Réponses B thymodépendantes et thymoindépendantes

BMC 423 (IF) - 2007

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PLAN

- **B cell development and classification**
- **B cell activation**
- **Thymodependent B(2) cell response**
- **Thymo-independent B cell response**
- **[Antibody effector mechanisms]**

TD vs TI humoral immune responses

- Most antibody (B cell) responses need "help"= "Thymus-Dependent" (TD) responses

  Antigens that activate in this way are said to be thymus-dependent antigens

  "Help" comes from T cells (signal 2)

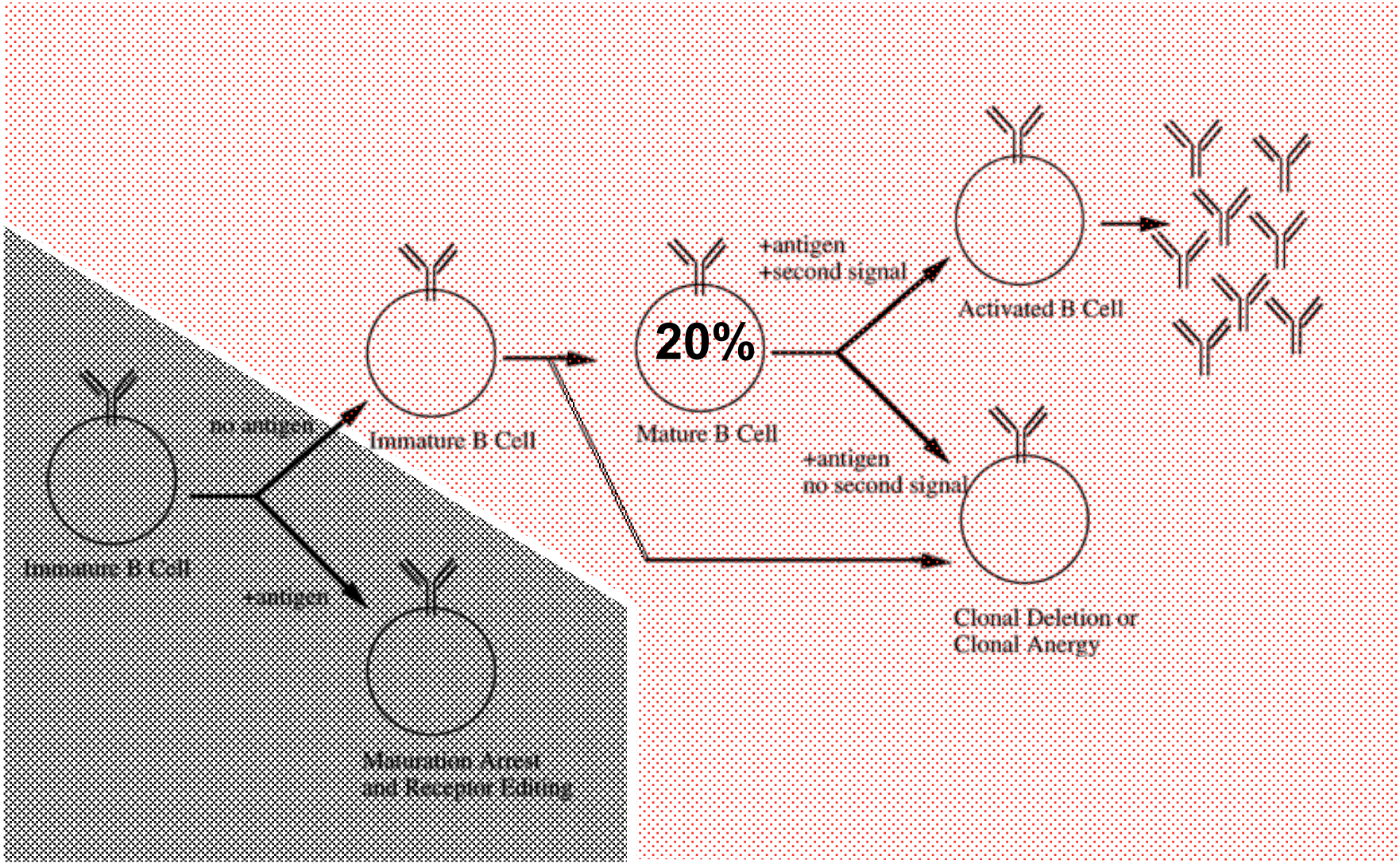
  Most help comes from T_H2 but T_H1 can also provide help

  T help controls or partly controls B cell proliferation, class switching, initiation of somatic mutations and memory

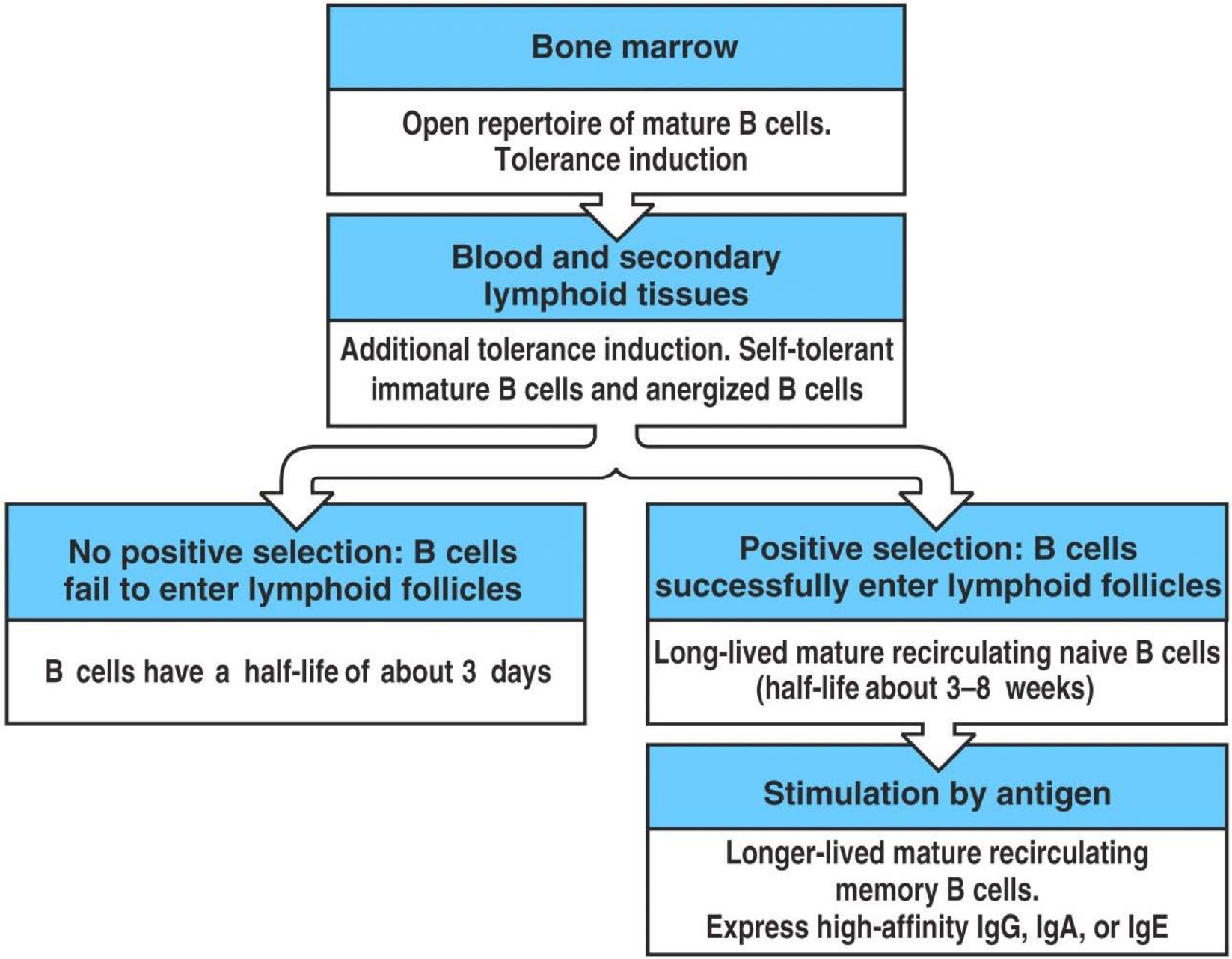
- There are also antibody responses that do not require T help ="Thymus-independent" (TI) antibody responses

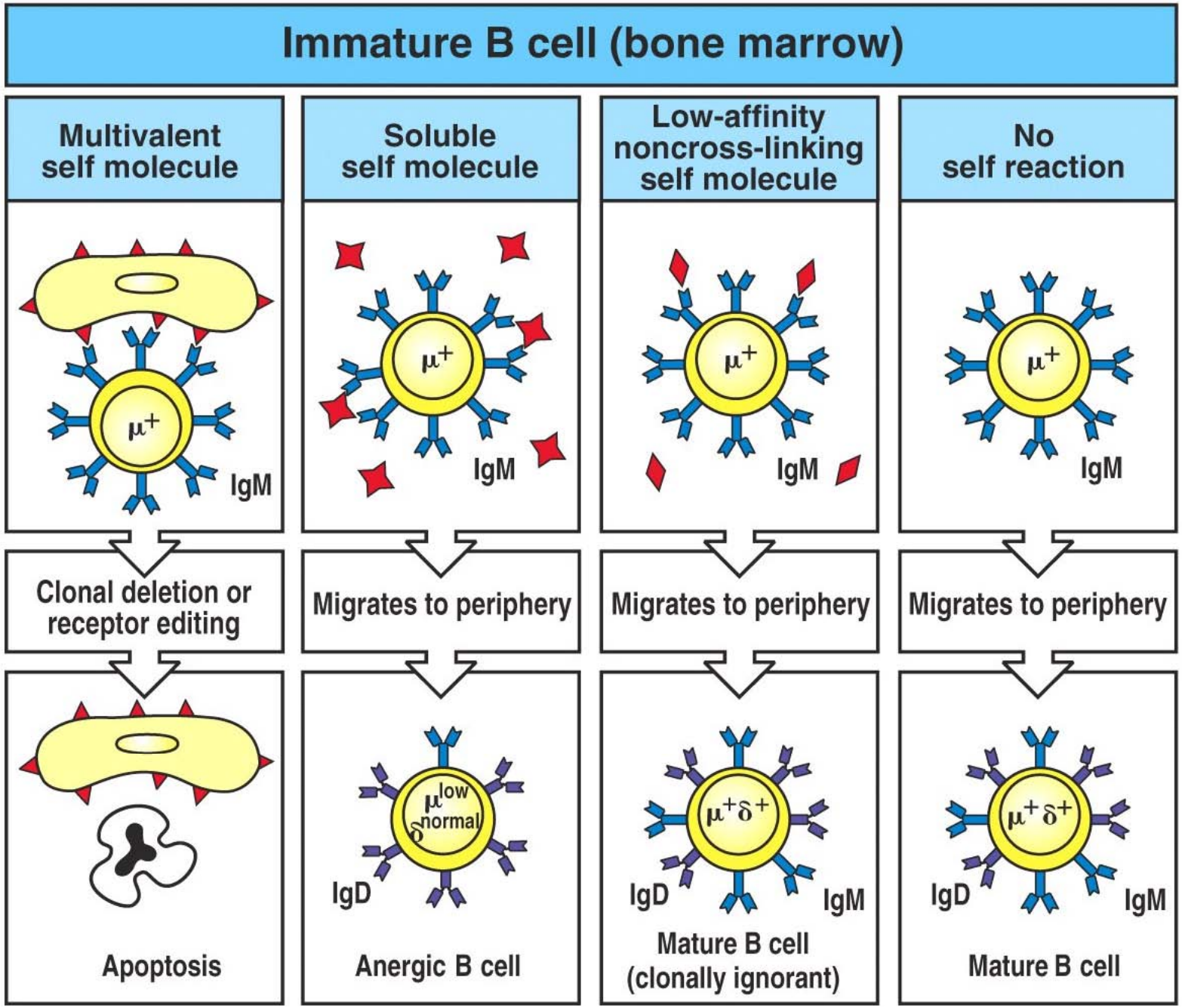
  Antigens that activate in this way are said to be thymus-independent antigens

B cell development and classification



Bone Marrow **Periphery**

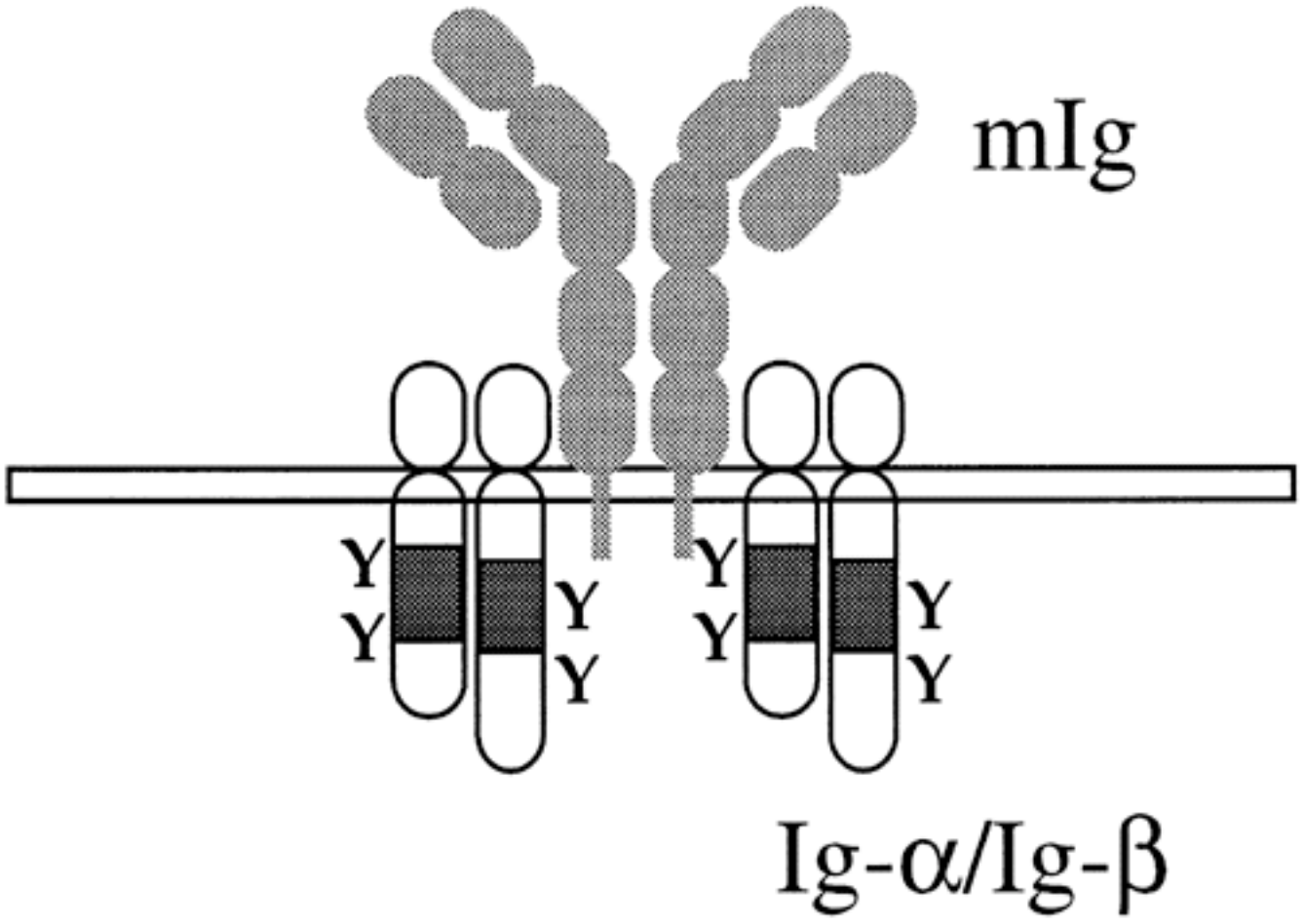

Bone marrow
Open repertoire of mature B cells.
Tolerance induction
Blood and secondary lymphoid tissues
Additional tolerance induction. Self-tolerant immature B cells and anergized B cells
No positive selection: B cells fail to enter lymphoid follicles
B cells have a half-life of about 3 days
Positive selection: B cells successfully enter lymphoid follicles
Long-lived mature recirculating naive B cells (half-life about 3–8 weeks)
Stimulation by antigen
Longer-lived mature recirculating memory B cells.
Express high-affinity IgG, IgA, or IgE


Immature B cell (bone marrow)
Multivalent self molecule
Soluble self molecule
Low-affinity noncross-linking self molecule
No self reaction
μ+
IgM
Clonal deletion or receptor editing
Migrates to periphery
Migrates to periphery
Migrates to periphery
Apoptosis
μlow normal δ+
IgD
Anergic B cell
μ+δ+
IgD
IgM
Mature B cell (clonally ignorant)
Mature B cell

