MCB 55 Plagues & Pandemics: Adaptive Immunity

ADAPTIVE IMMUNITY

1. General Properties of Adaptive Immune Responses (as compared to Innate Immune responses)

–slower (peak at ~5 days after infection) than innate immune responses (occur within hours of infection)

–more specific. Targets very specific antigens on pathogens. Can distinguish antigens that differ only very subtly. By contrast, the innate immune system does not discriminate among similar pathogens (though it can discriminate among classes of pathogens, e.g., gram-negative bacteria have LPS vs gram-positive that do not).

–exhibits memory. This means that the adaptive immune response, when rechallenged a second time by the same pathogen, is faster and more vigorous than the first (or primary) response. Innate immune responses do not exhibit memory – they are the same, regardless of how many times the pathogen is encountered.

–When we talk of "having immunity" to something, we mean that we were exposed to it once before, and thus our adaptive immune system is now ready to respond more rapidly and vigorously. The first time we are infected with a pathogen we might get sick for a long time (as the immune response gradually clears the infection), but our secondary immune responses to the same pathogen are much more effective and we are sick for much less time, if at all (i.e., we are "immune").

2. Main cells of the Adaptive Immune system

–Although adaptive immune responses depend in many ways on all the cells and responses of the innate immune system, there are two main cell types involved in adaptive immune responses:

1. B cells

– make antibodies (proteins that are capable of binding very specifically to precise structures (called antigens) on pathogens)

2. T cells

– There are two main types of T cells:

2A. Cytotoxic T cells. These cells are also sometimes called CD8 T cells because they express a special receptor molecule called CD8 on their cell surface (see more below).

– the function of cytotoxic T cells is to specifically kill virally-infected cells

2B. Helper T cells. These cells are also sometimes called CD4 T cells because they express a special receptor molecule called CD4 on their cell surface (see more below).

– the function of Helper T cells is primarily to produce cytokines (recall that cytokines are proteins that diffuse through the blood and alert other cells to the infection). In general, B cells need cytokines produced by Helper T cells in order to be turned on to produce antibodies. Similarly, Cytotoxic T cells need cytokines produced by Helper T cells in order to become maximally effective killers. For this reason, Helper T cells are considered by many to be the master regulators or 'generals' of adaptive immune responses. Ultimately, the important decision about whether to fully commit to making an immune response to an infection is often made by helper T cells (i.e., whether the helper T cells detect the antigen to which they are specific).

– B cells and T cells both belong to a family of cells called lymphocytes. Lymphocytes are recognizable because of their small size and round shape. Just by looking in a microscope, you can't distinguish B and T cells from each other.

3. B cells

– The main function of B cells is to produce antibodies. They are the only cells capable of producing antibodies. No B cells=No antibodies=increased susceptiblity to infections with viruses and extracellular bacterial pathogens. Antibodies produced by B cells circulate throughout the blood and lymph system.

– Another name for antibody is immunoglobulin (sometimes abbreviated as Ig). Immunoglobulins (i.e., antibodies) have two important parts:

1. One part binds specifically to antigens on pathogens. This part of the antibody is highly variable, since it must be able to bind to many different antigens. Thus, it is called the variable region. And it can be VERY variable. It is estimated that the body can generate ~100,000,000,000 ($=10^{11}$) different kinds of antibodies, each with its own specific ability to bind a specific antigen. Intriguingly, each individual B cell only produces a single kind of antibody.

2. The other part of antibodies is called the constant region, since it is not nearly as variable as the variable region. Despite its name, the constant region is not entirely constant: there are a handful of different constant regions that can be found on antibodies (e.g., constant regions A, G, M, E, etc.).

– The particular constant region found on the antibody endows the immunoglobulin with particular functions. For example:

- constant region A is found on Immunoglobulin A (IgA). IgA is secreted primary into mucosal sites, such as the thin layers of cells that line the lungs, the intestines and the reproductive tracts. The main function

of IgA is to neutralize pathogens. Neutralization does not require the involvement of other cell types. By binding to the pathogen, a neutralizing antibody itself prevents the pathogen from functioning properly (e.g., it may prevent a virus from binding to a host cell).

- constant region G is found on Immunoglobulin G (IgG). IgG is found circulating in the blood. Like IgA, IgG can also neutralize pathogens. But it has additional functions as well. For example, IgG is recognized by special receptors on macrophages, and promotes phagocytosis by macrophages. An IgG-coated bacterium is therefore much more likely to be phagocytosed (and destroyed) by a macrophage.

- constant region M is found on Immunoglobulin M (IgM). IgM is also found circulating in the blood. IgM is relatively poor at neutralization and promoting phagocytosis. Instead, IgM is a very potent activator of a blood toxin called complement. Complement circulates in the blood in an inactive form. When it encounters a bacterium that has been coated with IgM, it becomes activated and becomes deposited on the surface of the IgM-coated bacterium. Complement deposition eventually leads to the destruction of the pathogen via direct toxic effects or by increasing phagocytosis of the bacterium.

