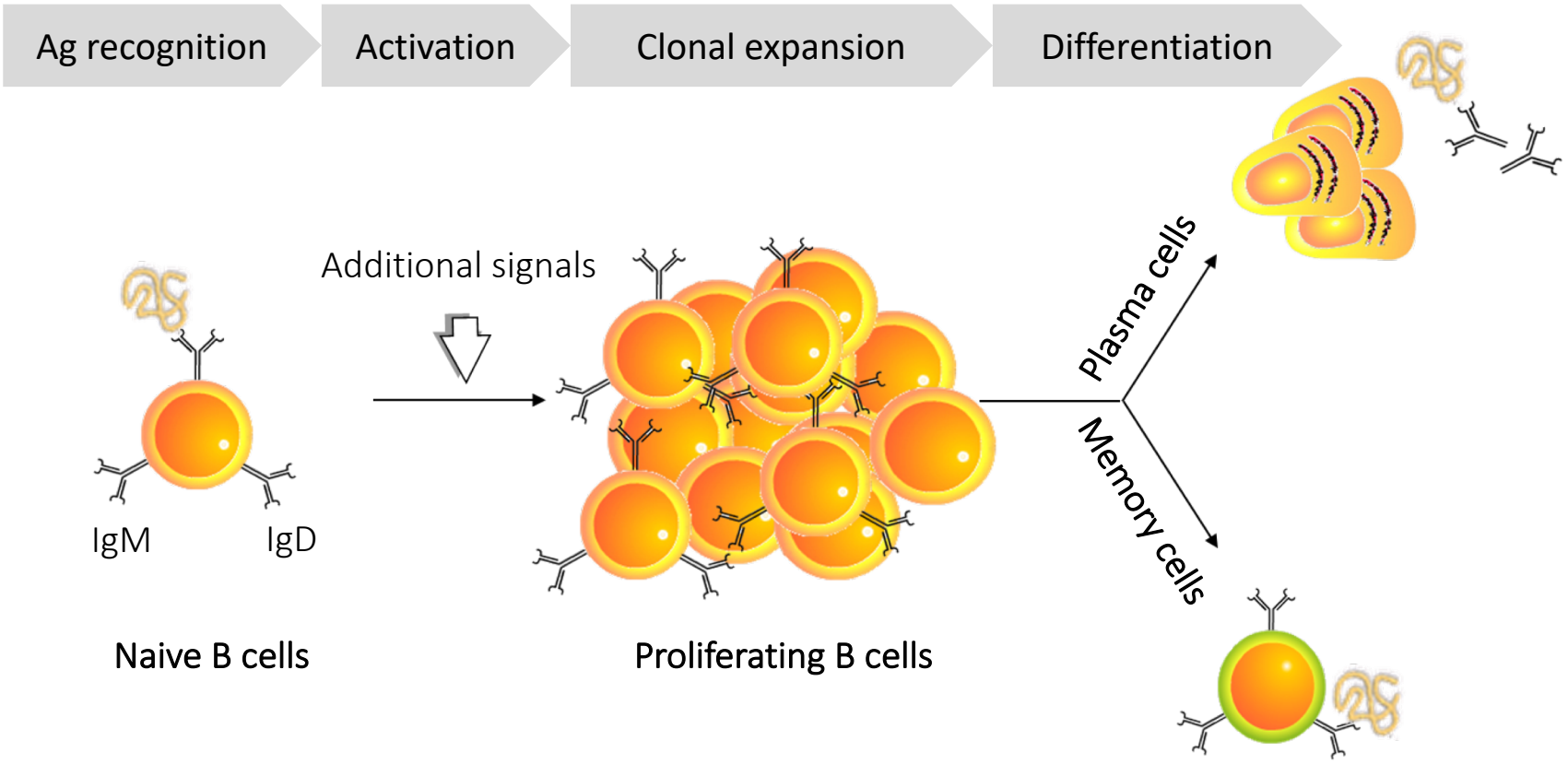


Adapted from Abbas, Cellular and Molecular Immunology

Sequence of events during a B cell response

Upon antigen encounter, B cells get activated: they stop migrating, proliferate and eventually differentiate into effector B cells (plasma cells) and memory B cells.

Plasma cells and memory B cells produce Igs that have the same specificity as the original membrane-bound Ig.

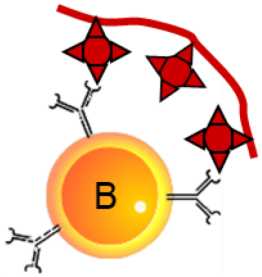


The activation phase: 2 signals

B cell activation requires **two signals:**

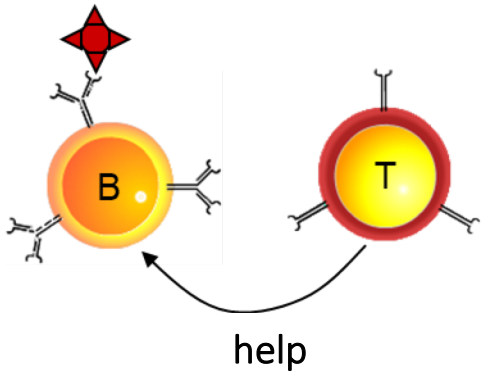
1. an intracellular signalling cascade triggered by **the B cell receptor (BCR) complex** [SIGNAL 1]
2. a **costimulatory signal** [SIGNAL 2] delivered to the B cells:
   - by the antigen itself (T-independent activation)
   - by cognate interaction with primed T helper cells.

High-valency antigens
(Polysaccharides, lipopolysaccharides, capsides…)
→ Strong signal 1



Low-valency antigens
Proteins

→ Weak signal 1

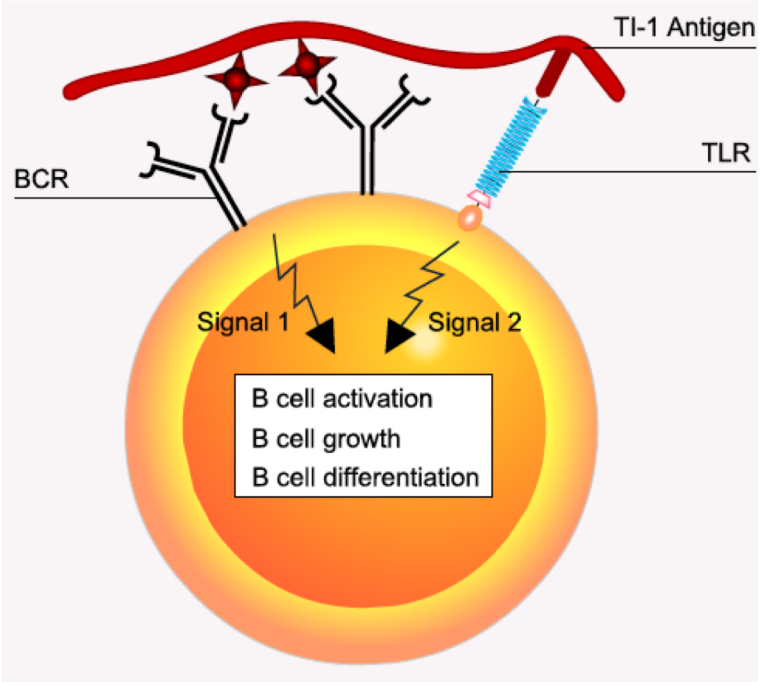


7.1 Antibody response to T-independent antigens

Antigen Recognition by B lymphocytes: TI-1

Thymus independent type 1 (TI-1) (Non specific)

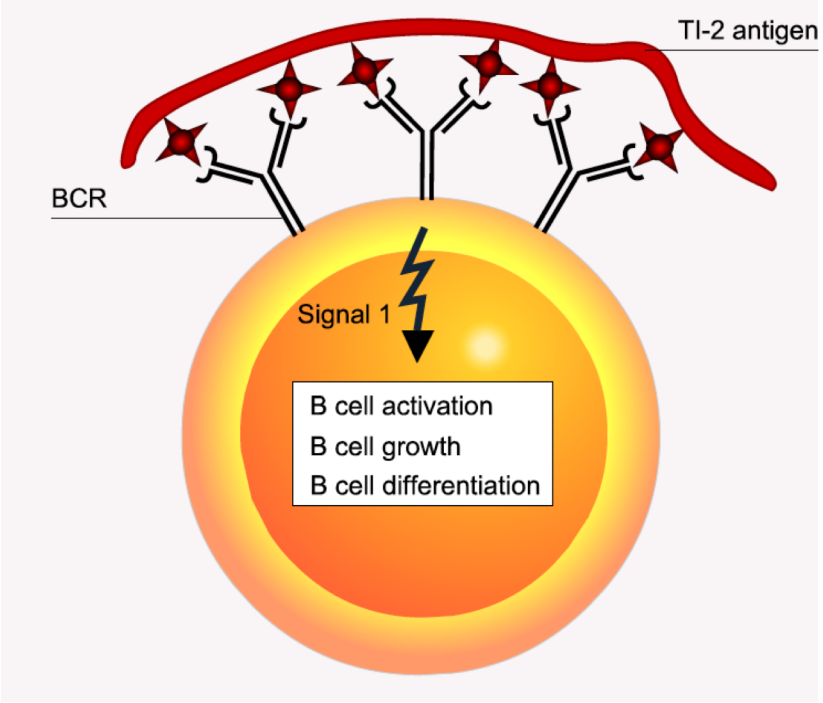
- TI-1 antigens are polyclonal, non antigen specific activators of B cells that engage co-stimulatory receptors on B cells but not the BCRs
- B cells function as innate immune cells
- Example: **lipopolysaccharide (LPS)** from Gram-negative bacterial cell wall which binds to TLR4.
- At **high concentration, LPS** can engage all TLR4-expressing B cells, irrespective of their BCR specificity (→ polyclonal response)
- At **low concentration of LPS**, only the B cells with TLR4 and anti-LPS BCR will be activated.



Antigen Recognition by B lymphocytes: TI-2

Thymus independent type 2 (TI-2) (Non specific)

- TI-2 antigens are molecules of high molecular weight with repetitive epitopes that cause extensive cross-linking of BCRs and stimulate B cell proliferation and differentiation without the cognate help of T lymphocytes.
- Prototype: high molecular weight polysaccharide such as the dextran B512.
- Only generate short-lived IgM responses with no memory
- Responsible for **natural antibodies** (constantly produced, probably due to antigens from the flora)



Conclusions | TI (thymus-independent) antibody response

- Many bacteria and viruses contain polysaccharide and lipid antigens with multivalent arrays of the same epitope.
- These antigens are able to cross-link multiple antigen receptors on a specific B cell or engage simultaneously a Pattern recognition receptor to elicit antibody responses without the participation of helper T cells.
- Antibody responses to T-independent antigens lead to short-lived plasma cells that release IgM of low affinity. They do not give rise to memory B cells.
- T-independent plasma cells provide a rapid effector response to specific antigens, that are associated with infection.
- Marginal zone B cells in the spleen are the major contributors to T-independent antibody responses to blood-borne antigens.
- B-1 B cells make T-independent responses to antigens of microbes in mucosal tissues and microbes that enter the peritoneum.

7.2 Antibody response to T-dependent antigens

7.2.1 Antigen recognition

7.2.2 B Cell activation

- B cell receptor
- B cell co-receptor Signaling
- B / T cell interaction

7.2.3. B cell differentiation

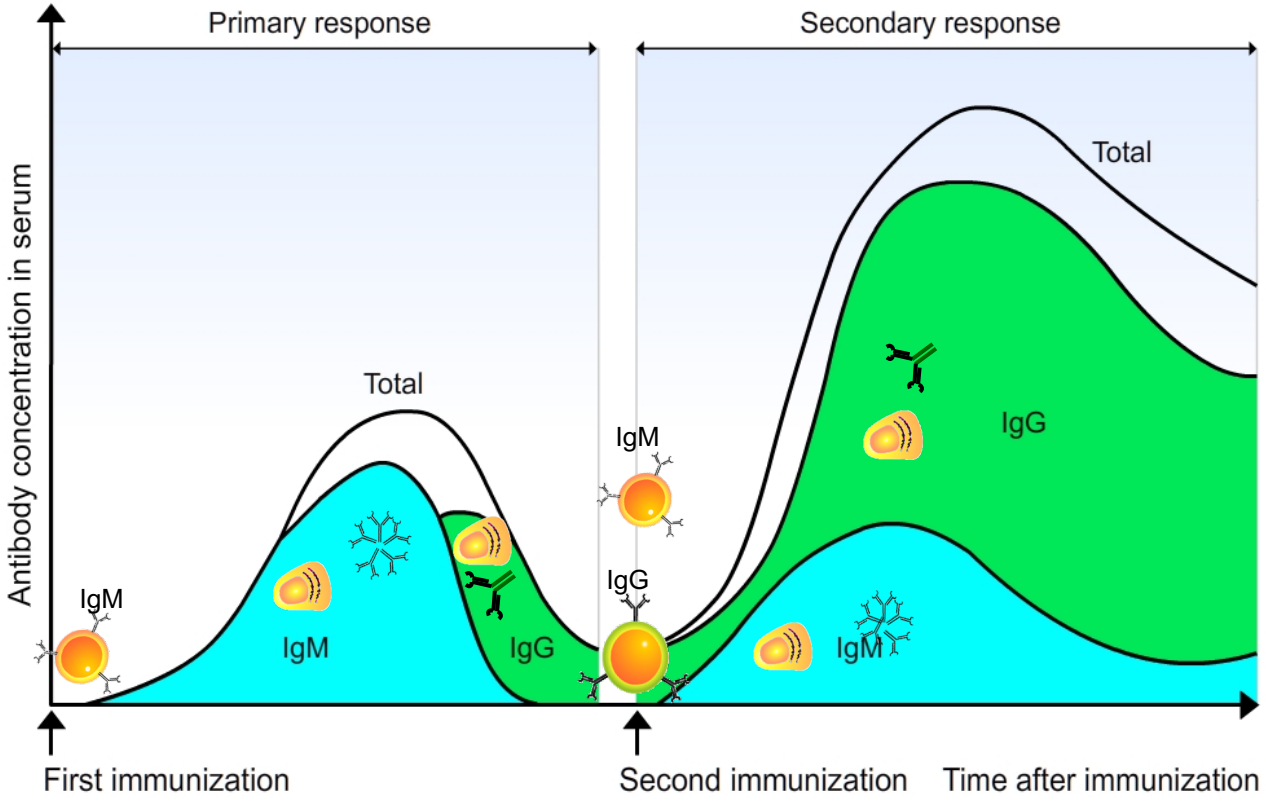
- Extrafollicular reaction
- Germinal center reaction
  - Affinity maturation
  - Class switch
- Plasma cellS and memory cells

Primary versus secondary B cell response

Primary antibody response

First contact with an antigen activates naïve B cells.

- long lag period (5-10 days)
- low magnitude
- IgM > IgG (low affinity)



Secondary antibody response

Second contact with an antigen activates memory B cells.