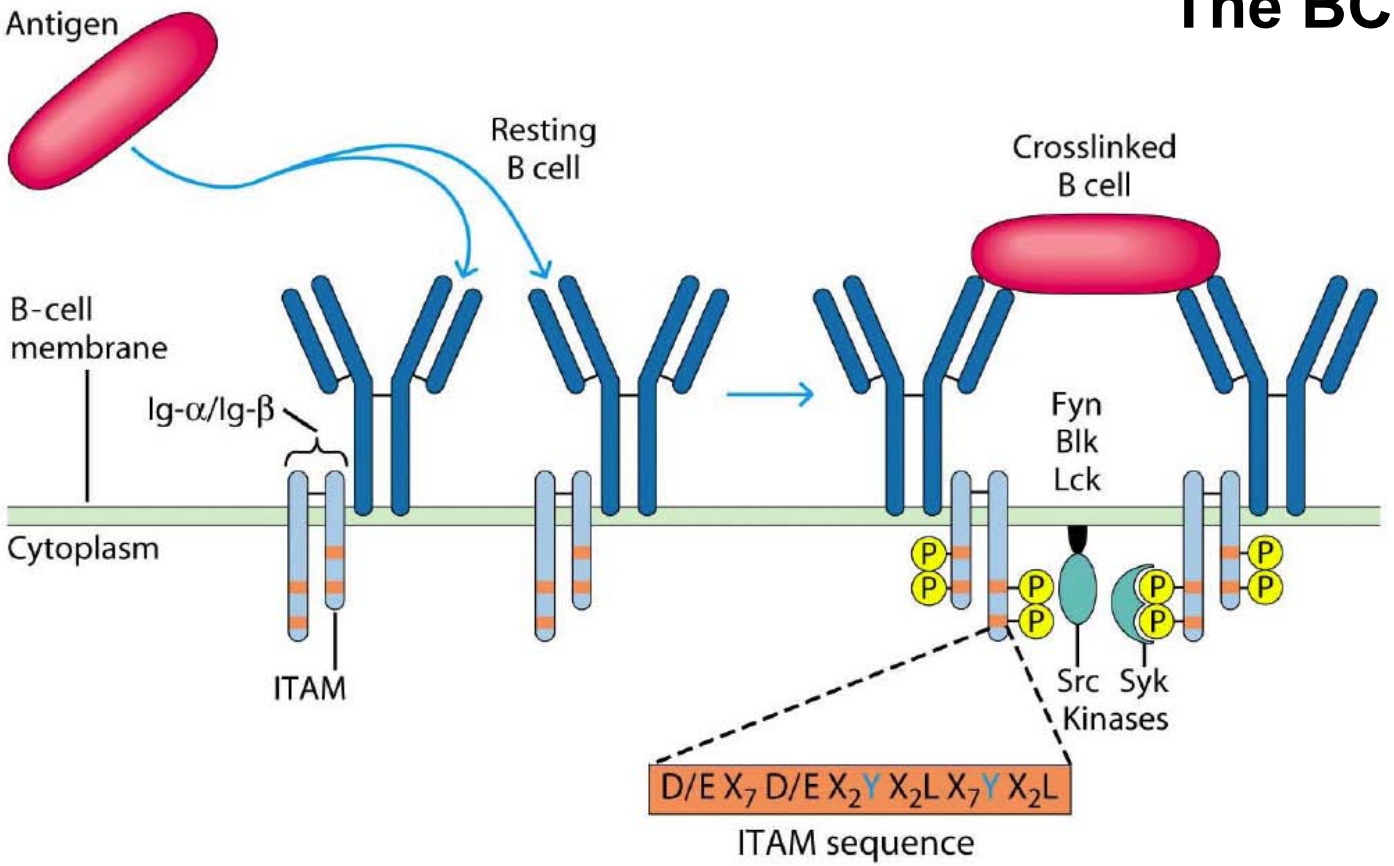
Property	B-1 cells	Conventional B-2 cells	Marginal zone B cells
When first produced	Fetus	After birth	After birth
N-regions in VDJ junctions	Few	Extensive	Yes
V-region repertoire	Restricted	Diverse	Partly restricted
Primary location	Body cavities (peritoneal, pleural)	Secondary lymphoid organs	Spleen
Mode of renewal	Self-renewing	Replaced from bone marrow	Long-lived
Spontaneous production of immunoglobulin	High	Low	Low
Isotypes secreted	IgM >> IgG	IgG > IgM	IgM > IgG
Response to carbohydrate antigen	Yes	Maybe	Yes
Response to protein antigen	Maybe	Yes	Yes
Requirement for T-cell help	No	Yes	Sometimes
Somatic hypermutation	Low–none	High	?
Memory development	Little or none	Yes	?

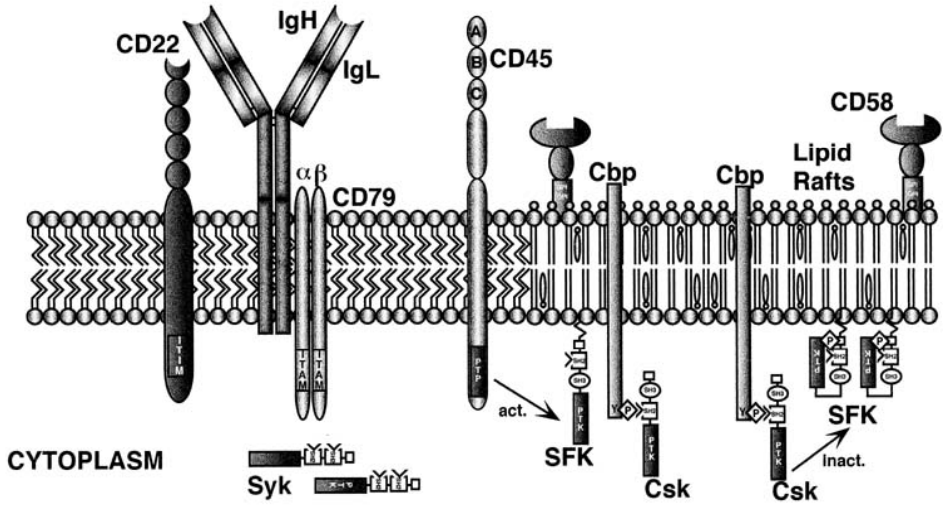
B cell activation

The BCR complex

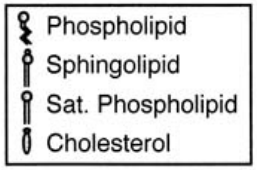


The BCR complex

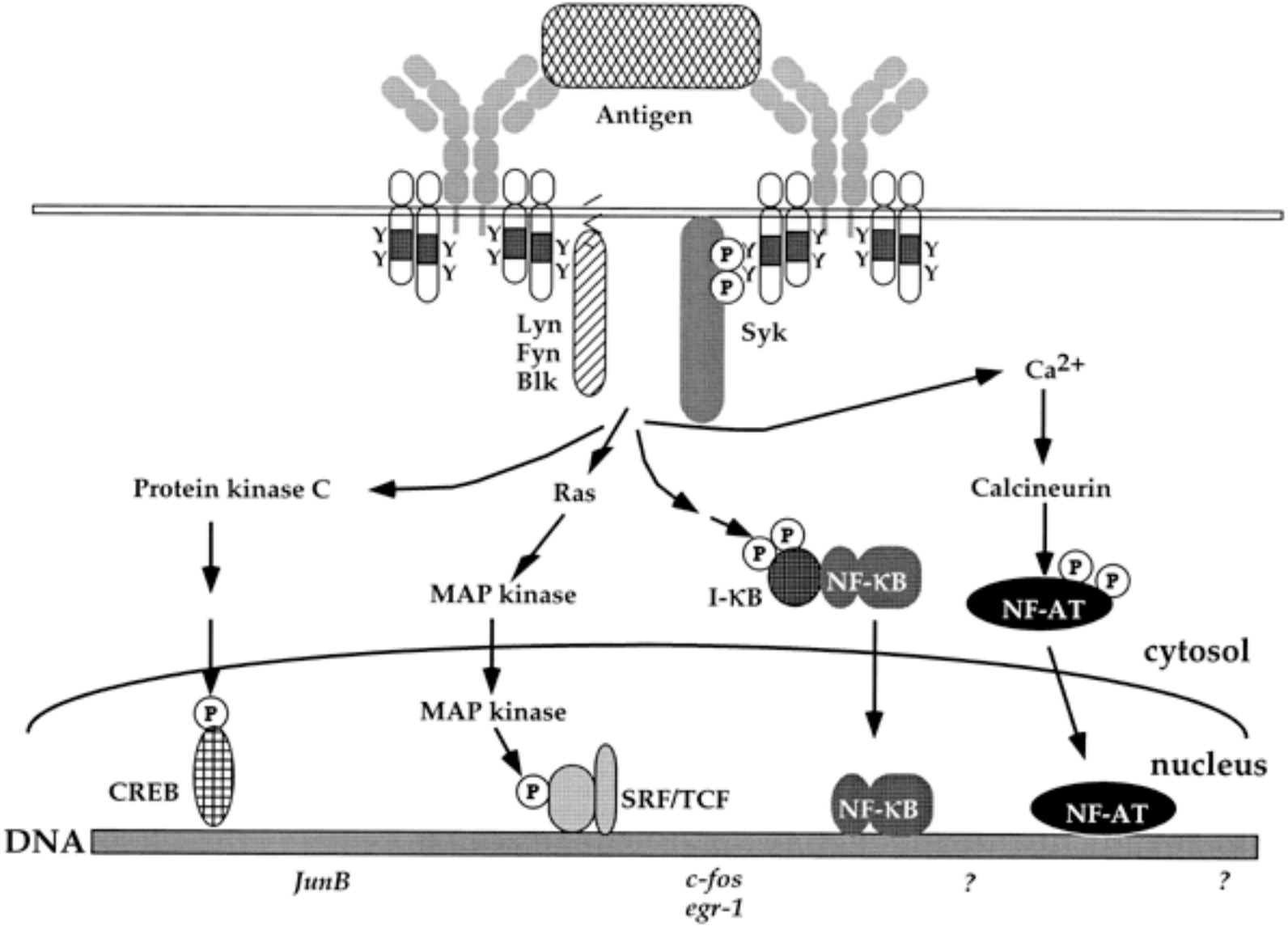




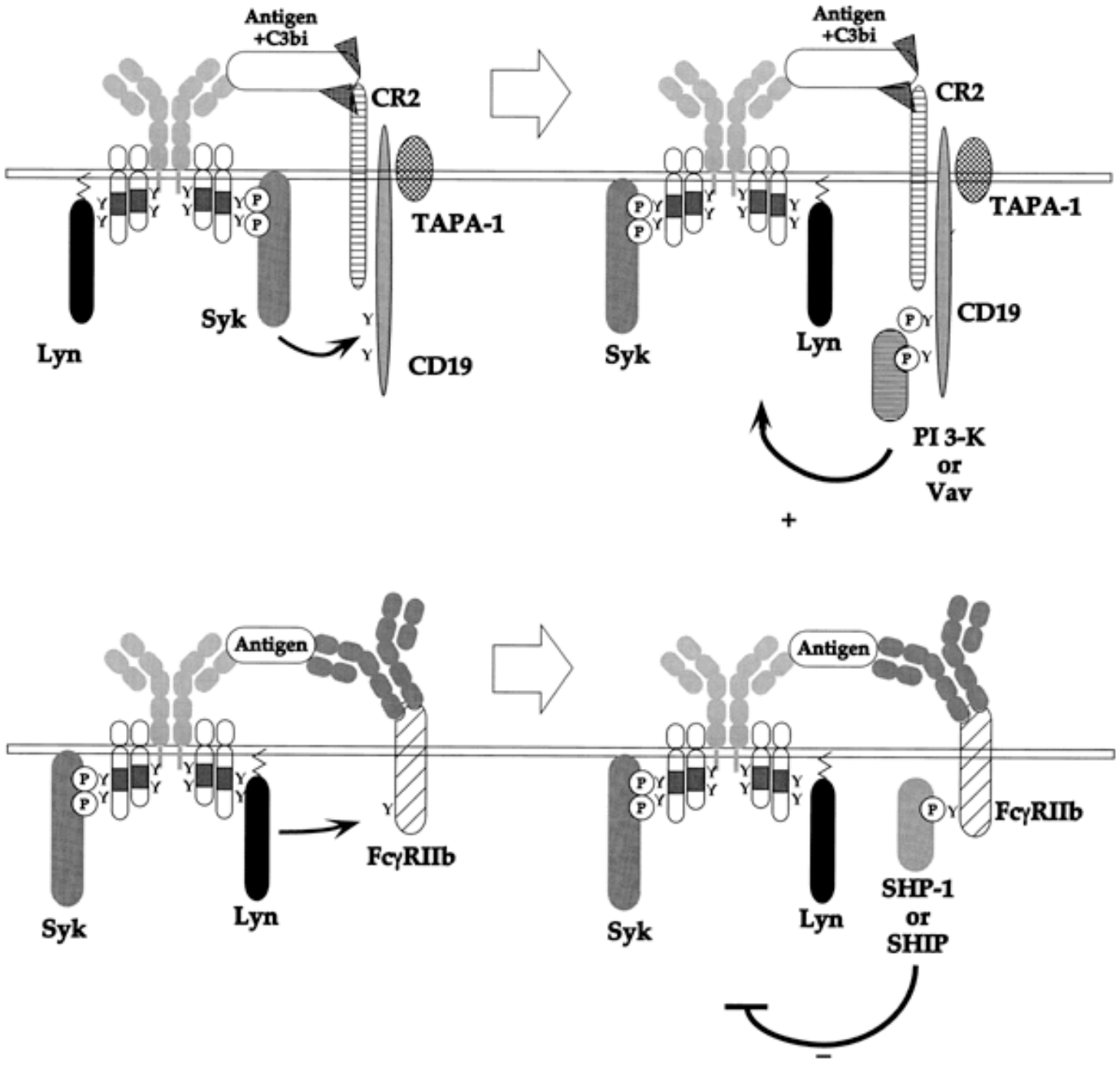
SFK= Src family kinase
Csk= C-terminal Src kinase
Cbp= Csk binding protein
PTP= Protein tyrosine phosphatase
PTK= Protein tyrosine kinase