- constant region E is found on Immunoglobulin E (IgE). The constant region of IgE is bound by special receptors on mast cells. Binding of IgE to mast cells causes the mast cells to release chemical mediators (e.g., histamines) that stimulate allergic responses.

– Important point: bacterial pathogens that replicate inside of host cells are largely impervious to the effects of antibodies, which circulate in the blood. Immunity to intracellular pathogens usually requires cytotoxic T cells (see below).

4. Antigen presentation

– Before explaining T cells, antigen presentation needs to be explained.

– Bacteria or viruses that replicate in host cells, or are engulfed by host cells, are often degraded, and small protein fragments of these bacteria and viruses end up being "presented" or displayed on the cell surface. The presentation of these small pathogen-derived fragments on the surface of host cells is called antigen presentation.

– Antigen presentation is a way for infected host cells to alert the adaptive immune system that they have been infected.

  – This is especially critical for immune responses to intracellular bacteria or viruses, which might otherwise be able to hide from the immune system and replicate inside of host cells

– Special proteins called Major Histocompatibility Complex (MHC) perform the job of displaying fragments of pathogens on the host cell surface.

– Certain cell types are specialized in the job of presenting antigens. Sometimes these cells are called professional antigen presenting cells. Dendritic cells are professional antigen presenting cells. They are very good at engulfing material (by phagocytosis), digesting it, and presenting it on their cell surface.

5. T cells

– T cells, whether CD4 helper T cells or CD8 cytotoxic T cells, are activated by a very special receptor on their surface called the T cell receptor (TCR)

– T cell receptors are in many ways similar to antibodies; for example, they have a variable region and a constant region. One important difference is that the TCR is a receptor on the surface of T cells (permanently there), whereas antibodies are often secreted by B cells (and diffuse away).

– Similar to the way in which the variable part of antibodies recognize antigen, the variable part of the T cell receptor recognizes antigen too, but a key difference is that TCR receptor only recognizes antigen presented by MHC. The TCR binds to the combination of antigen+MHC (it cannot bind to antigen alone).

– Like antibodies, T cell receptors are incredibly diverse. The body can make $>10^{11}$ different T cell receptors, each capable of binding to a unique combination of antigen+MHC (the specific combination of MHC+antigen that is recognized by a given T cell receptor is sometimes called that T cell receptors cognate MHC/antigen).

– Each T cell expresses only one unique T cell receptor.

– CD4 and CD8 molecules are called co-receptors, because they assist the T cell receptor by binding MHC (but CD4 and CD8 do not recognize the antigen: only the TCR recognizes the antigen).

– When the T cell receptor on a CD4 T cell is engaged by its cognate MHC/antigen, the T cell is stimulated and produces cytokines (secreted proteins) that promote antibody production and/or promote the activation of CD8 T cells

– When the T cell receptor on a CD8 T cell is engaged by its cognate MHC/antigen, the T cell is provoked into killing the cell that is presenting the MHC/antigen on its surface.

Figure 1. Immunological “memory”. The second exposure to an antigen results in a more potent immune response.

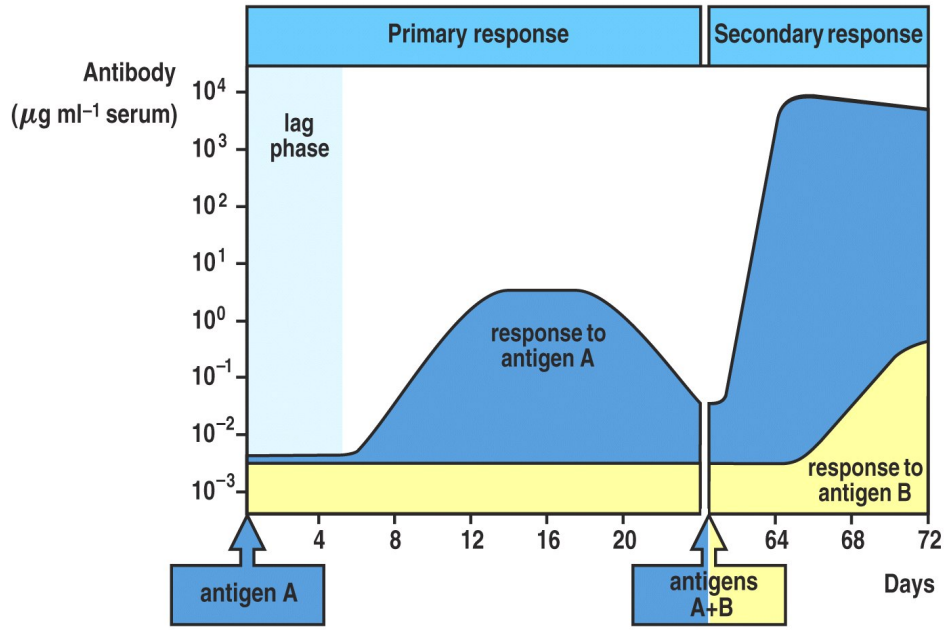

Figure 1-20 Immunobiology, 6/e. (© Garland Science 2005)