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B lymphocytes

Lectures 5 and 6 handout

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2017

PLEASE NOTE: this might look as if it's a large handout, but it is easy, and remember, these are actually two lectures.

Introduction

The specific immune system is composed of the B and the T lymphocytes. B cells produce antibodies (AB), also called immunoglobulins (Ig) which circulate in the blood, and this is called *humoral immunity* (humoral means something related to body fluids, and AB circulate in a body fluid, the blood), whereas T cells are responsible for *cellular immunity*. This handout describes B lymphocytes and their role in the adaptive immune system.

The main aim of stimulating a B cell is the production of antibodies. This process involves several steps: first the B cell must recognize an antigen through the B cell receptor (BCR), this causes stimulation of the receptor mainly via clustering of several receptors, and then the receptor must be activated. Activation of the receptor occurs through 2 mechanisms, one involves T cells (T cell dependent activation) and the other doesn't involve T cells (T cell independent activation). The activated receptor needs to send a message to the nucleus to start AB production. This message is conveyed via an associated part of the BCR called immunoglobulin alpha and immunoglobulin beta. Then a cascade of second messengers are stimulated to reach the nucleus. Now transcription and translation of gene segments starts to produce the AB. At the same time cytokines and growth factors cause proliferation of the stimulated B cell so it gives a large number of that particular B cell (clonal expansion). The activated B cells mature further during this process and undergo changes like increasing their affinity to bind to antigens.

This is an overview of the whole process and these two lectures describe the details of these steps.. *Relax and enjoy*

But first let's describe the origin and maturation of B cells

B cell development and maturation

B Cells originate from bone marrow stem cells where one billion B cells are produced each day.

While in the bone marrow, each B cell chooses the antibody arrangement (the mix and match we discussed in the first lecture). This antibody arrangement codes for the B cell receptor (BCR) and the antibody the B cell will produce. Actually, BCR is an antibody (AB). The only difference between BCR and AB is that the AB lacks the small protein sequence at the tip of the heavy chain. This sequences fixes the receptor to the B cell surface. Because the AB lacks this sequence it is not fixed to the surface, it circulates in the blood.

Note that B cells originate from bone marrow and also mature in the bone marrow.

All Lymphocytes (B , T, and NK) originate from multipotent hematopoietic stem cells in the bone marrow and they develop through a series of events that include:

1. *Commitment* of progenitor cells to the B lymphoid or T lymphoid lineage. This commitment depends on *signals from several cell surface receptors that induce transcriptional regulators* that drive development toward either B cells or T cells.

2. Proliferation of progenitors and immature committed cells at specific early stages of development, providing *a large pool of cells that can generate useful lymphocytes*. Early maturation is characterized by cell proliferation *induced by cytokines*

3. The sequential and ordered rearrangement (or recombination) of antigen receptor genes (the mix and match process) and the expression of antigen receptor proteins. The expression of antigen receptors is essential for the survival, expansion, and maturation of developing lymphocytes .This process of somatic gene recombination is mediated by *a recombinase enzyme complex made up of the lymphocyte-specific components Rag-1 and Rag-2.*

4. *Selection* events that preserve cells that have produced functional antigen receptor proteins and eliminate potentially dangerous cells that strongly recognize self antigens. During the gene rearrangement some cells fail to do an arrangement that produce BCR, others succeed but form receptors that recognize self-antigens, these both types of cells are deleted by apoptosis. Only cells that manage to produce BCR that recognizes non-self antigens survive… it's a tough life for the B cell!

5. *Differentiation* of B cells into functionally and phenotypically distinct subpopulations. The cells that survived step 4 mature further to become **follicular, marginal zone, or B-1 cells**.

Bone marrow–derived stem cells give rise to the majority of B cells. These cells, also called **B-2** cells, rapidly pass through two transitional stages and can commit to development either into **marginal zone B cells or into follicular B cells**.

B-1 cells represent a distinct lineage that develops from fetal liver and produce membrane-associated IgD in addition to IgM. B1 cells expresses antigen receptors with limited diversity

Most murine B-1 cells spontaneously secrete IgM antibodies .most IgM antibodies against ABO blood group antigens are derived from B-1 cells. *These antibodies are sometimes called natural antibodies because they are present in individuals without overt immunization,* although it is possible that microbial flora in the gut are the source of antigens that stimulate their production. B-1 cells contribute to rapid antibody production against microbes in particular tissues, such as the peritoneum. It's not obvious if B1 are important in humans.

Marginal zone B cells are located primarily in the vicinity of the marginal sinus in the spleen and in lymph nodes. Marginal zone B cells are similar to B-1 cells in terms of their limited diversity and their ability to respond to polysaccharide antigens and to generate natural antibodies.

Marginal zone B cells express IgM but no IgD and they don't have high levels of the CD21 coreceptor, which distinguishes them from follicular B cells (this means follicular cells have both IgM, IgD and also CD21.. don't worry I'll tell you what the CD 21 is later)

Marginal zone B cells respond very rapidly to blood-borne microbes and differentiate into short-lived IgM-secreting plasma cells. Marginal zone cells can also participate in T-dependent immune responses and can collaborate with NKT cells in response to antigens.

The majority of mature B cells are Follicular cells. These coexpress IgM and IgD on their surface and this helps them interact with antigens in an effective manner.

