The Wiley-Blackwell Handbook of Psychoneuroimmunology

Edited by

Alexander W. Kusnecov and Hymie Anisman
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During the past decade the biological and behavioral sciences have become increasingly intertwined, as research continues to reinforce the notion that physical and psychological health are a function of interactive biological systems. Mental ill-health as a reflection of deficits in neural functions is potentially precipitated and/or perpetuated by systemic factors engineered by immunological processes; for these are now understood to be modulators of neural activity, and ultimately the cognitive and emotional life of the organism. Similarly, environmental and physiological events, both prior to and after birth, can impact neurodevelopmental and behavioral processes, as well as endocrine and immunological functions. These circumstances serve as the basis for immunological theories for the formation of autistic spectrum disorders and schizophrenia, as well as potential vulnerabilities that set the stage for how later life events influence physiological and psychological adaptation during adult life and the ageing process. Debilitating neuropathological conditions, such as Alzheimer’s like dementia and Parkinson’s disease, in which neurodegeneration progressively destroys the motoric, cognitive and emotional lives of the individual, have resurrected and redefined the meaning of “neuroinflammation.” This is a hotly pursued process that involves parenchymal glial cells of the brain, as well as the contributions of systemic inflammatory processes that emanate from the immune system. This area has increased attention on the biological functions of astrocytes and microglial cells, and the recognition that they are as much a part of brain function, as oligodendrocytes, the myelinating cells that expedite communication between neurons. Finally, it has also become clear that nutritional, metabolic and cardiovascular health are intimately linked to inflammatory and/or immunological activities, emphasizing the importance of the immune system as both a contributor and reflection of health status across different provinces of physiological function.

In protecting the organism against infectious disease, the hematopoietic cells that give rise to the heterogeneity of lymphocytes, monocytes and other cellular forms – in short, the immune system – are intimately linked to the activities of the central nervous system. This now is an established fact, as the contents of this handbook make abundantly clear. Furthermore, this relationship has served to emphasize a multifactorial, integrative systems approach to the scientific investigation of disease. Of course, no one involved in this field, and especially the authors assembled for this volume, is surprised by this, since reductionistic approaches that seek unitary explanations for complex phenomena are bound to encounter disappointment. Indeed,
Robert Ader in his 1980 Presidential Address to the American Psychosomatic Society, given on the eve of his seminal publication, *Psychoneuroimmunology* (Ader, 1981), gave eloquent voice to this point:

Despite the most sophisticated strategies designed to achieve uniformity, variability remains one of the most ubiquitous results of all natural and contrived biological experiments. The biomedical scientist, operating within the conceptual and technical constraints imposed by the disciplinary boundaries of a reductionistic philosophy, attempts to control or minimize (or ignore) variability. For the psychosomaticist, such variability is the starting point of his research; it defines the operation of variables with which to be concerned. (Ader, 1980, p. 307)

The contents of this handbook continue to echo these thoughts, and provide a comprehensive source of information on the history, methodology, and conceptual development of different aspects of research into psychoneuroimmunology. In doing so, a balance between traditional and emerging topics of psychoneuroimmunological research is provided that focuses on the clinical and practical implications of findings from human and animal empirical research. While the specialist reader will appreciate the gains made in psychoneuroimmunology, the newcomer to this field will receive an informed introduction to the field, and some of the prominent approaches that currently are under investigation. Some stratification has been incorporated into the book, with initial chapters providing basic information on the immune system, “hard-wired” innervation of lymphoid organs, and neuroscience approaches to examining effects on immune function. These early conceptual and methodological chapters are followed by material that addresses entry of molecular and cellular elements of the immune system into the brain and spinal cord, and the consequences of this to neural function, nociception, or pain, and feedback regulation of immunological and metabolic processes. Immunomodulation through catecholamine, neuropeptide, and neuroendocrine processes is addressed at a basic level, but then moves on to the effects of stressors on immune function. Many of these and subsequent chapters address methodological issues and potential pitfalls when interpreting the results of human and animal studies.

