

Monocyte Populations Which Participate in Chronic Lung Inflammation

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Introduction

Monocytes are a member of the family of mononuclear phagocytes, which are composed of monocytes, macrophages, and dendritic cells. These cells play a crucial role in the innate immune response but are also essential for adaptive immunity. Very importantly, these cells also exert a major influence on both acute and chronic inflammatory reactions. Each of the members of this family is made up of multiple subtypes, and our understanding of the regulation of their function is still not fully developed. In this chapter we will review current knowledge regarding the function of monocytes and macrophages, and in particular we will examine the role of these cells in chronic inflammatory responses in organ systems such as the lung.

Monocyte Development

Monocytes develop from precursor cells in the bone marrow, and the precise nature of this maturation process is still not fully understood. It is possible to identify cell populations that give rise to mature monocytes and distinguish them based on the expression of certain cell surface markers. Monocytes develop from

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hematopoietic stem cells (HSCs) that are renewable, and these cells reside in the bone marrow for long periods of time [1–4]. These HSCs are pluripotent and have the capacity to develop into common lymphoid precursors and common myeloid precursor cell populations which, in turn, develop into mature lymphocytes, dendritic cells, monocytes, and granulocytes (Fig. 1). The development of the common myeloid progenitor (CMP) and common lymphoid progenitor represents the first branch point in the differentiation of the HSC, and the CMP express a phenotype which can be detected based on the expression of cell surface markers CD34 and CD117/cKit, together with the loss of the stem cell antigen (Sca1) (Fig. 1). These cells do not express the lineage-, monocyte-, dendritic-, or granulocyte-specific markers (i.e., Lin-) and at this stage are still capable of development into any of these hematopoietic cell types [2, 5]. In the bone marrow the CMP population gives rise to the granulocyte/macrophage progenitor (GMP), a population that acquires the expression of both CD16 and the receptor for colony-stimulating factor (CSF-1R).

The GMP population appears to be programmed to preferentially develop into erythrocyte progenitors, and this bias is only interrupted in the presence of certain myeloid colony-stimulating factors. Perhaps the most significant of these factors is CSF-1 (alternatively termed macrophage colony-stimulating factor (M-CSF)) [2, 5, 6], a cytokine which influences hematopoietic cell development only after the transition of the CMP population to GMP. A deficiency in CSF-1R in mice results in deficiency of macrophages in a number of organs and tissues, including the lung [7–9]. The expression of CSF-1R is preserved through the development of mature monocytes, and CSF-1 regulates the functional activity of mature monocytes and macrophages [10–12]. Of note is the ability of CSF-1 to induce the expression of CD16 by monocytes, and CD16+ monocytes express higher levels of MHC class II, express higher levels of the proinflammatory cytokines TNF- α and IL-1 β , but exhibit reduced phagocytic activity [13–16]. Recently it has become clear that IL-34 shares many of the activities of CSF-1, and like CSF-1, this cytokine also appears to work through the CSF-1R [7].

The GMP stage of development is followed by the emergence of cells which have committed to the development of monocytes or dendritic cells (Fig. 1), and these cells are designated monocyte/dendritic cell progenitors (MDP). These cells can be identified by a reduced expression of CD117/cKit, combined with expression of the CX3CR1 (the fractalkine or CX3CL1 receptor). These cells are capable of proliferation in response to a variety of signals, including CSF-1 under noninflammatory conditions. In contrast, during inflammatory conditions the expansion and further maturation of these cells can be strongly induced through the activation of Toll receptors TLR2 and TLR4 [17]. The proliferation of these cells in the bone marrow in response to Toll receptor ligands serves to expand the reservoir of monocyte progenitors during the initial period of inflammation and/or infection. This selective proliferation of monocyte precursors is coincident with a substantial loss of overall cellularity in the bone marrow following infection [17, 18].

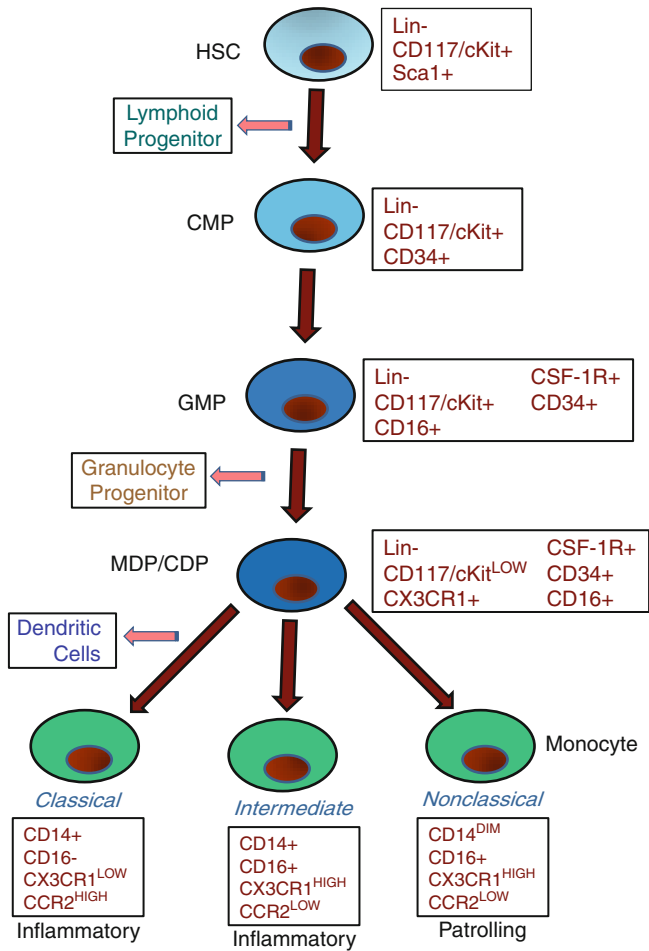


Fig. 1 Development of monocytes and dendritic cells from hematopoietic stem cells. Hematopoietic stem cells (HSC) reside in the bone marrow and give rise to common myeloid progenitors (CMP). These cells further develop into the granulocyte/macrophage progenitor (GMP) population and then into myeloid/dendritic progenitor cells (MDP). At this stage, these cells can further differentiate into either dendritic cells or monocytes before exit from the bone marrow

In humans, it is estimated that 3×10^{11} monocytes are released from the bone marrow per day [2]. However, the emigration of monocytes from the bone marrow is altered during periods of inflammation or in response to infection. Research carried out with mice suggests that the major stimulus of monocyte emigration from the marrow is mediated by CCL2 and its receptor CCR2. Moreover, during periods of inflammation or infection, blood levels of CCL2 increase, and CCR2, CCR5, and CX3CR1 are major regulators of greater monocyte traffic [19–25].

