Chapter

Macrophages: The Potent Immunoregulatory Innate Immune Cells

Vijay Kumar

Abstract

Macrophages are ubiquitously present innate immune cells in humans and animals belonging to both invertebrates and vertebrates. These cells were first recognized by Elia Metchnikoff in 1882 in the larvae of starfish upon insertion of thorns of tangerine tree and later in *Daphnia magna* or common water flea infected with fungal spores as cells responsible for the process of phagocytosis of foreign particles. Elia Metchnikoff received the Noble prize (Physiology and Medicine) for his discovery and describing the process of phagocytosis in 1908. More than 130 years have passed and different subtypes and roles of macrophages as innate immune cells have been established by the researchers. In addition to their immunoregulatory role in immune homeostasis and pathogenic infection, they also play a crucial role in the pathogenesis of sterile inflammatory conditions including autoimmunity, obesity, and cancer. The present chapter describes the immunoregulatory role of macrophages in the homeostasis and inflammatory diseases varying from autoimmunity to metabolic diseases including obesity.

Keywords: macrophages, monocytes, innate immunity, inflammation, cytokines, pathogens

1. Introduction

The innate immune system evolved to protect the host from invading foreign pathogens, allergens, and different xenobiotics. The system comprises of both its cellular and humoral (circulating complement proteins, defensins, certain cytokines and chemokines secreted by innate immune cells) components. The innate immune cells comprise of epithelial cells, endothelial cells (ECs), the granulocytes (i.e. neutrophils, basophils, eosinophils, and mast cells (MCs), monocytes, macrophages, natural killer (NK) cells, dendritic cells (DCs), invariant NKT cells (iNKT cells), γδT cells, and newly described innate immune T cells called mucosal invariant T cells (MAIT) cells and innate lymphoid cells (ILCs) [1–9] (**Figure 1**). These innate immune cells are crucial to maintain the immune homeostasis and regulate adaptive immune system via acting as antigen presenting cells (APCs) along with providing other signaling molecules/factors required in the effective adaptive immune response in response to infection or other sterile chronic inflammatory diseases including, allergy, autoimmunity, cancer, and metabolic diseases including type 1 diabetes mellitus (T1DM), and obesity etc.

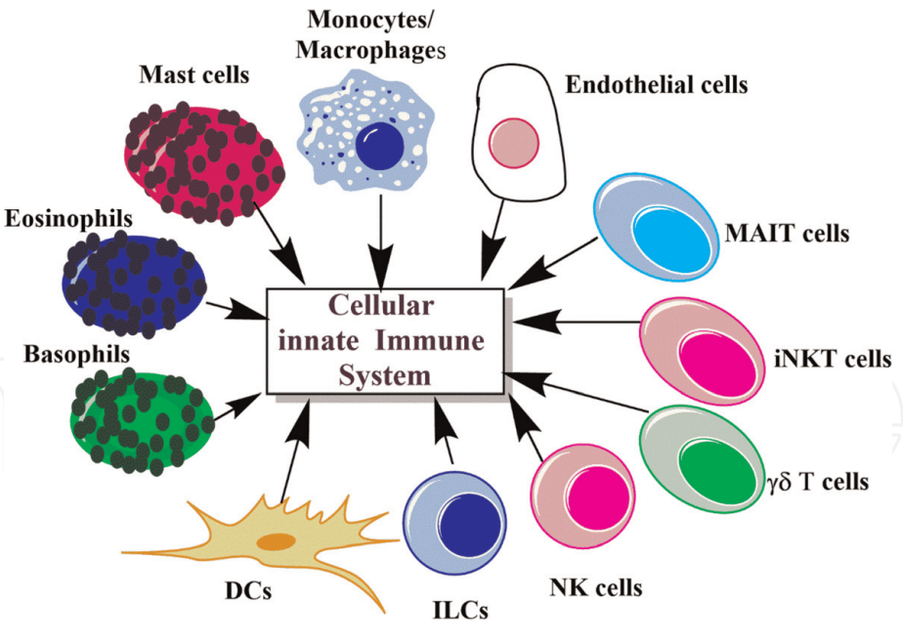

Figure 1.
Schematic representation of cellular components of innate immune system. Macrophages also comprise a very important component of innate immune system along with other innate immune cells mentioned in the figure and text.

Macrophages are type of innate immune cells that were first described by Elia Metchnikoff in 1882 in larvae of starfish upon the insertion of thorns of tangerine tree and later on in *Daphnia magna* or common water flea infected with fungal spores as cells responsible for the process of phagocytosis of foreign particles. Elia Metchnikoff received the Noble prize (Physiology and Medicine) for this discovery in the year 1908. Thus macrophages are first innate immune cells described almost 130 years ago. The continuous development in the field of immunology has established their role in various immunological and non-immunological processes including embryonic development. Along with acting as potential phagocytic cells involved in the phagocytosis of pathogens, xenobiotics, these cells also secrete various cytokines, chemokines, and growth factors including TNF-α, TGF-β, platelet-derived growth factor (PDGF), endothelial growth factor (EGF), and vascular endothelial growth factor (VEGF) [10–12]. Thus macrophages are very potent innate immune cells with diverse functions. The present chapter is intended to describe the immunoregulatory role of macrophages in the maintenance of immune homeostasis in the normal and disease stage.

2. Development of macrophages

Macrophages are the cells of the mononuclear phagocyte system (MPS) that was previously considered as reticuloendothelial system (RES), a system associated with the clearance and phagocytosis of dead cells [13]. They were included in the RES in 1924 to show their origin, residency, and renewal within RES. The RES was renamed to the MPS system in 1968 by Ralf van Furth, Zanvil Cohn and colleagues to distinguish them from polymorphonuclear leukocytes (PMNLs) or neutrophils and to show that all macrophages originate via terminal differentiation blood monocytes into different macrophages including pulmonary macrophages, liver macrophages (or Kupffer cells), and peritoneal macrophages etc. [14, 15]. The MPS comprises of monocytes, macrophages, and DCs involved in the maintenance of tissue and organismal homeostasis, the pathogenesis of inflammation, cancer,

autoimmune diseases, infection and the generation of immune response associated with the organ transplantation [16, 17].

Macrophages are developed during very early phase of embryogenesis called primitive hematopoiesis occurring at embryonic day 6.5 [E6.5]-E8.5 from precursor cells present in the extraembryonic yolk sac [18, 19]. The process of hematopoiesis in line with ontogeny progresses towards fetal liver at the beginning of E10.5 and finally to the bone marrow in the adult animal including humans [18, 19] (**Figure 2**). The primitive hematopoiesis occurring in the yolk sac of human embryos comprises of about 70% macrophages of the total nucleated blood cells at 4 weeks of gestational age, while in mice embryos macrophages predominate in the early stage of primitive hematopoiesis taking place in the yolk sac with the absence

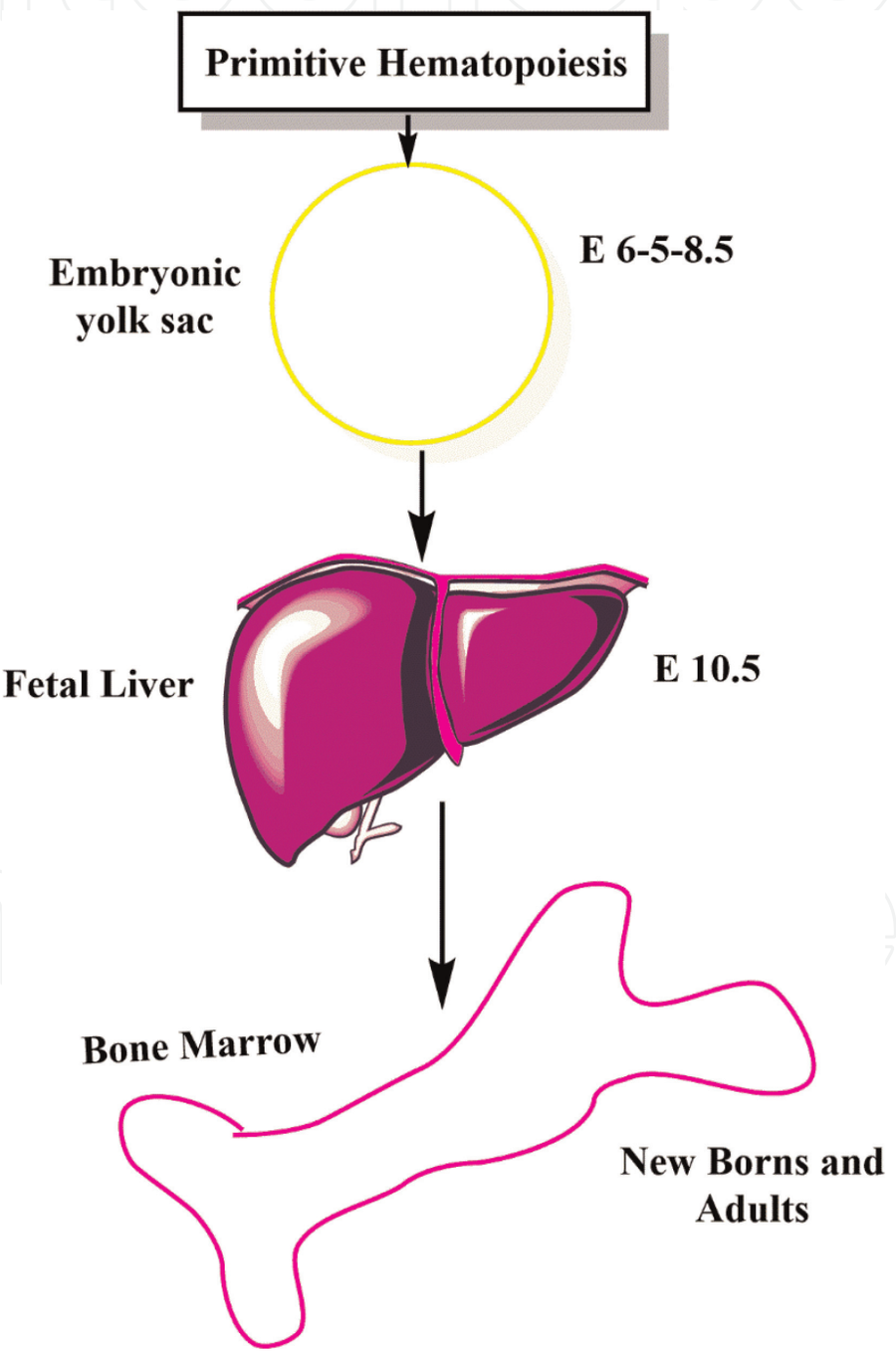

Figure 2.
Schematic representation of production of macrophages in various organs throughout the mammalian (mouse and human) development. For example, at embryonic day 6.5 [E6.5]-E8.5 macrophages develop in the extraembryonic yolk sac from precursor cells, thereafter at E10.5 they develop in fetal liver, and in neonates and adults they develop in bone marrow as mentioned in the text.