The second half of the book is focused on material that mixes basic and clinical findings to determine the degree to which neural–immune interactions or disruption of the neural–immune axis contributes to disease. An emerging theme is the operation of neural–immune processes throughout the lifespan. In recognition of this point, chapters are provided on how maternal exposure to immunologic and psychogenic stressors influences neural and cognitive development during the postnatal and early adult years, with special attention given to microglial cells and their emerging role in shaping the development of the central nervous system. This is revisited in a later chapter by a detailed treatment of whether immunologic activity can be considered as a plausible factor in the formation of autism, as well as schizophrenia. Ageing is an ever-present background process that late in life contributes to biological variability, and is given attention in two chapters focused on animal and human studies, respectively. As already mentioned, mental health and behavioral abnormalities are a recurring theme, and this is reemphasized in chapters that cover inflammatory processes in stress, depression, cardiovascular disease, and neurodegenerative diseases, such as Parkinson’s and Alzheimer’s. Related to this, are cognitive deficits, which have become a dominant theme in psychoneuroimmunological investigations. In the present volume, this literature is discussed with a focus on methodological issues and the interpretation of results from studies involving various immune
challenges, as well as those addressing the presence of immune-related transcription factors in the brain. Finally, given the prominence of obesity and eating-related disorders, a chapter is devoted to the role of immunologic processes in regulating food intake, energy regulation and metabolism.

We are indebted to the distinguished group of authors who devoted their time and energy to create this handbook. The excellent level of scholarship displayed in these chapters left very little for us to do, and only left us recognizing how impressive this multidisciplinary endeavor has become over the past three decades. We are, of course, cognizant that the full breadth of psychoneuroimmunology has not been represented in these pages. Important topics such as sleep, cancer and exercise have not been included, and this oversight is something for us to correct in future volumes. However, psychoneuroimmunology has become pleasantly unwieldy. One cannot cram everything into a finite number of pages, and volumes such as this are instruments for inspiration and the generation of ambitious research programs.

In coming to the end of this long process, we sadly acknowledge the loss of some dear friends. Dr Steven Zalcman, a contributor to this volume, unexpectedly passed away. Steve was a close friend and colleague who often shared perceptive thoughts about the field, as well as an encyclopedic knowledge of popular music and stand-up comedy – he was as equally comfortable exhorting about interleukins and the brain, as he was about the merits of the Beatles, Stones, and Monty Python!

Sadly, Dr. Robert Ader, a mentor and constant inspiration to all of us, passed away during the development of this volume, but left the field he helped create, quite fertile and fully alive. We are grateful to his support on this project. One of us (AWK) approached him and picked his brain in the simplest of ways: “Bob, should I do this?” No answer is simple, however, when it comes to Bob Ader, although mercifully, the answer was a resounding yes. This handbook has elements of his suggestions, real and implied. Ultimately, we are grateful that he was able to pen, along with his good friend and long-time colleague, Nicholas (Nick) Cohen, a foreword to the book. To paraphrase something Nick stated in a past correspondence, we note that this foreword not only offers a brief historical overview of the field of psychoneuroimmunology, but also represents the final scientific thoughts of Robert Ader.

The production values of this project owe their special touch to the hard work of the publishers. We are particularly grateful to Andrew Peart, Publisher for psychology books at Wiley-Blackwell, who initially approached us to undertake this project. Andy has been a constant source of encouragement and guidance with our various questions and concerns. We could not ask for a better interpreter of the book publishing process. Additional thanks go to Tori Halliday, Karen Shield, and Mirjana Misina, who queried and guided us – hands stretched across the Atlantic – tolerating the long process of reading and re-reading, copyright-getting and various other important details a forgetful editor rarely remembers to do.

Of course, as editors, we know that the buck stops with us. If there is anything to yell about, we are to blame. But we hope the excitement and proven success of psychoneuroimmunology will drown out the noise. This book may hold some hidden nuggets of thought and fact for the experienced and informed, but we are most hopeful that it may inspire new ambitions and promising careers for students and postdoctoral fellows who have yet to be smitten by the allure of this field. And while this book is dedicated to the memory of Robert Ader, I am sure, he will be the first to agree that this book is for you.

Alexander W. Kusnecov
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Preface

References

Just in case a prospective reader of this book doesn’t already know the simple definition of psychoneuroimmunology, it is the study of the interactions among behavior, neural and endocrine function, and immune system processes. The central premise of this interdisciplinary field is that adaptation is the product of a single, integrated network of defenses. Each component of this network evolved to serve specialized functions. These are the parochial interests of the “disciplines” into which we have divided the biological sciences. At the same time, though, each component of this defensive network monitors and responds to information (sometimes presented as shared molecules and/or receptors) derived from the others. Thus, we cannot fully understand immunoregulatory processes without considering the organism and the internal and external milieu in which immune responses take place. Immunoregulatory processes, once considered a self-regulating, autonomous agency of defense, have been revealed by research, most of which has been conducted over the past 35 years, to be, in reality, influenced by the brain; and, conversely, neural and endocrine functions and behavior have been shown to be influenced by the immune system.

