

## Overview of the Immune System in Transplantation

The immune system is complex, interactive and essential for survival. In transplant, however, some of the body's normal immune responses are counter-productive. Without modulating the normal immune response, transplantation could not be successful. This self-study continuing education program will review the foundation of immunity and the immune process to support understanding of the role of the immune system in transplant, including immunomodulation to create an environment with less risk of rejection.

Of the five primary roles of the immune system (see box), protection and tolerance are the most relevant to transplantation. Protection is essential in order to prevent infection. And tolerance would cause rejection in the solid organ transplant, or graft-versus-host disease (GVHD) in the stem cell transplant. Purposeful weakening of that response is necessary for successful transplantation; however, that same weakening places patients at greater risk of infection.

In solid organ transplant, it is the transplant recipient's immune system that recognizes the donor

organ (the graft) as foreign or "non-self" and attempts to "reject" it. In bone marrow or blood cell transplant, the transplant is not of an organ but of a new bone marrow and new hematologic and immune system. Thus, when cells from this graft develop and are released, they see the rest of the body tissues as foreign and try to reject them.

### Innate and Adaptive Immunity

**Innate immunity** refers to a natural, non-specific inflammatory response, such as the influx of T-cells at the presence of a pathogen, or the engulfing of a pathogen by a phagocyte. **Adaptive immunity** refers to an acquired, specific learned response, such as the development of antibodies. Both types of responses react to antigens. Antigens are the "foreign" cells that enter the body.

The immune system must be able to recognize and tolerate the body's own cells. Every cell in the body carries distinctive molecules or markers; it is the unique markers that identify a cell as "self." A molecule that is recognized as "non-self" — for example bacteria, pollen

for some people, and human tissue (as with organ and bone marrow transplantation) — is an antigen. The greater the difference between the antigens and the "self" cells, the stronger the immune response.

Antibodies are formed against a specific "non-self" antigen. For example, an antibody against one strain of cold virus would be ineffective against a different strain. Antibodies attack the antigen in order to destroy it, and upon reexposure to that antigen, rapidly attack it to prevent re-infection.

The innate immune system is also referred to as **cellular immunity**. As mentioned, T-cells are the first to respond to the presence of anything "non-self." Cellular immunity is particularly active against viruses, for example. The T-cells transfer their knowledge to B-cells for specific antibody production. This humoral immunity plays a major role against bacterial pathogens.

The cells, tissues and organs that are responsible for the immune response are found in the lymphoid system, primarily in the thymus (thymocytes) and bone marrow, but also in other sites throughout the body. Hematopoiesis is the formation and development of all of our blood cells from unique parent cells called **stem cells**.

Stem cells are primitive, undifferentiated blood cells. They have yet to declare themselves as, for example, T- or B-cells, red cells, white cells, or platelets. For that reason, stem cells are often referred

### The Primary Roles of the Immune System

- **Protection:** Defend against pathogens
- **Surveillance:** Recognize and destroy abnormal cells
- **Homeostasis:** Remove damaged cells
- **Tolerance:** Differentiate self from non-self
- **Regulation:** Turn the immune response on/off as appropriate

to as pluripotent — they differentiate into myeloid or lymphoid lineages (see Fig. A below). Stem cells give rise to **progenitor cells**, which gradually develop into specific functioning cells.

As mentioned above, the stem cell differentiates into two lineages, myeloid (eventual white cells) or lymphoid (eventual B-cells and plasma cells). Each step represents key components of the hematopoietic process and requires, for example, colony stimulating factors (CSFs) and interleukins (ILs).

On the lymphoid side, the bone marrow is the site of initial lymphocyte formation. However, the majority of circulating lymphoid cells, both T and B, are produced in the peripheral lymphoid tissue (lymph nodes, spleen, thymus and lymphoid tissues of the gastrointestinal and respiratory tracts). Lymphocytes make up less than 10% of the normal bone marrow amalgam. The cells in the group of white blood cells (neutrophils, eosinophils and basophils) are primarily phagocytes.

Along with lymphocytes, antibodies and complement, they function as the major defense against microorganisms.

The monocytes are immature-looking cells that spend only a short time in the marrow. They circulate in the blood for 20 to 40 hours until they move into tissue, where they may survive for several months or even years. The macrophage either removes the antigens or presents them to lymphocytes. The phagocytic cells form a network known as the reticuloendothelial system (RES) and are found in the organs, such as in Kupffer cells in the liver, in alveolar macrophages in the lungs, and in mesangial cells in the kidneys.

