B cells and Antibodies

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Adaptive immune system

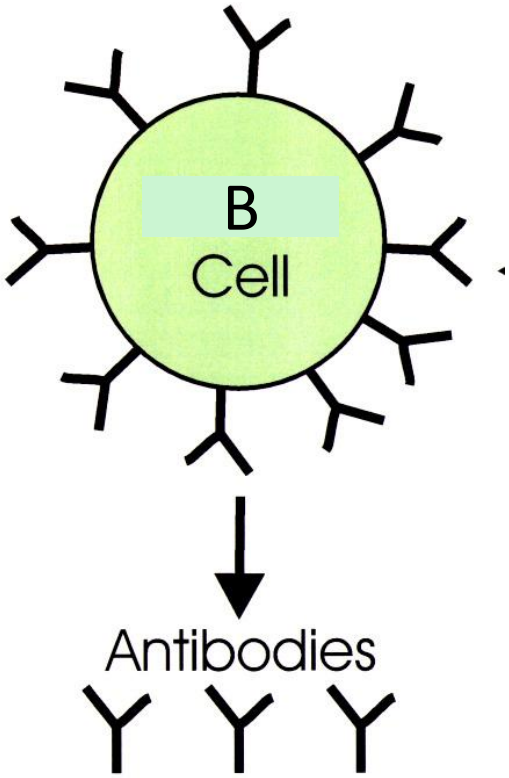
B Cells **T Cells**

B cells

Made in the bone marrow

Select gene segments to make immunoglobulins (Ig)

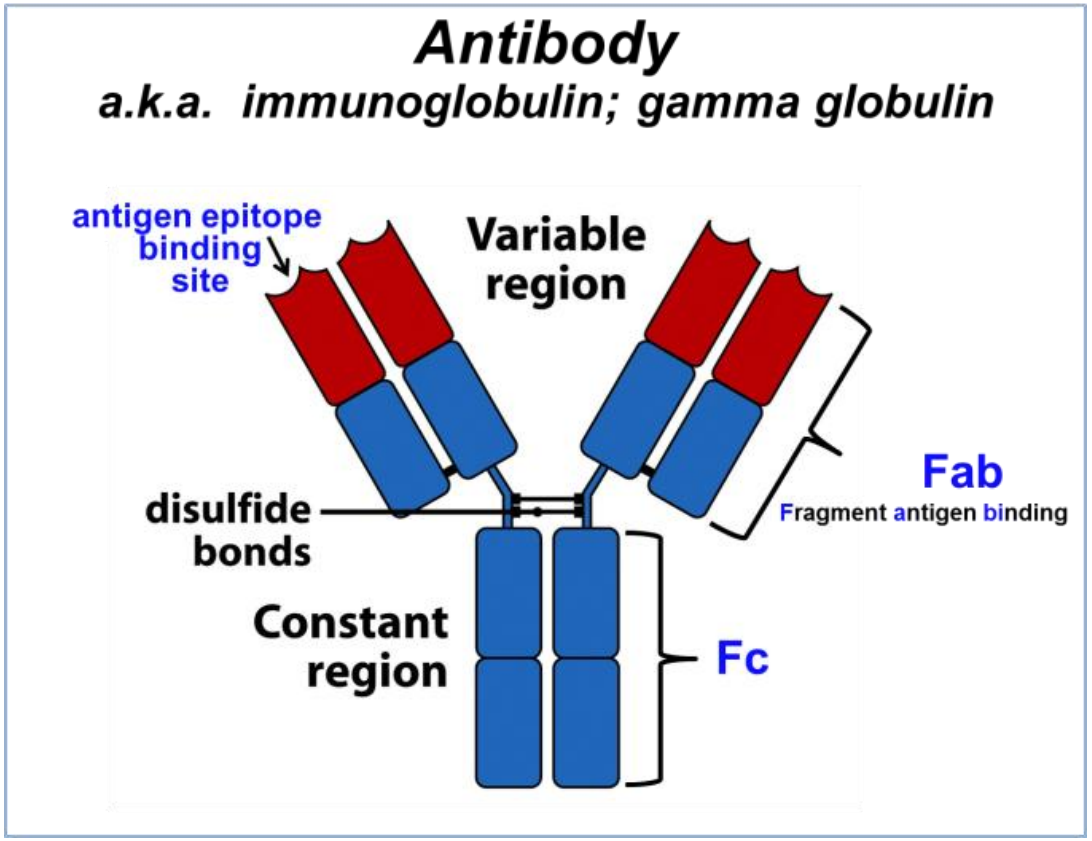
Some Igs are on the surface, others are secreted.



