

Innate Immune Defects



Chapter 18

Primary immunodeficiency diseases are disorders in which part of the body's immune system is missing or does not function properly. These disorders can be divided into two groups:

- 1) Those less common conditions with defects in the innate immune system, a system of cells and mechanisms that defend the host from infection in a non-specific manner.*
- 2) Those conditions due to defects of the adaptive immune system in which defense is carried out in a more specific manner by T-cells and antibody producing B-cells.*

This chapter focuses only on the following innate immune disorders: Toll-like receptor (TLR), natural killer (NK) and interferon- γ /interleukin 12 (IFN- γ /IL-12) defects.

Innate Versus Adaptive Immunity

The mechanisms by which the innate and adaptive (acquired) immune systems function are different: Innate immune responses are those that rely on cells that require no additional “training” to do their jobs. These cells include neutrophils, monocytes, natural killer cells, basophils and mast cells and complement proteins. Innate responses to infection occur rapidly and reliably. Even small infants have excellent innate immune responses. The innate immune system recognizes microbes through a class of proteins found on cells termed pattern recognition receptors (PRRs), which bind to unique proteins of various microorganisms. A major class of PRRs are called toll-like receptors (TLRs), molecules found on the surface and within cells.

Adaptive immune responses comprise the second category. These responses involve T-cells and B-cells, two cell types that require “training” or education to learn not to attack our own cells and to become more efficient for eliminating invading germs. In contrast to the innate immune system, adaptive immune responses recognize microbes by specific receptors found on T- and B-cells. The advantages of the adaptive responses are their long-lived memory and the ability to adapt to new germs. Each T- and B-lymphocyte acquires a unique receptor during development that can respond to a specific microbe. As a group, these cells are capable of recognizing virtually all microbial or other antigens found in nature.

Toll-like Receptors

There are ten human TLRs termed TLR1 to TLR10. The TLRs recognize microbes by forming pairs with each other. After recognizing a molecule on the microbe, the TLRs begin a series of chemical reactions that allow signals to enter the innate immune cell and allow it to function in the killing of the microbe. If one or more of these chemical molecules are defective, the innate immune cell cannot kill the microbe and patients with these defects present with recurrent infections.

The pairing of TLR1/2 or TLR2/6 recognizes bacteria such as those that cause tuberculosis. The TLR3 recognizes certain viruses; TLR4 recognizes certain molecules on bacteria found in the gastrointestinal tract such as *E. coli*; TLR5 recognizes whip-like structures on bacteria called flagella; TLR7, 8 and 9 recognize certain viruses such as influenza and human immunodeficiency virus I (HIV-I). The function of TLR10 is not yet known. In recent years several deficiencies of TLRs have been identified in patients who present with recurrent infections. The knowledge of the function of these TLRs has provided an important basis for the diagnosis and treatment of these disorders.

Toll-like Receptor (TLR) Deficiencies

As described previously, TLRs are proteins present on the surface of many types of white blood cells that react with proteins present on many microbes. Upon contact with these microbes TLRs send internal messages to the nucleus of the cell to secrete cytokines, which stimulate the immune system to combat invading microorganisms.

Cytokines are important proteins in the body that serve as hormones for the immune system. They are produced in response to a threat and represent the communication network for the immune system. In some cases, cells of the immune system communicate by directly touching each other, but often cells communicate by secreting cytokines that can then act on other cells either locally or at a distance. There are

several families of cytokines and two of these are called interleukins (ILs) that number 1 through 37 and a family of interferons, originally described by their ability to interfere with viral replication, and which include interferon-alpha (IFN- α), interferon-beta (IFN- β) and interferon-gamma (IFN- γ).

Several TLR immunodeficiencies have been described in which cellular proteins that should transmit the message from the TLRs to the nucleus are abnormal. These signaling defects result in a failure of cytokines to be produced in response to bacterial infection. Two of these are disorders termed MyD88 deficiency and IRAK-4 deficiency. Other disorders of this type include UNC93B deficiency and TLR3 mutations and ectodermal dysplasia with immunodeficiency (EDA-ID), an X-linked disorder associated with a defect of a gene termed NEMO. (*See chapter titled "Nemo Deficiency Syndrome."*)

Clinical Presentation of TLR Deficiencies

The typical presentation of TLR deficiencies is susceptibility to infection with either bacteria or viruses. The innate immune system defects also play a major role in allergy and asthma, atherosclerosis and human immunodeficiency virus (HIV) infection.

MyD88 Deficiency

All TLRs except TLR3 use a signaling protein called MyD88 (myeloid differentiation primary response protein 88), a protein that allows the innate immune cell to function normally. MyD88 deficiency was initially described in nine children suffering from recurrent and severe pus-forming or pyogenic bacterial infections. These children were susceptible to invasive infections with *S. pneumoniae*, *S. aureus*, and *P. aeruginosa*, but had normal resistance to other common bacteria, viruses, fungi, and parasites. Susceptibility to infection improved with age in affected patients, although MyD88 levels did not change, indicating that the function of

(Toll-like Receptors continued)

MyD88 can be replaced by other systems as the immune system matures. The defect in the children with this disorder displayed autosomal recessive inheritance.

