

THE IMMUNE SYSTEM AND THE HEPATITIS C VIRUS

Tina M. St. John, MD

SECTION

I

MEET THE IMMUNE SYSTEM

Introduction

The *immune system* is the body's defense against infections. Think of the immune system as the body's army, protecting it from invaders. Just as the army has soldiers trained to perform different jobs, the immune system also has many types of cells performing different jobs. The cells of the immune system circulate through every tissue of the body.

When the body is infected with the *hepatitis C virus (HCV)*, the immune system swings into action. The immune systems of approximately 15% to 45% of people infected with HCV are able to rid their bodies of the virus. This is called *spontaneous clearance*. However, 55% to 85% of people infected with HCV are unable to clear the virus and become chronically infected. In immunology terms, chronic infection is called "persistence."

Among those who are chronically infected, the immune system appears to have a role in the rate of disease progression and liver damage caused by HCV. Therefore, the interaction between the hepatitis C virus and the immune system is at the core of HCV disease and its treatment.

This chapter provides a brief introduction to the immune system, and how it relates to chronic hepatitis C. At first glance, the concepts in this chapter may seem very complex. Many of the terms are likely to be new to you. However, reading this information may help you better understand some of the logic behind current hepatitis C treatment and research.

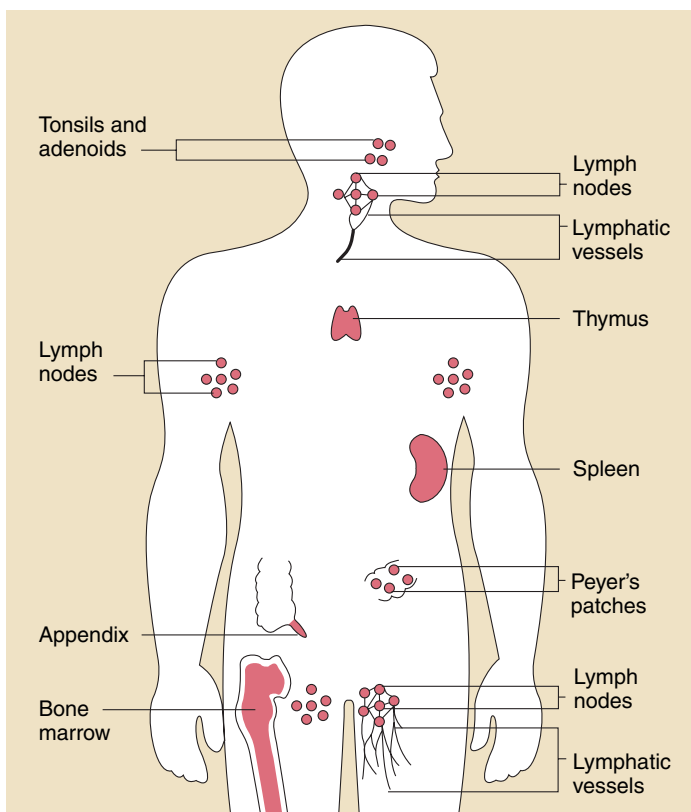
What Is the Immune System?

Every day, you are exposed to millions of germs or *microbes* including bacteria, viruses, fungi, and molds. Many of these microbes are harmless, but others can cause diseases ranging from the common cold to life-threatening infections such as pneumonia. The skin is the body's first line of defense against infections. It prevents most of the microbes we encounter from entering the body.

The immune system is the body's defense against those disease-causing microbes that get by our exterior defenses and enter the body.

The immune system runs through every tissue of the body. The primary parts of the immune system include the lymphatic vessels, *lymph nodes*, the *thymus gland*, the spleen, and the bone marrow (see Figure 1). Immune system cells and tissues are located throughout the body. Solitary immune system cells travel through the body via the blood and *lymphatic systems*, much like soldiers on patrol.

Figure 1. Immune System Tissues*



*Courtesy of the National Institute of Allergy and Infectious Diseases

Cells of the Immune System

The immune system has many different types of cells performing different jobs. The names of these cells can be confusing. Some of the most important cells of the immune system are listed in Figure 2. *White blood cells* called *lymphocytes* are the main “soldiers” of the immune system.

