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CHAPTER 9

Vaccines and Immunotherapy

CHAPTER FOCUS

To emphasize immunological principles as they relate to vaccination. The goal is to develop a perspective about active and passive immunization via vaccination against infectious agents of multiple classes. The discussion will demonstrate how principles in immunology combine with biotechnology to advance the field of vaccinology. Information regarding immunotherapeutics is presented as a way to provide homeostasis of normal immune function.

PRINCIPLES OF VACCINATION

The definition of immunity is centered on protection against infectious disease. This may be conferred most readily by immune responses generated through immunization or previous infection. Edward Jenner, an English country doctor, observed that people infected with cowpox virus often developed less severe smallpox disease. Consequently, he inoculated a boy with cowpox virus obtained from hand sores on a milkmaid. Six weeks later, after the boy recovered from cowpox, he was reinoculated with virulent smallpox virus. The boy survived. Thus was born the process of vaccination. Since that time, similar methodologies have been successfully adopted for immunization against a multitude of diseases.

Although unknown at the time, Jenner’s vaccination represented cross-reactivity of common antigens present on the cowpox virus with molecules present on the smallpox virus. Antibodies raised against the avirulent form also were able to neutralize virulent infection. It has been shown subsequently that the development of specific antibodies is a powerful tool to provide long-lasting immunologic protection against infectious agents. Indeed, it is now appreciated that a wide variety of responses are triggered via immunization; specific pathways can be
targeted to elicit the arm of the immune response that is most critical for protection against distinct pathogens (Table 9.1). Major advances in vaccine design are taking place. Improvements in methodologies to produce nonvirulent antigenic substances for use as vaccine antigens will dictate future successes in the immunization arena. These include novel ways to manufacture toxoids and synthetic peptides, improvements in recombinant DNA technology to allow live, avirulent (nondisease-causing) viral and bacterial agents to express other pathogen genes, development of DNA-based vaccines, and new methods of conjugation to achieve superior immunogenicity for both polysaccharide and protein antigens.

**BASIC CONCEPTS OF PROTECTIVE IMMUNIZATION**

The objective of immunization is to generate high levels of memory cells using vaccination methods (Fig. 9.1). The term primary immune response refers to a lymphocyte activation event following first recognition of foreign material, following which a memory response is generated. Immunological memory represents a pool of circulating, long-lived cells that remain present and available for action long after the initial response activities wane. If the antigen is reencountered at a later time, a secondary immune response occurs, in which memory cells are engaged and activated. This secondary response is faster, more focused, and more effective than the original encounter.

The development of disease is a complex equation that gives rapidity of response as a critical component related to disease outcomes. The

| Type of vaccine | Components | Examples |
|----------------|------------|----------|
| Live, attenuated | Viral or bacterial organism with reduced pathogenicity | Oral polio, varicella, measles-mumps-rubella (MMR), bacillus Calmette-Guerin (BCG) |
| Killed-inactivated | Whole killed organism | Inactivated polio, typhoid |
| Subunit Recombinant subunit | Inactivated or modified toxins, purified components Gene-derived proteins produced in another organism | Diphtheria, tetanus, influenza Hepatitis B toxoid, human papillomavirus (HPV) |
| Conjugate/polyvalent | Combined components isolated or genetically modified from multiple strains | Haemophilus influenzae type B, Streptococcus pneumoniae, Neisseria meningitidis |
incubation period during the establishment of infection is important because it dictates how much time is available to mount an immune response prior to disease initiation. A long pathogen incubation time results in an extended period where immune events can mature. This naturally leads to induction of a relatively stronger immune response, with significant development of immunological memory. In this case, secondary exposure results in protection to disease due to preestablished memory responses. Vaccines are especially useful in this example, as there is a shorter window of opportunity for fighting pathogens with them. Induction of protection can be achieved with a vaccine, provided that one is able to sustain high, long-term, reactive antibody titers. This is clinically achievable by giving several immunizations in a shorter time frame to raise sustained titers of specific antibody responses.
TYPES OF IMMUNIZATIONS

Immunizations may be active or passive. Active immunization is a result of direct exposure to an antigen, which allows the host to generate protective immunity. The objective is to provide long-lasting immunity against future exposures. **Active immunity** may be acquired naturally, through infection (and subsequent recovery), or artificially, through vaccination. **Passive immunity** also provides protection for the host, but it is conceived by the administration of humoral and/or cellular factors that provide immunity for the host. In this case, the host does not actively generate a protective response. The objective of passive immunity, therefore, is to provide immediate but temporary protection against an imminent or ongoing threat.