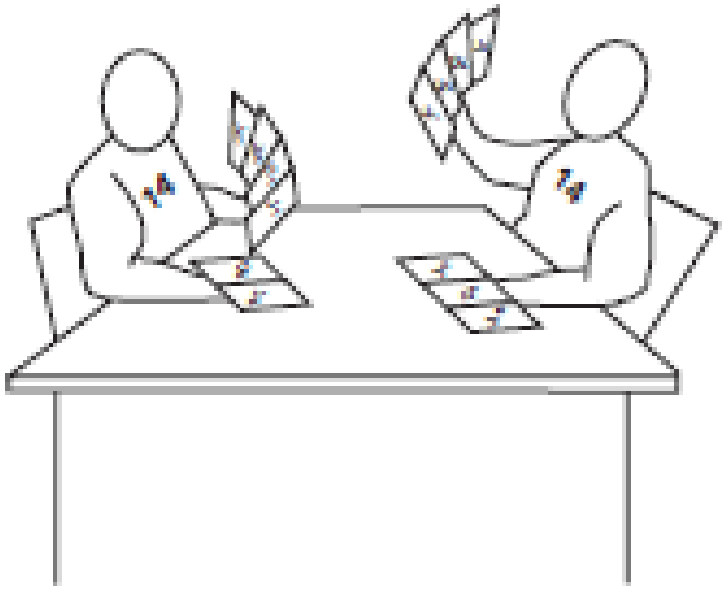
B Cell Receptor

Ig genes are on chromosome 14

We have two copies of each,
Which one will be used??



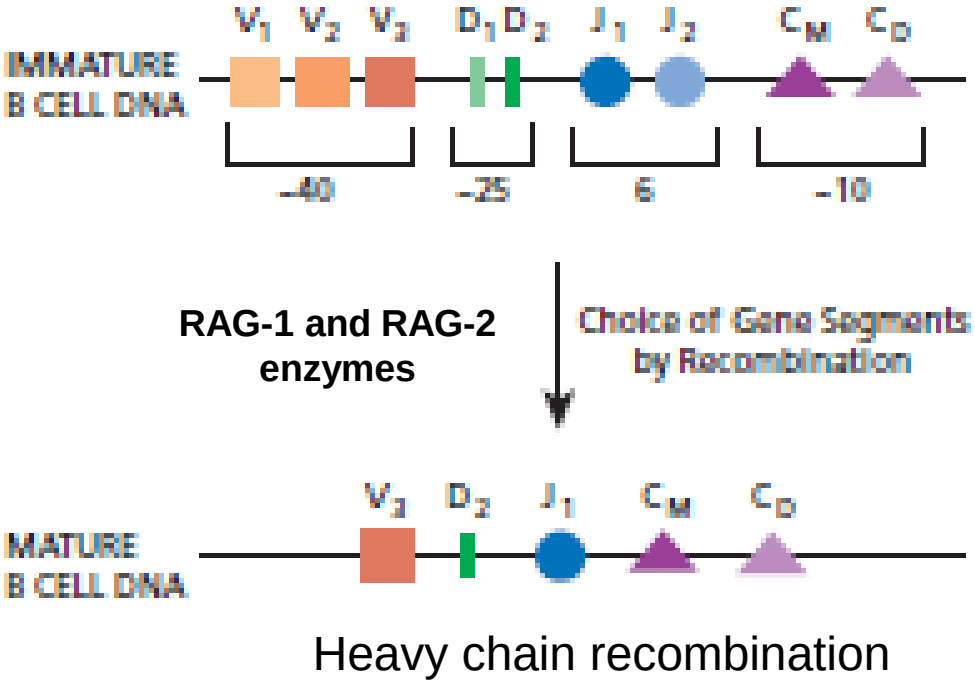
Card game- winner takes it all



Gene rearrangement test:

Full Heavy/light chain?
Did it load on cell surface?