Mature T-cells make up about 65–80% of the circulating lymphocyte population. The cell surface contains antigen receptors. T-cells mature in the thymus and migrate between blood and lymph fluid.

They have two major functions:

1. Regulation, such as aiding B-cell function, augmenting cytotoxic T-cell action and, when needed,

suppressing antibody and T-cell effect or function.

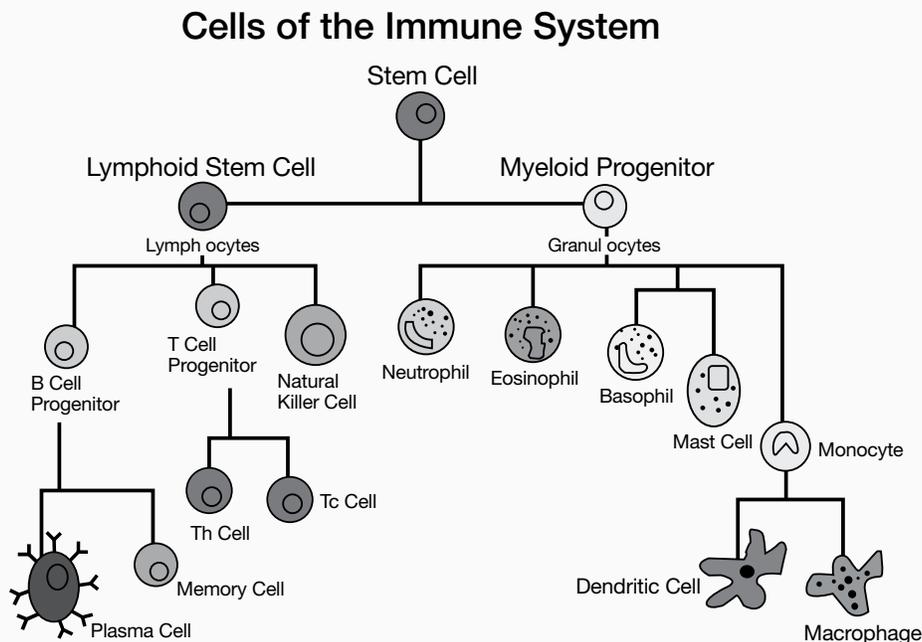
2. Initiation of delayed hypersensitivity reactions, lysis of antigens, and production of lymphokines.

Natural killer cells are a small population of lymphocytic cells that are able to kill tumor cells and cells virally infected. They are also involved in graft rejection.

Cytokines are produced primarily by the T-cells, but also by monocytes and macrophages. Cytokines include interleukins, lymphokines, interferons, tumor necrosis factor, and others. They bind to plasma membrane receptors and affect the growth and differentiation of white blood cells. Cytokines are the key to regulation of the immune system. They often work together to either potentiate or inhibit the immune response, depending on what is needed.

B-cell lymphocytes comprise 5–15% of the circulating lymphocytes. Mature B-cells are defined by the presence of immunoglobulin molecules, which

Fig A.



are produced endogenously (in the body). These molecules are on the cell's surface membrane, where they act as receptors for specific antigens.

## Histocompatibility in Transplant

The HLA (human leukocyte antigen) system, the major histocompatibility complex (MHC) in humans, is controlled by genes located on a section of the sixth chromosome. Histocompatibility refers to the tolerance or compatibility of human tissue to human tissue. The MHC consists of HLAs. The more alike the HLA of the donor and recipient, the less the immune system's effort to reject. This degree of compatibility is an important factor in transplant. "Tissue typing" is the name given to the test that identifies an individual's HLA and matches the donor tissue with the recipient by comparing HLA type.

There are many different HLA antigens, but the ones now known to be most important for transplantation are HLA-A, HLA-B, and HLA-DR. HLA antigens are "polymorphic," meaning their form is different in different individuals. Thus, within a population they can be found in many different forms. There are more than 25 forms of HLA-A, more than 50 forms of HLA-B, and more than 15 forms of HLA-DR.

Refer to Fig. B on page 4. Imagine that the second oldest child is the potential transplant recipient. Within a family, each child should be a "half-match," or 3/6 match, with each parent. There is a 25% chance that two siblings will be "perfect" 6/6 matches, a 25% chance that they will share no HLA antigens, and a 50% chance that they will be a half-match.

Often, however, there are no family members to consider as donors. In the case of solid organ transplant,

many patients have to look to an unrelated donor (either deceased or living). Many blood cell transplant (BCT) patients have to look outside the family as well, given that matching is particularly important in BCT.

