Macrophage Function Disorders

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Advanced article

Article Contents

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Macrophages are sentinel cells of the innate immune response. Macrophages recognise pathogen-associated molecular patterns (e.g. microbial products) and endogenous ligands (e.g. apoptotic cells) through a broad and adaptable range of pattern-recognition receptors. The consequence of this recognition is generally effective clearance via phagocytosis; however, when this is not effective, macrophages may become inappropriately activated and initiate an inappropriate inflammatory response. Because macrophages are extremely variable in phenotype and function and share a common ancestry with monocytes and dendritic cells, there are very few genes that are expressed exclusively in macrophages. Consequently, macrophage-specific immunodeficiencies are rare. There are, however, a number of genetic immunodeficiencies that affect macrophage function. In addition, as macrophages are exquisitely attuned to their microenvironment, their function appears to be adversely affected by and contributes to chronic inflammatory conditions such as cancer, atherosclerosis and obesity. Thus, genetic deficiencies, in addition to microenvironmental dysregulation, can contribute to macrophage function disorders.

Introduction

Macrophages are a heterogenous family of cells whose phenotype and function depend considerably on their tissue microenvironment and can change considerably with exposure to infectious and antigenic agents. They are relatively long-lived, biosynthetically active cells and express diverse surface receptors and secretory products. They adapt readily to changes in their milieu and help to maintain homoeostasis locally and systemically. If unable to deal adequately with an infectious or injurious stimulus, macrophages initiate a chronic inflammatory process, which can contribute to persistent tissue damage; they can also mediate acute, sometimes massive, responses from other cell types and organ systems (Mukhopadhyay *et al*., 2009).

Although primary deficiencies of macrophage function in human disease are relatively uncommon, macrophages contribute to, and play a central role in, many major disease processes. These include storage diseases, chronic infections and immunological disorders, as well as responses to metabolic injury (**Table 1**). Macrophages may participate in the pathology of disease by producing secretory products or by altering functional phenotype, which can be characterised by changes in the expression of their receptors (for further information see Taylor *et al*. (2005)). Herein the authors discuss a subset of macrophage functions, focussing especially on their role in infectious and chronic diseases, and highlight the recent advances in human genetics that contribute to our understanding of macrophage function disorders. **See also**: Inflammation: Chronic; Macrophages

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Macrophage Functions

In 1883, Ellie Metchnikoff described highly motile, amoeboid-like cells that were associated with phagocytosis or 'eating' particulates of either exogenous (e.g. bacterial) or endogenous (e.g. damaged host cells) origin (Metschnikoff, 1884). Since then it has become clear that the diversity of macrophage function is dazzling and includes such

Table 1 Diseases in which macrophages play a significant role

	Type	Example	Mechanism
1.	Storage	Gauche's disease	Genetic lysosomal hydrolase deficiency
		Haemosiderosis	Secondary Fe^{2+} accumulation in reticuloendothelial system
		Hasmochromatosis	Primary Fe^{2+} overload (also other tissues)
2.	Chronic inflammation	Silicosis and asbestosis	Nondegradable, bioactive particle accumulation in the lungs and the pleura
		Rheumatoid arthritis	Autoimmune destruction
		Inflammatory bowel disease	Defects in intracellular sensing of bacteria lead to a skewed cytokine response
3.	Infection	Septic shock (Gram-negative and -positive)	Release of vasoactive mediators and cytokines, especially tumour necrosis factor α and interleukin 1β
		Tuberculosis	Cellular immunity activates MØ, via interferon γ
		Malaria	Uptake of parasitised erythrocytes and release of mediators
		Acquired immune deficiency syndrome	Human immunodeficiency virus infects M0 and CD4 T cells leading to failure of cellular immunity
		Dengue virus	Antibody-dependent enhancement leads to increased infection of FcγR-expressing cells
4.	Metabolic injury	Atherosclerosis	Oxidised lipopratelns induce foam cell formation in major arteries
		Alzheimer disease	Nondegradable amyloid peptide induces MØ secretion of neuratoxic products
5.	Malignancy	Cancer	Mϕp within the tumour microenvironment facilitate angiogenesis, extracellular-matrix remodelling and promote tumour cell motility

disparate activities as memory generation (Derecki *et al*., 2011), thermoregulation (Nguyen *et al*., 2011) and embryonic development (Hopkinson-Woolley *et al*., 1994). Generally speaking, macrophages have two major functions, phagocytosis (and subsequent processing of internalised matter) (Whelan *et al*., 2012) and production of proinflammatory, antiinflammatory and angiogenic factors such as cytokines. These two functions are essential for both host defence and homoeostasis and require plasma membrane and cytosolic pattern-recognition receptors (PRRs).

Pattern recognition

Macrophages bind and phagocytose microbes and particulates, and initiate inflammatory responses that recruit leucocytes to a site of infection or tissue damage. This response is mediated by proinflammatory cytokines and chemokines produced by macrophages following pathogen or danger signal recognition. Macrophages express a variety of PRRs that are able to recognise conserved molecular patterns, both pathogenic and harmless. Molecular patterns derived from microbes and viruses, such as bacterial cell wall components and viral deoxyribonucleic acid/ribonucleic acid (DNA/RNA) sequences, are known as pathogen-associated molecular patterns (PAMPs), or microbe-associated molecular patterns as these conserved components are not unique to pathogens. Host molecules that are indicative of tissue injury, including heat shock proteins and extracellular adenosine triphosphate (ATP), can similarly be recognised by PRRs, and are known as danger-associated molecular patterns (DAMPs). Detection of PAMPs or DAMPs by PRRs activates signalling cascades that induce the production of proinflammatory molecules and ultimately activation and maturation of the macrophage (Mukhopadhyay *et al*., 2009). **See also**: Innate Immune Mechanisms: Nonself Recognition

