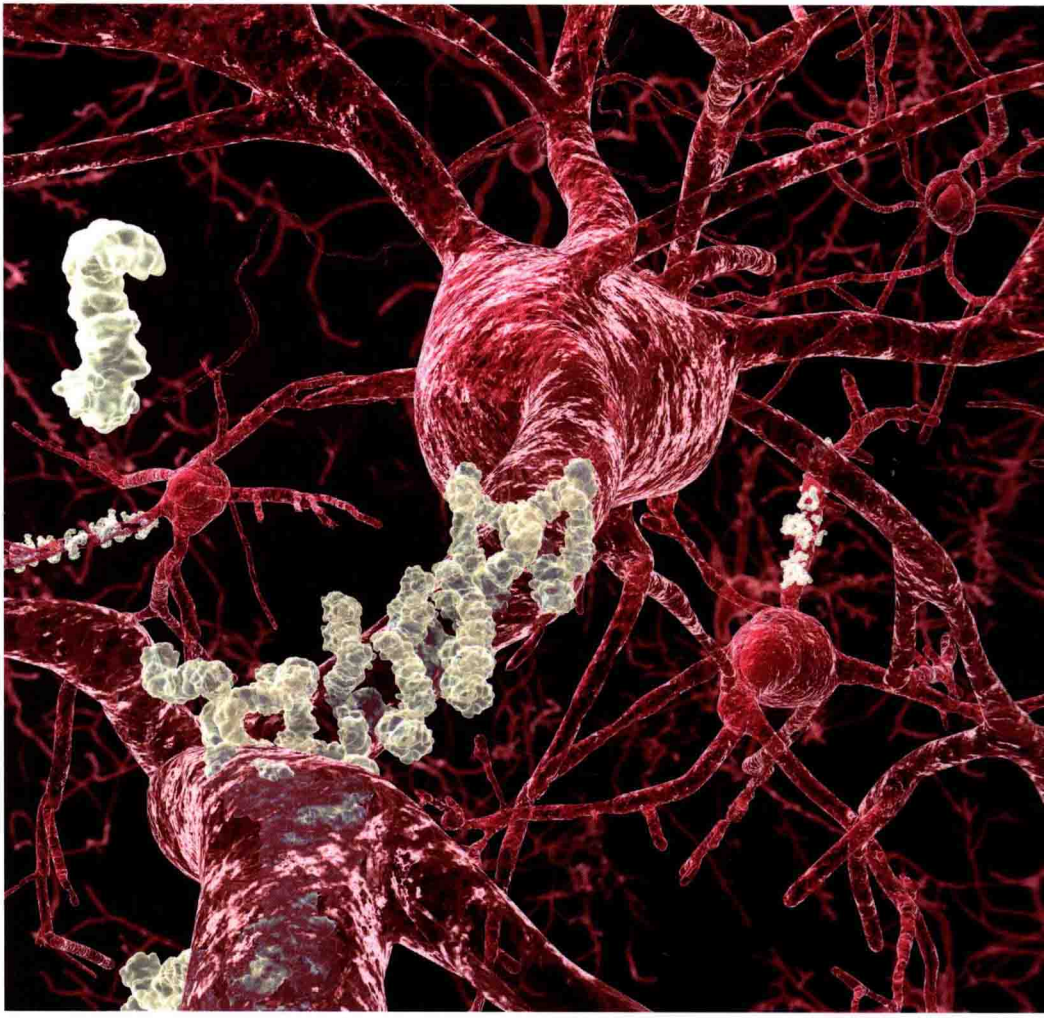
RSC Metallobiology Series

Edited by Roberta Ward, Robert Crichton and David Dexter

Mechanisms and Metal Involvement in Neurodegenerative Diseases



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Mechanisms and Metal Involvement in Neurodegenerative Diseases

Edited by

Roberta Ward and Robert Crichton
Catholique University of Louvain, Belgium
Email: roberta.ward@uclouvain.be; robert.crichton@uclouvain.be