As there are thousands of potential HLA combinations, it is extremely difficult to find a donor with any match to a recipient. That is why the donor marrow registry exists — to assess a large pool of potential donors. When cadaver organs are donated, the donor HLA is obtained and compared to that of the people waiting for that organ on the waiting list. Matching is often part of the determinant for organ distribution. Remember, the greater the match, the less immune response is expected.

Patients can also have antibodies against HLA antigens as part of prior exposure and the learned response. Patients may be exposed to human tissue antigens in several ways:

- **Through pregnancy.** The pregnant woman is exposed to the father's antigens through the fetus.
- **Through blood transfusions.** A patient is exposed to all the blood donors from whom they have ever received blood.
- **Through transplant.** A previous transplant exposes patients to that donor's six HLA antigens.

Some patients build antibodies against these antigens. They are "sensitized" — this means they have antibodies against human tissue and react against many potential donors. Some patients will only react toward a few HLA antigens; some will react to many. A transplant using a donor to whom the recipient has antibodies would result in rapid and irreversible rejection.

How many and even which specific HLA antibodies a patient has in

their blood can be determined with a blood test, thus allowing the transplant team to avoid those antigens when selecting an appropriate donor for a specific recipient.

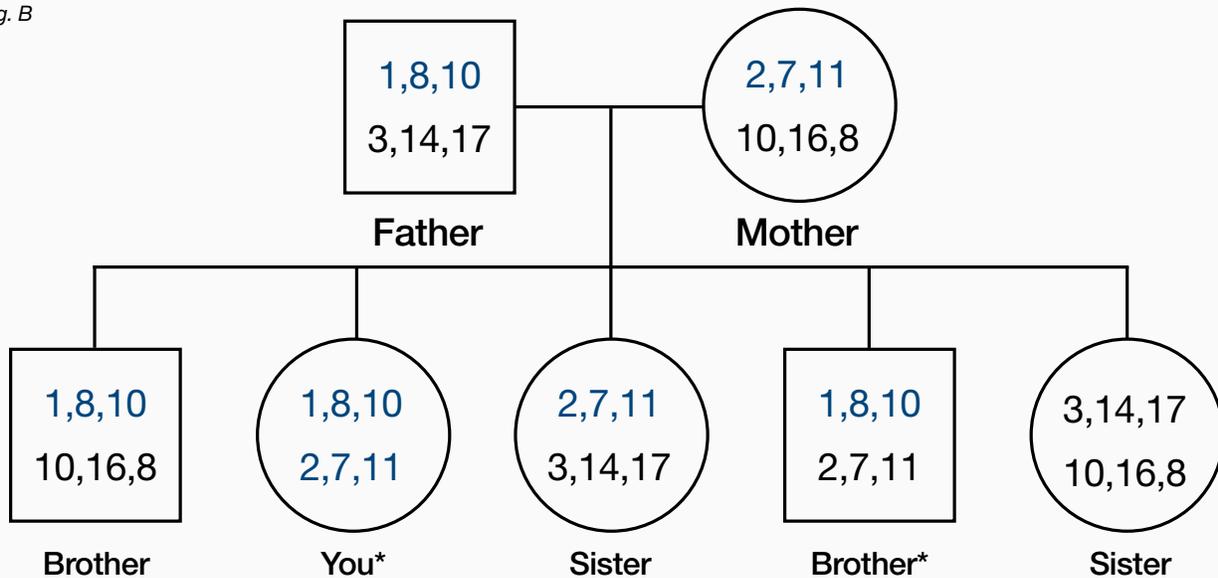
If the patient does not have HLA antibody to a possible donor, the test result will be negative. The antibody screening procedure also identifies how much HLA antibody the patient has. For example, if the patient reacts with 30 out of 60 cells, then the patient is said to have 50% antibody for that particular serum date. This percent antibody is called the PRA (panel reactive antibody). It is difficult to find a donor to which this patient would not react. Whether reacting against one or five antigens, a positive reaction dictates that the patient cannot receive that donor's organ.

Highly sensitized patients represent approximately 20–30% of transplant waiting lists. There is a limited chance for transplant for this patient population. At minimum, highly sensitized patients have a "wait time" (time on the cadaver transplant waiting list) of several years. If transplanted, sensitized patients are more likely to experience an increased number of rejection episodes and, ultimately, poorer graft survival.

## Immunomodulation in the Face of Sensitization

Fairly recently, protocols for "down-regulation" of the highly sensitized patient's immune system have been incorporated. Using plasmapheresis and/or intravenous immunoglobulin (IVIg) and a lymphocyte-reducing agent such as rituximab has proven to decrease the level of donor-specific antibodies. Since antibody levels eventually rebound, boosters may be required as the patient awaits a transplant opportunity.

