# How do B cells acquire memory?

In the germinal centers, the activated B cells not only under class switch recombination (CSR) but they also undergo rapid proliferation and accumulate mutations in their immunoglobulin (Ig) V genes. These B cells produce antibodies with different affinities for the antigen. Follicular dendritic cells (FDCs) display the antigen, and B cells that recognize the antigen are selected to survive. FDCs display antigens by utilizing Fc receptors to bind immune complexes or by using C3 receptors to bind immune complexes with attached C3b and C3d complement proteins. B cells also bind the antigen, process it, and present it to follicular helper T (Tfh) cells in the germinal centers, and signals from the Tfh cells promote survival of the B cells. As more antibody is produced, the amount of available antigen decreases, so only the B cells that express receptors with higher affinities can bind the antigen and are selected to survive.

Activated B cells in germinal centers may differentiate into long-lived **plasma cells** or **memory cells**. The antibody-secreting cells enter the circulation and are called plasmablasts. From the blood they tend to migrate to the bone marrow or mucosal tissues, where they may survive for years as plasma cells and continue to produce high-affinity antibodies, even after the antigen is eliminated. It is estimated that more than half of the antibodies in the blood of a normal adult are produced by these long-lived plasma cells; thus, circulating antibodies reflect each individual's history of antigen exposure. These antibodies provide a level of immediate protection if the antigen (microbe or toxin) reenters the body. Think about the antibody titers you've had checked post-vaccination before enrolling in medical school.

A fraction of the activated B cells, which often are the progeny of isotype-switched high-affinity B cells, do not differentiate into active antibody secretors but instead become memory cells. Memory B cells do not secrete antibodies, but they circulate in the blood and reside in mucosal and other tissues. They survive for months or years in the absence of additional antigen exposure, undergo slow cycling, and are ready to respond rapidly if the antigen is reintroduced. Therefore, memory from a T-dependent antibody response can last for a lifetime.

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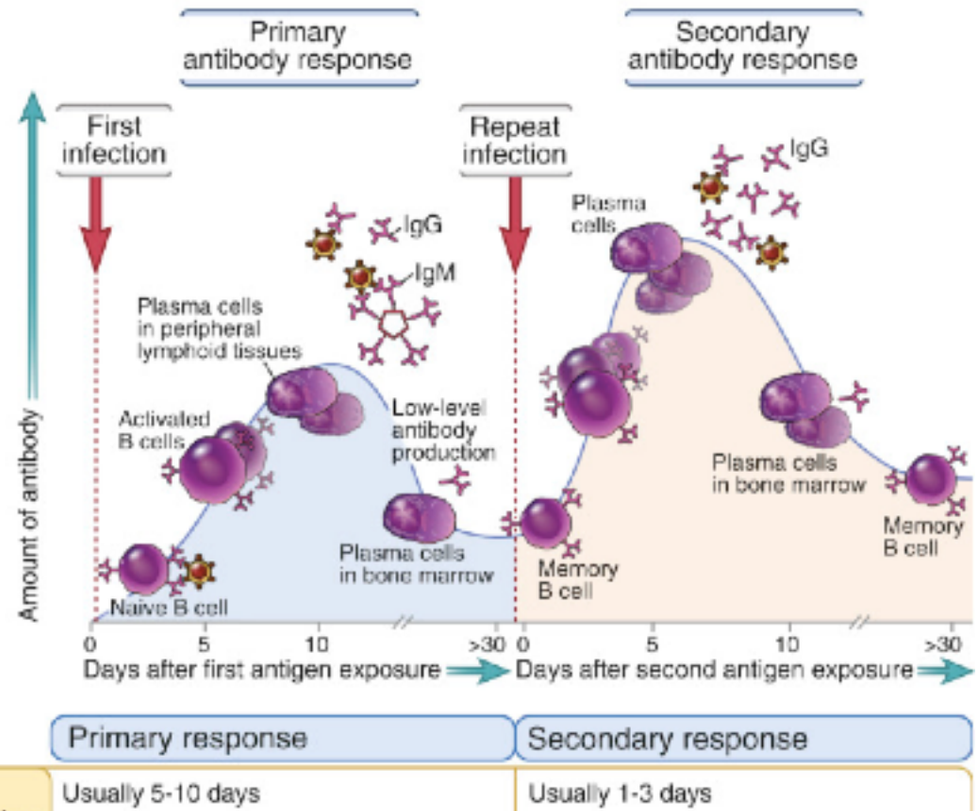


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|---|---|---|
| Lag after immunization | Usually 5-10 days | Usually 1-3 days |
| Peak response | Smaller | Larger |
| Antibody isotype | Usually IgM>IgG | Relative increase in IgG and, under certain situations, in IgA or IgE (heavy-chain isotype switching) |
| Antibody affinity | Lower average affinity, more variable | Higher average affinity (affinity maturation) |