There are two main groups of lymphocytes, *T cells* and *B cells*. T cells are grouped according to the jobs they perform and include *T helper cells*, *T suppressor cells*, *cytotoxic T cells*, and *memory T cells*. Similarly, B cells are grouped according to their function. *Plasma cells* and *memory B cells* are two types of B cells. A third type of lymphocyte called a natural killer or *NK cell* is also important in the immune system. The specific jobs performed by different types of lymphocytes are discussed throughout the chapter.

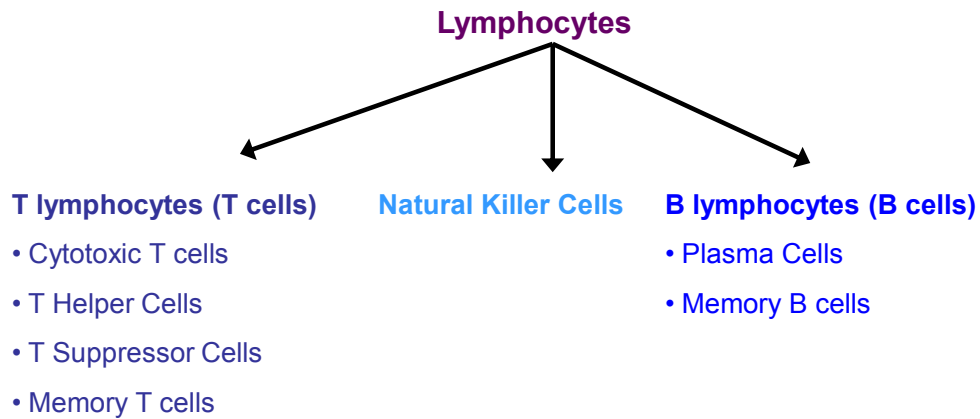
Identification of Invaders: Immune Recognition

Just as a soldier must be able to determine a friend from an enemy, the immune system must be able to recognize when a potentially harmful invader enters the body. In other words, the immune system must be able to distinguish between things that are supposed to be in the body (“self”) versus things that are invaders (“non-self”).

The immune system has a complex surveillance system to identify invaders. Some researchers believe HCV’s ability to “hide” from the immune system may explain, at least in part, how HCV is able to live in the body without being destroyed in those people with chronic infections.^{1,2}

The cells of the body and invading microbes each have many *proteins* on their surface. The combination of proteins on the surface of a cell or an invader enables the immune system to tell friend (self) from invader (non-self). Think of the surface proteins on cells as coats. All the cells of the body (self cells) have red coats. One day, an immune cell

Figure 2. Lymphocytes of the Immune System

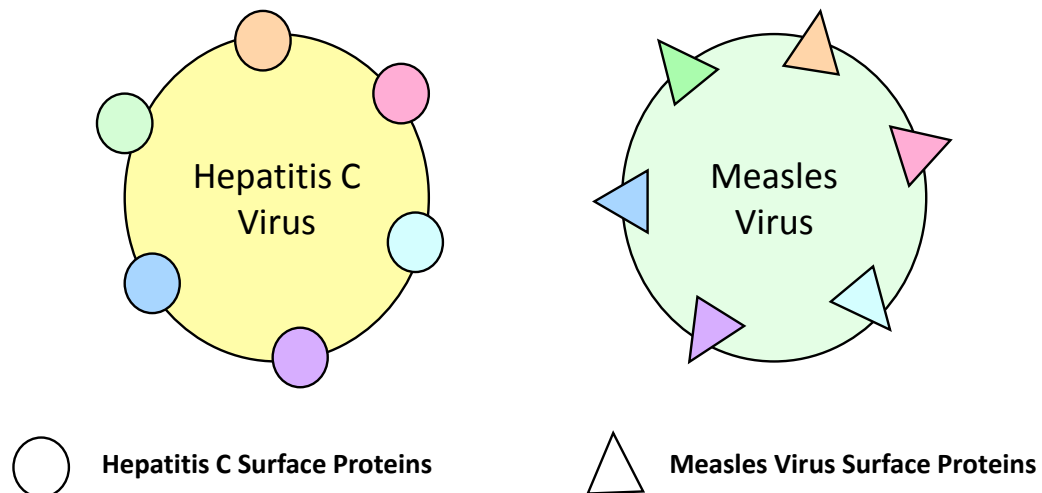


encounters a microbe in a green coat. The immune cell quickly recognizes that anything not in a red coat is an invader, and sounds the alarm to notify the rest of the immune system that an invader has made its way into the body. How HCV is able to subvert this critical recognition is the subject of much research, as is discussed in great detail in *Chapter 7.2, Immunology Takes on Hepatitis C*.