Our original study on behaviorally conditioned immunosuppression was published in 1975. We were not aware of it at the time, but Russian scientists had conducted studies on the classical conditioning of immune responses in the 1920s. A conditioned stimulus (e.g., heat, tactile stimulation) was repeatedly paired with injections of foreign proteins. Subsequent exposure to the conditioned stimulus alone was thought to have induced antibody production. These studies attracted little attention outside the Soviet Union. Within the Soviet Union, they provoked heated arguments since some investigators believed (but the scientific community rejected the notion) that an antibody response was the direct result of neural activity (i.e., that the nervous system, by itself, could stimulate antibody production).

Other early indications of CNS influences on immunity came from Andor Szentiványi’s studies in the late 1950s showing that hypothalamic lesions could prevent anaphylactic shock in animals. Similar lines of research were initiated sporadically following these findings.

One of the earliest pioneers in the study of behavioral influences on immunity was Fred Rasmussen a virologist intrigued by the possibility that emotional states could influence the course of infectious illness. Rasmussen teamed up with Norman Brill, a psychiatrist and James Marsh, a psychologist – probably the first such collaborative team – to start a program of research on stress and infectious disease. During the 1950s and 1960s, Rasmussen and his
colleagues examined the effects of various stressors on mice inoculated with different viruses.\(^1\) Susceptibility to infections was increased or decreased, depending on the nature of the stressor. These studies, with obvious implications for the neuroendocrine modulation of immunity, also failed to attract much attention, although they were forerunners of some of the research on early life experiences and disease susceptibility initiated by Drs George Solomon and Alfred Amkraut and others in the mid 1960s.

George Solomon, a psychiatrist, was one of the real pioneers in the development of psychoneuroimmunology. His initial research examined the life histories and personality characteristics of patients with autoimmune disease. In the best known of their studies, Solomon and Rudolf Moos compared rheumatoid arthritis patients with their “at risk,” but healthy, relatives. Their analysis also included the presence or absence of rheumatoid factor, an anti IgG antibody characteristic of rheumatoid arthritis. Compared to the patients, rheumatoid factor positive relatives were psychologically “healthy,” lacked anxiety, depression, or alienation and reported good relationships with spouses, relatives and friends. Psychological well-being seemed to have had a salutary effect in the face of a genetic predisposition to autoimmune disease.

Solomon was convinced that experimental research would be more persuasive, so he established a “psychoimmunology” laboratory to study the effects of behavioral, social, and endocrine manipulations in animals on immune function and responses to a bacterial antigen, virus-induced tumors, and adjuvant-induced arthritis. As in other such studies, the results varied depending on the stressor and the outcome measure.

During the 1970s, Hugo Besedovsky, another very prominent figure in the development of psychoneuroimmunology, was beginning to construct a neuroendocrine–immune system network with his studies of the effects of immune responses on neural and endocrine function. If, as he and his colleagues (the most “important” one being his wife Adriana del Rey) believed, immune function was integrated with other physiological processes, exposure to an antigen should evoke changes in neuroendocrine activity that, in turn, should have feedback effects on immunoregulatory processes and host defenses. There followed an innovative program of research that provided dramatic demonstrations that the nervous and endocrine systems could perceive and respond to signals emitted by an activated immune system.

The novel studies of several other figures played critical roles in the growing acceptance of this new discipline. There was the research of Ed Blalock and his colleagues (e.g., Eric Smith) who found lymphocytes could be a source of brain peptides and pituitary hormones. Now, it is accepted that brain peptides and their receptors exist within the immune system and that the products of an activated immune system can function as neurotransmitters. Another critical link was forged by investigators led by David Felten, Susanne Stevens, and Karen Bulloch, who described “hard-wired” connections from the nervous system to the immune system.

At a behavioral level, Roger Bartrop described immunologic changes associated with the bereavement that followed the sudden death of a spouse, and several other laboratories launched studies of the immune changes associated with stressful life experiences and emotional states. Marvin Stein, for example, who had studied the effects of hypothalamic lesions and stimulation on anaphylactic reactions in guinea pigs during the 1960s, returned to psychoneuroimmunology in the 1980s with a program of animal research on the immunologic effects of stressful experiences as well as human studies of the immunologic changes associated with

\(^1\) Rasmussen was the chair of the Department of Medical Microbiology and Immunology at UCLA in 1965 when one of us (NC) was there as a postdoctoral fellow in a transplantation immunogenetics lab and was unaware of this line of research.
loss and depression. Another interdisciplinary collaboration between Janice Kiecolt-Glaser, a psychologist and Ronald Glaser, a virologist, developed an extremely productive research program beginning with studies of stress-induced immune function and the reactivation of latent viruses. All the aforementioned research initiated in the 1970s and early 1980s was apparently “the right stuff at the right time!” It is likely that no one research program would have had quite the same impact had it not been for the converging evidence of brain–immune system interactions that was appearing in the literature at the same time. These initial studies legitimized questions that had not been asked before. And if the questions – and, sometimes, the questioners – were disparaged, a common experience, the data were compelling and then, undeniable. Thus, the coalescence of research initiated during the 1970s – and the identity provided by the label, psychoneuroimmunology, a book of the same name, a journal and a society – reactivated latent interests and attracted new investigators from different fields to this hybrid field.