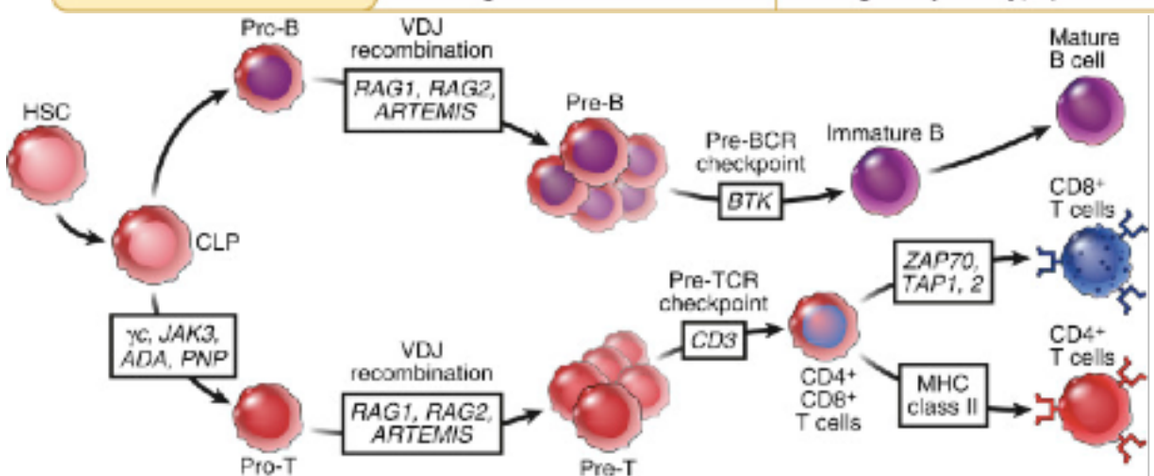
Primary and secondary antibody responses differ in several respects. In a primary response, naive B cells in peripheral lymphoid tissues are activated to proliferate and differentiate into antibody-secreting plasma cells and memory cells. Some plasma cells may migrate to and survive in the bone marrow for long periods. In a secondary response, memory B cells are activated to produce larger amounts of antibodies, often with more heavy-chain class switching and affinity maturation. These features of secondary responses are seen mainly in responses to protein antigens, because these changes in B cells are stimulated by helper T cells, and only proteins activate T cells (not shown). The kinetics of the responses may vary with different antigens and types of immunization.

# What happens if something goes wrong?
# Immunodeficiencies Part 1 of 2

| Severe combined immunodeficiency (SCID) | | |
|---|---|---|
| Disease | Functional deficiencies | Mechanism of defect |
| X-linked SCID | Markedly decreased T cells; normal or increased B cells; reduced serum Ig | Cytokine receptor common γ chain gene mutations, defective T cell maturation due to lack of IL-7 signals |
| Autosomal recessive SCID due to ADA, PNP deficiency | Progressive decrease in T and B cells (mostly T) | ADA or PNP deficiency leads to accumulation of toxic metabolites in lymphocytes |
| Autosomal recessive SCID due to other causes | Decreased T and B cells; reduced serum Ig | Defective maturation of T and B cells; may be mutations in *RAG* genes and other genes involved in VDJ recombination or IL-7R signaling |

| B cell immunodeficiencies | | |
|---|---|---|
| Disease | Functional deficiencies | Mechanism of defect |
| X-linked agammaglobulinemia | Decrease in all serum Ig isotypes; reduced B cell numbers | Block in maturation beyond pre–B cells, because of mutation in Bruton tyrosine kinase (BTK) |
| Ig heavy chain deficiencies | Deficiency of IgG subclasses; sometimes associated with absent IgA or IgE | Chromosomal deletion involving Ig heavy-chain locus at 14q32 |

| Disorders of T cell maturation | | |
|---|---|---|
| Disease | Functional deficiencies | Mechanism of defect |
| DiGeorge syndrome | Decreased T cells; normal B cells; normal or decreased serum Ig | Anomalous development of 3rd and 4th branchial pouches, leading to thymic hypoplasia |




CLP (common lymphoid progenitor) HSC (hematopoietic stem cell)

There are two big categories of immunodeficiency relevant to this case. Determining which parts of a patient's immune system are normal or abnormal can help narrow the underlying genetic cause, but also guide treatment, including prophylactic antibiotics, vaccination strategies, or determining if the patient is a candidate for a stem cell transplant. Newer treatment strategies of genome alteration may also become available.

**(1) Defects in Lymphocyte Maturation**

Many congenital immunodeficiencies are the result of genetic abnormalities that cause blocks in the maturation of B lymphocytes, T lymphocytes, or both. Some example proteins shown include JAK3 (Janus kinase 3), a kinase involved in signaling by many cytokine receptors; ARTEMIS, a protein involved in antigen receptor gene recombination; BTK (Bruton tyrosine kinase), a kinase that delivers signals from the pre–B cell receptor (BCR) and BCR; ZAP70, a kinase involved in TCR signaling; TAP proteins, which transport peptides for presentation by class I MHC molecules; ADA (Adenosine deaminase) and PNP (purine nucleoside phosphorylase), enzymes involved in purine metabolism important for lymphocytes; and RAG1, RAG2 (recombination-activating gene), enzymes which mediate V(D)J recombination.

# Index

If you would like to learn more or review any particular topic, the links below will take you to a text-based review of these concepts, or to the correlating video. You may also skip ahead to the post-module assessment.