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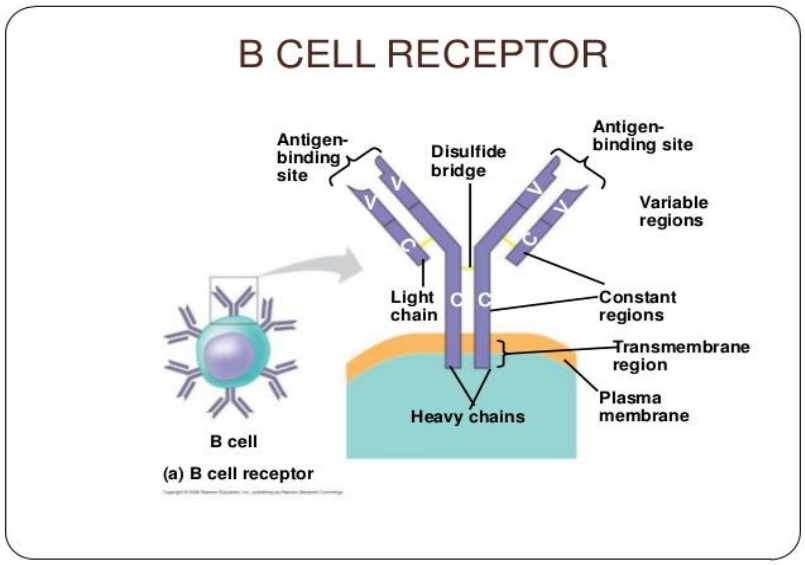
B cell receptor



Note from the picture above that BCR is an AB. Note the transmembrae region, this is a hydrophobic amino acid sequence that anchors the BCR to the cell membrane. This is not present in immunoglobulins and that's why Ig do not bind to the membrane, but circulate in blood instead

Each B cell has one unique BCR that is specific for one antigen. This receptor is selected through modular design during B cell maturation in the bone marrow (modular design is the mix and match process described in lecture 1)

Genes coding for both heavy chain and light chain are assembled through modular design. Genes for BCR heavy chain are found on chromosome 14. Each B cell contains 2 copies of chromosome 14 (maternal and paternal). Each copy starts a rearrangement of DJ segments of the heavy chain gene and delete the DNA in between. Then a V segment is chosen and joined to the DJ , again by deleting the DNA in between

Next to the J segment there are C segments that code for the constant region. Closest to the J are the c segments that code for IgD and IgM, so one of these is chosen for the BCR. This means that by default the BCR is of immunoglobulin class D or M, not any other!

There are several possible gene arrangements that occur during this process of modular design. Genes from both copies of chromosome 14 do these rearrangements, but one rearrangement is used to create the BCR. Actually not all of these rearrangements will work and be suitable to be translated to produce a heavy chain. What happens is that these arrangements are translated but the majority of them will have a **stop codon** and be useless.

One arrangement might work. Its protein product (BCR) is transported to the surface of the cell. The rearrangement that works is called **productive arrangement.**

Once the BCR is fixed to the surface it sends signals to the other chromosome to stop rearrangement so that chromosomal genes are silenced.

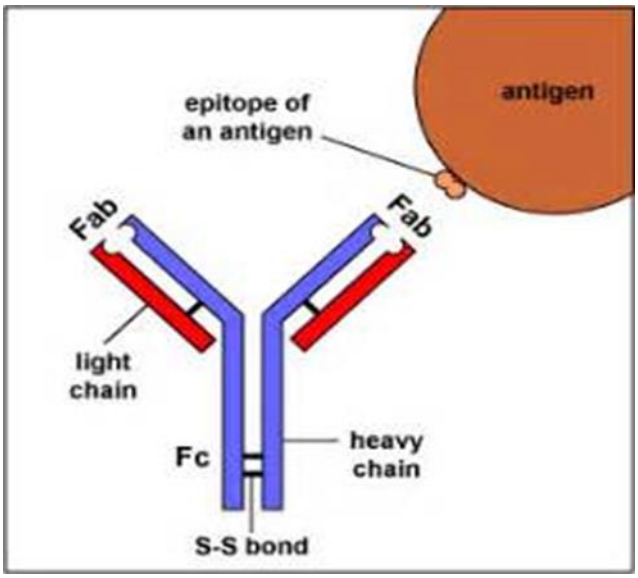
In some B cells no productive arrangement is achieved, these cells die by apoptosis.

Note that the BCR contains also a light chain, which is assembled through modular design. For the production of a BCR we need the B cell to have productive arrangement of the light chain but also it is must that the light and heavy chain in that cell fit together to create the BCR.

If no productive light arrangement or if the light and heavy do not complement each other, the cell dies by apoptosis .

How BCR recognize antigens

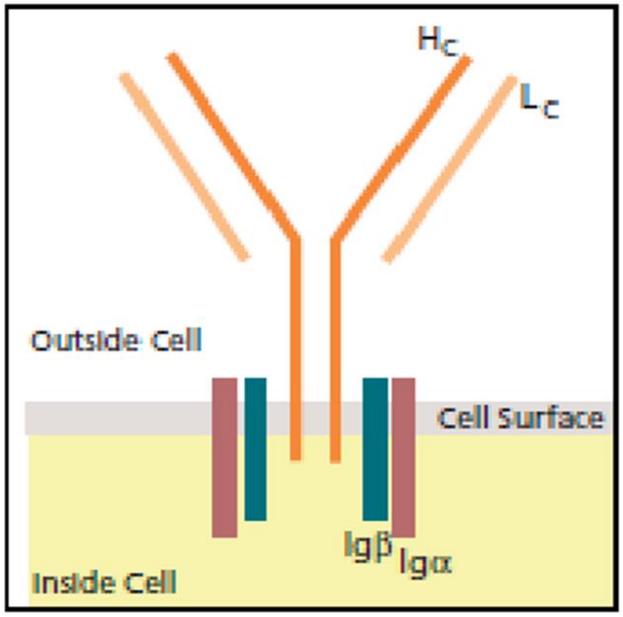
Each BCR recognizes one specific antigen called the **cognate** antigen (basically this means the complementary antigen) . BCR binds to a tiny part **(6-12 amino acids**) of the antigen. This is called **the epitope**.