If yes, inactivate other copy of chromosome 14



Heavy chain recombination

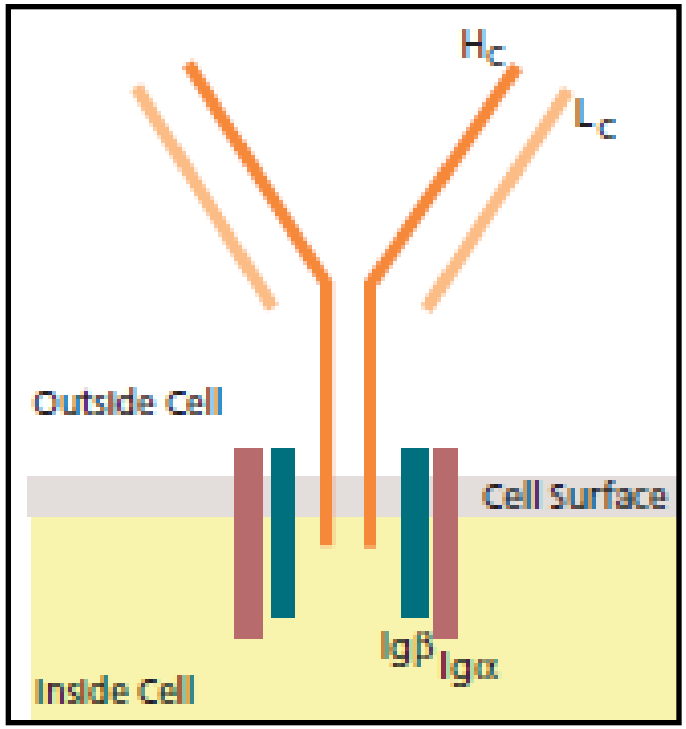
If both copies fail:

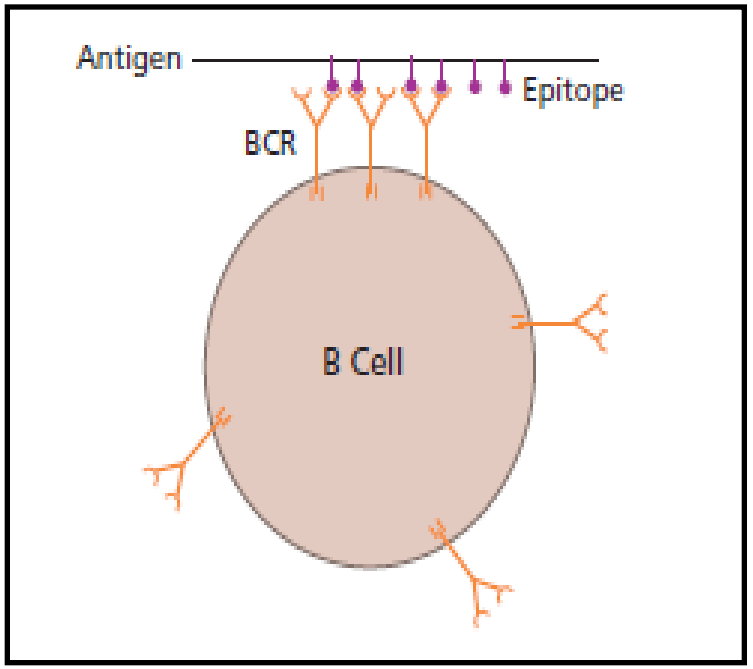
B cell dies, by apoptosis

One B cell→ **One** antibody (one heavy and one light chains)

Recombination options so many! We can produce antibodies to **every** organic molecule available.

