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The Interactive Role of Macrophages in Innate Immunity

Roland Osei Saahene, Precious Barnes and Samuel Victor Nuvor

Abstract

Macrophages are critical effector cells of the innate immune system that play central roles in the initiation and resolution of inflammation. They mediate resistance in response to pathogens and “danger” signals mainly through phagocytosis. Macrophages and other cells co-operate and complement one another in host defense. As innate immune cells, they also contribute to the initiation of adaptive immune responses. Therefore, appropriate activation of macrophages would aid effective immune response in curbing many infections. This chapter explores how the interaction and roles of macrophages influence outcomes during infections. It is expected that understanding these fundamental mechanisms may help stimulate research to exploit macrophages for therapeutic benefits.

Keywords: macrophage, phagocytosis, infection, innate immunity

1. Introduction

Macrophages are effector cells of the innate immune system that play central roles in the initiation and resolution of inflammation. They secrete a wide range of cytokines, chemokines, and antimicrobial mediators in response to pathogens and “danger” signals largely through phagocytosis [1]. Additionally, macrophages eliminate diseased and damaged cells and present antigens to activate the acquired immune system. Macrophages differentiate from hematopoietic stem cell-derived monocytes and embryonic progenitor cells. However, tissue macrophages mainly arise from the embryonic yolk sac and occur at sites of primary pathogen exposure [2–5]. Macrophages exist in the tissues of vertebrates, and phenotypes respond differently to different stimuli to direct the immune response. They are critical for the commencement of inflammatory responses. Pattern recognition receptors (PRRs) on the surface of macrophages recognize pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs) and as a result, activate intracellular signaling cascades for host defense. Pattern recognition receptors such as mannose receptor, dectin-1, scavenger receptors, dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin, toll-like receptors in macrophages recognize pathogens and initiate phagocytosis [6]. Plasticity and functional polarization are characteristics of macrophages. Macrophages exist in two different functional phenotypes: classically activated or M1 macrophages and alternatively activated or M2 macrophages. The M1 are activated by PAMPs and DAMPs as well as Type 1 T helper (Th1) cytokines, such
Macrophages - Celebrating 140 Years of Discovery

as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). They function as microbicidal and tumoricidal agents by producing proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6, IL-12, IL-23, and TNF-α, and also activate cytotoxic T cells [7]. M2 are induced by IL-4 and/or IL-13 and play a crucial role in phagocytosis, tissue remodeling, and wound repair and produces anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) and usually attract regulatory T cells [8, 9]. M1 potentially induces Type 1 T helper (Th1) and Th17 cells, while M2 induces Type 2 T helper (Th2) cells [10]. The interplay between macrophages and T cells is regarded as a critical link between the innate and adaptive immune systems and is essential for host defense. This chapter explores how the interaction and roles of macrophages influence outcomes during infections.

2. Macrophage-neutrophil co-operation

Macrophages and neutrophils originate from stem cells that differentiate through common myeloid progeny and play essential roles to protect the host. They employ a wide variety of antimicrobial mechanisms, such as the production of reactive oxygen species, reactive nitrogen species, and granules in their defense through phagocytosis. Macrophage-neutrophil interaction plays a critical role in both the initiation and resolution stages of inflammation. During the resolution of inflammation, macrophages produce IL-10 and downregulate IL-12, to promote tissue repair when apoptotic neutrophils are phagocytosed [11]. Macrophages secrete chemokines such as C-X-C motif chemokine ligand 8 (CXCL8) to attract neutrophils upon recognition of bacterial extracellular pathogens [12]. They secrete granulocyte colony-stimulating factor (G-CSF), IL-1β, TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF) which prolongs survival of recruited neutrophils to the site of infection [13–16]. Moreover, as principal scavengers of aging and apoptotic neutrophils, they acquire potent neutrophil antimicrobial molecules to enhance their antimicrobial capacity [17]. Neutrophils transfer intracellular microbes to macrophages to be cleared when they are phagocytosed. Neutrophils also interact with macrophages by secreting antimicrobial agents to aid in the clearance of bacterial intracellular pathogens in mycobacteriosis [18–22], in oral [23] listeriosis, in salmonellosis [24], and in legionellosis [25]. Notably, the antimicrobial capacity of macrophages in macrophage-neutrophil interaction depends on the pathogen encountered during the immune response. These include the use of neutrophil acquired lactoferrin, myeloperoxidase, against Candida albicans [26, 27], or Histoplasma capsulatum [28] and human neutrophil peptide-1 against Trypanosoma cruzi [29]. Therefore, macrophage-neutrophil co-operation boosts the antimicrobial capacity of macrophages to restore inflammation and homeostasis in innate immunity.