of monocytic cells [20, 21]. From embryonic day 8.5 [E8.5]-E10.5, the aorta-gonad-mesonephros give rise to hematopoietic stem cells (HSCs) giving birth to all immune lineages [19]. The cells committed to become macrophages within the mononuclear phagocyte lineage pass through morphologically-different but defined developmental stages including common myeloid progenitors (CMPs), shared with granulocytes giving rise to monoblasts, promonocytes and then monocytes that migrate to different tissues [22]. The differentiation of HSCs or hematopoietic progenitors (HPs) into different cell lineages including CMPs is governed by the activation of highly regulated gene expression programs integrated by different lineage-determining transcription factors (TFs) [23–25].

Pu.1 serves as an essential factor to reconstitute the myeloid cell lineage and for the development of macrophages and monocytes in concentration-dependent manner [24, 26, 27]. A high concentration of the TF called PU.1 promotes the macrophage development whereas a low level of PU.1 supports the B cell development due to the presence of many low- and high-affinity PU.1 binding sites in the genome [28, 29]. PU.1 is regulated by Runt-related transcription factor 1 (RUNX1) or Acute myeloid leukemia 1 protein (AML1) or Core-binding factor subunit-alpha 2 (CBFA2) that are members of core-binding factor family of TFs [30]. The gene *Csf1r* encoding the receptor for the cytokine IL-34 and monocyte-colony stimulating factor (MCSF) is one of the major targets of PU.1 in macrophage development [31, 32] *Cebp-α*, *-β*, and *-ε* are important towards the development of different myeloid cell types primarily including granulocytes, macrophages, and monocytes [33, 34]. *Irf8* also serves as a crucial TF for monocyte lineage along with DC lineage by establishing monocyte- and DC-specific enhancers [35–38]. The TF called ZEB2 is essential for the maintenance of tissue-specific macrophages and its loss causes tissue-specific changes in different macrophage populations including KCs and their subsequent loss [39]. Thus these lineage-determining TFs, establish the central macrophage program during the pre-macrophage stage. This core macrophage program includes the expression of CX3CR1, pattern-recognition receptors (PRRs), phagocytic receptors (PRs), FcγRs including FcγR1 or CD64 and various other genes including *Sirpα*, *Iba1*, *Mertk* and *Adgre1* (F4/80) expressed by almost all types of macrophages [40, 41]. A bZip TF called MAFB (c-Maf) regulates the self-renewal of macrophages and its induction is a specific and crucial determinant of monocytic program in hematopoietic cells [42, 43].

There are two principal subtypes of monocytes in mice (**Figure 3**): (1) classical Ly6c^{hi} monocytes (also called inflammatory monocytes expressing high levels of CC-chemokine receptor 2 (CCR2) but low levels of CX3C-chemokine receptor 1 (CX3CR1)) that descend directly from Ly6c^{+} monocyte progenitors [44], and (2) Ly6c^{low} non-classical monocytes expressing high levels of CX3CR1 and low levels of CCR2 that differentiate from Ly6c^{hi} monocytes through an Nr4a1 (nuclear receptor subfamily 4 group A member 1 or Nur77)-dependent transcriptional program and are less prevalent in blood [44–47]. The Ly6c^{hi} monocytes in mice represent approximately 2–5% population of the circulating white blood cells (WBCs) in a normal laboratory mouse without any infection and rapidly migrate towards the site of infection and inflammation [48]. However the deficiency of CCR2 significantly reduces the migration of Ly6c^{hi} monocytes at the site of infection and inflammation indicating the importance of CCR2 in the trafficking of these monocytes [49–51]. These Ly6c^{low} non-classical monocytes develop primarily to function within the vasculature and patrol the vasculature by crawling over the resting endothelium in an Lymphocyte function-associated antigen 1 (LFA-1) integrin and CXCR3-dependent manner [19, 52].

The non-classical monocytes patrol the vasculature to clear the damaged endothelial cells (ECs) for maintaining the integrity of endothelium, and thus the

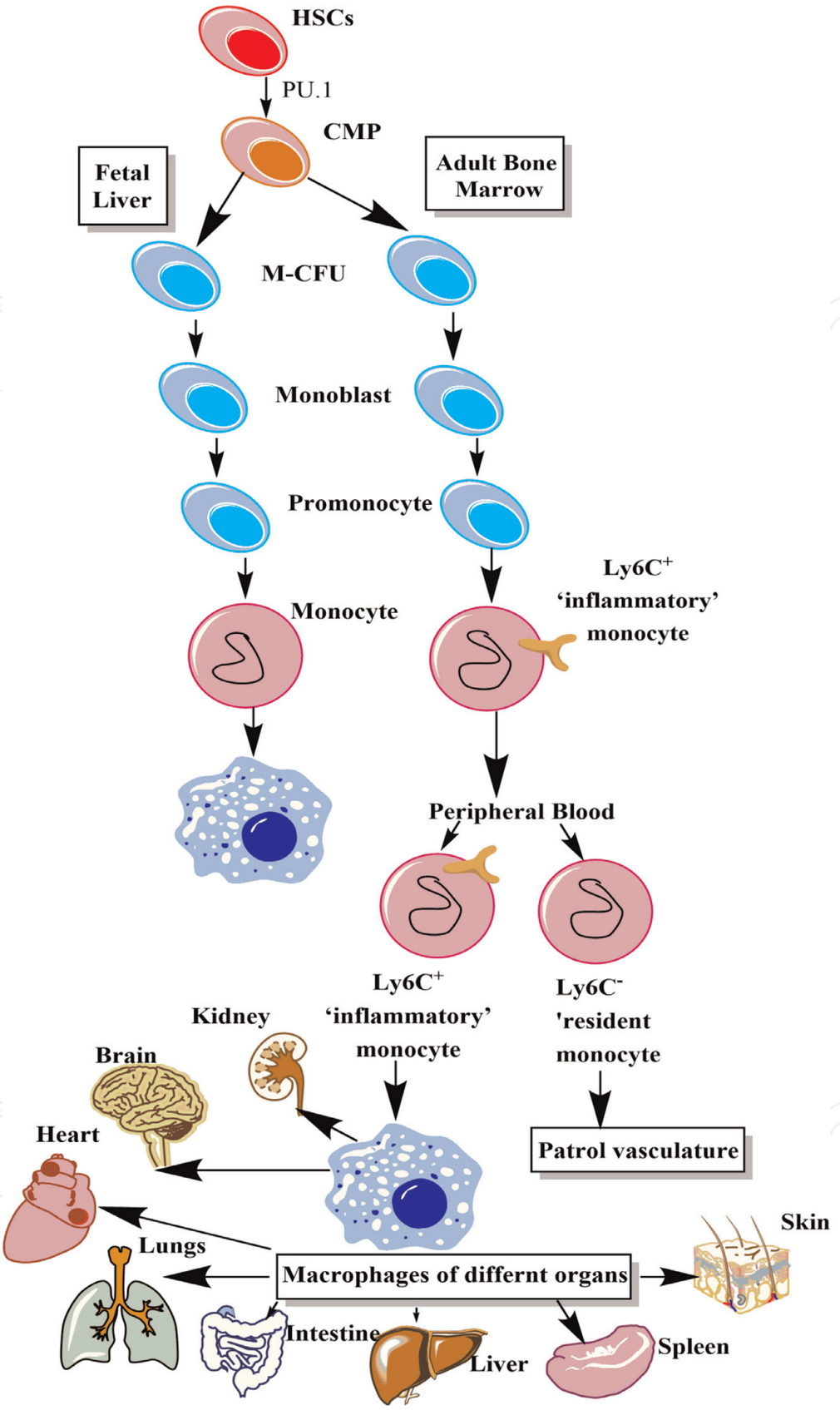

Figure 3.
Schematic representation of developmental stages of macrophages. HSCs, in the presence of TFs including PU.1 develop into CMP that further differentiates into promonocytes by undergoing different developmental stages. The promonocytes in fetal liver develop into monocytes that further differentiate into macrophages. Whereas in bone marrow promonocytes develop into Ly6C⁺ inflammatory monocytes also called classical monocytes. However, in peripheral blood circulation they are further differentiated into Ly6C⁺ inflammatory monocytes and Ly6C⁻ resident monocytes or non-classical monocytes residing in the blood and patrolling the vasculature. On the other hand Ly6C⁺ inflammatory monocytes or classical monocytes migrate to different organs and develop into different tissue/organ specific macrophages as described in the figure.

vasculature during homeostasis and inflammatory conditions [53, 54]. Thus, these Nr4a1-dependent non-classical monocytes serve as housekeepers for the endothelial vasculature and orchestrate the necrosis by neutrophils due to damaged ECs inducing the TLR7 signaling via *in situ* phagocytosis of cell debris derived from damaged ECs [53]. Hence these non-classical monocytes play a crucial role in the pathogenesis of various diseases associated with vasculature along with the process of wound healing and the resolution of the inflammation [54]. This patrolling nature of the monocytes distinguishes them from macrophages as macrophages have a very limited capacity to emigrate from their site of location. In humans monocytes are differentiated into two subsets on the basis of expression of surface expression of CD14 and CD16 [55]. In humans the $CD14^{++}CD16^{-}$ monocytes are known as classical monocytes and are most prevalent monocyte subset in the blood [56, 57]. Like mice $Ly6c^{hi}$ monocytes they also express CCR2 [58]. The $CD14^{+}CD16^{+}$ monocytes are considered as intermediate monocytes and $CD14^{low}CD16^{+}$ monocytes are called non-classical monocytes in humans [56].

