Immunological response to infection: inflammatory and adaptive immune responses

Peter J Wood

Abstract

The immediate response to infection involves the innate immune system, which consists of many cell types and factors. The cells of the innate immune system include the different types of white blood cells and tissue residing cells such as macrophages and mast cells. This immediate response to infection involves an inflammatory response which locally causes vasodilation and increased vascular permeability, thereby promoting the recruitment of cells and soluble factors from the bloodstream. Systemic inflammatory responses involve the brain, liver and bone marrow. If the infection is not resolved the second arm of the immune system, the specific immune system, generates new effector cells and mediators to deal with the infection. CD4 T cells are activated by antigens presented by dendritic cells and differentiate into helper T cells. Helper T cells are involved in the three major types of adaptive response: they help B cells to become antibody producing plasma cells; they help CD8 T cells differentiate into cytotoxic T cells that can kill cells infected with virus; they can activate macrophages to kill intracellular pathogens in a delayed-type hypersensitivity response.

Keywords Immune response; infection; mast cells; tissue macrophages

Royal College of Anaesthetists CPD matrix: 1A01

Learning Objectives

After reading this article, you should be able to describe:

- the roles played by tissue macrophages
- the components of the inflammatory response and its effects upon other tissues and organs
- the components of the immune response
- delayed hypersensitivity

When a microbe enters the body, it or its products encounter tissue macrophages. If the macrophage recognizes the pathogen it is activated to release a range of factors.

- Nitric oxide causes vasodilatation and has antimicrobial activity.
- Oxygen radicals have antimicrobial activity.
- Prostaglandins and leukotrienes are important inflammatory mediators that cause vasodilatation and increased vascular permeability, and are chemotactic for (attract) neutrophils and eosinophils.
- Platelet-activating factor causes platelet aggregation and is chemotactic for neutrophils and eosinophils.
- Cytokines are hormone-like molecules involved in immune responses. They are small proteins and act in an autocrine and paracrine manner but seldom in an endocrine fashion. Three of the most important cytokines secreted by macrophages in an inflammatory response are interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α).

Tissue damage and damage to the endothelium, which often accompany infection, result in activation of the clotting, kinin, fibrinolytic and complement systems. Activation of these systems leads to the generation of factors with many biological functions (Table 1) including vasodilatation, increased vascular permeability and activation of mast cells. Activated mast cells degranulate, releasing the contents of their granules into the surrounding tissue. The granules contain histamine, heparin and degradative enzymes. Histamine is a powerful mediator of vasodilatation and increased vascular permeability. The net result is increased blood flow to the area and the recruitment of blood proteins and cells to the site. Cytokines released in the area increase the expression of adhesion molecules on the

Systems activated during inflammatory responses

System	Component	Function of component or cleavage product
Clotting	Hageman factor	Activates clotting, fibrinolytic and kinin systems
	Fibrin	Forms clot
	Fibrinopeptides	Increase vascular permeability, neutrophil chemotaxis
Kinin	Bradykinin	Vasodilatation, smooth muscle contraction, pain
Fibrinolytic	Plasmin	Breaks down clots, activates complement system, activates Hageman factor
Complement	C1	Binds to antibody (C1q). Serine proteases (C1r, C1s)
	C4	Inflammatory mediator (C4a), binds C2
	C2	Serine protease (C2a)
	C3	Activates mast cells (C3a) Opsonin (C3b)
	C5a	Activates mast cells, chemotactic for neutrophils, monocytes, eosinophils and basophils
	C5–C9	Formation of pores in microbial cell walls causing cell lysis

Table 1

Peter J Wood *BSc (Hons) PhD is Senior Lecturer in Immunology in the Faculty of Life Sciences, University of Manchester, UK. Conflicts of interest: none declared.*

endothelium, and chemokines (chemotactic cytokines) attract neutrophils and monocytes to the site. The neutrophils and monocyte/macrophages attempt to phagocytose and kill the infectious microbes and monocyte/macrophages also remove dead cells and damaged tissue.

Acute-phase response

If the inflammatory response is large enough, cytokines produced by macrophages appear in the bloodstream in sufficient concentrations to affect other tissues and organs.

Brain – IL-1 acts on the hypothalamus to stimulate prostaglandin secretion which causes fever, somnolence and anorexia.

Bone marrow – IL-6 and TNF-α stimulate stromal cells and macrophages in the bone marrow to release factors that stimulate increased production of leukocytes.

Liver – IL-6 stimulates hepatocytes to produce increased amounts of acute-phase proteins, which are secreted into the blood and travel to sites of inflammation. Plasma levels of some of these proteins increase 100- to 1000-fold:

- serum amyloid A inhibits fever and platelet activation and provides a negative feedback loop
- C-reactive protein binds to phosphoryl choline present on bacteria and some fungi and can act as an opsonin in a similar fashion to antibody (see below)

Plasma levels of other factors increase only twofold to fivefold:

- fibrinogen is involved in clotting and some of its breakdown products (the fibrinopeptides) are chemotactic for (attract) phagocytes (Table 1)
- complement protein C3 has a number of biological activities, including activation of mast cells and promoting phagocytosis (Table 1)
- mannose-binding lectin can bind mannose-containing molecules on the surface of microbes and activate complement.

