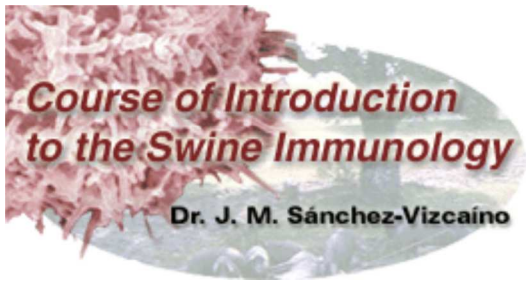
CHAPTER 7 Chapter 6 Next theme Course program



ACTIVATION MECHANISMS OF THE IMMUNE RESPONSE. NATURAL AND ADAPTIVE RESPONSES.

The activation of the immune response -natural or adaptive- takes place by several mechanisms that activate, in a coordinated way, different cell populations and the secretion of several molecules. The purpose is to eliminate foreign agents.

In previous chapters we learnt that the **immune system has different cell populations** (T and B lymphocytes, macrophages, antigen presenting cells, NK cells, etc.) **and molecules** (antibodies, cytokines and complement) **able to respond to foreign agents**. We already know that in order to enter the organism and produce an infection pathogens have to pass through different stages, each of which can be blocked by several defense mechanisms.

The first ones are the **mechanical-chemical barriers** (skin, mucus secretions, proteolytic enzymes, stomach pH, etc.). These prevent most infections from becoming established.They are followed by the **natural immune response** (or innate immunity) which **is the first non-specific immune barrier of the pig.** The innate immunity has a great capability of eliminating pathogens, thanks to the **activation of humoral factors, such as the complement, or cellular mechanisms such as phagocytosis or NK cell activation**. In the last place, and not always necessary because most infections do not progress, there is the adaptive immune response, that thanks to its characteristics of specifity and memory (**characteristics of the immune system**) is highly efficient and allows the immune system to recognize the pathogen in subsequent infections.

Phagocytosis activation takes place in four stages: **1. chemoatraction 2. adherence 3. ingestion 4. destruction.**

DEFENSE MECHANISMS

MECHANICAL AND CHEMICAL BARRIERS

- SKIN
- SECRETIONS
- STOMACH pH
- ENZYMES

NATURAL OR INNATE RESPONSE (NON-SPECIFIC IMMUNE RESPONSE) (HUMORAL AND CELLULAR FACTORS):

- ALTERNATIVE PATHWAY OF COMPLEMENT ACTIVATION
- PHAGOCYTOSIS
- NK CELL ACTIVATION
- CYTOKINES

ADAPTIVE RESPONSE (SPECIFIC IMMUNE RESPONSE)
(HUMORAL AND CELLULAR FACTORS)

- ANTIBODIES
- CLASSICAL PATHWAY OF COMPLEMENT ACTIVATION
- CYTOKINES
- CYTOTOXICITY: ADCC and CD 8+

This chapter will cover different mechanisms of activation of the immune response towards various types of infection.

How does the immune system respond during infections?

The microorganism that crosses over the **mechanical** (skin) **chemical** (stomach pH, enzymes, etc) or **biological** (saprophyte microorganisms in the gut, etc) **non immunological and non-specific barriers,** will trigger the **immunological mechanisms (humoral and cellular) that will respond to the infection in a consecutive and coordinated way.** The first reaction is mediated by the mechanisms of the **natural response**, that begin immediately after the entry of the infectious organism (4 minutes to 4 hours).