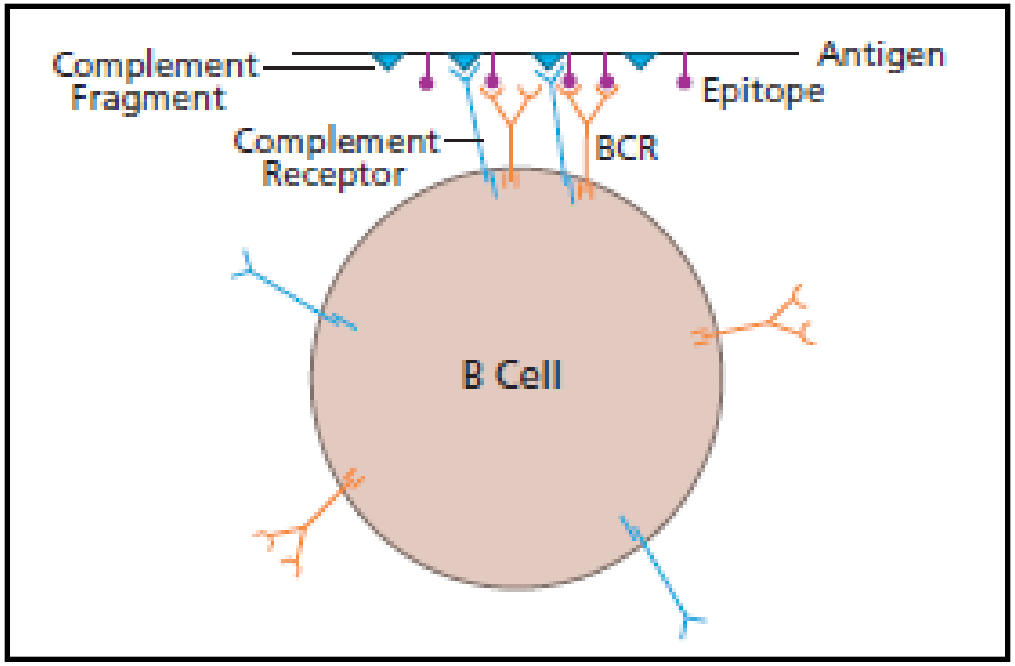
BCR signaling





Accessory proteins are required for signaling
but cross-linking of antibodies is key.

Opsonization by complement system greatly amplifies BCR signaling



Complement receptor engagement tightens BCR binding and signaling

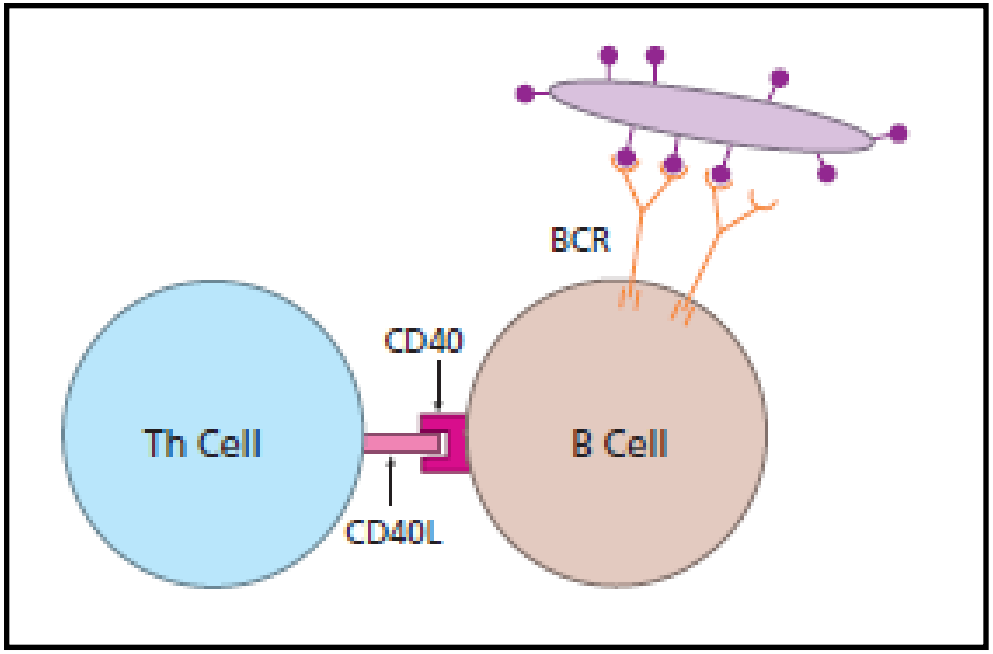
How are B cells activated?

Two-step activation system:

1- BCR engagement and clustering

2- Co-stimulatory signal

(T-cell-dependent: CD40L)
(T-cell independent: cytokines: IFN-γ)



What is the purpose of T-cell-independent activation??