- shorter lag period (1-3 days)
- higher magnitude
- IgG > IgM (high affinity)

B cell response

The B cell response can be divided into 4 sequential phases:

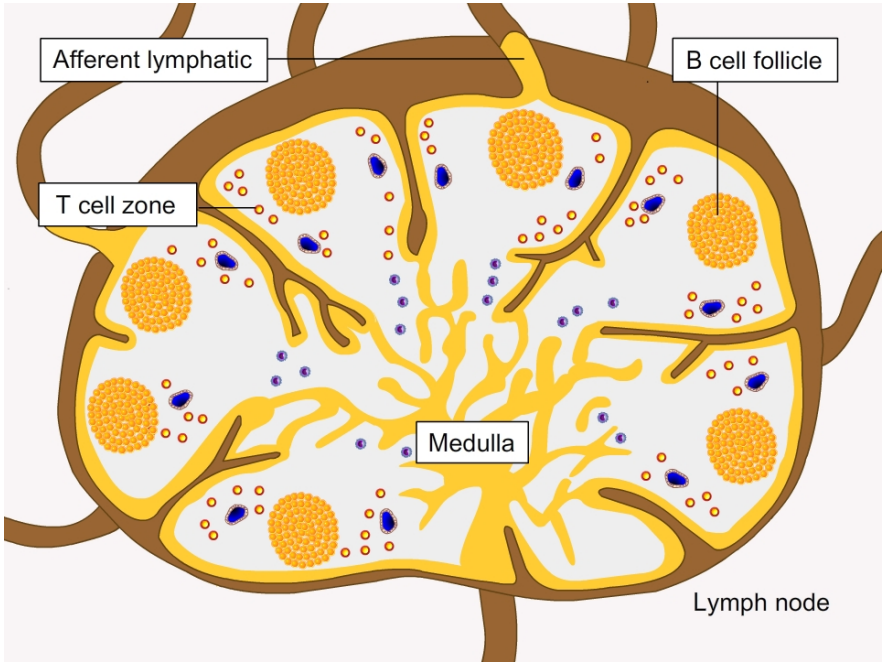
Recognition	B cells bind to the antigen for which they express specific membrane-bound Igs
Activation	B cells are triggered to proliferate and differentiate into plasma cells and memory cells
Effector phase	Antibodies released by plasma cells bind the antigen and cause its elimination
Contraction	As antigen is cleared from the body, most B cells and plasma cells die by apoptosis but a stable population of memory B cells for subsequent responses with the same antigen remains

Recognition: antigen transport to lymph nodes

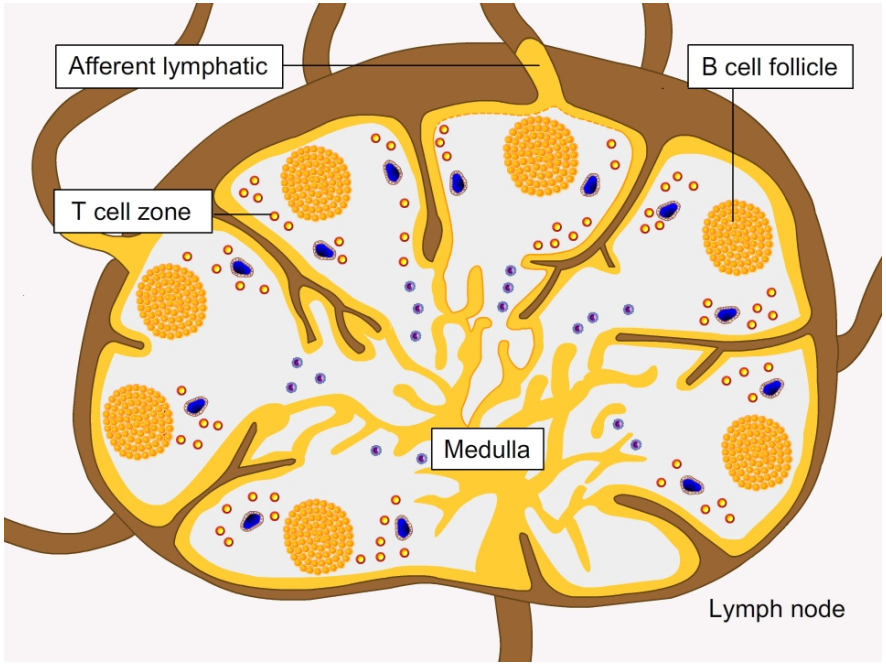
Antigens reach the B follicles of lymph nodes via afferent lymphatics:

- associated with dendritic cells
- as free antigens

DC pathway



Free antigen



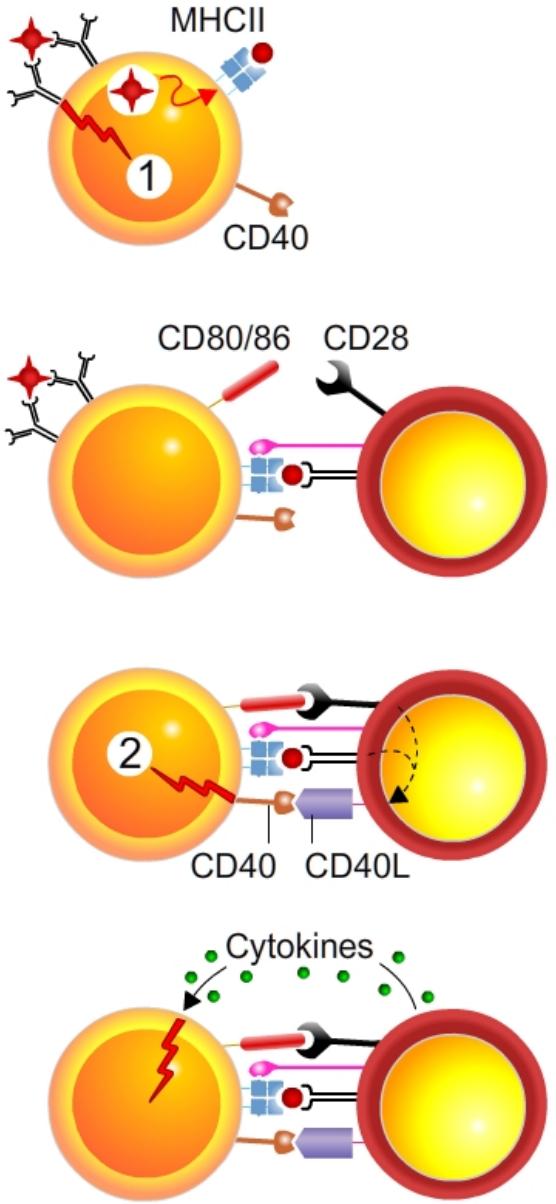
T-dependent antibody production

1. B cell activation by antigen-mediated crosslinking of BCRs
   - B cell activation and antigen processing
   - Upregulation of MHC class II and CD80/86

2. Antigen presentation to the T cell

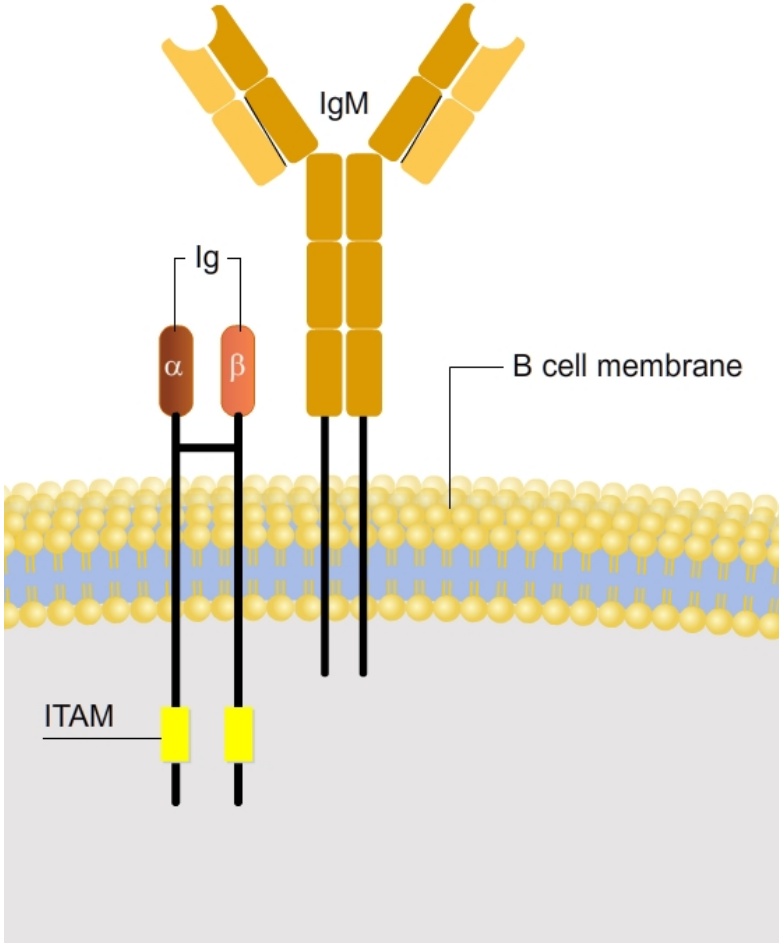
3. T cell activation, upregulation of CD40L, production of cytokines

4. CD40 and cytokine-mediated activation of the B cell



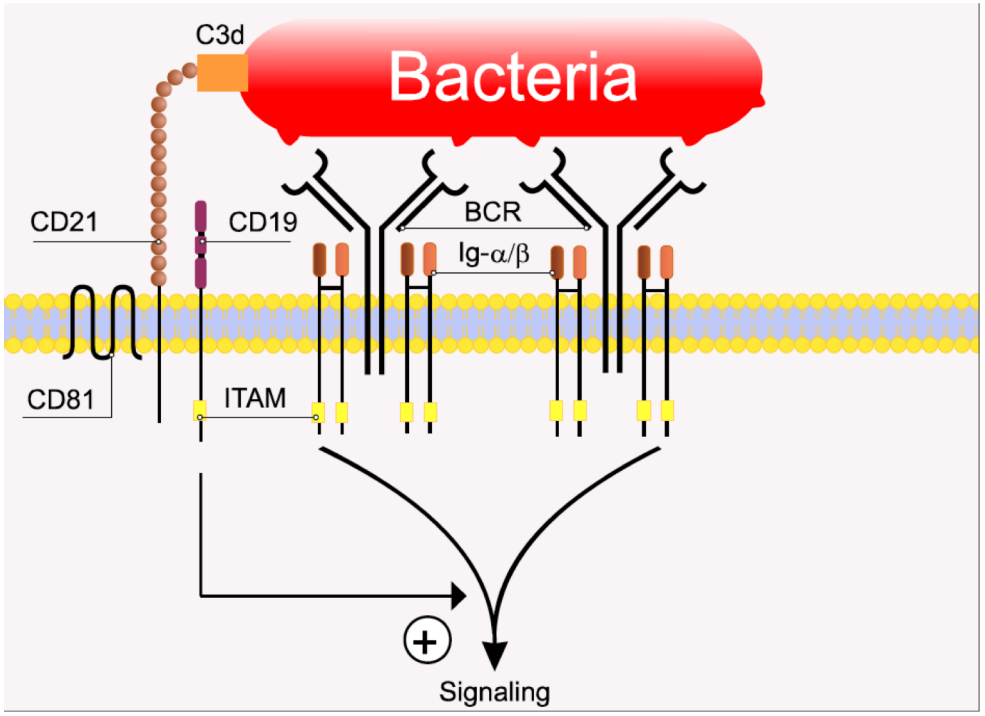
B cell response: recognition

- The B cell antigen receptor (BCR) complex is a **multimeric protein complex** consisting of:
  - membrane-bound immunoglobulin (IgM and IgD)
  - heterodimers of two polypeptides, Ig-α and Ig-β, non-covalently associated with the BCR in a 1:1 ratio.
- The BCR complex has **two functions**:
  - transmit signal into the interior of the B cell to inform about antigen binding
  - internalize the antigen for subsequent processing and presentation of antigen-derived peptides to T cells
- **Ig-α and Ig-β** are type I transmembrane polypeptides of the immunoglobulin (Ig) superfamily linked together by a disulfide bond and containing ITAM motifs.



B cell activation: activating co-receptors

- Co-receptors inform the B cell of its environment and thus provide a context for BCR signal transduction.
- Activating co-receptors include CD21/CR2: the **complement receptor 2 (CR2)** binds to antigen tagged with C3d. This reduces the amount of antigen required for B cell activation



Of note: Engagement of CD21/CR2 greatly enhances antigen-dependent activation responses of B cells. Thus, complement proteins provide additional signals for B cell activation, functioning in concert with antigen ("signal 1") to initiate B cell proliferation and differentiation. This role of complement in humoral immune responses again illustrates the idea that innate immune responses to microbes provide signals in addition to antigen that promote lymphocyte activation.

B cell activation: Signaling

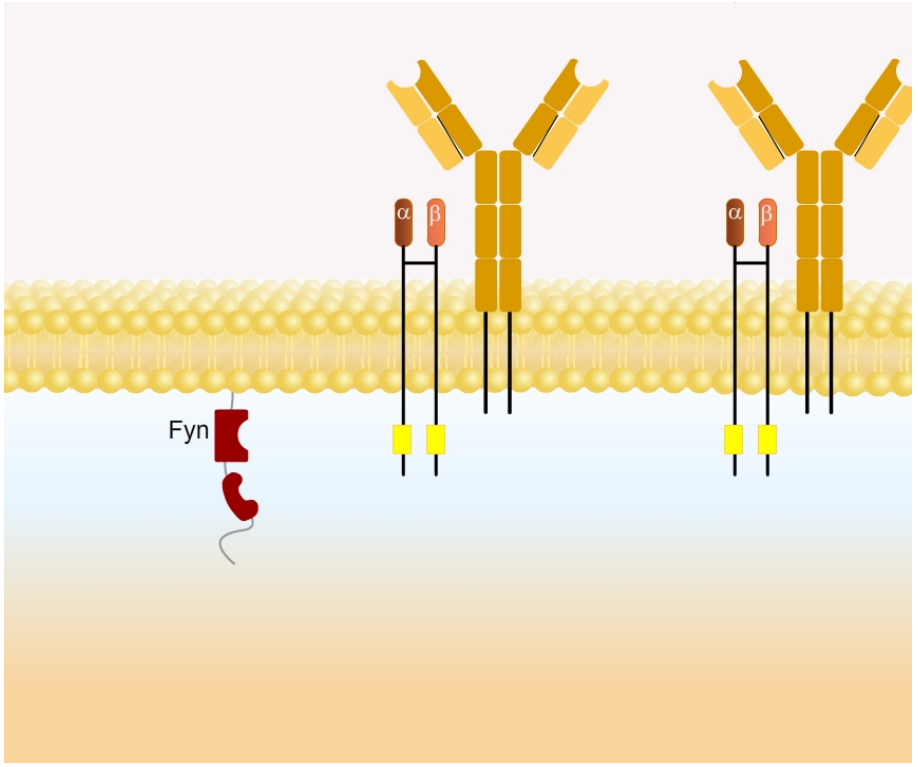
Three **pathways** are activated

- NFκB
- NF-AT
- MAP kinase

Consequences of antigen recognition by B cells:

- Expression of cytokine receptors
- Expression of co-stimulatory molecules (CD80/CD86)
- Expression of MHC II
- Expression of adhesion molecules → promotes interaction of B cells with T helper cells
- Internalisation of antigen and presentation by MHC II.