IRAK4 Deficiency

Another signaling defect with a similar clinical pattern similar to MyD88 deficiency is called IRAK 4 deficiency. Patients with IRAK4 deficiency have recurrent severe infections (cellulitis, arthritis, meningitis, osteomyelitis, organ abscesses and sepsis) mainly caused by *S. aureus*, *S. pneumoniae* (*pneumococcus*) and *Pseudomonas aeruginosa*. One report described recurrent bacterial infections, mostly localized to the upper respiratory tract and skin. No patients had severe viral, fungal or parasitic infections. Invasive pneumococcal infections caused the most disease and were the cause of death in 33 percent of affected

patients. Initial invasive infections occurred before the age of two years in 88 percent. The clinical status of patients with IRAK-4 deficiency seems to also improve with age, regardless of therapy, similar to patients with MyD88 defects.

UNC93B Deficiency and TLR3 Mutations

UNC93B1 is another signaling molecule involved in the production of interferon important in the killing of viruses. Signaling through TLRs 3, 7, 8, and 9 normally induces production of interferons following their binding to viral RNA. Deficiency of UNC93B1 or TLR3 leads to susceptibility to encephalitis caused by herpes simplex (HSV-1) (the virus that causes cold sores) due to decreased production of interferons in the central nervous system.

Human Natural Killer Cell Deficiencies

Natural killer (NK) cells are innate immune cells important in the killing of viral-infected or malignant cells. NK cells are so named because they kill cells without the presensitization needed for cytotoxic T-cells (part of adaptive immunity). NK cells are present in relatively low numbers in the bloodstream and in tissues.

NK cells kill virus-infected cells by inserting toxic proteins into their membranes. They are particularly important in the defense against herpes viruses. This family of viruses includes Herpes simplex virus (that causes cold sores and genital herpes), Epstein-Barr virus (that causes infectious mononucleosis) and varicella virus (that causes chicken pox and shingles).

Human NK cell deficiencies have been divided into two categories:

1. Quantitative defects: with decreased numbers of NK cells in the peripheral blood
2. Qualitative defects: with normal numbers of NK cells with abnormal function

NK cell deficiencies in the first category have been labeled “classical NK cell deficiencies” and those in the second “functional NK cell deficiencies.”

Two genetic causes of NK cell deficiency have been identified including an autosomal recessive CD16 functional defect and an autosomal dominant GATA2 mutation causing classic NK deficiency.

Defects in Interferon- γ (IFN- γ) and Interleukin-12 (IL-12) Signaling

A major way the cells of the innate immune system can kill microbes that are found within cells, such as the tuberculosis bacteria, is to cooperate with the T-cells of the adaptive system to stimulate interferon- γ (IFN- γ) production. IFN- γ /IL-12 pathway deficiencies are rare genetic disorders characterized by susceptibility to mycobacteria (the family of bacteria which cause

tuberculosis and related infections) and salmonella infections. Many of the affected infants become ill after receiving a live BCG tuberculosis vaccination, given routinely at birth in many countries, although not the U.S. Other patients have skin infections, swollen lymph nodes or blood stream infections with an enlarged liver and spleen.

Diagnosis of Innate Immune Defects

Most of patients with innate immune system defects have intact adaptive immune systems with normal immunoglobulins, antibodies and T-cells. A type of white blood cell called an eosinophil may be increased in the blood; elevated IgE immunoglobulin levels may also be present. The diagnosis is usually made by measuring cytokine production by white blood cells, activated by

microbial products that stimulate the cells. Testing of TLR function is becoming available through commercial reference laboratories. Abnormal tests need to be confirmed by repeat testing. Persistently abnormal tests may be followed up by specific genetic tests.

Treatment of Innate Immune Defects

The usual treatment for these defects is antibiotic therapy to treat acute infection. Prophylactic antibiotic therapy is also used. Some providers have also prescribed immunoglobulin therapy as infection prophylaxis.

New treatments of innate immune system defects have included new TLR-BASED THERAPIES. There are several new therapies in use or development that utilize emerging knowledge of TLR biology.

TLR7 agonists are drugs that activate TLR7 and have been found to slow the growth of malignancies and

inhibit viral replication. Imiquimod is a synthetic agonist of TLR7 that is effective topically on basal cell carcinoma and genital warts. Isatoribine is another TLR7 agonist used in the treatment of hepatitis C.

TLR9 agonists include CpG DNA — pieces of DNA that stimulate TLR9 activation to fight viruses. When added to hepatitis B vaccine (Engerix-B), they may boost the response to the vaccine. They may also be of value in augmenting cancer therapy.

Expectations for Patients with Innate Immune Defects

Patients with the defects of the innate immune system are being recognized with increasing frequency. Since these illnesses are rare and only recently identified, the long-term outlook has not yet been established. There is

considerable variability in the severity of their disease, and all the complications that may occur have not yet been identified. It is best to consult an immunologist who has specific expertise in this area.