Frequently, we have been asked if we had any idea of what we had “started” with our studies of conditioned alterations in immune function or where our studies would lead. Of course we did know that the concept challenged immunological dogma and could be very important, but we never anticipated how rapidly or how large the field would grow and expand and we continue to be amazed by the number of scientists working in various psychoneuroimmunology laboratories – named as such – all over the world. When the journal *Brain, Behavior, and Immunity* (BBI) was launched in 1987, it was overseen by an Editor-in-Chief (a behavioral scientist) and two Associate Editors (an immunologist and a neural scientist). This was sufficient to handle the topical diversity and number of submitted publications and to assign appropriate reviewers from the 31-member Editorial Board. Twenty-five years later, this high-impact journal is guided by an Editor-in-Chief, six Associate Editors and an Editorial Board of 64 scientists. Eight issues are published each year – twice the number that appeared in 1987. Of course, peer-reviewed publication of new data in psychoneuroimmunology is by no means restricted to BBI; high quality papers appear with regularity in a number of highly ranked journals. [The 20th annual meeting of the PsychoNeuroImmunology Research Society (PNIRS) took place in Stockholm, Sweden, in June 2013. ] The book *Psychoneuroimmunology*, first published in 1981, is in its fourth edition. Psychoneuroimmunology is now taught in many colleges and universities in this country and abroad. A few textbooks are now available to guide the novice, although multi-authored collections of chapters still prevail. Our guess is that, now, it is close to impossible for any normal mortal to write a single authored, integrated, and up-to-date inclusive psychoneuroimmunology text book in addition to running a funded productive laboratory.

Some contemporary news releases and numerous websites still refer to psychoneuroimmunology as an emerging field. That descriptor might have been appropriate 25 years ago but today, there can be no doubt that by any set of criteria, psychoneuroimmunology has fully emerged from a veil of skepticism as an exemplar of an integrated field of study. We’ve been afforded a wonderful and rare opportunity to witness this emergence of a new field of research and to chart, for nearly 40 years, its scientific development and its impact on, and integration into, mainstream scientific and medical thinking. This most recent edited volume, *Handbook of Psychoneuroimmunology*, is an exciting and up-to-date presentation of many of these advances.

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2 We have also seen psychoneuroimmunology become an exemplar of mind–body medicine, but have watched, with some dismay, how it is being exploited as a cash cow for some self-styled practitioners of non-scientifically validated approaches to patient care.
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Basic Principles in Immunology
Relevance for Studies in Psychoneuroimmunology

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Introduction

Over the past century our knowledge of the immune system and how it functions has grown exponentially. This is especially true in regard to how it relates to and interacts with various physiological systems, including the central nervous system. An important focus of the field of neuroimmunology is to elucidate the ways that the immune system influences neuronal function and subsequently, behavior and cognition through the modulation of cytokines and hormones, especially stress hormones such as corticosteroids. Since the intimate relationship between the immune system and brain function has come to light, research in this field has broadened into psychoneuroimmunology, which specifically addresses the role of the immune system in the development of psychiatric disorders, including depression and anxiety. The purpose of this section is to provide a general overview of basic immune function, describing both the components of the immune system and the various modes of immunity employed in an immune response. Additionally, we will explore the validity of some of the most widely used methods and models for psychoneuroimmunology applied to the study of interactions between immunological processes and behavior and cognition as they relate to mental disorders in humans.

The Components of the Immune System

To understand how the immune system influences the brain, and subsequently, behavior and cognition, it is vital to understand how the immune system functions. The immune system
comprises two major components: specialized cells that carry out the various functions of the immune process, and the chemical messengers that allow these cells to communicate, not only with each other, but with other cells and tissues within the body. These partners in immune function must perform a precise and complex dance in order to maintain homeostasis and, when necessary, to mediate an inflammatory response. In general, as part of the inflammatory response damaged or infected cells secrete chemical messengers called chemokines that serve to attract specific immune cells, which in turn release various cytokines that influence the types of cells and modes of immunity that will be employed to eliminate any potential pathogens. Once these threats have been neutralized the process continues, as immune cells and their chemical messengers also function to mediate tissue repair and regeneration. A lack of coordination from either partner can result in deleterious consequences, including the development of allergies, as well as autoimmune and immune-deficiency disorders.