The BCR complex

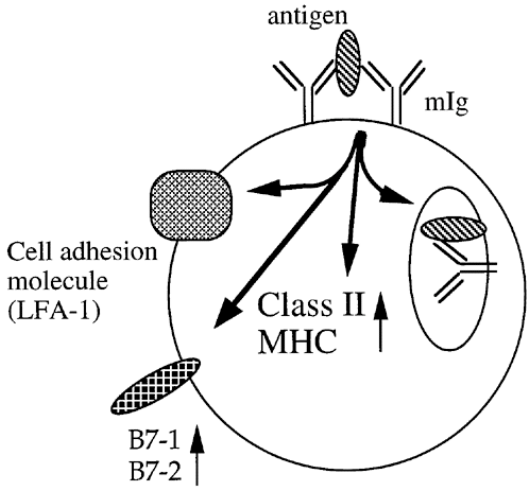


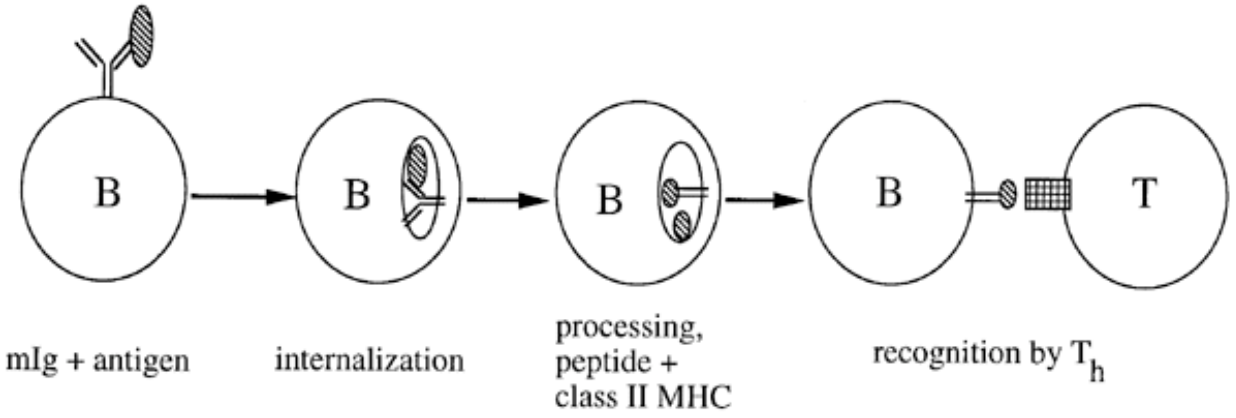
The BCR complex



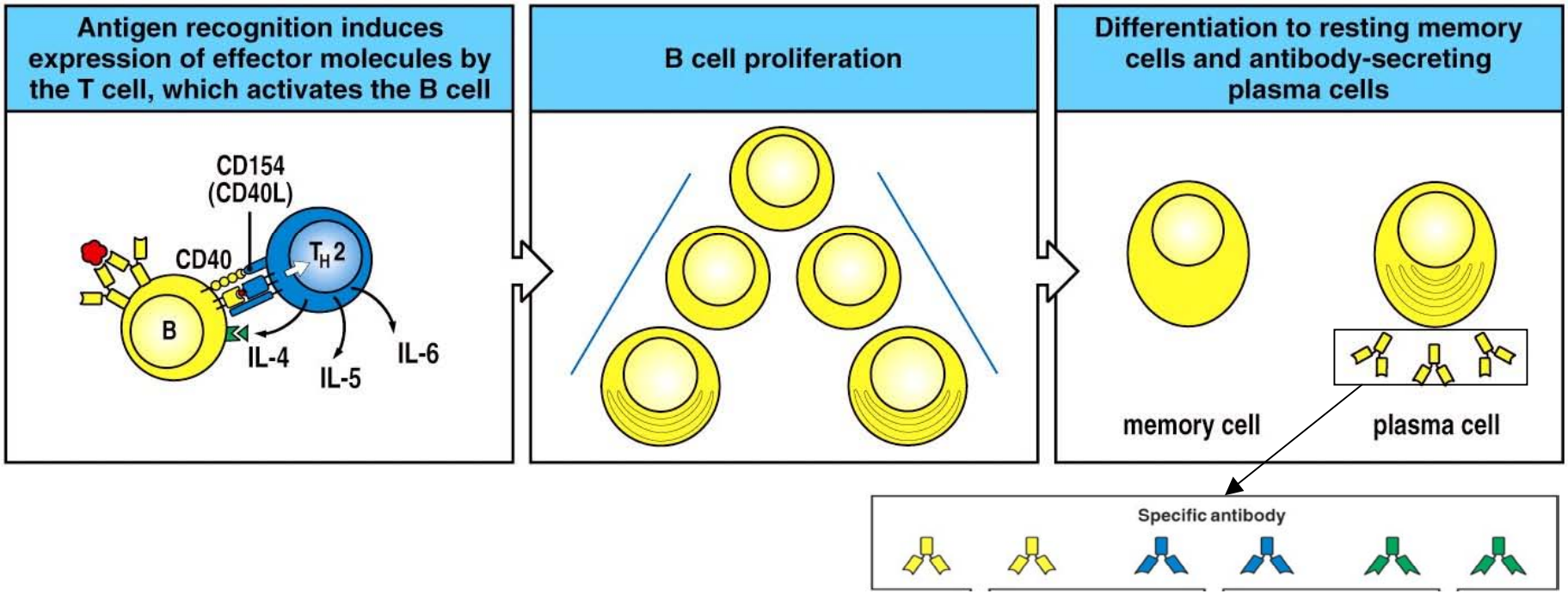
Thymodependent B(2) cell response

Activation by antigen binding and helper T cell interactions

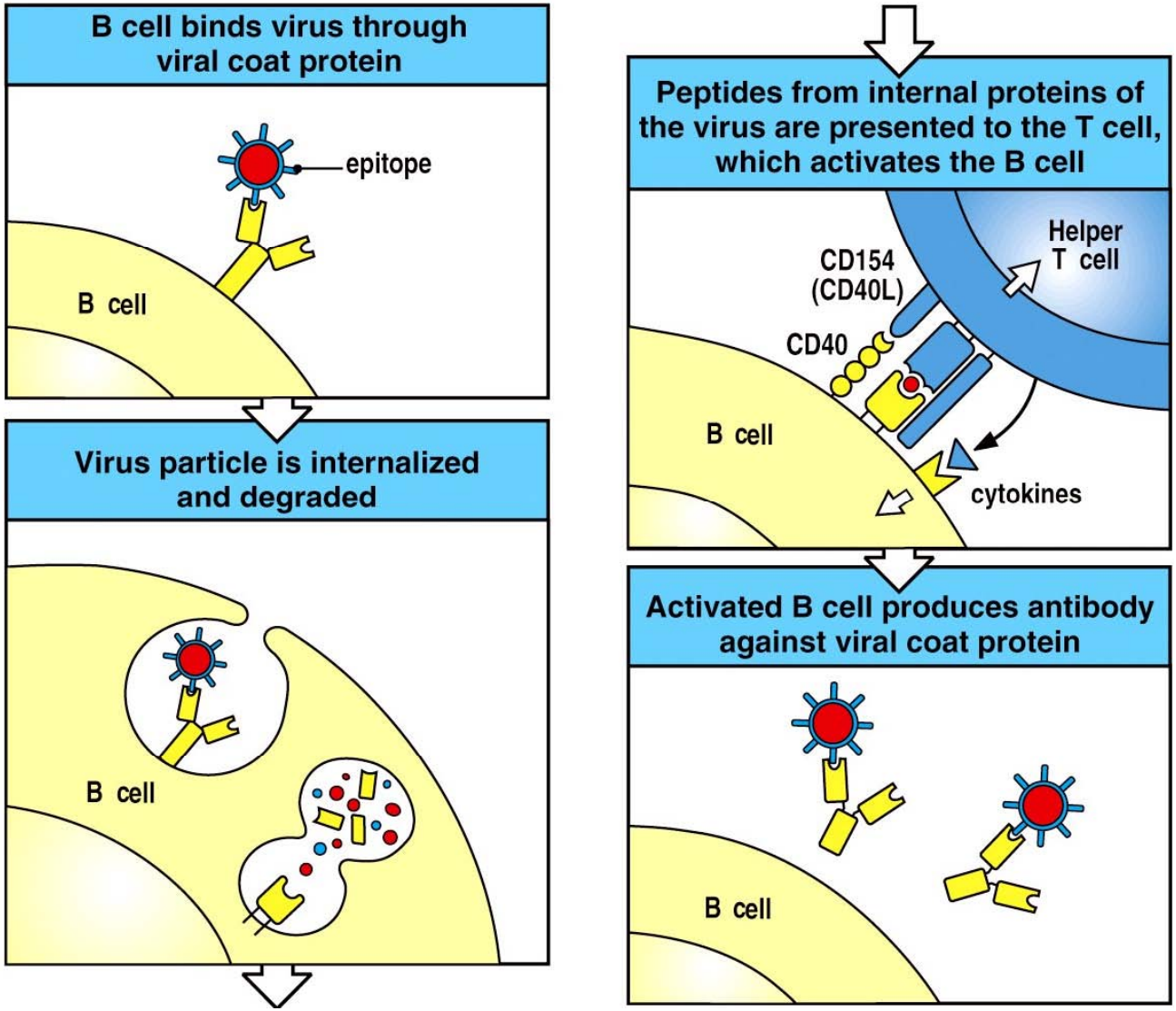




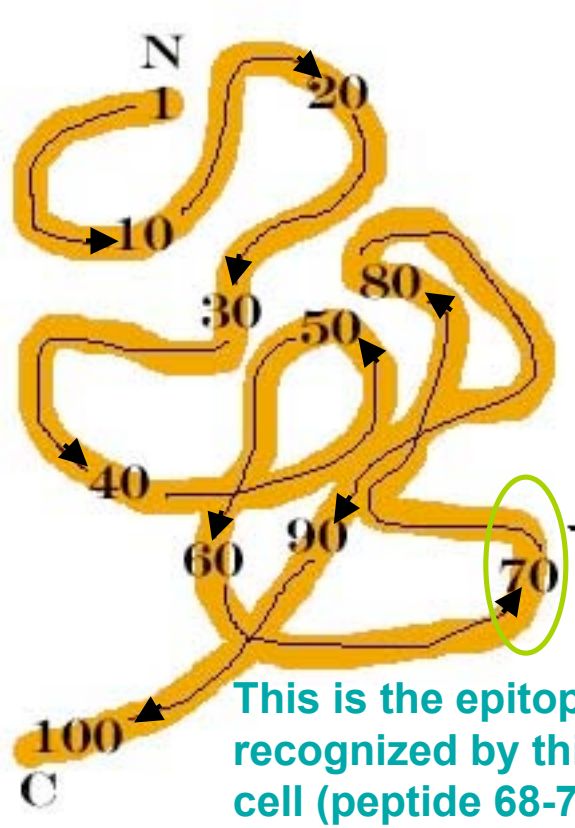
Activation = proliferation and differentiation



T cells activate B cells that recognize the same Ag but not necessarily the same epitope



=MHC class II



This is the epitope recognized by this B cell (peptide 68-74)

B cell

B cell binds antigen in BCR, endocytoses the antigen, process it in to many different peptides and presents several of the peptides in association with MHC class II

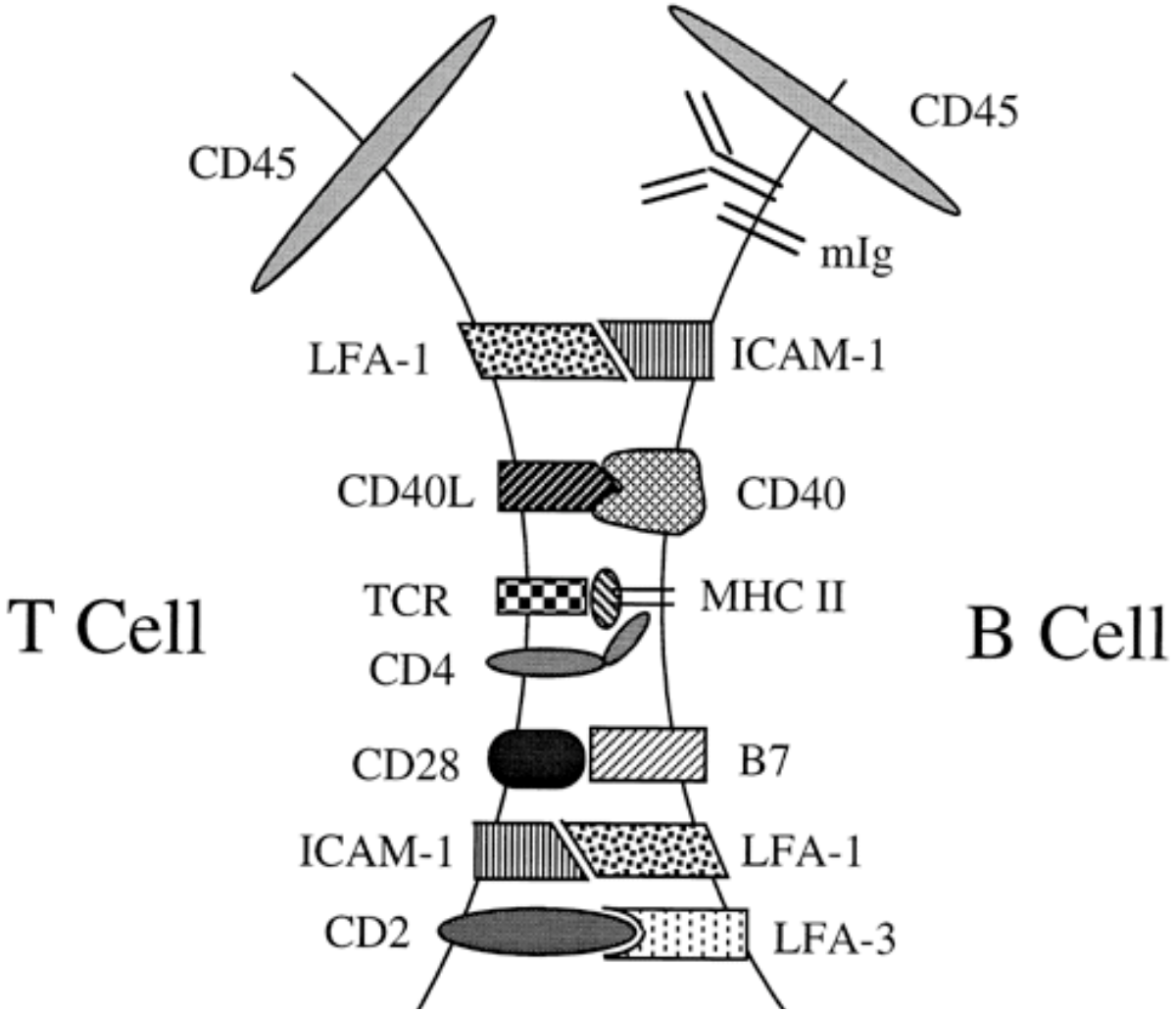
Peptide 34-48

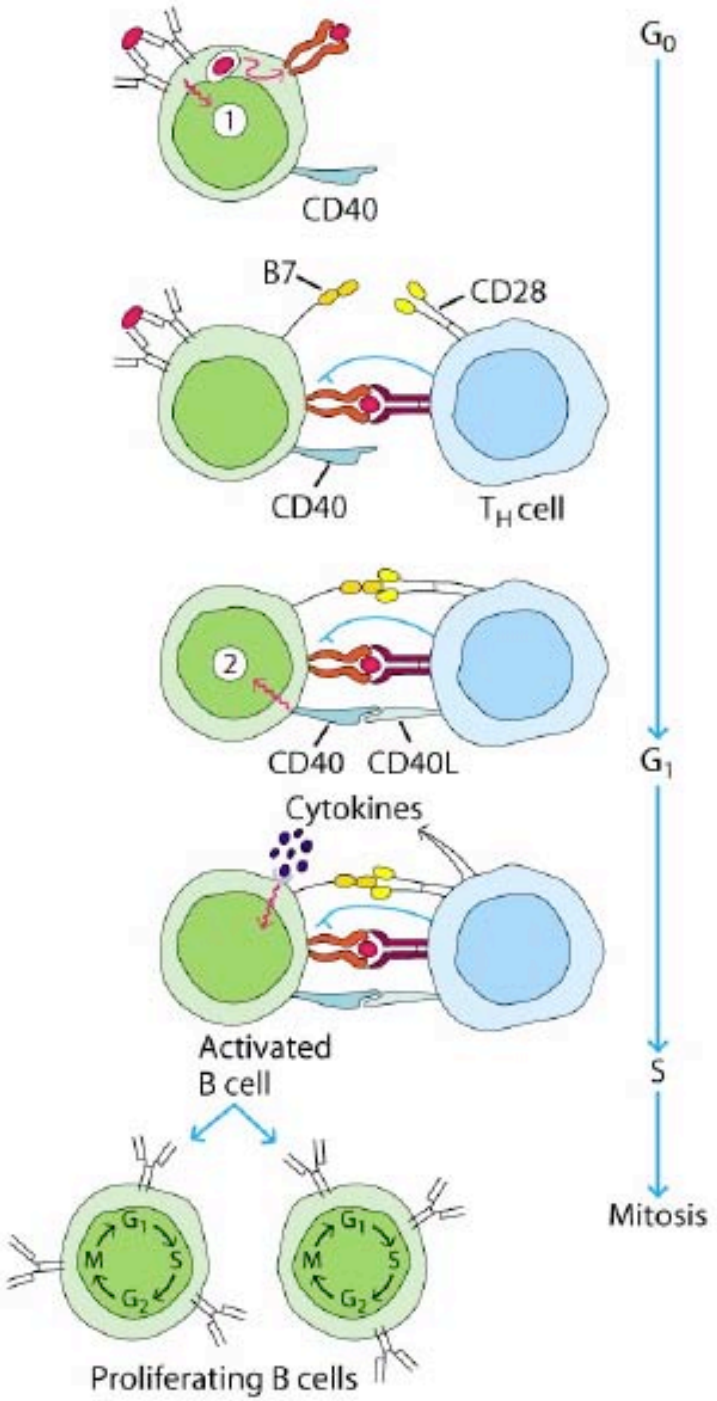
Peptide 80-93

Peptide 73-88

Peptide 12-25

Th cells can recognize any of these peptides and provide “help”


CD45
CD45
mIg
LFA-1
ICAM-1
CD40L
CD40
T Cell
TCR
MHC II
B Cell
CD4
CD28
B7
ICAM-1
LFA-1
CD2
LFA-3
B
T
1μ
B
T
1μ



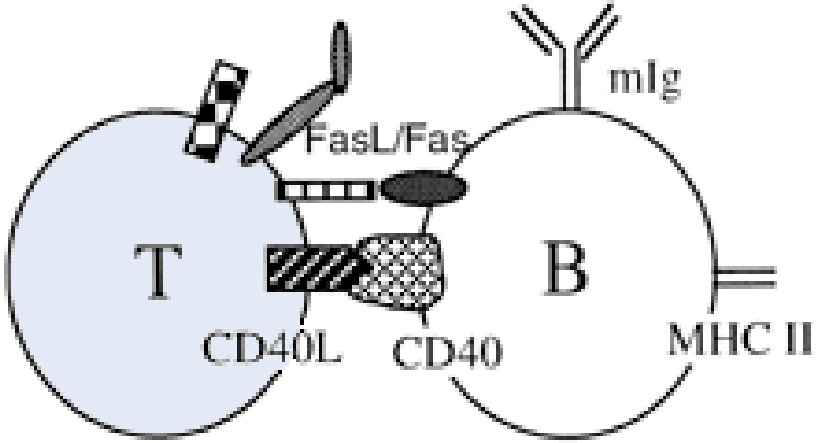
Binding of Ag stimulates MHC II and B-7 expression on B-cell.