AGE AND TIMING OF IMMUNIZATIONS

Vaccines are given to prevent life-threatening infections. It is critical, therefore, to relate factors such as patient age, demographics, geographical location, and pathogen incidence to the vaccines being administered (Table 9.2). For example, neonate or pediatric vaccines typically target pathogens that rapidly outpace an infant’s ability to respond effectively. The newborn is naturally delayed in the development of immune responses, especially in the production of immunoglobulin isotypes (Fig. 9.2). Newborns are immunocompetent but immune immature; fetuses make immunoglobulin M (IgM), but not immunoglobulin G (IgG) until birth. Maternal IgG provides protection against bacterial agents through the first months of life. While the total amount of all immunoglobulin IgG in newborn serum is at a level (mg/ml) close to that of a normal adult, almost all of it is of maternal origin. The half-life of IgG is 2–3 weeks; only 10% of maternal antibodies remain by 4 months of age, and only 3% by 6 months. Fortunately, at 2–3 weeks postpartum, supplemental antibodies of the immunoglobulin A (IgA), IgM, and IgG isotypes are delivered through colostrum and breast milk.

Children under 2 years of age remain immunologically disadvantaged, with limited ability to produce antibodies other than those of the IgM isotype to bacterial capsular polysaccharides (T-independent antigens). Vaccines are designed to work with the newborn’s developing immune system to elicit opsonizing antibodies of the IgG isotype. One trick is to link a polysaccharide molecule, or a hapten, to a carrier protein chemically to enlist a strong T-helper-cell response and induce accompanying antibody isotype-switching.
## TABLE 9.2  US Schedule for Active Immunization of Children and Adults

| Vaccine (birth to 18 years old) | Age (dosing dates for vaccination) |
|----------------------------------|------------------------------------|
| Hepatitis B                      | Birth, 1–2 months, 6–18 months     |
| Rotavirus                        | 2 months, 4 months                 |
| Diphtheria, tetanus, acellular pertussis (DTP) | 2 months, 4 months, 6 months, 15 months, additional dose after year 4 |
| *H. influenzae* type b (Hib); pneumococcal conjugate (PCV13) | 2 months, 4 months, 6 months, 15 months, additional dose after year 1 |
| Poliovirus                       | 2 months, 4 months, 6–18 months, and after year 4 |
| Influenza                        | Annual vaccination after month 6   |
| MMR; varicella                   | 1 year, additional dose after year 4 |
| Hepatitis A                      | 1 year, additional dose before year 2 |
| Influenza (childhood)            | Annual vaccination after month 6   |
| HPV                              | 3 doses in early teenage years     |
| Tetanus, diphtheria, pertussis (Tdap) | 1 dose annually, begin year 7, boost in year 11 and each decade after |
| Meningococcal                    | 11 years, boost in year 16         |
| Vaccine (19 years old plus)      | Age (dosing dates for vaccination) |
| Influenza (adult)                | 1 dose annually, begin year 19     |
| HPV                              | 2–3 doses over lifetime, depending on age at series initiation |
| Tetanus, diphtheria, pertussis (Tdap) | 1 dose annually, boost each decade |
| Varicella                        | 2 doses recommended over lifetime  |
| HPV                              | Boosting of individuals of high risk or immunocompromised |
| Pneumococcal conjugate (PCV13 or PPSV23) | Boosting of individuals of high risk, plus after year 65 |
| Meningococcal                    | 2 doses recommended over lifetime  |
| Hepatitis A, hepatitis B         | 2 doses recommended over lifetime  |
| *H. influenzae* type b (Hib)     | 1 or more doses dependent upon indication |
| Zoster                           | 50–60 years old, or older         |

An expanded recommended immunization schedule maintained by the Centers for Disease Control and Prevention (CDC) may be found at [http://www.cdc.gov/vaccines/schedules/index.html](http://www.cdc.gov/vaccines/schedules/index.html).
On the other end of the age spectrum, the elderly (i.e., > 60 years of age) exhibit a reduced capacity to mount primary responses to most antigens. Extreme age is a determinant for immune regulation; immune senescence occurs, in which the majority of memory responses remain available but poor primary (naive) response results in increased susceptibility to organisms and strains never before encountered. It is noteworthy that the immune-senescent individual retains a strong response to bacterial polysaccharides. The goal with elderly individuals, therefore, is to induce high levels of specific responses. It may be necessary to repeat vaccinations at more frequent intervals (years, rather than decades) to maintain a high functional response level.

In healthy individuals, multiple doses may be required to induce immunoglobulin isotype switching and to attain high levels of antibody titer sufficient for long-lasting protection. The critical factor is knowledge of which arm of the immune response is required to optimize protective responses against any particular infectious agent or pathogenic factor. Induction of B-cell responses for antibody production is a successful method of toxin or viral neutralization. Antibodies are also tremendously effective for opsonizing bacteria to prepare them for phagocytosis, as well as for targeted pathogen killing when combined with complement components.