David Dexter
Imperial College London, UK
Email: d.dexter@imperial.ac.uk

RSC Publishing

RSC Metallobiology Series No. 1

ISBN: 978-1-84973-588-9
ISSN: 2045-547X

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

Published by The Royal Society of Chemistry,
Thomas Graham House, Science Park, Milton Road,
Cambridge CB4 0WF, UK

Registered Charity Number 207890

For further information see our web site at www.rsc.org

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RSC Metallobiology Series

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1: Mechanisms and Metal Involvement in Neurodegenerative Diseases

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Published by the Royal Society of Chemistry, www.rsc.org

CHAPTER 1

Introduction

ROBERTA WARD,[b] DAVID DEXTER*[a] AND ROBERT CRICHTON[b]

[a] Imperial College London, UK; [b] Université Catholique de Louvain, Belgium
*Email: d.dexter@imperial.ac.uk

1.1 Outline

The complexity of the human brain is staggering, able to coordinate the fingers, hands and feet of an organist, all playing on three different keyboards, and to create three-dimensional images from light falling on a two-dimensional retina. While the brain regulates all aspects of the functions of our bodies, in our post-genomic era we are still a long way from understanding it, despite the enormous strides made in DNA sequencing. Weighing only about 1.4 kg (only 2% of body mass), the brain accounts for 20% of our total oxygen consumption and 25% of our glucose utilisation. However, as the human population lives longer and longer, hand in hand with our ever-increasing life expectancy goes an alarming increase in the incidence of neurodegenerative disorders, affecting both cognititive and motor function. Neurodegenerative disorders are set to overtake cancer to become the second most common cause of death by 2040.[1] The most common of these are *dementias*, the characteristic of which is decline in cognitive faculties and occurrence of behavioural abnormalities which interfere with the capacity of the afflicted individual to carry out normal daily activities. It usually affects elderly individuals and occurs in many different forms, of which the most common is Alzheimer's disease (AD). In the *World Alzheimer Report 2009*,[1] Alzheimer's Disease International (ADI) estimated that 36 million people

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worldwide are living with dementia, with numbers doubling every 20 years to reach 66 million by 2030, and 115 million by 2050. Dementia prevalence increases with age; in the USA, whereas 5.0% of those aged 71–79 years are affected, this climbs to 37.4% of those aged 90 and older.[2] Dementias are chronic, progressive, long-lasting and, so far, incurable diseases, the worldwide costs of which now represent more than 1% of global GDP. In other words, if dementia care were a country, it would represent the world's 18th largest economy.[3] Of the neurodegenerative diseases affecting motor function, Parkinson's disease is the most common, and it is estimated that 6.3 million people worldwide suffer from the disease.[4] It is the second most prevalent neurodegenerative disorder, affecting 1% of those over 60, and 4% of those over 80.

1.2 Interplay Between the Peripheral Circulation and Brain: Importance of the Blood–Brain Barrier

The brain contains about 10^{11} specialized nerve cells, called neurons, which send electrical impulses at high speeds over long distances, down their axons. Each neuron can interconnect with tens of thousands of other neurons, at junctions called synapses. The human brain contains more than 10^{14} of these synaptic connections, which forge enormously complex neural circuits, undergoing continuous remodelling. The brain also contains cells of a different type, called glial cells, which account for 90% of the brain's cells and more than half of its volume. An accumulating body of work over the last two decades[5–7] has revealed that the glial cells are important regulators of synaptic connectivity, involved in the control of synapse formation, function, plasticity and elimination, both in health and disease. Figure 1.1 presents a representation of neurons and the three main types of glial cells.