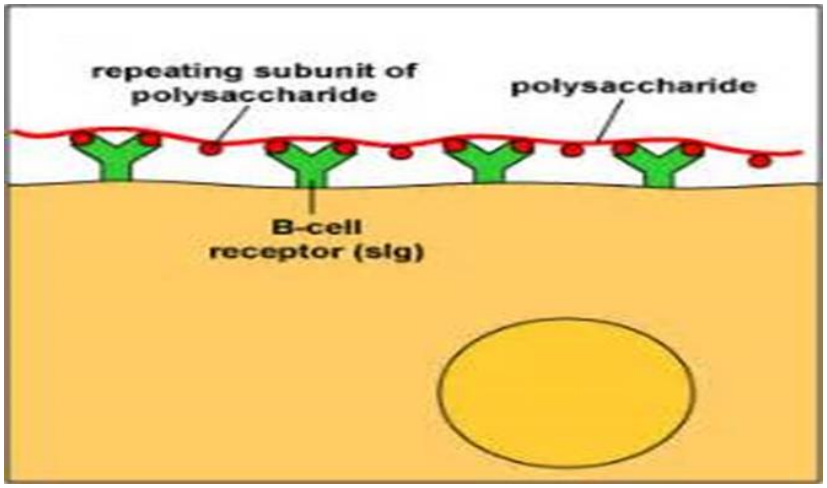
Note from this picture that the BCR binds only to a tiny part of the antigen, the epitope.

Once the B cell binds to the epitope it needs to send a signal to the nucleus in order to start immunoglobulin synthesis .This signalling is done through two segments that bind the intracellular part of the heavy chain, these are called **Ig alpha and Ig beta**

Note that Ig alpha and beta do not recognize antigens. They only act as second messengers.



For signaling to the nucleus to happen, we need clustering of B cell receptors. This clustering is called **cross linking**. Cross linking happens when adjacent BCR recognize repeated epitope sequences on an antigen or when the receptors recognize several epitopes from several closely located antigens on a bacterial surface



This pic shows cross linking of B cell receptors. This is essential for BCR stimulation.

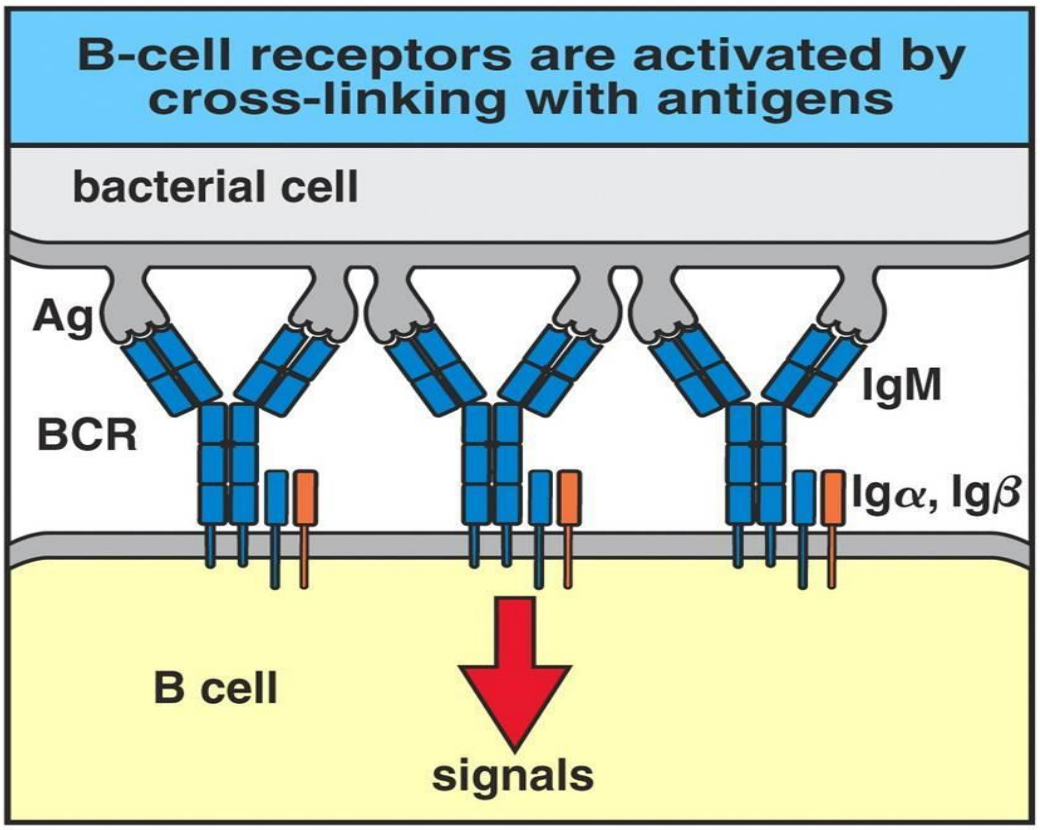


Figure 7-1 The Immune System, 2/e (© Garland Science 2005)

This cross linking is important because it allows enough signals to be transmitted to the Ig alpha and beta to start the cascade of second messengers to convey a message to the nucleus.

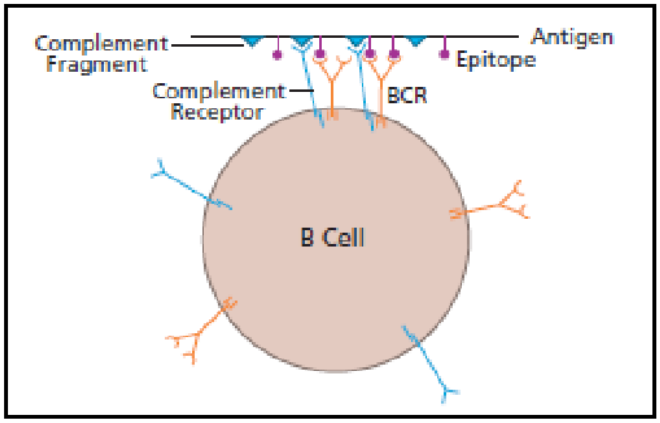
On B cells there is another type of receptor***; a complement receptor (CR2 or CD21)that binds complement opsonins like C3b (note that when c3b acts as an opsonin sometimes it's called iC3b, so don't be confused) and C3d which is recognized by the CD21***

If a bacterium is opsonized the B cell will recognize two things in the bacteria: the BCR (AB) recognizes the epitopes and the complement receptor will recognize the complement component (the opsonin)

If both receptors act together the need for crosslinking is decreased and the second messages are amplified.