Beyond distinguishing self from invader, surface proteins specifically identify cells and microbes. Think of surface proteins as a labeling system. Surface proteins are “read” by the immune system. For example, Figure 3 shows a cartoon of the surface proteins of a measles virus and a hepatitis C virus. The circles and triangles on the outside of the viruses represent their surface proteins. The surface proteins of the measles virus and the hepatitis C virus are different. The immune system reads this difference. The combination of the measles surface proteins tells the immune system, “I am a measles virus.” The surface proteins of HCV tell the immune system, “I am a hepatitis C virus.” Thus, the immune system can not only detect the presence of an invader, it can also tell one type of invader from another because of their different surface proteins.

A surface protein that is recognized by the immune system and leads to *antibody* production is called an *antigen* or *immunogen*. Detection of foreign antigens is the primary way the immune system is alerted to the presence of invading microbes.

Figure 3. Surface Antigens on Measles and Hepatitis C Viruses



What is an Antibody?

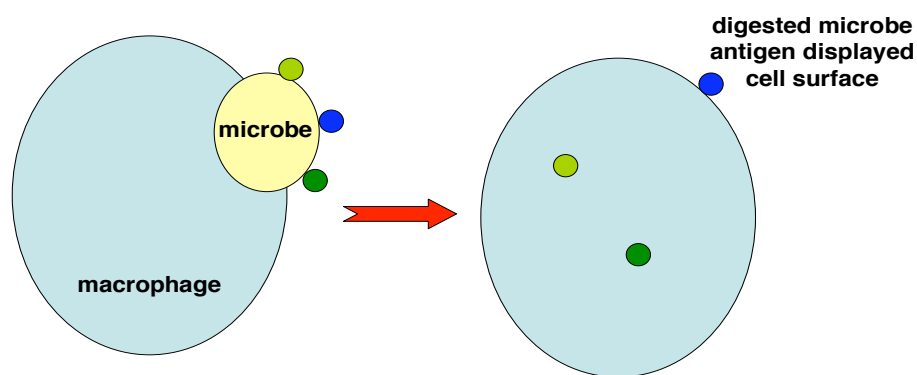
Antibodies are substances produced by the immune system that interact with microbes to kill them. *Immunoglobulin* is another term you may hear used for antibodies.

Antibodies are most effective against bacteria and viruses that live outside of cells (*extracellular* microbes). The immune cells that produce antibodies are special lymphocytes called *activated B cells* or plasma cells.

Several steps are required for the production of antibodies.

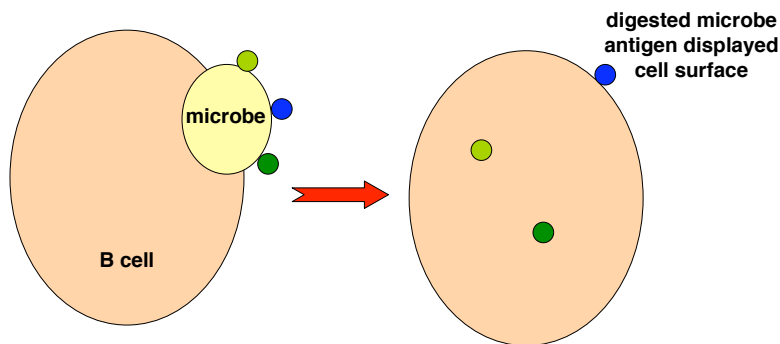
1. A white blood cell called a *macrophage* ingests (eats) an invading microbe. The microbe is digested by the macrophage (see Figure 4). Some of the microbe's digested proteins (antigens) are displayed by the macrophage on its surface to alert other cells of the immune system that an invader is present.

