7.7: Specific acquired immunity

What triggers specific immune responses? Antigens

Antigens trigger specific immune responses. Antigens are substances which can trigger specific immune responses. When the immune system is working correctly, antigens are any substance that is “foreign” or “non-self”, such as invading pathogens. (Sometimes the immune system malfunctions and one’s own cells or cell components trigger an immune response. When this occurs, it is referred to as “autoimmune” disease.) A bacterium can trigger production of antibodies and thus the bacterium is called “antigenic”. Different parts of the bacterium will trigger production of different antibodies. Each of these different parts is called an “antigenic determinant” or “epitope”. In class however, we will use the general term “antigen” to describe the part of a microbe to which antibodies bind.

Humoral immunity and antibodies/immunoglobulins

In humans, there are 5 classes of antibodies (Ab) also called immunoglobulins (Ig). The predominant class and most versatile antibodies are called “IgG”. They represent approximately 70-80% of the antibodies in a human and can be found in blood and other tissue fluids.

Structure of IgG

IgG is made of 4 polypeptide or protein chains. These chains are organized to form a roughly “Y” shaped molecule. The tips of the arms are called “antigen-binding sites”. The arm tips have grooves with a specific shape and size which permit the antibody to bind to complementary antigen. Once bound to the antigen, the
antibodies carry out several beneficial functions.

**Functions of Antibodies**

1. **agglutination** of cells: inhibit movement of pathogens, increase phagocytosis by neutrophils and macrophages (agglutination="clumping")

2. **neutralization**: antibodies binding to pathogen adhesins block attachment of pathogens to host cell surface receptors thus block colonization and disease. Antibodies can also bind toxins, preventing the toxin from binding host cells (antibodies to toxins are called “antitoxins”)

3. **opsonization**: recall opsonization (literally “preparing to eat”) is the process in which a pathogen is coated with a “sticky” substance such as complement, making the coated pathogen easier for the phagocytic cells to attach to and kill the pathogen. Antibodies can also opsonize pathogens. When an antibody binds to the surface of a pathogen, the antibody “tail” sticks outward (the antibody tail is called the Fc fragment). Phagocytic cells have surface receptors which can bind to the antibody tails, permitting them to attach easier to the pathogen, thus increasing pathogen killing.

4. **Complement activation**: when antibodies bind antigens, the antibodies can trigger activation of the complement pathway. Recall activation of the complement pathway has several advantages including:
   - triggering inflammation (increase blood flow, increase delivery of phagocytic cells, chemical gradients to guide phagocytic cells to sites of invasion)
   - complement proteins also act as opsonins thus help increase phagocytic killing of pathogens
   - complement proteins help guide phagocytic cells to site of injury/invasion
   - complement proteins can form membrane attack complexes “MAC attack” to help kill invading microbes by lysis.

**Classes of antibodies**

As mentioned earlier, IgG is one of 5 antibody classes in humans. The other classes include:

- **IgM**: a large pentamer (5 parts), the first antibody produced in specific immune reactions. So large it is difficult to leave blood vessels. Can activate complement, can cause agglutination but NOT opsonic
- **sIgA**: secretory IgA a dimmer (2 parts): VERY important antibody in mucous secretions. Important role in binding pathogens or toxins on mucous membrane to inhibit attachment to host cells. Essential component of specific mucosal immunity
- **IgE**: important in allergic/hypersensitivity reactions. Bind to mast cells, help trigger release of histamine when allergen is encountered.
- **IgD**: surface receptor on B lymphocytes

**Which cells make antibodies? B-lymphocytes/plasma cells**

When humoral immunity is triggered, antibodies are produced by **B lymphocytes**. Lymphocytes are one type of white blood cell or leukocyte which functions in the immune system. B lymphocytes are so named because they were first identified in chickens (!). Lymphocytes originate in bone marrow then mature under guidance
of special chemicals produced in different environments. Upon maturation they will carry out different functions. In chickens, lymphocytes which mature under the chemical influence of the “Bursa of Fabricus” mature into “B” (Bursa) lymphocytes. Humans lack a Bursa of Fabricus. It is thought B lymphocytes may mature in the bone marrow of human or in lymphoid tissue associated with the intestine (GALT=gut associated lymphoid tissue)

B lymphocytes are programmed to produce antibodies when stimulated by the appropriate antigen (more later). Once the B lymphocytes are stimulated, they mature into antibody producing plasma cells.