Note: the *complement receptor is considered a co-receptor*, because of its effect in helping the BCR to be stimulated and in decreasing the need for crosslinking.

Opsonization by complement system greatly amplifies BCR signaling



Complement receptor engagement tightens BCR binding and signaling

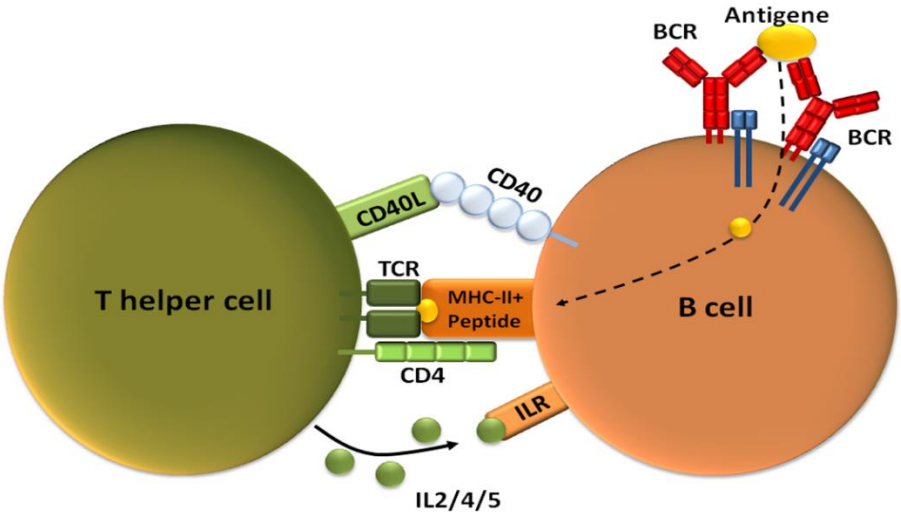
B cell activation

B cells that have never encountered their cognate antigen are called naïve B cells or virgin B cells. Activated B cells are called experienced B cells

Once the antibody recognizes its cognate antigen, the B cell can be activated. There are two ways of activating B cells: 1. T cell dependent and 2. T cell independent activation.

B cell activation always needs two signals, the **First signal is the BCR crosslinking**. The second **signal is called a co-stimulatory signal**, which can be achieved through T cell dependent or T cell independent activation.

In T cell dependent activation, the second signal occurs when a ligand on the surface of T helper (Th) cell is attached to its complementary molecule on the surface of a B cell. These molecules that produce the costimulatory signal are **CD40 on the B cell and CD40L (standing for CD40 ligand) on the T cell**



This pic shows T cell dependent activation, cross linking of the BCR is the first signal, the second occurs from T helper cells (CD40- CD40L attachment)

T cell independent activation occurs if the antigen has many repeated similar epitopes. This will cause clustering (cross linking) of many BCR. Bacterial carbohydrates usually have these repeated epitopes. However, **another signal is still needed, which is a danger signal usually recognized by toll like receptor**

Why the second signal is important? Because if the BCR recognizes repeated DNA sequences from the individual (self DNA) the clustering of BCR will happen. If no second signal is needed this will result in the B cells attacking self DNA. But because the second signal is essential this will not happen because Toll like receptors will not send a danger signals (they don't recognize self DNA).

T cell independent activation gives B cells a chance to be activated quickly without waiting for T cells to be activated.

This is important in: most B some bacterial infections. For example cells that are activated in the T cell independent activation are present in the spleen. These act quickly against Streptococcus pneumonia infection. People who have their spleen removed are at risk of having clinically significant streptococcus pneumonia infection.

Note that T cell recognizes only protein antigens presented to them. So if all the B cell activation will depend on T cells then the adaptive immune system will be able only to fight

against protein antigens. The presence of T cell independent activation allows B cells to act against non-protein antigens.

The presence of two signaling system is very important to keep AB response regulated so this decreases the chances of B cells reacting against self antigens

Note that T cell dependent and independent activation is specific to a certain antigen , so one clone of B cells will be activated and one type of AB will be produced (**monoclonal AB** production)

However, sometimes antigens cause polyclonal proliferation of B cells, so many types of B cells are activated and several classes of AB are produced… this is called **polyclonal activation**. The antigens that cause this polyclonal activation are called **mitogens** and mitogens are found mainly on **parasites**.

Signal transduction

Cross linking of BCR and subsequent activation of the B cell stimulates kinases (Src family kinase, don't worry too much about the name the idea is that there is kinase activation)– the kinase causes phosphorylation of the ITAM tyrosines of Igα and Igβ, followed by the recruitment and activation of Syk Activating receptors (again just get the idea not the name).

ITAM= immunoreceptor tyrosine-based activation motifs ,these contain tyrosine residues that become phosphorylated by cytoplasmic kinases after binding of ligands to the receptors. Other protein kinases are recruited to the modified ITAMs and become activated, and these kinases contribute to further signaling by phosphorylating additional proteins,

ITAMs also found in the cytoplasmic tails of several signaling receptors in the imune system, including the antigen receptor complexes of T and B cells as well as in NK signaling.

NOTE : in NK cells inhibitory motifs called **ITIMS = immunoreceptor tyrosine based inhibitory motifs are also present.**

SUMMARY OF BCR ACTION

BCR recognize a small sequence of the antigen; the epitope. After recognition, the receptor is stimulated via cross linking. Sometimes a co-stimulatory receptor (CD21) is engaged in the process, which is a receptor that recognizes complement opsonins. In both cases (cross linking alone or cross linking and costimulation with CD21) a second signal is needed to activate the B cell. There are two ways to activate B cells that provide the second signal: T cell dependent, where T helper's CD40l interacts with CD40 receptor on the B cell. The second way is the T cell independent where the Toll like receptor provides the second signal.