Figure 4. Macrophage Digesting Microbe and Displaying Antigen

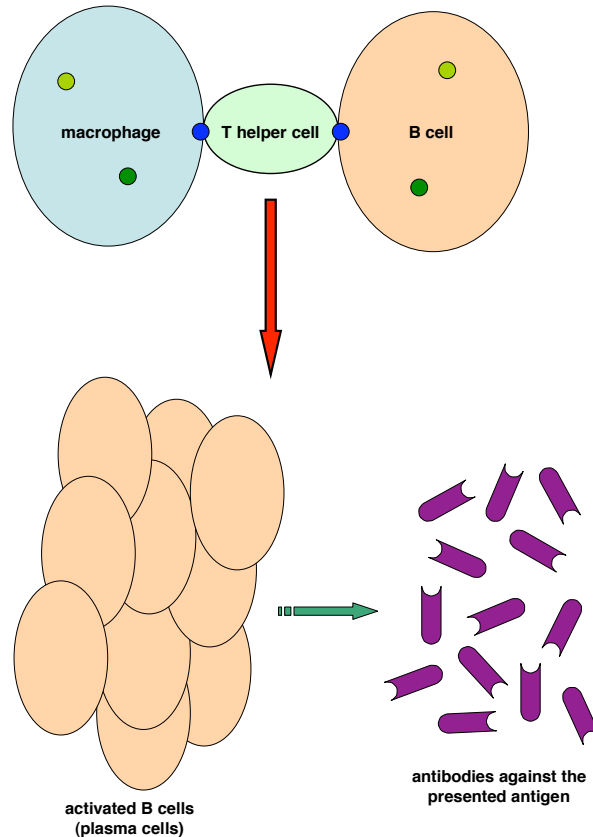


2. Lymphocytes called B cells also process and display the invader's proteins on their surfaces (see Figure 5).

Figure 5. B Cell Digesting Microbe and Displaying Antigen



3. When an immune cell called a T helper cell sees the same protein on the surface of a B cell and a macrophage, it sandwiches itself between the two other immune cells (see Figure 6). The formation of this bridge complex stimulates the B cell to begin dividing, making more copies of itself. The resulting group of activated B cells produces antibodies against the invading microbe's displayed proteins (antigens).

Figure 6. T Helper Cell Activates B Cell Causing B Cell Expansion and Antibody Production

The antibodies produced against an invader attach to antigens on its surface. The presence of antibodies on the surface of the invader serves as a “red flag” to the rest of the immune system and marks the invader for destruction. The killing takes place in one of two ways. The antibodies may cause leaks in the outer coat of the microbe; the leaky invader cannot recover and dies. More commonly, antibodies on the surface of the invader alert the killer cells of the immune system to ingest (eat) and destroy the invader.

Antigen-antibody interactions are very specific. Antibodies produced in response to a specific antigen normally react only with that antigen. Antigen-antibody interactions are often likened to a lock and key. A given lock can only be “activated” by a matching key. Similarly, a given antibody only reacts with its matching antigen.

In certain conditions, the immune system mistakes self antigens for foreign antigens. As a result, the immune system produces antibodies against self. These abnormal antibodies are called *autoantibodies*. Disease states caused by autoantibodies include:

- systemic lupus erythematosus (SLE)
- *autoimmune* hepatitis
- autoimmune *thyroiditis*
- rheumatoid arthritis

Examples of specific autoantibodies include *anti-liver-kidney microsomal antibodies (anti-LK)*, *anti-nuclear antibodies (ANA)*, *anti-smooth muscle antibodies (anti-SMA)*, and rheumatoid factor (RF).

More than half of all people with chronic hepatitis C have one or more autoantibodies in their blood. This is important because autoantibodies may cause additional symptoms and disease. Your doctor may test your blood for autoantibodies if you are having unexplained signs or symptoms. See *Chapter 6, Laboratory Tests and Procedures* for additional information about these tests.

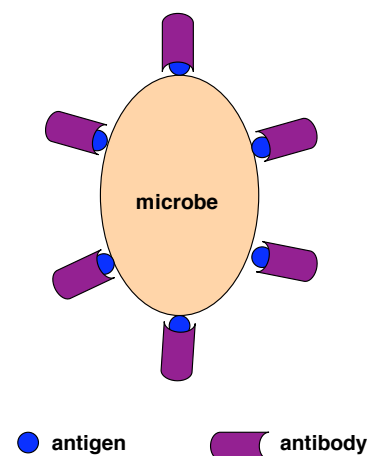
Cell-Mediated Immunity

Cell-mediated immunity is another tactic the body uses to defend itself against invaders through the direct actions of specific immune cells. Two important types of cells in the cell-mediated immune response are cytotoxic T cells and *natural killer cells* (NK cells).