The $CD14^{low}CD16^{+}$ monocytes in humans are similar to mice $Ly6c^{low}$ monocytes and patrol the vasculature or endothelium along with sensing the nucleic acids and virus via TLR7 and TLR8 receptors [59]. These monocytes have weak phagocytic potential and do not produce ROS and cytokines in response to cell-surface TLRs. However they produce TNF-α, IL-1β, and CCL3 in response to viruses and immune complexes containing nucleic acids due to the activation of TLR7 and TLR8 signaling pathways [59]. Thus it can be inference that mice and human monocytes do not precisely overlap in terms of their receptor expression including PPAR-γ (peroxisome proliferator-activated receptor-γ) that is signature for mouse monocytes but absent in humans, however, the process of their differentiation and the function in immune defense is apparently similar [60–62]. For example, approximately 270 genes in humans and 550 genes in mice monocytes (both types including classical or non-classical one) are expressed differentially and more than 130 of these gene expressions are conserved between mouse and human monocyte subsets [62]. Thus this difference between human and mouse monocytes should be kept in mind when developing and studying human diseases in mice.

The development of mononuclear phagocytes from monocyte/macrophage progenitor cells is directed by colony stimulating factors (CSFs) including M-CSF, granulocyte-monocyte colony-stimulating factor (GM-CSF), and fms-like tyrosine kinase 3 ligand (Flt3-ligand) [63–65]. The number of various tissue and organ monocytes/macrophages are regulated by M-CSF without any alteration in their activation stage [64]. However, GM-CSF is involved in the activation of both monocytes and macrophages along with its participation in the differentiation into DCs. The mature cells developed during fetal development and later in life are distributed accordingly as sinus-lining and interstitial resident macrophages in lymphohematopoietic and other organs including lungs, liver, spleen, gut, skin and brain. Major tissue-resident macrophages, including liver KCs, lung alveolar, splenic, and peritoneal macrophages, are established prior to birth and their maintenance starts subsequently by themselves independent of replenishment of blood monocytes during adulthood [47]. The macrophages present in endocrine and reproductive organs including testes, adipose, vascular, musculoskeletal and connective tissues are less well characterized.

3. Macrophage polarization

The polarization of macrophages gives a diverse heterogenic function and phenotypes to them depending on their activation in respect to their duration of

stimulation and spatial localization [66]. The macrophage polarization is not a fixed process due the plasticity of the macrophages to integrate multiple signals (different pathogens and their PAMPs, DMAPs, and normal tissue environment). Thus macrophage polarization occurs in response to cell-cell interaction and cell-molecule interaction within the host tissues or organs to maintain the homeostasis or during different pathological conditions [67, 68]. Thus macrophage polarization is regulated by at least three different mechanisms: (1) epigenetic and cell survival mechanisms, (2) external stimuli (pathogens, PAMPs, and allergens), and (3) tissue environment including DAMPs [66]. The inflammation and associated immune response is a good pathogenic condition to study the macrophage polarization as this process impacts the inflammation from its initiation to the resolution phase. The details of macrophage polarization are discussed elsewhere [66, 67, 69].

Depending on their polarization status the macrophages can be categorized in to M0, M1 (classically activated macrophages (CAMs) or pro-inflammatory), and M2 (alternatively activated macrophages (AAMs) or anti-inflammatory) macrophages (**Figure 4**). M0 macrophages can be considered as naïve macrophages that have not been exposed to any pro- or anti-inflammatory stimuli or environment. M1 or CAMs are developed when M0 macrophages are exposed to bacterial moieties including LPS and Th1 cytokines including IFN-γ, IL-2, IL-12, IL-18 and TNF-β (lymphotoxin β (LT-β)) etc., whereas M2 or AAMs are developed upon exposure to Th2 cytokines including IL-4, IL-5, IL-6, and IL-10 [70, 71]. The M2 macrophages can further be divided into M2a, M2b, and M2c depending on their stimulus for the activation. The M2 macrophages induced by IL-4 or IL-13 are called M2a (a stands for alternative), M2b macrophages are induced by poly I:C or TLR or IL-1R agonists, and M2c are induced by IL-10 and glucocorticoids [72]. M2 macrophages exhibit a higher phagocytic activity, higher expression of scavenging, mannose and galactose receptors, produce higher concentration of ornithine and polyamines due to high arginase pathway, secrete high amount of IL-10 and express higher levels of the IL-1 decoy receptor and IL-1RA [40]. Thus, M2 macrophages in general exert an anti-inflammatory action and play a crucial role in anti-parasitic immune response required for parasite clearance, promote tissue remodeling, vasculogenesis, tumor progression [70, 72, 73]. The M1 macrophages express Th1 cell-attracting chemokines including CCL5 or regulated upon activation, normal T cells expressed, and secreted (RANTES), CXCL9 and CXCL10, whereas M2 macrophages express the chemokines CCL17, CCL22 and CCL24 [74].

The M1 macrophages highly express cyclo-oxygenase 2 (COX 2) enzyme, inducible nitric oxide synthase (iNOS or NOS2) involved in nitric oxide ($NO^{\cdot}$) synthesis, whereas M2 macrophages express COX 1 and arginase is expressed in M2a and M2c required to synthesize ornithine and polyamines but not in M2b macrophages activated by Poly I:C and LPS [72, 74, 75]. The metabolic process of macrophages governing their pro-inflammatory and anti-inflammatory action also differs in M1 and M2 macrophages. M1 macrophages exhibit a shift from normal oxidative phosphorylation (OXPHOS) to increased glycolysis, increased release of lactate, a decreased oxygen consumption and glutaminolysis. On the other hand M2 macrophages are dependent on fatty acid oxidation (FAO) as a major source of energy along with the mitochondrial OXPHOS. The detailed description of macrophage (both M1 and M2) immunometabolism is beyond the scope of the chapter and described elsewhere [76, 77]. Succinate (a signaling metabolite) regulates the macrophage polarization via succinate receptor 1 (SUCNR1) and regulates the process of inflammation [78]. The myeloid-specific deficiency of SUCNR1 promotes a local pro-inflammatory or M1 phenotype among macrophages, disrupts glucose homeostasis in mice, exacerbates the metabolic effects of diet-induced obesity and impairs the browning of the adipose-tissue under cold conditions [78]. On the other

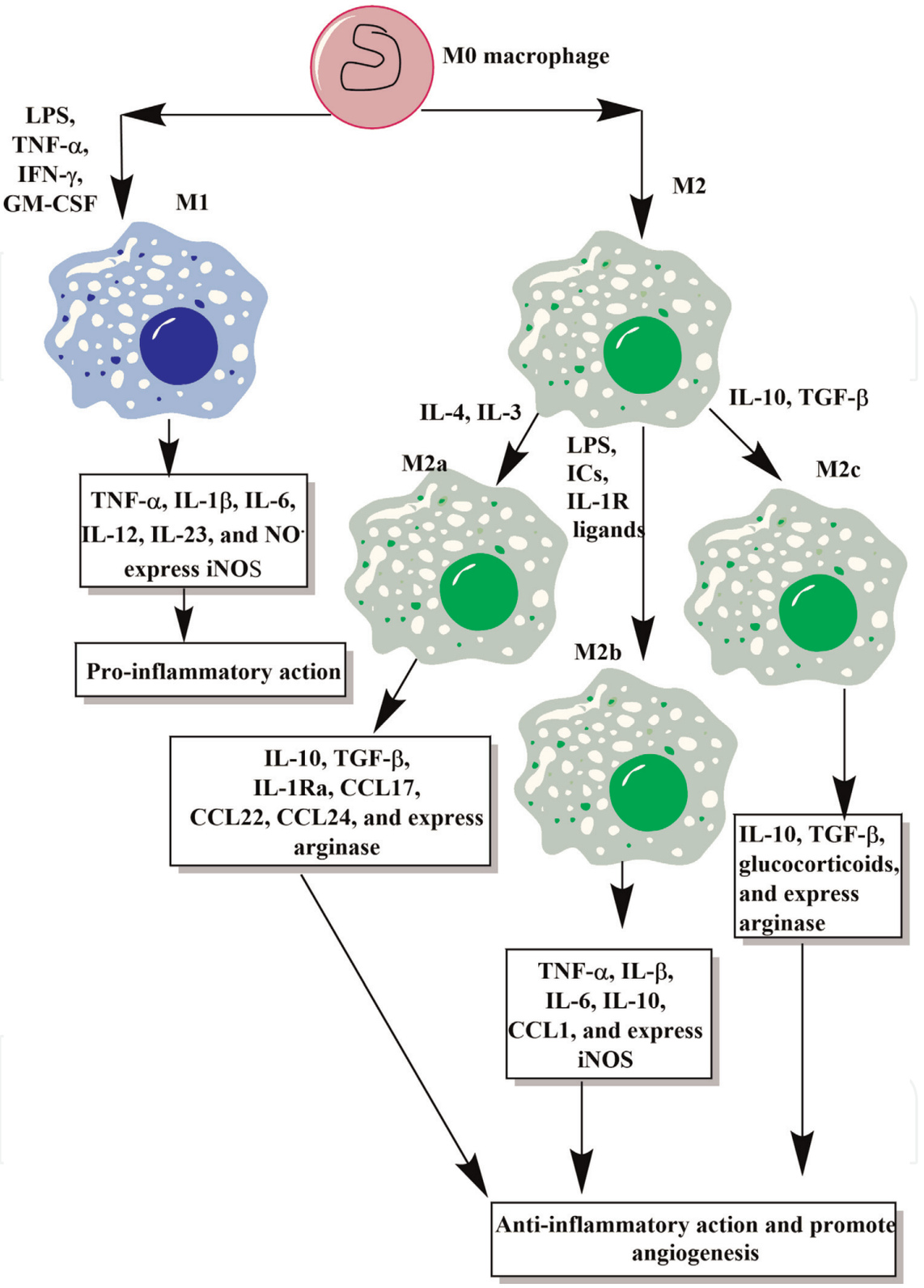

Figure 4.
Schematic representation of macrophage polarization. Naïve or M0 macrophages upon different stimulation as describe in the figure and the text differentiate into pro-inflammatory M1 macrophages or classically activate macrophages (CAMs) and anti-inflammatory macrophages called alternatively activated macrophages (AAMs) or M2 macrophages. These M2 macrophages are further differentiated into M2a, M2b, and M2c macrophages depending on the stimulus as mentioned in the figure and the text.