Once activated a signal to produce AB is transmitted to the nucleus and this occurs through activation of tyrosine kinases of Ig alpha and beta (ITAMS) and then by second messengers.

B cell maturation

Once B cells are activated, they mature

Maturation involves three things

1. **AB class switching**, remember that the first AB (the default Ab produced by any B cell is IgD or IgM) but once B cells mature they can change the AB class they produce to the class suitable for the specific situation.

2. somatic hyper-maturation or **affinity maturation**, this is a process through which B cells can increase affinity of their immunoglobulins to antigens

3. **differentiation**, B cells decide if they will become plasma cells or memory cells.

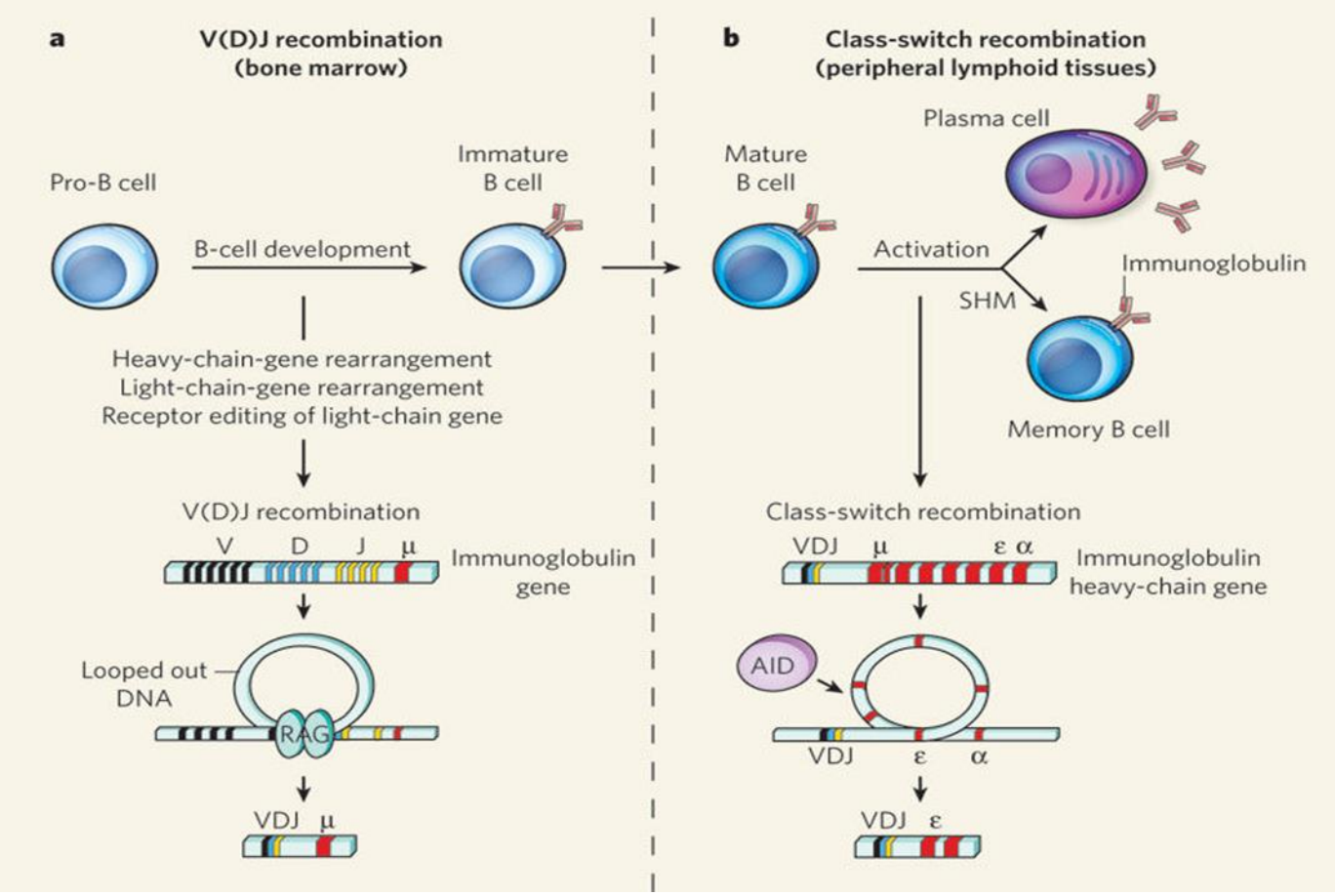
AB Class switching

The default Ig type secreted by B cells is IgM or IgD.. Refer to the beginning of the lecture if you have already forgotten! IgM is much more than IgD and it is not clear if IgD has any function in our cells apart from acting as a receptor.

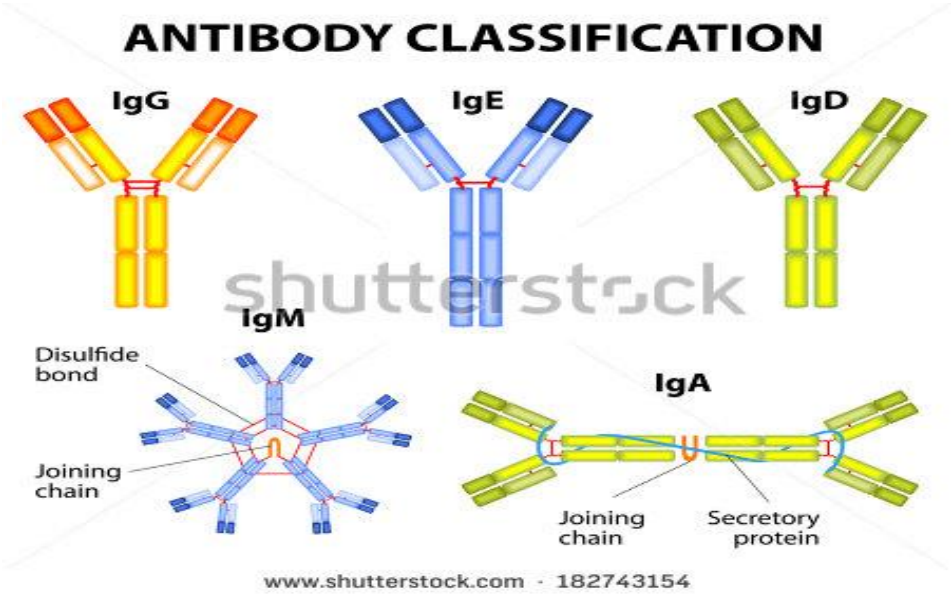
This means that when BCR is activated the signal sent to the nucleus will always cause production of IgM, not any other type! IgM has a large structure suitable for the first defense action, but it has a limited half life, so switching to another AB class is needed.