PRRs are expressed both on the cell surface and intracellularly (**Figure 1**). Intracellular PRRs can be localised to either the endosomes or to the cytosol, allowing macrophages to recognise both extracellular and intracellular PAMPs. Three broad classes of PRRs exist, namely toll-like receptors (TLRs), nucleotide-binding domain and leucine-rich repeat (LRR) containing receptors (NLRs), and retinoic acid-inducible gene I-like receptors (RLRs). Genetic studies in mice and rare cases of mutations in humans have demonstrated that these receptors are vital for the host defence against infectious diseases. As such, mutations and polymorphisms in PRR genes can contribute to autoimmune disorders, chronic inflammatory conditions and conditions such as septic shock, in which an overactive immune response can lead to death. **See also**: Pattern Recognition Receptor

TLRs

TLRs recognise a broad range of microbial products, host-derived molecules and synthetic agents (**Table 2**; Kawai and Akira, 2010). The 13 known mammalian TLRs (10 human and 13 mouse) can be divided into those found

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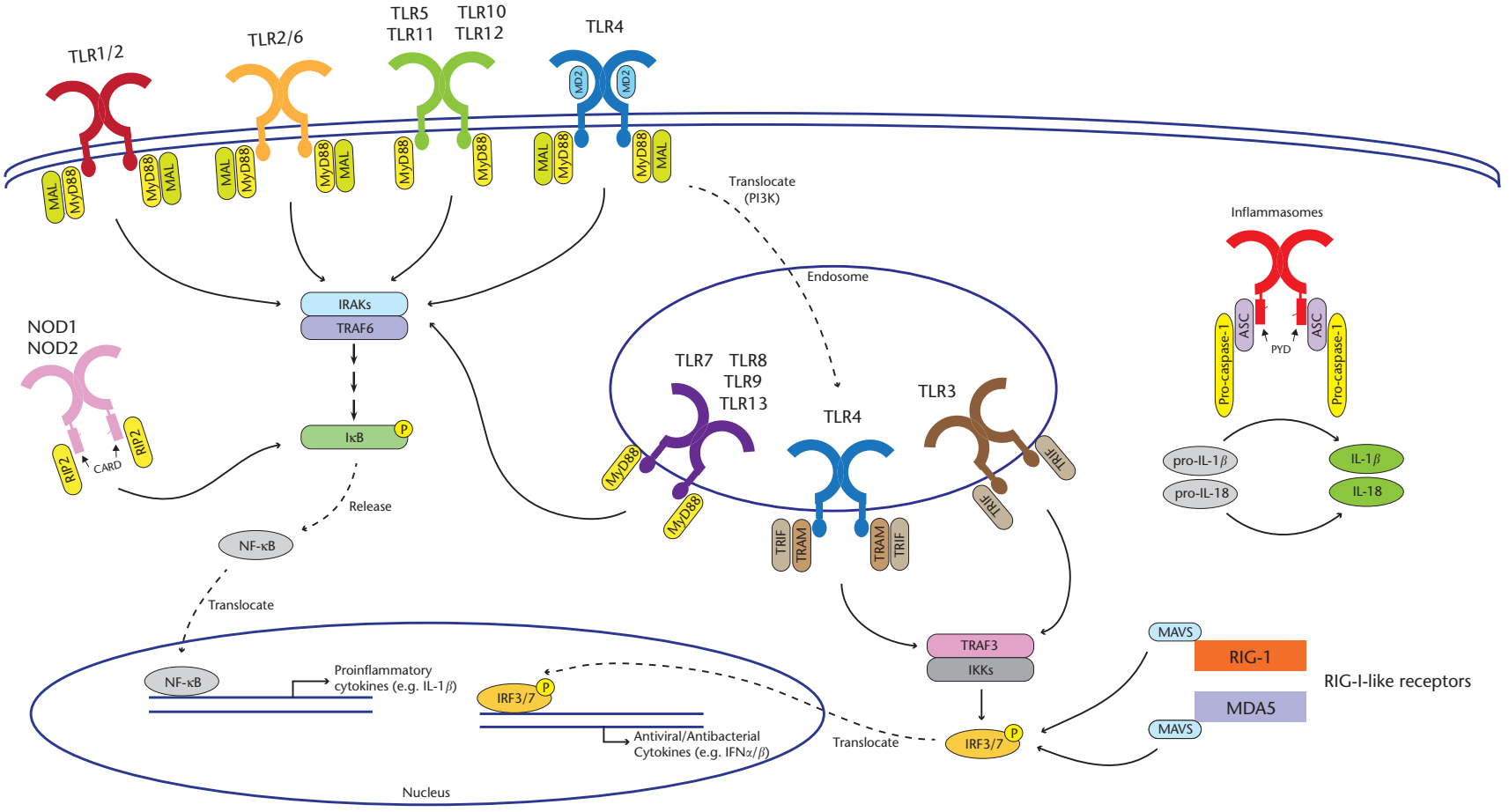

Figure 1 Inflammatory PRRs expressed by macrophages. The surface expressed TLRs (TLR1,2,4,5,6,10,11 and 12), recognised conserved bacterial and fungal components including both bacterial cell wall components (LPS, LTA and lipoproteins), flagellin components and some host ligands. Most of these surface expressed TLRs require coreceptors (e.g. CD14 and MD2, CD36) for efficient binding and signalling (not pictured). These receptors use the common adaptor protein MyD88 and some (TLR2 and TLR4) may also signal from the endosome using alternative adaptor proteins to induce an interferon response. The endosomal-restricted receptors, TLR3, 7, 8 and 9 recognise bacterial and viral nucleic acids and induce NF-κB and in the case of TLR3 an antiviral response via the induction of interferon. The cytosolic RIG-1 or MDA5 sense viral nucleic acids and induce interferon responses, whereas the inflammasome recognises bacterial cell wall components (e.g. peptidoglycan) and other ligands to induce formation of the inflammasome and production of IL-1β.

