

Fundamentals of Vaccine Immunology

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ABSTRACT

From a literature review of the current literature, this article provides an introduction to vaccine immunology including a primer on the components of the immune system, passive vs. active immunization, the mechanism(s) by which immunizations stimulate(s) immunity, and the types of vaccines available. Both the innate and adaptive immune subsystems are necessary to provide an effective immune response to an immunization. Further, effective immunizations must induce long-term stimulation of both the humoral and cell-mediated arms of the adaptive system by the production of effector cells and memory cells. At least seven different types of vaccines are currently in use or in development that produce this effective immunity and have contributed greatly to the prevention of infectious disease around the world.

Key words: Adaptive immunity, Immune system, Immunization, Vaccines

INTRODUCTION

As early as the fifteenth century, both the Chinese and the Turks were attempting to induce immunity to smallpox using dried crusts from smallpox lesions by either inhaling the crushed lesions or inserting them into small cuts. These initial crude attempts at immunization led to further experimentation with immunization by Lady Mary Wortley Montagu in 1718 and Edward Jenner in 1798. Edward Jenner's experiments with cowpox to stimulate smallpox immunity are better known than these earlier attempts at immunization.^[1]

These early endeavors have led to the plethora of vaccines that are available today. Although these attempts were successful in providing immunity, the underlying processes required to produce this immunity were unknown.

From a literature review of the current literature, this article will provide an introduction to vaccine immunology including a primer on the components of the immune system, passive vs. active immunization, the mechanism(s) by which immunizations stimulate(s) immunity, and the types of vaccines available.

COMPONENTS OF THE IMMUNE SYSTEM

The immune system can be divided into two main subsystems, the innate/general resistance system and the adaptive system. Both the innate system and the adaptive system continually interact with each other to provide an effective immune response.

The innate immune system or general resistance includes a variety of protective measures which are continually functioning and provides a first-line of defense against pathogenic agents. However, these responses are not specific to a particular pathogenic agent. Instead, the innate immune cells are specific for conserved molecular patterns found on all microorganisms. This prevents the innate immune system from inadvertently recognizing host cells and attacking them. However, this prevents the innate immune responses from improving their reactions with repeated exposure to the same pathogenic agent. In other words, the innate immune system does not have memory.

The protective defenses of the innate immune system begin with the anatomic barriers such as intact skin and mucous membranes which prevent the entrance of many microorganisms and toxic agents. The skin also has an acidic environment of pH 3–5 which retards the growth of microorganisms. In addition, the normal microorganisms or flora, which inhabit the skin and mucous membranes compete with other microorganisms for nutrients and

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DOI:
10.4103/0974-777X.77299

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attachment sites. Further, the mucus and cilia on the mucous membranes aid in trapping microorganisms and propelling them out of the body.^[1]

Next, the innate immune system includes such physiologic barriers as the normal body temperature, fever, gastric acidity, lysozyme, interferon, and collectins. The normal body temperature range inhibits a variety of microorganisms; and, the development of a fever can further inhibit many of these pathogenic organisms. The gastric acidity of the stomach is also quite effective in eliminating many ingested microorganisms. Lysozyme, which is a hydrolytic enzyme found in tears and mucous secretions, can cleave the peptidoglycan layer of the bacterial cell wall thus lysing the microorganism.^[1] Interferon(s), which include(s) a group of proteins that are produced by virally infected cells, can bind to noninfected cells and produce a generalized antiviral state.^[1] Collectins are surfactant proteins that are present in serum, lung secretions, and on mucosal surfaces. They can directly kill certain pathogenic microorganisms by disrupting their lipid membranes or indirectly by clumping microorganisms to enhance their susceptibility to phagocytosis.^[1,2]

The complement pathways are also a part of the defensive measures of the innate immune system. There are three complement pathways. The classical pathway is triggered when IgM antibodies or certain IgG antibody subclasses bind surface markers/antigens on microorganisms. The alternative or properdin pathway is triggered by the deposition of complement protein, C3b, onto microbial surfaces and does not require antibodies for activation. The third pathway, the lectin pathway, is triggered by the attachment of plasma mannose-binding lectin (MBL) to microbes and does not require antibodies for activation. These three pathways merge into a common pathway which leads to the formation of the membrane attack complex that can form pores in the membrane of targeted cells. The complement pathways are also integral in the opsonization (or increased susceptibility) of particulate antigens to phagocytosis and in triggering a localized inflammatory response.^[3]