MHC/B7 interaction with T-cell receptor induces expression of CD40L on T-cell.

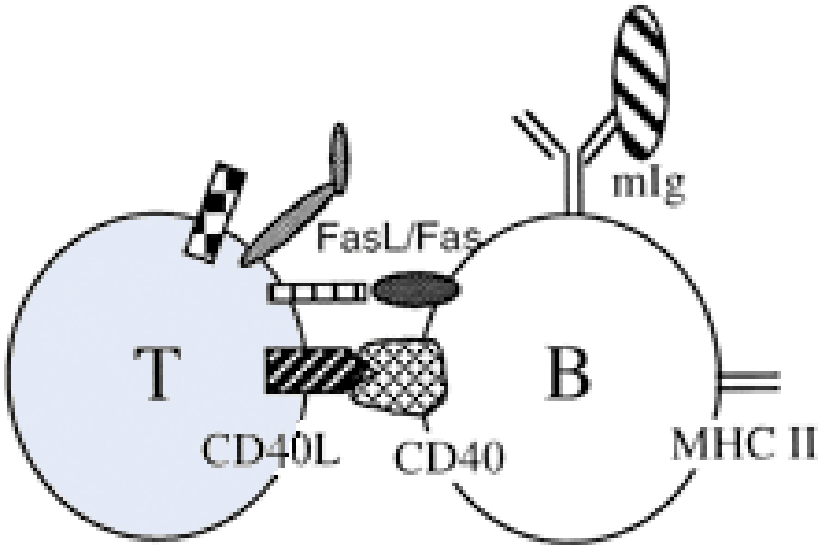
CD40/CD40L interaction provides co-stimulatory interaction necessary for activation of B-cell.

B-cells induce expression of receptors for cytokines secreted by T-cell. T-cell reorients golgi toward B-cell.

B-cells begin to proliferate and differentiate. Undergo Class switching and affinity maturation



CD40L without Ag: B cell susceptible to Fas Killing: **Apoptosis**



CD40L with Ag: B cell resistant to Fas killing: **Activation**

(T cell activation up-regulates T cell expression of CD40L)

Signal 2 (CD40L) is required for class switching but T_H cells make cytokines that influence isotype switching

Role of cytokines in regulating Ig isotype expression

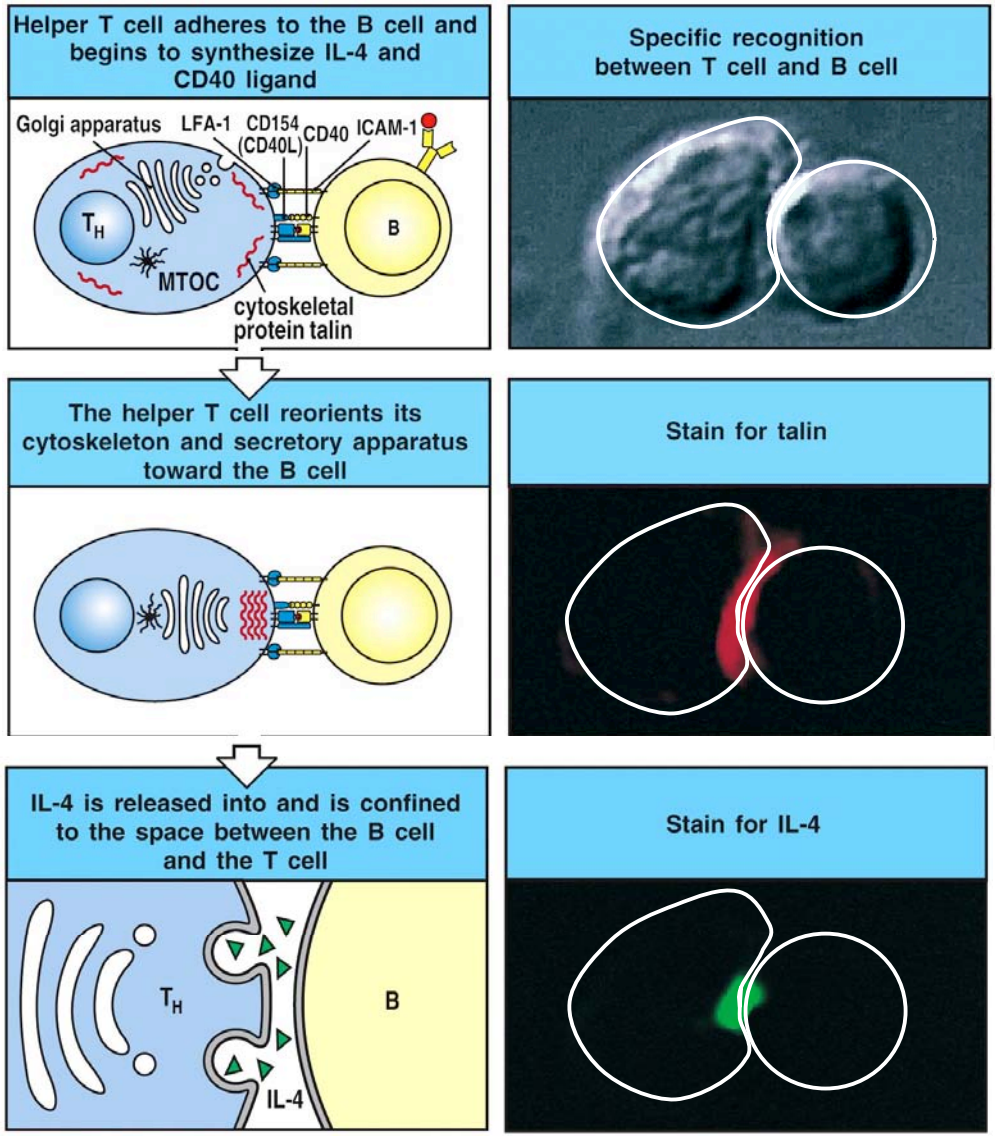
Cytokines	IgM	IgG3	IgG1	IgG2b	IgG2a	IgE	IgA
IL-4	Inhibits	Inhibits	Induces		Inhibits	Induces	
IL-5							Augments production
IFN-γ	Inhibits	Induces	Inhibits		Induces	Inhibits	
TGF-β	Inhibits	Inhibits		Induces			Induces

Figure 9-7 Immunobiology, 6/e. (© Garland Science 2005)

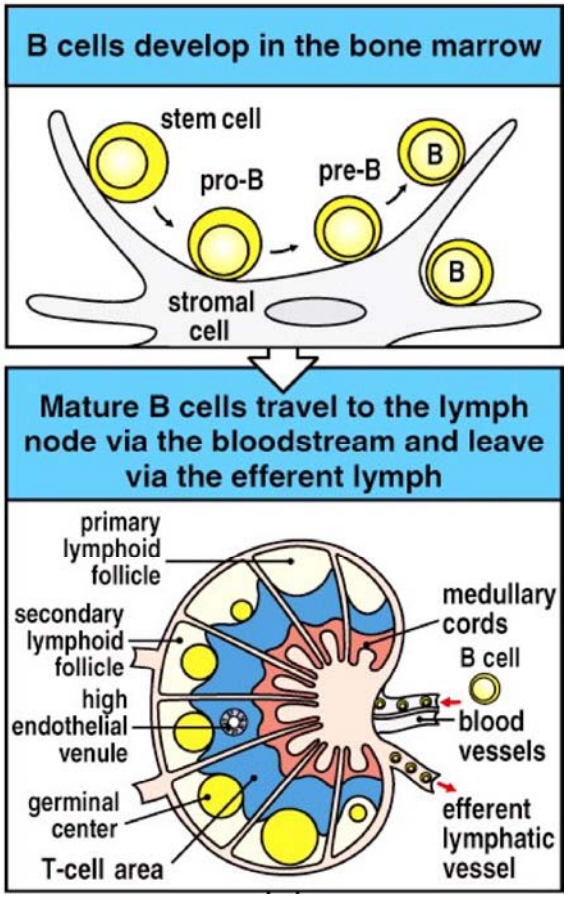
IFN-g is a hallmark of cell-mediated immune responses so IgG3 and IgG2a are also associated with T_H1 responses

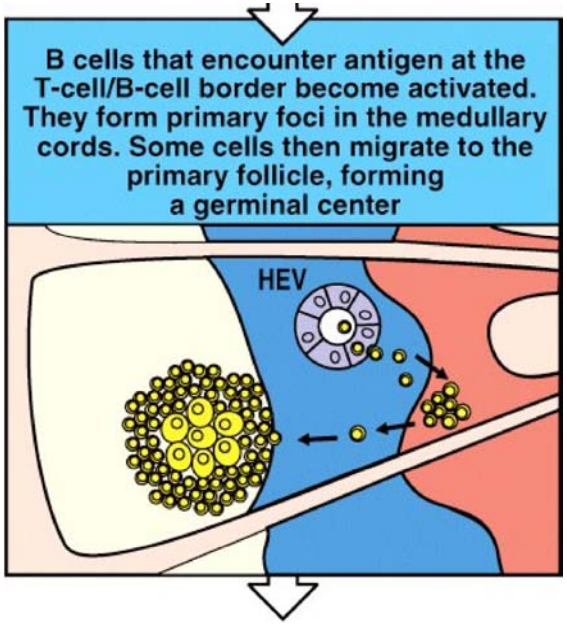
(Mouse data)

IL-4 is secreted in the direction of the B cell so there is little bystander effect on neighboring B cells



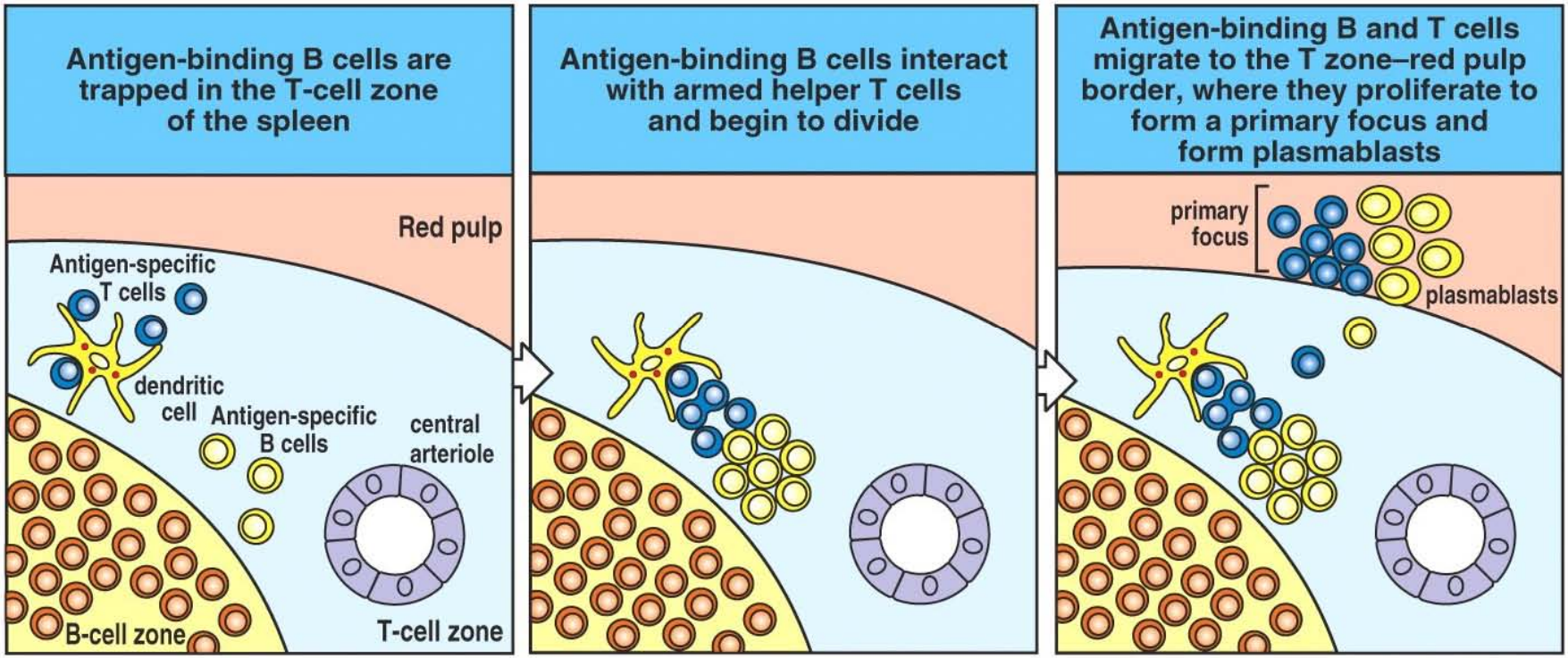
Topology of the thymodependent B cell response





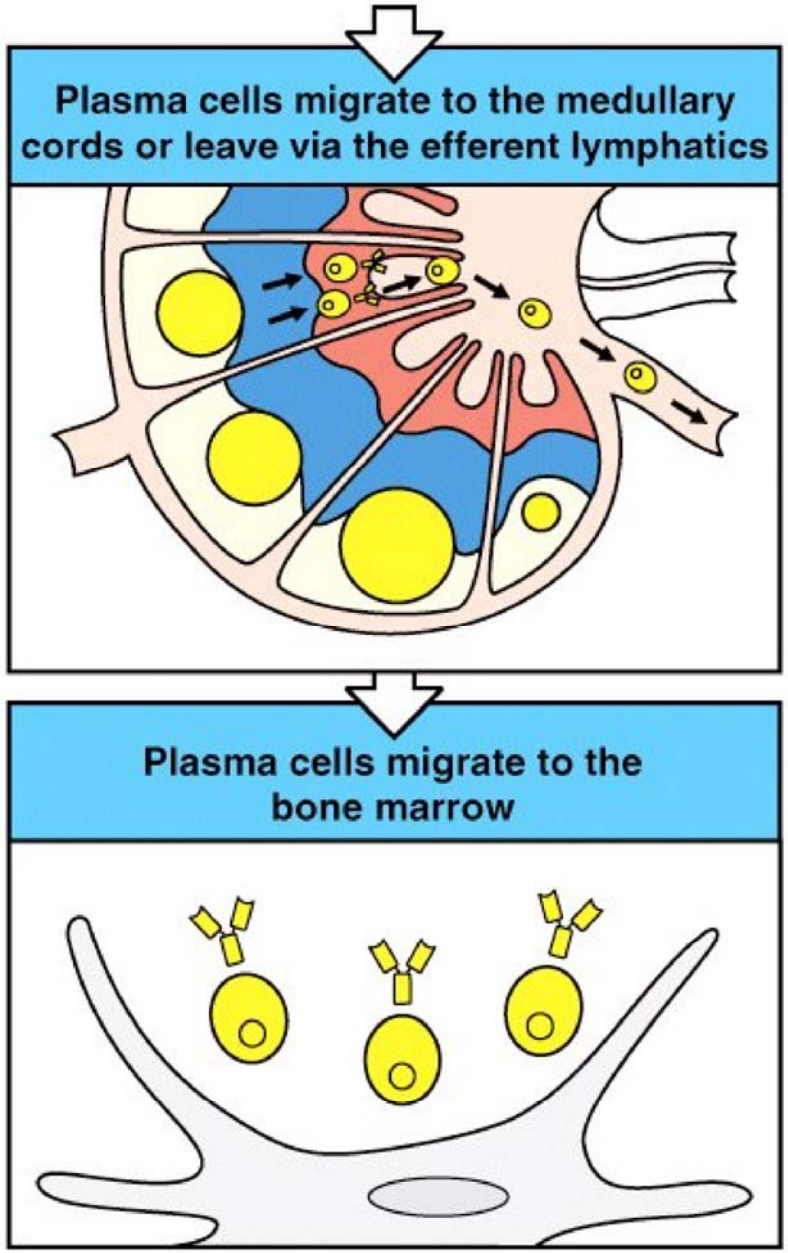
Those B cells and T cells that bind antigen are trapped in the T cell zone of the peripheral lymphoid organ where they can both get activated and interact

Topology of the thymodependent B cell response



Some B cells in the primary focus differentiate into plasmablasts and plasma cells, leave the area and make antibody. Others go to the B cell zone