Clonal Selection, Expansion and Memory Cells

How are we able to specifically respond to the antigens of an invading pathogens? The key is the surface receptors on our lymphocytes. We have an incredible variety of lymphocytes circulating in our blood stream and through our lymphatic system. Each lymphocyte carries a different surface receptor. Each surface receptor can bind to a different antigen. Once the surface receptor binds its specific antigen (selection), it helps trigger the lymphocyte to start dividing (clonal expansion) and to start maturing into a functional lymphocyte. When a lymphocyte starts dividing, it divides into two populations of cells: effector cells and memory cells.

1. **Effector cells**: these lymphocytes start immediately “to work”, they carry out the specific function of the lymphocyte. For example B lymphocyte effectors are the B lymphocytes which actually start producing antibodies (they have the specific name “plasma cells” when they start making antibodies)

2. **Memory cells**: these memory lymphocytes do not start to work immediately. Instead, their job is to “live long” and “remember” the antigen which first triggered the immune response, if it is ever encountered again. The memory cells increase the number of lymphocytes which could respond to the antigen if it is ever encountered again. The memory cells are also “primed” to trigger a faster immune response the second time the antigen is encountered. The memory cells are what proved us with “immunological memory”, the reason vaccines work and the reasons some people develop “life-long” immunity once they recover from some infectious diseases. When memory cells are subsequently triggered by exposure to the same antigen that triggered the first (primary) immune response, the memory cells trigger a “secondary” immune response.

The secondary immune response is faster, stronger and longer lasting than the primary immune response.

Are only B lymphocytes involved in antibody production?

Although it would make our lives easier as students if only B lymphocytes were involved in antibody production, the process is much more complicated. The BEST humoral immunity is triggered when antigens trigger activation of 3 types of leukocytes/WBC’s. The 3 types of cells are called:

1. **Antigen-Presenting Cell** or “APC”; a macrophage is a classic example of an APC
2. **T helper lymphocyte**: The MOST IMPORTANT cell of our immune system. T helpers literally help all the other cell of the immune system to function properly. The T helpers have a surface molecule called “CD4”. For this reason, T helpers are also called “CD4+” cells or “CD4+” lymphocytes. Tragically, HIV targets and destroys our CD4+ T helper lymphocytes, thus crippling our immune system, causing AIDS. (note: T lymphocyte originate in the bone marrow then travel to the thymus gland where they mature into T (thymus) lymphocytes)

3. **B lymphocyte**: the actual antibody producer

**Note**

There 3 cells interact with specific antigen and produce chemical messengers which enable each to carry out specific functions. Although we will briefly go over the process in lecture, what is most important to remember is that **B cells need T helper lymphocytes to produce memory cells and to “switch” to IgG production.**

Summary of how APC, T helper and B lymphocytes interact with antigen to trigger antibody production—YOU DO NOT NEED TO KNOW DETAILS:

1. APC ex macrophage phagocytizes a pathogen (example a bacterium). The macrophage hydrolyzes the pathogen, processes the pathogen antigens, binds the pathogen antigens to a special molecule called the MHC-II molecule and “presents” the pathogen antigen on the surface of the macrophage linked to the MHC-II molecule.

2. A T helper lymphocyte with a complementary surface receptors binds to the pathogen antigen “presented” on the MHC-II molecule of the macrophage. This binding and chemicals (interleukins) which the macrophage synthesizes helps to “activate” the Th helper lymphocyte. The Thelper starts to divide, forming effector cells and memory cells.

3. Meanwhile, a B lymphocyte with surface receptors for the same antigen (IgD molecules) has also bound antigen from the pathogen and is partially activated. The B lymphocyte brings the antigen into its cell, processes them and binds them to MHC-II molecules and (just like the macrophage), “presents” the pathogen antigen on its surface, linked to the MHC-II molecule.

4. One of the activated effector T helpers (from step 2 above) encounters the B lymphocyte and using its complementary surface receptor (T cell receptor or TCR), binds the pathogen antigen the B lymphocyte is presenting on its surface. This holds the T helper in close contact with the B lymphocyte. The T helper secretes chemicals (interleukins) to further activate the B lymphocyte. Now the B lymphocyte can start dividing, forming antibody producing plasma cell and B memory cells.

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