Cytokines and chemokines – the immune system’s messengers

Cytokines and chemokines are protein and glycoprotein molecules synthesized and secreted by cells as part of the immune response. Chemokines are a specialized class of cytokines that derive their name from their role in chemotaxis; a majority of these soluble factors are chemoattractants that serve to guide immune cells to the site of infection. They are characterized by their small size and the presence of four cysteine residues (named C) which contribute to their tertiary structure. They are divided into four families (C, CC, CXC and CX3C) based upon the location of the first two C residues. Chemokines in the C group differ from the other chemokine families in that they contain only two cysteines; secretion of these chemokines attracts T-cell progenitors to the thymus. The CC chemokines have two adjacent cysteines near the amino terminus, while the relevant cysteines in the CXC chemokines can be found at the N-terminus separated by a single amino acid (X). Similarly, the CX3C chemokines have three intervening amino acids; thus far, fractalkine is the only chemokine with this structure that has been identified. In addition to their role in immune function, chemokines contribute to a variety of biological functions, especially in the brain, as will be discussed later.

The major cytokines consist of interleukins (IL), interferons (IFN) and colony-stimulating factors, as well as various growth factors and eicosanoids, including prostaglandins. Cytokines are mainly produced by immune cells and also by a variety of other cell types including brain cells. The specificity of the elicited immune response is dictated by the expression of cytokine receptors that are widely expressed in tissues and organs. Additionally, some cytokine receptors exist in a soluble form and can act as inhibitors of cytokine activity through competitive binding of their ligands. To differentiate between cytokines’ biological activity they are often described as either pro-inflammatory or anti-inflammatory; upon damage to or infection of cells and tissues, pro-inflammatory cytokines are produced and secreted to stimulate immune system activation. The induction of cytokine expression tends to occur in a step-wise manner, with the expression of certain cytokines dependent upon the prior expression of others; for example, IL-1 is necessary to induce the production of IL-2, IL-6 and tumor necrosis factor (TNF). Anti-inflammatory cytokines, such as IL-10, are also released during inflammation in order to dampen and eventually terminate pro-inflammatory cytokine activity. In many instances, the cytokines IL-4 and IL-13 are referred as anti-inflammatory because they oppose the effects of inflammatory cytokines IL-2 and IFN-γ. However, many inflammatory processes such as allergic inflammation are mediated by the actions of IL-4 and IL-13. Thus, describing
cytokines purely by their pro- or anti-inflammatory properties can be misleading since they are pleiotropic in nature and are involved in many biological processes. Maintaining a balance in cytokine and chemokine signaling is vital for sustaining immune homeostasis and stimulating the appropriate immune cells as part of the immune response.

The cells of the immune system

The circulatory system serves as the main highway for the cells of the immune system, so it is not surprising that immune cells are derived from the same source as the other major components of blood. During prenatal development the spleen and liver are responsible for producing both red blood cells and white blood cells; however, once the skeleton begins to develop and the bone marrow becomes established, this responsibility shifts to hematopoietic stem cells (HSCs) within the bone marrow. HSCs give rise to the three cell lineages of the blood and immune system: the erythroid lineage, the myeloid lineage, and the lymphoid lineage (see Figure 1.1). Currently, the general consensus for how these lineages arise is that the initial progeny of HSCs are multipotent progenitor cells (MPPs) which in turn give rise to common myeloid progenitor cells (CMPs). Progeny of these CMPs maintain expression of myeloid specific genes, but can undergo further restriction into either erythroid or lymphoid progenitors. Thus, the myeloid lineage may be considered the default fate for CMPs unless directed towards either erythroid or lymphoid lineages through changes within the milieu of the stem cell niche, including alterations in cytokine expression. Ultimately, the erythroid lineage will develop into red blood cells and platelets while the myeloid and lymphoid lineages will give rise to the cells of the immune system.

The myeloid lineage

Members of the myeloid lineage include monocytes, granulocytes and mast cells. The primary function of monocytes is to migrate out of the vasculature and into tissues where they mature into macrophages that will monitor the body and destroy potential pathogens through phagocytosis. Macrophages can be further classified into mobile or fixed macrophages. The alveolar macrophages of the lungs and the dendritic cells of the epidermis are examples of mobile macrophages that can freely travel within the interstitial space, whereas the Kupffer cells of the liver remain fixed in place.