There are three types of neurons: multipolar neurons, motor neurons and sensory neurons. Some collect information about our environment (both external and internal), which they transmit to other neurons, where the data are either processed or stored, while others respond to this information to regulate the control of muscle contraction, hormone synthesis, *etc.* Sensory neurons collect all sorts of information, concerning light, smell, sound, pressure, touch, *etc.*, through specialized receptors, and transform this information into electrical signals, whereas multipolar neurons receive synaptic signals from several hundred other neurons and transmit them to many other neurons at the lateral branches of their terminals. Motor neurons transmit nerve impulses to muscle cells, and their single, often very long, axons extend from the cell body of the neuron to the effector muscle cell. They have an insulating sheath of myelin, a kind of biological insulating tape, covering all parts of the axon except for the nodes of Ranvier and the axon terminals at the neuromuscular synapse. This allows them to propagate nerve impulses at velocities of up to 100 m s^{-1}, around ten times faster than in unmyelinated nerves.

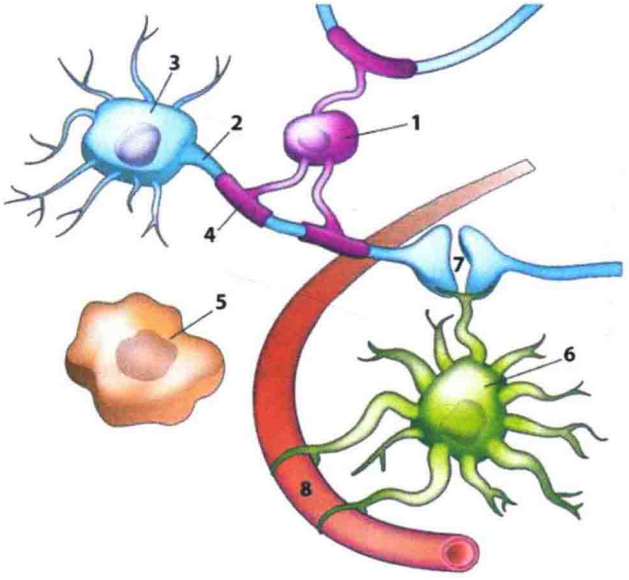

Figure 1.1 A representation of neurons and the three main types of glial cells. Oligodendrocytes (1) send projections that wrap the axons (2) – of neurons (3) – in sheathes of myelin (4), speeding signal conduction. Microglia (5) are the brain's immune cells, but they also monitor neighbouring brain cells for damage which they remove, and also have other functions. Astrocytes (6) carry out a host of activities. They can monitor levels of neuronal activity along axons at synapses (7) and, when neuronal activity is high, signal to local blood vessels (8) to dilate, increasing blood supply to the neurons. Adapted from Standmed 2009.

There are three principal types of glial cells, namely astrocytes, oligodendrocytes and microglia. Astrocytes are star-shaped glial cells which are the major cell type in the central nervous system (CNS). The network of astrocytic processes forms the infrastructure on which all other CNS cells and vessels are anchored. They have a multitude of functions, including regulation of the ionic milieu in the intercellular space, uptake and/or breakdown of some neurotransmitters, supplying nutrients to the neurons and formation of the blood–brain barrier (BBB). Astrocytes also produce and secrete substances that have a major influence on the formation and elimination of synapses.

Oligodendrocytes are involved in the electrical insulation of nerve fibres (axons), wrapping up to 150 layers of myelin sheath approximately 1 μm thick around the axons of neurons, rather like electrical insulating tape. One oligodendrocyte can extend its processes to up to 50 neuronal axons. In the peripheral nervous system the function of the oligodendrocytes is replaced by Schwann cells, which however can wrap around only one axon. High numbers of proliferating oligodentroglial progenitor cells are present to ensure remyelination can occur when necessary. New studies of human brain using magnetic resonance imaging (MRI) have demonstrated that myelinating

oligodendrocytes sense electrical activity in axons, revealing that white matter changes after learning complex tasks.