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Table 2 Selected pattern-recognition receptors and their ligands

Localisation	Receptor	Ligands
Cell surface	TLR1/2	Triacylated lipopeptides
	TLR2/6	Diacylated lipopeptides, lipoteichoic acid, and zymosan
	TLR4	Lipopolysaccharide, host proteins (e.g. heat shock protein and fibrinogen), viral proteins (envelope and fusion proteins) and taxol
	TLR5	Flagellin monomers
	TLR10	Unknown
	TLR11[a]	Profilin
	TLR12[a]	Unknown
	SR-AI/II	Lipid A, LTA, bacterial lipoproteins, asbestos, modified LDL and apoptotic cells
	MARCO	LPS, environmental particles, bacteria (ligands unknown) and trehalose dimycolate
	CD36	Modified LDL and *Plasmodium falciparum* parasitised erythrocytes
	MINCLE	Trehalose dimycolate and SAP130 (endogenous nuclear protein)
	Dectin1 and2	β-glucan
Endosomal	TLR3	dsRNA, poly(1:C), siRNA, and viral ribonucleic acid (RNA)
	TLR7	single-stranded RNA (ssRNA) and synthetic agonist R848
	TLR8	ssRNA
	TLR9	Unmethylated ssDNA containing CpG motifs
	TLR13[a]	Vesicular stomatitis virus, conserved bacterial 23S ribosomal RNA (rRNA) sequence
Cytosolic	NOD1	meso-diaminopimelic acid (m-DAP) (l-Ala-gamma-d-Glu-m-diaminopimelic acid), iE-DAP
	NOD2	Muramyl dipeptide
	NLRP1	Toxin from *Bacillus anthracis*
	NLRP3	*Staphylococcus aureus*, influenza A virus, extracellular adenosine triphosphate (ATP) and hyaluronan
	IPAF	Bacterial flagellin
	RIG-I	5′ triphosphorylated short double-stranded RNA (dsRNA)
	MDA5	dsRNA

[a]Mouse only.

intracellularly and those expressed on cell surfaces. TLR3, 7, 8, 9 and 13 are expressed on endoplasmic reticulum membranes or in endosomal compartments, where they detect microbial nucleic acids. TLR9 recognises microbial unmethylated single-stranded DNA (ssDNA) containing CpG motifs, whereas TLR3, 7 and 8 recognise microbial single-stranded RNA (ssRNA) or double-stranded RNA (dsRNA). TLR13 has been recently identified as an intracellular TLR that recognises vesicular stomatitis virus and a conserved bacterial 23S rRNA sequence. The remaining TLRs (TLR1, 2, 4, 5, 6, 10, 11 and 12) are expressed on the cell surface, where they detect whole bacteria or their components (Barbalat *et al*., 2011).

Crystal structures of TLRs suggest that they share a common structure that includes an extracellular LRR domain, a transmembrane helix and an intracellular toll/interleukin-1 receptor (TIR) domain. The LRR domain contains 20–25 LRR modules, each of which is composed of 20–30 amino acids and contain a characteristic LxxLxLxxN motif. Together, the LRRs form a horseshoe-shaped solenoid structure. Crystal structures of various TLR–ligand complexes suggest that TLR ligands bind this extracellular LRR domain directly or with the help of an accessory protein, as in the case of TLR4, which associates with the MD-2 protein to bind lipopolysaccharide (LPS). A single transmembrane α-helix connects the *C*-terminus of the extracellular LRR domain to an intracellular TIR domain, composed of a parallel β-sheet surrounded by α-helices. These TIR domains recruit TIR-domain-containing adaptor proteins to initiate a signalling cascade.

TLR–ligand binding induces homo- or heterodimerisation of the respective extracellular LRR domains, with both *C*-termini coming in close proximity. Although most TLRs form homodimers, several exceptions exist. TLR2 heterodimerises with TLR1 or TLR6. TLR4 can form a TLR4–TLR4 homodimer, it can also form a heterodimer with TLR6. Dimerisation induces conformational changes in the TLR, resulting in the recruitment of a limited number of adaptor proteins (myeloid differentiation primary response gene 88 protein (MyD88), TRIP, TIR-domain-containing adaptor-inducing interferon-β (TRIF)-related adaptor molecule (TRAM), MyD88-adaptor-like protein or TIR-domain-containing adaptor protein (Mal/TIRAP) and SARM). These adaptor proteins mediate signal transduction, resulting in the activation of various transcription factors, such as nuclear factor kappa-light-chain-

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enhancer of activated B cells (NF-κB). The recruitment of different adaptor proteins and the subsequent differences in kinetics and the type of transcription factors activated determine the specificity of the response generated.

All TLRs, with the exception of TLR3, recruit MyD88 to the cytoplasmic TIR domain on activation. TLR2 and TLR4 require Mal/TIRAP as a bridging adaptor to recruit MyD88 to the TIR domain. MyD88 subsequently recruits serine–threonine kinases IRAK1, 2 and 4, forming a large signalling complex that then associates with tumour necrosis factor (TNF)α receptor-associated factor 6 (TRAF6). As an ubiquitin protein ligase, TRAF6 catalyses additions of K63-linked ubiquitin chains on itself, NF-κB essential modulator (NEMO), transforming growth factor-β-activated kinase-1 (TAK1) and TAK1 binding proteins (TAB1, TAB2 and TAB3). A TRAF6/IRAK-1/TAK1/TAB2/NEMO complex is formed and phosphorylates inhibitor of nuclear factor kappa-B kinase subunit alpha (IKKα) and IKKβ, kinases that phosphorylate IκB. This results in the release of the transcription factor NF-κB, which is normally sequestered in the cytoplasm by IκB. NF-κB then translocates to the nucleus and induces expression of genes encoding proinflammatory cytokines such as interleukin (IL)-1β, IL-6 and TNFα. These cytokines act systemically to induce fever, stimulate the production of acute phase proteins and act locally to activate macrophages and induce the production of chemokines, which triggers cellular recruitment to the site of infection.