These studies have been confirmed by work showing that CCR2 knockout mice exhibit substantial monocytopenia, and this duplicated in genetically normal mice treated with inhibitors of CCR2 [26]. Current evidence using experimental animals suggests that the influence of CCL2 is greater for the Ly6c⁺ monocyte subset (roughly equivalent to the human CD14⁺⁺CD16⁻ population) [19, 20, 24, 27], and this is likely due to the greater expression by these cells of CCR2 (Fig. 1). There is also evidence that monocyte emigration is promoted by chemokines which activate the chemokine CX3CR1 and CCR5, although the role of these receptors appears to be less significant [20, 25].

There are also retention mechanisms in the marrow which act to resist the emigration of monocytes. The most notable of these is mediated by the chemokine receptor CXCR4. The ligand for CXCR4 (CXCL12) is produced by marrow stromal cells, and the activation of CXCR4 on monocytes in the marrow appears to lead to the arrest of marrow monocytes. Moreover, in certain circumstances, the production of CXCL12 can lead to the loss of monocytes from the blood and into the bone marrow reservoir [5]. These results are consistent with studies which show that pharmacological inhibition of CXCR4 leads to a rapid emigration of bone marrow monocytes into the blood [26].

Monocyte Subpopulations

Monocytes comprise about 5–10 % of the circulating leukocytes in humans, and this is typically a stable frequency in the absence of inflammation or infection. Three populations of monocytes can be identified in humans based on the expression of cell surface markers CD14 and CD16, and these subpopulations exhibit the following phenotype: CD14⁺⁺CD16⁻; CD14⁺CD16⁺, and CD14^{DIM}CD16⁺ (Table 1) [2, 5]. The CD14⁺⁺CD16⁻ “classical” population is the major monocyte subset (80–90 % of circulating monocytes) and expresses high levels of the chemokine receptor CCR2 and low levels of CX3CR1 [29]. The differential expression of these receptors directs these cells to migrate prominently toward sites of inflammation, by virtue of the elevated level of CCL2 expression at these sites. These cells exhibit a weak TNF- α and IL-1 β response, but a strong IL-6, IL-8, CCL2, CCL3, and IL-10 response to bacterial LPS, a TLR4 agonist, and are typically considered “proinflammatory” [14, 30].

The CD14⁺⁺CD16⁺ “intermediate” monocyte subpopulation represents 5–7 % of the total blood monocytes, and these cells express low levels of CCR2, but high levels of both CX3CR1 and CCR5. While these cells are unlikely to migrate strongly toward tissue sources of CCL2, the expression of CCR5 presumably allows these cells to migrate to sites of inflammation where the CCR5 agonists CCL3, CCL4, and CCL5 are typically produced at elevated levels. These cells are responsive to bacterial LPS and in general produce an intermediate to high level of proinflammatory cytokines (Table 1). These cells are proinflammatory, although the precise function of these cells *in vivo* remains somewhat uncertain.

Table 1 Characteristics of human monocyte subpopulations

Feature	“Classical” CD14++CD16-	“Intermediate” CD14++CD16+	“Nonclassical” CD14 ^{DIM} CD16+
Function	Inflammatory	Inflammatory	Patrolling
Frequency (%)	80–90	5–7	6–8
Receptor expression	CCR2 ^{HIGH} CX3CR1 ^{LOW} CCR5 ^{HIGH} CD163+	CCR2 ^{LOW} CX3CR1 ^{HIGH} CCR5 ^{HIGH} CD163+	CCR2 ^{LOW} CX3CR1 ^{HIGH} CCR5 ^{LOW} CD163-
Size	Large	Large	Small
LPS-induced:			
Cytokine expression	TNF- α ^{LOW} IL-1 β ^{LOW} IL-6 ^{HIGH} IL-10 ^{HIGH}	TNF- α ^{HIGH} IL-1 β ^{HIGH} IL-6 ^{HIGH} IL-10 ^{MEDIUM}	TNF- α ^{LOW} IL-1 β ^{LOW} IL-6 ^{LOW} IL-10 ^{LOW}
Chemokine expression	CCL2 ^{HIGH} CCL3 ^{HIGH}	CCL2 ^{LOW} CCL3 ^{MEDIUM}	CCL2 ^{LOW} CCL3 ^{LOW}
TLR7/8-induced:			
Cytokine expression	TNF- α ^{LOW} IL-1 β ^{LOW}	TNF- α ^{MEDIUM} IL-1 β ^{HIGH}	TNF- α ^{HIGH} IL-1 β ^{HIGH}
Chemokine expression	CCL3 ^{LOW}	CCL3 ^{LOW}	CCL3 ^{HIGH}

Information derived from Cros et al. [28]

Finally, the CD14^{DIM}CD16+ “nonclassical” monocytes contribute approximately 5–8 % to the total circulating monocytes and express low levels of both CCR2 and CCR5 and high levels of CX3CR1. The absence of both CCR2 and CCR5 significantly restricts the ability of these cells to traffic into the extravascular tissue in response to inflammatory stimuli, since these receptors provide strong signals for extravasation. However, recent work has demonstrated that the expression of CX3CR1 provides these cells with the ability to interact with the chemokine CX3CL1 (fractalkine) expressed on the luminal surface of vascular endothelial cells [28]. This interaction results in prolonged “crawling” of these cells along the blood vessel surfaces. This prolonged crawling activity is not exhibited as prominently by either classical or intermediate monocytes. However, these cells do traffic into extravascular tissues during inflammatory reactions, so their complement of chemoattractant receptors is sufficient to permit mobilization to sites of tissue inflammation. Finally, studies conducted in mice suggest that once these cells leave the blood, they differentiate into the type of macrophage which is designated “M2” or “alternatively activated” [5]. The features of the M2 macrophages will be discussed in a section below.

The nonclassical monocytes express low levels of CD14 (which is a coreceptor with TLR4 for bacterial LPS), and this results in a much weaker cytokine and chemokine response to bacterial LPS (Table 1). However, analysis of the nonclassical monocytes shows that they are very responsive to stimulation by viral pattern Toll receptors TLR7 and TLR8 [28]. The implication of these findings is that the

nonclassical monocyte subpopulation is relatively unresponsive via bacterial pattern receptors (i.e., TLR4) but highly responsive to viral pattern receptors (i.e., TLR7 and TLR8). This suggests that these cells are very likely responsible for “patrolling” in search of anatomical sites where there might be a viral infection, but unlike the other monocyte subpopulations, these cells would be hyporesponsive to bacterial stimulation (Table 1) [28].

The capacity of the classical and intermediate monocyte subpopulations to respond via bacterial pattern receptors is consistent with the functional activity of these cell types. For example, both of these populations are highly phagocytic, and the classical subtype exhibits strong reactive oxygen and myeloperoxidase activities [28]. This is in contrast to the nonclassical subtype which is poorly phagocytic and exhibits a very weak reactive oxygen and myeloperoxidase response. These populations appear to have specialized their abilities to participate in an effective response to either bacterial or viral pathogens.