hand SUCNR1 via succinate binding stimulates the anti-inflammatory (M2) phenotype among macrophages as indicated by the release of type 2 or anti-inflammatory cytokines including IL-4. Thus succinate exerts the anti-inflammatory action via SUCNR1 on macrophages via controlling their polarization [78]. The macrophages

involved in the resolution of inflammation are called resolution-phase macrophages (rMs). The rMs differ from both M1 and M2 macrophages in terms that they have weak bactericidal properties and express an alternatively activated phenotype along with higher expression of markers of M1 macrophages (i.e. inducible cyclooxygenase (COX 2) and nitric oxide synthase (iNOS)) [79]. This phenotype of rMs is controlled by cyclic adenosine monophosphate (cAMP) as its inhibition converts rMs into M1 macrophages [79]. On the other hand the upregulation of cAMP in M1 macrophages converts them in rMs. Although rMs are nonessential to clear neutrophils during self-limiting inflammation but are required for the initiation of post resolution lymphocyte repopulation signaling event via COX 2 lipids. Thus, rMs are the hybrid of both M1 and M2 macrophages and play an important role in the post resolution innate-lymphocyte repopulation and the restoration of tissue/organ homeostasis. **Table 1** is showing the major differences between M1 and M2 macrophages. The detailed mechanism of macrophage polarization (M1 and M2), its

	M1 macrophages	**M2 macrophages**
1. Phenotype	Express high levels of MHC-II, CD68, and CD80 and CD86 costimulatory molecules	Express higher levels of CD206, CD200R, CD163 and transcription factor called CMAF (musculoaponeurotic fibrosarcoma) and response gene to complement 32 (RGC-32)
2. Upregulated genes	Suppressor of cytokine signaling 3 (SOCS3), iNOS or NOS2, M*acrophage* receptor with collagenous structure (Marco), Il12B, Il23a (Il23p19) and Ptgs2 (Cox2)	Arg1, MMR (Mrc1), resistin-like molecule α (FIZZ1) or Relma or Retnla, Ym1, Irf4, Cxcl12, Cxcl13, Ccl24 and Klf4
3. Action	Pro-inflammatory	Anti-inflammatory
4. Cytokines and chemokines produced	IFN-γ, IL-8, TNF-α, IL-1β, RANTES (CCL5), CXCL10	IL-13, IL-10, CCL17, CCL18, CCL22
5. Metabolic pathway	Glycolysis and glutaminolysis	FAO and OXPHOS
6. HIF-1α expression	High	Low
7. Inducers or stimuli	IFN-γ, PAMPs (i.e. LPS), GM-CSF	Glucocorticoids, IL-10, IL-4, IL-13 and M-CSF
8. ROS and RNS production	High ROS and $NO^{\cdot}$ production	Low ROS and $NO^{\cdot}$ production
9. Rate of acidification	Low	High
10. Antimicrobial action	High	Low
11. Glucose uptake	Mainly depends on HIF-1α and Akt/mTORC1 activation	Mainly depends on Akt/mTORC1 activation
12. Macrophage galactase-type C-type lectins	Low	High
13. Autophagy	Induce autophagy during tuberculosis (TB) infection	Decrease autophagy during TB infection

Table 1.
Differences between M1 and M2 macrophages.

regulation and impact on inflammatory process including in cancer are described somewhere else [66, 70–73, 75, 80, 81].

4. Role of monocytes and macrophages in host defense

Macrophages are present in almost every tissue or organ system including the barriers system comprising of respiratory tract (pulmonary alveolar and interstitial macrophages), skin, gastrointestinal tract (GIT), and reproductive tract [82–91]. Thus their presence in the every organ system along with the mucosal sites serving as potential sites for the entry of pathogens, toxins, allergens and xenobiotics makes them first line of defense.

Monocytes/macrophages are one of the major innate immune cells involved in the process of recognition of pathogens and the cell debris originated as a result of apoptosis and their engulfment by the process of phagocytosis. Thus along with other innate immune cells including neutrophils, dendritic cells (DCs), mast cells, monocytes, and macrophages are considered as 'professional' phagocytes. The professional phagocytes are differentiated from non-professional phagocytes on the basis of their effectiveness in mediating the phagocytosis [92]. The major factor contributing to the effectiveness of the phagocytosis and characteristic of professional phagocytes is the expression of various receptors on their cell surface involved in the recognition of molecules or ligands that are not normally expressed by normal and healthy cells [93]. For example, scavenger receptors (SRs) play important role in the recognition and binding of apoptotic and necrotic cells, opsonized pathogens (i.e. pathogens opsonized by complement protein C5a and C3a), and cell debris. The scavenger receptor-A1 (SR-A1)-mediated phagocytosis of low density lipids (LDLs) or oxidized lipids causes the formation of foam cells and this phenomenon is involved in the pathogenesis of atherosclerosis [94]. The absence of SR-A1 in macrophages increase their pro-inflammatory action due to the increased p42/44 mitogen-activated protein kinase (MAPK) phosphorylation, interferon regulatory factor-3 (IRF-3) and NF-κB nuclear translocation and increased production and secretion of TNFα, IL-6 and IFN-β due to the increased activation of TLR4 signaling pathway [95]. Thus SR-A1 antagonizes the TLR4-mediated phagocytosis and pro-inflammatory immune response of macrophages in the presence of LPS and gram-negative bacteria in a competitive manner [95].

Additionally, alveolar macrophages expressing SR-A1 and class A scavenger receptors (SRAs) called macrophage receptor with collagenous structure (MARCO) protect the host from inhaled toxicant and pathogens by phagocytosing the oxidized lipids and decreasing the inflammatory damage [96]. The detailed information of scavenger receptors is beyond the scope of the chapter and is described elsewhere [97–101]. In addition, professional phagocytes including monocytes and macrophages express various Toll-like receptors (TLRs) [93]. However the interplay between phagocytic receptors (which initiate and assist in the mechanics of phagocytosis) and pattern recognition receptors (PRRs, such as TLRs, which detect PAMPs or DAMPs) is complex. The interplay between these receptors may involve both synergistic and antagonistic interactions, including downstream signaling mechanisms within the phagocytic cell that remain largely unknown [102, 103].

During and following phagocytosis, PRRs (including TLRs, C-type lectin receptors (CLRs), scavenger receptors, retinoic acid-inducible gene 1 (RIG1)-like helicase receptors (RLRs) and NOD-like receptors (NLRs)) recognize different PAMPs and DAMPs along with different xenobiotics including silica or asbestos [104, 105]. Some PRRs including mannose receptor, DC-specific ICAM3-grabbing non-integrin (DC-SIGN) and MARCO are also involved in the process of pathogen

recognition and phagocytosis, whereas signaling PRRs (which include the TLRs, NLRs and RLRs) sense microbial products and aberrant self-molecules on the cell surface or in the cytoplasm of cells and activate transcriptional mechanisms that lead to phagocytosis, cellular activation and the release of cytokines, chemokines and growth factors [106–109]. During phagocytosis of the pathogens, the TLR2 recruits into the phagosome and discriminates between pathogens along with initiating the pro-inflammatory immune response [110]. The TLR-induced phagocytosis of bacteria is reliant on MyD-88-dependent signaling via interleukin-1 receptor-associated kinase-4 (IRAK-4) and p38 MAP kinase causing an up-regulation of SRs [111]. TLR9 is the strongest inducer of phagocytosis among all the TLRs, whereas TLR3 is the weakest inducer of the process [111]. However, TLR4-stimulated phagocytosis also requires the activation of MyD-88-independent actin-Cdc42/Rac pathway [112, 113].

Macrophages also express various complement receptors (CRIg, C1qR, CR3, C5aR, C5L2 or C5bR, etc.) and Fc receptors on their cell surface that bind and phagocytose the opsonized pathogens or other molecules and activate the complement system (CS)-mediated immune response for increasing the process of phagocytosis [114–116]. CRIg is a member of complement receptor of the immunoglobulin superfamily that binds to complement fragments C3b and iC3b opsonizing the pathogens to initiate their phagocytosis [115]. The expression of CRIg on macrophages increases in the presence of dexamethasone and IL-10, but decreases in the presence of IFN-γ, IL-4, TGF-β1, arachidonic acid (AA) [117]. AA decreases the expression of CRIg on macrophages by activating the protein kinase C (PKC) independent of its metabolism via cyclooxygenase and lipoxygenase pathway [117]. The CR3-mediated phagocytosis of the pathogens is mediated by the activation of Syk-kinase that becomes tyrosine-phosphorylated and accumulates around the nascent phagosomes [114]. However, it also negatively regulates the phagocytosis of degenerated myelin sheath by activating Syk-kinase and cofilin (an actin-depolymerizing protein controlling F-actin remodeling) in microglia and macrophages [118]. C1q component of the CS plays a crucial role in the process of phagocytosis by triggering the rapid enhancement of the phagocytosis independent of its role in direct activation of the classical complement pathway [119]. The engulfment of the membrane attack complex (MAC) deposited on pathogens by the macrophages during the process of phagocytosis activates the NALP3 (NACHT, LRR and PYD domains-containing protein 3 or cryopyrin) inflammasome via inducing K^+ efflux and ROS generation [120]. The NALP3 activation activates caspase 1 (CASP1) to cause the maturation and release of IL-1β and IL-18 [120]. This also induces the differentiation of T cells into Th17 cells when these macrophages are used as antigen presenting cells (APCs). Thus, macrophages use various surface receptors and secreted molecules to monitor and respond to changes in the vicinity of their tissue environment.