The inflammatory response is another essential part of the innate immune response. The inflammatory response is the body's reaction to invasion by an infectious agent, antigenic challenge, or any type of physical damage. The inflammatory response allows products of immune system into area of infection or damage and is characterized by the cardinal signs of redness, heat, pain, swelling, and loss of function.^[1]

In addition to the anatomic and physiologic mechanisms,

there are also Pattern recognition receptors or PRRs which contribute to the innate immune response. Pattern recognition receptors are not specific for any given pathogen or antigen, but can provide a rapid response to antigens. PRRs are classified as membrane proteins because they are associated with the cell membrane; and, they can be found in all the membranes of the cells in the innate immune system. Although there are several hundred varieties, all the genes of the PRRs are encoded in the germline to ensure limited variability in their molecular structures. Examples of PRRs include MBL, pulmonary surfactant protein, C-reactive protein, toll-like receptors (TLRs), C-Type lectin, NOD, and MX. The PRRs recognize PAMPs or pathogen associated molecular patterns which can trigger cytokine release. Examples of PAMPs include LPS (endotoxin), peptidoglycan (cell walls), lipoproteins (bacterial capsules), hypomethylated DNA (CpG found in bacteria and parasites), double-stranded DNA (viruses), and flagellin (bacterial flagella). These antigens are produced by microbial cells and not by human cells. Recognition of PAMPs by PRRs leads to complement activation, opsonization, cytokine release, and phagocyte activation.^[1,4-6]

Finally, the mononuclear phagocytes and granulocytic cells are also important to the innate response and help link the innate immune response to the adaptive immune response. Mononuclear phagocytes include monocytes which circulate in the blood and macrophages which are in the tissues. Monocytes and macrophages are highly important in antigen presentation, phagocytosis, cytokine production, and antimicrobial and cytotoxic activities.^[7]

Upon maturity of the monocytes, the monocytes circulate in the blood for approximately 8 h, then migrate into the tissues and differentiate into specific tissue macrophages or into dendritic cells. There are several types of dendritic cells which are involved in different aspects of immune functions. Many dendritic cells are important in presenting antigen to T-helper cells. However, follicular dendritic cells are found only in lymph follicles and are involved in the binding of antigen-antibody complexes in lymph nodes.^[1,6,7]

Granulocytic cells include neutrophils, eosinophils, and basophils/mast cells. Neutrophils are highly active phagocytic cells and generally arrive first at a site of inflammation. Eosinophils are also phagocytic cells; however, they are more important in resistance to parasites. Basophils in the blood and mast cells in the tissues release histamine and other substances and are important in the development of allergies.^[1,7]

The innate system may be able to eradicate the pathogenic agent without further assistance from the adaptive system; or, the innate system may stimulate the adaptive immune system to become involved in eradicating the pathogenic agent.^[1,4]

In contrast to the innate immune system, the actions of adaptive immune system are specific to the particular pathogenic agent. This response will take longer to occur than the innate response. However, the adaptive immune system has memory which means that the adaptive immune system will respond more rapidly to that particular pathogen with each successive exposure.^[4]

The adaptive immune response is composed of the B-cells/antibodies and T-cells. These are the two arms of the adaptive immune system. The B-cells and antibodies compose humoral immunity or antibody-mediated immunity; and, the T-cells compose cell-mediated immunity. As a note, natural killer cells are also from the lymphocyte lineage like B-cells and T-cells; however, natural killer cells are only involved in innate immune responses.^[1,7]

The first arm of the adaptive immune system is humoral immunity, functions against extracellular pathogenic agents and toxins. B-cells are produced in the bone marrow and then travel to the lymph nodes. Within the lymph nodes, naïve B-cells continue to mature and are exposed to pathogenic agents caught in the particular lymph node. Unlike T-cells, B-cells can recognize antigens in their native form which means that B-cells can recognize antigens without requiring that the antigen be processed by an antigen-presenting cell and then presented by a T-helper cell.^[4] These antigens are called T-independent antigens because T-cell activation is not required to activate the B-cells. Examples of these T-independent antigens include lipopolysaccharide, dextran, and bacterial polymeric flagellin. These antigens are typically large polymeric molecules with repeating antigenic determinants. These antigens can also induce numerous B-cells to activate; however, the immune response is weaker and the induction of memory is weaker than with T-helper cell activation. In contrast, activation of B-cells with T-helper cell activation results in a much better immune response and more effective memory. This long-term, effective immune response is the type of reaction that is the goal of immunizations.^[1] With the binding of the antigen to the Fab region on the B-cell receptor and secondary signaling from cytokines released by T-helper cells, B-cells begin somatic hypermutation at the Fab region which further increases the corresponding fit between the Fab region and the antigen. This process then stimulates the B-cell(s) to mature into a plasma cell(s) which

then begins production of the particular antibody with the best corresponding fit to the antigen.^[1]