Monocyte Traffic to the Lung

Studies on the capacity of monocytes to move to sites of inflammation have led to the conclusion that monocytes have at least two distinct phenotypes. The first phenotype has previously been referred to as “patrolling” monocytes, and the second has been designated “inflammatory” [30]. The patrolling monocytes were shown to circulate in the blood and populate tissues in the absence of an inflammatory response, while the inflammatory cells traffic preferentially to sites of inflammation. These cell types can be distinguished on the basis of the expression of cell surface marker, and the major difference was found to be the expression of the two chemokine receptors CCR2 and CX3CR1 [30]. In humans, these phenotypes are now designated classical (inflammatory) and nonclassical (patrolling), and the trafficking properties of these cells now appears to be much more complex. For example, there is evidence from studies in mice that classical monocytes can convert to nonclassical monocytes *in vivo* [31–33]. In addition, classical monocytes can differentiate to dendritic cells *in vivo* under conditions of inflammation [34]. Furthermore, unlike nonclassical monocytes, the classical monocyte population is capable of transport from the blood to the marrow and back unless exposed to an inflammatory signal which mobilizes these cells to inflamed tissue [30, 31]. The influences which regulate emigration of monocytes from the marrow to the blood must be sustained in order to maintain a normal level of circulating classical monocytes.

Recent work has shown that nonclassical, but not classical, monocytes traffic to the normal lung, and these cells undergo extravasation and differentiate into lung macrophages [34]. These cells express low levels of CCR2 and CCR5, but a high level of CX3CR1. The tissue signals responsible for the transport of these cells out of the blood vessel into the lung are not understood. Classical monocytes do not appear to have the capacity to develop into lung macrophages in normal (noninflamed) tissue, but these cells do differentiate into lung dendritic cells. In contrast, classical

monocytes are strongly mobilized to the lung tissue during lung inflammation, and these cells differentiate into lung macrophages. Evidence in mice suggests that the major signal for traffic of these cells into inflamed tissue is provided by CCL2 [35].

Macrophages

Macrophages and their phagocytic capacity for microorganisms and other cellular debris were described in detail by Metchnikoff in 1905 [36]. Since that time, two key events propelled our understanding of macrophages and their functions. The first was the discovery of interferon (IFN- γ) in the early 1980s [37]. IFN- γ induces macrophages to produce proinflammatory cytokines and other mediators as well as enhancing phagocytic activity and increased antigen presentation capacity. The second was the elucidation of Toll-like receptors (TLRs) and their role in innate immunity [38, 39]. Signaling through TLRs once the macrophage has been primed with IFN- γ results in a potent antimicrobial response with the most obvious phenotype being phagocytosis and destruction of the invading pathogen. Together these two discoveries rapidly advanced our understanding of the molecular mechanisms of innate immunity to a wide variety of organisms.

Macrophages are found in all tissues and organs of the body in the absence of inflammation or tissue injury, and they serve homeostatic roles and as sentinels of infection or injury. These macrophages are considered “resident” within the tissue and are thought to be derived and replenished from the blood by CD14^{DIM}CD16+CX3CR1^{HIGH} monocytes [28, 30]. Examples of these macrophages include alveolar and interstitial macrophages in the lung, Langerhans cells in the epidermis, Kupffer cells in the liver, microglial cells and perivascular macrophages in the CNS, renal interstitial macrophages in the kidney, and osteoclasts in the bone. Macrophages can also be recruited to sites of inflammation in a number of tissues, or where tissue damage/injury has occurred. In these situations, monocytes in the blood with a CD14++CD16- phenotype are typically recruited to the site infection/inflammation in a CCR2-dependent manner [30]. Upon transit from the blood into the tissue, these monocytes differentiate into macrophages and this differentiation is highly dependent on the tissue microenvironment.

Microbial Pattern Recognition Receptors

Our understanding of innate immunity has greatly advanced with the sequencing of the human, murine, and *Drosophila* genomes. Comparative analysis of these genomes resulted in the identification of a family of ten Toll orthologues (in human), termed Toll-like receptors. These receptors play a critical role in the innate immune response, and the TLRs are expressed in several cell types of the immune system, including monocytes, macrophages, fibroblasts, and endothelial cells. The TLRs are

Table 2 General characteristics of human TLRs

Receptor	Cellular location	Microbial ligand	Organism
TLR1	Cell surface	Triacyl lipoprotein	Bacteria
TLR2	Cell surface	Peptidoglycan	Bacteria
TLR3	Intracellular	dsRNA	Viruses
TLR4	Cell surface	LPS	Bacteria
TLR5	Cell surface	Flagellin	Bacteria
TLR6	Cell surface	Diacyl lipoprotein	Bacteria, viruses
TLR7/TLR8	Intracellular	ssRNA	Viruses
TLR9	Intracellular	CpG DNA	Bacteria, viruses, protozoa
TLR10	Unknown	Unknown	Unknown
TLR11	Cell surface	Profilin-like molecule	Protozoa

Information derived from several sources [39–41]

“pattern recognition” receptors, and together with other microbial recognition receptors, these proteins play a role in the inflammatory response [39–43].

Toll receptors have the capacity to recognize conserved components and products of a wide range of microbial organisms (Table 2). These receptors have some common structural characteristics including leucine-rich repeats (LRR) that are arranged in tandem domains. This structure confers the ability of these receptors to recognize a wide range of molecules. For example, TLR4 has the capacity to recognize lipopolysaccharide (LPS), as well as the fusion protein of respiratory syncytial virus (RSV), paclitaxel, and fibronectin [42]. Furthermore, some of the TLRs can form heterodimers, and this creates additional structural diversity and expands the capacity to recognize microbial products. Examples of this are TLR1/TLR2, TLR1/TLR6, and TLR6/TLR2. Ligation of TLRs initiates a complex set of signaling cascades that are predominantly mediated through MyD88 and ultimately via the transcription factor nuclear factor- κ B (NF- κ B). The specific outcome of these signaling events varies depending on the cell type but can include cytokine and chemokine production, enhanced phagocytic activity, and production of reactive oxygen species (ROS) and nitric oxide (NO). Macrophage function and activity depends on sensing cues from the environment which are delivered primarily via cytokine/chemokine receptors in combination with TLRs.

Classically Activated Macrophages

Traditionally, activation of macrophages has been studied through the examination of events/functions of macrophages following stimulation with IFN- γ in combination with LPS. These are the macrophages described above which are designated “classically activated” or more recently “M1” cells. Upon sensing a pathogen via opsonic (antibody-mediated) or non-opsonic (pattern recognition receptors) mechanisms, these resident macrophages differentiate (or “polarize”) to the M1 phenotype.