TLR4 is also capable of signalling through a MyD88-independent pathway to upregulate type 1 interferon (IFN) expression. Initially, LPS activation of TLR4 forms the aforementioned TLR4–TIRAP–MyD88 cell surface complex and induces the production of proinflammatory cytokines through NF-κB. Through the actions of p110δ isoform of phosphatidylinositol-3-OH kinase (PI(3)K), TLR4 releases the TIRAP–MyD88 complex and is subsequently internalised into an endosomal compartment. Here, TLR4 associates with TRAM, which recruits TRIF allowing TLR4 to signal through a TRIF-dependent pathway. This pathway independently activates both NF-κB and interferon regulatory factor 3 (IRF3) transcription factors. TRIF is able to recruit TRAF6, inducing NF-κB in a fashion similar to MyD88 pathway. TRIF is also able to form a complex with TRAF3 and other IKKs. This complex phosphorylates IRF3, which then translocates as a dimer to the nucleus and upregulates the transcription of IFNα and IFNβ, crucial components of antiviral responses that have also recently been demonstrated to be important in the antibacterial responses. TLR2 has also been demonstrated to induce IFNα/β signalling, although the signalling pathways are less well characterised.

TLR3 can only signal through the MyD88-independent, TRIF-dependent pathway and functions similarly to TLR4 but can bind TRIF directly without TRAM. The resultant upregulation of antiviral, type 1 IFNs is appropriate given that TLR3 is an endosomal and nucleic-acid-sensing TLR. Although the other nucleic-acid-sensing TLRs (TLR7, 8, 9 and 13) can only signal through MyD88, they are still able to induce type 1 IFNs (IFNα/β) via IRF7, a constitutively expressed transcription factor found within the plasmacytoid dendritic cells. IRF7 is phosphorylated by a complex of MyD88 and other adaptor proteins and consequently able to translocate to the nucleus and upregulate IFNα/β-inducible genes. **See also**: Toll-like Receptors

NLRs

NLRs are soluble, cytoplasmic sensors of PAMPs and DAMPs (Rathinam *et al*., 2012). In humans, 23 NLRs have been identified. These NLRs can be categorised into subfamilies, including nucleotide-binding oligomerisation domain-containing proteins (NODs), NACHT, LRR and PYD domain-containing proteins (NLRPs) and ICE-protease-activating factor (IPAF). All NLRs contain three distinct domains, a *C*-terminal ligand-sensing LRR domain, a central nucleotide-binding and oligomerisation (NACHT) domain and a variable *N*-terminal domain that could either be a caspase activation and recruitment domains (CARD), an effector pyrin domain (PYD) or a baculoviral IAP repeat (BIR).

NOD1 and 2 recognise certain bacterial peptidoglycan motifs. On activation, NOD1 and 2 self-oligomerise via their NACHT domains. The CARDs of NOD1 and 2 then bind the CARD domain of receptor-interacting protein 2 (RIP2), also known as RIPK. In a fashion similar to the MyD88 pathway, IκB becomes phosphorylated, allowing NF-κB to translocate to the nucleus, where it upregulates genes involved in host defence.

NLRs also lead to the release of proinflammatory cytokines, such as IL-1β and IL-18, via the formation of cytosolic inflammasome complexes. On ligand binding, several NLRs, including NLRP1, NLRP3 and IPAF, assemble inflammasomes composed of a homoligomerised NLR, procaspase-1 and apoptosis-associated speck-like protein containing a CARD (ASC). The NLR within the inflammasome is responsible for recognising a variety of PAMPs and DAMPs. For example, NLRP3 recognises various viruses and endogenous danger signals, such as the extracellular ATP, whereas IPAF responds to bacterial flagellin. When the inflammasome is activated, procaspase-1 matures into caspase-1 and cleaves pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18, inducing a proinflammatory response. However, for the NLR, which has a PYD but not a CARD, to associate with the CARD of the procaspase-1, ASC is required to link the molecules, as it itself contains both a PYD and a CARD.

RLRs

The RLRs are a second class of PRRs that recognise cytosolic products of viral replication, such as dsRNA, and induce a strong antiviral type 1 IFN response. The RLR family includes retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5) and laboratory of genetics and physiology 2 (LGP-2). All three RLRs share a central RNA helicase domain that has

ATPase activity and a *C*-terminal repression domain that can bind dsRNA. Subtle differences to the modifications of dsRNA confer specificity to either RIG-I or MDA5. For example, RIG-I recognises RNA that is 5′-triphosphorylated, including that derived from orthomyxoviruses and flaviviruses. MDA5, however, appears to be specific to Picornaviruses, whose RNA is covalently linked to a small protein, virion protein genome-linked protein (Vpg) rather than possessing triphosphorylated 5′ ends. RIG-I and MDA5, but not LGP-2, also have *N*-terminal CARDs, which are involved in signal transduction on RIG-I dimerisation. As such, LGP-2 is unable to induce downstream signalling and likely functions as a negative regulator of RIG-I and MDA5.

On RNA binding, RIG-I and MDA5 dimerise and recruit interacts with adaptor protein mitochondrial antiviral signalling (MAVS), also known as IPS-1, CARDIF and VISA, via CARD–CARD interactions. In addition to a CARD domain, MAVS also contains a *C*-terminal transmembrane domain that targets MAVS to the outer mitochondrial membrane. The purpose of such a localisation sequence has yet to be determined. MAVS then activates an IKK-related kinase, which in turn activates IRF3 and IRF7, transcription factors that upregulate the expression of antiviral type I interferons. Additionally, MAVS recruits other adaptor proteins that activate NF-κB, thereby inducing a proinflammatory response.