The granulocytes, named for the multiple granules found within their cells, comprise three types of cells: neutrophils, eosinophils, and basophils. These polymorphonuclear cells (PMNs) are confined primarily to the blood stream until activation by cytokines and chemokines released by damaged cells and tissues. These messengers prompt the PMNs to migrate into the interstitial space where they will hunt down and destroy invading pathogens. Neutrophils, which make up the greatest proportion of PMNs, are phagocytic cells that are among the first cells recruited to eliminate invading pathogens. In addition to destroying foreign cells by phagocytosis, neutrophils can also degranulate and release anti-microbial chemicals such as gelatinase and cathepsin. Interestingly, neutrophils have also been observed extruding filaments of DNA and associated proteins that can act as nets to entrap microbes; these extracellular structures provide an alternate method of destroying pathogens and may prevent their spread into the surrounding tissue. Lastly, neutrophils also release cytokines and thus can enhance the inflammatory response by recruiting more immune cells to the site of infection. The other two types of granulocytes, the eosinophils and basophils, make up a relatively small proportion of the total leukocyte population, but are vital in mitigating the effects of pathogens, especially
Figure 1.1  **Cells of the immune system.** Hematopoietic stem cells (HSCs) within the bone marrow are relatively quiescent stem cells whose progeny, multipotent progenitor cells (MPPs), can differentiate into both erythrocytes and leukocytes. There are three potential lineage fates: the erythroid lineage, which gives rise to both red blood cells (RBCs) and platelets, and the myeloid and the lymphoid lineages, which produce the cells of the immune system. Myeloid progenitor cells differentiate within the bone marrow to produce monocytes, granulocytes and mast cells, which then migrate to their target environments within the blood and tissue. Lymphoid progenitors can also be found within the bone marrow, however these cells will differentiate into precursor B-cells that will then migrate into the lymphatic tissues and organs. In contrast, T-cell progenitors leave the bone marrow and migrate directly to the thymus where they will undergo further proliferation and selection for immunocompetency.

for their role in mediating the innate and adaptive immune responses. Although eosinophils and basophils are perhaps best characterized for their anti-parasitical activities, in recent years their role in tissue and immune homeostasis has been further clarified. As part of the adaptive immune response, eosinophils are rapidly recruited to the site of infection by T-helper 2 (T\textsubscript{H2}) cells, where they release cytokines and lipid mediators, such as prostaglandin 2, as well as cytotoxic chemicals that can destroy invading pathogens. Additionally, they have the capability of acting as antigen-presenting cells to activate both naïve and memory T-cells. Finally, both eosinophils and basophils have also been implicated in the development of hypersensitivity and allergies, perhaps due to their relationship with T\textsubscript{H2} cells and mast cells.

Mast cells are functionally and morphologically similar to eosinophils and basophils; they play a vital role in the immunity against parasites, and facilitate tissue repair by stimulating angiogenesis, the growth of new blood vessels. However, these myeloid cells are found mainly within tissues adjacent to the external environment, especially within the mucosae of the respiratory and gastrointestinal tracts, and are perhaps best-known for their role in allergic responses. Mast cells are also found in the brain, particularly in some nuclei of the thalamus.
The granules within mast cells store a variety of cytokines and chemokines that facilitate the inflammatory process, as well as histamine which not only dilates blood vessels and is responsible for the pain and itchiness associated with an allergic reaction, but which can also act as a neurotransmitter. Another neurotransmitter, serotonin, has also been found within mast cells, and although the role of these neurotransmitters is not yet clear, they may be involved in cross talk between the immune system and neurons, especially those of the enteric nervous system. Interestingly, in addition to direct damage or the binding of antigens, degranulation of mast cells can also be initiated by various neuropeptides, further supporting the possibility that mast cells represent a link between the immune system and the nervous system.

**The lymphoid lineage**  
Lymphocytes derive their name from the fact that they reside primarily within the tissues of the lymphatic system. These tissues include a network of reticular fibers that can be found in virtually every organ of the body; these fibers converge upon the lymph nodes and the two major organs of the lymphatic system: the spleen and the thymus. The main function of the lymph nodes is to filter out and clear lymph as it travels along the lymphatic vessels. Resident macrophages remove and destroy any microbes or cellular debris while lymphocytes monitor the lymphatic stream for the presence of foreign antigens. The lymphocytes include B-lymphocytes, T-lymphocytes and natural killer (NK) cells.

