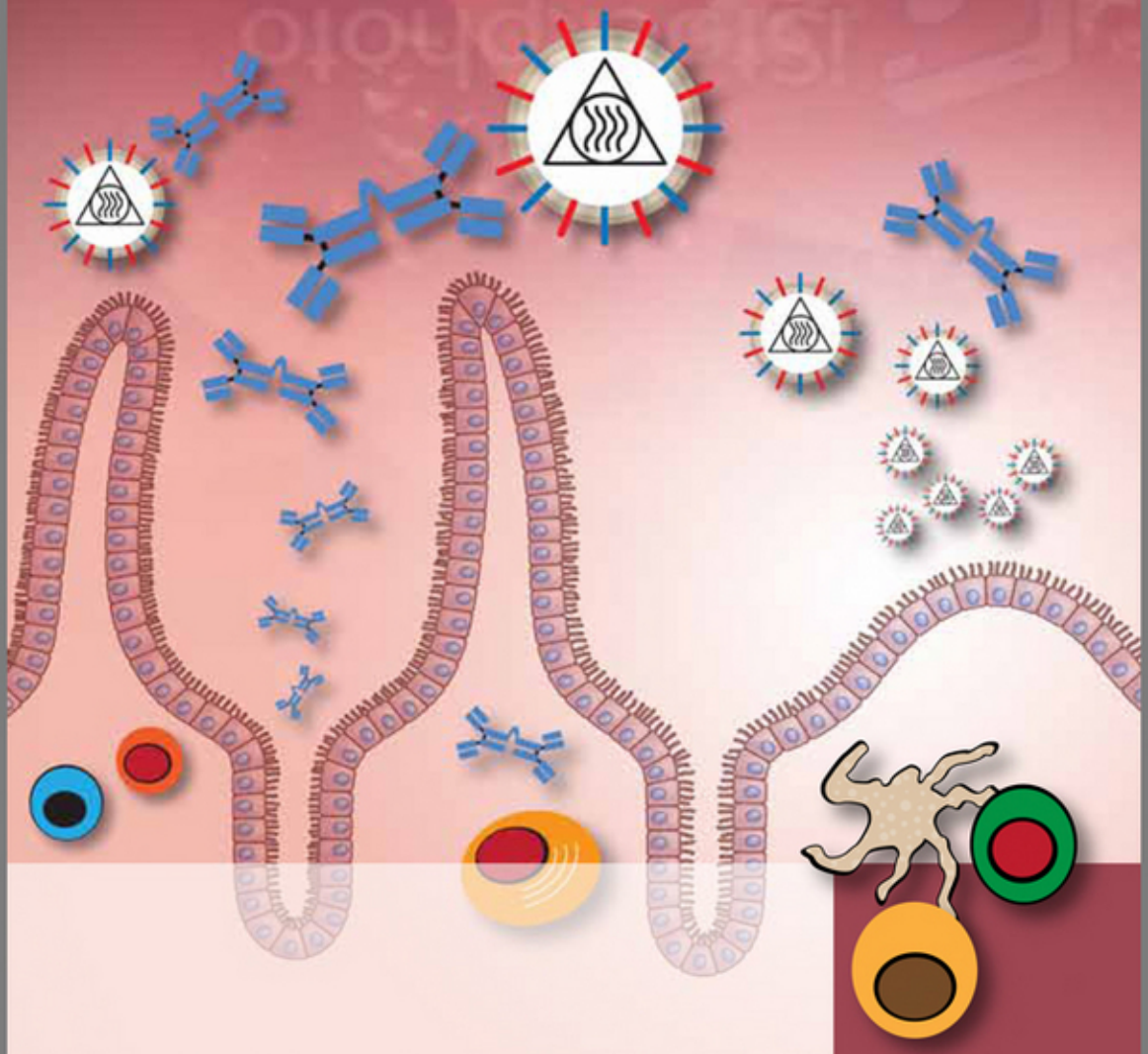
Andrew E. Williams

Immunology

Mucosal and Body Surface Defences



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Mucosal and Body Surface Defences

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A John Wiley & Sons, Ltd., Publication

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

Registered office: John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

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Library of Congress Cataloging-in-Publication Data

Williams, Andrew, E. 1975-
Immunology : mucosal and body surface defences / Andrew E. Williams – 1st ed.
p. cm.
Includes index.
ISBN 978-0-470-09003-9 (cloth) – ISBN 978-0-470-09004-6 (paper)
1. Immunology – Textbooks. I. Title.
QR181.W67 2011
616.07′9 – dc23

2011021727

A catalogue record for this book is available from the British Library.

This book is published in the following electronic formats: ePDF 978-0-470-09005-3; ePub 978-1-119-97988-3; Wiley Online Library 978-1-119-99864-8; Mobi 978-1-119-97989-0

Set in 9.25/11.5pt Minion by Laserwords Private Limited, Chennai, India

First impression 2012

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Preface

For thousands of years humans have marvelled at how the body is able to protect itself from infectious pathogens. Even the ancient Chinese and Greeks acknowledged the protective effects of the immune system, noting how one is rendered resistant to catching the same disease a second time. The first empirical studies were performed by Edward Jenner, and later Louis Pasteur, who developed vaccines against smallpox and anthrax, respectively. Indeed, vaccination has become such an important aspect of human health it is sometimes easy to forget the central role the immune system plays in affording protection against so many diseases.

The vast majority of medically important pathogens infect their host across a body surface such as the skin, or across a mucosal tissue such as the respiratory tract or intestines, as these sites are the ones exposed to the external environment. Vertebrates have therefore evolved elaborate immune defence mechanisms to protect against infection across mucosal linings and body surfaces. Mucosal immune defence mechanisms are therefore integral to our survival. However, conventional immunology textbooks largely overlook this aspect of the immune system, even though it remains fundamental for the prevention of infectious disease. Many have continued to teach immunology based on knowledge of the central immune system of the blood and spleen, rather than teaching immunology from the perspective of mucosal and body surfaces. After all, these are the places where host–pathogen interactions actually take place. Therefore I have tried to redress this bias by focusing on immunity at mucosal and body surfaces. This book should therefore prove useful for science undergraduates studying immunology, medical students undertaking academic studies, postgraduate students working toward a higher degree and the broad spectrum of professional academic and clinical scientists working in the field of immunology.