B cell maturation

1- Class Switching

2- Somatic hypermutation

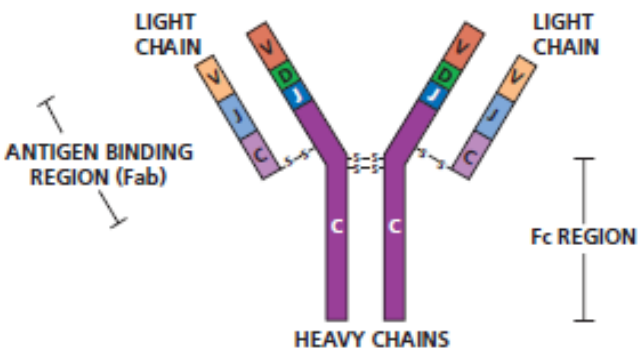
3- Career Decision

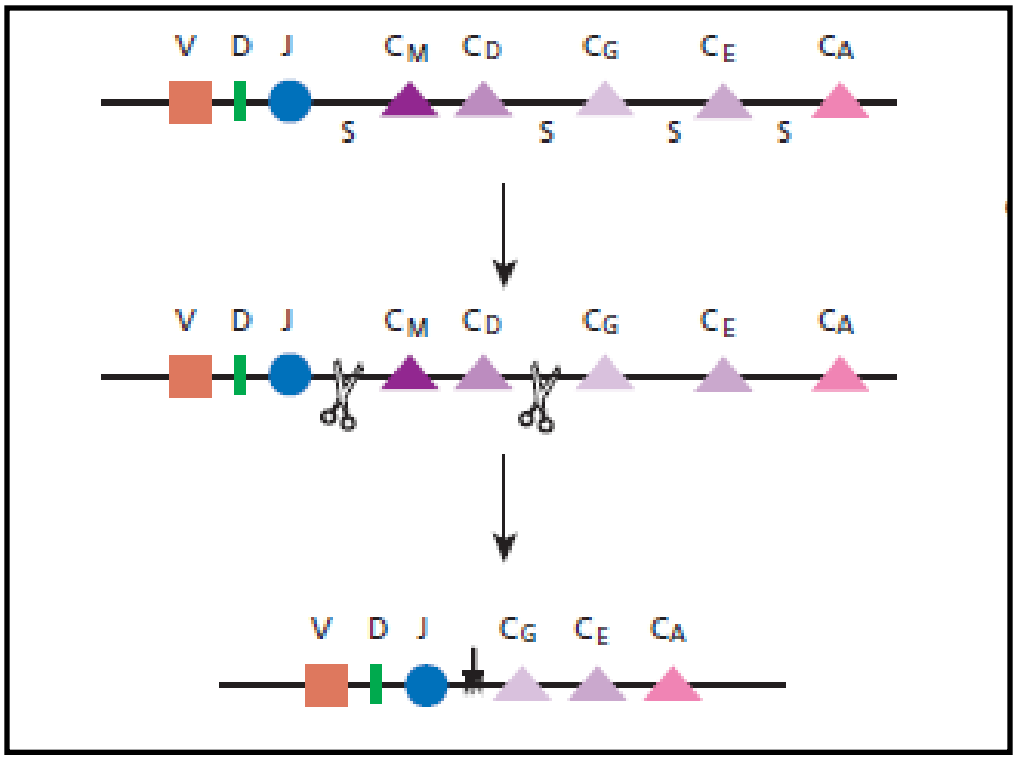
Class Switching

Changing antibody class from IgM or IgD **to** IgG, IgA, or IgE.

Why?

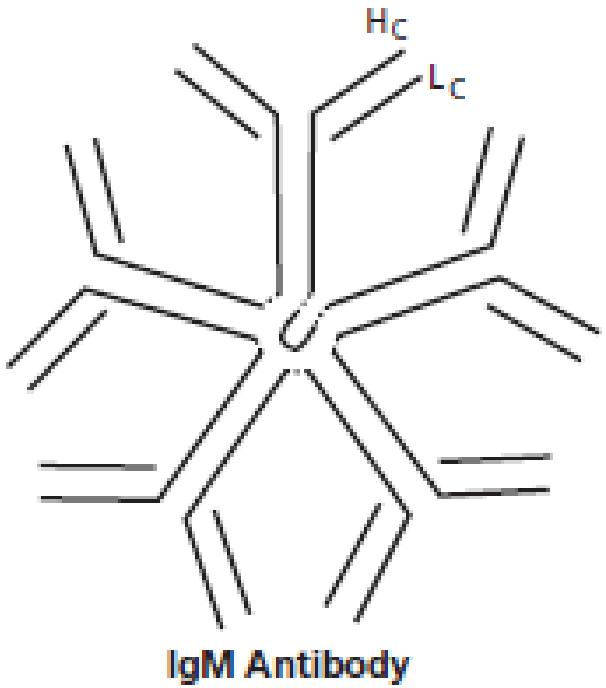
Class switch from IgM to IgG





Antibody classes and their function

IgM Antibodies



IgM Antibody

Pentamer, first antibody to be produced.

Can trigger classical complement pathway
through bringing C1 molecules in close proximity.

C1s bind to Fc portion, get activated and subsequently
Activate the C3 convertase causing a complement
cascade on the surface of the pathogen.