Cytotoxic T cells are specific in their destructive action. They kill only cells that display the antigens they are programmed to seek-and-destroy. In contrast, natural killer cells are not very selective. An NK cell may kill any of a number of different cells. Both NK cells and cytotoxic T cells kill their targets directly and almost immediately after binding to them. Think of this as “the kiss of death” because once an immune system killer cell binds to an invader, that invader is doomed to die.

Cell-mediated immunity defends the body against fungi, parasites, cancer cells, foreign tissue (transplanted organs), and viruses that live inside cells (*intracellular viruses*) such as the hepatitis C virus. Specific actions of the cell-mediated branch of the immune system in response to HCV infections are discussed in *Chapter 7.2, Immunology Takes on Hepatitis C*.

Figure 7. Antibody Tags Microbe Marking It for Immune System



The Immune Response to Hepatitis C

Since the discovery of the hepatitis C virus in 1992, researchers have focused on trying to unravel the mysteries of how the immune system responds to HCV. Much has been learned, but there remain more questions than answers. For example:

- Why do some people spontaneously clear the virus while others develop chronic infection?
- How does the virus “outwit” the complex and sophisticated immune system?
- How does the interaction of the virus and the immune system cause liver damage?

These questions are easy to pose, but the answers are very complicated. Many highly skilled researchers continue to work diligently to find answers to these and other questions. This section provides an overview of some basic information scientists have discovered about the immune response to the hepatitis C virus. Each of these topics is explored in detail in *Chapter 7.2, Immunology Takes on Hepatitis C*.

Antibody Response to Hepatitis C

In a person with a normal immune system, HCV infection quickly leads to the production of antibodies against the virus. Anti-HCV antibodies are usually detectable in the blood within 3 to 12 weeks after infection. These antibodies persist even in people who spontaneously clear the virus. The presence of these antibodies is the basis for hepatitis C screening tests, which detect anti-HCV antibodies. The presence of anti-HCV antibodies in the blood indicates exposure to the virus, but does not indicate whether the virus is still present in the body.

While HCV circulates in the blood of an infected person, the virus spends most of its life inside liver cells. Once inside, HCV “hijacks” the liver cell’s production equipment in order to produce more copies of itself. The rate at which a virus

is able to make copies itself is called its *replication rate*. HCV has an extremely high replication rate with 10^{12} (that is 1,000,000,000,000) virus particles produced each day in an infected person.^{3,4}

With so many copies of the virus being made each day, there is some variation in the virus particles produced. Think of the *replication* process as a very rapid assembly line of HCV production. With the assembly line running at such a high rate of speed, the viruses produced are not perfect copies of the original. Therefore, as an HCV infection persists, several slightly different versions of the virus emerge. The process leading to these slight variations is called *mutation*, and the variant viruses produced are called *quasispecies*. Research findings suggest that the production of HCV quasispecies may contribute to HCV's ability to persist in the body. It appears that some HCV quasispecies are not recognized by the immune system as invaders. As such, these quasispecies are not attacked by the immune system.

The fact that HCV is predominantly an intracellular virus also appears to help it survive even in the face of a strong antibody response from the immune system. Recall that antibodies work best against invaders that live outside of cells. With HCV living primarily inside liver cells, most virus particles are able to escape antibody destruction. In the end, it appears that an antibody response alone is unable to rid the body of HCV. For a thorough review of this topic including the latest research findings, see *Chapter 7.2, Immunology Takes on Hepatitis C*.

Cell-Mediated Immune Response to Hepatitis C

Since HCV is an intracellular virus, the cell-mediated branch of the immune system is the predominant responder to HCV infection. Studies have proven that HCV lives inside the liver cells of an infected person. Some evidence suggests that HCV may also live inside specific types of immune cells.^{5,6}

The cell-mediated immune response to HCV is complex, and we have much yet to learn. However, several theories exist about the role of cell-mediated immunity in hepatitis C that have sufficient supporting evidence to warrant mentioning.