Initial steps



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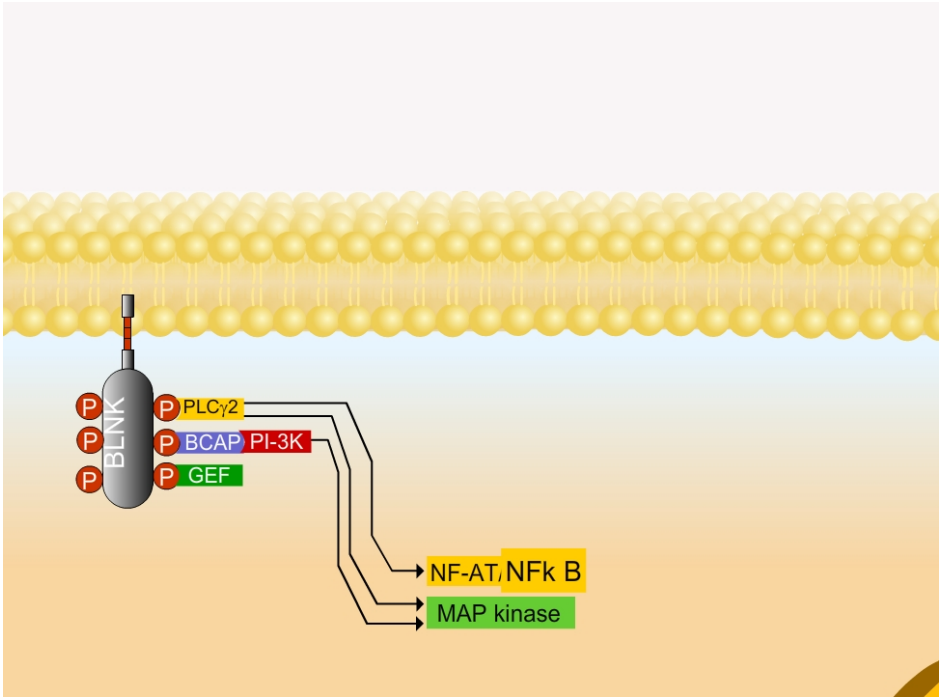
Activation of the NFκB pathway



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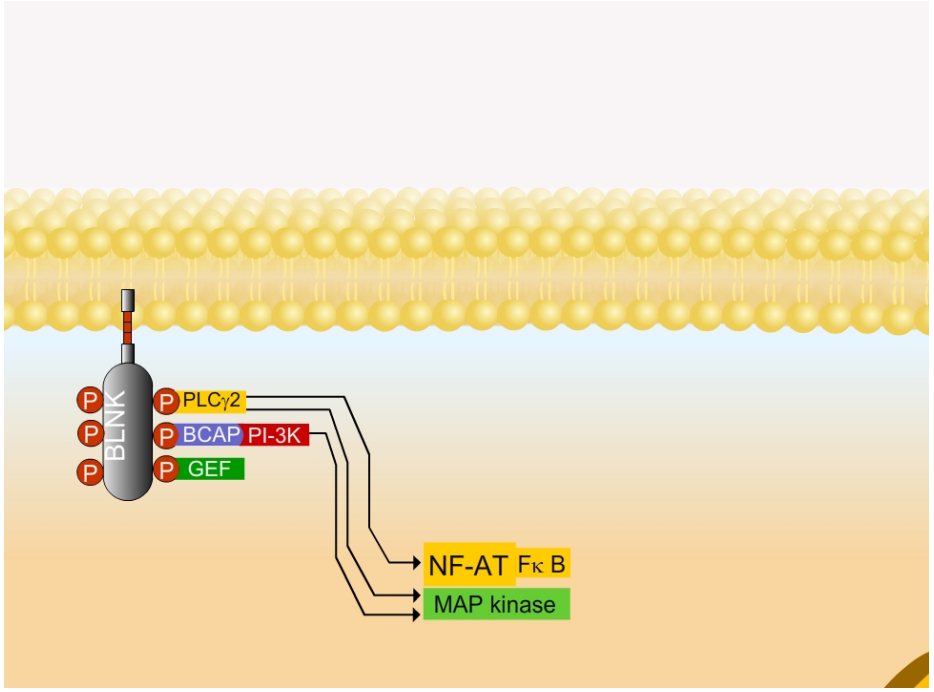
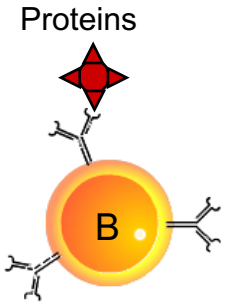
Activation of the NF-AT pathway

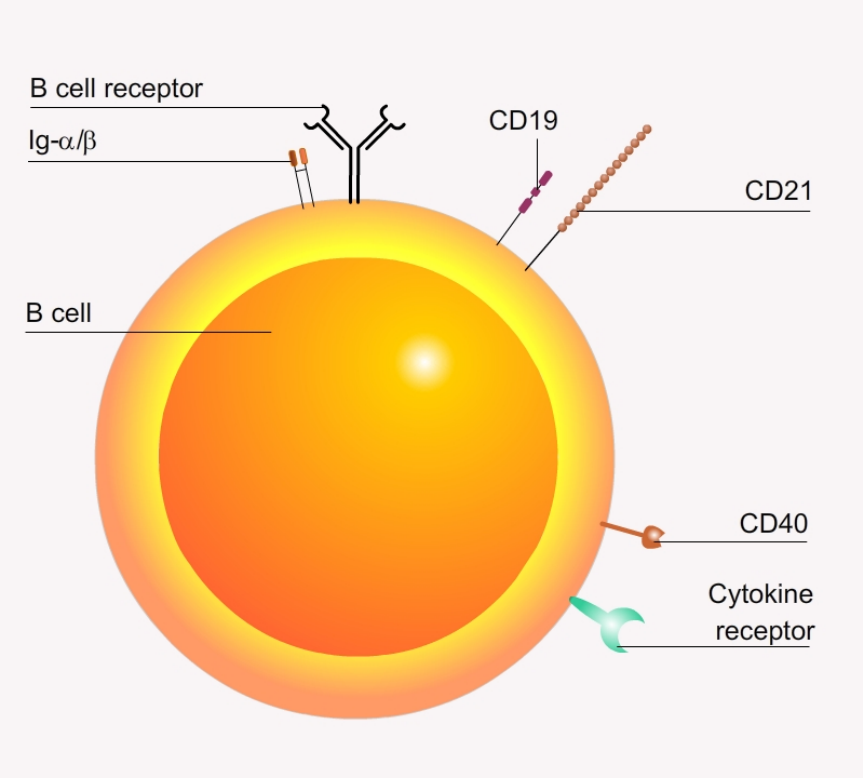


Activation phase: signal 2



Co-stimulatory signal (2) is required for full B cell activation.

- delivered by T helper cells previously activated by DCs presenting epitopes from the antigen
- B cells have to internalize BCR bound antigens, process and present them on MHC class II molecules
- Signal 2 is mediated by co-stimulatory surface molecule CD40L (which binds to CD40 receptor on B cells) and cytokines (which engage cytokine receptors on B cells)

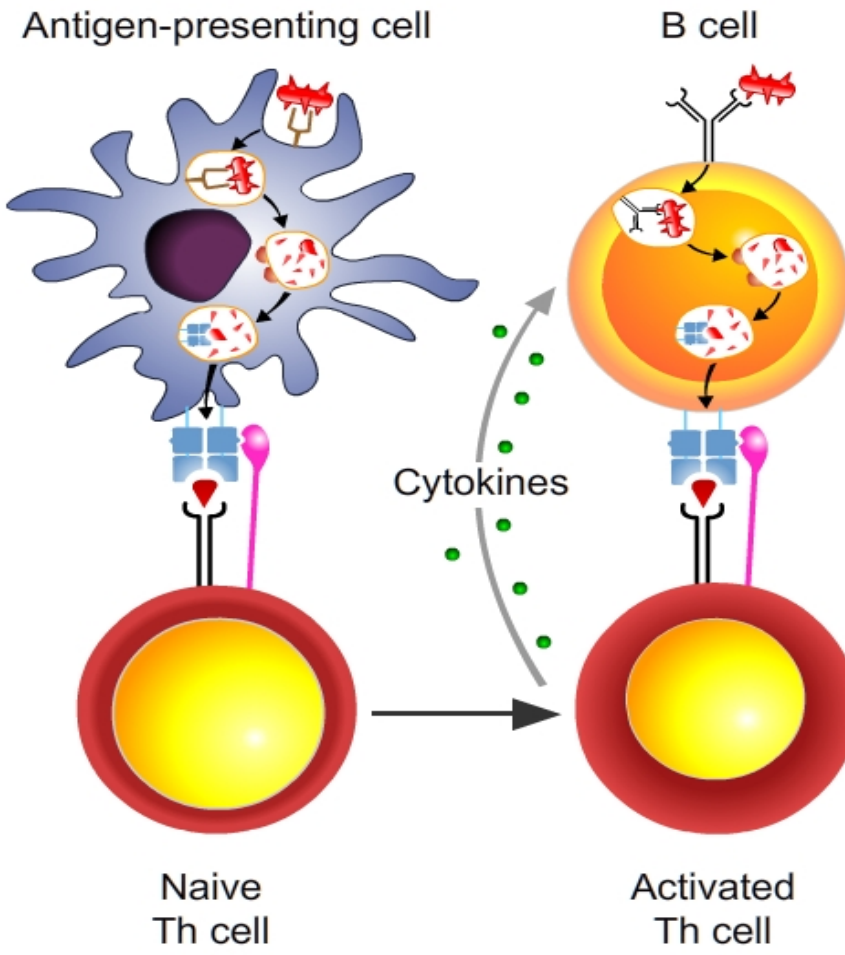


Consequences of B cell activation:

- clonal expansion
- IgM secretion
- differentiation:
  - extrafollicular
  - follicular (formation of a germinal center, affinity maturation, isotype switch)

Conclusions | T-dependent B cell response and B / T cell interactions

- B cell activation by proteins requires two signals
  1. Binding of protein antigen on the BCR
  2. T helper (CD4) previously activated by a DC
- The BCR signaling complex includes the BCR and the Ig-α/Ig-β co-receptors
- Antigen-BCR signaling can be modulated by co-receptors
- Signal 1 transforms the B cell into an APC expressing MHC II and co-stimulatory molecules, CD40, which internalizes and presents the antigen.
- Signal 1 and Signal 2 lead to B cell activation
  - clonal expansion
  - secretion of IgM
  - differentiation into plasma cells
- B2 cells make T-dependent responses in lymph nodes and spleen.

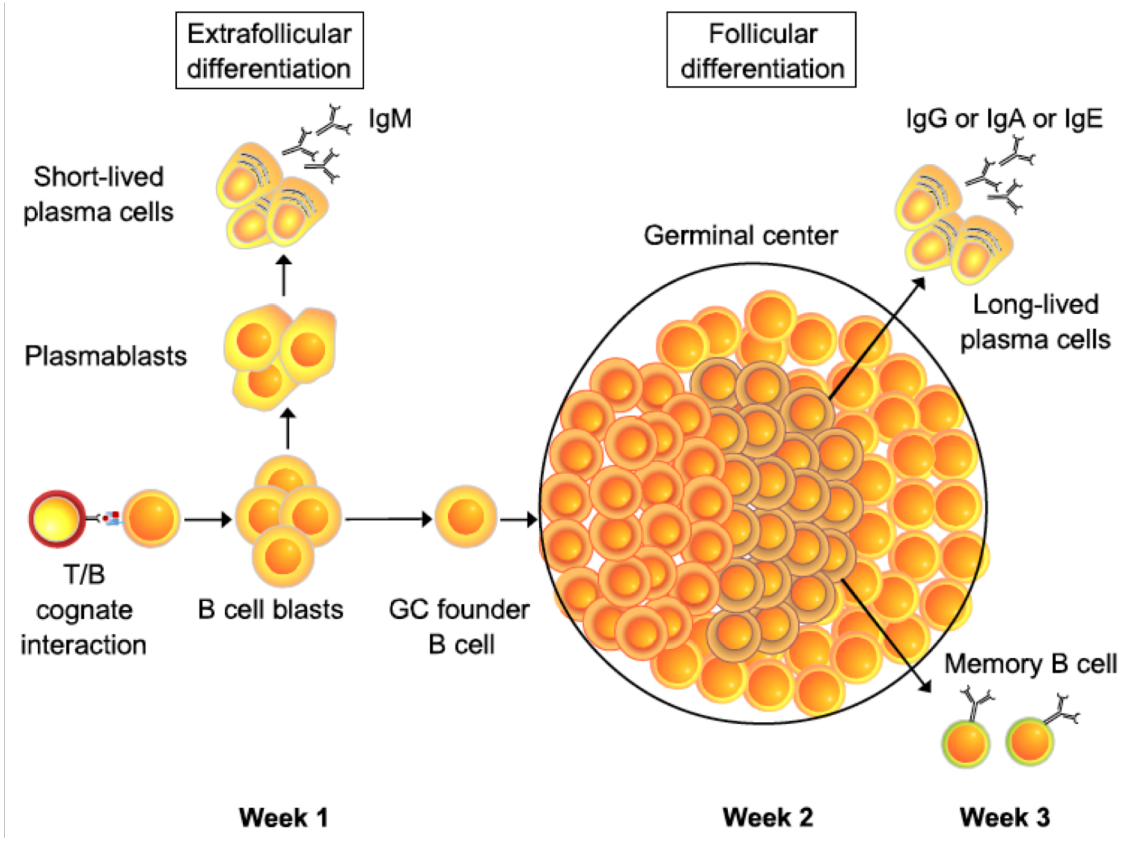


B cell differentiation

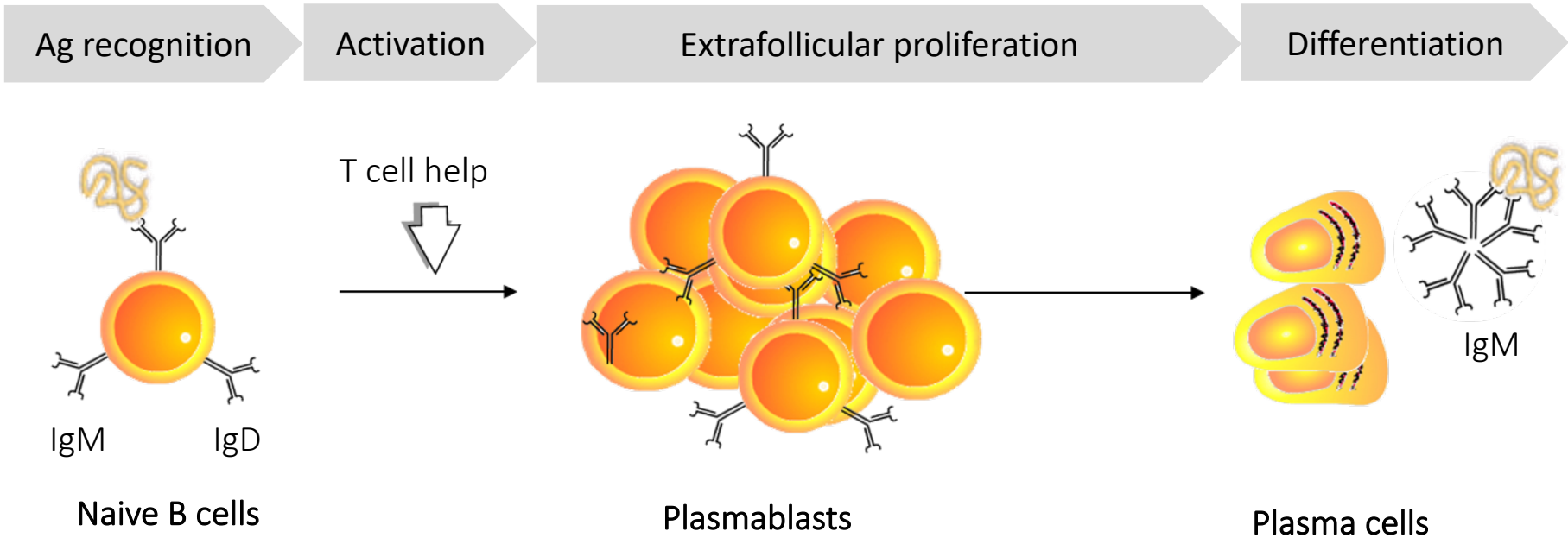
- After priming with antigen in B cell follicles or T cell zones, B cells move towards the border area between follicles and T cell zones to interact with antigen-specific helper T cells.
- B cells start to proliferate and enter one of **two possible differentiation pathways**:

Extrafollicular differentiation: differentiate in extrafollicular foci within the T cell area

Follicular differentiation: migrate back to follicles and initiate the germinal center (GC) reaction