5. Role of macrophages in homeostasis (angiogenesis, wound repair, and regeneration) and diverse inflammatory conditions (metabolic diseases and autoimmunity)

5.1 Macrophages in angiogenesis

Macrophages play a crucial role in the immune homeostasis via regulating the process of inflammation under both sterile and infectious inflammatory conditions. In addition to this they also play a crucial role in the process of angiogenesis (**Figure 5**), metabolism, and salt and water balance [121]. For example, myeloid

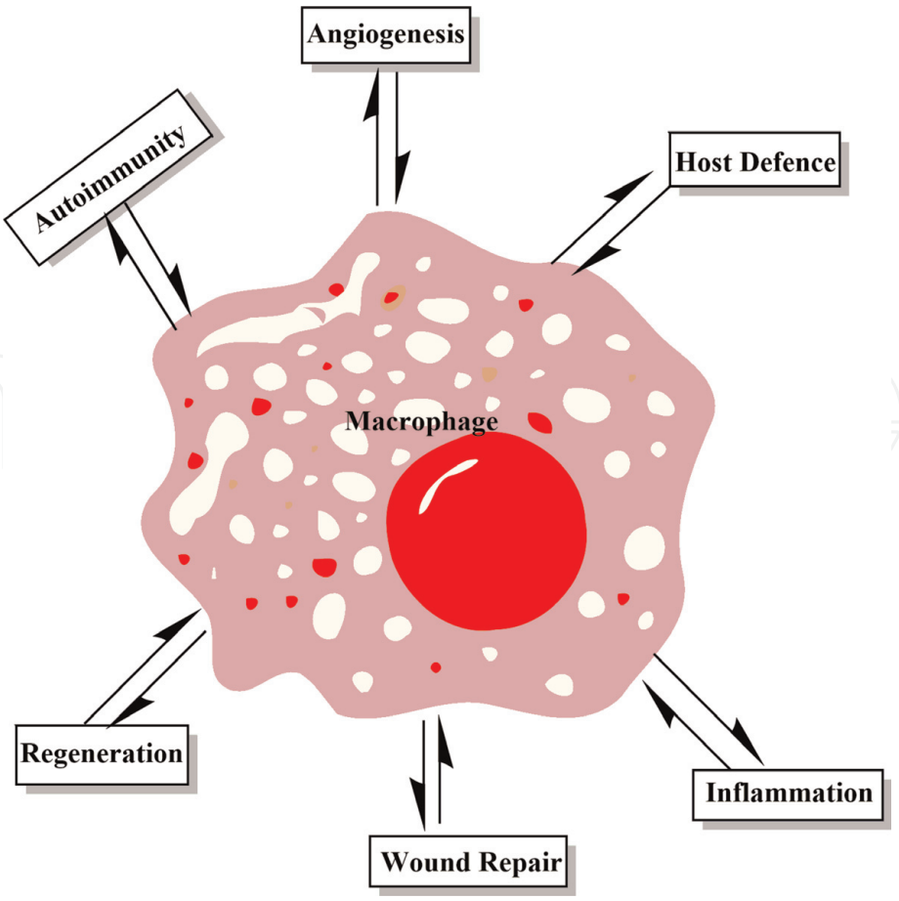

Figure 5.
Macrophages play important role in host defense, immune homeostasis, regeneration, and inflammation. The detailed mechanisms of macrophages impact on the processes mentioned in the figure are described in the text.

cells including monocytes and neutrophils are the first innate immune cells migrating through post capillary venules (PEVs) at the site of inflammation and tissue injury or tissues requiring microvascular growth and remodeling including several tumors due to the expression of CCR2 that binds to the chemokine called CCL2 [122, 123]. Furthermore an inhibition in the chemo-attraction and migration of monocytes at the site of tissue ischemia causes a flap necrosis due to impaired neovascularization [124]. Macrophages also synthesize, release, and respond (or reprogram themselves) to various pro- and anti-angiogenic factors including vascular endothelial growth factor-A (VEGF-A), and several angiopoietins including angiopoietin (ANG) 1 and ANG 2 [125–127]. Thus these recruited monocytes or tissue macrophages reprogram themselves in the presence of theses angiogenic factors to serve as angiogenic and arteriogenic professional cells (APCs) [125]. For example, ANG1 exerts its angiogenic action on macrophages via repressing the expression of prolyl hydroxylase domain protein 2 (PHD2) through angiopoietin (ANG)-TIE2 (angiopoietin-1 receptor or CD202B) signaling that supports their reprograming into angiogenic and APCs [127, 128]. ANG2-dependent TIE2-signaling in macrophages plays a crucial role in the induction of angiogenesis during inflammation and tumor growth as both condition are associated with increased hypoxia causing an induction of hypoxia inducible factors (HIFs) including HIF-1α and HIF-2α enhancing the generation of tumor and angiogenesis promoting molecules and cytokines (CXCR4, GLUT1 (glucose transporter 1), VEGF A, IL-1β, IL-8, adrenomedullin, and ANG 2) [129–131].

These angiogenesis supportive macrophages exhibit the similarity with M2 macrophages and in tumor environment they are called tumor-associated macrophages

(TAMs) with higher levels of IL-6, iNOS, and TIE2 [132]. These M2 macrophages and TAMs support the growth, proliferation, and migration of endothelial cells (ECs) and blood vessel formation or sprouting by releasing VEGF-A as well as promoting the synthesis and release of VEGF-A and fibroblast growth factor-2 (FGF-2) or basic-FGF (b-FGF) from the tissue or tumor microenvironment cells [133]. The TAM-mediated support of angiogenesis and tumor growth is determined by TIMP-1 (tissue-inhibitor of matrix metalloproteinase-1) levels free of or complexed with pro-MMP-9 (matrix metalloproteinase-9) [134]. For example, MMP-9 null macrophages are non-angiogenic. In addition to secreting the angiogenic factors, macrophages also interact with cells including pericytes, ECs, and vascular smooth muscle cells for regulating angiogenesis observed during embryonic development, adult responses to injury, and in tumor microenvironment [135]. Furthermore the depletion of macrophages disrupts the process of vascular patterning in response to insufficient vascular pruning due to decreased phagocytosis of endothelial cells and pericytes during both embryonic and postnatal development of organs [135–137].

5.2 Macrophages in wound repair

Macrophages also serve as crucial immune cells involved in the process of wound repair in response to stimuli generated in the local tissue milieu [138, 139]. The phenomenon of wound repair is mainly regulated by AAMs or M2 macrophages due to their anti-inflammatory action, induction of angiogenesis, and decreased apoptosis that induces the extracellular matrix remodeling and the process of wound repair and regeneration [138, 139]. These wound repair macrophages are characterized by the higher production of various growth factors including platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), transforming growth factor-α (TGF-α), TGF-β, and VEGF-A causing angiogenesis and supporting cell proliferation to alleviate the hypoxia caused by the inflammatory tissue insult [140]. The TGF-β stimulates the differentiation of the local and recruited tissue fibroblasts into myofibroblasts facilitating the contraction and closure of the wound area along with the synthesis of the extracellular matrix (ECM) components [141]. Additionally macrophages also release amphiregulin (AREG) that serves as an epidermal growth factor receptor ligand (EGFRL) to play a role in the restoration of tissue homeostasis after injury or wound healing [142, 143]. The wound healing or repair mechanism by AREG involves the release of TGF-β from latent complexes via integrin-α_V activation that induces the differentiation of mesenchymal stromal cells (pericytes) into myofibroblasts to restore the vascular barrier function within injured tissue during the process of wound healing [142].

These wound repair macrophages also augment the proliferation and expansion of many neighboring parenchymal and stromal cells along with activating stem cells and local progenitor cells to participate actively in tissue repair response during chronic or severe injury [144]. Hence, the disruption of monocyte recruitment and the inhibition of local macrophages and their conversion into M2 or AAMs may dampen the process of wound repair. For example, in some cases the disruption in the process of wound repair may lead to the development of tissue or organ fibrosis or scarring due to the overactivation of wound repair macrophages that can further impair organ's normal function causing ultimate organ failure and death of the patient [145, 146]. For example, idiopathic pulmonary fibrosis (IPF), hepatic fibrosis and systemic sclerosis, are tightly regulated by 'pro-fibrotic' macrophages producing PDGF, IGF-1, TGF-β1 (induces myofibroblast transdifferentiation and promotes matrix accumulation), and directly activating fibroblasts [93, 147–150]. These pro-fibrotic macrophages also secrete pro-inflammatory cytokines including

IL-1β that stimulates Th17 cells to secrete IL-17 involved in the bleomycin pulmonary fibrosis, MMPs and TIMPs that regulate the inflammatory cell recruitment and the ECM turnover [146, 151–154]. Hence macrophages are involved in the process of wound repair and the impairment in their function may lead to the poor wound healing and the development of fibrosis causing organ failure and the death of the patient. Therefore targeting of the pulmonary macrophages and their mediators play a crucial role in the process of pulmonary fibrosis [155].