Microglia are also found in the vicinity of the BBB. The microglia are the resident macrophages of the central nervous system, which can communicate with the astrocytes and neurons and with cells of the immune system by a large number of signalling pathways. They are the most susceptible sensors of brain pathology, and when they detect any signs of brain lesions or nervous system dysfunction, they undergo a complex, multistage activation process that converts them into "activated microglia". Activated microglial cells have the capacity to release a large number of substances that can act detrimentally or beneficially upon surrounding cells; they can also migrate to the site of injury, proliferate and phagocytose cells and cellular compartments. However, it has become clear that microglia have a role in the maintenance of synaptic integrity and are capable of removing defunct axon terminals, thereby helping neuronal contacts to remain intact. In the healthy CNS, microglia do not present as macrophages, indicating that their day-to-day function is different, and these specific non-macrophagic microglial functions are now beginning to be explored.

The brain is unique among all the organs of the body, hidden behind a relatively poorly permeable vascular barrier, which limits its access to plasma nutrients, such as metal ions. There are three principal barrier sites which constitute the interface between the peripheral circulation and the brain.[8] These are (Figure 1.2) the endothelium of the brain microvessels (forming the BBB proper); the epithelium of the choroid plexus, which secretes cerebrospinal fluid (CSF) into the cerebral ventricles; and the epithelium of the arachnoid mater covering the outer brain surface above the layer of subarachnoid CSF. Together the choroid plexus and the arachnoid form the blood–CSF barrier (BCSFB). The BBB is created at the level of the cerebral capillary endothelial cells, and is essentially composed (Figure 1.3) of the cerebral capillary endothelial cells, joined by tight junctions, a basal lamina, pericytes and astrocyte end-foot processes. The types of cells found at the BBB, and their associations, are illustrated in Figure 1.3. The endothelial cells form tight junctions which seal the paracellular pathway between the cells, such that substances which enter the brain must use dedicated endothelial cell transport systems. Pericytes, the connective tissue cells which occur around small blood vessels, are distributed along the length of the cerebral capillaries, partially surrounding the endothelium. Both the cerebral endothelial cells and the pericytes are enclosed by the local basement membrane, forming a distinct perivascular extracellular matrix (basal lamina 1, BL1), different from the extracellular matrix of the astroglial end-feet bounding the brain parenchyma (BL2). Foot processes from astrocytes form a complex network surrounding the capillaries.

In brain endothelium, adsorptive and receptor-mediated transcytosis allow restricted and regulated entry of certain large molecules that have particular growth factor and signalling roles within the CNS. Once the BBB is crossed, diffusion distances for solutes to neurons and glial cells are short. Unlike other