Natural or innate immune response

The natural or innate response is the first NON SPECIFIC barrier of the immune system. It is mediated by several **humoral mechanisms** (complement activation and some cytokines) and **cellular mechanisms** (macrophage activation and NK cells), which can be grouped together depending on their sequences of action:

A. Rapid action (4 minutes to 4 hours) mediated by:

1. Alternative pathway of complement activation
2. Macrophage activation

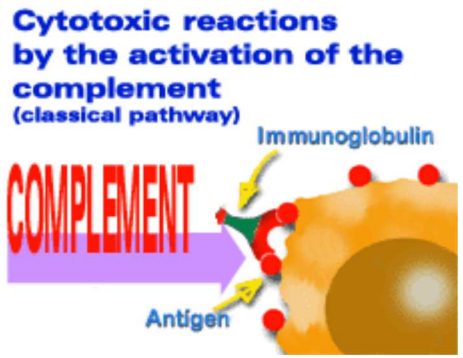
B. Medium and slow action (4 hours to 4 days) mediated by:

1. Inflammation
2. Activation of NK cells
3. Production and liberation of Interferon

A.1.Complement activation. The complement system is made up of a large number of **plasma and membrane proteins that trigger a cascade of reactions aimed towards the elimination of the pathogen. This can occur directly (microorganism destruction) or indirectly (phagocytosis, inflammation and chemoattraction, and elimination of antigen-antibody immunocomplexes). The complement is one of the most important defense mechanisms of the immune system, both in the natural and the adaptive responses.** There are three pathways by which the effector functions of complement can be activated:

- **Classical pathway**
- **Alternative pathway**
- **Lectin pathway**

The classical pathway of complement activation is only **triggered by an antigen-antibody reaction** (adaptive response). There is a cascade of protein activations which leads to the formation of the **membrane-attack complex,** which reacts with the membrane of the microorganism or of the infected cell and brings about its **destruction**.



Cell destruction by the activation of the complement (classical pathway)

The activation of the complement by the alternative and lectin pathways occurs as a response to many foreign particles. It is part of the first line of defense in the natural response. The alternative pathway is triggered by the fragment C3b, which is produced either spontaneously or by the classical pathway

The recently-described lectin pathway, is activated by a lectin present in the **membrane of a large number of microorganisms known as MBL** (**M**annose **B**inding **L**ectin). **MBL can activate the attack complex and so produce the destruction** of the membrane of several microorganisms without activating antibodies.

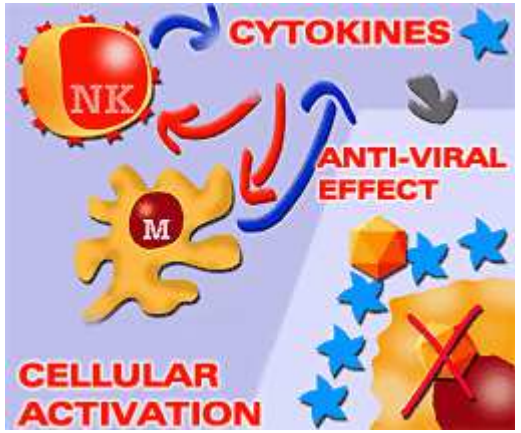
A.2. Macrophage activation.

Macrophages play a key role in the phagocytosis and destruction of microorganisms, either directly (**natural or innate immunity**), through their complement receptors (C3b) or during the **adaptive immune response** through their receptors for the **Fc** fraction of **immunoglobulins**. **Macrophages are activated in this way during the innate response by their receptors for the complement and during the adaptive response by the Fc**

fragment of immunoglobulins. Macrophage activation can be triggered by the liberation of several **cytokines**, such as interferon. Moreover, its own activation produces the secretion of cytokines, which induce inflammation (the second phase of the innate response).

Macrophage phagocyting *Candida albicans* cells
© James A. Sullivan, Cells Alive!

Inflammation. Macrophages and stimulated NK cells produce different cytokines that induce local inflammation and other general effects, such as the elevation of body temperature. These actions have a key defensive role during the innate response, because they stimulate the attraction of immune cells to the affected area. The main cytokines that intervene in this type of response were studied in **How do cytokines intervene in the natural or innate immune response?** In this chapter we will review the activation of NK cells and the production and functions of the complement.