3. Macrophage-dendritic cell interaction

Macrophages and dendritic cells may impact the Th1/Th2 response and respond to T and B cells, through cellular co-operation and cytokine secretion. These include the use of interferon γ, IL4, IL 13, and antibodies which modulate their phagocytic and microbicidal activities. A recent study indicated that macrophages could transfer phagocytosed antigens to dendritic cells for effective antigen presentation to enhance T cell activation [30].
4. Macrophage-basophil co-operation

Until recently, the function of basophils was not investigated as they were considered as small relatives of mast cells. Basophil-derived IL-4 causes monocyte differentiation into M2 macrophage which suppresses allergic inflammation or provides immunity against helminths [31]. Lung-basophil alveolar macrophage niche is essential in the differentiation, compartmentalization, and phagocytic effects of alveolar macrophage [32].

5. Macrophage and T cell interaction

Macrophages are professional antigen-presenting cells that initiate host protection by phagocytosing pathogens circulating in the host for destruction during inflammation. They recognize a broad array of PAMPs or DAMPs using PRRs. After phagocytosis, they present pieces of foreign antigens within a major histocompatibility complex (MHC I or II) bound to its membrane surface to activate T cells. T cell activation requires three main signals which include T cell receptor (TCR)-MHC peptide, costimulatory and polarizing cytokines. T cells recognize MHC–peptide complex through TCR complexed with a cluster of differentiation 3 (CD3) for onward transmission into the cell. TCR-MHC II–peptide interaction triggers several signaling cascades within T cells. The activation of Lck and zeta-chain associated protein 70 (ZAP-70) in turn activate downstream phospholipase C-γ. This gives rise to diacylglycerol and inositol triphosphate to switch on the cell’s transcription machinery [33]. The activation of phosphorylated tyrosine-based immunoreceptor motifs of TCR/CD3 complex activates various pathways such as Ras/extracellular-signal-regulated kinase, mitogen-activated protein kinase cascade, the protein kinase C/nuclear factor-kappa B, and Ca/calcineurin/nuclear factor [34].

Macrophages express costimulatory and/or coinhibitory molecules to induce activation or inhibition of T cells. The modulation of costimulatory and coinhibitory molecules is vital to highlight the significance of macrophage functional role in T cell activation and suppression. The ultimate subset differentiation, survival, and role of T cell are determined by the costimulatory and coinhibitory ligand-receptor signal interaction between the macrophage and T cell. Different costimulatory molecules have been characterized, including coreceptor CD28, commonly expressed by naïve and primed T cells. CD28 interact with B7–1 (CD80) and B7–2 (CD86) on macrophages. The activation of T cells requires TCR-MHC–peptide complex and CD28-B7 costimulation. This interaction is essential as it promotes T cell proliferation, survival, and cytokine production. Moreover, it induces an increase in response to the production of B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra large (Bcl-xL) anti-apoptotic proteins [35]. However, failure of CD28-B7 interactions results in anergy and apoptosis of T cells.

On the contrary, several key coinhibitory molecules including cytotoxic T-lymphocyte antigen 4 (CTLA4; CD152), programmed cell death-1 (PD-1), and killer inhibitory receptors interact with ligands on macrophages to suppress T cell activation [36, 37]. CTLA-4 binds with a much higher affinity to the B7 proteins on antigen-presenting cells (APCs) than CD28. However, CTLA-4 expressed ensuing T cell activation is predominantly high compared to that of naïve T cells. During the initial priming event, T cells experience cell-cycle arrest if CTLA-4 binds to the B7 proteins and prevent CD28 engagement. T cell-expressed PD-1 binds with PD-L1 on
Macrophages and serves as a negative regulator during T cell activation. This engagement can affect the positive signals between CD28 and CD80/CD86 and inhibit T cell activation [38].