Knowledge of how the immune system operates has increased extensively in the past 50 years, including our insight into mucosal immunology. The first three chapters describe the basic architecture of the immune system and the elements of innate and adaptive immunity that contribute to protective immune responses. A more focused description of the innate immune system is given in Chapter 2, including aspects of barrier, chemical and mechanical defence, components of innate immunity which are so often overlooked. A description of the effector functions of the cells of the innate immune system, such as macrophages, granulocytes and NK cells, is also given. A similar approach is used in Chapter 3 to illustrate the ways in which adaptive immune responses are orchestrated, including how B cells produce antibodies and how T cells elicit their effector functions. This includes a discussion of B cell and T cell selection and the generation of memory cells, which are key to providing long-lasting protection and is a central concept in immunology.

The next two chapters focus on two important families of signalling molecules, the cytokines and chemokines, which have fundamental roles in orchestrating the spatial and temporal mechanics of an immune response. These chapters define just how important cytokines and chemokines are to the organization of the immune system.

Chapters 6 to 10 describe the central thesis of this textbook, in that they describe the workings of the mucosal immune system. An introductory chapter outlines the central concepts of the mucosal immune system that differentiates it from the central or peripheral immune systems. The key structural and cellular components and the common themes that link mucosal tissues are explored. For example, epithelial barrier formation, aggregation of organized lymphoid tissues, the importance of secretory IgA in mucosal defence and the need to balance immunity with homeostasis, are discussed. The concept of inductive sites, where immune responses are initiated, and effector sites, where immune cell functions take place, are discussed. From there, a description of the major tissues that form mucosal associated lymphoid tissue (MALT) is described, including the gastrointestinal tract, respiratory tract, urogenital tract and the conjunctiva of the eye. In addition, the importance of the skin in body surface immunity is examined.

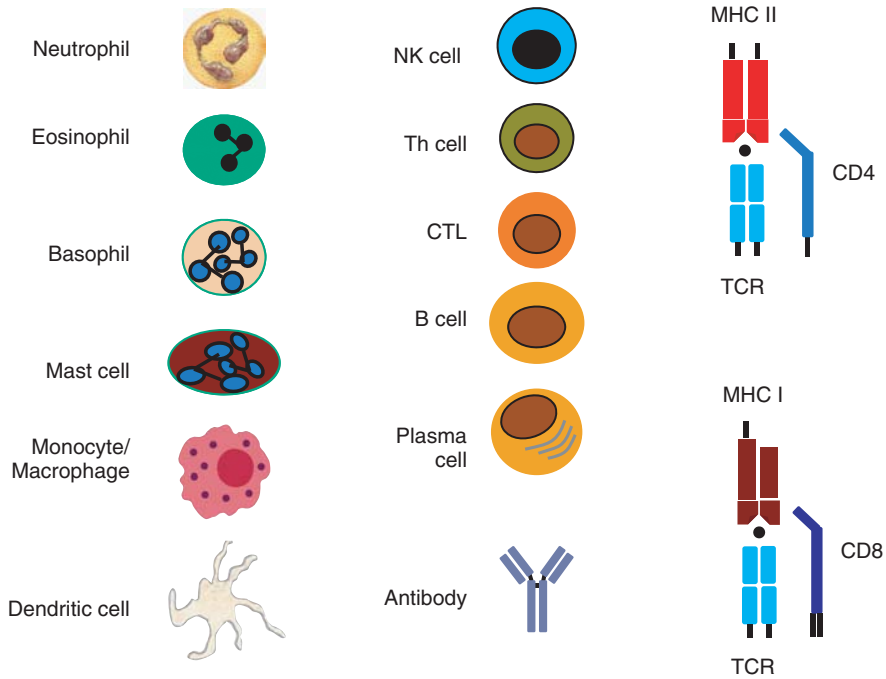
The next four chapters are devoted to studying immunity against the four major groups of pathogen,

the viruses, bacteria, fungi and parasites, with particular emphases on those infectious microorganisms that infect mucosal or body surfaces. This discussion includes the innate and adaptive immune mechanisms that are responsible for protection and the evasion strategies that these pathogens employ in order to subvert host immune responses.

Chapter 15 focuses on immune-mediated diseases that affect mucosal and body surfaces, including hypersensitivity reactions, allergies and autoimmunity. Chapter 16 details the various aspects of mucosal tumour immunology, in particular how the tumour and the immune system are constantly competing with each other. Finally, Chapter 17 describes the process of vaccination, from the conventional strategies most commonly used today, to novel regimens that specifically target the mucosal immune system and to cutting edge technologies used in modern vaccine development.

List of Standard Cells and Symbols

KEY –Standard cells and symbols



1 Basic Concepts in Immunology

1.1 The immune system

The immune system evolved so as to defend our bodies against infectious microorganisms such as viruses, bacteria, fungi and parasites. Throughout history it has been observed that people who survive an infectious disease acquire protection against that disease, which is otherwise known as immunity. As far back as the fifteenth century attempts have been made to induce immunity against infectious diseases, a process referred to as vaccination. The realisation that immunity can be transferred from one person to another demonstrated that soluble factors exist in the blood and body fluids that protect against pathogens. It is now known that cellular components of the immune system are also present throughout the entire body and that these immune cells engage with any harmful substance or microorganism in order to preserve the integrity of host tissues. The defence against microorganisms is fought on many fronts and there are immune cells and innate components of the immune system within every tissue and organ. There are a multitude of cells and soluble factors that can be considered part of the immune system. For example, the barrier function of the outer layers of the skin, the mucus produced in the airways, the antibodies secreted into the gut lumen or the circulating lymphocytes that destroy virus-infected cells. The immune system comprises a number of different cell types and a multitude of secreted factors and surface bound molecules.

The immune system has a multi-layered organisation that provides immunity to infectious organisms (Figure 1.1). Each layer of the immune system can also be considered to have an increasing complexity. The first layer is provided by physical barriers such as the skin and the mucosal epithelium of the respiratory and gastrointestinal tracts. These barriers aim to prevent pathogens gaining access to underlying tissue. The next layer is the non-specific chemical barrier that consists of antimicrobial compounds and factors of the humoral immune system (soluble factors found in body fluids). Other chemical immune defence mechanisms include the acidic environment of the stomach and the proteolytic enzymes produced in the intestines. The third layer is composed of all the cells of the immune system. Therefore, if a pathogen breaches the physical barriers and chemical barriers then the immune system utilizes its immune cells.