Fig. B



### Rejection in Transplant: Solid Organ Transplant vs. Blood Cell Transplant

In solid organ transplant the patient is the host and the new organ is the graft. The graft is the foreign object so the host naturally tries to reject it, i.e. host versus graft.

In allogeneic blood cell transplant the graft is the new blood cells (new immune system) and it is that graft that carries the immune cells. In allogeneic transplant it is another donor supplying the immune system so, as that new system engrafts and replicates, and is sent out into circulation, it is the patient (the host's) tissues and cells that are foreign to the new immune system, i.e. graft versus host.

### Cross-match

If the patient has antibodies to the donor HLA, this is referred to as a

“positive crossmatch.” A positive crossmatch signifies that the patient will react against and destroy the donor’s cells, injuring the donated organ. Therefore, a positive crossmatch is a contraindication to transplant with that donor. A negative crossmatch indicates that the patient does not have the HLA antibody against that particular donor, and a transplant can be performed.

### Rejection

As described, it is a natural function of the immune system to “reject” something foreign, as the system does not differentiate between a beneficial foreign object (the transplant) or a harmful one. Rejection is a common occurrence in both organ and blood cell transplant. Immunomodulation continues post-transplant, with the use of immunosuppressive medications, in order to weaken the rejection response. The goal of immunosuppression is to weaken the immune system in order to

prevent rejection or GVHD. The consequence is a weakened immune system. It's a double edged-sword, and getting the right balance for each individual patient is challenging. Too much and the patient is at risk for infection; too little and the risk is for rejection or GVHD. ♦

### References

1. Vo, AA, Peng, A, Toyoda, M et al. Use of intravenous immune globulin and rituximab for desensitization of highly HLA-sensitized patients awaiting transplantation. *Transplantation*. May 15, 2010;89(9):1095-1102.

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# Self-Assessment Quiz: Overview of the Immune System in Transplantation

## LEARNING GOAL

To understand the complexities of the immune system and the implications for solid organ and blood cell transplant.

## LEARNING OBJECTIVES

Upon completion of this continuing education program, the reader will be able to:

1. Describe the concepts of “self” and “non-self.”
2. Differentiate between innate and adaptive immunity.
3. Describe the role of the stem cell.
4. Identify the primary roles of T and B lymphocytes.
5. Define the major histo-compatibility system and HLA antigens.

## SELF-ASSESSMENT QUESTIONS

**In the Quiz Answers section on the next page, fill in the correct answer for each question. To obtain two (2.0) contact hours toward CE credit, the passing score is 100%.** Return your Self-Assessment Quiz to Coram via email or fax. See the next page for details on how to return to your quiz. Please allow approximately seven days to process your test and receive your certificate upon achieving a passing score.

1. Tolerance is the ability of the body to differentiate between self and non-self.
  - a. True
  - b. False
2. Non-self refers to anything that is foreign to the immune system.
  - a. True
  - b. False
3. In blood cell transplant, non-self is the patient's own tissue/cells.
  - a. True
  - b. False
4. Innate immunity is:
  - a. Non-specific.
  - b. The natural response of the body to a foreign antigen.
  - c. The early response of the immune system to a foreign antigen.
  - d. All of the above.
  - e. A and B.
5. Adaptive immunity:
  - a. Centers around non-specific antibody formation.
  - b. Centers around specific antibody formation.
  - c. Provides lifelong immunity.
  - d. A and C.
  - e. B and C.
  - f. C.
6. B-cells are the first to respond in the presence of an antigen.
  - a. True
  - b. False
7. T-cells act to kill invading pathogens.
  - a. True
  - b. False
8. The stem cell:
  - a. Is pre-determined as to which type of cell it will eventually develop into.
  - b. Divides into myeloid cell lines and lymphoid cell lines.
  - c. A and B.
9. “Tissue typing” is the name given to the test that identifies an individual's HLA and matches the donor tissue with the recipient by comparing HLA type.
  - a. True
  - b. False
10. A positive crossmatch indicates HLA incompatibility between recipient and donor.
  - a. True
  - b. False

# Healthline

VOLUME 9

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### QUIZ ANSWERS

Fill in the key below with the correct answers to receive 2.0 Continuing Education credits.\*\*

1. (a) (b)
2. (a) (b)
3. (a) (b)
4. (a) (b) (c) (d) (e)
5. (a) (b) (c) (d) (e) (f)
6. (a) (b)
7. (a) (b)
8. (a) (b) (c)
9. (a) (b)
10. (a) (b)

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