5.3 Macrophages in regeneration

Macrophages also play a crucial role in the process of tissue and organ regeneration that refers to the process of proliferation of cells and tissues to replace the damaged and lost structures [156]. The organs and tissues including skeletal muscles and liver exhibit a higher degree of regenerative capacity through the regeneration of parenchymal cells involving monocytes and hepatocytes [157]. In most tissues the complete regeneration of intact tissues is not achieved and results in the formation of scar [158]. Macrophages play a very important role in the regeneration process of skeletal muscle by coordinating the inflammation and regeneration [157]. They act as essential immune cells for the recovery of tissue integrity and function following the injury [150]. The macrophages involved in the process of regeneration of skeletal muscle are located in the interstitial space between myofibers, specifically in the perimysium (the connective tissue surrounding muscle fascicles), epimysium, (the connective tissue surrounding the whole muscle), and perivascular space that recruit circulating neutrophils and monocytes following the muscle injury to initiate the process of inflammation [157]. The monocytes infiltrated into the damaged skeletal muscle undergo the process of *in situ* transition to develop into $Ly6C^{hi}$ (inflammatory) and $Ly6C^{low}$ (regenerative or repair) macrophages that is independent of NR4A1 (nuclear receptor subfamily 4 group A member 1) or NUR77 or nerve growth factor IB (NGFIB) [159]. The NUR77 belongs to the family of the *Nur* nuclear receptors acting as intracellular transcription factors and plays a crucial role in the macrophage-mediated inflammatory immune response generation [160]. The transition of monocytes into $Ly6C^{hi}$ (inflammatory) and $Ly6C^{low}$ (regenerative or repair) macrophages plays a crucial role in the process of muscle regeneration [161]. The $Ly6C^{low}$ macrophages in the skeletal muscle exhibit a distinct pro-resolving signature [specialized pro-resolving lipid mediators (SPMs), including resolvins (for example, RvD1, RvD2, RvE1)] that helps in the functional improvement in the process of muscle regeneration [162]. On the other hand $Ly6C^{hi}$ inflammatory monocytes further differentiate into skeletal tissue macrophages (both M1 and M2) and secrete pro-inflammatory cytokines (i.e. FN-γ, TNF-α, IL-1β, and IL-6) that are also integral component of myogenic precursor cells (MPCs) or myoblasts. The M2 macrophages on the other hand promote the differentiation and maturation of MPCs [157, 163, 164]. In addition macrophages are also shown to involve in the process of regeneration of heart/cardiomyocytes in different animals (Zebra fish, Salamander, and the laboratory mouse) [165–167]. Even studies have also shown the involvement of macrophages in the regeneration of spinal cord and tail fin of Zebra fish [168, 169]. Wnt signaling in macrophages plays a critical role in driving parenchymal regeneration in animal models of liver injury [170]. After the death of hepatocytes phagocytic uptake of the cell debris by macrophages synthesizes Wnt3a that in nearby hepatic progenitor cells (HPCs) induces the canonical Wnt signaling cascade facilitating their specification to hepatocytes [171]. Even the regeneration of hair follicles also involves the macrophage-mediated key signals to local stem cells facilitating the regeneration of hair follicles upon plucking of hairs [172]. The plucking of hairs causes the local generation of CCL2 that promotes

pro-inflammatory TNF-α generating macrophages and initiates the process of hair-follicle regeneration [172]. Thus the fine tuning of macrophages is essential for their protective function during would healing or repair, regeneration or the induction of fibrosis due to the loss of this fine tuning leading to the organ damage and failure.

5.4 Macrophages in autoinflammation and autoimmunity

The uncontrolled activation of macrophages in response to DAMPs recognized by various PRRs and apoptotic cells (uncontrolled phagocytosis) may lead to chronic and uncontrolled inflammation that may induce autoinflammation and autoimmune diseases including severe autoimmune anemia, systemic lupus erythematosus (SLE), and chronic arthritis [173–176]. The increased infiltration of macrophages into the brain (i.e., in meninges surrounding the CNS, the perivascular space, and the choroid plexus) is also reported in experimental autoimmune encephalitis (EAE), an animal model for multiple sclerosis (MS) [177, 178]. The chronic up-regulation of CCR2, CCL2, CCL3, CCL4, and CCL22 stimulates the process of macrophage accumulation at the sites of the brain affected during EAE [179, 180]. Both M1 and M2 macrophages play a crucial role in the pathogenesis of EAE or MS [180, 181]. Macrophages also play a very important role in the pathogenesis of rheumatoid arthritis (RA) by secreting various pro-inflammatory cytokines, controlling the generation and function of regulatory T cells (Tregs) via binding and release of transforming growth factor-β (TGF-β), and their therapeutic targeting proves beneficial to the patients [182–185]. Sjogren's syndrome (SS), a chronic autoimmune disease of exocrine glands specifically salivary glands and lacrimal glands causing also systemic autoimmune lesions also shows the accumulation of monocytes and macrophages in the inflamed lesions [185–187]. In addition to these autoimmune diseases, both M1 and M2 macrophages also play a crucial role in the pathogenesis of type 1 diabetes mellitus by contributing to the destruction of β cells of the pancreas through controlling the generation of Th1 cells and acting as antigen presenting cells (APCs) to stimulate cytotoxic $CD8^+$ T cells (T1DM) [188–190].

5.5 Macrophages in metabolic diseases

Obesity is an altered stage of metabolism originating due to the increased availability of nutrients (except in the genetically impaired conditions causing the deposition of the white adipose tissue (WAT)) [191]. However, both obesity caused by the genetic factors or due to the increased food intake and sedentary life style cause a low-grade systemic chronic inflammation that may lead to the development of type 2 diabetes mellitus (T2DM) and atherosclerosis [192–194]. The death of adipocyte serves as a major trigger for the recruitment of inflammatory $LY6C^{hi}CCR2^+$ monocytes and the accumulation of macrophages in the WAT as more than 90% of the macrophages in WAT are localized to the dead adipocytes [195, 196]. These macrophages then fuse to form syncytia sequestering and scavenging the residual "free" adipocyte lipid droplets and ultimately forming the multinucleate giant cells that serve as a hallmark of chronic inflammation. Furthermore, these macrophages recognize fatty acids (FAs) as potential inflammogens and reprogram themselves into classical macrophages (M1 macrophages) during obesity [104, 197, 198]. For example, saturated but not unsaturated fatty acids promote the inflammatory activation of macrophages via the activation of TLR4 as TLR4 is essential for high-fat diet-induced insulin resistance in adipose tissue and liver [199–203]. Additionally, Fetuin A (FetA or AHSG, a secreted glycoprotein) serves as an endogenous ligand for TLR4 for promoting the lipid-induced insulin resistance, lipotoxicity in β cells of the pancreas, and T2DM [204, 205]. However, M2 macrophages generated in the

environment promote the health of the WAT and the insulin sensitivity by an unknown mechanism in a lean state [206]. It can be hypothesized that the M2 macrophages via maintaining the health of adipocytes in WAT prevent the generation of signals including the death of adipose tissue that chemo-attract the pro-inflammatory monocytes reprogramming later into classical M1 macrophages. The genetic depletion of the M2 gene or M2 macrophages cause the induction of metabolic diseases upon high-fat-diet [206]. IL-6 promotes the generation of AAMs or M2 macrophages in adipose tissue environment during obesity [207]. The depletion of CD11b also increases the number of AAMs in adipose tissue during obesity and prevents the development of obesity-induced insulin resistance [208]. Thus targeting CD11b during obesity may prevent obesity-induced insulin resistance. Recently, a population of sympathetic neuron-associated macrophages (SAMs) has been identified controlling the obesity by engulfing and clearing norepinephrine (NE) [209].

6. Conclusion and future perspective

Macrophages are innate immune cells that serve as a first line of defense against invading pathogens almost in every organ system including lungs, liver, intestine, kidneys, and brain. Along with acting as first line of defense against pathogens, PAMPs, DAMPs, and other xenobiotics they act as antigen presenting cells (APCs) and provide processed antigens to activate the adaptive immune response comprising of B and T cells. Thus macrophages are sentinel innate immune cells taking part in the generation of both acute and chronic inflammation induced during both sterile and infectious tissue damaging conditions via controlling the migration and activation of other innate immune cells including neutrophils and dendritic cells (DCs) as well as cells of the adaptive immune system. In addition to their role in controlling the process of inflammation they are also involved in the process of wound repair and regeneration, autoimmunity, obesity and associated insulin tolerance, angiogenesis and embryonic development of the fetus. Thus macrophage are the potent immunoregulatory cells of the innate immune system involved in host defense against infections and other inflammatory diseases including cancer and autoimmunity along with the maintenance of immune homeostasis involving the process of resolution phase during inflammation [210–212]. Hence macrophages are very important innate immune cells with immune regulatory function depending on their fine tuning or polarization during diverse inflammatory conditions as described here in the chapter.

Although macrophages have been discovered a century ago and revolutionized the immunology research and opened the road to the branch of immunology called innate immunity but much more is still remaining to explore in macrophage biology and their role in the regulation of development, homeostasis, immune homeostasis, inflammation, and disease pathogenesis. For example, macrophage immunometabolism and epigenetic mechanisms regulating their polarization and pro-and anti-inflammatory phenotype and action have started to answer the several previously unknown questions that may influence the future immunotherapeutics and immunomodulatory approaches to target several immune-based diseases varying from autoimmune diseases to several cancers to metabolic diseases.

Author details

Vijay Kumar[1,2]

1 Children's Health Queensland Clinical Unit, School of Clinical Medicine, Faculty of Medicine, Mater Research, University of Queensland, St Lucia, Brisbane, Queensland, Australia

2 School of Biomedical Sciences, Faculty of Medicine, University of Queensland, St Lucia, Brisbane, Queensland, Australia

*Address all correspondence to: vij_tox@yahoo.com

References

[1] Kumar V, Ahmad A. Role of MAIT cells in the immunopathogenesis of inflammatory diseases: New players in old game. International Reviews of Immunology. 2018;**37**:90-110

[2] Kumar V. Innate lymphoid cells: New paradigm in immunology of inflammation. Immunology Letters. 2014;**157**:23-37

[3] Kumar V. Innate lymphoid cells: Immunoregulatory cells of mucosal inflammation. European Journal of Inflammation. 2014;**12**:11-20

[4] Kumar V, Sharma A. Mast cells: Emerging sentinel innate immune cells with diverse role in immunity. Molecular Immunology. 2010;**48**:14-25

[5] Kumar V, Sharma A. Neutrophils: Cinderella of innate immune system. International Immunopharmacology. 2010;**10**:1325-1334

[6] Van Kaer L, Parekh VV, Wu L. Invariant natural killer T cells: Bridging innate and adaptive immunity. Cell and Tissue Research. 2011;**343**:43-55

[7] Brennan PJ, Brigl M, Brenner MB. Invariant natural killer T cells: An innate activation scheme linked to diverse effector functions. Nature Reviews. Immunology. 2013;**13**:101-117

[8] Konigshofer Y, Chien Y-h. γδ T cells —Innate immune lymphocytes? Current Opinion in Immunology. 2006;**18**: 527-533