The cellular components of the immune system can be divided into the innate immune system and the adaptive immune system. The innate immune system provides a rapid, early response and is considered to be the first line of cellular immune defence. If the innate immune response is overcome by an infectious pathogen then the adaptive immune system comes into play. Only jawed vertebrates have evolved a complex adaptive immune system, which provides highly specific immune protection against microorganisms. The immune protection afforded by the adaptive immune system is retained by the host over a prolonged period of time and is capable of generating immunological memory. It is this immunological memory that confers immunity to subsequent infections with the same pathogen.

1.2 Tissues and cells of the immune system

The organs and tissues of the immune system can be compartmentalized (Figure 1.2). There are certain areas that are more susceptible to infection than others and these usually correspond to areas that come into contact with the environment. Therefore the mucosal immune system has evolved over millions of years in answer to selection pressures forced upon it as a result of host-pathogen interactions. The immune system therefore comprises a series of specialized organs and tissues that function by counteracting the threat of pathogens. The areas of the body at

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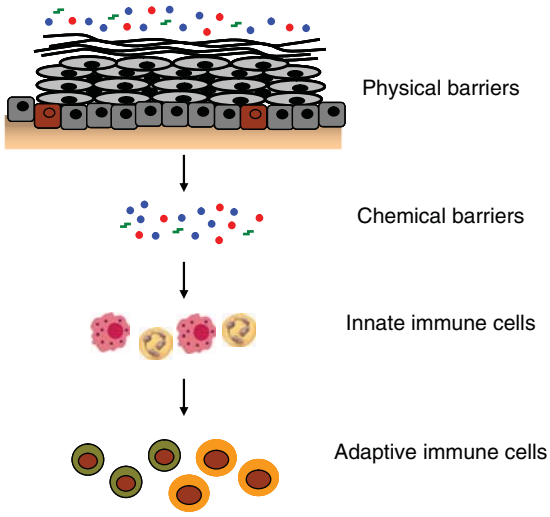

Figure 1.1 The multiple layers of the immune system.

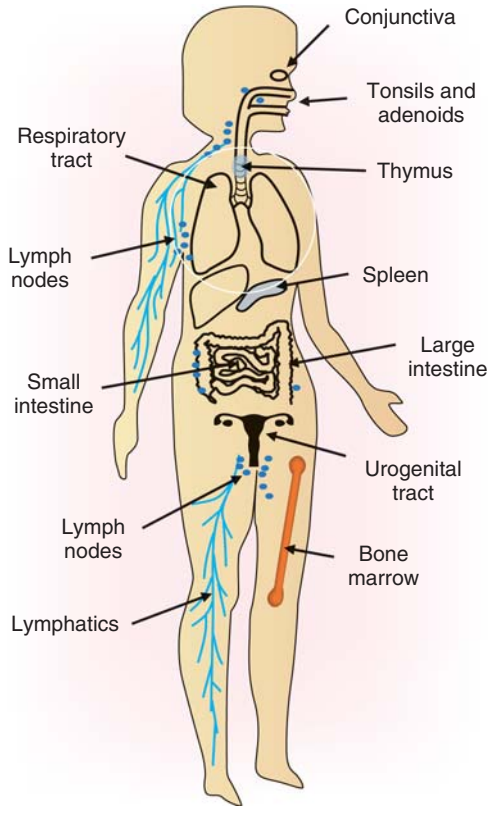

Figure 1.2 Tissues of the immune system.

most risk are the ones that are most frequently exposed to the outside, the most visually obvious tissue being the skin. Other tissues come into direct contact with the outside including the urogenital tract, gastrointestinal tract and the respiratory tract. For example, the lungs sample in the region of 11,000 litres of air every day and with each breath there is the risk of inhaling a harmful substance or potentially pathogenic microbe. Likewise the intestines are constantly exposed to material ingested through swallowing and, in addition, the gut has to cope with the billions of commensal bacteria that reside there. These tissues have therefore developed a series of immunological barriers to prevent infectious disease. The common mucosal immune system and mucosal-associated lymphoid tissue (MALT) are phrases that have been used to describe the composition of the immune system at sites that possess a mucosal lining. The respiratory, gastrointestinal and genital tracts are the major components of the MALT and function as immunological barriers at sites that are exposed to external substances.

Other tissues, which are not classified as mucosal, also contribute to the immune system. Central to haematopoiesis is the bone marrow, which is located within cavities of the long bones and is the site where all cells of the blood are derived. The bone marrow is home to multipotent stem cells that give rise to red blood cells, platelets and all the different types of white blood cell. The thymus is another important organ responsible for the differentiation and maturation of a population of white blood cells known as T cells and is located in the chest cavity just above the heart and surrounding the trachea.

Both the bone marrow and thymus are known as primary lymphoid organs, as these are the sites of immune cell development. There are also secondary lymphoid organs such as the spleen, which is located within the upper left hand quadrant of the abdomen. The spleen is responsible for the removal of moribund red blood cells and the initiation of immune responses directed toward blood borne antigens. Other secondary lymphoid organs include the lymph nodes, which are part of the lymphatic system. Lymph nodes are critical for the proper initiation of many immune responses. They are found throughout the body and are concentrated in regions that drain large body parts such as the neck, thorax and abdomen. They provide sites for the initiation of immune responses to antigens derived from body tissues that have been filtered into lymph nodes via the extensive lymphatic system. The tonsils and adenoids are further examples of organized

secondary lymphoid organs, which play an important role in the initiation of immune responses to pathogens that enter the body through the oral cavity.

The cells of the immune system are sometimes referred to as immunocytes, the most important of which are the white blood cells (otherwise known as leukocytes; from the Greek leuko (white) and cyte (cell)). All leukocytes originate within the bone marrow from precursor stem cells and can be divided into three groups, depending on their ontogeny (Figure 1.3). The first group are the granulocytes, which include neutrophils, eosinophils, basophils and mast cells. The second group are the myeloid cells that include the monocytes, macrophages and dendritic cells (DCs). The third and final group are the lymphocytes that comprise the natural killer (NK) cells, T cells and B cells. This classification is based on developmental lineage, which will be discussed further in this chapter, as a result of a process known as haematopoiesis. However, when studying the immune system it is sometimes more helpful to classify the different cell types in accordance with cell function. To this end the immune system is often divided into the innate immune system and the adaptive immune system (discussed later in the chapter). Alternatively, the immune system can be studied in terms of the type of immune response it generates and can therefore be classified as either being antibody-mediated or cell-mediated (Figure 1.4). These terminologies will be become clearer as we proceed through the subsequent chapters.