LIVER INJURY

The word "hepatitis" means inflammation of the liver. Indeed, liver cell injury and death are the features of HCV infection that threaten health. Some experts believe the liver injury associated with chronic HCV is caused by an ongoing but relatively low level, cell-mediated immune attack on the liver. It is believed that cytotoxic T cells attack and kill infected liver cells in an attempt to rid the body of HCV.^{7,8} If this theory is correct, it follows that while the attack of the cytotoxic T cells is at least partially responsible for the slowly progressive liver damage seen in chronic hepatitis C, it is at the same time inadequate to rid the body of the virus.

Research suggests that an individual's T cell response to HCV infection may play an important role in whether the virus is spontaneously cleared or becomes chronic. A strong initial T cell response has been associated with *viral clearance*, while a weak initial response that builds in strength over time has been linked to chronic infection.⁹

EARLY T HELPER CELL RESPONSE AND VIRAL PERSISTENCE

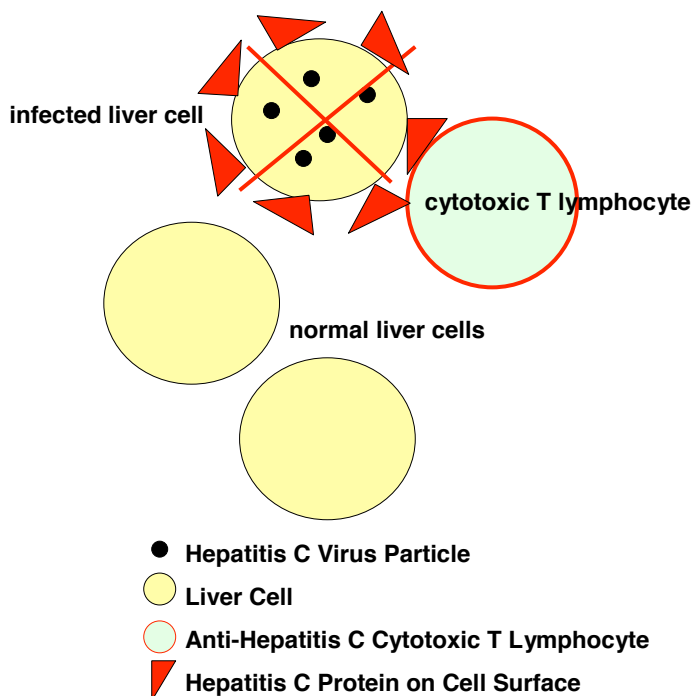
T helper cells are members of the T lymphocyte family of white blood cells. T helpers are also sometimes called *CD4 cells*. There are two types of T helper cells, Th1 and Th2. Th1 cells are cell-mediated immunity helpers. Th2 cells are *humoral immunity* helpers.

Research suggests that a person's T helper cell response in the first few months after HCV infection may be an important factor in whether the infection becomes chronic.^{10,11} A strong, sustained Th1 response appears to be important in spontaneous clearance of HCV. Scientists continue to explore the details of this important finding.

CYTOTOXIC T LYMPHOCYTES AND VIRAL PERSISTENCE

Cytotoxic T lymphocytes (CTLs or *CD8 cells*) are targeted killers of infected cells. When a virus invades a cell, some of the virus' proteins are displayed on the surface of the infected cell. The displayed virus proteins are "red flags" to the CTLs. CTLs attach to cells bearing the "I'm infected with a virus" red flag and deliver "the kiss of death." With HCV, infected liver cells are killed to stop additional HCV production and release of new viruses. The seek-and-destroy mission of CTLs is specific. That is to say, an anti-hepatitis C CTL will only bind to and kill a cell with HCV proteins displayed on its surface

Figure 8. Anti-HCV Cytotoxic T Lymphocytes Destroy Infected Liver Cells



(those with the HCV “red flag”). Thus, only HCV infected cells are killed by anti-HCV CTLs (see Figure 8). A strong and prolonged anti-HCV CTL response appears to be important in spontaneous clearance of HCV.^{12, 13, 14} Weak and/or limited CTL responses have been suggested as possible factors in the development of chronic HCV infection. Some evidence suggests that *interferon-based therapy* may act, at least in part, by enhancing the body’s cytotoxic T cell response to HCV.^{15, 16}

A person’s *genetic* makeup strongly influences how he or she responds to immune system challenges. Researchers continue to study exactly how genetic factors affect an individual’s immune response to HCV infection. Each of these topics and other cutting edge immunology research findings are discussed in detail in *Chapter 7.2, Immunology Takes on Hepatitis C*.