Remember that the C region determines the classes of the antigen because it codes for the Fc region of the AB .To switch antibody class the B cell changes gene arrangement of the C module.

So with class switching only the Fc region changes without changing the variable region which means antigen recognition is not changed


a
V(D)J recombination
(bone marrow)
Pro-B cell
B-cell development
Immature
B cell
Heavy-chain-gene rearrangement
Light-chain-gene rearrangement
Receptor editing of light-chain gene
V(D)J recombination
V D J μ
Immunoglobulin
gene
Looped out
DNA
RAG
VDJ μ
b
Class-switch recombination
(peripheral lymphoid tissues)
Mature
B cell
Plasma cell
Activation
SHM
Immunoglobulin
Memory B cell
Class-switch recombination
VDJ μ ε α
Immunoglobulin
heavy-chain gene
AID
VDJ ε α
VDJ ε

AB classes:



General antibody structure and function

Antibodies (AB) (also called immunoglobulins (Ig)) are a family of glycoproteins produced by B lymphocytes and function as mediators of specific humoral immunity antigens. The antigen-binding regions of antibody molecules are highly variable, and we have the potential to produce millions of different antibodies, each with distinct antigen specificity.

All antibodies have a common symmetric structure composed of two identical covalently linked heavy chains and two identical light chains, each linked to one of the heavy chains. Each chain consists of two or more independently folded Ig **domains** of about 110 amino acids containing conserved sequences and intrachain disulfide bonds. Each domain contains 2 layers of beta pleated sheet, each layer is composed of 3-5 strands of polypeptide chains

The N-terminal domains of heavy and light chains form the variable regions (V regions) of antibody molecules, which differ among antibodies of different specificities. The V regions of heavy and light chains each contain three separate hypervariable regions of about 10 amino acids that are spatially assembled to form the antigen-combining site of the antibody molecule (the binding site, called the fab region) . These **hypervariable regions** are also called **complementarity- determining regions (CDR**), the three hypervariable regions are called CDR1, CDR2, CDR3 and **CDR3 is the most variable and has the most genetic diversity**. Note that there are 3 CDR regions for the heavy chain and three for the light chain.

Antibodies are classified into different classes or isotypes and subtypes on the basis of differences in the heavy chain constant regions (C regions) , which consist of three or four Ig C domains, and these classes and subclasses have different functional properties. The antibody classes are called IgM, IgD, IgG, IgE, and IgA.

Both light chains of a single Ig molecule are of the same light chain isotype, either κ or λ, which differ in their single C domains.

Most of the effector functions (killing, interaction with other components of the immune system) of antibodies are mediated by the C regions of the heavy chains, but these functions are triggered by binding of antigens to the combining site in the V region.

Monoclonal antibodies are produced from a single clone of B cells and recognize a single antigenic determinant. Monoclonal antibodies can be generated in the laboratory and are widely used in research, diagnosis, and therapy.

Antigens are substances specifically bound by antibodies or T lymphocyte antigen receptors. Antigens that bind to antibodies include a wide variety of biologic molecules, including sugars, lipids, carbohydrates, proteins, and nucleic acids. This is in contrast to most T cell antigen receptors, which recognize only peptide antigens.

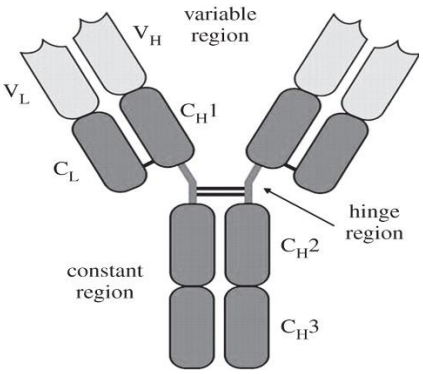
Macromolecular antigens contain **multiple epitopes**, or determinants, each of which may be recognized by an antibody. Linear epitopes of protein antigens consist of a sequence of adjacent amino acids, and conformational determinants (epitopes) are formed by folding of a polypeptide chain. **Antibodies can bind to two or, in the case of IgM, up to 10 identical epitopes simultaneously, leading to enhanced avidity of the antibody–antigen interaction.**(more details later)

Recognition of antigens involves noncovalent reversible binding like electrostatic forces, hydrogen bonds. The strength of binding between AB and epitope is called **affinit**y**. Affinity is measured by dissociation constant Kd which indicate how easy it is to separate an Ag-AB complex. The smaller the Kd the higher the affinity**

So AB have certain affinity to antigens, this measures the strength of binding between the epitope and the AB binding site. However, AB can have more than one binding site, at least two, the sum of the affinities of all the binding sites is called **avidity**.