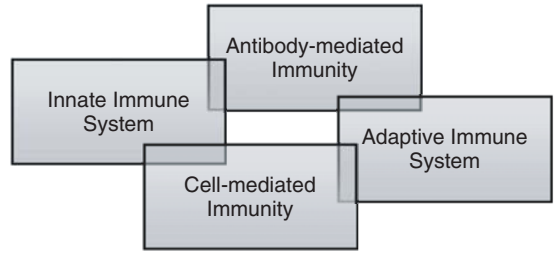

Figure 1.4 The immune system can be compartmentalised based on function. Certain components overlap, although innate and adaptive systems are considered separate.

There are several key concepts that must be addressed when considering how the immune system works. The first is why the immune system exists at all? It can be argued that the immune system has evolved in order to defend our body against invading pathogens. It is therefore important to understand how the immune system is organized in terms of the cell types responsible for orchestrating an immune response and in terms of the tissues that provide an appropriate environment for the generation of an immune response. It is then important to understand how immune responses are initiated and, once active, how these responses are regulated. Finally, it is important to gain an understanding of how the immune system is able to provide us with immunological protection against a pathogen that we have previously encountered, a process known as immunological memory. Some

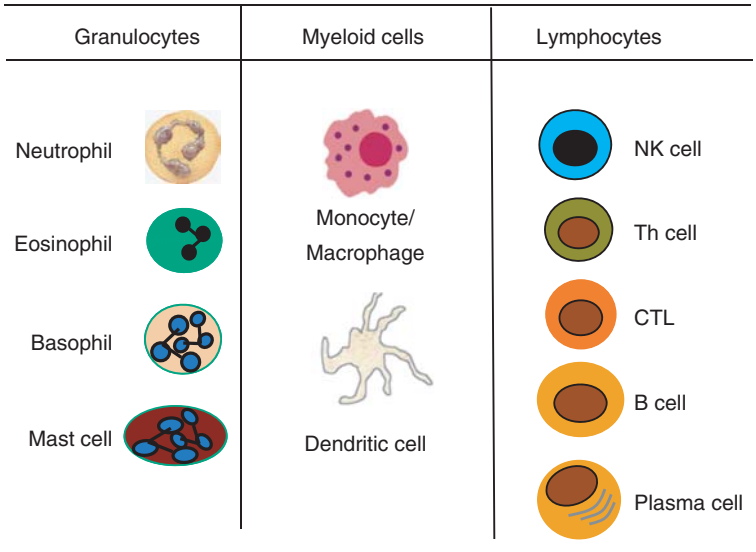

Figure 1.3 Cells of the immune system, which are divided into granulocytes, myeloid cells and lymphocytes.

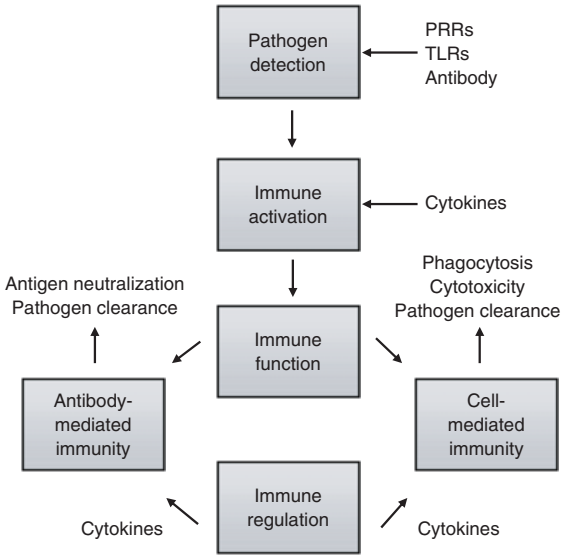

Figure 1.5 Key concepts in the development of an immune response. First pathogens must be detected and recognised as a threat. This pathogen recognition then activates the immune system and results in immune function, which can be divided into antibody-mediated or cell-mediated immunity. The functional activity must then be regulated after the pathogen has been dealt with and is known as immune regulation.

of these key concepts and immunological terms will be introduced in this chapter (Figure 1.5), while subsequent chapters aim to provide detailed descriptions of specific immunological mechanisms.

1.3 Activation, regulation and functions of immune responses

One of the most important concepts in immunology is the recognition of foreign substances by the immune system. For example, microorganisms such as bacteria and viruses produce a multitude of proteins, carbohydrates and glycolipids, which can all be recognized by cellular receptors expressed on the surface of immune cells. The most widely studied family of microbial recognition receptors are known as pattern recognition receptors (PRRs), because they recognize evolutionary conserved molecular patterns produced by microorganisms. The recognition of microbial products, which are known as pathogen associated molecular patterns (PAMPs), is one of the first steps in the activation of an immune response. Numerous cells of the immune system, and also tissue cells such as epithelial cells, express these PRRs. Probably the most ubiquitous family of PRRs are known as the toll-like receptor (TLR) family, which are responsible for the recognition of a host of PAMPs (discussed further in Chapter 2). The recognition of foreign molecules activates immune cells and results in the initiation of an immune response. For these reasons PAMPs are often referred to as danger signals. This is one way in which the immune system is able to discriminate between foreign substances (non-self) and its own molecules (self).

The interaction between immune cells, and indeed between immune cells and tissue cells, can dictate the phenotype, magnitude and duration of an immune response. It is often the case that an individual immune cell relies on signals derived from the extracellular environment in order to become activated or initiate one or more of its effector functions, for example through the recognition of danger signals. A key family of molecules, known as cytokines, play a central role in the initiation and regulation of immune responses (discussed in detail in Chapters 4 and 5). Cytokines are produced from all types of immune cells and from tissue cells such as epithelial cells of the respiratory or gastrointestinal tracts. Cytokines are normally produced and released from a cell in response to an external substance, such as an invading bacteria or virus. The released cytokine then exerts its biological effects on a target cell. For example, an epithelial cell will respond to an invading bacteria and will secrete several cytokines. These cytokines then signal to nearby immune cells and cause a functional response in those immune cells. This response may involve one or more effects including the cell activation, proliferation, migration, further cytokine secretion or initiation of effector functions. There are several families of cytokine including the interleukins, interferons, growth factors and chemokines, all of which provide a network of soluble mediators that regulate the immune response.