Table 3 Genes transcriptionally upregulated in M1 macrophages

Gene name	Gene symbol
Chemokine (C-X-C motif) ligand 11	CXCL11
Chemokine (C-C motif) ligand 19	CCL19
Chemokine (C-C motif) receptor 7	CCR7
Chemokine (C-X-C motif) ligand 10	CXCL10
Chemokine (C-X-C motif) ligand 9	CXCL9
Chemokine (C-C motif) ligand 5	CCL5
Interleukin 2 receptor, alpha	IL-2RA
Complement component 2	C2
Interleukin 15 receptor, alpha	IL-15RA
Fas (TNF receptor superfamily, member 6)	FAS
Interleukin 15	IL-15
Complement component 1, s subcomponent	C1S
Complement component 1, r subcomponent	C1R
CD40 molecule, TNF receptor superfamily member 5	CD40
Interleukin 32	IL-32
Interleukin 7 receptor	IL-7R
Chitinase 3-like 2	CHI3L2
Superoxide dismutase 2, mitochondrial	SOD2
Mucin 1, cell surface associated	MUC1
Interleukin 12B	IL-12B
CD80 molecule	CD80
Poliovirus receptor	PVR
Interleukin 6	IL-6
Tumor necrosis factor (TNF superfamily, member 2)	TNF- α
Chemokine (C-X-C motif) ligand 13	CXCL13
Chemokine (C-C motif) ligand 20	CCL20
Major histocompatibility complex, class II, DO beta	HLA-DOB
Fc fragment of IgG, high affinity Ib, receptor (CD64)	FCGR1B
Information derived from Martinez et al. [44]. M1 cells are induced by treatment of macrophages with the combination of IFN- γ and LPS	

These cells produce several proinflammatory cytokines including TNF- α , IL-6, IL-1 β , and IL-12, express MHC class II, and other costimulatory molecules then drive the inflammatory process for both innate and acquired immunity. In addition, a number of chemokines are produced, including CXCL8, 9, 10, and 11 and CCL2, 3, and 5, which can call into the site of infection additional macrophages, neutrophils, and other granulocytes to assist in the elimination of the invading pathogen. At the same time, M1 cells develop enhanced phagocytic activity which is specifically designed to engulf the pathogen. Once phagocytized, the pathogen resides in a compartment called a phagosome which merges with another intracellular compartment called the lysosome. It is within the lysosome that inducible nitric oxide (iNOS), ROS, and superoxide dismutase (SOD) are present, and these agents are important elements of the antimicrobial mechanism of the macrophage. Table 3 shows a partial list of genes reported to be upregulated in expression in human M1 macrophages.

Alternatively Activated Macrophages

It has recently become apparent that macrophages can be activated in ways that do not necessarily require the presence of a pathogen, IFN- γ , or stimulation via TLRs. These macrophages are collectively referred to as “alternatively activated” or M2 macrophages. This nomenclature of M1 versus M2 cells parallels that of Th1 versus Th2 designations, but it should not be assumed that M2 polarization is tied exclusively to Th2 responses. Although Th2 cells are the major source of IL-4 and IL-13 production, there are other cells of both the innate and acquired immune systems that also produce IL-4 and IL-13 [2, 45].

There are currently three subpopulations of M2 cells that have been identified. First, M2a cells are induced by either IL-4 alone or in combination with IL-13. These cells exhibit increased expression of mannose receptor (CD206), scavenger receptors, DC-SIGN (CD209), fibronectin, complement component 5a receptor (C5aR), and IL-10 [2, 44–46]. Genes that are upregulated by IL-4 (Table 4) and are characteristic of M2 cells include the mannose receptor (CD206) and other scavenger receptors (important for pathogen sensing and lipoprotein clearance) and CD209 (involved

Table 4 Genes transcriptionally upregulated in M2 macrophages

Gene name	Gene symbol
Mannose receptor, C type 1	MRC1
CD36 molecule (thrombospondin receptor)	CD36
Insulin-like growth factor 1 (somatomedin C)	IGF1
Chemokine (C-C motif) ligand 13	CCL13
Fibronectin 1	FN1
CD209 molecule	CD209
Interleukin 1 receptor, type I	IL-1R1
Chemokine (C-C motif) ligand 18 (pulmonary and activation regulated)	CCL18
Scavenger receptor class B, member 1	SCARB1
CD14 molecule	CD14
Macrophage scavenger receptor 1	MSR1
Chemokine (C-X-C motif) receptor 4	CXCR4
Chemokine (C-C motif) ligand 23	CCL23
Toll-like receptor 5	TLR5
Complement component 5a receptor 1	C5AR1
Transforming growth factor, beta receptor II (70/80 kDa)	TGFBR2
Major histocompatibility complex, class II, DM beta	HLA-DMB
Chemokine (C-C motif) ligand 17	CCL17
Fc fragment of IgG, low-affinity III receptor	CD16
Chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)	CXCL12
Transforming growth factor, alpha	TGFA
Major histocompatibility complex, class II, DMA/B	HLA-DMA/B
CD4 molecule	CD4
Interleukin 17 receptor B	IL-17RB

Information derived from Martinez et al. [44]

in antigen presentation and costimulation) [47]. Fibronectin expression is particularly significant because it is involved with tissue repair and is also important in the development of fibrosis. Dysregulated overexpression of fibronectin may be an important factor in the lung fibrosis observed in idiopathic pulmonary fibrosis (IPF) [48].

M2b macrophages are induced by treatment with the combination of immune complexes (IC) and either LPS or IL-1 β . M2b cells exhibit an anti-inflammatory cytokine expression profile but do produce low levels of IL-1, IL-6, and TNF- α . In addition, Th2 responses and immunoglobulin class switching in B cells are promoted by these cells [2].

Finally, M2c macrophages are induced by stimulation with either glucocorticoids, IL-10, or TGF- β [2, 45]. These cells produce elevated levels of the anti-inflammatory cytokine, IL-10, and these cells can promote tissue repair, remodeling, and wound healing [2, 49]. The relationship of M2b and M2c remains uncertain, and it is not clear that the M2b and M2c phenotypes are truly distinct.

Tumor-associated macrophages (TAMs) appear to represent a hybrid of macrophage subset phenotypes. These cells reside within many solid tumors and appear to regulate angiogenesis, lymphogenesis, and tissue repair functions which promote tumor progression [50–53]. These cells share many of the characteristics of M2 cells such as expression of CD206, scavenger receptors, and TGF- β and can inhibit proinflammatory processes [54]. However, TAMs can also express certain M1 cytokines including TNF- α , IL-1 β , and IL-6 but have little capacity to produce NO or ROS [46, 55, 56]. This is an active area of research understanding the relationship between tumor cells and TAMs.

We would hypothesize that the induction and resolution of immune responses by macrophages are dependent upon local environmental status [5]. For example, in a situation where tissue has been damaged, the resident macrophages would be directed toward an M2 program of tissue remodeling, wound repair, and angiogenesis in an effort to repair the physical damage that has occurred. During an infection, one might expect an M2 macrophage response to occur near the termination of an M1 macrophage response, which would normally have resolved the infection. At the same time, the M2 macrophages would be involved in tissue remodeling and wound repair as needed. However, aberrant or chronic activation of M2 cells would likely result in inappropriate tissue remodeling, and potentially fibrosis which is observed in chronic inflammatory diseases such as idiopathic pulmonary fibrosis (IPF), or scleroderma.