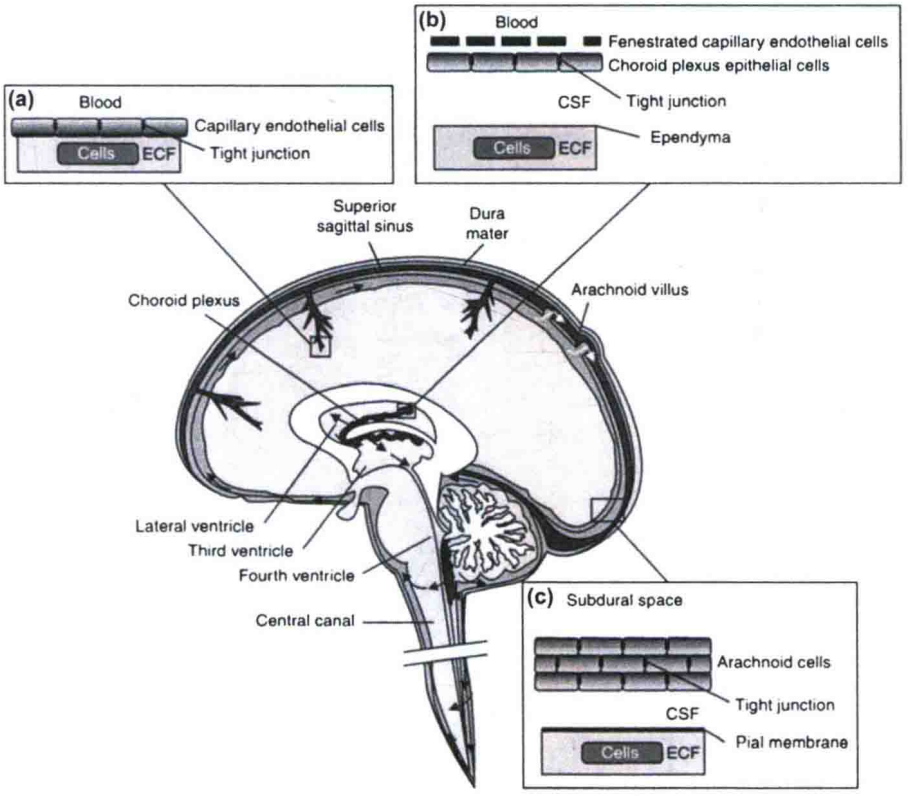

Figure 1.2 Barriers of the brain. There are three principal barrier sites between blood and brain: (a) the BBB proper; (b) the blood–CSF barrier; and (c) the arachnoid barrier.
(Reproduced from Abbott *et al.*[8] with permission from Elsevier).

blood vessel epithelia, the BBB epithelia express different receptors at the luminal membrane (facing the circulation) compared to the abluminal membrane, surrounded by astrocyte end-feet, neuronal processes and interstitial fluid.

1.3 Immune Function in Neurodegenerative Diseases

The immune system can be divided into two interactive systems: the innate and the adaptive immune systems. Innate immunity is the first line of defence, which mobilizes a rapid response to endogenous or exogenous molecules, by distinguishing self from non-self. Innate immunity is rapidly mobilized initially when endogenous ligands are released, which in turn alert the immune system and activate toll-like receptors (TLRs). In contrast, the adaptive immune system is involved in the elimination of pathogens during the later phase of infection and is elicited by B and T lymphocytes, which utilize immunoglobulins and T cell receptors, respectively, as antigen receptors to recognize "non-self" molecules.