Specialized lymphocytes, known as B cells, can also secrete numerous proteins called antibodies, which are found in bodily fluids such as the blood serum and lymphatics. The role of antibodies within the immune system is to recognize and bind to foreign proteins derived from microorganisms. Any protein that can be bound by an antibody is known as an antigen. The interaction between an antibody and an antigen is a key principle in immunology. The binding of an antibody to an antigen has several downstream consequences, including the neutralisation and clearance of the antigen, and the activation of the effector functions of numerous immune cells. Often the word antibody is interchanged with the word

immunoglobulin, as these two terms describe the very same molecule. The functional consequences of antibody and antigen interactions will be discussed further in this chapter and in subsequent chapters. Immune responses generated as a result of antibody and antigen interactions are commonly referred to as antibody-mediated immunity, which can be considered to be part of the humoral immune response. Any immune component that affords protection and is not associated with the cellular fraction of body fluids is considered humoral.

In addition to PRRs, released soluble mediators and antibody, the immune system utilizes a number of specialized cells that participate in cell-mediated immunity. The mechanisms of cell-mediated immunity are largely independent of antibody and other humoral factors (such as complement proteins). Cell-mediated immunity involves the activation of immune cells and the subsequent deployment of cellular effector functions. For example, macrophages and neutrophils participate in cell-mediated immunity by phagocytosing invading pathogens, or infected host cells, and releasing a cascade of antimicrobial products. Phagocytosis is an important process that engulfs foreign substances and microbes and clears them from the body. NK cells and T cells also participate in cell-mediated immunity by recognizing and lysing virally infected cells. This mechanism is known as cytotoxicity, which kills infected or abnormal cells. The cells that are involved in cell-mediated immunity also secrete a number of cytokines, which regulate any ongoing immune response. Historically, cell-mediated immunity has been separated from antibody-mediated immunity or humoral immunity, depending on whether immunological protection can be found in the cellular fraction or the cell free fraction of body fluids, respectively.

Therefore, the key concepts in immunology can be summarized as components that activate immune cells and initiate immune responses, soluble mediators that signal to immune cells and regulate the immune response, components of antibody-mediated immunity (and also other humoral components), and constituents of cell-mediated immunity.

1.4 Innate versus adaptive immunity

Components of the immune system can be conveniently grouped into either the innate immune system or the adaptive immune system (Table 1.1). The innate immune system encompasses all those aspects of non-cellular immunity, including epithelial barrier defence, antimicrobial peptide secretion, chemical barriers and the complement system. The innate immune system also involves aspects of cellular immunity associated with granulocytes (neutrophils, eosinophils, basophils and mast cells), monocytes, macrophages, DCs and NK cells. Cells of the innate immune response are rapidly initiated and are considered to be the first line of cellular defence against invading microorganisms (Figure 1.6). Essentially, innate immune cells provide protective immunity against infectious microorganisms until adaptive immune responses can be initiated.

Table 1.1 Comparison between the innate and adaptive immune systems.

Innate Immune System	Adaptive Immune System
Rapid response (hours)	Delayed response (days)
Non-specific response to conserved molecules	Highly specific response to antigen
Response fixed (not adaptive)	Response adaptive (changes over time)
No immunological memory	Immunological memory
Humoral and cell-mediated components	Humoral and cell-mediated components
Components found in all animals	Only found in jawed vertebrates

The cell receptors expressed by innate immune cells recognize evolutionary conserved molecules derived from invading pathogens or damaged host tissues, for example through the recognition of danger signals. Each of these receptors recognizes the same molecular motifs, irrespective of the cause or progression of an immune response, and is therefore considered to be part of a

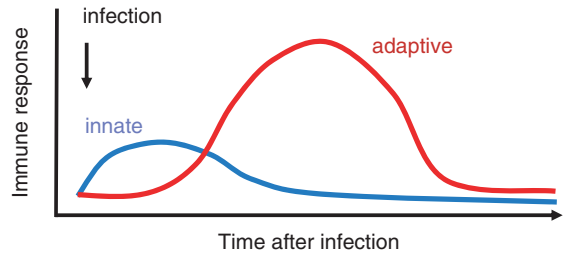

Figure 1.6 Kinetics of a primary immune response. Innate immunity precedes the adaptive immune response.

non-specific response. For example, different bacteria will be recognized by macrophages in much the same way and will activate the same process of phagocytosis. Activation of non-specific innate immune receptors often leads to the development of an inflammatory reaction at the site of tissue damage. This also results in the release of several pro-inflammatory mediators that increase blood vessel permeability, stimulates the migration of more inflammatory cells into the area and is the first step in the activation of the adaptive immune system.

The adaptive immune system takes longer to establish itself and principally involves the T lymphocyte and B lymphocyte populations. Cells of the adaptive immune system are considered to be part of the specific immune response, due to the nature of the receptors that they express. T cell receptors (TCRs) and B cell receptors (BCRs) recognize very specific components of external substances, usually proteins, which are known as antigens. The entire T cell population is thought to consist of as many as 10^9 different T cells, each of which displays a slightly different TCR. Similarly, the number of B cells, each capable of expressing a slightly different BCR, probably exceeds 10^9. Therefore, the adaptive immune system has the capacity to identify a sizeable number of antigens, through the generation of antigen receptor diversity (discussed in detail in Chapter 3). T cells and B cells are therefore part of a highly evolved adaptive immune system that aims to maximize the recognition of as many different pathogens as possible. Furthermore, the mechanisms by which these receptors are produced enable the adaptive immune system to fine tune its response to antigen, so that subsequent responses are more effective. The plasticity built into the generation of antigen receptor diversity has the capacity to alter itself in response to new pathogenic challenges, hence the term adaptive immunity.