Topology of the thymodependent B cell response

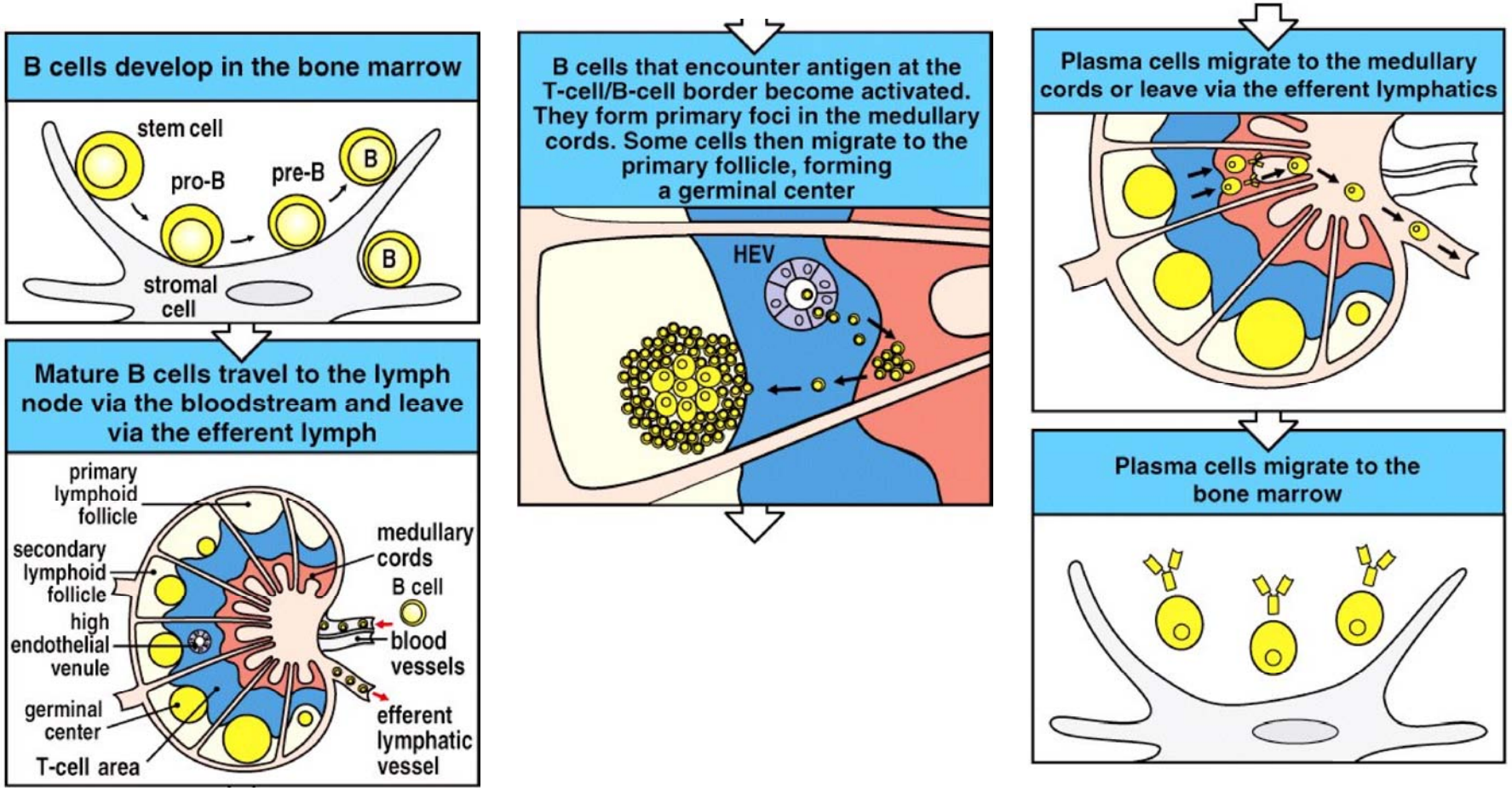


Activated B cells eventually differentiate into **plasma cells** for the secretion of antibody and **memory B cells**.

Most plasma cells survive for a few day to a few week. Some are long-lived (account for much of the circulating antibodies).

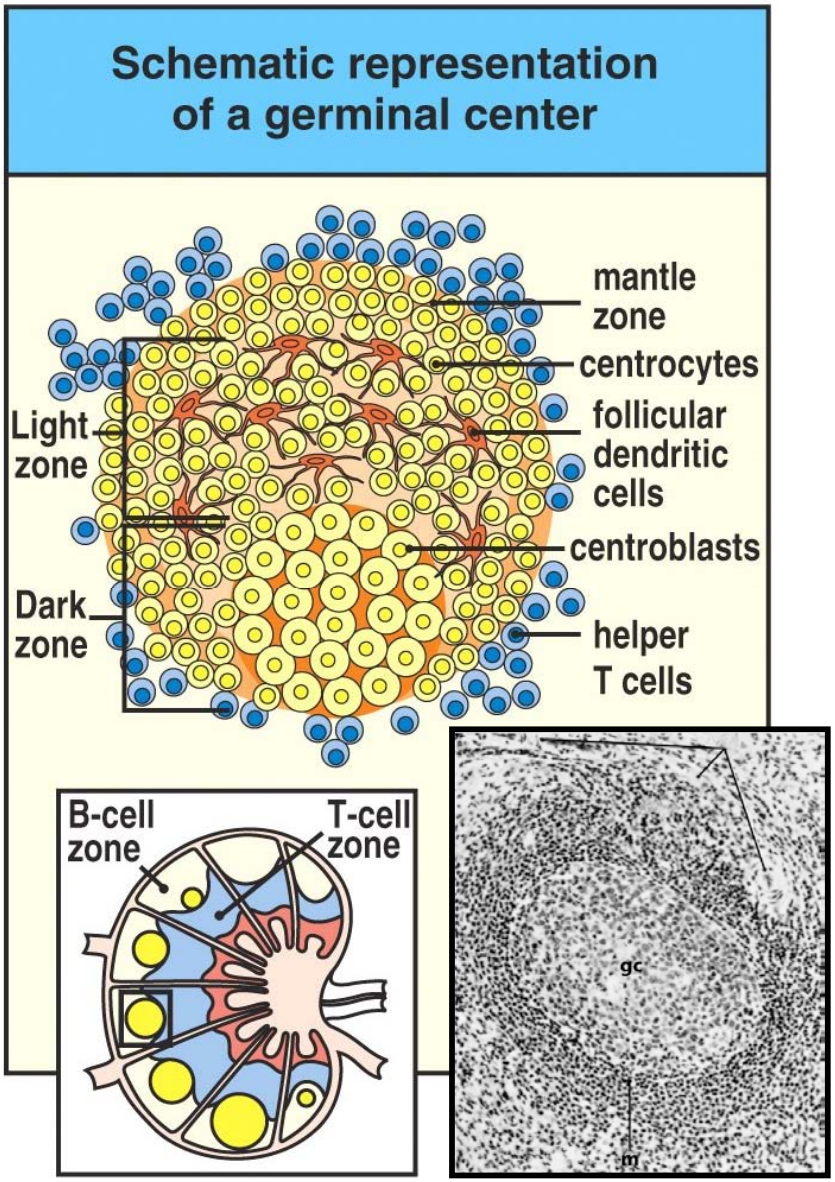
Memory B cell live a long time (years). Memory B cells keep the changes that they acquired in the germinal centers (e.g., class switched, somatic mutations).

Topology of the thymodependent B cell response



Although 50-100 different antigen-specific B cells originally comprise a GC, by the end of the response all the B cells are from 1 or a few clones

Germinal centers (GC) contain antigen-specific B cells, follicular dendritic cells (FDC) and antigen-specific T cells



Germinal centers are mostly proliferating B cells but also contain many (10%) T cells

In the germinal centers, B cells undergo:

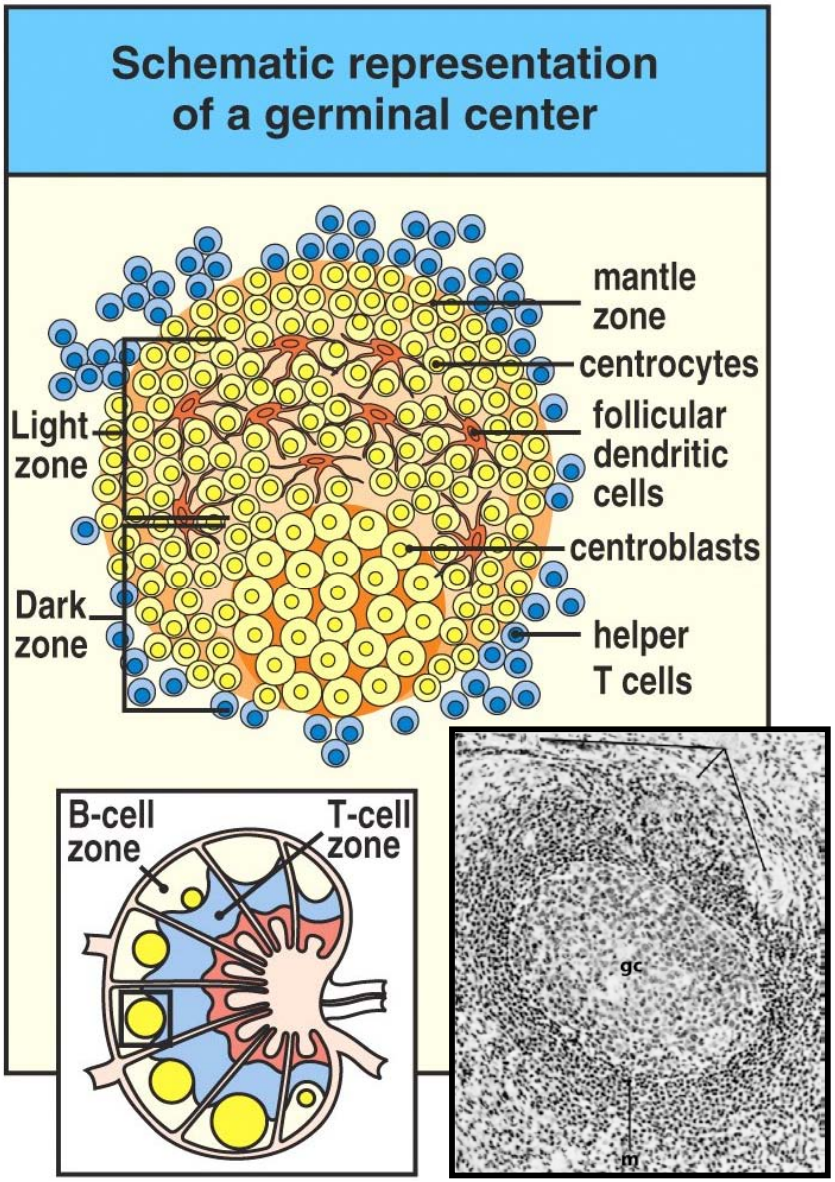
1. somatic hypermutations
2. affinity maturation
3. isotype switching

⇩

Modification of the amount (proliferation), of the function (switch) and of the efficiency (affinity) of the antibodies

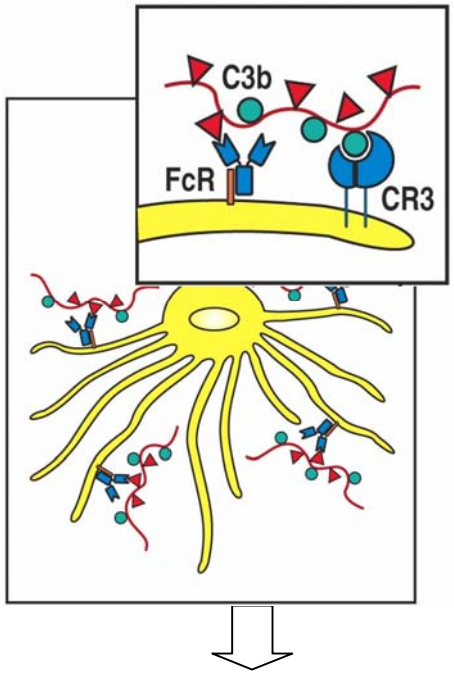
Centrocyte = B cell;
Centroblast = dividing B cell

Germinal centers (GC) contain antigen-specific B cells, follicular dendritic cells (FDC) and antigen-specific T cells

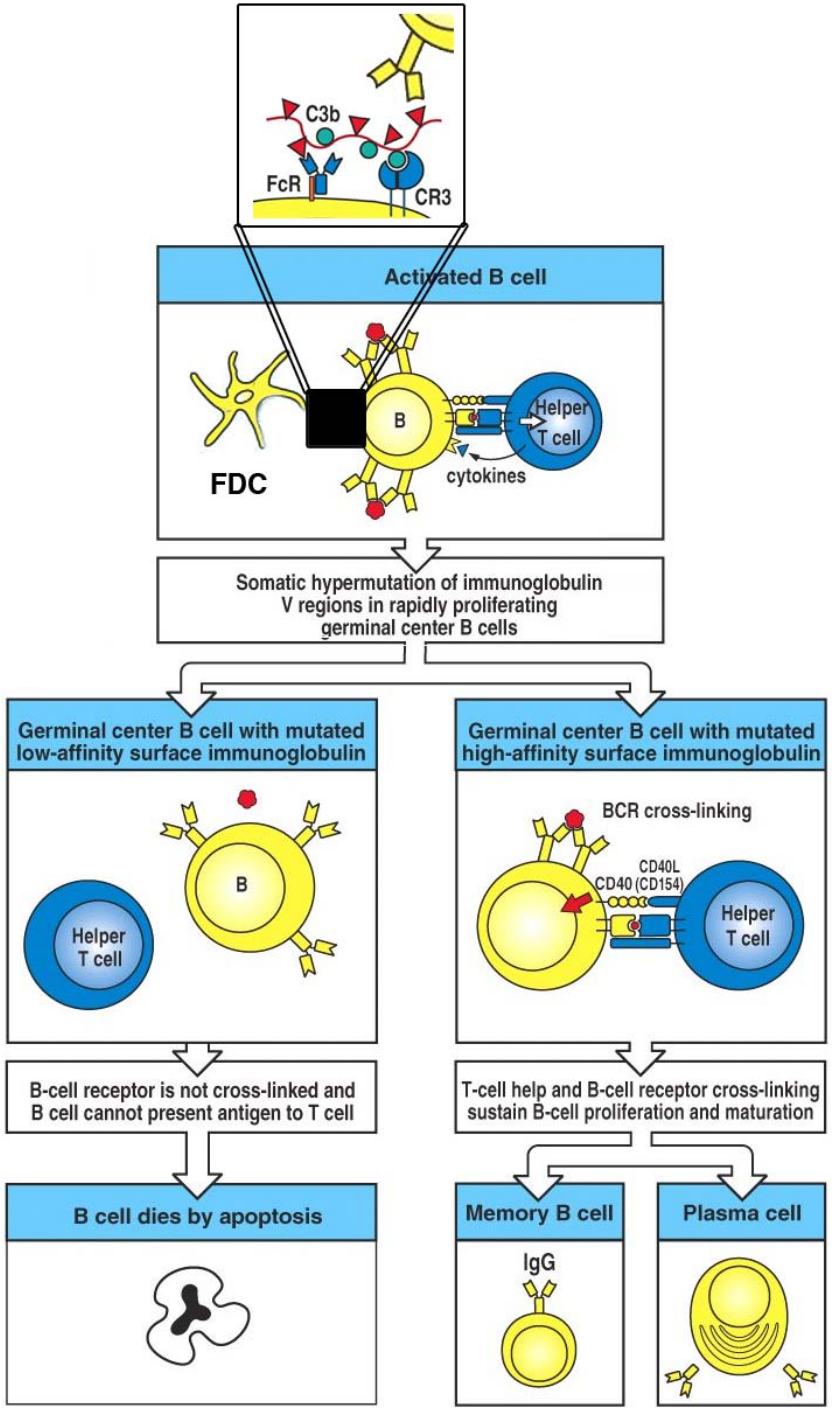


FDC present native antigen:

1. bound by antibody and FcR
2. bound by complement and complement receptors



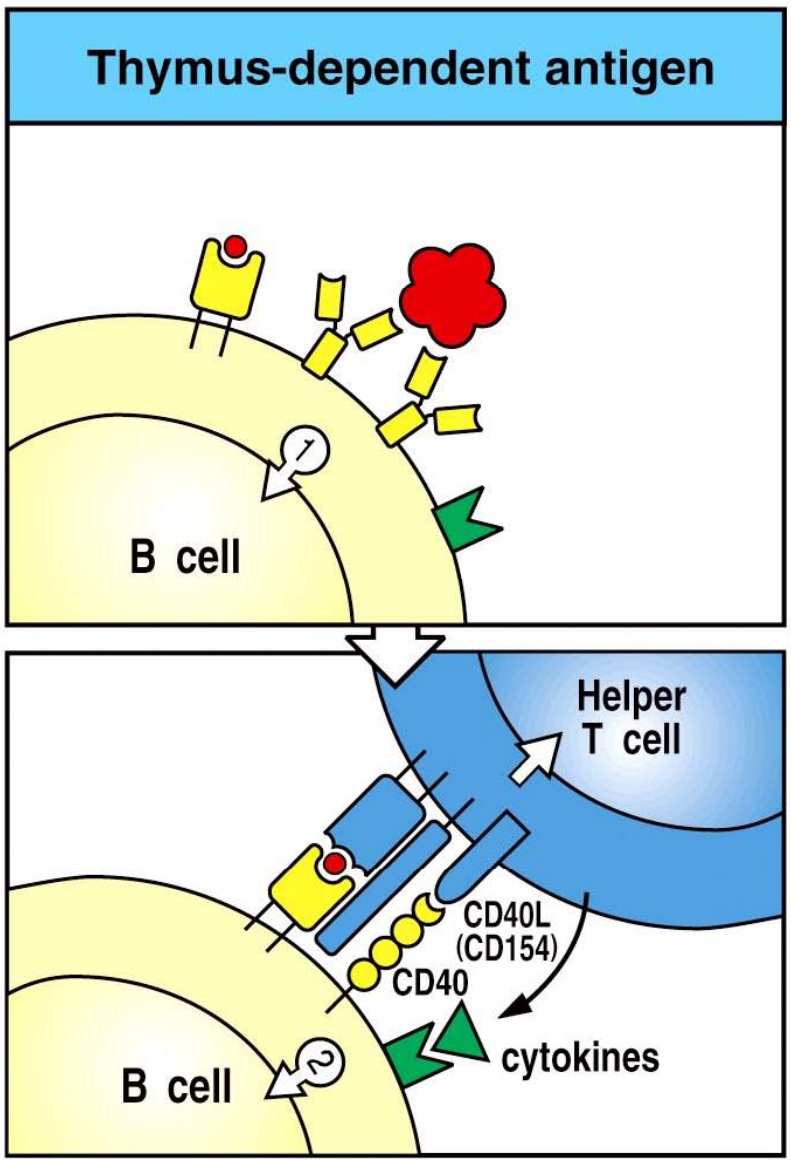
B cells competing to bind the antigens presented by FDCs= competition that drive affinity maturation

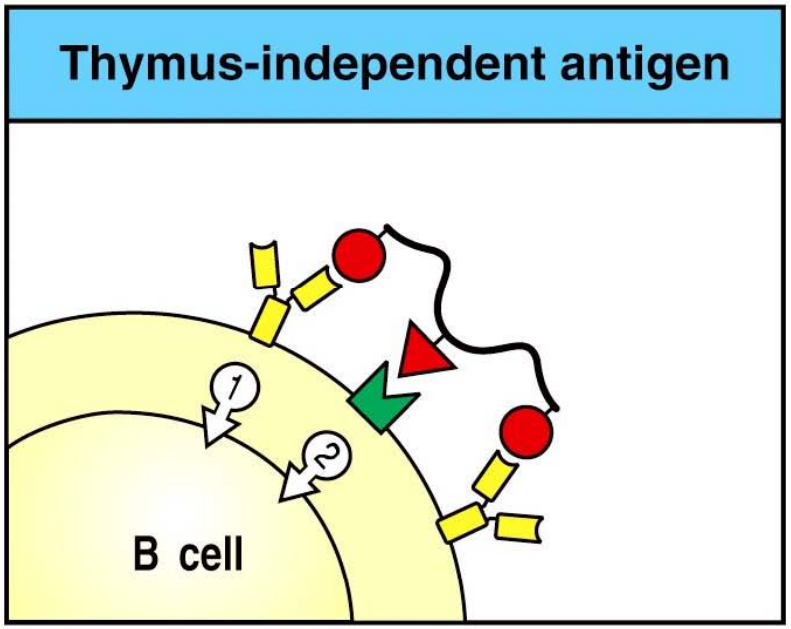

C3b
FcR
CR3
Activated B cell
FDC
B
Helper T cell
cytokines
Somatic hypermutation of immunoglobulin V regions in rapidly proliferating germinal center B cells
Germinal center B cell with mutated low-affinity surface immunoglobulin
B
Helper T cell
Germinal center B cell with mutated high-affinity surface immunoglobulin
BCR cross-linking
CD40L
CD40 (CD154)
Helper T cell
B-cell receptor is not cross-linked and B cell cannot present antigen to T cell
T-cell help and B-cell receptor cross-linking sustain B-cell proliferation and maturation
B cell dies by apoptosis
Memory B cell
IgG
Plasma cell

If T cells recognize only peptides, how do you make antibodies to polysaccharides or other non-protein macromolecules?

Thymo-independent B cell response

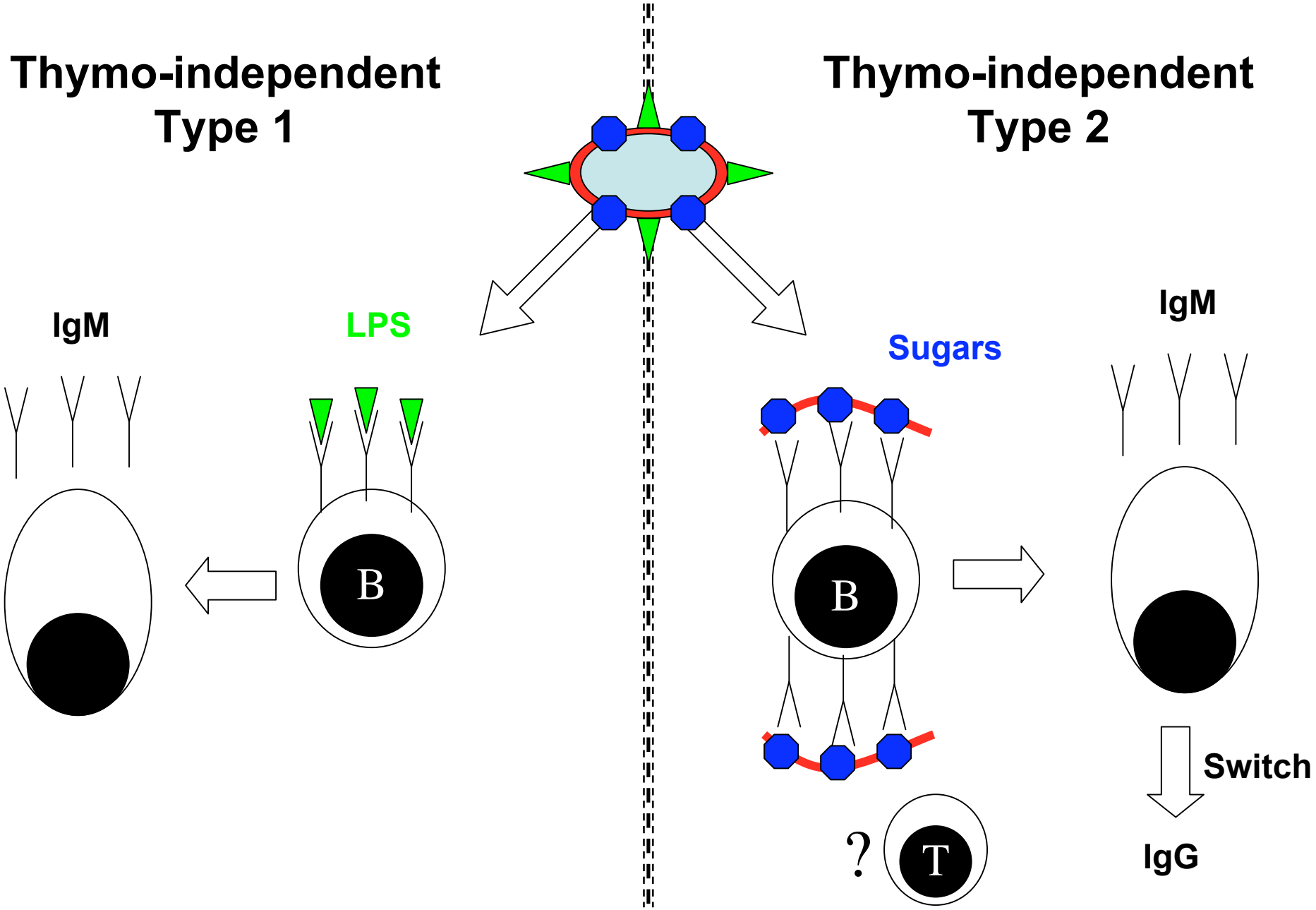
Some B cell responses require T help whereas other do not





T-independent antibody response generally have

1. no memory
2. no isotype switching
3. no somatic mutations

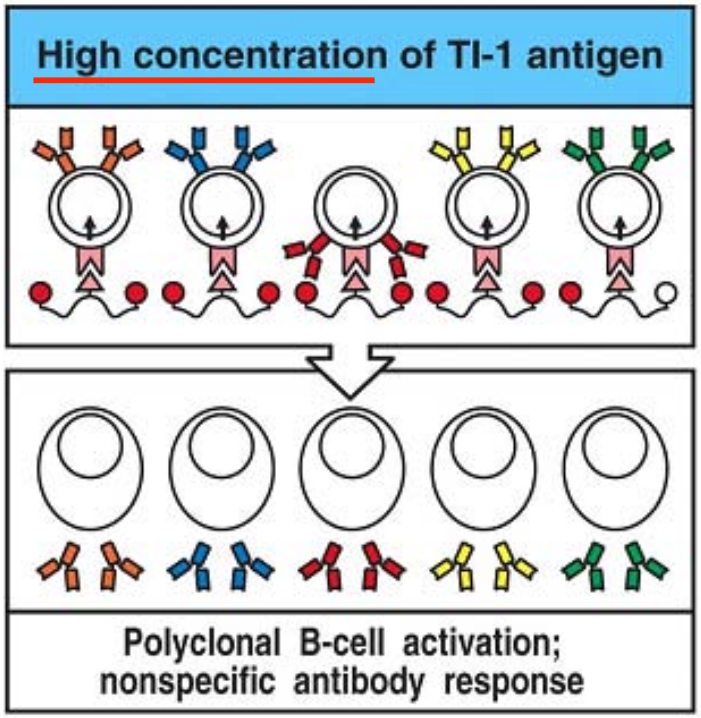


B cells that respond to these Ags are mostly B1a cells

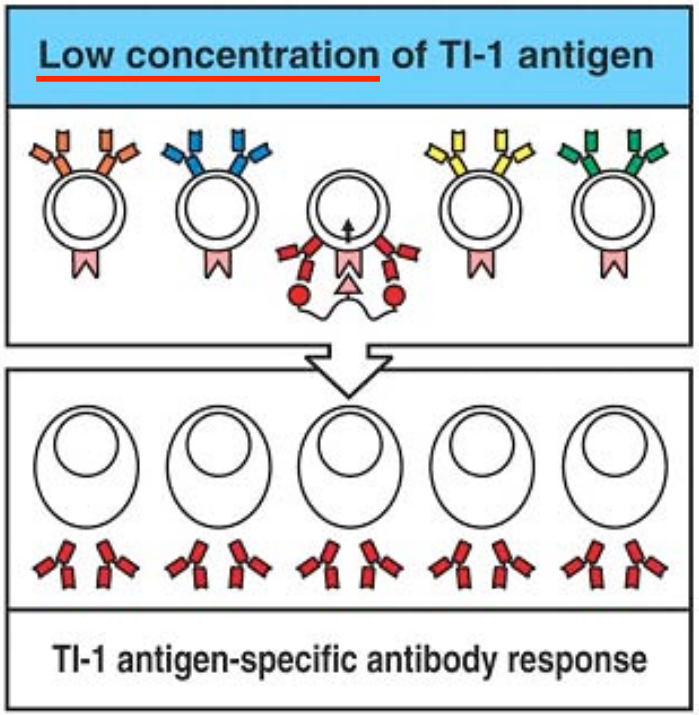
Properties of thymus-dependent and thymus-independent antigens

	TD ANTIGENS	TI ANTIGENS
Property		Type 1
Chemical nature	Soluble protein	Bacterial cell-wall components (e.g., LPS)
Humoral response		
Isotype switching	Yes	No
Affinity maturation	Yes	No
Immunologic memory	Yes	No
Polyclonal activation	No	Yes (high doses)
BCR signaling	"Classic"	Use the BCR as a focusing component that concentrates the polyclonal activator
Cytokines	Required (from Th)	Required (from non-lymphoid cells)
Target B cells	Mature only	Mature and immature

B cell response to TI-1 antigens



These are polyclonal B cell activators or B cell mitogens. These can be dangerous because they deregulate B cell responsiveness



At low doses, the TI-1 antigens activate only the antigen-specific B cells but they do it without T cell help. This can be helpful in getting rid rapidly of bacteria (without the need to expand Th cells)

Bacterial lipopolysaccharides (LPS) is the prototypical TI-1 antigen

Properties of thymus-dependent and thymus-independent antigens

	TD ANTIGENS	TI ANTIGENS	
Property		**Type 1**	**Type 2**
Chemical nature	Soluble protein	Bacterial cell-wall components (e.g., LPS)	Polymeric protein antigens; capsular polysaccharides
Humoral response			
Isotype switching	Yes	No	Limited
Affinity maturation	Yes	No	No
Immunologic memory	Yes	No	No
Polyclonal activation	No	Yes (high doses)	No
BCR signaling	"Classic"	Use the BCR as a focusing component that concentrates the polyclonal activator	Vigorous and prolonged
Cytokines	Required (from Th)	Required (from non-lymphoid cells)	Required (not necessarily from Th cells)
Target B cells	Mature only	Mature and immature	Mature only

B cell response to TI-2 antigens

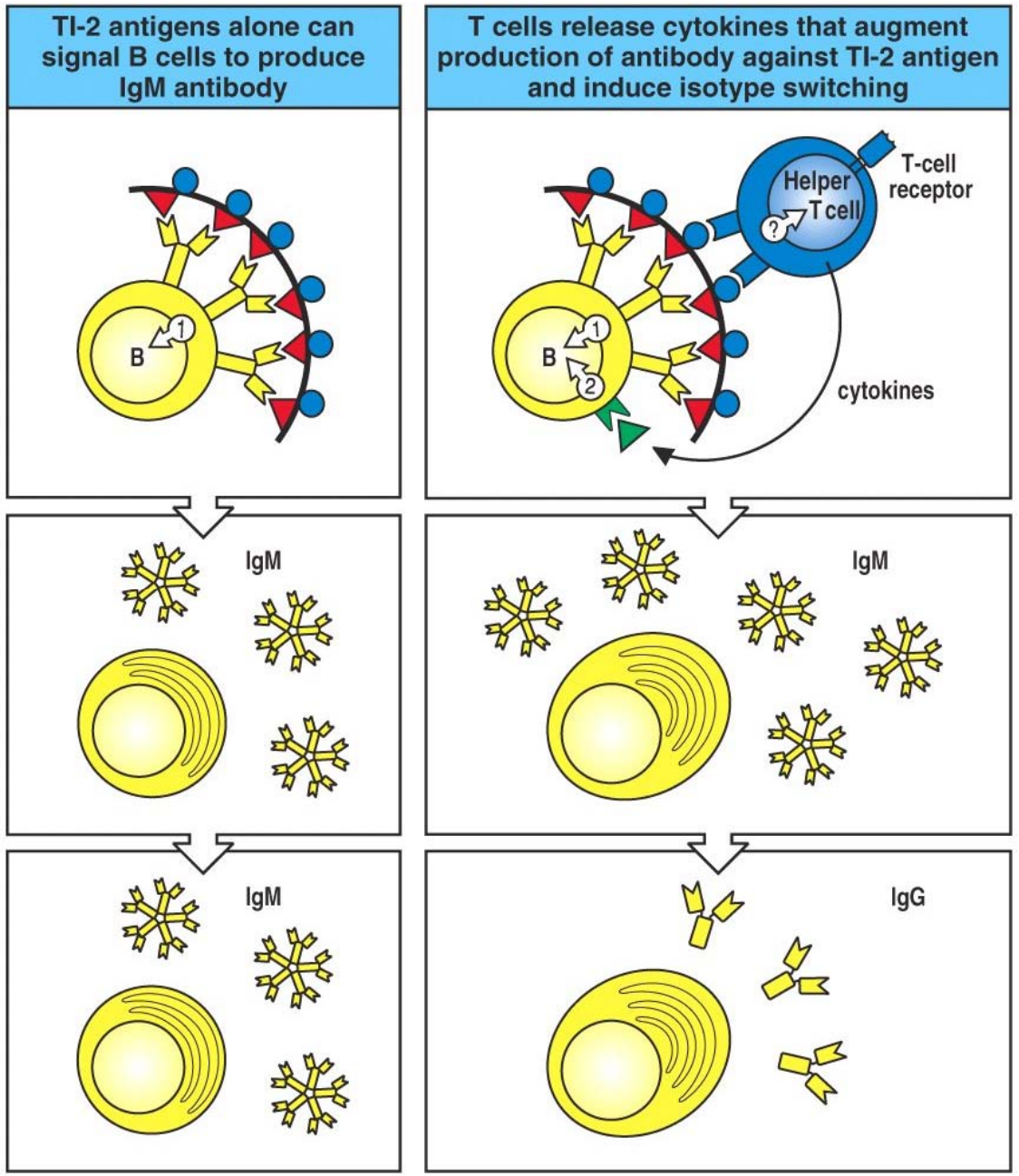
TI-2 antigens contain highly repetitive structures (epitopes)

Highly repetitive epitopes cross-link the BCRs and that activates the B cells

Bacterial capsule polysaccharides are prototypic TI-2 antigens

Too low a density of repeating epitopes and they do not activate

Too high a density of repeating epitopes and they anergize.