Monocyte Subtype and Bacterial Infection

Macrophages are dynamic and heterogeneous cells; they undergo activation in response to various inflammatory and immune stimuli, and the mode of their activation will determine the success or failure of the host response to the infection [57]. Benoit et al. [58] compared microarray data from 12 studies on the response of human and mouse macrophages to several bacteria and bacterial components and found that the common response of macrophages to bacterial infections mainly

involves upregulation of genes involved in M1 polarization. For example, during the acute infection with *Salmonella typhi*, control of the infection is associated with an upregulation of M1 genes [58]. However, during the convalescence period, M1 macrophages are replaced by M2 macrophages. Convalescent patients who retain the M2 phenotype for prolonged periods may be more susceptible to reinfection, relapse, or the establishment of a carrier state [59].

As stated before in this chapter, the CD14^{DIM} CD16+ monocytes represent about 5–10 % of monocytes in healthy adults, they produce high levels of TNF- α [23], and they are considered to represent an activated or more mature subset than the CD14++CD16- monocytes [60]. These proinflammatory monocytes have been shown to be elevated in bacterial sepsis in adults [61–63], in neonates, and small children [64] compared to normal control subjects. In a case of self-induced urinary tract infection and sepsis with gram-negative bacteria, there was an increase in the level of TNF- α , IL-6, and monocyte colony-stimulating factor (M-CSF) followed by a rise in the number of circulating blood CD14^{DIM} CD16+ monocytes 24 h after the infection [65]. These data suggest that the accumulation of peripheral blood nonclassical monocytes is induced as a part of the response to bacterial infection.

Herra et al. [66] found an increase number of circulating CD16+ monocytes in patients with evidence of systemic or localized bacterial infection when compared to healthy controls. Sixteen patients had positive blood cultures, four patients had gram-negative pneumonia, one patient had peritonitis due to *E. coli*, and another patient had *Clostridium difficile*-associated diarrhea. In this study, infection with gram-negative bacilli appeared to promote a higher level of circulating nonclassical monocytes than gram-positive bacteria. Similar results have been reported which show an elevation of peripheral blood CD14^{DIM} CD16+ monocytes during bacterial infections including patients with erysipelas [67], hemolytic uremic syndrome (HUS) [68], and pulmonary tuberculosis [69].

Macrophage Subtypes and Bacterial Infection

In the acute phase of *Mycobacterium tuberculosis* infection, macrophages exhibit an M1 phenotype [70]. However, there is growing evidence that macrophages infected with *M. tuberculosis* can also induce an M2 polarization. There is a subset of patients who present upregulation of genes involved in Th2 immune responses who can be reversed to a Th1 response after successful treatment [71–73]. Rajaram et al. [74] demonstrated that *Mycobacteria* upregulates the expression and activity of peroxisome proliferator-activated receptor (PPAR)- γ in macrophages. The upregulation of PPAR- γ induces an M2 phenotype which in turn increases the intracellular survival of mycobacteria [74].

Leprosy is a disease that presents as a clinical and immunological spectrum. Patients develop a clinically progressive or disseminated lepromatous form versus a self-limited or tuberculoid form of the disease depending on the type of immune response that results from the infection of macrophages by the *Mycobacterium leprae* [75]. The M2 phenotype predominates in lepromatous lesions whereas the tuberculoid lesions are

dominated by M1 macrophages [76]. There is also a dynamic change in macrophage functional programs in which a shift from an M2 to an M1 phenotype occurs in patients who convert from the disseminated to the tuberculoid form of the disease.

Whipple's disease is a chronic bacterial infection caused by *Tropheryma whipplei*. In this disease, there are elevated numbers of CD163+ monocytes in the peripheral blood, and M2 cells are the predominant macrophage phenotype in the infected duodenum [77]. Moreover, M2-type chemokines and cytokines (CCL2 and IL-10) are elevated in the duodenum and in peripheral blood of patients infected with *T. whipplei* compared to healthy controls. Therefore, in Whipple's disease, there is polarization toward an alternative macrophage activation which is apparent both locally in the duodenum and also systemically in the circulation. In addition, these macrophages and monocytes produce low levels of nitrite and have a decreased capacity to exhibit an oxidative burst compared to healthy individuals. The overall anti-inflammatory milieu may facilitate the invasion of the intestinal mucosa by macrophages with impaired function, carrying *T. whipplei* which can sustain of the infection in the tissue [77].

Chronic rhinosinusitis (CRS) with nasal polyps is characterized by Th2 inflammation, and CRS without polyps by a Th1 immune response [78]. Krysko et al. [79] demonstrated that the mucosa of CRS patients with nasal polyps had an increased number of M2 macrophages when compared to CRS without polyps and controls, while the number of M1 macrophages among the patient groups was not different. This shift may be caused by IL-33, which is increased in patients with CRS with polyps, and it is known to switch the phenotype of alveolar macrophages to an M2 phenotype [80]. In addition, evidence suggests that the macrophages from patients with CRS with polyps exhibit deficient phagocytosis of *Staphylococcus aureus* [79]. This finding could explain the higher rate of colonization by *S. aureus* seen in this condition compared to controls [81]. The M2 signature combined with the deficient phagocytosis could work to prolong the inflammation in chronic rhinosinusitis with nasal polyps.

Monocyte and Macrophage Subtypes in Viral Infection

Monocytes and macrophages play a crucial role in HIV-1 persistence and contribute to the reservoir of cell-associated virus. A number of investigators have described an increase in the percentage of CD14^{DIM}CD16+ monocytes in patients infected with HIV-1 compared to seronegative controls [82–86]. In normal individuals, this subset of monocytes represents less than 10 % of the monocyte population [1]. However, Thieblemont et al. [85] found that in patients with AIDS the percentage of CD14^{DIM}CD16+ monocytes may represent up to 40 % of the total circulating monocyte cell population, and Pulliam et al. [86] found this percentage to be the highest in patients with HIV-associated dementia.

Monocytes are nearly refractory to HIV-1 infection but become susceptible to infection when they differentiate into macrophages in culture [87, 88]. As stated above, CD14^{DIM}CD16+ monocytes are a more mature subpopulation of monocytes,

and data shows that they are more susceptible to HIV-1 entry, are more permissive for replication, and harbor the virus long term [89, 90]. Furthermore, the apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3 (APOBEC3G) is associated with resistance to HIV infection. CD14⁺ monocytes express elevated levels of APOBEC3G whereas this protein is inactive in CD16⁺ monocytes [89] which may explain the increased susceptibility to infection of nonclassical monocytes. Finally, the chemokine receptor CCR5 serves as a coreceptor for M-tropic HIV-1 entry into CD4 expressing cells, and the increased susceptibility may also be explained by the enhanced CCR5 expression following monocyte differentiation [91, 92]. However, little is known regarding the effects of macrophage polarization on susceptibility to HIV infection. Results suggest that polarization into an M1 phenotype is associated with resistance to CCR5-dependent HIV-1 infection [93].