Following the stimulation of antigen specific T cells and B cells, a proportion of those cells differentiate into memory cells (Figure 1.7). These memory T cells and B cells are retained within various tissues of the immune system, until they are required at a later time point, when an individual becomes re-infected with the same pathogen. The adaptive immune system is sometime referred to as the acquired immune system, due to its ability to form populations of T cells and B cells that furnish the immune system with immunological memory.

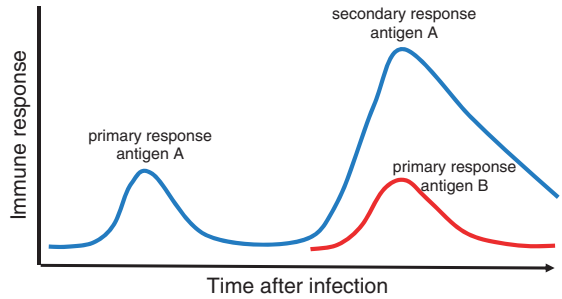

Figure 1.7 Primary and secondary adaptive immune response. Secondary infections with the same pathogen elicits a more rapid and heightened response compared to a primary response.

1.5 Primary and secondary immune responses

The first time that the body encounters a new pathogen a primary immune response is triggered. It usually takes up to 7 days for a T cell response to become established, while it may take as long as 10–14 days for B cells to produce a significant amount of antibody that can be detected in the bloodstream. The reason for such a delay is that neither the B cell nor the T cell population has encountered such an antigen in the past and for this reason these cells are known as naïve B cells or naïve T cells. Therefore, these immune cells require sufficient time to recognize the antigen and start proliferating in order to produce sufficient numbers of antigen-specific clones. In the meantime, while the adaptive arm of the immune system becomes established, the innate immune system plays a vital role in controlling pathogen replication and dissemination. Once fully activated, the adaptive immune system prevents further infection and eventually eliminates the pathogen from the body. The primary immune response is then downregulated so that antigen-specific antibodies become less frequent and T cell numbers return to normal (Figure 1.7).

A secondary immune response occurs when an individual encounters the same pathogen for a second time and principally involves B and T cells of the adaptive immune system. For example, if a person has recovered from influenza infection and encounters the same strain of virus on a subsequent occasion, a secondary immune

response is initiated. A secondary immune response is much quicker in establishing itself than a primary immune response is, because the antigens derived from the pathogen have been encountered before. The magnitude of a secondary immune response is also higher, meaning that more cells participate in the reaction, which results in a much more effective response (Figure 1.7). There is a rapid elevation in antibody levels within the bloodstream, which remain elevated for a longer period of time. This heightened response involves the activation of memory B cells, which can directly differentiate into antibody secreting plasma cells, without having to undergo the various stages of B cell development that a naïve B cell has to undergo. A secondary immune response is also dominated by the production of highly specific antibodies for a particular antigen. The antibodies produced during a secondary immune response are much more specific than those produced during a primary response (Figure 1.8). This is due to a process known as affinity maturation and antibody isotype switching (discussed in detail in Chapter 3), which involves a switch in IgM production to IgG production. Likewise, memory T cells are much more readily activated and they too have a heightening effector response, which is capable of responding more rapidly and with a greater magnitude than during a primary response.

The effectiveness of a secondary immune response relies on the generation of memory B cells and memory T cells (Figure 1.9), which develop following the initiation of a primary immune response. These memory cells reside in various lymphoid tissues throughout the body and contribute to what is known as immunological memory. The term immunity was first used to describe the ability of the immune system to provide protection against infectious diseases and relies on the activation of memory B and T cells. Importantly, vaccination relies on the ability of the immune system to respond more effectively to a secondary encounter with antigen. Many infectious diseases can be prevented by vaccination (Figure 1.10), through the generation of antigen-specific memory cells that become activated in response to a challenge from the real pathogen.

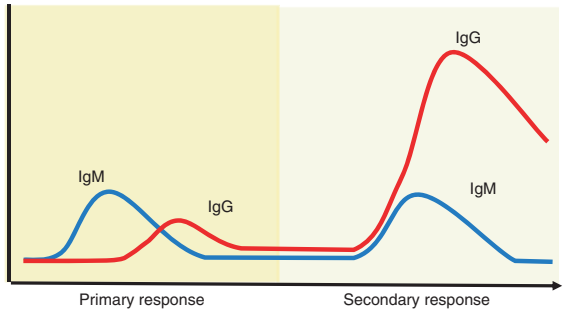

Figure 1.8 Antibody production in primary and secondary immune responses. Primary antibody responses are initially dominated by IgM, while secondary responses are dominated by elevated IgG.

1.6 Immune cell development

Before the array of different immune cells can exert their effector functions and prevent infection, they must first undergo a highly controlled series of developmental stages, collectively known as haematopoiesis. The bone marrow is extremely important for this process and for the continuity of the immune system. It is situated at the centre of all the long bones in the human body and consists mostly of a fatty substance surrounding a stroma of dividing stem cells. The major function of the bone marrow is to produce new lymphoid and myeloid cells, which originate from pluripotent haematopoietic stem cells. In fact, these special stem cells can give rise to any blood cell, hence the term haematopoietic, meaning blood forming. These cells then divide and develop into mature lymphocytes from the lymphoid line or monocytes, dendritic cells and granulocytes from the myeloid line (Figure 1.11). The common myeloid stem cell is also capable of differentiating into red blood cells and platelets. The differentiation of the many cells of the immune system occurs in precise developmental stages and at each of these stages a particular cell lineage is formed. This involves a complicated series of differential gene expression events that subsequently determines the commitment to a certain cell lineage. The genetic potential of a pluripotent haematopoietic stem cell is expansive and it is possible for that stem cell to differentiate into any one of a number of available cell types. As haematopoiesis proceeds, the haematopoietic stem cell becomes more and more specialized and its genetic potential becomes increasingly restricted. This eventually leads to cell fate