Extrafollicular differentiation

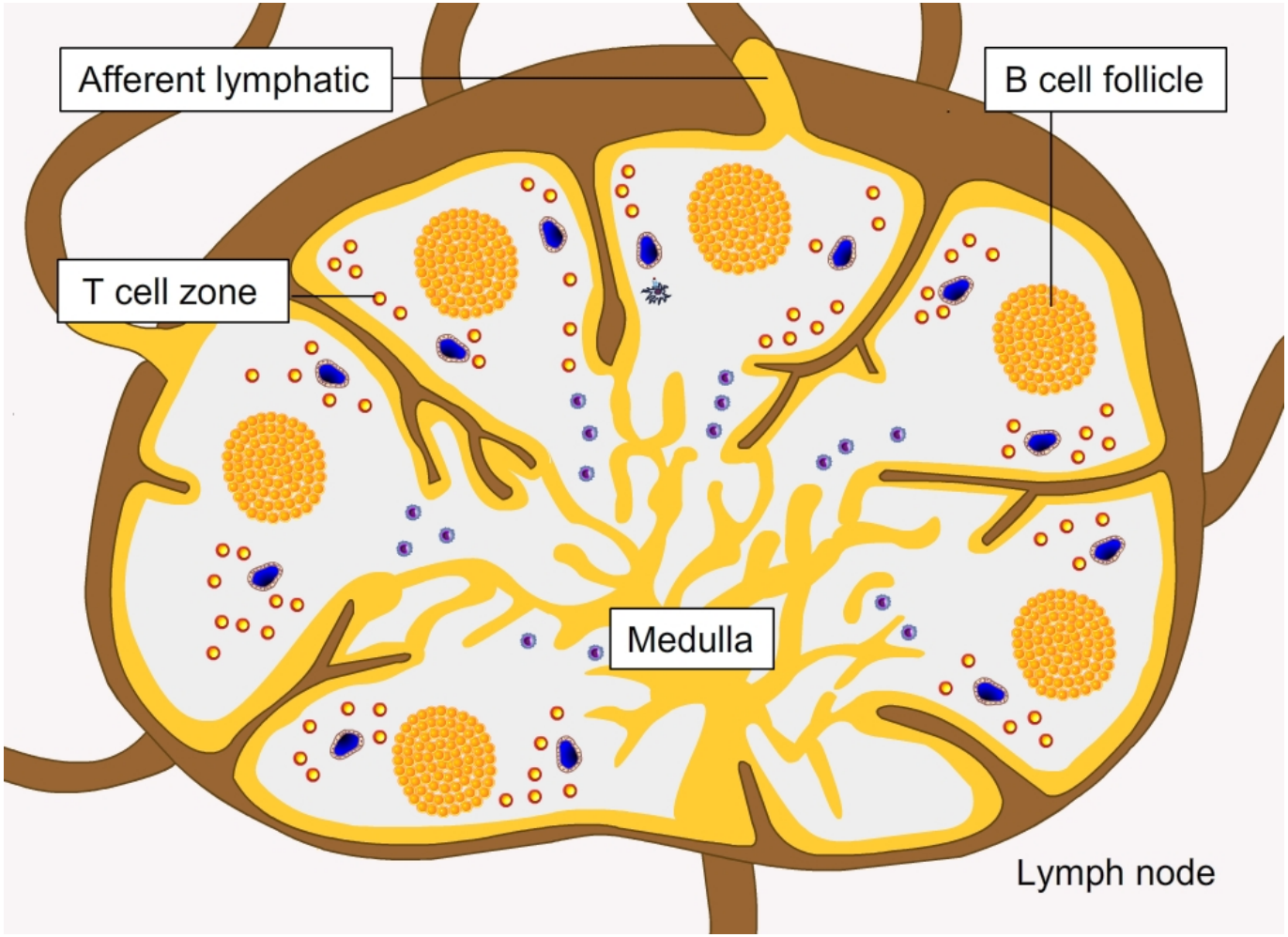


Extrafollicular plasma cells

- are short-lived and secrete antibodies within 48h of infection
- release mostly IgM of low-affinity
- provide a rapid effector response that allows a quick control of pathogens during the time the follicular reaction develops
- do not give rise to memory B cells

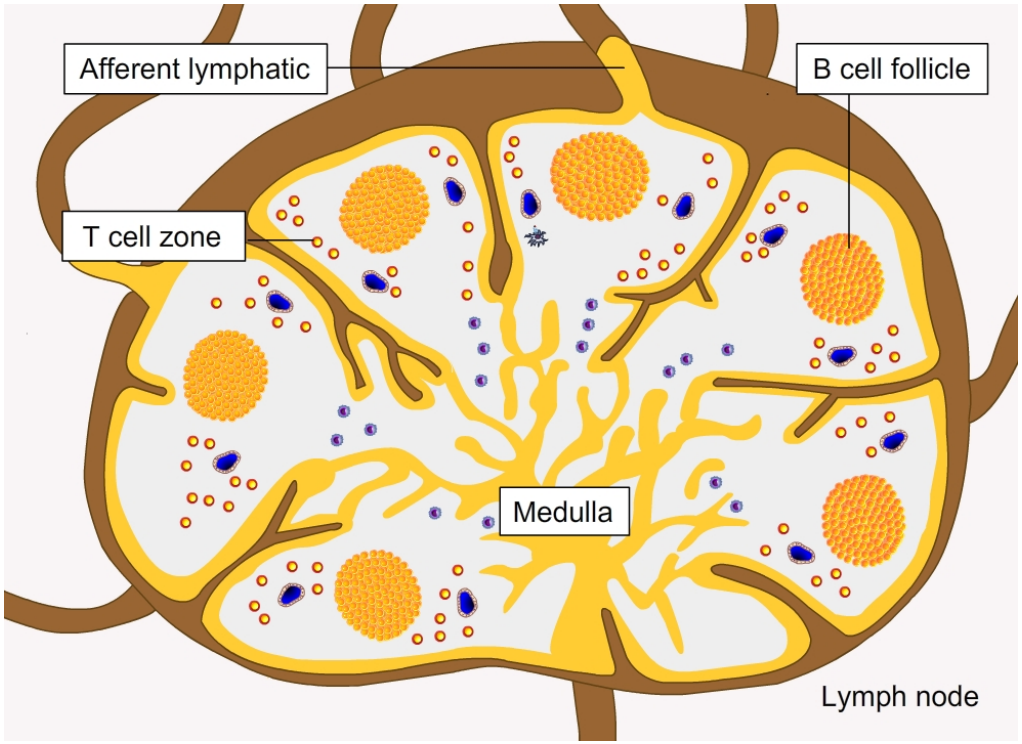
Extrafollicular reaction

differentiate in extra-follicular foci within the T cell area and migrate to medulla



Germinal center (GC) reaction

- In follicles, GC founder B cells undergo clonal expansion, giving rise to rapidly dividing centroblasts that form the dark zone.
- Over time, a portion of centroblasts stop dividing, and migrate toward the distal pole rich in FDCs. These non-cycling cells are termed centrocytes and form the light zone.
- Centrocytes ultimately differentiate into plasma cells and memory cells.
- Plasma cells and memory B cells express high-affinity IgG, IgA or IgE.



Germinal center reaction

Three major events take place in the GC:

- Somatic hypermutation (SHM) (Dark zone)

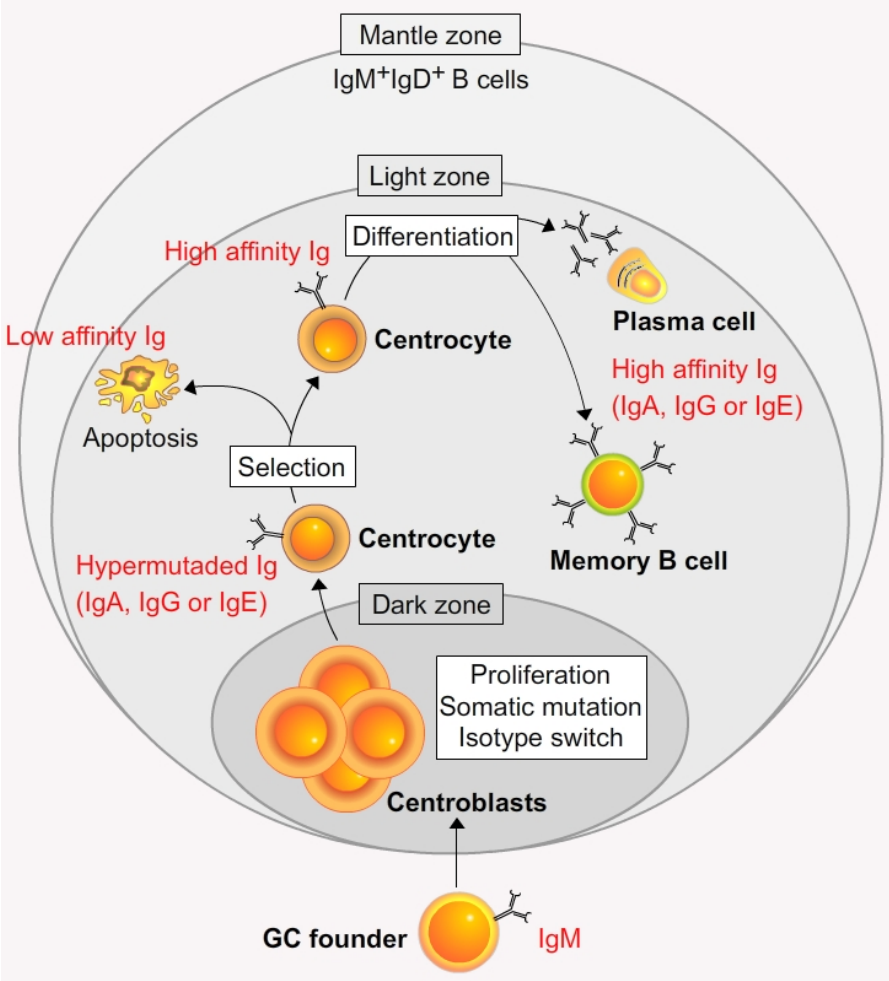
This process introduces point mutations in the V regions of immunoglobulins, and thus generates B cell variants with new affinity or new specificity.

- Class switch recombination (CSR) (Dark zone)

This event changes the class of heavy chain of Ig to be produced (from IgM to the IgG, IgA, or IgE isotypes). This is initated in the dark zone.

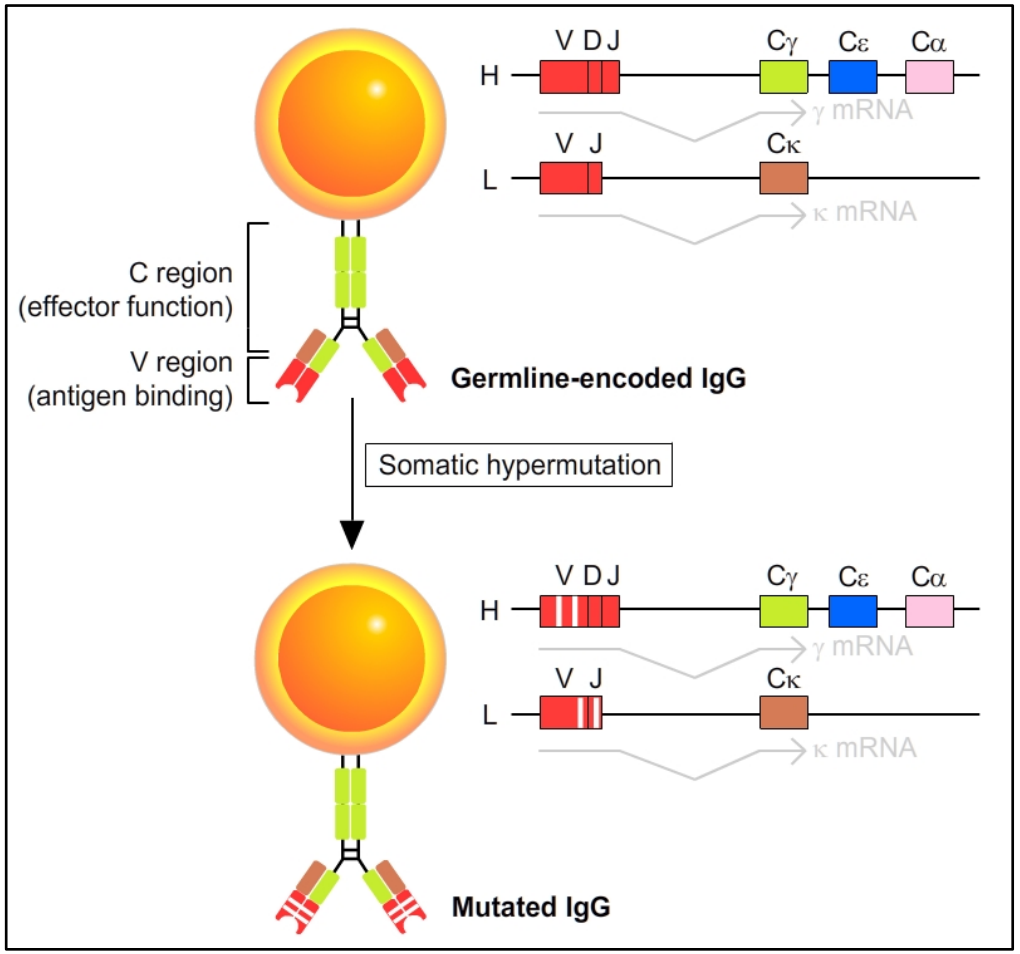
- B cell selection (Light zone)

This process serves to select for B cell variants with high affinity (positive selection) and to eliminate those with low affinity or self-reactivity (negative selection).



Affinity maturation: Somatic hypermutation

- Somatic hypermutations (SHM) operate by introducing point mutations into the variable region of both heavy and light chains that encode the antigen-binding site of Ig molecules.
- SHMs change the affinity of the antigen-binding sites of Igs and thus potentially increase the affinity for the immunizing antigen.
- Mediated by the activation-induced-deaminase (AID) which transforms cytosine to uracil. AID can induce mutations in genes that are highly transcribed even in heterologous systems.



Affinity maturation: B cell selection

B cell selection serves 3 functions:

- to rescue B cell variants with high affinity for the stimulating Ag

Two cell types provide survival signals to B cells:

  - Follicular dendritic cells (FDC) provide new antigens to be internalized by the antibody
  - Antigen-primed CD4 T cells send the survival signals

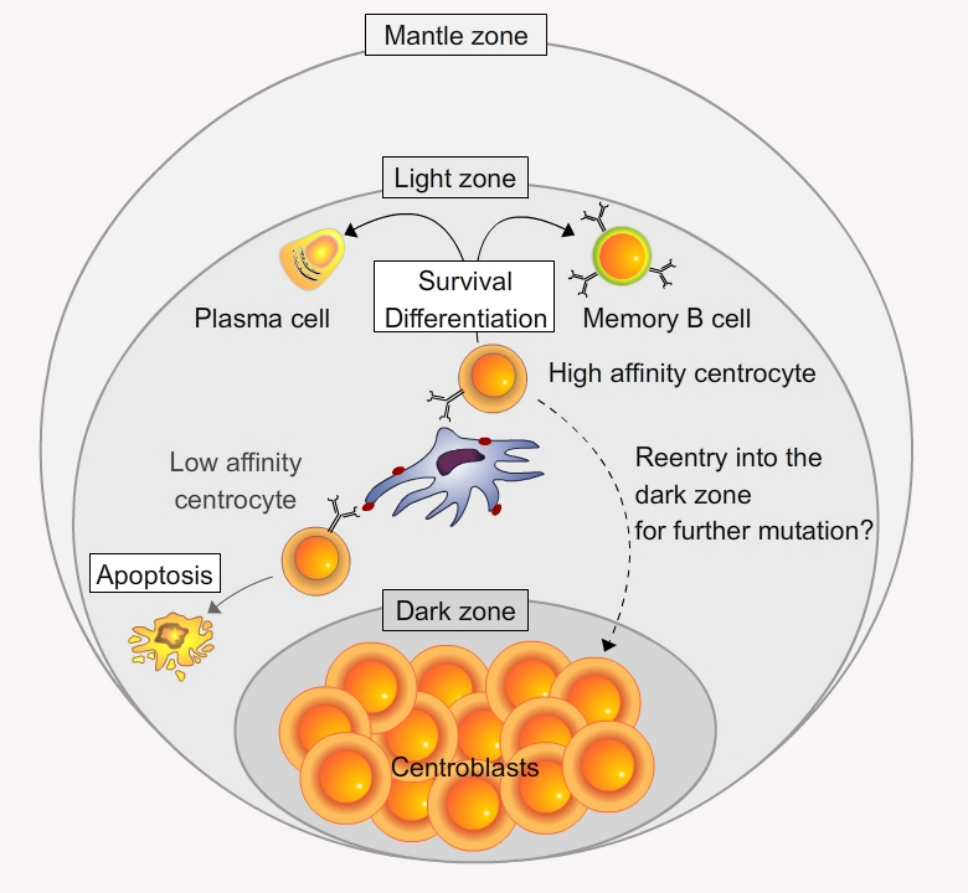
- to eliminate B cell variants with low affinity

Low-affinity B cell variants have no chance to contact antigen on FDCs and present it to antigen-specific GC T helper cells. They thus die by neglect (they do not receive a survival signal).