While the immune response to viruses is often largely Th1 mediated, in the case of dengue virus (DV), there is evidence to suggest that a Th2-mediated response is also involved [94]. Miller et al. [94] showed that the dengue virus binds to the macrophage mannose receptor (MR), a protein preferentially expressed by M2 macrophages, and that the type 2 cytokines IL-4 and IL-13 increase the susceptibility of macrophages to DV infection. These cytokines induce M2 macrophage polarization and MR expression. Additionally, these investigators showed that DV infection can be blocked by using an anti-MR antibody.

Merkel cell polyomavirus (MCPyV) is a new member of the two previously known human polyomaviruses JCV and BKV. MCPyV has been implicated in the oncogenesis of Merkel cell carcinoma (MCC) [95], an uncommon but aggressive neuroendocrine skin neoplasia [96]. The transmission route and the reservoir of this virus have not been fully established. There is evidence that monocytes can harbor viruses and establish a long-term reservoir. For example, the nonclassical monocytes CD14^{dim}CD16⁺ have been reported to harbor HIV [89], while Mertz et al. [97] identified two patients in which the classical inflammatory monocytes CD14⁺⁺CD16⁻ where the only reservoir of the MCPyV virus in the blood.

Human cytomegalovirus (HCMV) is an opportunistic pathogen that poses a significant health risk in immunocompromised individuals. It has the ability to evade the immune response and establish a chronic infection, and monocytes are the primary target [98]. HCMV induces an accelerated rate of differentiation of blood monocytes into macrophages, promoting migration, viral replication, and dissemination to host organ tissues [99]. Furthermore, HCMV infection induces simultaneous upregulation of genes and chemokines implicated in M1 and M2 macrophage activation with a predominance of the M1 phenotype [100].

Monocyte and Macrophage Subtypes in Parasitic Infection

Our current understanding of alternatively activated macrophages has been driven in part because of extensive investigation of these cells in parasitic infections. While most of the data comes from animal studies, there are interesting studies conducted in humans, some of which will be reviewed in this section.

Helminthic Infections

Nematodes

Intraperitoneal infection of mice with *Brugia malayi* (a nematode responsible for filarial infection) induces an IL-4-mediated Th2-type response and the recruitment of M2 macrophages. Furthermore, these alternatively activated macrophages can suppress T cell proliferation [101]. Similar results were found in studies with *Litomosoides sigmodontis*, another nematode that causes filariasis [102]. However, the role of M2 macrophages in filariasis is uncertain.

Nippostrongylus brasiliensis is an intestinal nematode that infects through the skin and migrates to the lung where it induces a strong Th2 cell-mediated immune response and activates M2 macrophages [103]. The larvae are then coughed up and swallowed. Even though *N. brasiliensis* is not retained in the lungs, there is evidence that lungs from mice infected with the parasite develop damage to the alveoli and severe airway hyperresponsiveness resembling emphysema and chronic obstructive pulmonary disease (COPD) [104].

Heligmosomoides polygyrus is a gastrointestinal nematode that triggers a Th2-type response and can induce chronic infections. An interesting fact about this parasite is that alternatively activated macrophages in this case protect the host against reinfection [105]. In this infection as in *B. malayi*, *L. sigmodontis*, and *N. brasiliensis* infection, M2 macrophages were only detected at the site of infection [102].

Trematodes

Schistosoma mansoni causes schistosomiasis, a disease that affects millions of people worldwide. Alternatively activated macrophages isolated from liver granulomas of a mouse model infected with this parasite were able to anergize T cell (CD4 and CD8) responses [106]. During this infection, a Th2 immune response dominates over a Th1 response and is thought to be protective. This is consistent with the observation that infected IL-4^{-/-} mice are unable to mount a Th2 immune response and die from acute schistosomiasis [107].

Cestodes

Taenia crassiceps infection represents a good model to study the immunopathological mechanisms involved in the parasite-host interactions that occur in cysticercosis [108, 109]. The initial response to *T. crassiceps* infection is a brief Th1 response, followed by a mixed Th1/Th2 response, and finally a predominant Th2 response [110, 111]. Alternatively activated macrophages induced by this parasite have suppressive activity and low proinflammatory properties which could be a defense mechanism to prevent a dangerous inflammatory burst [102]. In human neurocysticercosis (caused by

Taenia solium), a Th2 response promotes a silent resolution of the infection and was associated with asymptomatic neurocysticercosis [112, 113], whereas a high inflammatory profile was associated with severe disease symptoms [114].

Protozoan Infections

During the acute phase of infection with protozoan parasites such as *Leishmania*, *Toxoplasma*, *Plasmodium*, and *Trypanosoma*, a type 1 immune response with classically activated macrophages predominates [115]. However, during the course of the infection, Th2-type anti-inflammatory immune responses can also occur and attenuate exaggerated type 1 responses to avoid damage to host tissue. In human malaria, excessive production of TGF- β and IL-10 inhibit type 1 immune responses and facilitate parasite replication. However, failure to produce these cytokines is associated with severe malaria. Walther et al. [116] found significant interindividual variability in innate responses from 18 healthy subjects with recent *Plasmodium falciparum* exposure and divided them into groups depending on their proinflammatory responses. The group that mounted the highest proinflammatory response had a more rapid control of parasite growth but at the expense of developing clinical symptoms. The group that had an undetectable inflammatory response were less likely to control parasite growth but had no symptoms [116]. A balance between proinflammatory and anti-inflammatory responses is crucial for host survival. In *Plasmodium* infection, early elevated levels of IL-10 and TGF- β resulted in death from overwhelming infection from inhibition of the proinflammatory cytokines IFN- γ and TNF- α [117]. Conversely, *Toxoplasma gondii* infection of IL-10^{-/-} mice induced an uncontrolled immune response with lethal overproduction of IFN- γ and TNF- α [118].

Blood monocytes from patients with human malaria also exhibit interesting changes. In healthy malaria-exposed individuals, the majority of monocytes are classical monocytes, and in patients with acute uncomplicated malaria, the percentage of intermediate and proinflammatory monocyte subsets increases [119]. Additionally, patients with elevated levels of a unique phenotype of the CD14⁺⁺ monocyte subset that expresses CCR2 and CX3CR1 had low levels of parasitemia, suggesting that activation of this particular monocyte subset is associated with effective infection control [119].

Trypanosoma cruzi is an intracellular parasite that resides in macrophages and B cells and causes Chagas disease. As with other protozoan infections, there is an initial Th1 immune response with a subsequent switch to a Th2 response and induction of alternatively activated macrophages. These M2 macrophages downregulate the inducible nitric oxide synthase (iNOS) and hence are responsible for persistent *T. cruzi* intracellular growth and might favor chronic infection [101].