B-cells differentiate within the bone marrow and migrate into the lymph nodes and spleen. Here they will remain in a precursor stage until activated by an antigen, at which time they will undergo rapid proliferation and maturation into antibody-secreting plasma cells. Membrane-bound immunoglobulins (Ig), including IgM and IgD, on the surface of precursor B-cells act as receptors for intact antigens. The binding of the antigen stimulates the production of secretory immunoglobulins, usually referred to as antibodies, including IgM, IgG, IgA and IgE. These antibodies consist of a conserved region and a variable region. It is the conformation of the variable region (the product of the genetic recombination of several genes within the immunoglobulin super-gene family) that makes the antibodies specific for their target antigen. Interestingly, lymphocytes are the only somatic cells that rearrange DNA to produce new protein variants as part of their phenotype.

Once antibodies have been secreted into the extracellular space they can facilitate the removal of pathogens in a variety of ways. By binding to antigens on the surface of pathogens they can make the pathogen more visible to macrophages. That is, the antibody serves as an opsonin (from the latin “to relish”), that marks the pathogen as a target for phagocytosis by macrophages; this will be facilitated by the Fc region of the antibody molecule binding to Fc receptors on the macrophage. Additionally, some immunoglobulins are capable of binding to and activating other effector cells, including granulocytes and mast cells. In the case of IgG, binding to platelets allows for the transfer of immunity across the placenta, which is vital for the development of the fetal immune system. The binding of the Fc region of IgE to the Fc receptor on mast cells results in mast cell degranulation and release of inflammatory mediators such as histamine. The production of IgE antibodies against harmless compounds such as pollen or albumin is responsible for the establishment of allergies.

Although the role of different antibodies in the immune response is quite varied, their primary function is to facilitate the removal of pathogens; however, in order to do so, they must be able to bind to antigens. Individual immunoglobulins are specific for only one or two closely related antigens, though they may be able to bind to other related antigens with lower affinity. However, the immune system cannot sustain an army of B-cells for every possible antigen that the body may encounter. Instead, precursor B-cells expressing a specific antibody
monitor the spleen, lymph nodes, and other peripheral lymphatic organs for the antigen that matches its antibody, much like pairing up two pieces of a puzzle. Upon successful binding of the antibody and antigen, the B-cell will undergo a period of rapid proliferation, or clonal expansion, making multiple replicas that will then mature into antibody-secreting plasma cells. Additionally, a subset of B-cells will become memory B-cells, which can rapidly mature into plasma cells should they encounter their specific antigen again.

Unlike the B-cells, T-cells do not differentiate in the bone marrow. Progenitors of T-cells instead migrate to the thymus where they continue to proliferate and undergo thymic selection, a process that ensures that T-cells are immunocompetent. Although initially considered a minor player in the immune response, the importance of T-cells in maintaining immune homeostasis and in modulating the immune response has become abundantly clear. The establishment of their critical role in autoimmune diseases and allergies, as well as immune-deficiency disorders such as HIV/AIDS, has been a major advance in immunology. A naïve T-cell (T_0) has the potential to differentiate into a variety of effector T-cells, which can be distinguished by the expression of recognition proteins known as cluster of differentiation (CD) proteins. Helper T-cells (T_H), also referred to as CD4^+ T-cells, modulate both the innate and adaptive immune response; among their many functions, they assist in the maturation of B-cells into plasma cells and memory B-cells, and activate cytotoxic T-cells as well as macrophages. Cytotoxic T-cells (T_C), which are CD8^+, attack and destroy virally infected cells as well as tumor cells. The major role of regulatory T-cells (CD4^+, CD25^+, FoxP3^+, T_reg), sometimes referred to as suppressor T-cells, is to shut down T-cell mediated immune responses. Finally, memory T-cells are antigen-specific subsets of CD4^+ and CD8^+ T-cells which have been previously activated and have the capacity to remain viable for long periods of time. Upon re-exposure to the antigen they will rapidly proliferate and activate both T_H and T_C cells so that the immune system can specifically target and destroy the invading pathogen.

The final class of lymphocytes is the natural killer (NK) cells; these cells take part in the innate immune response and act primarily against cells infected by viruses or rogue cells that have become cancerous. Unlike phagocytes, NK cells destroy their targets through the release of perforins, cytolytic enzymes that punch holes in the membrane of the targeted cell. In addition, NK cells discharge a class of proteases called granzymes, which enter the perforated cell and catalyze cell death via apoptosis. Since many of the cells that NK cells target are infected by viruses it is vital that the destruction of the cell is contained; if the cell was merely lysed any viruses that had succeeded in reproducing would be released to infect other cells.

In order to maintain immune and tissue homeostasis myeloid and lymphoid cells work together in a precise and coordinated dance choreographed by cytokines and chemokines. Although each partner is responsible for specific facets of an immune response, they are also dependent upon each other in order to provide the best protection for the host. So as to provide an optimal defense against potential pathogens these components of the immune system employ diverse strategies for identifying and eliminating various microbes.