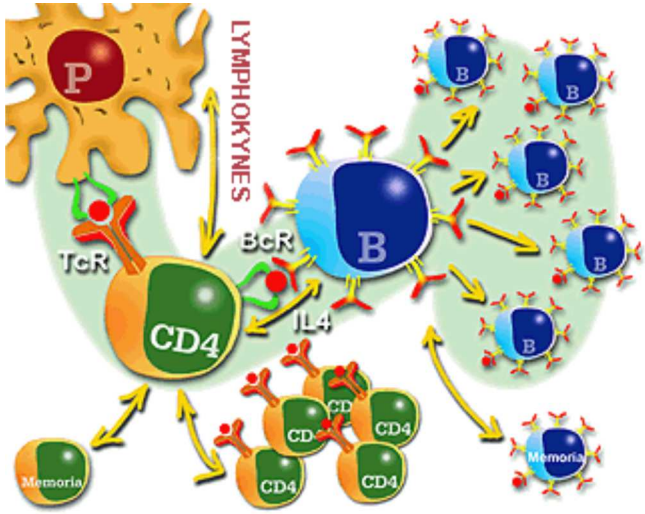


Cytokines play a main role in the innate response with direct mechanisms of action against the pathogen (avoiding infection of cells by different viruses) or with mechanisms of cellular activation (NK cells and macrophages) that produce the liberation of more cytokines.

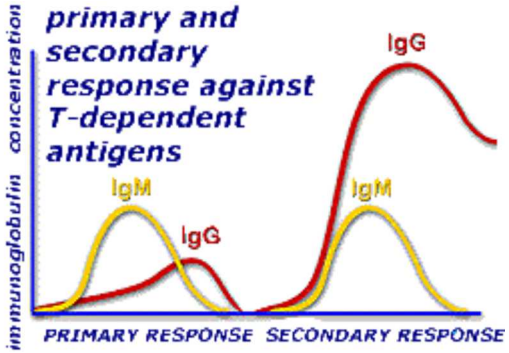
Only if an infectious organism can break through the first lines of defense of the innate immunity will an adaptive immune response ensue.

Adaptive immune response

The adaptive immune response is a SPECIFIC response, induced by a given antigen that generates a response that specifically targets that same antigen. It takes place after the failure of the innate response starting 96 to 120 hours after the infection. The infectious organisms or **antigens**, which have not been eliminated during the innate response, are transported by the macrophages to the **secondary lymphoid organs** (**lymph nodes**). There the antigen presenting cells will process the antigen in order to present it to the CD 4+ T lymphocytes (**How are B lymphocytes stimulated?**)



Mechanisms of antigen presentation. Cellular cooperation between antigen presenting cells and CD4 T lymphocytes and B lymphocytes. The participation of different cytokines is essential for this process.



and stimulation of B lymphocytes thanks to the cooperation of **Th 2 lymphocytes** and the subsequent **antibody production**. This type of response can be **primary** or **secondary**. During the primary response, **memory lymphocytes** will be produced, and which allow the immune system to respond during the secondary response more rapidly and effectively to pathogens that have been encountered previously. **This type of immune response allows animals to win their fight against infections that have surpassed the innate mechanisms. Thanks to the lasting memory, they become resistant to further infections.**

The antibodies produced during the adaptive immune response can react with the antigen and trigger different **biological functions** such as:

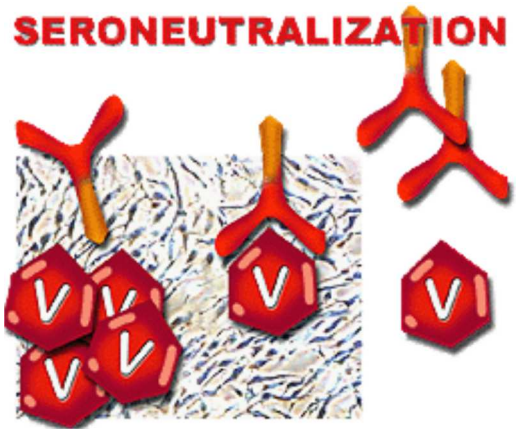
The classical pathway of complement activation.

Agglutination.