- to eliminate B cell variants with self-reactivity

1. lack of specific T help in the GC

2. constant stimulation of self-reactive B cells with self-antigen, which leads to apoptosis.

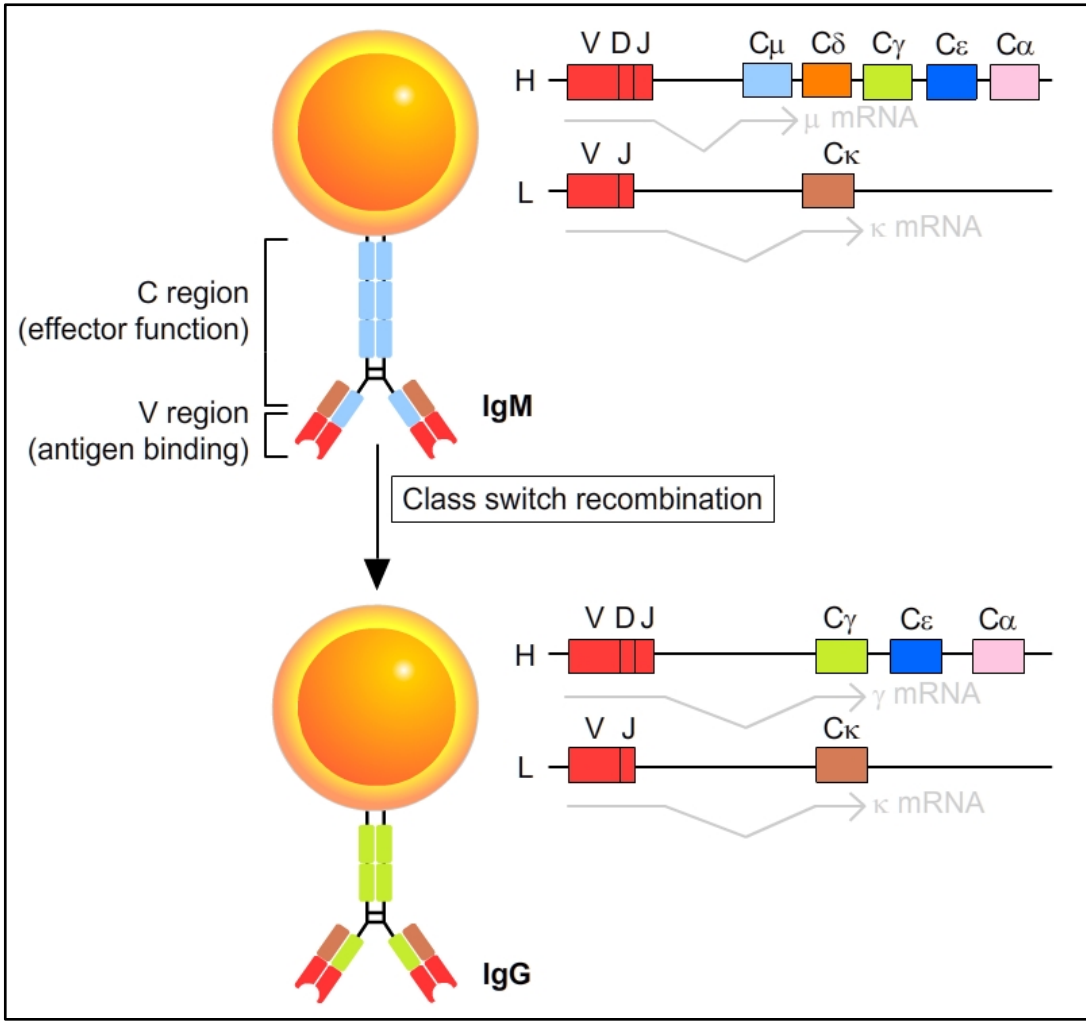


Summary | Affinity maturation

- 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. This increase in affinity is due to point mutations in the V regions, and particularly in the antigen-binding hypervariable regions, of the antibodies produced.
- Affinity maturation is seen only in responses to helper T cell-dependent protein antigens.
- 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 by antigen. Some of the progeny of activated B lymphocytes enter lymphoid follicles and form germinal centers. Within these germinal centers, the B cells proliferate rapidly, with a doubling time of approximately 6 hours, so that one cell may produce about 5000 progeny within a week. (The name "germinal center" came from the morphologic observation that some follicles have central regions that stain lightly because they contain large numbers of dividing cells, once believed to be sites of production of lymphocytes.) During this proliferation, the Ig genes of the B cells undergo numerous point mutations. The enzyme AID also plays a critical role in somatic mutation by changing nucleotides in the Ig genes and making them susceptible to the mutational machinery. The frequency of Ig gene mutations is estimated to be one in 10^3 base pairs per cell per division, which is 1000-fold greater than the mutation rate in most other genes.
- 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.
- Germinal center B cells die by apoptosis unless they are rescued by antigen recognition or T cell help. At the same time as somatic hypermutation of Ig genes is going on in germinal centers, the antibody that was secreted earlier during the immune response binds residual antigen. The antigen-antibody complexes that are formed may activate complement. These complexes are displayed by cells, called follicular dendritic cells, that reside in 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. Thus, B cells that have undergone somatic hypermutation are given a chance to bind antigen on follicular dendritic cells and be rescued from death. B cells may also bind free antigen, process it, and present peptides to germinal center helper T cells, which then provide survival signals.
- As the immune response to a protein antigen develops, and especially with repeated antigen exposure, the amount of antibody produced increases. As a result, the amount of available antigen 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. The selected B cells leave the germinal center and secrete antibodies, resulting in increasing affinity of the antibodies produced as the response develops.

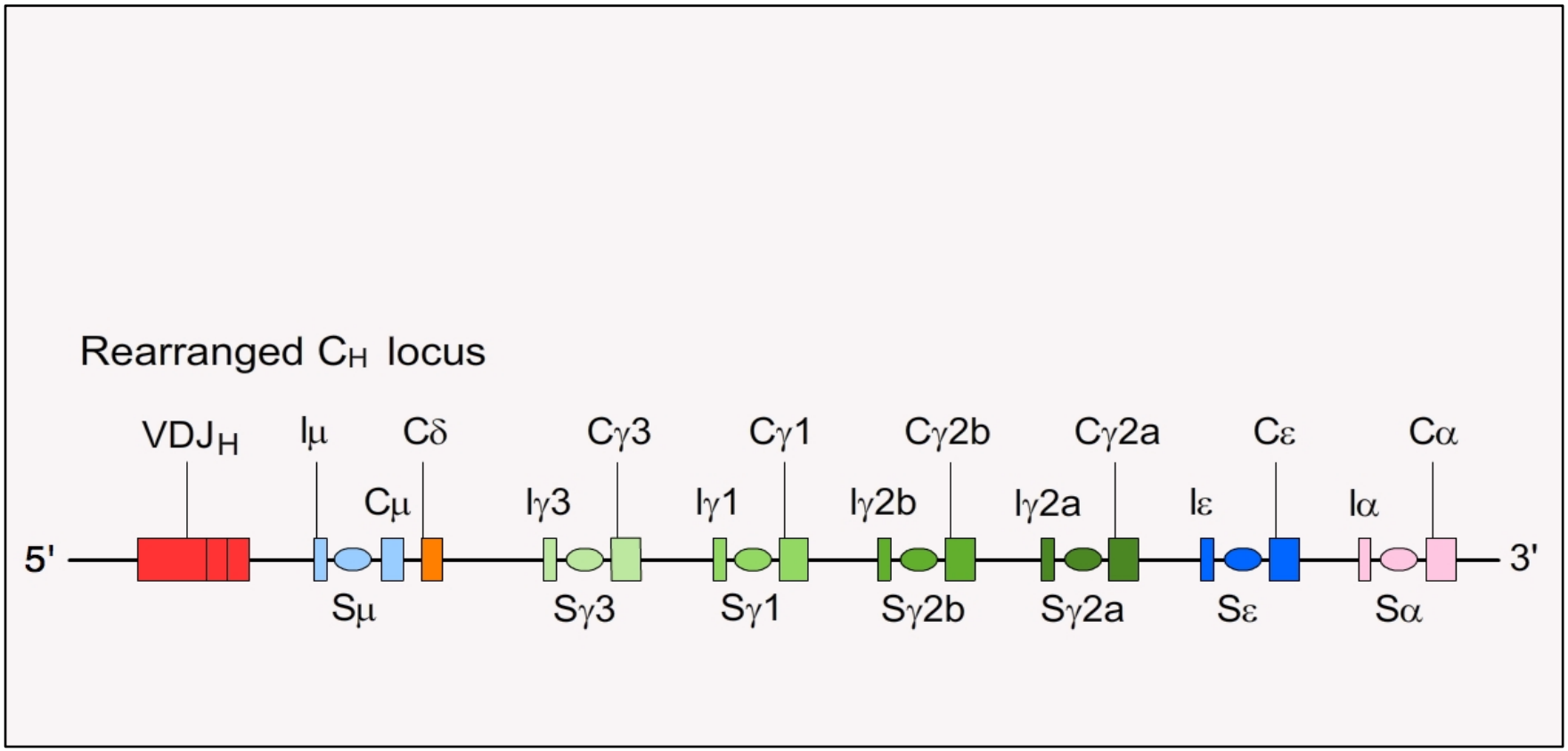
Class switch recombination (CSR)

- Class switch recombination (CSR) enables B cells **to change their isotype** from IgM to other isotypes (IgG, IgE or IgA) without changing their antigen-binding specificity.
- CSR is a **deletional recombination** reaction that juxtaposes the rearranged VDJH exon from Cμ to one of the downstream CH genes such as Cγ, Cε or Cα.



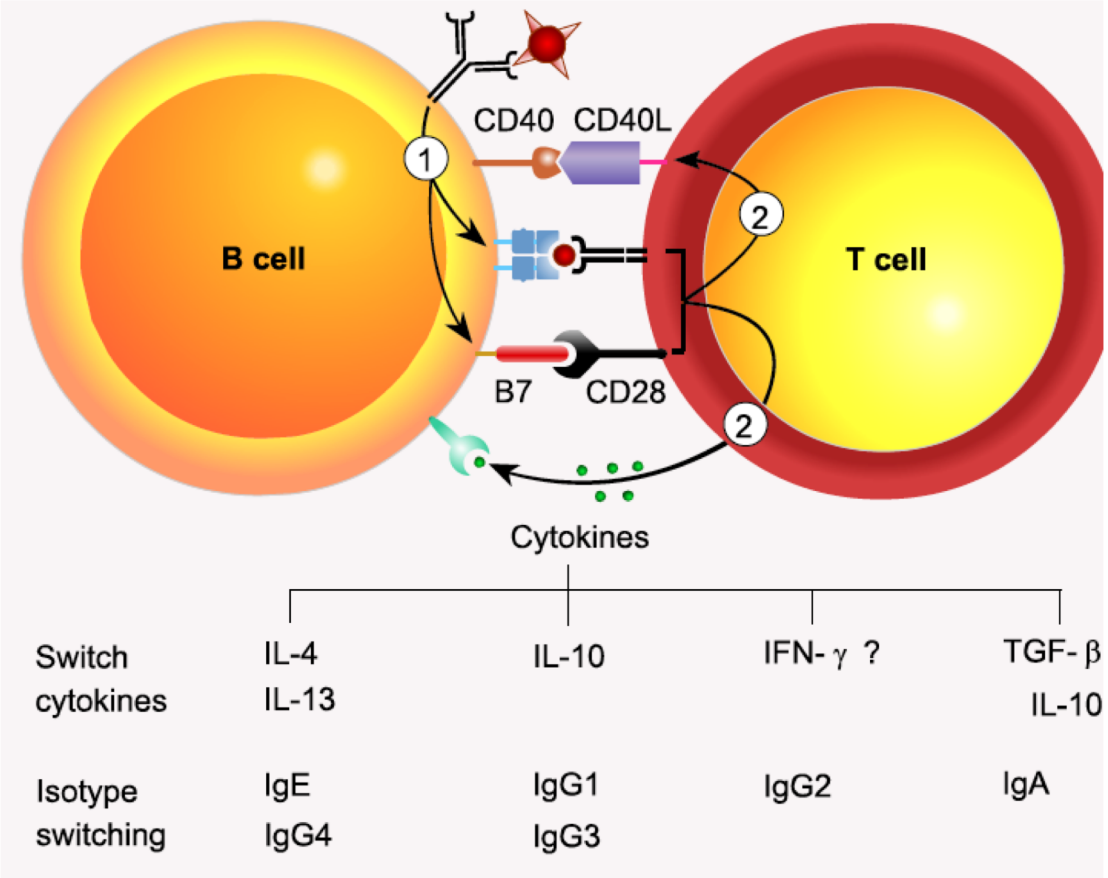
Class switch recombination (CSR)

Isotype switching is not random but **regulated by cytokines** that open the chromatin of the two participating S regions.



Class switch recombination

- Switching cytokines are produced by antigen-specific activated T cells.
- Cytokines elicit the type of antibody that is appropriate to fight the type of pathogen encountered.

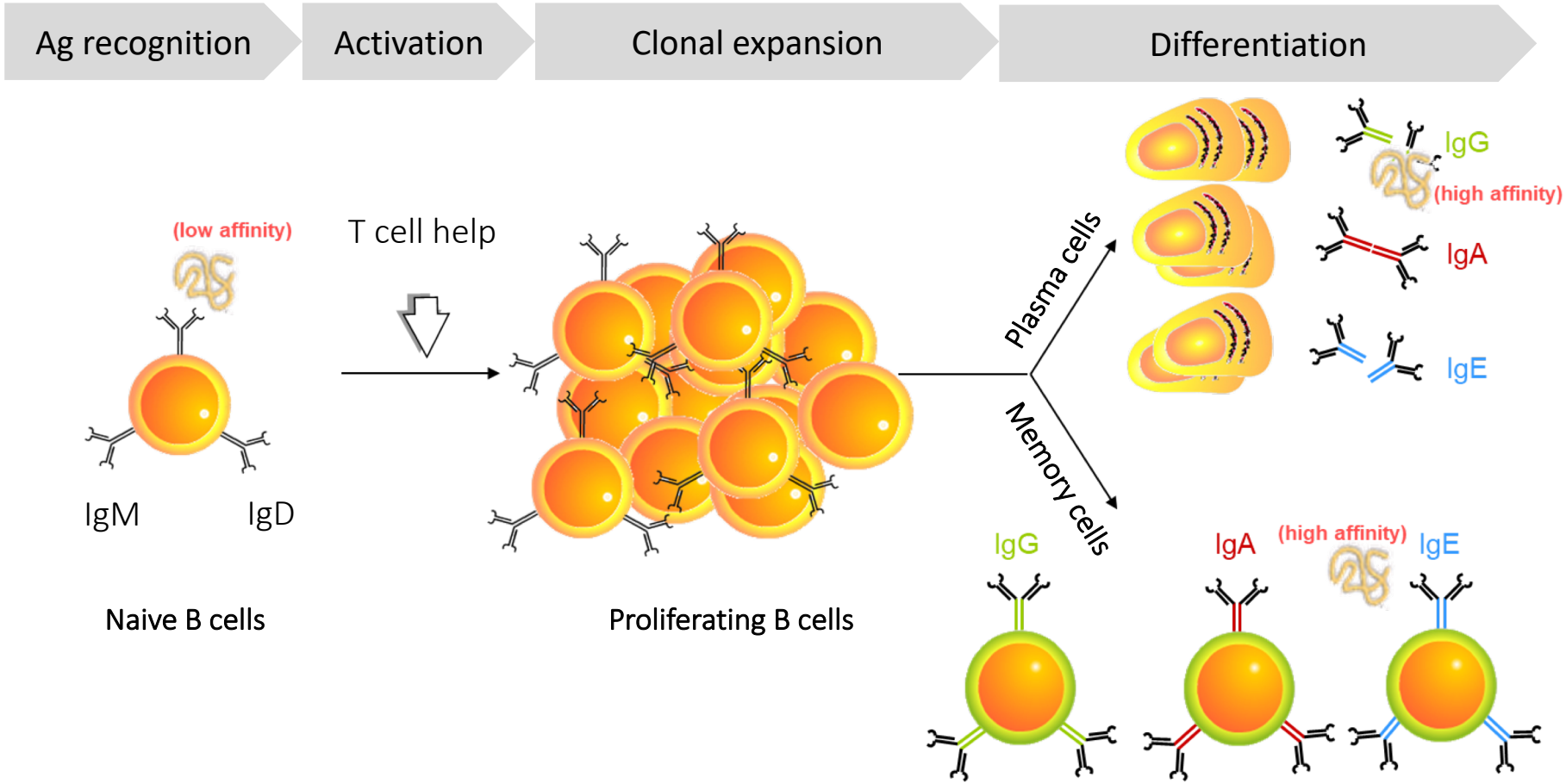


(in humans)