It is evident that each of the monocyte subtypes can play an important role in the innate immune response to certain parasitic infections. Excessive activation of M1 or M2 macrophages can be either protective or destructive. Hence, modulation of macrophage activation is paramount since the outcome is dependent on a careful balance between proinflammatory and anti-inflammatory responses.

Monocyte and Macrophage Subtypes in Fungal Infections

Aspergillus fumigatus is a mold that causes severe infections in the immunocompromised host. It is the leading cause of infection-related death in patients undergoing stem cell transplantation and in patients with acute leukemia [120]. Following inhalation of the conidia, the process of germination takes place within the alveolar space of individuals who are unable to mount an appropriate innate immune response. This leads to the formation of hyphae which have invasive and pathogenic properties [121]. During *Aspergillus fumigatus* infections in mice, M2 cells are the predominant alveolar macrophages present in the lungs, and they appear to have a protective effect for effective conidial phagocytosis [122]. While alveolar macrophages are the first line of defense against inhaled conidia [121], there is also evidence that circulating blood monocytes contribute to the innate immune response against these fungal elements. Serbina et al. [123] demonstrated that both human monocyte subtypes have effective phagocytosis capabilities against conidia but, interestingly, only CD14⁺⁺CD16⁻ monocytes inhibit germination. These results are surprising because CD14^{DIM}CD16⁺ nonclassical monocytes are thought to be superior to the CD14⁺⁺CD16⁻ classical monocytes in terms of their inflammatory properties [23]. Consistent with these findings are the results seen in the response of human monocytes to *Candida albicans* [124]. Even though both monocyte subsets inhibited the germination of *C. albicans* and did not differ in their phagocytosis capabilities, only CD14⁺⁺CD16⁻ cells were able to induce a strong Th17 response to effectively kill the fungus. Th17 responses induce IL-17A, an important cytokine that protects the host against systemic, mucosal, and chronic mucocutaneous candidiasis [124].

Both monocyte and macrophage subpopulations play important but different roles in the innate immune response to infection with bacteria, viruses, fungus, and parasites. Understanding the different immune mechanisms involved in various infectious diseases could lead to the development of novel biomarkers or provide targets for therapeutic intervention.

Interstitial Lung Diseases

Interstitial lung diseases (ILD) are a heterogeneous group of rare diseases that are classified together because of similar clinical, pathological, or radiographic manifestations. In general, ILD is characterized by lung parenchyma injury resulting in inflammation and/or fibrosis [125]. There is increasing evidence that suggests a profibrotic role of alternatively activated alveolar macrophages in the pathogenesis of a variety of ILD. Recent studies have shown that bronchoalveolar lavage (BAL) cells from patients with sarcoidosis, scleroderma, and idiopathic pulmonary fibrosis (IPF) exhibit elevated levels of IL1-RA, CCL17, CCL18, and CCL22 compared to healthy controls [48]. These cytokines are M2 markers, indicating an alternatively activated phenotype of alveolar macrophages in patients with these fibrotic lung diseases. Moreover, in patients with IPF, there was an enhanced expression of CD206 and additional marker of M2 macrophages. Additional results showed that while stage I

and II sarcoidosis patients had little radiological evidence of lung fibrosis, stage III and IV had much greater radiological evidence of fibrosis. Interestingly in this study, the stage I patients had similar levels of M2-associated cytokine production compared with controls, but stage III and IV patients had a substantial increase in the production of CCL17, CCL18, and CCL22. These studies also showed that stimulation of alveolar macrophages and monocytes from normal individuals with Th2 cytokines IL-10 or IL-4 induced an M2 phenotype *in vitro*, and this induction was even more pronounced in patients with fibrotic lung disease. It appears that production of CCL18 by alternatively activated macrophages induces collagen production by fibroblasts, and fibroblast production of collagen enhances CCL18 production by M2 macrophages which sustain the fibrotic process [126]. In line with these findings, several other authors have reported an upregulation of M2-associated cytokines in IPF, sarcoidosis, scleroderma, idiopathic interstitial pneumonias, asbestos-induced lung disease, and hypersensitivity pneumonitis [126–131].

CCL18 has been suggested as a biomarker of disease progression in patients with pulmonary fibrosis [127]. Studies by Prasse et al. [127] showed that there was spontaneous expression of CCL18 by normal macrophages but its production was significantly higher in BAL of patients with pulmonary fibrosis (more than 100-fold). Additionally, there was an inverse correlation between the CCL18 levels in BAL and serum, with total lung capacity (TLC) and diffuse lung capacity for carbon monoxide (DLCO). Furthermore, patients whose TLC improved over the following 6 months had a decrease in CCL18 serum concentration and patients with progressive disease had an increase in CCL18 levels [127]. A more recent study confirmed the latter results showed that patients with serum CCL18 levels above 150 ng/ml exhibited a higher mortality rate and a higher risk of disease progression [132].

As stated before in this chapter, peripheral blood monocytes are the precursors to several cell lineages including macrophages and fibrocytes. There is evidence that peripheral blood monocytes from patients with scleroderma-associated ILD have a fibrogenic potential [133]. LPS stimulation of CD14+ monocytes caused an increased upregulation of the scavenger receptor CD163 (M2 marker) and the profibrotic chemokines CCL18 and IL-10 compared to age matched controls [133]. These are interesting findings because LPS is traditionally associated with classical activation (M1), and in this case, LPS stimulation of peripheral blood monocytes of patients with scleroderma led to an M2 phenotype. Moreover, this phenotype was found on blood monocytes before their transformation into alveolar macrophages and entry into the lungs. These data suggest that monocyte phenotypes may be preprogrammed to mature into M2 macrophages while still in the bloodstream [133, 134].

Chronic Obstructive Pulmonary Disease

Alveolar macrophages play a major role in the pathogenesis of chronic obstructive pulmonary disease (COPD). The number of alveolar macrophages is increased in the lungs of patients with COPD compared to smokers without COPD even after

partial matching for cigarette exposure [135]. Macrophages from COPD patients have been reported to have impaired phagocytic activity compared with cells from healthy smokers or nonsmokers [136]. In line with these findings are the results from another study that found impaired phagocytosis to non-typeable *Haemophilus influenzae* of alveolar macrophages from COPD patients [137]. The defective phagocytic activity may promote bacterial colonization of patients with COPD and increase their susceptibility to exacerbations. Moreover, there is evidence that both healthy smokers and patients with COPD acquire an M2-polarized phenotype with a concomitant downregulation of M1-related genes [138]. These data suggest that cigarette smoke alters the polarization state of alveolar macrophages, and this would be expected to alter the status of the inflammatory response. This downregulation of M1 activity may potentially decrease host defense, leading to higher susceptibility to respiratory infections and the increased airway bacterial colonization in smokers and COPD smokers [138, 139]. The finding that cigarette smoke suppresses the expression of macrophage inflammatory genes in COPD is consistent with these results [140].