Finally, simultaneous engagement of TCR-MHC–peptide complex and costimulatory molecules requires cytokines produced by macrophages, other cells as well as

Figure 1. *Macrophages activate T cells through a series of critically important stepwise signals. After phagocytosis, macrophages (APCs) present peptide antigen within major histocompatibility complex (MHC)-II for T cell recognition. Effector T cells develop following appropriate costimulation and release of polarizing cytokines in the environment which also activates macrophages* [40].
T cells to effect cell activation. The activation of naïve CD4+ T cells by cytokines produces different subsets and dictates their functional outcome [39]. Th1 cells are produced by activation of CD4+ T cells with IL-12 and IFN-γ from APC (macrophages). Th1 cells secrete IFN-γ and TNF that activate macrophages to destroy pathogens and CD8+ T cells to combat infected cells. CD8+ T cells require cytokine signaling through IL-12 and type 1 IFN-α/β to maximize immune response. Effector CD8+ T cells kill infected cells through apoptosis by releasing perforin to act on membranes of the target cell and granzyme to enter and induce apoptosis (Figure 1) [41, 42].

6. Macrophages as a phagocytic cell

Macrophages defend the body against pathogens and play a key role in homeostasis through the removal of internal waste products and tissue repair. Phagocytosis, ingestion of large particles (>0.5 μm) into macrophages initiates the process of digestion and clearance. During phagocytosis, macrophages migrate in a chemotactic fashion toward the particles to be phagocytosed. Adhesion and particle uptake begin with the interaction of specific PRR with PAMPs or DAMPs of the particles or infected cells [6, 43]. Several PRRs have been identified to initiate phagocytosis upon recognition of PAMPs or DAMPs. These include scavenger receptor A (SR-A), c-type lectin receptors (dectin-1), and opsonin receptors (Fc receptor mainly immunoglobulin G (IgG) antibodies conserved domain, complement receptor 1 (CR1) and CR3) that binds to bacterial and fungal cell wall molecules [6, 43, 44]. The adhesion leads to polymerization of actin at the ingestion site, and the uptake through an actin-based technique [45, 46]. After absorption, F-actin is shed from the phagosome, and the newly formed phagosome matures through a series of fusion and fission events. The microbes and apoptotic cells are then destroyed by an oxygen-dependent or oxygen-independent killing mechanism.

The phagosomal NADPH-oxidase generates reactive oxygen species (ROS) and phospholipase A2 generates fatty acids for sterilization [47, 48]. Subsequently, myeloperoxidase (MPO), several hydrolases, and lysosomes fuse with the phagosome and deliver molecules that kill and degrade microbes. During this event, phagosomal pH is lowered by proton ATPase to activate an oxygen-dependent mechanism through halogenation or an oxygen-independent mechanism with lysosomal enzymes and basic sterilization proteins [49, 50]. Macrophages produce Fe2+ ions that bind with adenosine to substitute MPO.

7. The macrophage and complement system interaction

Macrophages and complement systems closely interact during which complement migrate in a chemotactic fashion and cover pathogens with C3b for efficient elimination through phagocytosis [51]. In human macrophages, a variety of complement components, including C1, C1q, C1s, C2, and C4 proteins, are expressed in the classical pathway; C3, factor B (FB) and factor D (FD) in the alternative pathway and C5 at the terminal pathway. Additionally, regulators such as factor H, factor P, factor I, and C1 inhibitor are secreted [52–55]. C2, C3, and FB are expressed, but C3 is upregulated if macrophages are stimulated with oxidized low-density lipoprotein, acetylated low-density lipoprotein, IgA or IgG immune complexes [56]. Complement regulators, such as CD46, CD55, and CD59, have been demonstrated to be expressed
by cultured macrophages isolated from peripheral blood monocytes [57, 58]. Several complement receptors including the anaphylatoxin receptors C3aR, C5aR1, and C5aR2 [59–61] and the CR1, CR3, and CR4 have been found to be expressed on the surface of macrophages [62]. Complement immunoglobulin receptor (CRIg) an opsonin receptor is known to be expressed on several tissue-resident macrophages, such as Kupffer cells [63, 64].