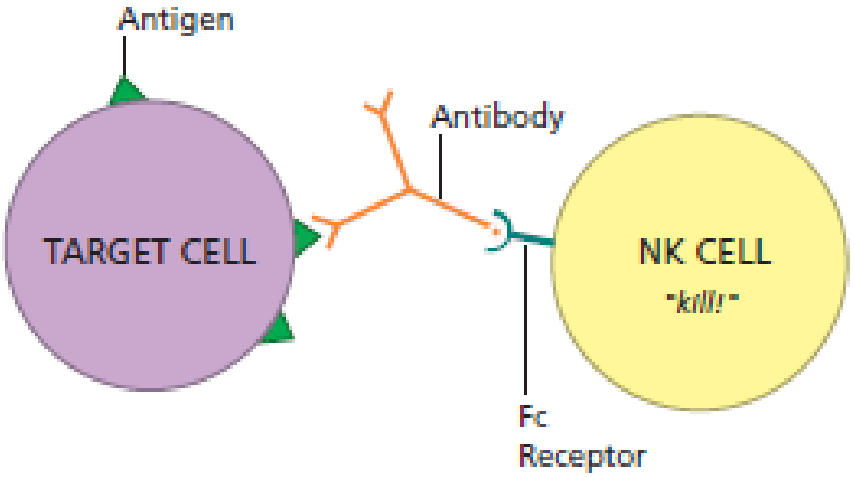
Why is the classical pathway needed?

Why IgM not IgG first??

Better complement fixer, better neutralizing ability

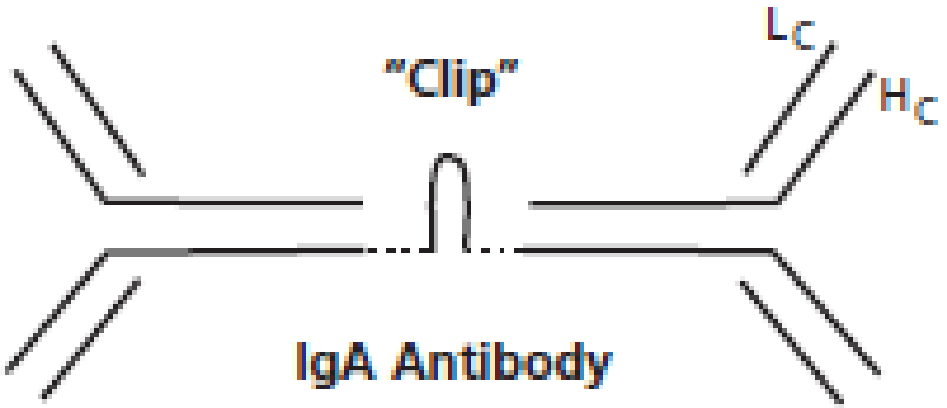
IgG Class

Called Gamma globulins. Bad complement fixers, good virus inactivators.
Can cross placenta, half-life about 3 weeks, how long does IgM live??
Four subclasses: IgG1, IgG2, IgG3, IgG4
IgG1 is a good opsoniser. Macrophages and neutrophils have receptors for IgG1-Fc
IgG3 fixes complement better than other subclasses. NK cells have receptors for it.



Antibody-dependent cellular cytotoxicity (ADCC)

IgA class



Main Ab class that guards the mucosal surfaces of the body.

Its structure facilitates its transport to intestines, and makes it resistant to acids and enzymes

Dimeric structure helps clump bacteria together to be swept out with mucus or feces.

Secreted into the milk of nursing mothers. Why?