Environmental factors in the lungs of COPD patients can influence macrophage activation and polarization. Macrophages incubated with sputum from patients with acute exacerbation of COPD (AECOPD) induced arginase and mannose receptor but no TNF- α induction which is suggestive of a shift to the M2 phenotype [141]. The cytokine IL-4, a known inducer of alternative activation of macrophages, is also increased in BAL from patients with AECOPD [142]. Taken together, these data suggest that there may be a shift to the M2-like phenotype in the lungs during AECOPD. Moreover, even though it was initially thought that COPD was predominantly a Th1-mediated disease, there is now evidence that macrophages in COPD exhibit the alternative activation phenotype [138, 143]. The role of these M2 macrophages in COPD and AECOPD is still unclear. Further research is necessary to elucidate whether they play a beneficial role by suppressing the inflammatory response or whether they are harmful either by promoting the development of destructive tissue remodeling or by increasing susceptibility to opportunistic infections.

Asthma

There is evidence that the innate immune response of children with poorly controlled asthma is impaired. This was suggested by the finding that the phagocytic activity of alveolar macrophages of children with poorly controlled asthma was decreased by 50 % when compared with that seen in adults or pediatric control subjects [144]. Current guidelines for the treatment of persistent asthma include steroid therapy [145]. However, there is a subset of patients with asthma who are corticosteroid resistant. In an effort to characterize this subset of patients, Goleva et al. [145] performed gene microarray analysis of BAL cells from patients with corticosteroid-resistant asthma and found significantly higher levels of M1-related genes and decreased levels of M2-related genes when compared to patients with

corticosteroid-sensitive asthma. These results were further confirmed by results obtained from RT-PCR and analysis of protein expression. Of note, corticoid-resistant asthma patients had elevated levels of LPS and in vitro exposure of monocytes to LPS induced cellular steroid resistance. These findings suggest that endotoxin exposure may contribute to corticoid resistance in these patients [145]. Of course, it is well established that there is upregulation of Th2-type cells and cytokines in asthma [146, 147]. Furthermore, flow cytometric analysis of peripheral blood monocytes from patients with untreated asthma show that there is an increase in the proportion of the CD14^{DIM}CD16⁺ nonclassical monocyte subset in these patients [148]. Finally, the number of macrophages is increased in the lungs of asthmatic patients but, in contrast to COPD, the role of these cells in pathogenesis of asthma remains uncertain [149].

Cystic Fibrosis

Cystic fibrosis (CF) is characterized by chronic airway inflammation. Patients with CF experience recurrent cycles of pulmonary infections that are responsible for the increased mortality and morbidity of this disease. By age eighteen, 80 % of the patients are chronically colonized with *Pseudomonas aeruginosa* [150, 151]. Initial studies on peripheral blood monocytes of patients with CF showed that the patients infected with *P. aeruginosa* produce more IL-4 and less IFN- γ compared to the noninfected patients, upon exposure to *P. aeruginosa* outer membrane proteins [150]. Studies evaluating BAL alveolar macrophages from patients with CF infected with *P. aeruginosa* reported increased levels of IL-4 and IL-13 expression and decreased levels of IFN- γ , and IL-4 and IL-13 levels are inversely correlated with lung function [152]. These findings are consistent with a Th2-type immune response. Murphy et al. [153] evaluated markers of alternative and classical macrophage activation in the lungs of patients with CF with and without *P. aeruginosa* infection. These investigators found that patients infected with *P. aeruginosa* exhibited increased expression of the M2 marker, mannose receptor, and higher arginase activity, consistent with M2 activation of alveolar macrophages. Furthermore, both markers inversely correlated with the forced expiratory volume in one second (FEV1). Of note, more than half of the patients were receiving treatment with azithromycin, especially the patients who had *P. aeruginosa* infection. Murphy et al. [154] have demonstrated that azithromycin can polarize mouse macrophages to the M2 phenotype. However, in a subgroup analysis, these investigators found no difference in expression of macrophage activation markers (arginase and mannose receptor) between the CF patients treated with or without azithromycin. It appears that CF patients infected with *P. aeruginosa* exhibit an enhanced expression of M2 macrophages that is not dependent on azithromycin treatment. However, the long-term consequences of an accumulation of alternatively activated macrophages in CF are still uncertain.

Atherosclerosis

Monocytes and macrophages play a crucial role in vascular plaque formation, and the available data suggests that differences in monocyte subtype populations contribute to the pathogenesis of atherosclerosis in humans. In a group of hypercholesterolemic patients, the number of CD14^{DIM}CD16+ monocytes correlated negatively with high-density lipoprotein (HDL) cholesterol levels and was associated with an increased expression of charged apo E4, which is related to higher plasma cholesterol levels [155]. Moreover, in a large group of 247 patients with angiographic evidence of coronary artery disease (CAD), the numbers of CD14^{DIM}CD16+ monocytes were elevated compared to the control group and correlated with serum levels of TNF- α [156]. Altogether, these data suggest that the proinflammatory CD14^{DIM}CD16+ monocytes may have a potential role in the development of atherosclerotic lesions.

There is evidence that classical monocytes also play a role in the pathogenesis of this disease. Patients with acute myocardial infarction (AMI) have increased levels of both CD14⁺⁺CD16- and CD14^{DIM}CD16+ monocyte subsets. In addition, peak levels of CD14⁺⁺CD16- monocytes correlate negatively with the extent of myocardial salvage 7 days after AMI as well as with the recovery of left ventricular function 6 months after AMI [157]. This study suggests that CD14⁺⁺CD16- monocytes may promote cardiac injury and remodeling; however, the precise mechanism remains unclear.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects multiple synovial joints. Monocytes and macrophages contribute to the perpetuation of chronic inflammation as well as for the joint damage in RA [158]. The nonclassical monocytes have been implicated in several inflammatory diseases including RA. The percentage of CD14^{DIM}CD16+ monocytes is significantly increased in patients with RA when compared to healthy subjects [159, 160]. Furthermore, patients with an increased frequency of CD14^{DIM}CD16+ monocytes have more active disease indicated by tender and swollen joints, elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF). In addition, patients who respond to therapy have a decrease in the frequency of nonclassical monocytes, while the nonresponders experience an increase in frequency [159]. Baeten et al. [161] found that CD14^{DIM}CD16+ monocytes express human cartilage gp-39 (HC gp-39), a glycoprotein that has been proposed as an autoantigen in RA. These investigators also found that this monocyte subtype is increased in the peripheral blood as well as in the synovium of RA patients with active disease, and the presence of HC gp-39 in the synovial tissue correlates with radiological joint destruction [161]. Furthermore, the expression of the chemokine receptors CCR1, CCR5, and ICAM-1

is stronger in CD14^{DIM}CD16⁺ monocytes of patients with active RA [159]. Altogether, these findings suggest that nonclassical monocytes have an enhanced ability to infiltrate the inflamed joint and may contribute to joint destruction and persistence of inflammation in RA.

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