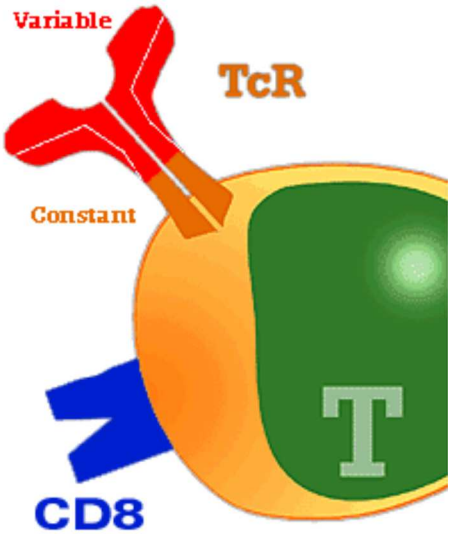
Neutralization (seroneutralization).

ADCC cytotoxicity.

Phagocytosis activation.



The seroneutralization technique assesses the capability of the test serum to neutralize the infectivity of a virus. This is done by using a sensitive cell line, at different concentrations. If the test antibody can neutralize the virus, no viral replication will take place (absence of cytopathic effect). If the antibody does not neutralize the virus, there will be viral replication (cytopathic effect). Some viruses do not produce any cytopathic effect, and in this case the potential viral replication can be assessed using immunofluorescence or peroxidase techniques.



Other cytotoxic processes take place in the adaptive response in addition to the cytotoxicity induced by antibodies (ADCC) and the activation of the complement through the classical pathway.They are mediated by **CD 8+ lymphocytes** that are specialized in the elimination of cells that express antigen fragments in their membranes (antigens associated to the **SLA I**). The recognition by the antigen-SLA I complex allow CD 8+ lymphocytes to discriminate between infected and non-infected cells.

Finally, just as it happens in the natural immune response, a large number of **cytokines** take part in the adaptive response.

Humoral and cellular response.

During the description of the mechanisms of innate and adaptive immune response we studied how **humoral and cellular factors are essential in both**

types of responses . Thus, we can say that there are both **humoral and cellular immune responses; in fact, both mechanisms act together. The most important humoral mechanism in the innate response is the complement** (alternative pathway); while during the **adaptive response, antibodies are the most outstanding humoral components**. The most important mechanism of the **cellular response** during the **innate response is the activation of macrophages and NK cells;** while in **adaptive immunity, it is the activation of CD 4+ and CD 8+**. **Cytokines play an essential role in both responses .**

In general, **humoral response refers to that response which is mediated by molecules,** this means that it is possible to transfer immunity from one animal to another just by transferring those molecules (which are **mainly antibodies)**.**Cellular immunity can also be transferred among animals using cells** (especially cytotoxic lymphocytes). **Both types of responses occur in a coordinated and simultaneous way in the animal**, even though one of the responses may be more relevant than the other. This depends on the kind of infectious agent, as we shall see in future chapters.

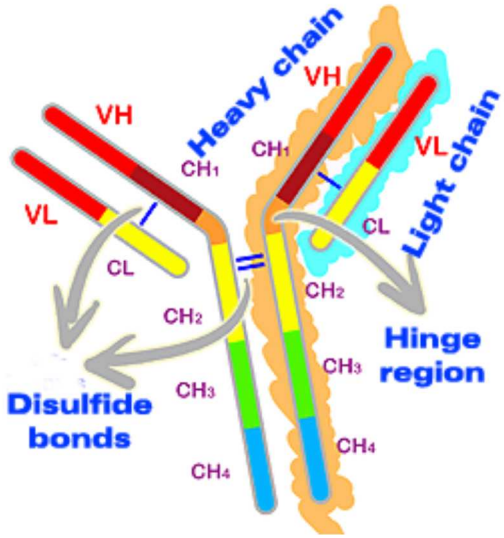


Diagram showing the structure of an immunoglobulin .

CHAPTER 7 Chapter 6 Next theme Course program