B cell response to TI-2 antigens and the role of T cells

- TI-2 responses exist in athymic mice
- Elimination of all $\alpha\beta$ and $\gamma\delta$ T cells blocks TI-2 B cell responses
- May be $\alpha\beta$ or $\gamma\delta$ CD4-/CD8- DN T cells with an extrathymic development which may interact with non classical MHC molecules (such as CD1)

Summary of different classes of antigens

	TD antigen	TI-1 antigen	TI-2 antigen
Antibody response in infants	Yes	Yes	No
Antibody production in congenitally athymic individual	No	Yes	Yes
Antibody response in absence of all T cells	No	Yes	No
Primes T cells	Yes	No	No
Polyclonal B-cell activation	No	Yes	No
Requires repeating epitopes	No	No	Yes
Examples of antigen	Diphtheria toxin Viral hemagglutinin Purified protein derivative (PPD) of *Mycobacterium tuberculosis*	Bacterial lipopoly-saccharide *Brucella abortus*	Pneumococcalpoly-saccharide *Salmonella* polymerized flagellin Dextran Hapten-conjugated Ficoll (polysucrose)

How can we help the immune system to make Abs to TI Ags such as polysaccharides and other non-protein macromolecules?

Haemophilus influenzae type b vaccine

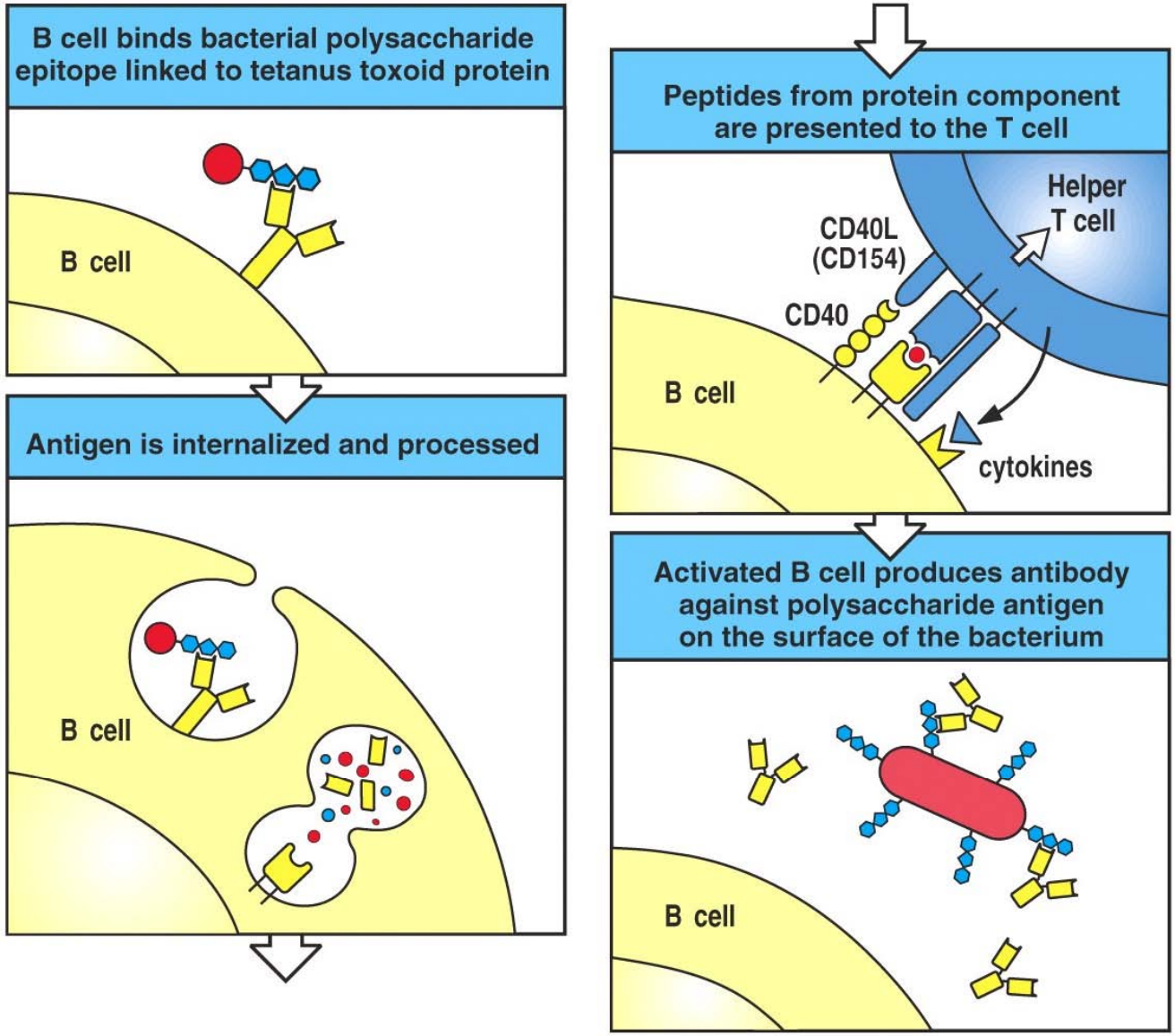
- Prior to the introduction of effective Hib vaccines 20 years ago, Hib = the most common etiologic agent of serious bacterial infections in young children (<5 years)
- Though neonates <3months were ('are' in developing countries) rarely affected
- Anti-Hib PS = TI-2 Ag. Anti-Hib PS Abs=IgM (also IgG in humans)
- First generation vaccine: purified Hib PS: poor efficacy in children <2 years
- Second generation vaccines: Hib PS conjugated with one protein carrier
  - Diphteria toxoid (PRP-D): poor efficacy
  - Non-toxic diphteroia toxin (HbOC or HibTiter): OK with 3 inj
  - Meningococcal outer membrane (PRP-OMPC): OK with 1 inj <2 mo of age but not efficient >6 mo
  - Purified tetanus toxoid (PRP-T) : has the advantage of HbOC+PRP-OMPC

How can we help the immune system to make Abs to TI Ags such as polysaccharides and other non-protein macromolecules?

Haemophilus influenzae type b vaccine

= protein

= polysaccharide



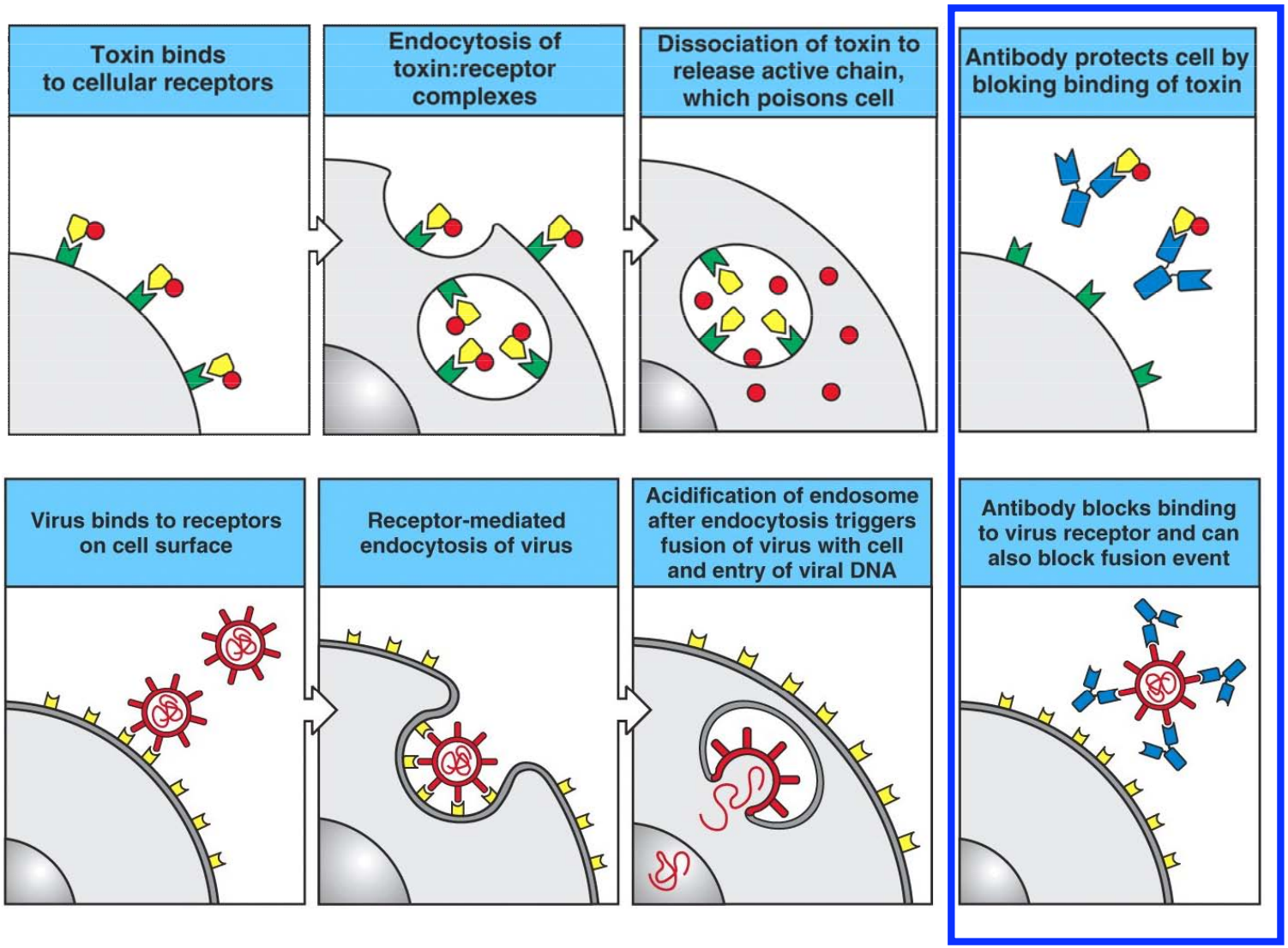
[Antibody effector mechanisms]

(how antibodies help get rid of antigens)

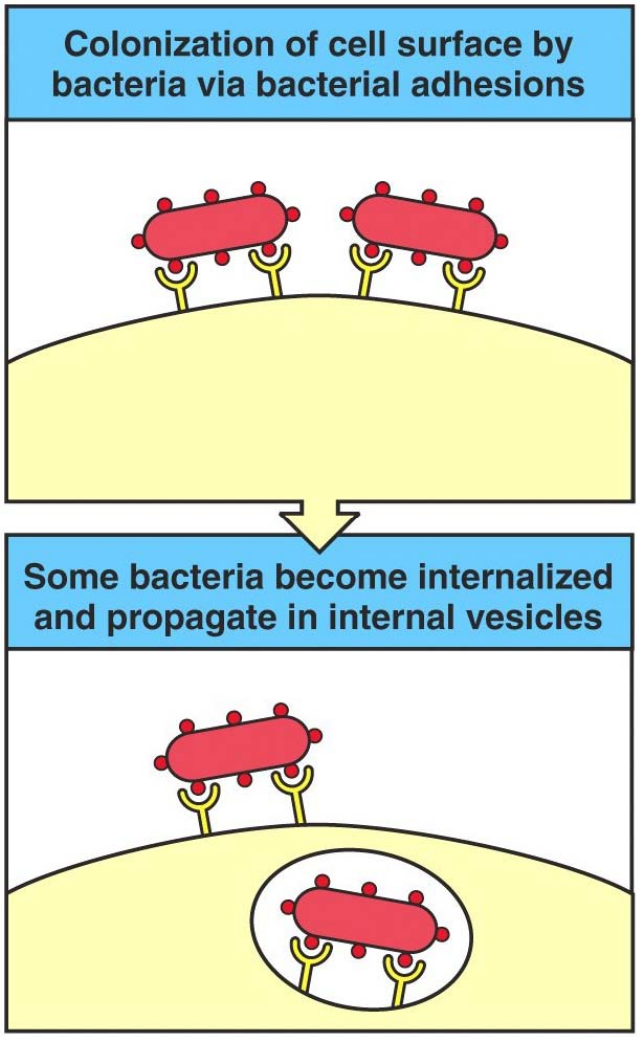
Some of the way that antibodies function to protect against infections

- ✓ Neutralization and inhibition of adherence
- ✓ Opsonization
- ✓ Complement activation
- ✓ Immune complex clearance by RBC
- ✓ ADCC
- ✓ Mast cell degranulation
- ✓ Eosinophil degranulation

Neutralization of microbial agents

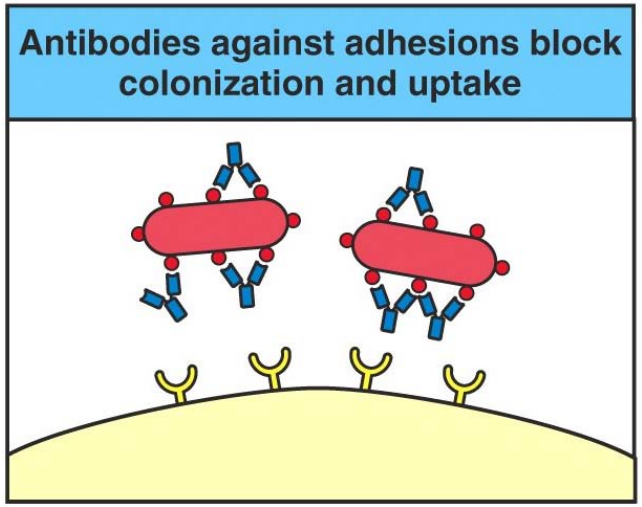


Neutralization of microbial agents



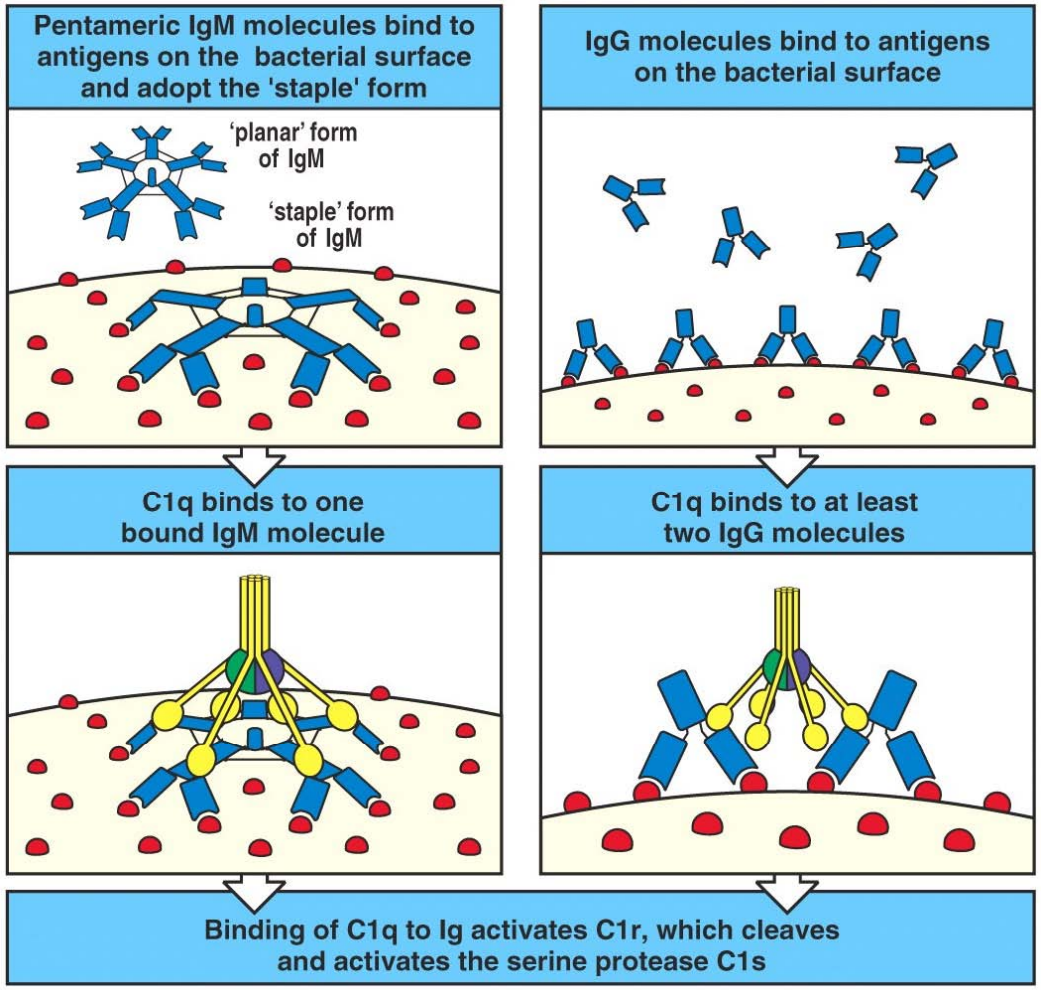
Most bacteria need to attach to a surface to initiate an infection