[9] Ferreira LM. Gammadelta T cells: Innately adaptive immune cells? International Reviews of Immunology. 2013;**32**:223-248

[10] Bhat A, Wooten RM, Jayasuriya AC. Secretion of growth factors from macrophages when cultured with microparticles. Journal of Biomedical Materials Research. Part A. 2013;**101**: 3170-3180

[11] Shimokado K, Raines EW, Madtes DK, Barrett TB, Benditt EP, Ross R. A significant part of macrophage-derived growth factor consists of at least two forms of PDGF. Cell. 1985;**43**:277-286

[12] Nathan CF. Secretory products of macrophages. The Journal of Clinical Investigation. 1987;**79**:319-326

[13] Martinez FO, Gordon S. The evolution of our understanding of macrophages and translation of findings toward the clinic. Expert Review of Clinical Immunology. 2015;**11**:5-13

[14] Davies LC, Jenkins SJ, Allen JE, Taylor PR. Tissue-resident macrophages. Nature Immunology. 2013;**14**:986-995

[15] van Furth RCZ, Hirsch JG, Humphrey JH, Spector WG, Langevoort HL. The mononuclear phagocyte system: A new classification of macrophages, monocytes, and their precursor cells. Bulletin of the World Health Organization. 1972;**46**:845-852

[16] Chow A, Brown BD, Merad M. Studying the mononuclear phagocyte system in the molecular age. Nature Reviews Immunology. 2011;**11**:788

[17] Hume DA, Irvine KM, Pridans C. The mononuclear phagocyte system: The relationship between monocytes and macrophages. Trends in Immunology. 2019;**40**(2):98-112

[18] Samokhvalov IM. Deconvoluting the ontogeny of hematopoietic stem cells. Cellular and Molecular Life Sciences. 2014;**71**:957-978

[19] Epelman S, Lavine KJ, Randolph GJ. Origin and functions of tissue macrophages. Immunity. 2014;**41**:21-35

[20] Takahashi K, Yamamura F, Naito M. Differentiation, maturation, and proliferation of macrophages in the mouse yolk sac: A light-microscopic, enzyme-cytochemical, immunohistochemical, and ultrastructural study. Journal of Leukocyte Biology. 1989;**45**:87-96

[21] Takahashi K. Development and differentiation of macrophages and related cells historical review and current concepts. Journal of Clinical and Experimental Hematopathology. 2001; **41**:1-31

[22] Hume DA. Probability in transcriptional regulation and its implications for leukocyte differentiation and inducible gene expression. Blood. 2000;**96**:2323-2328

[23] Moignard V, Macaulay IC, Swiers G, Buettner F, Schutte J, Calero-Nieto FJ, et al. Characterization of transcriptional networks in blood stem and progenitor cells using high-throughput single-cell gene expression analysis. Nature Cell Biology. 2013;**15**:363-372

[24] Graf T, Enver T. Forcing cells to change lineages. Nature. 2009;**462**: 587-594

[25] Orkin SH, Zon LI. Hematopoiesis: An evolving paradigm for stem cell biology. Cell. 2008;**132**:631-644

[26] Kurotaki D, Sasaki H, Tamura T. Transcriptional control of monocyte and macrophage development. International Immunology. 2017;**29**:97-107

[27] Pang SHM, de Graaf CA, Hilton DJ, Huntington ND, Carotta S, Wu L, et al. PU.1 is required for the developmental progression of multipotent progenitors to common lymphoid progenitors. Frontiers in Immunology. 2018;**9**:1264

[28] DeKoter RP, Singh H. Regulation of B lymphocyte and macrophage development by graded expression of PU.1. Science. 2000;**288**:1439-1441

[29] Pham T-H, Minderjahn J, Schmidl C, Hoffmeister H, Schmidhofer S, Chen W, et al. Mechanisms of in vivo binding site selection of the hematopoietic master transcription factor PU.1. Nucleic Acids Research. 2013;**41**: 6391-6402

[30] Imperato MR, Cauchy P, Obier N, Bonifer C. The RUNX1–PU.1 axis in the control of hematopoiesis. International Journal of Hematology. 2015;**101**: 319-329

[31] T'Jonck W, Guilliams M, Bonnardel J. Niche signals and transcription factors involved in tissue-resident macrophage development. Cellular Immunology. 2018;**330**:43-53

[32] Zhang DE, Hetherington CJ, Chen HM, Tenen DG. The macrophage transcription factor PU.1 directs tissue-specific expression of the macrophage colony-stimulating factor receptor. Molecular and Cellular Biology. 1994;**14**: 373-381

[33] Liu H, Shi B, Huang CC, Eksarko P, Pope RM. Transcriptional diversity during monocyte to macrophage differentiation. Immunology Letters. 2008;**117**:70-80

[34] Laiosa CV, Stadtfeld M, Xie H, de Andres-Aguayo L, Graf T. Reprogramming of committed T cell progenitors to macrophages and dendritic cells by C/EBP alpha and PU.1 transcription factors. Immunity. 2006; **25**:731-744

[35] Paul F, Ya A, Giladi A, Jaitin Diego A, Kenigsberg E, Keren-Shaul H, et al. Transcriptional heterogeneity and lineage commitment in myeloid progenitors. Cell. 2015;**163**:1663-1677

[36] Becker AM, Michael DG, Satpathy AT, Sciammas R, Singh H, Bhattacharya

D. IRF-8 extinguishes neutrophil production and promotes dendritic cell lineage commitment in both myeloid and lymphoid mouse progenitors. Blood. 2012;**119**:2003-2012

[37] Kurotaki D, Yamamoto M, Nishiyama A, Uno K, Ban T, Ichino M, et al. IRF8 inhibits C/EBPα activity to restrain mononuclear phagocyte progenitors from differentiating into neutrophils. Nature Communications. 2014;**5**:4978

[38] Kurotaki D, Nakabayashi J, Nishiyama A, Sasaki H, Kawase W, Kaneko N, et al. Transcription factor IRF8 governs enhancer landscape dynamics in mononuclear phagocyte progenitors. Cell Reports. 2018;**22**: 2628-2641

[39] Scott CL, T'Jonck W, Martens L, Todorov H, Sichien D, Soen B, et al. The transcription factor ZEB2 is required to maintain the tissue-specific identities of macrophages. Immunity. 2018;**49**: 312-325.e5

[40] Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K. Development of monocytes, macrophages, and dendritic cells. Science. 2010;**327**:656-661

[41] Gautier EL, Shay T, Miller J, Greter M, Jakubzick C, Ivanov S, et al. Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. Nature Immunology. 2012;**13**:1118-1128

[42] Aziz A, Soucie E, Sarrazin S, Sieweke MH. MafB/c-Maf deficiency enables self-renewal of differentiated functional macrophages. Science. 2009; **326**:867-871

[43] Kelly LM, Englmeier U, Lafon I, Sieweke MH, Graf T. MafB is an inducer of monocytic differentiation. The EMBO Journal. 2000;**19**:1987-1997

[44] Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. Nature Reviews Immunology. 2011;**11**:762

[45] Hanna RN, Carlin LM, Hubbeling HG, Nackiewicz D, Green AM, Punt JA, et al. The transcription factor NR4A1 (Nur77) controls bone marrow differentiation and the survival of Ly6C− monocytes. Nature Immunology. 2011;**12**:778

[46] Hettinger J, Richards DM, Hansson J, Barra MM, Joschko AC, Krijgsveld J, et al. Origin of monocytes and macrophages in a committed progenitor. Nature Immunology. 2013; **14**:821-830

[47] Yona S, Kim KW, Wolf Y, Mildner A, Varol D, Breker M, et al. Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. Immunity. 2013;**38**: 79-91

[48] Serbina NV, Jia T, Hohl TM, Pamer EG. Monocyte-mediated defense against microbial pathogens. Annual Review of Immunology. 2008;**26**:421-452

[49] Kurihara T, Warr G, Loy J, Bravo R. Defects in macrophage recruitment and host defense in mice lacking the CCR2 chemokine receptor. The Journal of Experimental Medicine. 1997;**186**: 1757-1762

[50] Kuziel WA, Morgan SJ, Dawson TC, Griffin S, Smithies O, Ley K, et al. Severe reduction in leukocyte adhesion and monocyte extravasation in mice deficient in CC chemokine receptor 2. Proceedings of the National Academy of Sciences of the United States of America. 1997;**94**:12053-12058

[51] Maus U, von Grote K, Kuziel WA, Mack M, Miller EJ, Cihak J, et al. The role of CC chemokine receptor 2 in alveolar monocyte and neutrophil immigration in intact mice. American

Journal of Respiratory and Critical Care Medicine. 2002;**166**:268-273

[52] Auffray C, Fogg D, Garfa M, Elain G, Join-Lambert O, Kayal S, et al. Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. Science. 2007;**317**: 666-670

[53] Carlin LM, Stamatiades EG, Auffray C, Hanna RN, Glover L, Vizcay-Barrena G, et al. Nr4a1-dependent Ly6C(low) monocytes monitor endothelial cells and orchestrate their disposal. Cell. 2013;**153**: 362-375

[54] Thomas G, Tacke R, Hedrick CC, Hanna RN. Nonclassical patrolling monocyte function in the vasculature. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015;**35**:1306-1316

[55] Ziegler-Heitbrock L. The CD14+ CD16+ blood monocytes: Their role in infection and inflammation. Journal of Leukocyte Biology. 2007;**81**:584-592

[56] Ziegler-Heitbrock L, Ancuta P, Crowe S, Dalod M, Grau V, Hart DN, et al. Nomenclature of monocytes and dendritic cells in blood. Blood. 2010;**116**: e74-e80

[57] Guilliams M, Ginhoux F, Jakubzick C, Naik SH, Onai N, Schraml BU, et al. Dendritic cells, monocytes and macrophages: A unified nomenclature based on ontogeny. Nature Reviews. Immunology. 2014;**14**:571-578

[58] Geissmann F, Jung S, Littman DR. Blood monocytes consist of two principal subsets with distinct migratory properties. Immunity. 2003;**19**:71-82