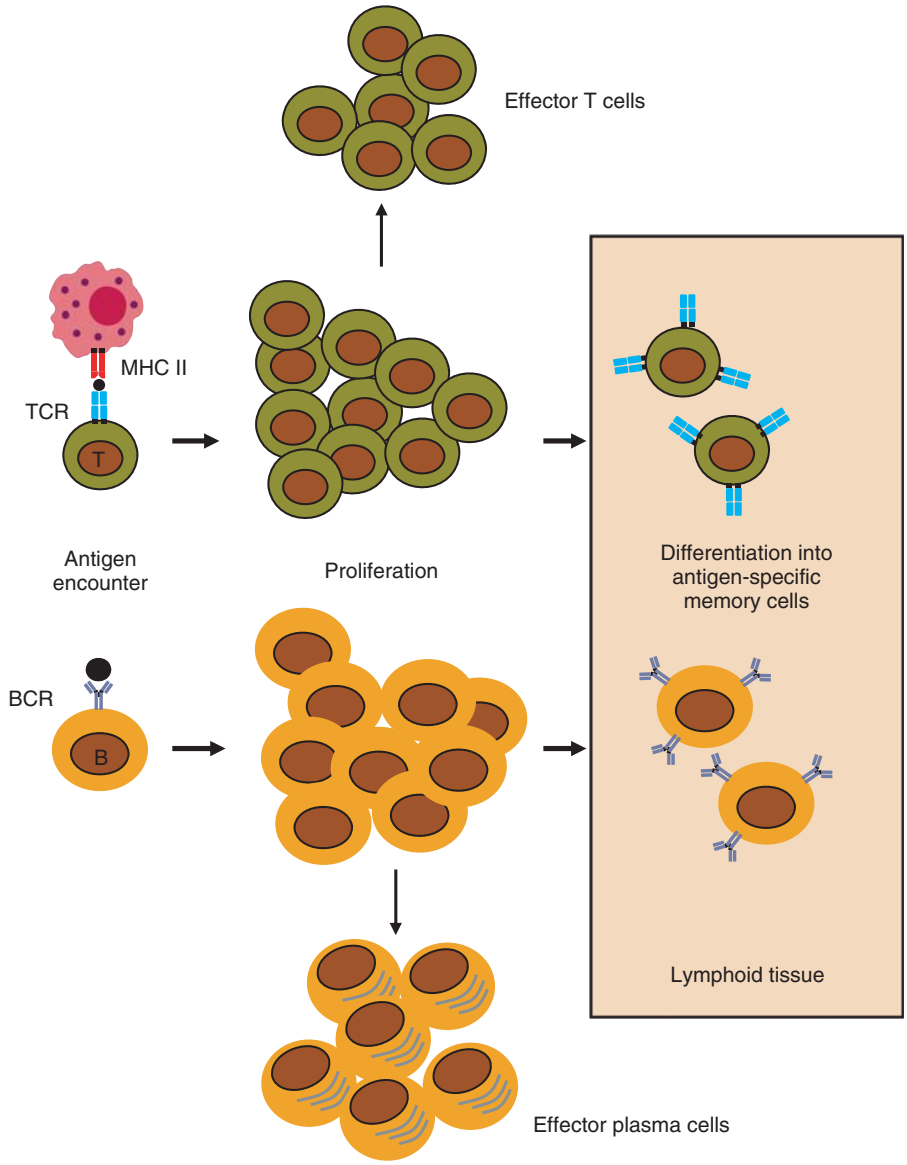

Figure 1.9 Generation of memory lymphocytes. Antigen stimulation leads to lymphocyte differentiation into effector cells. A subpopulation of lymphocytes differentiate into long-lived memory cells.

decisions that are irreversible and forces progenitor cells to continue down a particular cell lineage, for example the lymphocyte lineage.

The haematopoietic stem cell is driven to differentiate into a particular cell lineage based on what signals it receives from the extracellular environment within the bone marrow. One set of signals instructs the stem cell to differentiate into a common lymphoid progenitor cell and the other into a common myeloid progenitor cell. In other words, certain signals favour lymphocyte development, while other signals favour myeloid cell development. The lymphoid progenitor cell is capable of

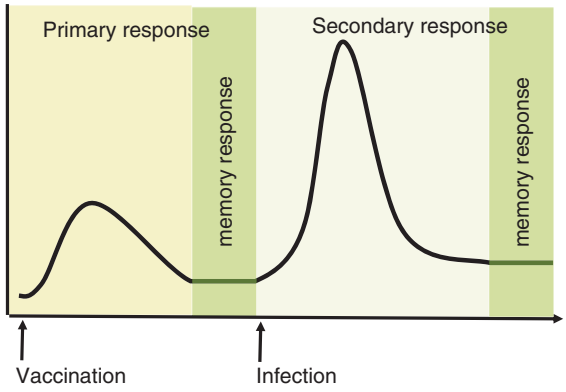

Figure 1.10 Vaccination induces immunological memory. Pathogen-specific memory cells are generated following vaccination. Infection with the wild type pathogen reactivates these memory cells and a rapid and robust secondary immune response follows.

either differentiating into an NK cell precursor, or into a lymphocyte precursor that eventually gives rise to T cells and B cells. Several soluble factors are involved in driving this differentiation. For example, stem cell factor (SCF) is associated with both NK cell precursor and lymphocyte precursor development, while IL-7 signalling is specifically associated with T and B cell differentiation. T cell precursors leave the bone marrow and migrate to the thymus, where the final stages of T cell development take place. This results in the differentiation of immature T cells into either CD4+ T cells or CD8+ T cells. These two specialized T cell subsets will be discussed further in this chapter and extensively in Chapter 3. Following the migration of B cells out of the bone marrow, further B cell maturation takes place in other lymphoid organs such as the lymph nodes, spleen and organized lymphoid follicles associated with MALT. Within these lymphoid structures B cell maturation occurs whereby they mature into antibody secreting plasma cells.

Haematopoiesis also gives rise to all the cells of the granulocyte and myeloid lineages. For instance, the common myeloid progenitor cell can differentiate into erythrocytes, thrombocytes (platelets), granulocytes and monocytes, thereby demonstrating its pluripotent capacity within the haematopoietic system. The precursor cells of erythrocytes (red blood cells) are called reticulocytes, which leave the bone marrow and complete their maturation in the circulation. Myeloid progenitor cells also give rise to megakaryocytes that are the precursors for thrombocytes. The main precursor for all the cells of the granulocyte lineage is the myeloblast, while the main precursor that gives rise to monocytes and macrophages is the monoblast. Mast cells, eosinophils, neutrophils and basophils diverge from the myeloblast lineage via independent precursor cells, while differentiated monocytes can subsequently mature into macrophages, once resident in tissues, or into myeloid DCs. Again, a number of growth factors and cytokines are involved in granulocyte and macrophage differentiation, including granulocyte/macrophage-colony stimulating factor (GM-CSF), G-CSF and M-CSF.