From these stimulated B-cells, clones of B-cells with the specificity for the particular antigen will arise. These cells may become plasma cells producing antibodies or memory cells which will remain in the lymph nodes to stimulate a new immune response to that particular antigen. This occurs during the primary immune response when the immune system is first exposed to a particular antigen.^[4]

This process of clonal selection and expansion will take several days to occur; and, primarily involves the production of IgM. IgM is the first antibody produced during a primary immune response.^[7]

As the immune response progresses, the activated plasma cells will begin producing IgG specific to the particular antigen. Although IgM is the first antibody produced and is a much larger antibody, IgG is a better neutralizing antibody. IgG binds more effectively to the antigen and aids in opsonization.^[1]

As a note, other antibodies can be produced by plasma cells. These antibodies include IgD, IgA, and IgE. IgD is primarily found as a receptor bound to the surfaces of mature B-cells. While, IgA is the antibody found in secretions such as mucous, saliva, tears, and breast milk; and, IgE is the antibody involved in allergic reactions and parasitic infections. However, the most important antibody for vaccines is IgG.^[7]

With the memory cells that have been produced with the primary immune response, any succeeding exposures to the antigen will result in a more rapid and effective secondary immune response. With this secondary immune response, the reaction will be quicker, larger, and primarily composed of IgG.^[7]

As for the other arm of adaptive immunity, cell-mediated immunity, it functions primarily against intracellular pathogens. T-cells mature in the thymus and are then released into the bloodstream. There are two main types of T-cells, CD4 cells and CD8 cells.^[1,4]

CD4 cells or T-helper cells have the CD4 co-receptor and only recognize the major histocompatibility complex (MHC) II protein. The MHC II protein is found on all immune cells and acts as a marker of immune cells.

CD4 cells are essential for antibody-mediated immunity and in helping B-cells control extracellular pathogens. There are two subsets of CD4 cells, Th1 and Th2. Th1

cells help promote cell-mediated immunity; and, Th2 cells help promote antibody-mediated immunity.^[1,4]

CD8 cells or T-cytotoxic cells have the CD8 co-receptor and only recognize the major histocompatibility complex (MHC) I protein. The MHC I protein is found on all nucleated body cells except for mature erythrocytes and acts as a marker of body cells. CD8 cells are essential for cell-mediated immunity and in helping control of intracellular pathogens.^[1,4]

Unlike B-cells, T-cells can only recognize antigen that has been processed and presented by antigen-presenting cells. There are two types of antigen processing.^[4,7]

The first type of antigen processing involves attaching intracellular antigens along with MHC I proteins to the surface of antigen-processing cells. This occurs with viral antigens and tumor cells.^[1]

The other type of antigen processing involves attaching extracellular antigens along with MHC II proteins to the surface of antigen-presenting cells. This occurs with bacterial and parasitic antigens.^[1]

Once the T-cell has been activated by the antigen-presenting cell, it begins to carry out its functions depending on whether it is a CD4 cell or a CD8 cell. As with B-cells, activated T-cells also undergo clonal expansion which produces additional effector T-cells for the current infection and memory T-cells for future infections with this antigen.^[1]

TYPES OF IMMUNIZATION

Immunization can be derived from either passive or active means. These means can be from either natural or artificial sources. Natural sources are due to exposure to the environment, humans, and animals. In contrast, artificial sources are due to medical interventions.

Passive immunization occurs with the transfer to preformed antibodies to an unimmunized individual. This individual would then develop a temporary immunity to a particular organism or toxin due to the presence of these preformed antibodies. Once these preformed antibodies have been destroyed, the individual would no longer have immunity to this microorganism or toxin.^[8]

Passive immunization can occur either naturally or artificially. Excellent examples of natural passive immunization are the passage of maternal antibodies through the placenta to the

fetus and the passage of these maternal antibodies to the infant through the colostrum and milk.^[1,9]

Excellent examples of artificial passive immunization include the administration of pooled human immune gamma globulin and antivenin. These gamma globulins and antivenins provide temporary immunity to either a particular illness or venom. Concurrent with these effects of this temporary immunity from the preformed antibodies, the individual's own body is likely to be in the early stages of developing its own active immune response.^[1]

Active immunization occurs with the exposure of an unimmunized individual to a pathogenic agent. The immune system of this individual then begins the process of developing immunity to this agent. In contrast to passive immunization, active immunization typically produces long-term immunity due to the stimulation of the individual's immune system. The process of stimulating the immune system against a pathogenic agent will be further discussed in this article.^[9]

Active immunization can occur either naturally or artificially. An excellent example of natural active immunization is exposure to influenza. The body then begins the process of developing long-term immunity to the influenza virus.