Vaccines that drive T-cell development are effective against both intracellular and extracellular agents and to help monocytes to stimulate inflammatory responses that are critical to destroying invading pathogens.

FIG. 9.2 Changes in relative antibody titers and isotypes in the newborn.

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Cytotoxic lymphocytes are necessary for the targeted destruction of intracellular pathogens, such as viral agents, in which a lethal hit delivered to infected target cells is required to limit the spread of infection. Adjuvants, discussed later in this chapter, are essential for directing the immune response in a way that will benefit protective outcomes.

Vaccines are especially effective for use in selected populations. These include military personnel, as well as travelers to high-risk areas, who may be exposed to pathogens not typically encountered in local environments. Vaccines will be an especially important tool to control outbreaks (and future outbreaks) of rare illnesses, and this is especially urgently needed for the Ebola virus, the Zika virus, and the Middle East Respiratory Syndrome (MERS)- and Severe Acute Respiratory Syndrome (SARS)-associated coronavirus agents.

Similarly, veterinarians and animal handlers should consider vaccination against pathogens found in the workplace. College students should be vaccinated against sexually transmitted diseases and against agents that are easily spread in high-contact areas. Obviously, health care workers and physicians should be vaccinated against pathogens transferred through accidental blood product exposure. Also, although not completely obvious, it is recommended that those in high-risk lifestyles [e.g., high human immunodeficiency virus (HIV) demographics or intravenous (IV) drug users], as well as those that are immunocompromised, should undertake regular reviews of vaccines for prophylactic protection. Finally, while less common, therapeutic vaccines may be used to treat infected individuals with slow-growing pathogens. These include vaccines that may be used as a targeted therapeutic to treat diseases such as rabies and hepatitis.

A short but frank discussion of relative vaccine safety is warranted. Vaccines are a safe and proven mechanism to induce strong protective immunity. They can elicit minor temporary inflammation following administration; however, those effects are limited in duration and quickly dissipate (2–3 days) postinjection. In some cases, elevated levels of hypersensitivity can occur, and there are rare cases of arthritis and arthralgia in individuals prone to these reactions. The US Food and Drug Administration (FDA) set strict rules for the removal of toxic products during formulation of vaccines. The current public reports of deaths in infants and the elicitation of neurological impairment due to vaccination are false. In addition, there is no proven link of infant vaccines to developmental disorders, such as those causing autism; data to back up those claims were falsified and the report has since been retracted.

While increased hygiene is protective, vaccines are critical to keep disease at bay. Herd immunity is a social concept relating that vaccination of a significant portion of a population (or “herd”) gives a measure of protection for individuals who have not developed immunity; vaccines
protect us as well as those around us due to the subsequent limitation of infection spread. Multiple vaccinations work; the child’s immune system is robust and cannot be overwhelmed by multiple immunizations. Indeed, a child is exposed to more antigens in their daily routine than through all the vaccines combined that they receive during childhood. Care should be taken with live vaccines, even if the organisms are attenuated. They should not readily be given to immunocompromised patients or to those with severe immune disorders. Likewise, patients undergoing concurrent immunosuppressive therapy, or even pregnant women, should avoid being vaccinated with live organisms.

**Immunologic adjuvants** are excipient components added to vaccines to potentiate immune responses. In essence, they function to direct antigenic responses toward achieving the desired immune outcome and allow the vaccine to be a more effective prophylactic candidate. In general, adjuvants are capable of assisting in the generation of immunity, through stabilization of the antigen delivered and direct triggering of cellular responses.

The only adjuvants approved for use in the United States are the mineral salts (*aluminum salts; alum*) and an oil-based emulsion capable of stabilizing functional delivery of the antigen. However, many novel molecules are under active research for inclusion as approved adjuvants in vaccine preparations. They include plant saponins, cytokines, bacterial cell wall products, particulates, viral-like particles, and nucleic acid motifs. Some function by stimulating antigen-presenting cells (APCs) through interaction with pathogen-associated molecular patterns (PAMPs) or Toll-like receptors (TLRs). Others function to stabilize the antigen for targeted presentation by APCs to T lymphocytes.

### PASSIVE IMMUNIZATION

An example of passive immunization was mentioned previously when describing how newborns are protected with maternal IgG. As a therapeutic class, passive immunization is an extremely useful clinical tool. Immunoglobulins are routinely given to patients to prevent or treat disease, and they are especially potent in immune-deficient individuals. Pooled antibodies from immune donors can be given intravenously. These *intravenous immunoglobulins* (IVIG) used to treat primary immune deficiencies can restore regular immune function, although continued administration is required every 3–4 weeks due to the half-life of the IgG isotype given.