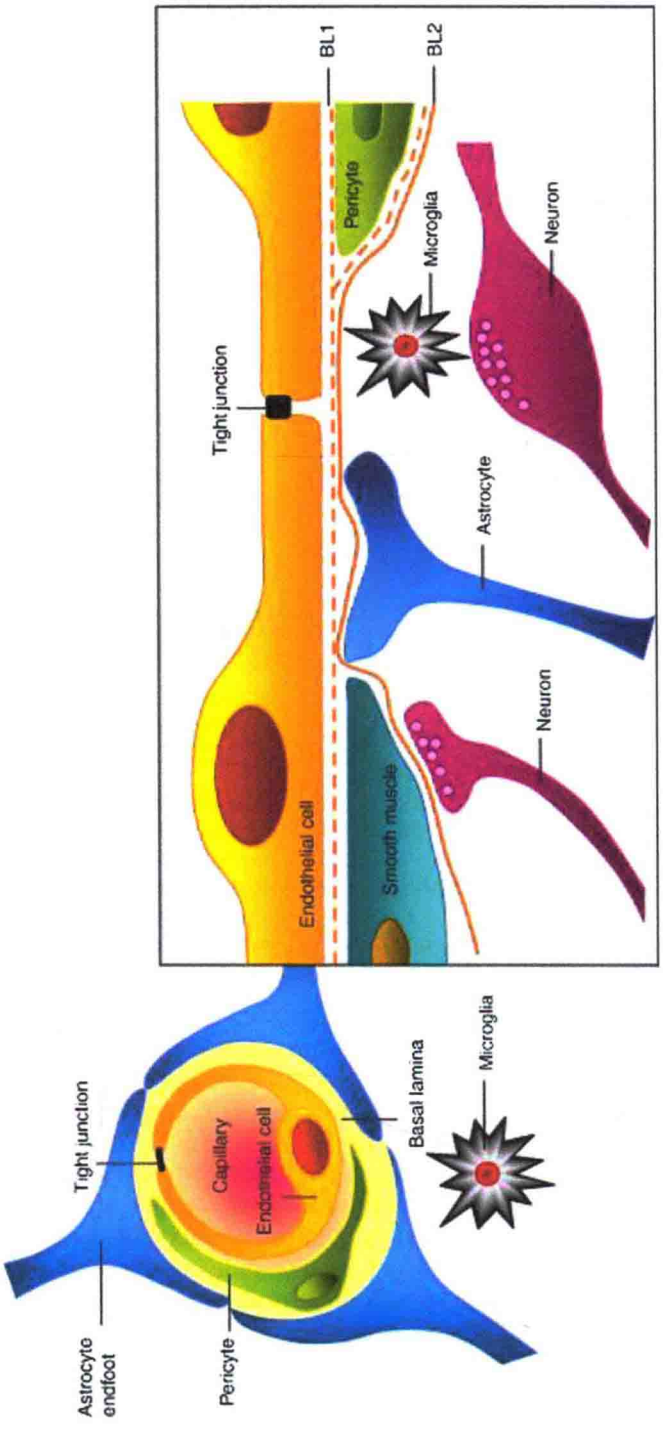

Figure 1.3 The cell associations at the BBB.
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Although the innate immune system is the dominant system of host defence in most organisms, it offers no long-term protection, whereas the adaptive immune system allows for both a stronger immune response and immunological memory.

The brain represents an immunologically privileged site which was long considered to be isolated from the central immune system owing to the presence of the BBB, lack of a draining lymphatic system to allow the uptake of potential antigens and the reputed immunoincompetence of microglia. CNS autoimmunity and neurodegeneration were presumed to be automatic consequences of the encounter of immune cells with CNS antigens. However, is now recognized[9] that the CNS is neither isolated nor passive in its interactions with the immune system and that it is involved in a constant interplay with the innate and the adaptive immune systems. Peripheral immune cells can cross the intact BBB, CNS neurons and glia actively regulate macrophage and lymphocyte responses, and microglia are most certainly immunocompetent but differ from other macrophage/dendritic cells in their ability to direct neuroprotective lymphocyte responses, playing an important role in innate immune responses of the CNS. How neuroimmune cross-talk is homeostatically maintained in neurodevelopment and adult plasticity is still not clear, although accumulating evidence suggests that neurons may also actively participate in immune responses by controlling glial cells and infiltrated T cells.[10] Many diseases of the CNS, such as stroke, multiple sclerosis (MS) and neurodegeneration, elicit a neuroinflammatory response with the objective of limiting the extent of the disease and supporting repair and regeneration.[11] However, various disease mechanisms lead to neuroinflammation contributing to the disease process itself.

Neuroinflammation occurs when there is chronic activation of the immune response in the CNS. Microglia are key players of the immune response in the CNS and the innate and adaptive immune responses triggered by microglia include the release of proinflammatory mediators. Microglia within the CNS parenchyma are activated in virtually all CNS diseases.[12] TLRs, a major family of pattern recognition receptors that mediate innate immunity but also link with the adaptive immune response, provide an important mechanism by which microglia are able to sense both pathogen- and host-derived ligands within the CNS. Upon recognition of their cognate ligands, TLR proteins initiate a signalling cascade[13] in order to turn on both common and unique pathways (Figure 1.4). All receptors of the superfamily, except TLR3, use MyD88 to initiate their signalling pathways.[14] Depending on which of the TLRs are activated, the subsequent signalling will either be MyD88 dependent or MyD88 independent, although some receptors have the ability to activate both types of pathway. Once MyD88 is bound to the TLR, IL receptor associated kinases (IRAK) 1 and 4 are phosphorylated and form oligomers with the tumour necrosis factor receptor associated factor-6 (TRAF-6). The oligomer interacts with transforming growth factor β-activated kinase (TAK1), *via* the TAK1-binding protein (TAB2), to activate IκB kinase (IκK). IκK is responsible for tagging IκB for degradation by phosphorylation and once IκB