Phagocytosis

Macrophages phagocytose pathogens or particulates using opsonins such as complement or antibodies via complement and Fc receptors, respectively (Swanson and Hoppe, 2004). Alternatively, phagocytosis may occur through recognition of conserved patterns on the bacteria or particle directly. Although it is not clear how phagocytic receptors generate signals, it is clear that they transmit information about the size and shape of the particle that they engulf (Champion *et al*., 2008, 2007) and possibly even irrespective of whether the particle is immunogenic or nonimmunogenic, and these observations are controversial (Blander and Medzhitov, 2004; Russell and Yates, 2007). Opsonin-dependent phagocytosis has been covered in many excellent reviews (Swanson and Hoppe, 2004). Descriptions of the major nonopsonic phagocytic receptors are given below. **See also**: Phagocytosis; Phagocytosis: Enhancement

Scavenger receptors

The scavenger receptors are a diverse family of receptors, which share the common function of binding modified lipoproteins. These receptors are involved in both host defence by recognising bacteria, viruses and microbial products such as bacterial proteins, LPS, double-stranded RNA and lipoproteins. These receptors are also associated with motility, antigen presentation, and modulation of inflammatory TLR signalling. Knockout mice are susceptible to infectious disease, autoimmunity and an atherosclerosis-like phenotype (Mukhopadhyay *et al*., 2009; Greaves and Gordon, 2009). In humans polymorphisms are associated with an increased cancer risk for certain types of cancer (Rennert *et al*., 2005) and infectious disease (Ma *et al*., 2011). **See also**: Scavenger Receptors: Structure, Function and Diversity

C-type lectins

The C-type lectins were originally defined as containing a calcium-dependent carbohydrate domain that binds to carbohydrates; however, many proteins with extremely high homology do not bind carbohydrates or do not require calcium for binding. Consequently, membership to this super family is based on evolutionary conservation rather than a strict adherence to the original definition. C-type lectin receptors include the mannose receptor, dectin-1, DC-SIGN and the soluble receptors mannose binding lectin. These receptors bind bacterial and yeast cell wall components such as mannose, β-glucan or other sugars. These receptors often signal through immunoreceptor tyrosine-based activation motifs, or through the Syk kinase pathway. In addition to their role in phagocytosing bacteria and fungi, they are also associated with cell adhesion, tissue remodelling, complement activation and endocytosis (Kerrigan and Brown, 2009, 2011). Decreased expression of phagocytic receptors and subsequent defects in phagocytosis are associated with COPD (Hodge *et al*., 2003) and patients who have mutations that prevent dectin-1 expression or function are susceptible to fungal infections (Ferwerda *et al*., 2009). **See also**: Immunity to Fungi

Macrophage Phenotypic Diversity

Macrophage phenotypes are extremely diverse. In the 1980s it was discovered that treating murine macrophages with a bacterial LPS and the cytokine interferon gamma resulted in synergistically increased killing capacity and enhanced antigen presentation (Pace and Russell, 1981). This phenotype is called ‘classically activated’ or ‘M1’. Subsequently, it was found that stimulating macropahges with IL4 or IL13 resulted in an increase in phagocytic capacity but reduced killing capacity (Stein *et al*., 1992). These macrophages were termed ‘alternatively activated’ or the ‘M2’. Since then, changes in macrophage phenotype have been associated with engulfment of apoptotic cells, adhesion, exposure to IL10, binding immune complexes and interactions with tumours. Although attempts have been made to create a unified nomenclature (Martinez *et al*., 2008), this has been complicated by differences between humans and mice and has led some macrophage biologists to speculate there are probably as many macrophage phenotypes as there are microenvironments in the body. In fact, tumour-associated macrophages consist of at least six distinct phenotypic and functional phenotypes (Qian and Pollard, 2010). Macrophages are under constant instruction from cytokines and other soluble factors in

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their immediate vicinity. The most common macrophage phenotypes are described below but although they are useful learning tools for describing macrophage phenotypes, there is considerable variation within species, experimental models and even within *in-vitro* systems.

Classical activation (M1)

Exposure to interferon Γ (IFNΓ) and a TLR agonist (e.g. microbes or their products) results in macrophages that are said to be classically activated. These macrophages express high levels of major histocompatibility complex (MHC) and CD80/86, which increases their capacity as antigen presenting cells. Immune activation by IFNΓ is central to host resistance to many intracellular pathogens as it induces the production of nitric oxide synthase (iNOS), superoxide radicals and a number of proteolytic enzymes. Failure to produce or respond to this cytokine as a result of recessive genetic defects results in persistent or disseminated mycobacterial and other infections in mice and humans.

IFNΓ-activated macrophages also contribute to tissue injury in delayed-type hypersensitivity reactions, by enhancing cytolytic activity and proinflammatory mediator production. Such macrophages are primed to respond to LPS and other microbial ligands by massive release of cytokines such as TNFΓ, contributing to direct endothelial injury and septic shock. **See also**: Hypersensitivity: T Lymphocyte-mediated (Type IV)

Alternative activation (M2)

The presence of a parasitic infection or certain allergens results in T-cell polarisation to a Th2 phenotype and results in the subsequent production of IL-4 and IL-13. Exposure to IL-4 or IL-13 results in alternatively activated macrophages. These cytokines enhance endocytosis, due in part to the expression of the phagocytic receptors mannose receptor and dectin-1, and an increased MHC class II expression. In mice, alternatively activated macrophages produce arginase but decrease the expression of iNOS, thereby reducing the capacity of these cells to kill intracellular pathogens. Alternatively activated macrophage*s* have been implicated in the host response to parasites, allergic asthma, fibrosis and may promote healing of inflammatory reactions.

Innate activation

The presence of IFNΓ is not characteristic of all infectious diseases and thus, there is a hypothetical niche for a macrophage subset that is altered in response to microbial pathogens in the absence of a secondary cytokine stimulus. Macrophages exposed to TLR agonists increase the expression of several receptors (e.g. macrophage receptor with a collagenous structure (MARCO) and CD200) independent of a secondary stimulus (Mukhopadhyay *et al*., 2006). The scavenger receptor MARCO increases the phagocytic capacity of the macrophage towards broad classes of bacteria (which can be completely unrelated to the initial stimuli) and bacterial products. The role of these innately activated macrophages is only beginning to be explored.