Historically, antibodies raised in animals also could be administered to humans to treat infections. For example, antibodies against tetanus toxoid isolated from serum of immunized horses could be given to neutralize the
tetanus toxin. Unfortunately, the heterologous antisera, being nonhuman in nature, were recognized as foreign when given more than once. This led to hypersensitive responses.

Fortunately, science has evolved the technology to produce monoclonal antibodies in the laboratory that are homologous in their physical amino acid structure (antibodies of the same species), which limits cross-reactivity to heterologous epitopes. The FDA now has a panel of approved antibody-based products for passive immunization and targeted immunotherapy, many of which have been “humanized” (via molecular engineering) to include human-constant regions while retaining the antigenic specificity targeted by the original immunoglobulin. This allows the monoclonal to be used with little or no chance of foreign reactivity developing.

**THERAPEUTIC USES OF IMMUNOGLOBULINS**

The ability to utilize passive antibodies as therapeutic agents has exploded in the last decade. In addition to IVIG, monoclonal antibodies have been successfully used to treat multiple autoimmune disorders. Specifically, antibodies that either neutralize or inhibit the binding of tumor necrosis factor (TNF) to its receptors are important therapeutic tools to fight the manifestation of pathology during autoimmune responses. Likewise, monoclonals can play a targeted role in the fight against cancers of both hematologic and solid tumor forms. These directly target B-cell malignancies, breast cancer, chronic myelogenous leukemia (CML), and chronic lymphocytic leukemia (CLL), to name just a few.

Another example for antibody use as a therapeutic agent is of clinical importance in a specific complication of red blood cell (RBC) surface antigen incompatibility between mother and fetus. Rh antigens, also called *Rhesus antigens*, are transmembrane proteins expressed at the surface of erythrocytes. They appear to be used for the transport of carbon dioxide (CO₂), ammonia, or both across the plasma membrane. RBCs that are Rh positive express a specific antigen designated the D type (RhD antigen). About 15% of the population have no RhD antigens and thus are Rh negative. An Rh-negative mother who carries a Rh-positive fetus runs the risk of producing immune antibodies to the Rh antigens on the fetal RBC. The exposure during primary pregnancy is minimized. However, the mother may generate Rh antibodies after birth if the mother comes into contact with fetal blood cells during placenta rupture. Some fetal RBCs enter the mother’s bloodstream, thus allowing the production of maternal-derived anti-Rh antibodies.

Upon subsequent pregnancies, the next Rh-positive fetus also will be at risk because the mother will retain a low level of circulating antibodies against the Rh antigen. Destruction of fetal erythrocytes will occur via
the passive immune transfer of maternal antibodies to the fetus, resulting in erythroblastosis fetalis (a hemolytic disease of the newborn). It is of great clinical importance to identify Rh-mismatched mothers and fetuses. If there is such a mismatch, the mother is clinically treated with anti-Rh antibodies [Rh immune globulin (RhIG) or Rhogam], which react with the fetal RBC. The ensuing antibody-antigen complexes are removed prior to maternal recognition of foreign Rh antigens.

Monoclonal antibodies are now being used regularly to treat diseases with immunological etiology. The essence of this technology (mentioned previously in this chapter and in Chapter 7) takes advantage of the exquisite binding capabilities of antibody-variable domains to recognize specific biological targets. These targets may be receptors on cells, or they may be inflammatory mediators released during disease. These biologically-based therapeutic agents have the advantage of being produced in the laboratory under quality-controlled conditions. Recent advances in this field have included the extension of these therapeutics for use in nonimmune-related disorders.

OTHER WAYS OF MODIFYING IMMUNITY

Finally, it should be noted that the removal of pathogenic antibodies and other immune factors is an important immunotherapeutic option. Another example again relates to a child born to a mother suffering specific autoimmunity. Maternal antibodies are passed to the child, and the child exhibits disease symptoms that mimick those in the mother.

A specific case can be seen with a mother who has active Graves’ disease; maternal antibodies passed to the newborn initiate relatively high activation of the thyroid gland, leading to clinical symptoms of hyperthyroidism. Successful treatment can be accomplished by plasmapheresis, in which reactive maternal antibodies are filtered from the serum of the newborn; elimination of reactive antibodies eliminates clinical presentation in the child.

SUMMARY

- Vaccines are a safe and proven mechanism to induce strong immunity. Immunization has had a tremendous impact on the quality and longevity of human life by eliminating devastating pathogens.
- Vaccines vary to accommodate the targeted immune recognition of pathogens in advance of encountering the infectious agent. Strategies incorporate the physical basis and nature of the antigen with stabilizing delivery vehicles. Adjuvants can be added to promote directed immune function.
The nature of the antigen used in immunization is critical to eliciting the subsequent response. Technological advances in molecular production allow a broad range of antigens for use in vaccination.

Passive administration of immunoglobulins or immune factors allows short-term protection in the absence of preexisting immune responses.