1.7 Mast cells and basophils

Mast cells and basophils are both granulocytes that are capable of rapidly releasing pro-inflammatory mediators into the extracellular environment, through a process known as degranulation. The release of pro-inflammatory mediators is a key process that initiates an inflammatory reaction. Examples of pro-inflammatory mediators include histamine, prostaglandins and cytokines, which will all be discussed in detail throughout the proceeding text. It was once thought that mast cells and basophils belonged to the same cell lineage; the circulating basophils giving rise to the mature, tissue residing mast cell. It is now clear that mast cells are derived from a separate precursor cell in the bone marrow, although they only fully mature once they reach their target organ. Mast cells can be detected in most tissues where they usually reside adjacent to connective tissue. They are also present in mucosal tissues such as the digestive, respiratory and urogenital tracts and the skin. Mucosal mast cells have slightly different characteristics to tissue dwelling mast cells, as they require the help of T cells to become fully activated, while tissue dwelling mast cells do not.

The primary function of mast cells is to provide an early response to the presence of microbial antigens. In order to recognize the presence of microorganisms, mast cells rely on antibodies interacting with their specific antigen. The interaction between an antibody and an antigen is then detected by the mast cells through the expression of a cell surface receptor that recognizes antibody, known as an immunoglobulin Fc receptor (FcR). When enough antigen is present, many antibody molecules cross link several adjacent FcRs. This antigen cross-linking is essential for receptor activation and in turn subsequent mast cell activation, degranulation and release of pro-inflammatory

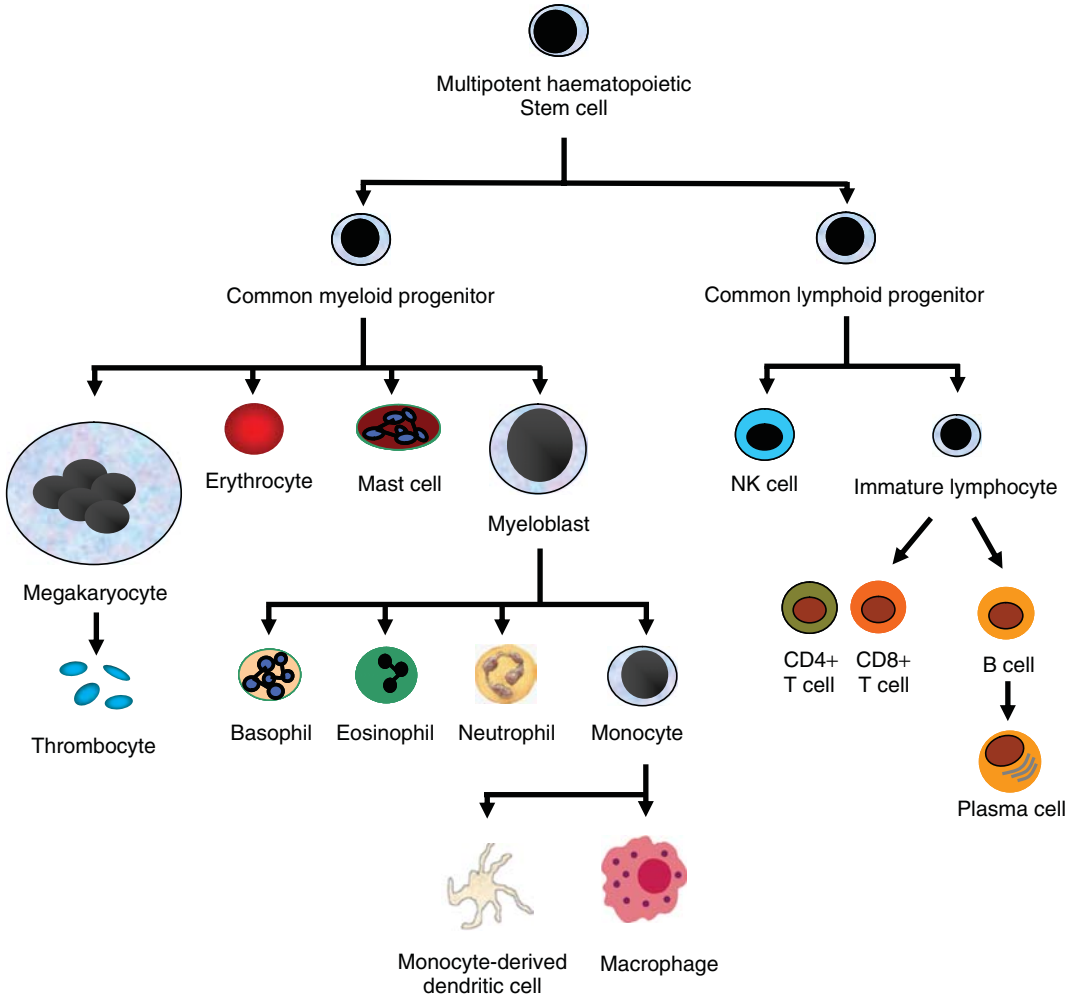

Figure 1.11 Formation of blood cells through the process of haematopoiesis.

mediators. The biological importance of receptor cross-linking should be emphasized, as numerous receptors rely on cross-linking for proper activation. FcR cross-linking on mast cells results the release of an active mediator called histamine, which causes the dilation of blood vessels and stimulates lymphocyte migration into sites of inflammation. Mast cells and histamine have been implicated in the pathology associated with allergic asthma, whereby an allergen (an antigen involved in allergic reactions) cross links FcRs on the cell surface and causes bronchial constriction of the airways. Mast cells also release cytokines and chemokines, which attract eosinophils and other inflammatory cells.

Basophils have a similar function to mast cells and also participate in the release of histamine following FcR cross-linking. Although associated with allergic reactions, basophils and mast cells are thought to have evolved to combat parasitic infections. The degranulation of basophils results in the recruitment of other immune effector cells, following the release of histamine, leukotrines and the cytokine interleukin-4 (IL-4). The cytokine IL-4 is a critical cytokine for the development of T cell responses associated with both parasitic and allergic immune reactions. Although they are the least common of the leukocytes in the blood, basophils can constitute a significant proportion of cells migrating into