Regulatory macrophages

As mentioned above, classically activated macrophages are essential for host defence; however, the inflammatory response must be controlled in order to protect the host from unnecessary tissue damage. Macrophages that are stimulated with a TLR and high-density antibody–antigen (immune) complexes, which are found during the resolution of inflammation, adenosine, which is released during cell damage, or prostaglandin E2, which is required for the resolution of infection, produce high levels of IL10 and inhibit IL-12 production. These macrophages express high levels of MHCII and B7, present antigen and do not appear to be involved in the wound-healing process. These regulatory macrophages are functionally distinct from classically and alternatively activated macrophages (Fleming and Mosser, 2011).

Deactivated macrophages

The presence of IL-10 or other antiinflammatory mediators, such as glucocorticoids, can induce a state of deactivation in macrophages that have been exposed to bacterial products. IL-10 is produced during the course of infection and inflammation and acts in an autocrine manner to reduce proinflammatory cytokine production, which results in a decrease in T cell activation. The importance of IL-10 is confirmed in IL-10 knockout mice, which have increased mortality in response to a number of experimental infections due to overwhelming inflammatory responses. Systemic treatment with IL-10 has been proposed as a therapy for a number of diseases characterised by chronic inflammation including inflammatory bowel disease, rheumatoid arthritis, chronic viral infections and fibrosis, with limited success.

Role in Disease

Chronic inflammatory diseases

Chronic low-grade inflammation (as measured by elevated circulating cytokines) is observed in a number of diseases such as cardiovascular disease, obesity and cancer. Whether chronic inflammation is a cause or a correlate of disease is not entirely clear; however, macrophages, as major producers of inflammatory cytokines have been implicated as a source of this inflammation. The cause of dysregulated inflammation is unclear but macrophage function is further altered in the context of the microenvironment, and this contributes to the progression of many chronic inflammatory conditions. **See also**: Inflammation: Chronic

Cancer

Macrophages contribute to tumour formation, cancer progression, metastasis and invasion but are also required for effective control of cancer (Coussens and Pollard, 2011; Joyce and Pollard, 2009). Cancer is considered a chronic inflammatory disease because the inability of macrophages to eliminate cancerous cells leads to an inflammatory response. This inflammatory microenvironment seems to contribute to tumour progression. Distinct macrophage phenotypes have been identified that are associated with invasion, metastasis, angiogenesis, immunosuppression and successful tumour control (Qian and Pollard, 2010). Studies in animals and humans have demonstrated that modifying the number of macrophages within a tumour, reducing macrophage antigen presentation or motility, altering their ability to take up apoptotic cells and reducing the amount of macrophage-produced angiogenic cytokines all affect the rate of cancer progression (Coussens and Pollard, 2011; Yi *et al*., 2011). Modulation of macrophage responses may lead to novel cancer immunotherapies (Coussens *et al*., 2013). (For a detailed explanation of how chronic inflammation contributes to macrophage impairment and promotes cancer, see Coussens *et al*. (2013).)

Obesity

Macrophages regulate metabolism both during the course of infection and in the steady state (Nguyen *et al*., 2011; Biswas and Mantovani, 2012). During the course of infection, glucose, lipid, amino acid and iron metabolism all undergo profound changes in order to release energy for the metabolically costly processes of macrophage activation or to sequester nutrients from pathogens. These changes in metabolism are regulated by proinflammatory cytokines. Obesity has a number of defining metabolic features including insulin resistance, impaired glucose tolerance, dyslipidaemia and increased adiposity. Obesity is a chronic inflammatory condition in which adipocytes release a number of proinflammatory cytokines and chemokines that attract macrophages (Weisberg *et al*., 2003; Xu *et al*., 2003). As macrophages accumulate in the adipose tissue, their phenotype changes to become more like a classically activated macrophage and they become avid producers of proinflammatory cytokines. Manipulation of macrophage phenotype has been demonstrated to reduce obesity in a number of experimental models (reviewed in Johnson *et al*. (2012).)

Atherosclerosis

Atherosclerosis is a thickening of the arterial wall due to the accumulation of fatty acids and cholesterol. A hallmark of atherosclerosis is the accumulation of lipid-laden macrophages, known as foam cells, at the sites of atherosclerotic lesions. The uptake of modified low-density lipoproteins via surface-bound lipid and scavenger receptors cause the macrophages to acquire a 'foamy' appearance. Although these macrophages may be effective in retaining cholesterol in plaques within the endothelial wall of the aorta for decades, eventually plaque rupture can cause myocardial infarction or strokes. Macrophages within plaques contribute to inflammation by secreting cytokines such as TNF-α and IL-1β, which further supports oxidised low-density lipoprotine (oxLDL) uptake (Koltsova *et al*., 2012; Hashizume and Mihara, 2012). OxLDL is itself a mediator of inflammation because it is a ligand for TLR-4 and consequently oxLDL uptake by macrophages induces the production of reactive oxygen species (ROS) and the expression of proinflammatory cytokines (Bae *et al*., 2009). The inflammatory microenvironment of the atherosclerotic plaque is chemoattractive to inflammatory monocytes, which contribute to the inflammatory microenvironment. Although macrophages certainly contribute to the pathology of atherosclerosis, individuals whose macrophages maintain efficient lipid and cholesterol metabolism in the absence of robust inflammation, the progression of the disease may be slow and macrophages may be atheroprotective. (For a comprehensive discussion of the role of macrophages in the promotion of and protection from atherosclerosis, see Swirski and Nahrendorf (2013).) **See also**: Macrophage Foam Cells

Primary Immunodeficiencies in Macrophage Function

Infectious disease

Primary immunodeficiencies are hereditary defects in one or more components of the immune system. Many primary immunodeficiencies have been identified and they vary considerably in aetiology, severity, patient prognosis, mode of heredity and pathology (Al-Herz *et al*., 2011). These disorders are rare, and most are confined to a few families. Nevertheless, primary immunodeficiencies are of considerable interest to clinicians and scientists as they present an opportunity to study the effects of specific immune defects in humans. Primary immunodeficiencies where function or regulation of macrophages is disrupted have the potential to offer insights into the normal activity of these cells. **See also**: Primary Immunodeficiency Affecting the Innate Immune System

To date, much of what is known about the function of the various cells of the immune system comes from the study of mouse models of disease. Mouse models have been critical in developing our understanding of macrophages in diseases such as atherosclerosis and cancer. However, it is becoming increasingly evident that mouse models are reaching their limit. Despite great similarity between the human and mouse genomes, the immune systems of these two species do have some key differences. Some striking differences between the structure of the immune system in humans and mouse include the balance of lymphocytes and neutrophils (mice have a much higher proportion of

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lymphocytes), differences in macrophage response to inflammatory mediators in the innate immune system and differences in immunoglobin isotypes in adaptive immunity (Mestas and Hughes, 2004). These and other differences in key immunobiological processes present a challenge to researchers attempting to translate observations made in mice back to humans.