Excellent examples of artificial active immunization include the different types of immunizations that will be discussed in this article. These immunizations mimic the stimulation necessary for immune development yet do not produce active disease.^[1,9]

STIMULATION OF IMMUNITY BY VACCINES

As with any challenge to the immune system, the body must first detect the threat whether it is a pathogenic agent or an immunization. This initial detection typically is done by the innate immune system; although, B-cells may also perform this function. This detection process begins when the immune system recognizes epitopes on antigens. Epitopes are small subregions on the antigens that simulate immune recognition.

Multiple components of the innate immune system will then respond to this challenge. These components of innate immunity will opsonize or bind to the agent and aid in its engulfment by antigen-presenting cells such as macrophages or monocytes. These antigen-presenting cell(s) will then process the antigens from this pathogenic agent and insert the processed antigen along with the MHC protein onto the surface on the antigen-presenting cell.^[10]

If it is a viral antigen, the antigen will be bound with MHC I protein and presented by the antigen-presenting cell to a CD8 cell which will likely trigger cell-mediated immunity. If it is a bacterial or parasitic antigen, the antigen will be bound with MHC II protein and presented by the antigen-presenting cell to a CD4 cell which will likely trigger antibody-mediated immunity.^[1]

CURRENT/UNDER DEVELOPMENT VACCINE TYPES

There are a variety of vaccine types that are either currently in use or in development for the prevention of infectious diseases. Under ideal conditions, vaccines should trigger the innate immune system and both arms of the adaptive immune system.^[11] However, each vaccine type has both advantages and disadvantages which can affect the stimulation of the immune system and thus limit the usefulness of the vaccine type.^[12]

First, live, attenuated vaccines as exemplified by the vaccines against measles, mumps, and chickenpox contain laboratory-weakened versions of the original pathogenic agent. Therefore, these vaccines produce a strong cellular and antibody responses and typically produce long-term immunity with only one to two doses of vaccine. Typically, it is less difficult to create live, attenuated vaccines with viruses rather than bacteria because viruses have fewer genes so it is easier to control the viral characteristics. However, because these vaccines contain living microorganisms, refrigeration is required to preserve potency; and, there is the possibility of reversion to the original virulent form of the pathogenic agent. In addition, live vaccines cannot be given to individuals with weakened immune systems because the vaccine produces actual disease.

Inactivated vaccines as exemplified by the inactivated influenza vaccine are produced by destroying a pathogenic agent with chemicals, heat, or radiation. This inactivation of the microorganism makes the vaccine more stable. These vaccines do not require refrigeration and can be freeze-dried for transport. However, these vaccines produce weaker immune responses therefore additional booster shots are required to maintain immunity.^[12]

In experiments with mice by Raz *et al.*, a vaccine made from irradiated *Listeria monocytogenes* bacteria, rather than heat-killed bacteria, showed protection against a challenge with live *Listeria*. The irradiated vaccine also stimulated a protective response from T-cells which previously had only been shown to occur with vaccines made from live, weakened *Listeria* bacteria.^[11]

Subunit vaccines as exemplified by the recombinant hepatitis B vaccine include only epitopes (specific parts of antigens to which antibodies or T-cells recognize and bind) that most readily stimulate the immune system. Because these vaccines only use a few specific antigens, this reduces the likelihood of adverse reactions; however, this specificity increases the difficulty of determining which antigens should be included in the vaccine.

Toxoid vaccines as exemplified by the diphtheria and tetanus vaccines are produced by inactivating bacterial toxins with formalin. These toxoids stimulate an immune response against the bacterial toxins.

Conjugate vaccines as exemplified by the *Haemophilus influenzae* type B (Hib) vaccine are a special type of subunit vaccine. In a conjugate vaccine, antigens or toxoids from a microbe are linked to polysaccharides from the outer coating of that microbe to stimulate immunity (especially in infants).

Naked DNA vaccines are still in the experimental stages of development. These vaccines would use DNA specific for microbial antigens to stimulate immunity. This DNA would be administered by injection and then body cells would take up the DNA.