Summary | Heavy Chain Isotype (class) switching

- Helper T cells stimulate the progeny of IgM and IgD-expressing B lymphocytes to produce antibodies of different heavy chain isotypes.
- Heavy chain isotype switching is induced by a combination of CD40L-mediated signals and cytokines. In the absence of CD40 or CD40L, B cells secrete only IgM and fail to switch to other isotypes, indicating the essential role of this ligand-receptor pair in class switching.
- The molecular basis of heavy chain isotype switching: IgM-producing B cells, which have not undergone switching, contain in their Ig heavy chain locus a rearranged VDJ gene adjacent to the first constant region cluster, which is Cμ. Thus, the first antibody produced by B cells is IgM. Signals from CD40 and cytokine receptors stimulate transcription through one of the constant regions that is downstream of Cμ. In the intron 5' of each constant region (except Cδ) is a conserved nucleotide sequence called the switch region. When a downstream constant region becomes transcriptionally active, the switch region 3' of Cμ recombines with the switch region 5' of that downstream constant region, and the intervening DNA is deleted. The enzyme called activation-induced deaminase (AID) plays a key role in these events by making nucleotides susceptible to cleavage and thus accessible to recombination. Predictably, CD40 signals induce the expression of AID. This process is called switch recombination. It brings the rearranged VDJ adjacent to a downstream C region. The result is that the B cell begins to produce a new heavy chain isotype (which is 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 rearranged VDJ).
- Cytokines produced by helper T cells determine which heavy chain isotype is produced. For instance, the production of opsonizing antibodies, which bind to phagocyte Fc receptors, is stimulated by interferon (IFN)-γ, the signature cytokine of TH1 cells. By contrast, switching to the IgE class is stimulated by interleukin (IL)-4, the signature cytokine of TH2 cells. Thus, the nature of the helper T cell response to a microbe guides the subsequent antibody response, making it optimal for combating that microbe. These are excellent examples of how different components of the immune system are regulated in a coordinated fashion 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 nature of antibody isotypes produced is also influenced by the site of immune responses. For instance, IgA antibody is the major isotype produced in mucosal lymphoid tissues.

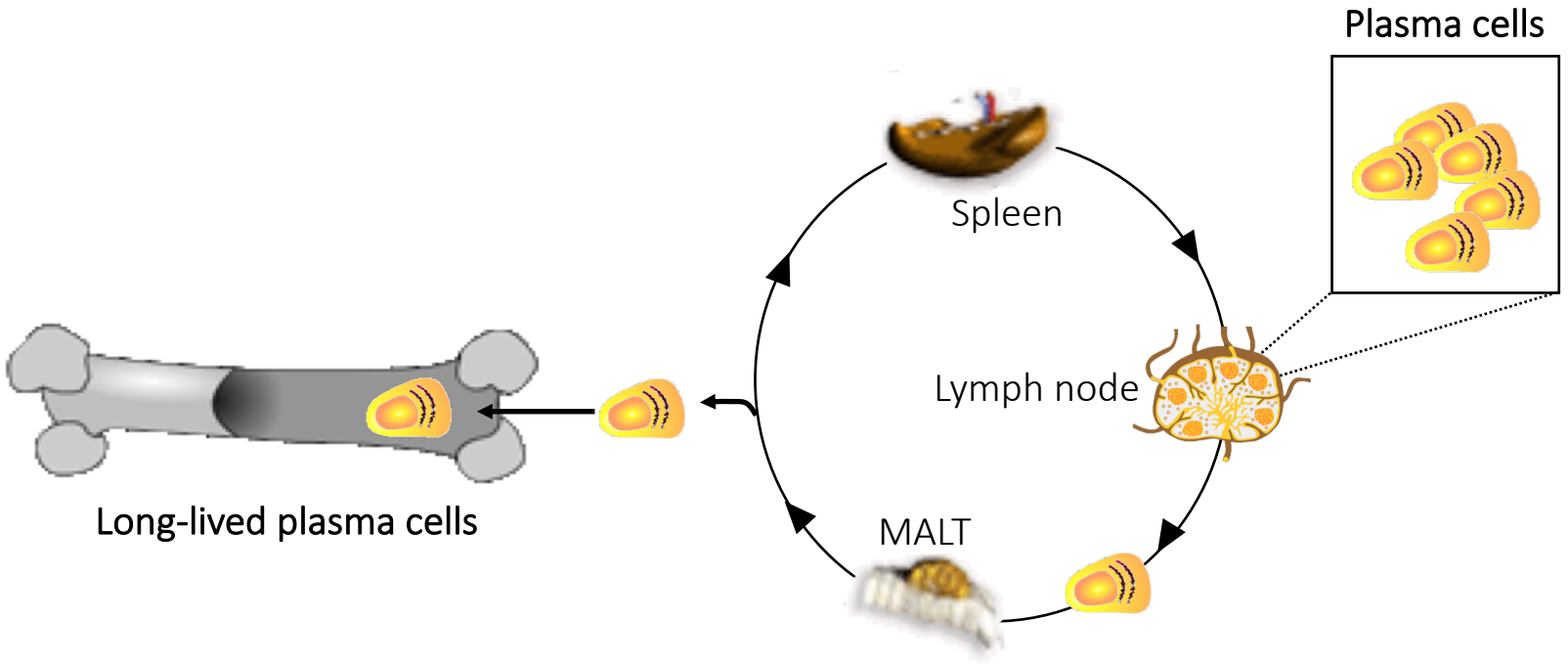
Germinal center reaction: consequences



- The follicular reaction gives rise to class-switched plasma cells and memory B cells. Memory B cells no longer express membrane-bound IgD and IgM. Instead, they carry membrane-bound Igs with IgG, IgA or IgE heavy chains.
- The follicular reaction gives rise to high-affinity Igs.

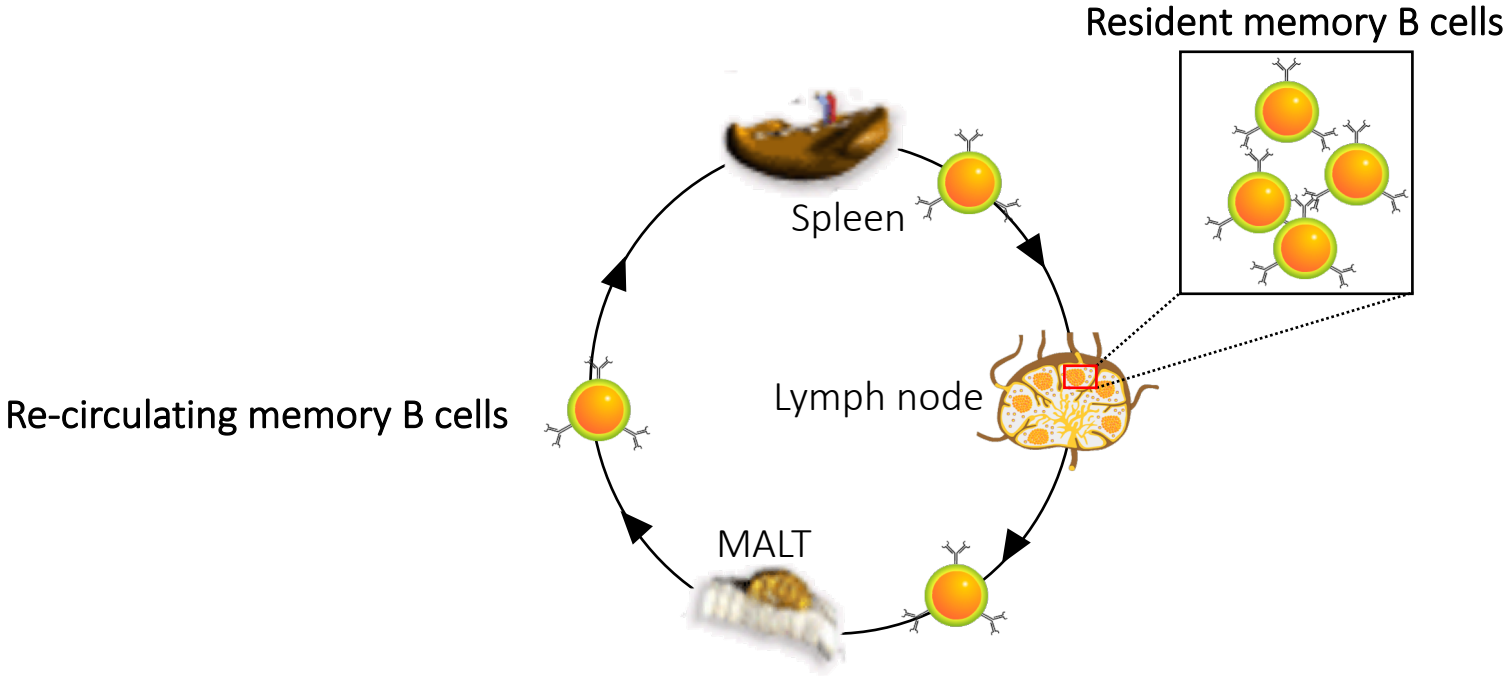
Follicular plasma cells

- Follicular plasma cells go to survival niches such as the bone marrow.
- Follicular plasma cells continually produce secreted antibodies which make an important contribution to the maintenance of serum antibody levels for a long time after antigen exposure and protect the host against re-infection.



Memory B cells

- Memory B cells may stay in the lymphoid organ where they were primed or recirculate between secondary lymphoid organs, like naive B cells.
- Memory B cells survive for years. Upon re-exposure to the same antigen, they re-expand and re-express effector functions faster than naive lymphocytes.



T-dependent B cell response | The follicular reaction

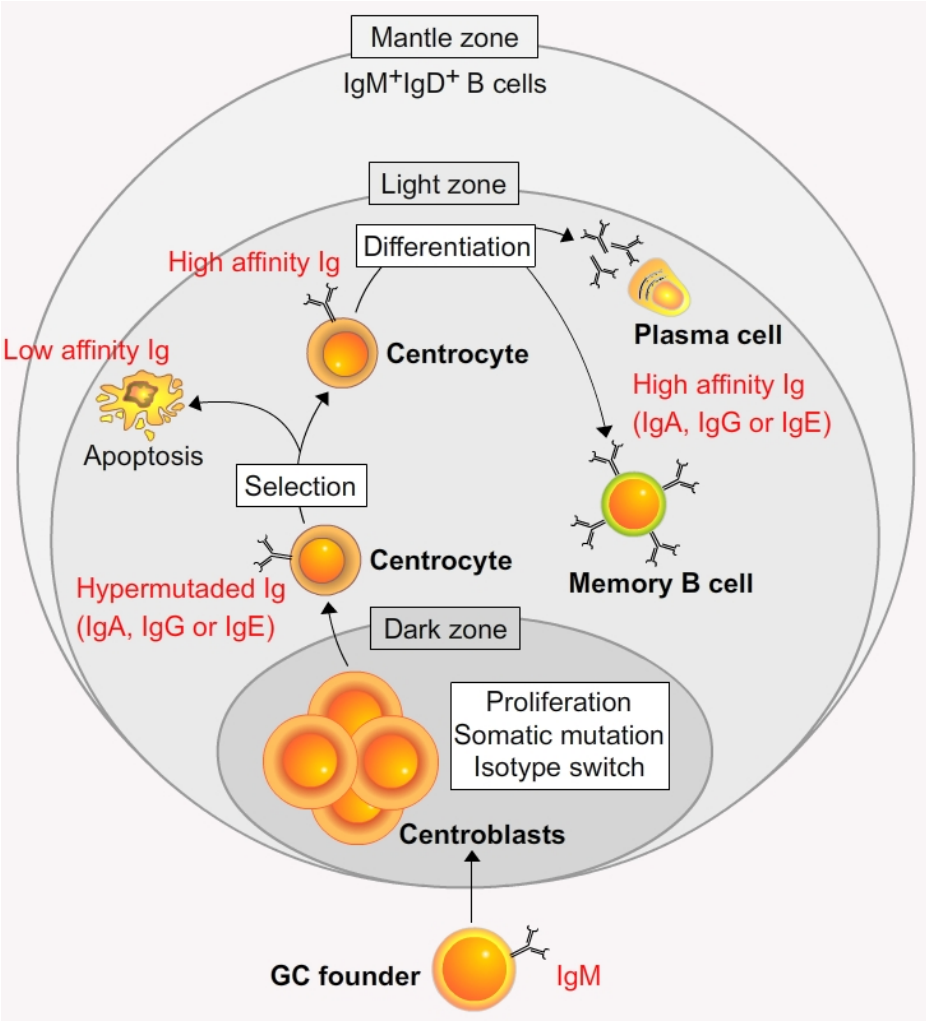
Signal 1 and 2 lead to B cell clonal expansion and to differentiation (extrafollicular and follicular reaction).

Extrafollicular reaction:

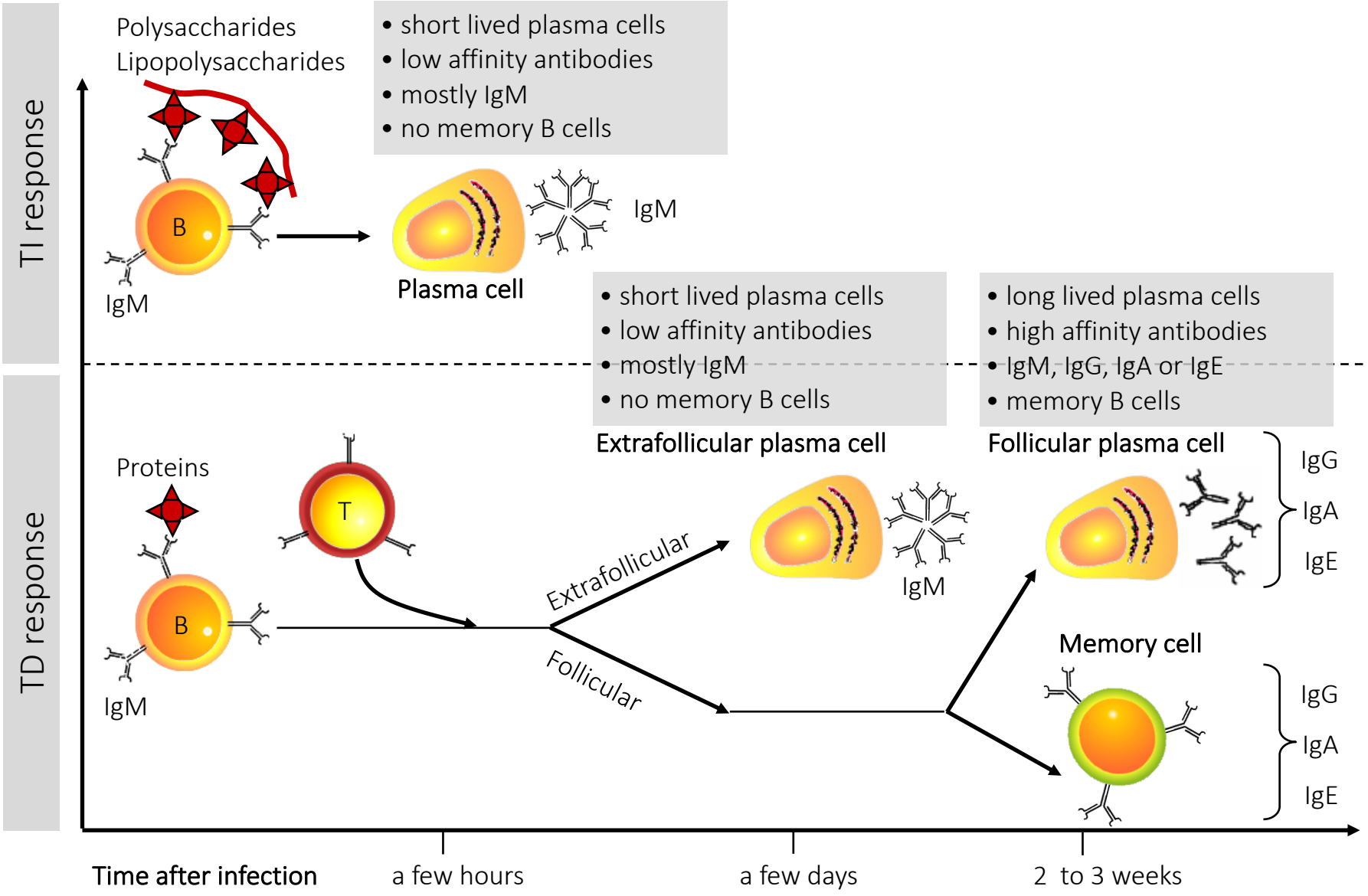
- A group of B cells immediately differentiate into plasmatocytes producing IgM
- Rapid, no memory, low affinity
- Provides a first line of defense

Follicular reaction: several phases

- B cells actively divide in the follicle
- Somatic hypermutation increases Ig affinity
- Class switch recombination (IgM → IgA, IgG or IgE)
- Selection (FDC, Th) ensures the specificity of the response
- Gives rise to memory B cells with high affinity
- Involves irreversible DNA modification
- Takes place in the germinal center of secondary lymphoid organs



Conclusion | B cell responses



7.3 Effector phase

7.3.1 Neutralization

7.3.2 Complement activation

7.3.3 Opsonization

7.3.4 ADCC

7.3.5 Transcytosis and IgA

Antibodies: effector functions

- Antibodies mediate effector functions:
  - at distance from their site of induction by circulating in the bloodstream and extracellular fluids
  - only when bound to the antigen that induced their formation
  - can cross epithelial barriers (i.e. transcytosis)

- Not all antibodies mediate all effector functions: antibody-mediated effector functions are dictated by their heavy chain isotype.