In contrast, primary immunodeficiencies offer researchers the opportunity to directly study immune function in humans. Significant advances in the understanding of how the human immune system defends against infection and maintains tissue homoeostasis have been gleaned through studying the aftermath of these 'experiments of nature'. Thus, primary immunodeficiencies offer crucial insights into the human immune system and highlight discrepancies that arise from studies in model organisms. Several documented forms of primary immunodeficiency have an impact on macrophage function. Owing to the systemic nature of most primary immunodeficiencies, these diseases are rarely restricted to impairing only macrophage function. Here, a selection of primary immunodeficiencies that are known to affect macrophage function is presented. However, because very few genes are expressed exclusively by macrophages, these deficiencies inevitably affect other types of immune cells, particularly other members of the phagocyte system.

Defects in macrophage activation

Macrophages are able to recognise a broad range of pathogens and respond by becoming activated and initiating an inflammatory response and processing antigens for presentation to naïve T cells. Defects in macrophage activation interfere with the ability of the immune system to recognise danger and mount the appropriate response. These diseases are characterised by recurrent infection and muted T- and B-cell responses.

One of the better studied of these diseases is inherited IFNγ receptor deficiency. IFNγ receptor deficiency is autosomal recessive and rare, but has been well studied in at least three families with a history of this defect. In all cases of this deficiency, mutations were identified in *IFNGR1*, which encodes IFNγR1 – one component of the IFNγ receptor heterodimer. Macrophages isolated from patients with this deficiency cannot become conventionally activated and consequently do not secrete the inflammatory cytokines needed for effective ROS production, inflammatory cytokine (e.g. IL-12) secretion and Th1-cell activation. Interestingly, these patients are primarily susceptible to infection by environmental mycobacteria (e.g. *Mycobacterium avium*) and the vaccine strain, Bacillus Calmette-Guérin, with relatively few confirmed cases of *Mycobacterium tuberculosis* infection. IFNγ receptor deficiency clearly illustrates the importance of IFNγ in host defence against environmental mycobacteria but indicates that its importance in *M. tuberculosis* infection is not fully elucidated in humans. A similar phenotype is observed in patients with mutations in genes encoding IL-12 Rβ1 and IL12-p40, presumably due to the requirement of IL-12 for IFNγ production (Moilanen *et al.*, 2009; Zhang *et al.*, 2008). **See also**: Genetics of Susceptibility to Mycobacterial Disease

Defects in PRRs and signalling

Macrophages are able to recognise a large repertoire of pathogens through binding of conserved ligands found on these pathogens to TLRs. Activation of TLR signalling results in the recruitment of a number of adaptor and signalling proteins and ultimately the nuclear translocation of NF-κB, eliciting a strong inflammatory response. Deficiencies in TLR signalling pathways result in the so-called 'cold infections', or infections that lack inflammation and the resulting fever response. The signalling components most commonly affected in primary immunodeficiencies include MyD88, IRAK4 – two proteins that play a role in the initial propagation and amplification of TLR signalling – and NEMO, a component of the complex that inhibits NF-κB translocation and which is ubiquitinated and degraded in the course of TLR signal transduction. Curiously, MyD88 and IRAK4 deficiencies render patients susceptible to only a narrow range of infections caused by pyogenic bacteria, particularly streptococci, without significantly impairing resistance to infection by fungi, viruses and other bacterial pathogens. This is in stark contrast to murine models of MyD88 or IRAK4 deficiency, in which mice are susceptible to a wide range of Gram positive and negative bacteria in addition to viruses and fungi, indicating that there are either differences in innate immune signalling or pathogen recognition between mice and humans (von Bernuth *et al.*, 2008).

Despite a number of defects in shared TLR adaptor proteins that have been identified, primary immunodeficiencies of the TLRs themselves are rare and the only such immunodeficiency identified to date is TLR3 deficiency. TLR3 is an intracellular receptor that primarily detects viral infections. Deficiency of this receptor results in an impaired type I interferon response and increased susceptibility to infection by viruses, particularly the herpes simplex virus. Deficiency of UNC93B1, a coordinator of intracellular TLR transport, is also known to cause similar susceptibilities.

Defects in phagocytosis and bacterial killing

On recognition of a pathogen, macrophages are able to engulf the invading microorganism through phagocytosis and proceed to destroy it through the production of ROS and activation of proteases and other antimicrobial compounds in what is referred to as the 'respiratory burst'. This process is essential to control infection. Deficiencies in the process of bacterial uptake exist, but are still poorly studied. Known deficiencies include a defect in actin polymerisation that impairs phagocytic vesicle formation. Deficiencies in the respiratory burst that kills engulfed pathogens are better studied and tend to result in severely compromised immune function.