The ability to bind to more than one epitope needs a certain flexibility in the Ig structurs so it fits the location of the epitope on the antigen, this flexibility is achieved via the **hinge site** of the AB structure.. see picture below:

<u>The hinge region</u> *is a short sequence of amino acids that lies between two longer sequences and allows the latter to bend about the former. This gives the AB flexibility so AB can bind an antigen at more than one binding site. The overall binding of all sites is the* ***avidity****.*



Each AB class has a different half life , half life is the average time at which the number of AB is reduced by half. IgE has the shortest half life 2 days. IgG has the longest half life of 21-28 days

<u>The long half life of IgG is due to its ability to bind to a receptor called neonatal fc rector FcRn</u> which is also involved in the transport of IgG across the placenta and to fetal blood. <u>Binding to this receptor sequesters IgG away from lysosomal degradation giving it this long half life</u>

Antibodies eliminate microbes by several mechanisms:

1. Neutralization of microbes and their toxic products
2. Activation of complement (classical pathway)
3. opsonization of pathogens to enhance phagocytosis
4. Antibody mediated cell dependent cytotoxicity (ADCC).. details later
5. Antibody mediated mast cell activation fight parazites

IMPORTANT NOTE: Ab are specific however AB produced against one antigen might bind to different but structurally related antigen. This is called **cross reaction**. That's why sometimes autoimmune diseases occur.

Classes of AB and their properties:

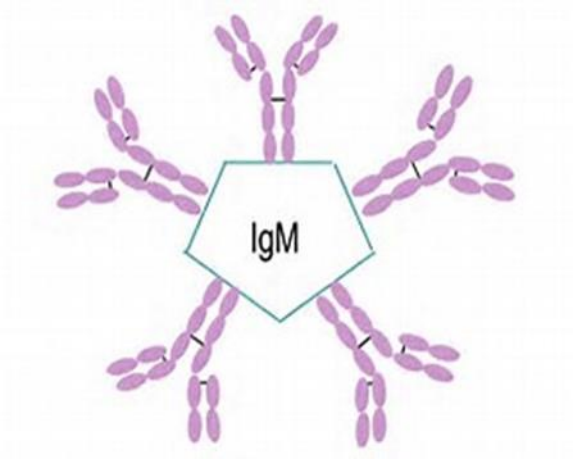
IgM:

IgM is the first AB type produced during infections. IgM is a massive molecule! Which looks similar to five IgG molecules (pentamer)

IgM can neutralize viruses but it also activates complement through the classical pathway .IgM has five Fc regions that can bind C1 complex and start the cascade to create the classical pathway convertase (refer to lecture 2)

Note that complement activation through this pathway is specific to the antigen recognized by the IgM.

REMEMBER: also IgG can stimulate the classical pathway but IgM is more efficient in this because of its five Fc portions that bring the C1 complexes .

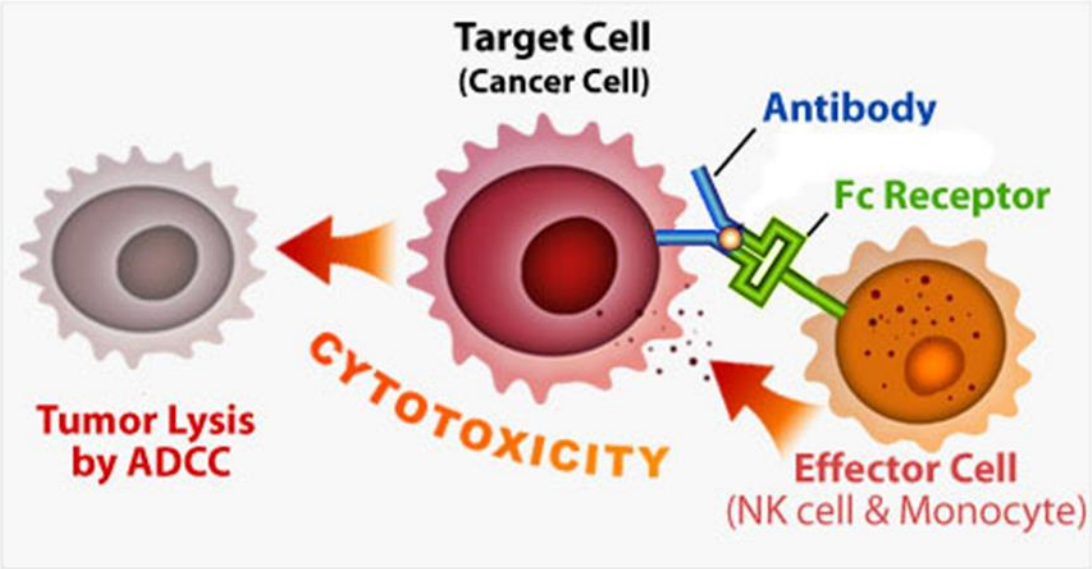


IgG

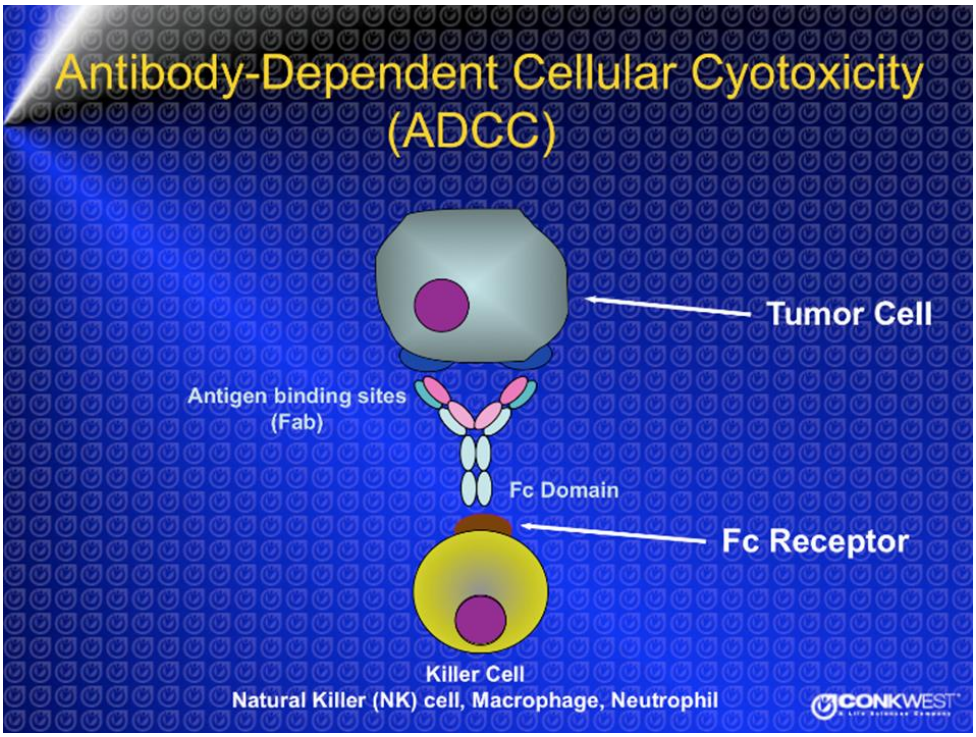
There are different subclasses of IgG (IgG1, 2, 3 and 4) that have slightly different Fc regions. Each subclass has a different function. For example IgG1 acts as an opsonin. IgG3 fixes complement (stimulates the classical complement pathway). IgG3 also can form a bridge between bacteria and NK cells. It binds the bacterial antigen via the Fab region and the NK by the Fc region which binds to a receptor on NK. This brings the bacteria close to the NK but also stimulates the NK to kill! This is called ADCC = antibody dependent cellular cytotoxicity.