8. Macrophage and infection

8.1 Bacterial infection

M1 macrophages have strong microbicidal and tumoricidal agents that promote resistance against bacterial toxins and destroy infected cells [65–67]. Pathogen-associated molecular patterns recognition by PRRs stimulates macrophages to secrete M1-like cytokines, including IFN-γ, TNF-α, IL-1, IL-6, and IL-12 [68]. These induce M1 polarization to promote prolonged production of ROS to kill invading microbes [7]. However, some intracellular bacteria promote the production of IL-4, IL-13, IL-10, and TGF-β to induce M2 phenotype polarization to reduce Th1 inflammatory response [69]. Mycobacterium tuberculosis (MTB) induces M2 phenotype by stimulating the production of IL-10 to inhibit the maturation of phagosomes and promote their survival [70, 71]. Alveolar macrophages have distinctive M2 phenotypic characteristics that promote the secretion of IL-10 and TGF-β with low oxidants and small antigen presentation capacity [72]. M1 promotes the potential bactericidal properties of macrophages during MTB infection and M2 the vice versa [73, 74]. Granulomatous macrophages within the lungs of MTB patients polarize to co-express proinflammatory and anti-inflammatory markers, signifying polarization is not binary and can occur continuously [75]. Helicobacter (H) pylori, induce M1 phenotype in patients with atrophic gastritis [76]. However, a mixture of M1/M2 phenotypes has been observed in the biopsy of the gastric mucosa in patients infected with H. pylori [77]. Salmonella typhi-infected patients have also demonstrated M1-like/M2-like phenotypic transition [78].

8.2 Viral infection

Viruses attack macrophages and polarize their activation during viral infections. Polarization is essential in reducing damage to tissues. M1 phenotype polarization is key in anti-viral immunity [79]. In acute and chronic human immunodeficiency (HIV) infection, M1 macrophages are crucial in early and late anti-viral immune responses. Additionally, macrophages infected with HIV are associated with the clearance of CD8+ T cells [79–82]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) disease induce M2 phenotype [83, 84]. However, HCV suppressed monocyte polarization to M1-like or M2-like phenotype via TLR2. This leads to an impaired transducer and activator of the STAT pathway [85] or promotes a mixture of M1-like/M2-like cytokines [86]. Abnormal function of M1-like and M2-like phenotypes results in HCV infections. During human cytomegalovirus infection, infected monocytes are induced to promote M1-like/M2-like polarization in favor of M1 phenotype to upregulate IL-1, IL-6, and TNF-α secretion [87]. However, viral elimination is restricted in the late phase of the infection because of upregulated IL-10 secretion that promotes M2 phenotype activation [88]. M1 and M2 macrophages play crucial roles in both
early and late viral infection. Therefore, therapies that can inhibit M1/M2 polarization will promote better clinical outcomes.

8.3 Parasitic infection

Macrophages undergo a shift toward M1 or M2 with respect to the causative agent. M1 phenotype promotes parasite clearance and resistance to leishmaniasis while M2 phenotype mediates the growth and survival of the parasite in the host [56, 58]. Th2-derived IL-4 and IL-13 mediate worm killing in granulomas and induce clearance by the contraction of smooth muscle [89–91]. M2 macrophages in hookworm disease suppress glucose absorption and function in various immune responses [69, 92]. M2-polarized macrophage in helminthic infection plays an important role in worm elimination but predisposes infected organs to cancer [89–91]. Protozoans, such as Plasmodium, Toxoplasma, Leishmania, and Trypanosoma, induce M1 macrophage phenotype that destroys the parasite to control the infection. M1 to M2 switch occurs partially to inhibit inflammatory-associated tissue damages but promotes chronic infection [9, 71, 89–91, 93–95].

8.4 Fungal infection

Disease-causing microbes induce a favorable environment inside their host to support proliferation, invasion, and survival of the microbes [96]. Activation of macrophage polarization is a mechanism used by the fungus to aid invasion and colonization of the host [96]. The macrophage polarization state of fungal pathogens within the lungs control disease progression or resolution [72]. M2-polarized macrophages possess a potent fungicidal effect against Pneumocystis pneumonia. M2 polarization inhibition can suppress the growth of Aspergillus and several fungal pulmonary diseases that result in allergic airway infection [96]. Aspergillus fumigatus, Cryptococcus neoformans, and Histoplasma capsulatum infections are favored by M1 polarized phenotypes [96]. Candida albicans induce an M1-like to M2-like phenotype to evade the host immune response [97].

9. Conclusions

Macrophages, other cells, and complement systems have overlapping and complementary potentials that are employed in a concerted first-line defense to fight infections. Macrophage-neutrophil co-operation aid each other to fight intracellular and extracellular pathogens, respectively. Macrophages play central roles in T cell activation by initiating a cascade of step-wise signals without which T cell apoptosis or anergy occurs. Macrophage activation is not fixed as they integrate many signals, such as those from microbes, dead cells, damaged and dying cells, and the normal tissue micro-environment to dictate phenotypes and direct the immune response. Different macrophage phenotypes have both protective and pathogenic decisive roles in a large array of infections. Therefore, appropriate activation of macrophages would aid effective immune response in curbing many infections developing to diseases.

Conflict of interest

The authors declare no conflict of interest.
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