These body cells would then start producing the antigen and displaying it on their surfaces which would then stimulate the immune system. These vaccines would produce both a strong antibody response to the free antigen and a strong cellular response to the microbial antigens displayed on the cell surfaces. These vaccines are also considered relatively easy and inexpensive to create and produce. Naked DNA vaccines for influenza and herpes are still in the developmental stages.^[12]

Recombinant vector vaccines are experimental vaccines that use either an attenuated virus or microbe to introduce microbial DNA into body cells. These viral vaccines would readily mimic a natural infection thus stimulating the immune system.

Attenuated bacteria could also have genetic material for antigens from a pathogenic microbe inserted. These antigens from the pathogenic microbe would then be displayed on the harmless microbe this mimicking the pathogen and stimulating the immune system. Both bacterial and viral-based recombinant vectors vaccines for HIV, rabies, and measles are in the experimental stages.^[12]

In addition to these vaccines, there have been studies examining the possibility of improving vaccine adjuvants

which would target the innate immune system. These adjuvants would fall into two classes, either delivery systems (such as cationic microparticles) or immune potentiators (such as cytokines or PRRs). The delivery systems would possibly be used to concentrate and display antigens in repetitious patterns, to assist in localizing antigens and immune potentiators, and to target the antigens in the vaccine to the antigen-presenting cells. While, the immune potentiators would be used activate the innate immune system directly.^[6]

SUMMARY

Both the innate and adaptive immune subsystems are necessary to provide an effective immune response whether to an actual pathogenic agent or to an immunization. Further, effective immunizations must induce long-term stimulation of both the humoral and cell-mediated arms of the adaptive system by the production of effector cells for the current infection and memory cells for future infections with the pathogenic agent. At least seven different types of vaccines are currently in use or in development that produce this effective immunity and have contributed greatly to the prevention of infectious disease around the world.

REFERENCES

1. Goldsby RA, Kindt TJ, Osborne BA, Kuby J. Immunology. 5th ed. New York: Freeman; 2003.

2. Hartshorn KL, White MR, Crouch EC. Contributions of the N- and C-terminal domains of surfactant protein D to the binding, aggregation, and phagocytic uptake of bacteria. *Infect Immun* 2002;70:6129-39.
3. The Merck Manuals Online Medical Library. 2008. Complement System. Available from: <http://www.merck.com/mmpe/sec13/ch163/ch163d.html> [Last cited on 2009 Nov 22].
4. Margolick JB, Markham RB, Scott AL. The immune system and host defense against infections. In: Nelson KE, Masters CF, editors. *Infectious Disease Epidemiology: Theory and Practice*. Chapter 10. 2nd ed. Boston: Jones and Bartlett; 2006. p. 317-43.
5. Janssens S, Beyaert R. Role of toll-like receptors in pathogen recognition. *Clin Microbiol Rev* 2003;16:637-46.
6. Pashine A, Valiante NM, Ulmer JB. Targeting the innate immune response with improved vaccine adjuvants. *Nat Med* 2005;11:S63-8.
7. The Merck Manuals Online Medical Library. 2008. Components of the Immune System. Available from: <http://www.merck.com/mmpe/sec13/ch163/ch163b.html> [Last cited on 2009 Nov 26].
8. The Merck Manuals Online Medical Library. 2008. Passive Immunization. Available from: <http://www.merck.com/mmpe/sec14/ch169/ch169c.html> [Last cited on 2009 Dec 5].
9. Centers for Disease Control and Prevention. 2009. Immunity Types. Available from: <http://www.cdc.gov/vaccines/vac-gen/immunity-types.htm> [Last cited on 2009 Dec 20].
10. Schijns VE. (2001). Activation and programming of adaptive immune responses by vaccine adjuvants. Available from: <http://www.vetscite.org/publish/articles/000027/index.html> [Last cited on 2010 Jan 7].
11. NIH News. 2006. Radiation-killed bacteria vaccine induces broad immune response in mice. Available from: http://www3.niaid.nih.gov/news/newsreleases/2006/raz_listeria.htm [Last cited on 2010 Jan 7].
12. National Institute of Allergy and Infectious Diseases. 2009. Types of Vaccines. Available from: <http://www3.niaid.nih.gov/topics/vaccines/> [Last cited on 2009 Dec 22].

How to cite this article: Clem AS. Fundamentals of vaccine immunology. *J Global Infect Dis* 2011;3:73-8.
Source of Support: Nil. **Conflict of Interest:** None declared.