What is ADCC?

ADCC: Antibody-Dependent Cell-Mediated Cytotoxicity



ADCC is a major mechanism for killing tumor cells by therapeutic antibodies.



IgG can neutralize viruses and it can pass through the placenta which gives protection to the infant

Also because they are long lived they can be used to protect from infections like hepatitis A if one is exposed to the infection

IgA

IgG is the most abundant AB in blood… But IgA is the most abundant in the body!!

IgA is the AB that protects mucosal surfaces. IgA molecule looks like **2 IgG clipped together**.

This clip is important for the IgA function: it allows its movement through intestinal wall and protects it from the intestinal acidity and enzymes.

IgA

In the intestinal lumen IgA coat the invading pathogen preventing it from attacking the intestinal cells.

Because IgA has four Fab regions it can attach to bacteria and produce a large enough particle to pass through mucus or stool

IgA is secreted in mothers' milk and taken by the baby during breast feeding, they coat the baby's intestine and protect it

IgA cannot fix complement, which is good because if they do our mucosal membranes will be always attacked by complement in response to bacteria that is always there in the mucosal membranes

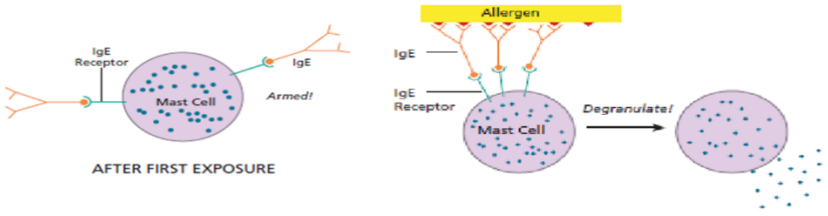
IgE: Synthesized against allergens. It can coat mast cells and it defend against parasites.

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

CLASS SWITCHING

The aim of class switching is to use the correct AB to the specific situation. So at first encounter with a pathogen IgM is always the first Ig secreted.. But according to the type and site of infection, switching occurs.

If infection of mucosal membrane : IgA produced (switching to IgA)

If parasitic infection: IgE

AB switching is controlled by the cytokines encountered by B cells

IL4 and IL5 : switching to IgE

Interferon gamma causes switching to IgG3

TGFb : IgA switch

These cytokines are secreted by T helper which decides which ones to secrete according to the situation and the AB needed

Isotype switching requires the induction of Activation induced deaminase enzyme(AID), a cytidine deaminase that converts cytosine to uracil in single-stranded DNA, and different cytokines allow AID to access distinct downstream heavy chain loci**. (our next case study will shed more light on AID and its importance)**

Somatic hypermaturation= affinity maturation.

In the VDJ region the mutation rate is high, much higher than in other cells. The increased mutation rate occurs late in the maturation of the B cell .Outcome of these mutations can be increased, decreased or unchanged affinity to antigen. Those B cells with higher affinity compete with other B cells and they predominate

Affinity maturation: the ones with higher affinity are selected. This affinity maturation occurs in germinal centers and leads to increased affinity of antibodies during the course of a T cell–dependent humoral response. Affinity maturation is a result of somatic mutation of Ig heavy and light chain genes induced by AID (Activation induced Deaminase), followed by selective survival of the B cells that produce the high-affinity antibodies and bind to antigen displayed by follicular dendritic cells in the germinal centers. T cells also participate in selection of high-affinity B cells.

So: B cells can change their class by changing their Fc region. They also change their binding capacity (affinity) by hyper mutation of the fab region .These two processes need T helper signaling, that's why B cells which are co-stimulated without T helper (T helper independent stimulation) don't undergo these change (they don't have class switching or hypermutation)

B cell differentiation: Career choice

B cells choose to be Plasma cells or memory cells. Plasma cells are short lived, they go to spleen or bone marrow to secrete AB. Memory cells are important for quicker recognition of antigens previously encountered by B cells.

How B cells choose to become plasma or memory? Mechanisms not understood. But T helper cell is thought to be important in producing memory cells. T cell independent activation doesn't produce memory cells.

Antibody feedback mechanisms

Antibody feedback is a mechanism by which humoral immune responses are downregulated when enough antibody has been produced and soluble antibody–antigen complexes are present. B cell membrane Ig and the receptor on B cells for the Fc portions of IgG, called FcγRIIB, are clustered together by antibody-antigen complexes. This activates an inhibitory signaling cascade through the cytoplasmic tail of FcγRIIB that terminates the B cell activation. So this is an important regulatory mechanism in order to keep AB production controlled.