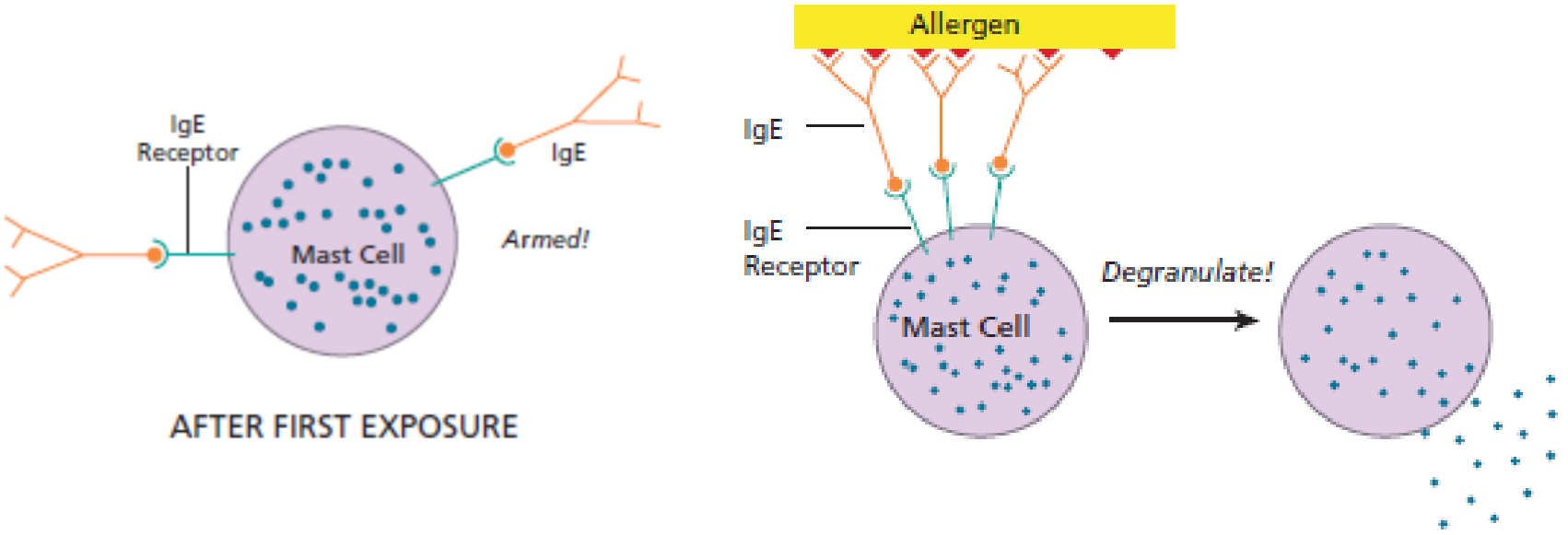
Good or bad complement fixers??

IgE class

1-Parasitic Infections: IgE is made, Fab binds to parasite, Fc binds to mast cell

Mast cell releases histamine and cytokines such as TNF and IL-3,4,5 to kill parasites.

2- **Allergies:**



Allergic reaction, anaphylactic shock in some cases!

Ab Classes and functions

ANTIBODY CLASS	ANTIBODY PROPERTIES
IgM	Great complement fixer Good opsonizer First antibody made
IgA	Resistant to stomach acid Protects mucosal surfaces Secreted in milk
IgG	OK complement fixer Good opsonizer Helps NK cell kill (ADCC) Can cross placenta
IgE	Defends against parasites Causes anaphylactic shock Causes allergies

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

Property	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	–	–	–	–	–	+++ (dimer)	–
Transport across placenta	–	–	+++	+	++	++	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg/ml)	1.5	0.03	9	3	1	0.5	2.5	5×10^{-5}

Figure 4.32 The Immune System, 3ed. (© Garland Science 2009)

What triggers class-switch?

Cytokines produced by Th cells

IL-4 and **IL-5** favour a switch to **IgE** (Parasitic infections)

IFN-γ favours switch to **IgG** (Fights bacteria and viruses)

TGF-β favours a switch to **IgA** (Common colds, intestinal infections).

Somatic Hypermutation

Mutation rate in our genome is approximately 1:100,000,000 b.p. per replication cycle.

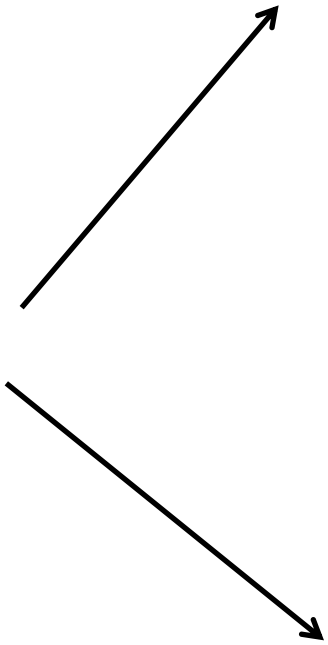
After VDJ segments have been selected, this region undergoes very high mutation rate: (As high as 1:1000 b.p. per generation).

This somatic hypermutation affects affinity of Fab region of B cell antibody.

B cells with higher affinity are better stimulated by antigen and so proliferate more And take over.

B cells can change both their Fc region (Class-switch) and Fab region (somatic hypermutation) to become better adapted to fight invaders.