Generation of the specific immune response

The local inflammatory and acute-phase responses may be enough to resolve an infection. If not, the next response of the immune system is to generate a specific immune response, which can be divided into two stages (Figure 1):

- activation of CD4 T cells so that they divide and differentiate into helper T (Th) cells
- generation of effector cells and molecules that mediate the removal or neutralization of the pathogen (the generation of these cells is controlled by Th cells produced in the first stage of the response).

Generation of Th cells

Specific immune responses occur in specialized lymphoid tissue. Responses against tissue pathogens generally occur in lymph nodes and responses against blood-borne organisms in the spleen. A crucial cell in the initiation of specific immune responses is the dendritic cell (DC). DCs are located throughout lymphoid and non-lymphoid tissue and bear extensive dendritic processes. Some tissue DCs have specialized features such as Langerhans cells in the skin, which possess Birbeck granules. Tissue DCs bear receptors for pathogen-associated molecular patterns (PAMPs) and have strong phagocytic activity. They are able to take up microbial products and are stimulated by them to migrate; tissue DCs enter the local lymphatic vessels and travel to the lymph node draining the site of infection. If there is vascular damage, DCs may enter the bloodstream and travel to the spleen.

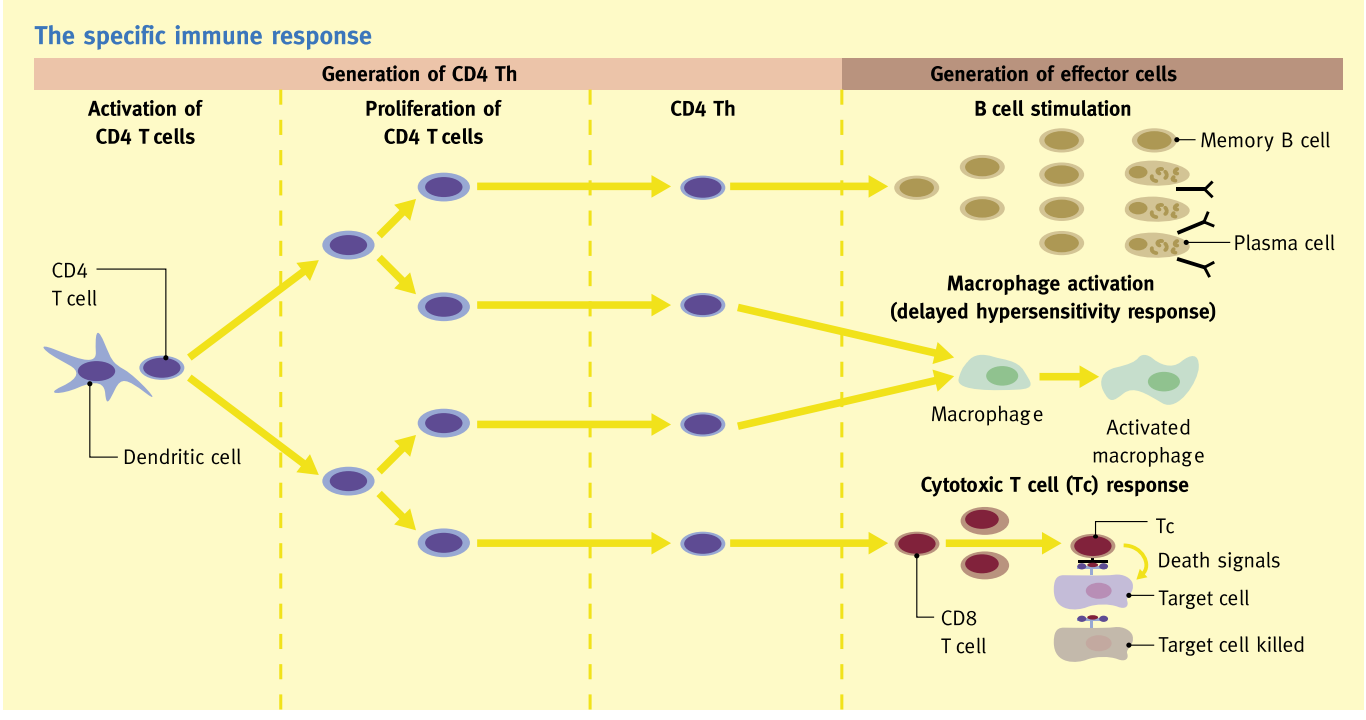

Figure 1