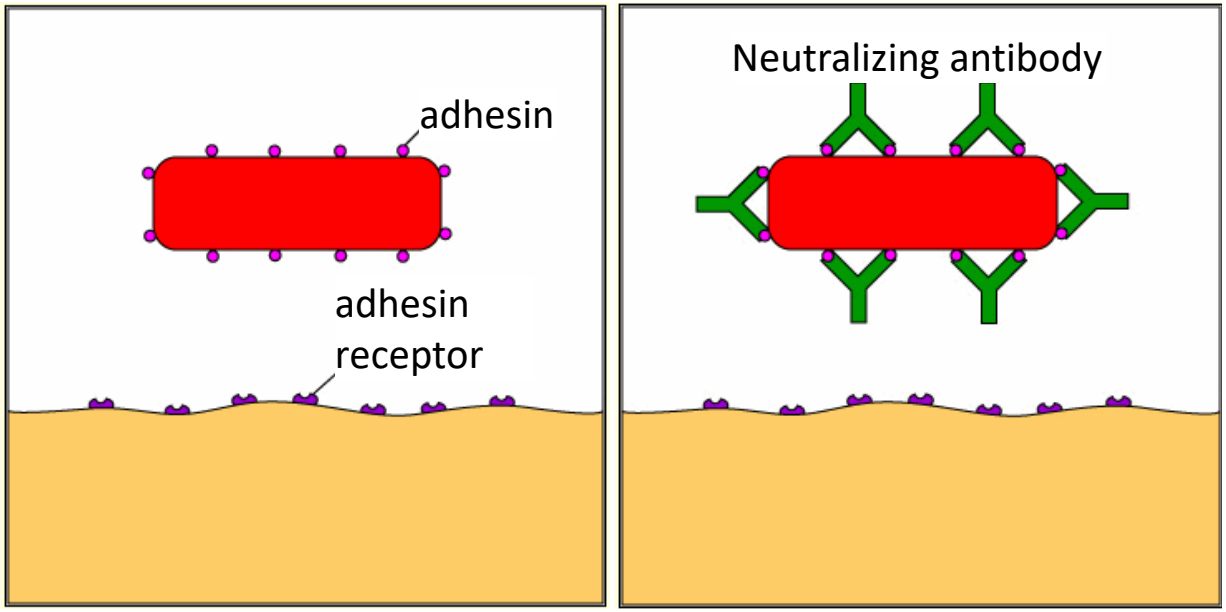
- Antibody effector functions include:
  - neutralization
  - complement activation
  - opsonization
  - ADCC (antibody-mediated cell-dependent cytotoxicity)
  - mastocyte activation

Antibody function: Neutralization

Process whereby antibodies

- bind to bacteria and viruses and inhibit their infectivity.
- interfere with the biological activities of bacterial toxins by preventing their interaction with their cellular receptor.
- **IgM and high-affinity IgG and IgA** are efficient for neutralization.

Isotype	Pathogen neutralization
IgM	+
IgD	-
IgG	+
IgA	+
IgE	-

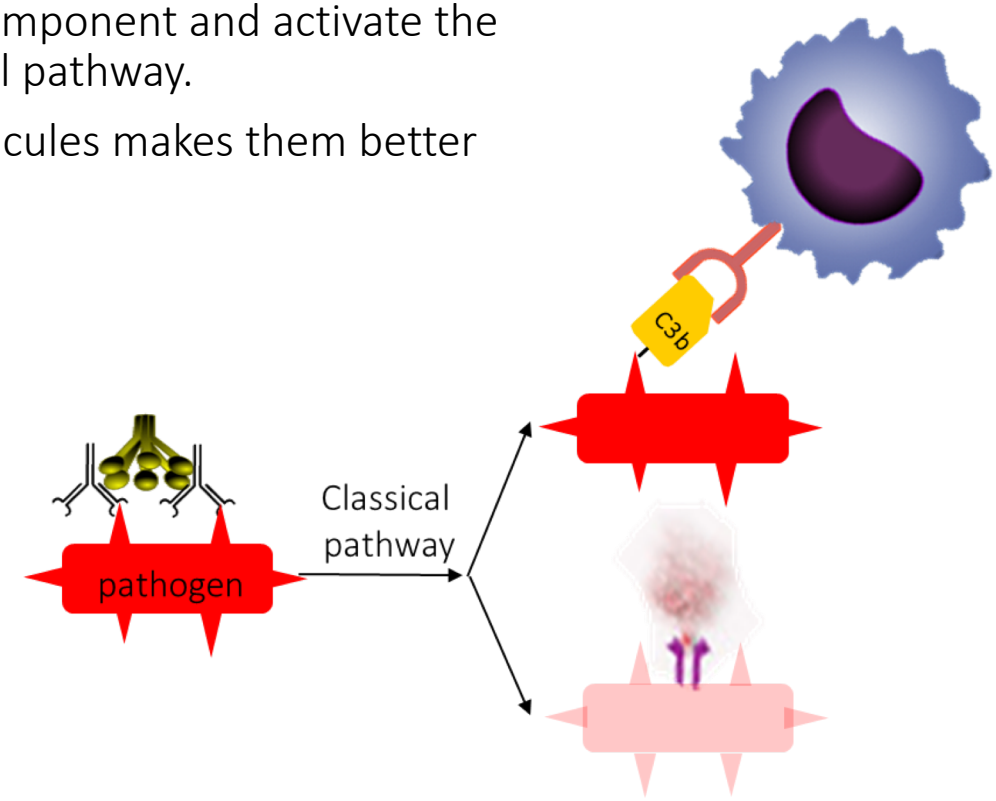


Antibody function: Complement activation

Process whereby antibodies

- bind to pathogens, fix **C1q component**, and activate the complement cascade via the **classical pathway**
- trigger the covalent **deposition of C3b** components onto pathogens, which prepares them for ingestion by phagocytes.
- promote **assembly of the membrane attack complex (MAC)** and the death of pathogen by osmotic lysis
- Only **IgM and IgG** can fix the C1q component and activate the complement system via the classical pathway.
- The pentameric nature of IgM molecules makes them better activators than IgG.

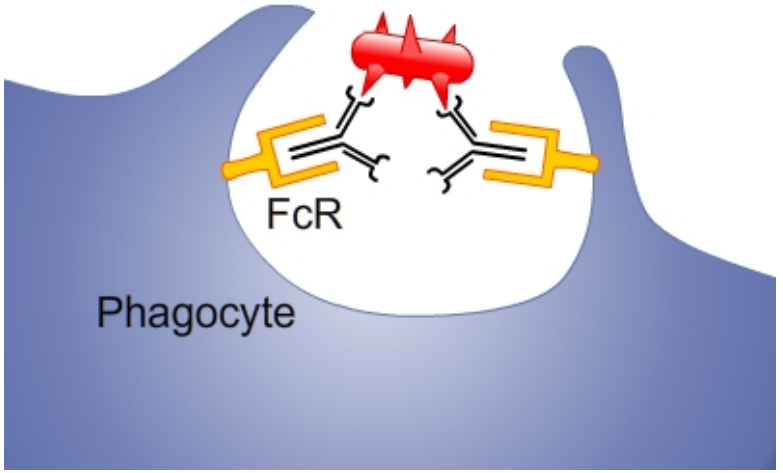
Isotype	Pathogen neutralization	Complement activation
IgM	+	+++
IgD	-	-
IgG	+	+
IgA	+	-
IgE	-	-



Antibody function: Opsonization

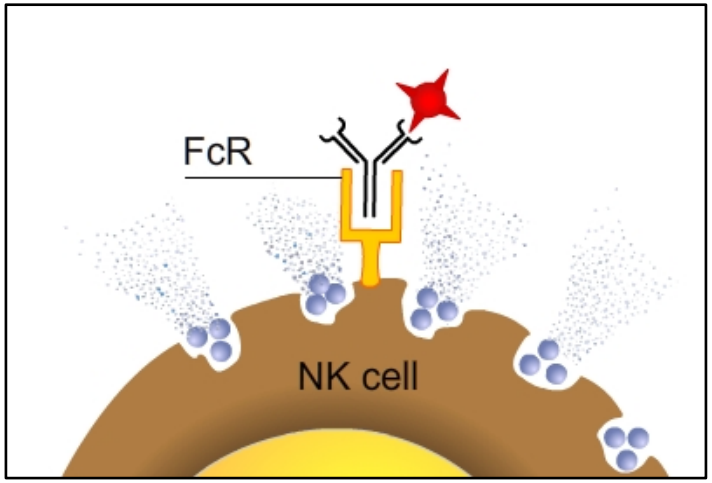
- Stimulates **phagocytosis** by macrophages and neutrophils via FcR.
- Cross-linking of FcR induces signaling which induces bactericidal state of phagocyte (enzymatic digestion, oxidative damage, antibacterial peptides)
- Two Ab classes function as opsonins: **IgG and IgA**
- IgG is a more potent opsonin than IgA

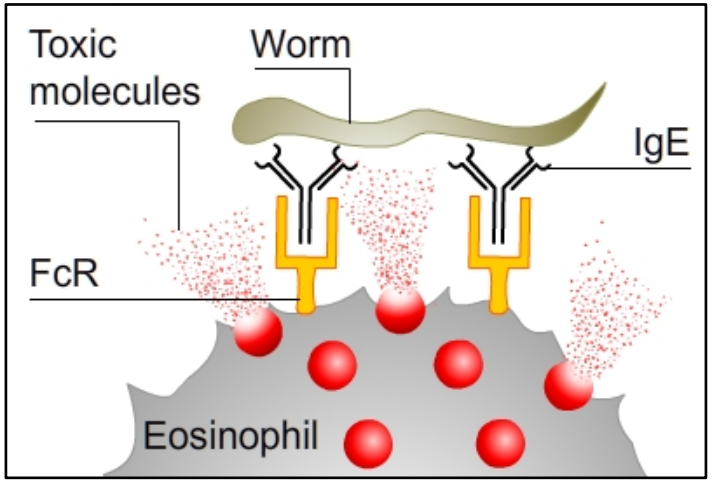
Isotype	Pathogen neutralization	Complement activation	Binding to macrophages
IgM	+	+++	-
IgD	-	-	-
IgG	+	+	+
IgA	+	-	+
IgE	-	-	-



Antibody function: Antibody-dependent cellular cytotoxicity (ADCC)

- process whereby Abs bind to pathogens or infected cells and cause the **degranulation of killer cells**, such as **NK cells and eosinophils**, onto the target cell. ADCC leads to the death of the target.
- Two Ab classes function in ADCC: **IgG and IgE**
  - IgG activates NK cell degranulation
  - IgE activates eosinophil degranulation

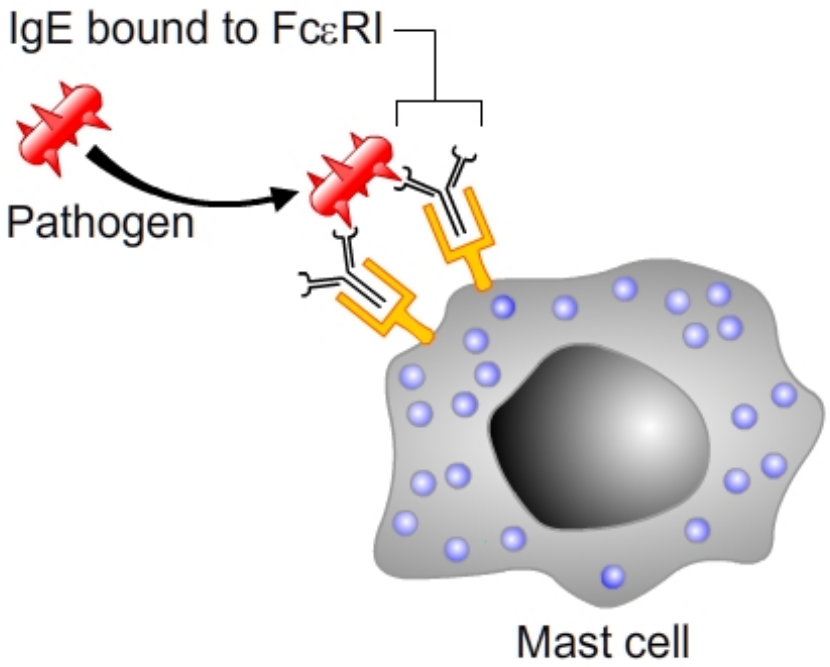




Isotype	Pathogen neutralization	Complement activation	Binding to macrophages	ADCC
IgM	+	+++	-	-
IgD	-	-	-	-
IgG	+	+	+	+
IgA	+	-	+	-
IgE	-	-	-	+

Antibody function: Mast cell degranulation

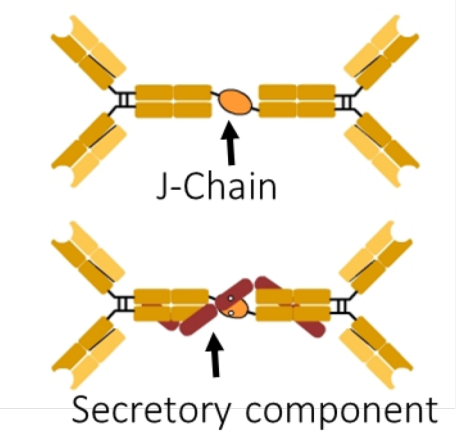
- occurs when IgE pre-bound to FcεR on mast cells are cross-linked by parasitic worms or allergens
- promotes local vascular changes that recruit effector cells and smooth muscle contractions that facilitate worm expulsion



Isotype	Pathogen neutralization	Complement activation	Binding to macrophages	ADCC	Activation of mast cells
IgM	+	+++	-	-	-
IgD	-	-	-	-	-
IgG	+	+	+	+	-
IgA	+	-	+	-	-
IgE	-	-	-	+	+