B cells make a career choice



Plasma Cell

Go to spleen or bone marrow and secrete Abs (up to 2000 Abs/sec)

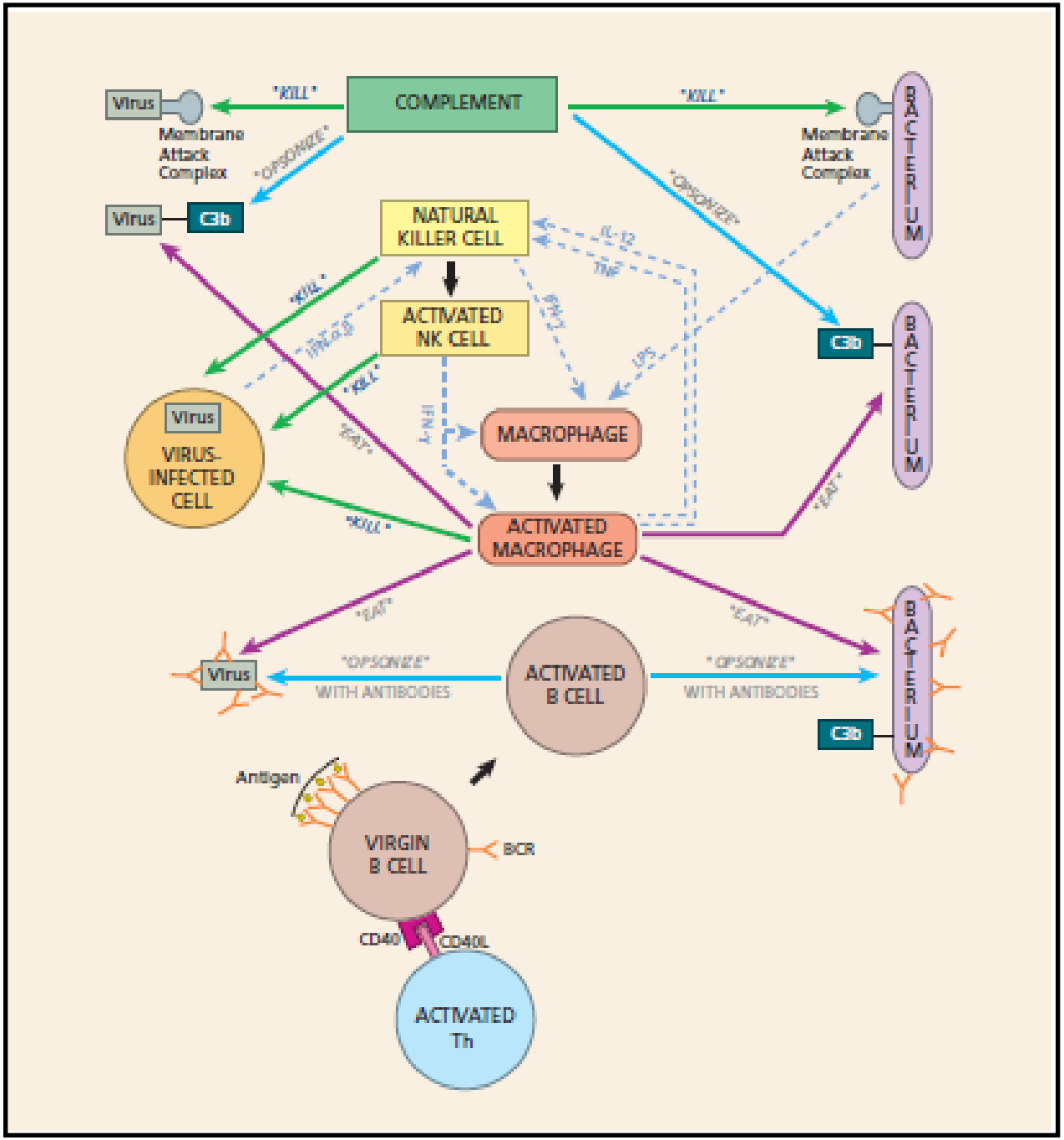
Short-lived (few days)

Memory Cell

Cells that remember the first exposure

Defend against subsequent exposure

Need Th cells to develop (CD40L)


Virus
"KILL"
COMPLEMENT
"KILL"
Membrane Attack Complex
"OPSONIZE"
Membrane Attack Complex
BACTERIUM
Virus
C3b
"OPSONIZE"
NATURAL KILLER CELL
IL-12
TNF
"KILL"
ACTIVATED NK CELL
IFNγ
"KILL"
IFNγ
LPS
C3b
BACTERIUM
Virus
VIRUS-INFECTED CELL
"EAT"
IFNγ
MACROPHAGE
"KILL"
ACTIVATED MACROPHAGE
"EAT"
"EAT"
"EAT"
Virus
"OPSONIZE" WITH ANTIBODIES
ACTIVATED B CELL
"OPSONIZE" WITH ANTIBODIES
C3b
BACTERIUM
Antigen
VIRGIN B CELL
BCR
CD40
CD40L
ACTIVATED Th

Thank you!

Questions???