Relatively well studied respiratory burst deficiencies include chronic granulomatous disease (CGD) and Chediak–Higashi syndrome. CGD results primarily from deficiency of one of the four components of nicotinamide adenine dinucleotide phosphate ($gp91^{phox}$, $p22^{phox}$, $p47^{phox}$ and $p67^{phox}$). A defect in any one of these four peptides will result in clinical CGD, but by far the most common form of CGD is caused by mutations in $gp91^{phox}$, which is encoded by an X-linked gene. Symptoms of CGD are severe, and typically manifest within the first year after birth. These symptoms include severe and recurrent infection, pneumonia caused by *Burkholderia cepacia* and cutaneous abscess formation. Patients with CGD form granulomas, but these granulomas are unable to mature and eliminate the infection completely. CGD, being a disease that affects superoxide production, will affect neutrophils in addition to macrophages. Defects in both these cell types contribute to the CGD phenotype (Mahoney *et al*., 1980). **See also**: Neutrophil Functional Disorders

Defects in myeloid migration

On infection, tissue-resident macrophages at the site of infection releases chemokines that attract other leucocytes to the area to help fight off the pathogen. Monocytes are amongst the recruited leucocytes and proceed to differentiate into macrophages once they have extravasated. The process of leucocyte migration and tissue invasion is tightly controlled and can be adversely affected by a number of primary immunodeficiencies. There are two distinct stages of leucocyte transmigration, the first being rolling adhesion of leucocytes in the bloodstream to epithelial tissue through the binding of receptors on the leucocyte to P- or E-selectins on the epithelial cell in what is known as rolling adhesion. The second step involves the migration of the leucocyte to the site of infection by following a chemokine gradient. Deficiencies in the molecules that mediate this process prevent the differentiation of monocytes into macrophages and thus interfere with macrophage function (Badolato, 2004).

Two major primary immunodeficiencies impair monocyte rolling adhesion, leucocyte adhesion deficiency type 1 (LAD-1) and LAD-2. LAD-1 is caused by a mutation in the gene encoding the leucocyte integrin common B_2 subunit CD18, which forms a component of LFA-1 and MAC-1 receptors, members of the CD11/CD18 glycoprotein family. These receptors mediate monocyte migration in response to a chemokine gradient and their abolishment results in impaired monocyte transmigration. Clinically, LAD-1 manifests with increased susceptibility to staphylococcal and Gram-negative infections, as well as periodontitis and gingivitis.

LAD-2 is caused by a deficiency of the guanine diphosphate (GDP)-fructose-specific transporter, which plays a role in the synthesis of the sialyl-Lewis x receptor. This receptor mediates monocytes rolling adhesion by recognising selectins on the surface of epithelial tissues. LAD-2 has similar pathology and gives rise to similar symptoms as LAD-1 (Badolato, 2004).

Chronic disease

Primary macrophage immunodeficiency has recently been implicated in a number of diseases previously thought to be unrelated, including osteopetrosis, Crohn's disease and even some types of cancer. These examples serve to illustrate the importance of macrophages in both control of infection, and in the maintenance of a number of other critical functions in the body.

Osteopetrosis

Osteopetrosis is a hereditary disease resulting from dysfunction of osteoclasts, cells that resorb cartilage during remodelling events. Osteoclasts are derived from the same precursors as monocytes/macrophages and a primary immunodeficiency would affect both cell types. Symptoms of osteopetrosis include bone brittleness and anaemia. The mechanism underlying this disease is still unknown, but it has been found that osteoclasts in patients with osteopetrosis are deficient in carbonic anhydrase. Bone marrow transplantation has been shown to be an effective treatment for osteopetrosis, in combination with the finding that monocyte function is unaffected, led to the hypothesis that osteopetrosis should be categorised as a macrophage primary immunodeficiency (Atkins and Findlay, 2012).

Crohn's disease (CD)

CD is an inflammatory disorder of the bowel commonly attributed to T-lymphocyte-mediated chronic inflammation. However, the aetiology and the underlying biochemical mechanisms contributing to CD pathology remains poorly defined. Recent studies have implicated a primary immunodeficiency of macrophages as a likely candidate for the causative agent of CD. Macrophages isolated from CD patients are defective in the production of chemotactic cytokines, which in turn translates into impaired neutrophil recruitment and bacterial clearance in response to bacterial invasion of tissues. The accumulation of bacteria then results in the chronic inflammatory phenotype that is clinically associated with CD patients.

The genetic basis of this deficiency in cytokine production has remained elusive. Defects in gene expression and translation have been ruled out and it now appears that the cytokines are degraded in the cytosol before they can be secreted. This appeared to be a lysosome-mediated effect, as treatment with lysozyme inhibitors restored normal cytokine levels. Taken together, these observations lead to a model of CD whereby an unknown defect in cytokine trafficking leads to a primary deficiency in tissue-resident macrophages, which in turn results in a secondary chronic inflammatory condition (Korzenik and Dieckgraefe, 2000). **See also**: Molecular Genetics of Crohn Disease

Cancer

Single nucleotide polymorphism linkage studies have identified an association between mutations in *MSR1* and prostate cancer. *MSR1* encodes CD204, a member of the

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macrophage class A scavenger receptors, and seven single amino acid substitutions have been identified in patients with a family history of prostate cancer. Two of these mutations are predicted to result in nonfunctional copies of CD204: Arg293X and Asp174Tyr. Arg293X results in a truncation that results in a product lacking most of the collagenous domain and the cysteine-rich domain. Asp174Tyr lies in the α-helical coil domain of CD204 and has been predicted to result in the inability of CD204 to assume its proper homotrimer conformation. Although much further work remains to be done, the results of these linkage analyses suggest that a macrophage scavenger receptor deficiency may play a role in the aetiology of prostate cancer (Yi *et al*., 2011).

Concluding Remarks

Macrophages are extremely adaptable cells that respond to microenvironmental changes and inflammatory insults, whether sterile or infectious. They are involved in every disease process in which there is persistent tissue injury or metabolic disturbance. They mediate acute as well as chronic inflammation, and promote repair through removal of dead cells and fibrin by phagocytosis and fibrinolysis, induce blood vessel ingrowth (angiogenesis) and modulate fibroblast invasion and production of extracellular matrix. They produce mediators that mobilise systemic responses of the host including fever, release and catabolise stress and other hormones, increase metabolic activity of other cells and influence blood flow to tissues and capillary permeability. They display considerable heterogeneity in both phenotype and functions. The study of macrophage biology and their involvement in human disease is therefore an avenue for potential therapeutic intervention.

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