Antibodies can prevent attachment of bacteria to cell surfaces



Prevention of adhesion on mucus membranes is particularly important; this is a major role for secretory IgA

Complement activation



IgM is highly efficient at fixing (activating) complement (A single molecule of IgM bound to a surface can initiate a complement cascade

IgGs can fix complement but are less efficient (2 IgG can initiate a complement cascade but getting 2 bound molecules of IgG close together can take lots of IgG

Free Ig does <u>not</u> bind efficiently to FcR whereas antigen-antibody IC do bind efficiently (IgE-FcRε is an exception)

=> free Igs and IC (Ig+Ag) do not compete with each other for FcR. This allows "innate immunity" to focus on targets already recognized by antibody

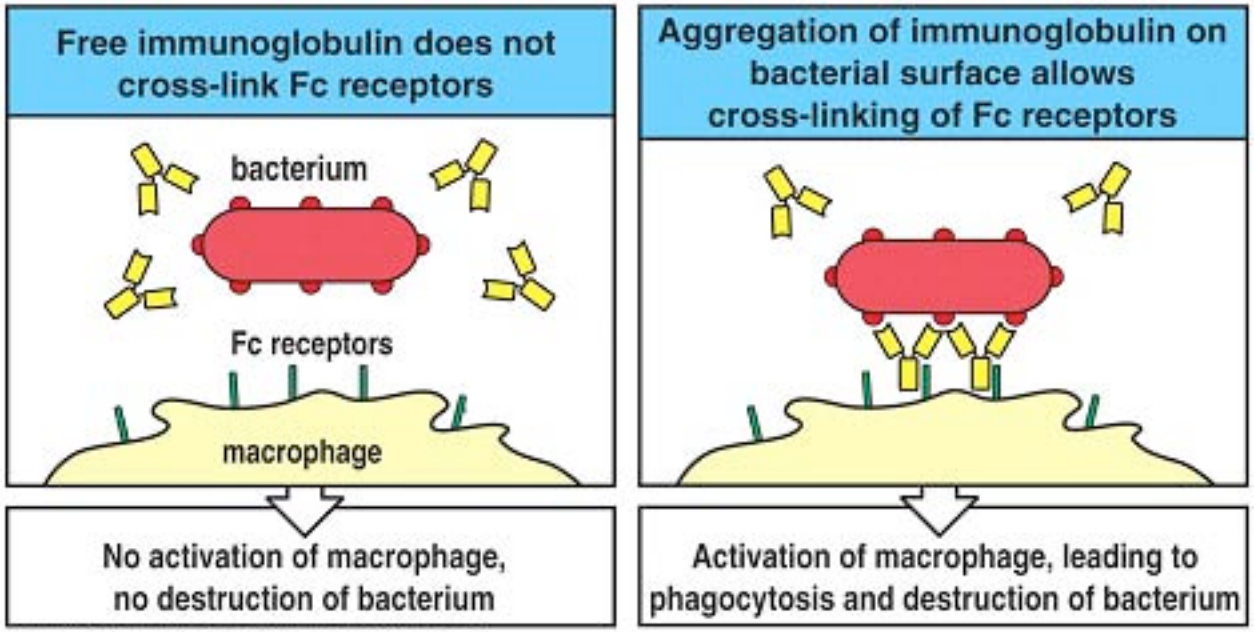


Figure 9-31 Immunobiology, 6/e. (© Garland Science 2005)

IgM does not have free Fc regions and there are few Fc receptors for IgM. But IgM is efficient at complement activation and uses C3b for an opsonin (IgM is not an opsonin but it is very efficient at inducing production of C3b, a good opsonin).

Fc receptors and complement receptors synergize to make phagocytosis of bacteria and other organisms very efficient

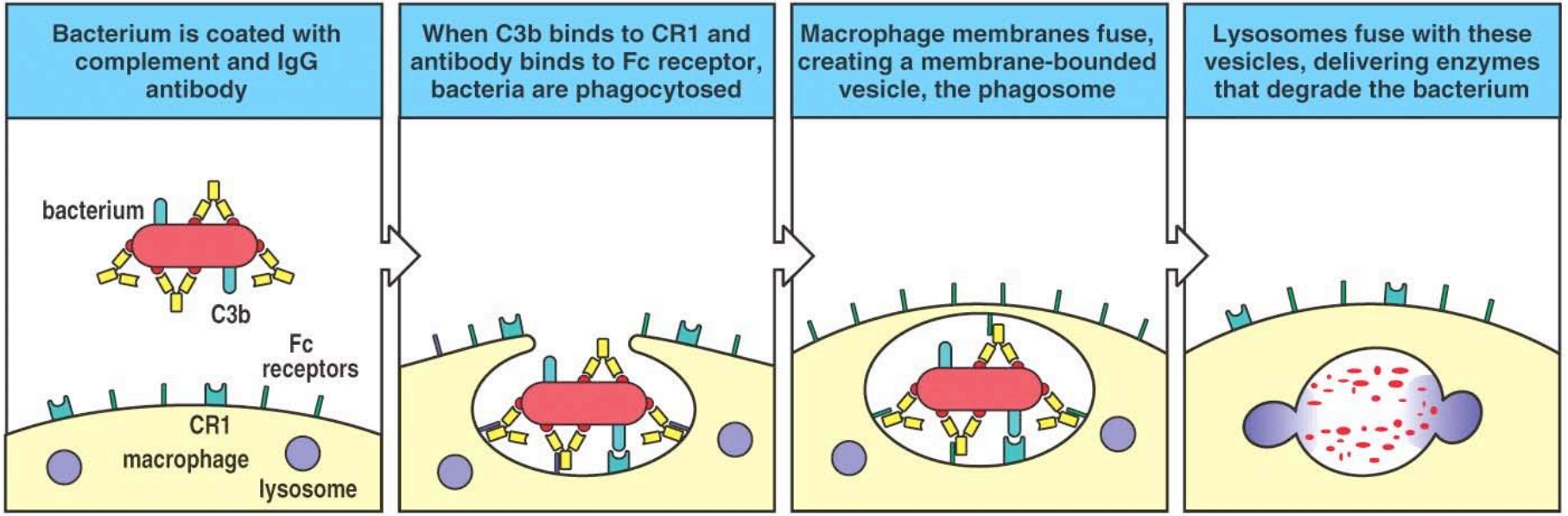


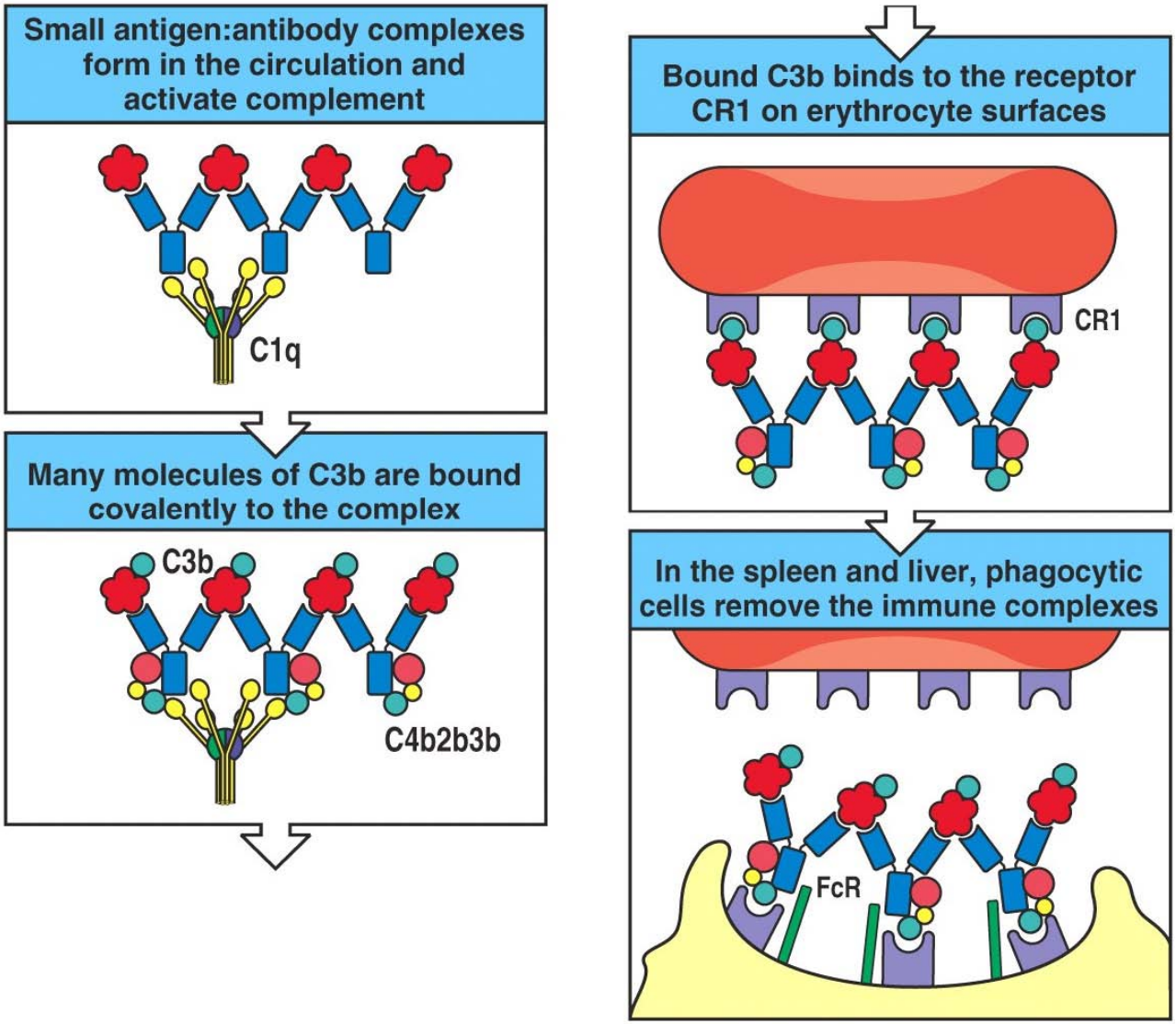
Figure 9-32 Immunobiology, 6/e. (© Garland Science 2005)

Antibodies can activate complement

but

complement can be activated without antibody

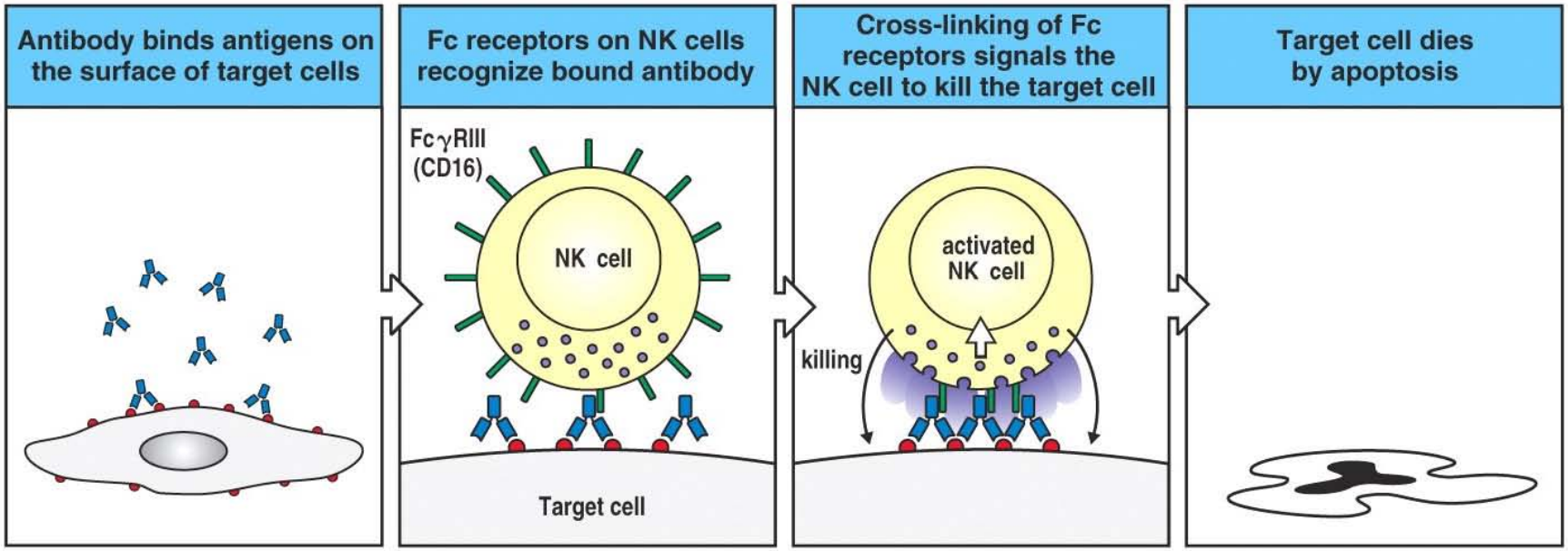
Red blood cells (RBC) help clear immune complexes (antigen-antibody complexes) from the blood via complement receptors on the RBCs.



Immune complexes that are not removed from the blood in the liver or spleen tend to get deposited in the kidneys

This can cause glomerulonephritis (inflammation of the glomeruli) and kidney failure

Antibody dependent cell-mediated cytotoxicity (ADCC)



NK has two ways to recognize targets:

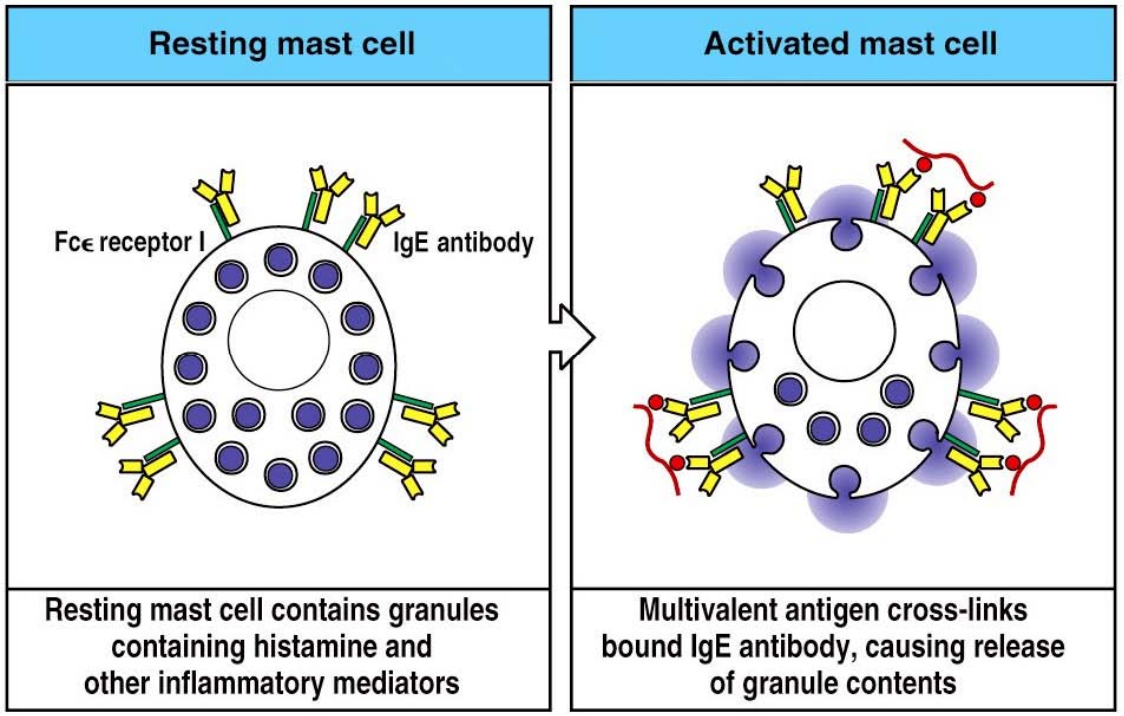
(1) lack of MHC class I on the target (innate immunity)

(2) antibody on the target (adaptive immunity)

IgE plus antigen causes degranulation of mast cells (granules contain histamine and other compounds that cause inflammation)

Mast cells can bind antibodies with FcεR in the absence of antigen (unlike other FcRs)

The binding affinity of FcεR for IgE is 100 to 50,000 time greater than the affinity of most other FcRs for antibody



Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	–	++	++	++	++	++	–
Opsonization	+	–	+++	*	++	+	+	–
Sensitization for killing by NK cells	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+	–	+	–	–	+++
Activates complement system	+++	–	++	+	+++	–	+	–