**Modes of Immunity**

The immune system must be able to cope with a variety of potential pathogens, as well as tumor cells and other damaged host cells, while mitigating possible damage to healthy cells and tissue. This requires the correct identification of potentially deleterious microbes and cells followed by their targeted elimination. In order to accomplish this the immune system
utilizes two distinct, though interdependent, forms of protection which work together in a complex yet highly coordinated assault on pathogens that attempt to invade the body. The innate immune system is a general, non-specific form of defense comprised of anatomical barriers, which serve as a blockade against a majority of microorganisms, and immune cells, including granulocytes, mast cells, macrophages and NK cells, which can recognize and attempt to destroy potential pathogens that breach the barricades of the skin and mucosae. The function of the innate immune system is modulated and enhanced by the adaptive immune system, a specific form of defense which targets and marks pathogens for elimination. However, unlike the innate immune system, a hallmark of the adaptive immune system is that it displays memory, a trait that has been exploited in the development of vaccines. The adaptive immune system evolves in response to the pathogens it encounters over the lifetime of the host, selecting and maintaining a pool of memory B-cells and T-cells specific for antigens the body has been exposed to, so that should the body be invaded by the same pathogen in the future, it can rapidly and specifically target it for destruction.

In order to convey how the immune system contends with the variety of extracellular and intracellular pathogens the host may encounter, the type of defense utilized by immune cells is often described as either cell-mediated immunity or humoral immunity. Cell-mediated immunity is typically modulated by helper T-cell class 1 (TH1) cells, which orchestrate attacks against intracellular bacteria and viruses, as well as tumor cells. This is often through the release of cytokines, such as interferon, that catalyze the programmed cell-death pathways of infected cells; this process results in the elimination of the pathogen and limits its ability to spread to other cells. In contrast, humoral immunity is targeted against extracellular pathogens, including bacteria, fungi, and helminthes; this form of immunity is mediated by TH2 and, to a lesser degree, TH17 cells, which enlist granulocytes and mast cells to facilitate the destruction of these pathogens. Additionally, TH2 cells can stimulate the release of antibodies from B-cells; these antibodies can then bind to pathogens and mark them for destruction by macrophages.

To function correctly, the immune system must be able to distinguish between healthy host cells and potential pathogens, as well as damaged host cells, including infected or cancerous cells, in order to identify which ones must be destroyed. Members of the innate immune system utilize a set of pattern-recognition receptors (PRRs) that recognize highly conserved motifs that are unique to non-mammalian cells, including components of the bacterial cell wall, such as lipopolysaccharide (LPS) and peptidoglycan, as well as viral nucleic acid structures, such as single-stranded (s.s.) and double-stranded (d.s.) RNA. These molecular structures are referred to as pathogen-associated microbial patterns, or PAMPs; the binding of a PAMP to its receptor triggers signaling pathways that activate transcription factors, such as NF-κB, and induce the expression and secretion of pro-inflammatory cytokines and chemokines. This process initiates an inflammatory response that involves both the innate and adaptive immune systems, with the ultimate goal of eliminating the invading pathogens.

As shown in Figure 1.2, there are four main families of PRRs: Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-1-like receptors (RLRs) and C-type lectin receptors (CLRs). Of these, the TLRs are the best characterized; however, ongoing research into the other three classes of PRRs, as well as other lesser-known receptors, indicates that the innate immune system, although non-specific, is efficient at identifying potential pathogens. TLRs are transmembrane proteins with a leucine-rich extracellular domain and a conserved region, the Toll/IL-1 receptor domain, on the cytoplasmic tail. These receptors are expressed in tissues involved in immune function, including the spleen and leukocytes, and on cells within the lungs and gastrointestinal tract, as well as other environments that are exposed to the external environment.
Figure 1.2 The innate immune system. A) Activation of the inflammatory response requires the recognition of highly conserved non-mammalian motifs referred to as pathogen associated molecular proteins (PAMPs). These include bacterial cell wall components such as lipopolysaccharide (LPS) and peptidoglycan (PPG), as well as the protein flagellin, viral nucleic acids (both s.s. and d.s. RNA) and fungal cell-wall components. B) These PAMPs can be identified by a wide assortment of pattern recognition receptors (PRRs) found on a variety of cells, especially those of the innate immune system. The lower panel illustrates how activation of PRRs within the cell by various pathogens initiates signaling pathways that culminate in the production of pro-inflammatory cytokines which will ultimately serve to stimulate the adaptive immune response.