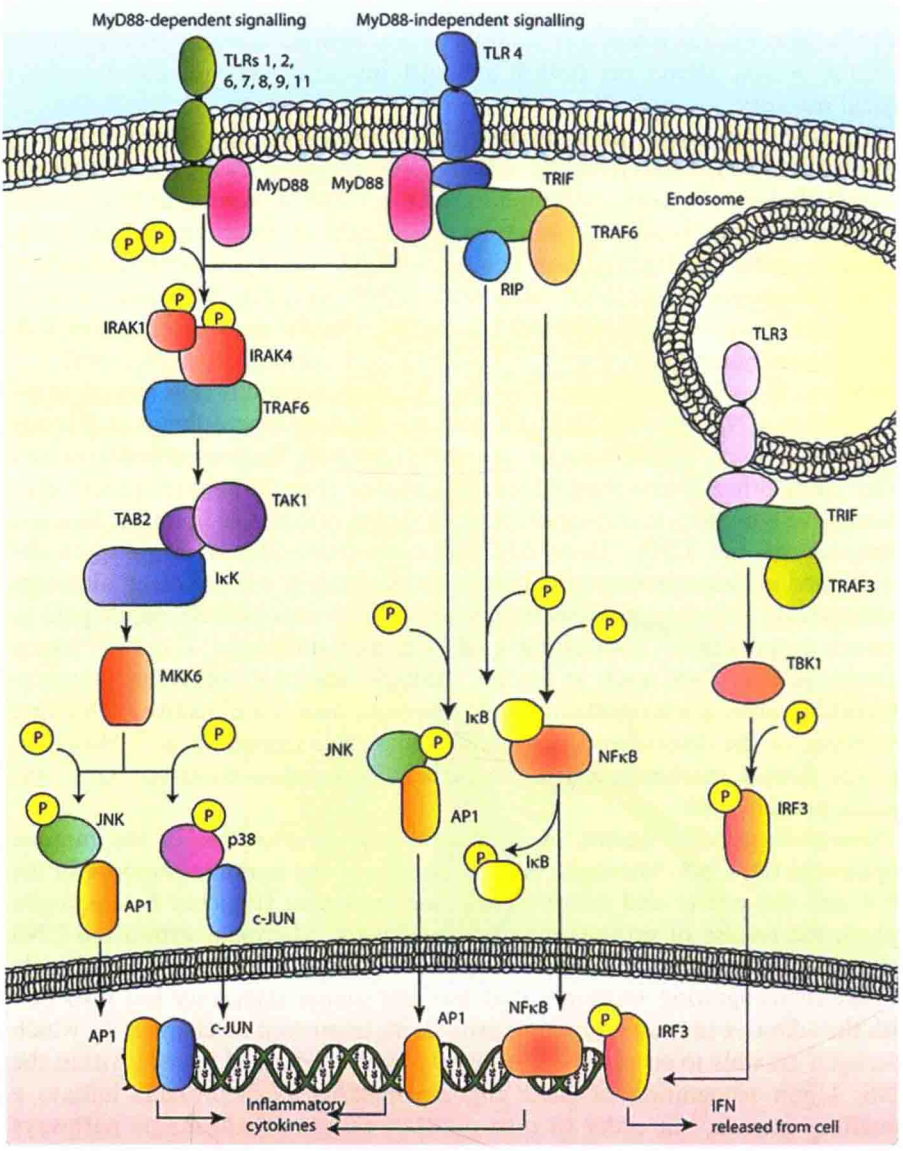

Figure 1.4 A diagram of the toll-like receptor (TLR) pathways, indicating MyD88-dependent signalling on the left, MyD88-independent signalling on the right and TLR3 only signalling on the upper right.
(Reproduced from Downes and Crack[14] with permission from Wiley).

is degraded, NFκB is free to move to the nucleus and begin transcription of various inflammation-associated genes. TAK1 is also responsible for the activation of mitogen-activated kinase kinase 6 (MKK6), which phosphorylates c-Jun N-terminal kinase (JNK) and p38. Their activation leads to