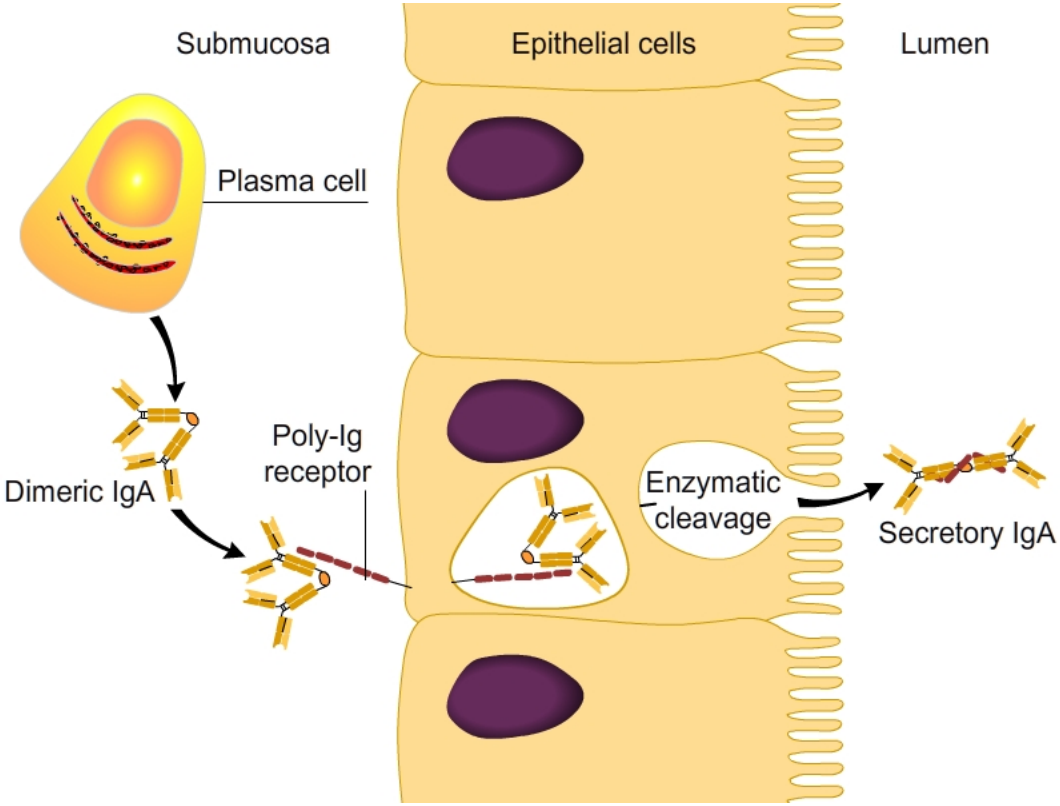
Antibody function: IgA

- 10-15% in serum, predominant in breast milk, saliva, tears, mucus of bronchial, digestive and urogenital tract
- Secretory IgA consists of a dimer or tetramer covalently linked by a J-chain and a secretory component produced by the mucosal epithelium
- Daily production of secretory IgA: 5-15g!
- IgA-secreting plasma cells are concentrated along mucous membrane surfaces (e.g. in jejunum of small intestine: 2.5×10^{10} – these are more plasma cells than in bone marrow, lymph and spleen combined)



Isotype	Pathogen neutralization	Complement activation	Binding to macrophages	ADCC	Activation of mast cells	Serum (%)	Mucosal secretions
IgM	+	+++	-	-	-	10	+
IgD	-	-	-	-	-	0.2	-
IgG	+	+	+	+	-	75	+/-
IgA	+	-	+	-	-	15	+
IgE	-	-	-	+	+	0.004	-

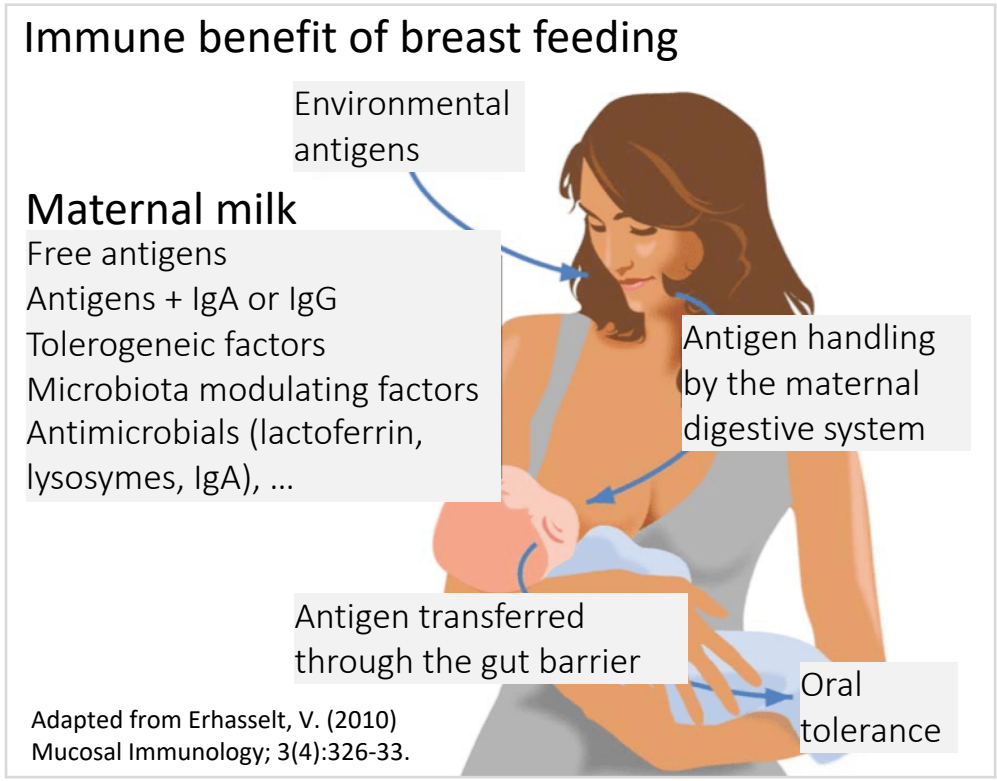
Antibody function: Transcytosis of IgA



- secretory component protects IgA from digestion in protease-rich mucosal environment
- cross-links large epitopes with multiple epitopes
- prevents binding of pathogens to mucosal cells

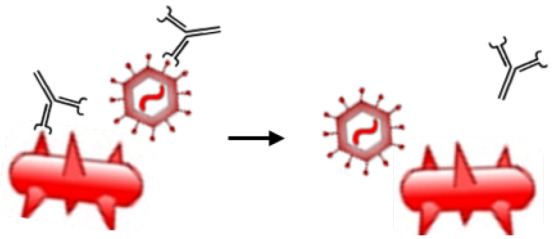
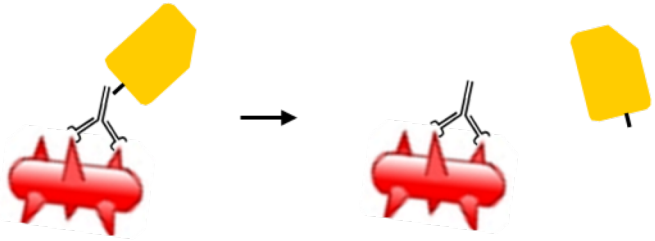
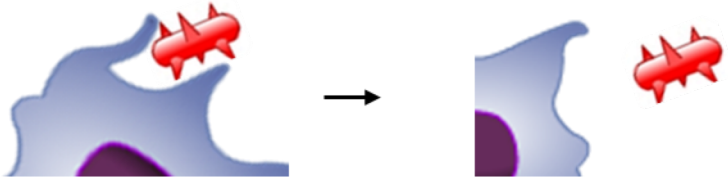
Antibody function: placental transfer

- Some antibodies can cross epithelial layers to reach mucosal surfaces (in respiratory, gastrointestinal and urogenital tracts) and to be exported into breast milk.
- Mostly IgA, but also IgG from mother to child during gestation



Isotype	Pathogen neutralization	Complement activation	Binding to macrophages	ADCC	Activation of mast cells	Serum (%)	Mucosal secretions	Placental transfer
IgM	+	+++	-	-	-	10	+	-
IgD	-	-	-	-	-	0.2	-	-
IgG	+	+	+	+	-	75	+/-	+
IgA	+	-	+	-	-	15	+	-
IgE	-	-	-	+	+	0.004	-	-

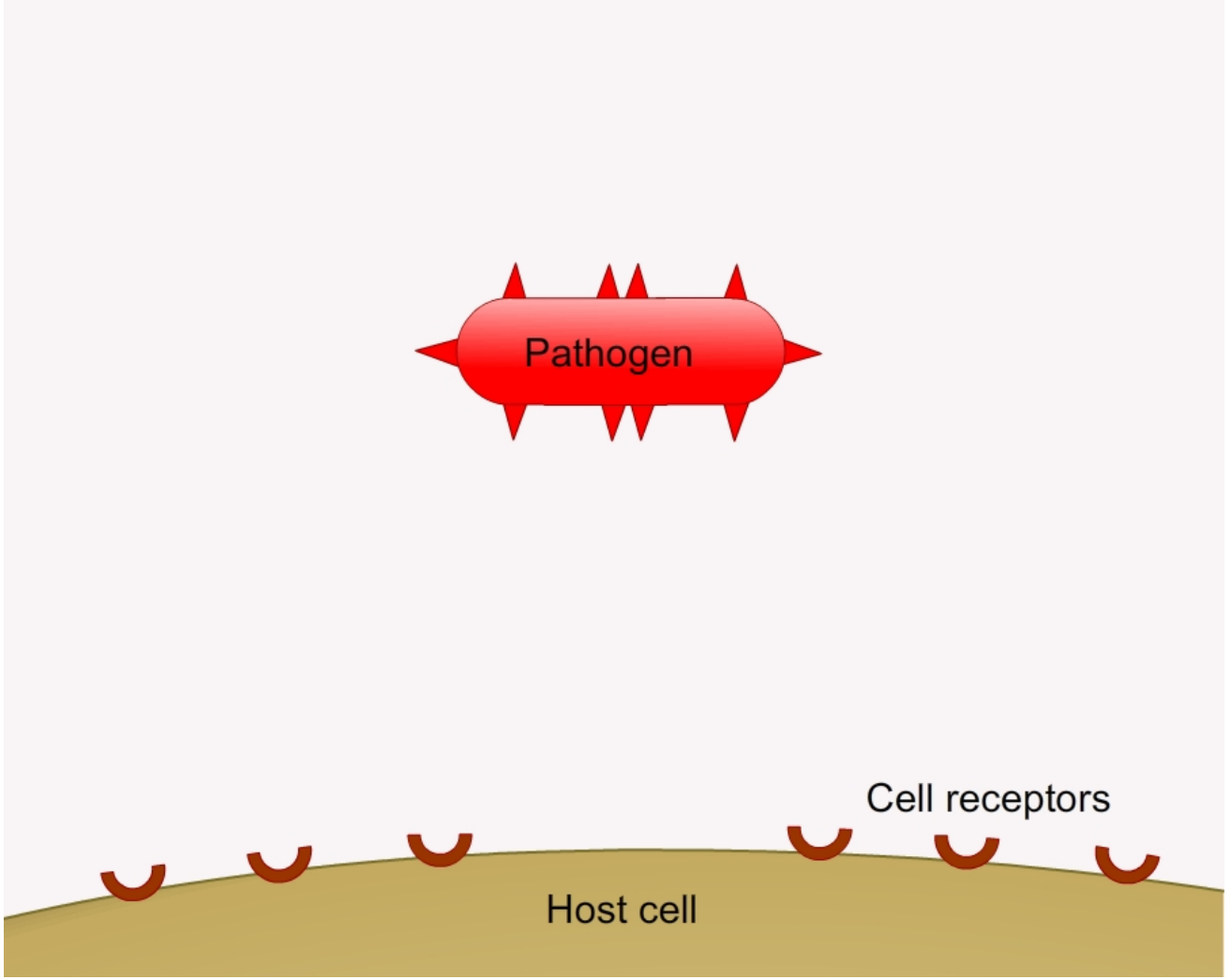
Evasion of humoral immunity by microbes

Mechanism	Example
Antigenic variation	Many viruses (e.g. Influenza, HIV) Bacteria (*Neisseria gonorrhoeae, E. coli, Salmonella typhimurium*) 
Preventing complement activation	Many bacteria 
Escaping phagocytosis	*Pneumococcus* 

Adapted from Abbas, Cellular and Molecular Immunology

Summary | Antibody function

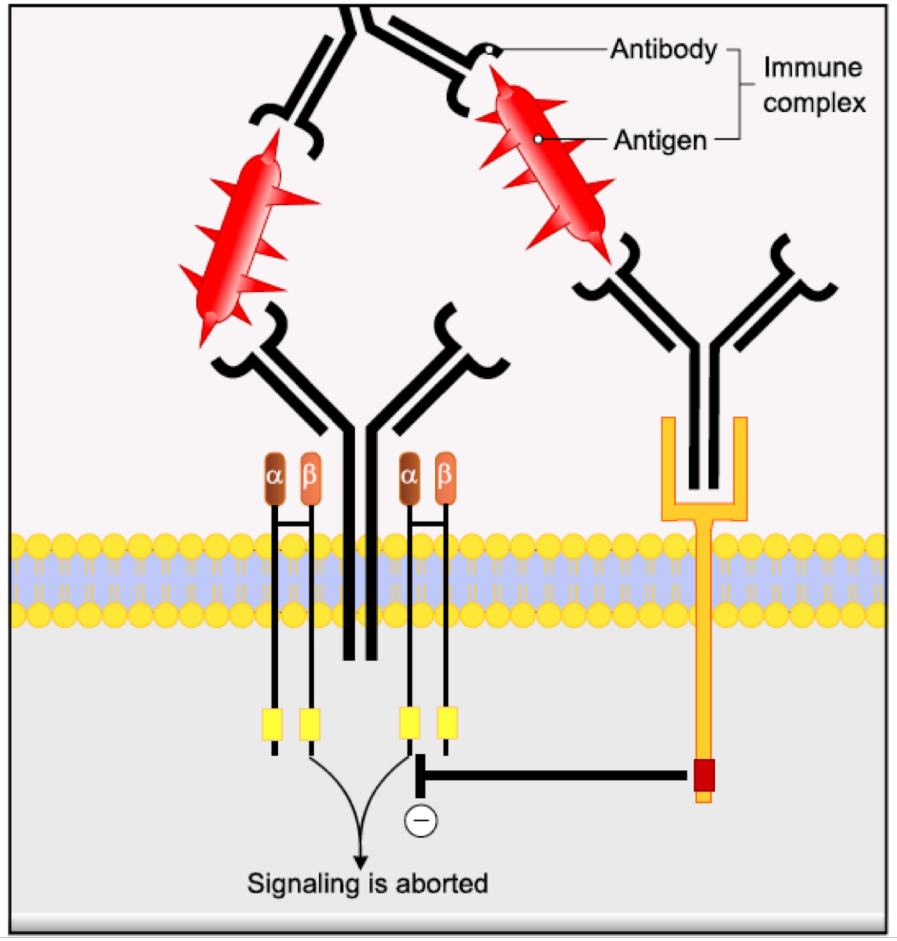
1. Neutralisation
2. Complement activation
   - Phagocytosis (C3b)
   - MAC formation
3. Opsonization
4. ADCC
5. Mast cells degranulation



7.4 Contraction phase

Termination of the B cell response

- B cell responses terminate when IgG-coated antigens, that appear late during primary antibody responses, bind the inhibitory IgG Fc receptor (FcγRIIb) which is constitutively expressed on B cells.
- FcγRIIb opposes B cell receptor (BCR) signaling.



Learning objectives

- B cell activation - Describe the sequence required to generate a B cell response
  - Where and how are antigens sampled and presented to B lymphocytes?
  - Which molecules are involved in triggering a B cell response?
  - How is tolerance induced?
- B cell differentiation - Describe the steps required to trigger a secondary response
  - What is affinity maturation?
  - How are high-affinity BCR bearing B cells selected?
  - What controls the differentiation of B cells into memory / effector cells?
- B cell function - Describe the effector functions mediated by B lymphocytes
  - How do antibodies control microbial infections?
  - How do antibodies activate the complement system?
  - What is opsonization?