Extrahepatic Immune Syndromes and Chronic Hepatitis C

HCV lives primarily in the liver, and many of the symptoms of the disease are related to liver damage. However, approximately 38% of people with *chronic hepatitis C* also have immunologic disorders.¹⁷ Although the association between HCV and *extrahepatic* (outside the liver) immune syndromes is accepted by most experts, the interaction between chronic hepatitis C and immunologic disorders such as *cryoglobulinemia*, kidney disease, Sjögren’s syndrome, and *neuropathy* is not completely understood. Immune syndromes most often develop during the course of long-standing hepatitis C, and most frequently occur in people whose liver disease has progressed to *cirrhosis*.

Cryoglobulinemia

Cryoglobulins are abnormal immunoglobulins (antibodies). Cryoglobulins can get stuck and block tiny blood vessels causing symptoms. The location of the blocked vessels determines what symptoms a patient experiences. The portion of people with hepatitis C who also have cryoglobulinemia has been reported from <1% to almost 60% in various studies conducted throughout the world.¹⁷ Differences in the quality of the tests used to detect cryoglobulins may be responsible for some of this wide variation. Regardless of the portion of HCV patients affected, the association

between chronic hepatitis C and cryoglobulinemia is strong. Although some people with cryoglobulinemia do not experience symptoms, others experience one or more of a range of signs and symptoms as shown in Table 1. The signs and symptoms are listed from most to least common. The best treatment for symptoms caused by HCV-associated cryoglobulinemia is to rid the body of the virus. Nearly all symptoms gradually resolve with viral clearance.

Lymphoma

A recent analysis examining the results of 23 separate studies concluded that chronic hepatitis C increases the risk for development of *non-Hodgkin's lymphoma* greater than 5-fold compared to those without HCV.¹⁸ Non-Hodgkin's lymphoma (NHL) is a form of lymphatic system cancer. Although it is unclear precisely how HCV enhances the risk of developing NHL, the presence of the increased risk is certain.

Table 1. Common Signs and Symptoms Associated with Cryoglobulinemia

Symptom	Description/Notes
Weakness	Approximately 2/3 of people with cryoglobulinemia experience this symptom.
Kidney disease	Several kidney disorders can be seen with cryoglobulinemia. The most common is membranoproliferative glomerulonephritis (MPGN). In some cases, people are initially diagnosed with MPGN and unsuspected chronic hepatitis C is diagnosed in the process of trying to uncover the cause for this disorder. Approximately ¼ of people with cryoglobulinemia have kidney involvement.
Neuropathy	Neuropathy is numbness, tingling, or other abnormal sensations in the hands and feet. These sensations make work their way up the arms or legs over time. Neuropathy is experienced by approximately ¼ of people with cryoglobulinemia.
Raynaud's phenomenon	Raynaud's phenomenon describes intermittent episodes when the arteries of the fingers or toes suddenly go into spasm causing the skin to become very pale, cold, and numb. Attacks are usually brought on by exposure to the cold or emotional stress. This phenomenon is experienced by approximately ¼ of people with cryoglobulinemia.
Skin disorders	Purpura (dark red to purple lesions on the skin) are the most common skin manifestation of cryoglobulinemia. These lesions usually appear on the lower legs, but can be present elsewhere. Around 20% of people with cryoglobulinemia have associated skin disorders.
Sjögren's syndrome	Sjögren's syndrome is a drying of the normally moist membranes of the eyes, mouth, and upper airway. This syndrome affects approximately 20% of people with cryoglobulinemia.
Joint disease	Approximately 15% of people with cryoglobulinemia experience joint pain that may be confused with rheumatoid arthritis.

Summary

The interaction between the immune system and the hepatitis C virus is a complex mystery that we are just beginning to unravel. Ongoing research will continue to provide insights into the interactions between hepatitis C and the immune system. A detailed review is presented in *Chapter 7.2, Immunology Takes on Hepatitis C*. With each new discovery, we come one step closer to new methods to intervene in the hepatitis C disease process.

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