[59] Cros J, Cagnard N, Woollard K, Patey N, Zhang SY, Senechal B, et al. Human CD14dim monocytes patrol and sense nucleic acids and viruses via TLR7 and TLR8 receptors. Immunity. 2010; **33**:375-386

[60] Grage-Griebenow E, Flad HD, Ernst M. Heterogeneity of human peripheral blood monocyte subsets. Journal of Leukocyte Biology. 2001;**69**:11-20

[61] Yona S, Jung S. Monocytes: Subsets, origins, fates and functions. Current Opinion in Hematology. 2010;**17**:53-59

[62] Ingersoll MA, Spanbroek R, Lottaz C, Gautier EL, Frankenberger M, Hoffmann R, et al. Comparison of gene expression profiles between human and mouse monocyte subsets. Blood. 2010; **115**:e10-e19

[63] Hamilton JA, Achuthan A. Colony stimulating factors and myeloid cell biology in health and disease. Trends in Immunology. 2013;**34**:81-89

[64] Ushach I, Zlotnik A. Biological role of granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) on cells of the myeloid lineage. Journal of Leukocyte Biology. 2016;**100**: 481-489

[65] Hamilton TA, Zhao C, Pavicic PG Jr, Datta S. Myeloid colony-stimulating factors as regulators of macrophage polarization. Frontiers in Immunology. 2014;**5**:554-554

[66] Murray PJ. Macrophage polarization. Annual Review of Physiology. 2017;**79**:541-566

[67] Parisi L, Gini E, Baci D, Tremolati M, Fanuli M, Bassani B, et al. Macrophage polarization in chronic inflammatory diseases: Killers or builders? Journal of Immunology Research. 2018;**2018**:25

[68] Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, et al. Macrophage plasticity, polarization, and function in health and disease. Journal of Cellular Physiology. 2018;**233**: 6425-6440

[69] Atri C, Guerfali FZ, Laouini D. Role of human macrophage polarization in inflammation during infectious diseases. International Journal of Molecular Sciences. 19 Jun 2018;**19**(6):E1801. DOI: 10.3390/ijms19061801

[70] Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: Cancer as a paradigm. Nature Immunology. 2010; **11**:889-896

[71] Locati M, Mantovani A, Sica A. Macrophage activation and polarization as an adaptive component of innate immunity. Advances in Immunology. 2013;**120**:163-184

[72] Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends in Immunology. 2004;**25**: 677-686

[73] Mantovani A, Biswas SK, Galdiero MR, Sica A, Locati M. Macrophage plasticity and polarization in tissue repair and remodelling. The Journal of Pathology. 2013;**229**:176-185

[74] Martinez FO, Gordon S, Locati M, Mantovani A. Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: New molecules and patterns of gene expression. Journal of Immunology. 2006;**177**:7303-7311

[75] Mosser DM. The many faces of macrophage activation. Journal of Leukocyte Biology. 2003;**73**:209-212

[76] Kumar V. Targeting macrophage immunometabolism: Dawn in the darkness of sepsis. International Immunopharmacology. 2018;**58**:173-185

[77] Van den Bossche J, Saraber DL. Metabolic regulation of macrophages in tissues. Cellular Immunology. 2018;**330**: 54-59

[78] Keiran N, Ceperuelo-Mallafré V, Calvo E, Hernández-Alvarez MI, Ejarque M, Núñez-Roa C, et al. SUCNR1 controls an anti-inflammatory program in macrophages to regulate the metabolic response to obesity. Nature Immunology. 2019;**20**(5):581-592

[79] Bystrom J, Evans I, Newson J, Stables M, Toor I, van Rooijen N, et al. Resolution-phase macrophages possess a unique inflammatory phenotype that is controlled by cAMP. Blood. 2008;**112**: 4117-4127

[80] Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: Time for reassessment. F1000prime Reports. 2014;**6**:13

[81] Chávez-Galán L, Olleros ML, Vesin D, Garcia I. Much more than M1 and M2 macrophages, there are also CD169+ and TCR+ macrophages. Frontiers in Immunology. 2015;**6**:263. DOI: 10.3389/fimmu.2015.00263

[82] Tamoutounour S, Guilliams M, Montanana Sanchis F, Liu H, Terhorst D, Malosse C, et al. Origins and functional specialization of macrophages and of conventional and monocyte-derived dendritic cells in mouse skin. Immunity. 2013;**39**:925-938

[83] Yanez DA, Lacher RK, Vidyarthi A, Colegio OR. The role of macrophages in skin homeostasis. Pflugers Archiv: European Journal of Physiology. 2017; **469**:455-463

[84] Pepe G, Locati M, Della Torre S, Mornata F, Cignarella A, Maggi A, et al. The estrogen-macrophage interplay in the homeostasis of the female reproductive tract. Human Reproduction Update. 2018;**24**:652-672

[85] Lee SK, Kim CJ, Kim D-J, Kang J-H. Immune cells in the female reproductive tract. Immune Network. 2015;**15**:16-26

[86] Cipriani G, Gibbons SJ, Kashyap PC, Farrugia G. Intrinsic gastrointestinal

macrophages: Their phenotype and role in gastrointestinal motility. Cellular and Molecular Gastroenterology and Hepatology. 2016;**2**:120-130.e1

[87] Grainger JR, Konkel JE, Zangerle-Murray T, Shaw TN. Macrophages in gastrointestinal homeostasis and inflammation. Pflugers Archiv: European Journal of Physiology. 2017; **469**:527-539

[88] De Schepper S, Stakenborg N, Matteoli G, Verheijden S, Boeckxstaens GE. Muscularis macrophages: Key players in intestinal homeostasis and disease. Cellular Immunology. 2018;**330**: 142-150

[89] Mossadegh-Keller N, Sieweke MH. Testicular macrophages: Guardians of fertility. Cellular Immunology. 2018; **330**:120-125

[90] Joshi N, Walter JM, Misharin AV. Alveolar macrophages. Cellular Immunology. 2018;**330**:86-90

[91] Liegeois M, Legrand C, Desmet CJ, Marichal T, Bureau F. The interstitial macrophage: A long-neglected piece in the puzzle of lung immunity. Cellular Immunology. 2018;**330**:91-96

[92] Mantovani B, Rabinovitch M, Nussenzweig V. Phagocytosis of immune complexes by macrophages. Different roles of the macrophage receptor sites for complement (C3) and for immunoglobulin (IgG). The Journal of Experimental Medicine. 1972;**135**: 780-792

[93] Murray PJW, T.A. Protective and pathogenic functions of macrophage subsets. Nature Reviews. Immunology. 2011;**11**:723-737

[94] Ricci R, Sumara G, Sumara I, Rozenberg I, Kurrer M, Akhmedov A, et al. Requirement of JNK2 for scavenger receptor A-mediated foam cell formation in atherogenesis. Science. 2004;**306**:1558-1561

[95] Ohnishi K, Komohara Y, Fujiwara Y, Takemura K, Lei X, Nakagawa T, et al. Suppression of TLR4-mediated inflammatory response by macrophage class A scavenger receptor (CD204). Biochemical and Biophysical Research Communications. 2011;**411**:516-522

[96] Dahl M, Bauer AK, Arredouani M, Soininen R, Tryggvason K, Kleeberger SR, et al. Protection against inhaled oxidants through scavenging of oxidized lipids by macrophage receptors MARCO and SR-AI/II. The Journal of Clinical Investigation. 2007;**117**:757-764

[97] Peiser L, Gordon S. The function of scavenger receptors expressed by macrophages and their role in the regulation of inflammation. Microbes and Infection. 2001;**3**:149-159

[98] Peiser L, Mukhopadhyay S, Gordon S. Scavenger receptors in innate immunity. Current Opinion in Immunology. 2002;**14**:123-128

[99] Zani IA, Stephen SL, Mughal NA, Russell D, Homer-Vanniasinkam S, Wheatcroft SB, et al. Scavenger receptor structure and function in health and disease. Cell. 2015;**4**:178-201

[100] Pluddemann A, Neyen C, Gordon S. Macrophage scavenger receptors and host-derived ligands. Methods. 2007;**43**: 207-217

[101] PrabhuDas MR, Baldwin CL, Bollyky PL, Bowdish DME, Drickamer K, Febbraio M, et al. A consensus definitive classification of scavenger receptors and their roles in health and disease. Journal of Immunology. 2017; **198**:3775-3789

[102] Erwig LP, Henson PM. Clearance of apoptotic cells by phagocytes. Cell Death and Differentiation. 2008;**15**: 243-250

[103] Hajishengallis G, Lambris JD. Microbial manipulation of receptor crosstalk in innate immunity. Nature Reviews Immunology. 2011;**11**:187-220

[104] Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Nature Reviews. Immunology. 2005;**5**:953-964

[105] Iborra S, Sancho D. Signalling versatility following self and non-self sensing by myeloid C-type lectin receptors. Immunobiology. 2015;**220**: 175-184

[106] Elinav E, Strowig T, Henao-Mejia J, Flavell RA. Regulation of the antimicrobial response by NLR proteins. Immunity. 2011;**34**:665-679

[107] Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity. 2011;**34**:637-650

[108] Osorio F, Reis e Sousa C. Myeloid C-type lectin receptors in pathogen recognition and host defense. Immunity. 2011;**34**:651-664

[109] Blander JM, Medzhitov R. Regulation of phagosome maturation by signals from toll-like receptors. Science. 2004;**304**:1014-1018

[110] Underhill DM, Ozinsky A, Hajjar AM, Stevens A, Wilson CB, Bassetti M, et al. The Toll-like receptor 2 is recruited to macrophage phagosomes and discriminates between pathogens. Nature. 1999;**401**:811-815

[111] Doyle SE, O'Connell RM, Miranda GA, Vaidya SA, Chow EK, Liu PT, et al. Toll-like receptors induce a phagocytic gene program through p38. The Journal of Experimental Medicine. 2004;**199**: 81-90

[112] Kong L, Ge BX. MyD88-independent activation of a novel actin-Cdc42/Rac pathway is required for Toll-like receptor-stimulated phagocytosis. Cell Research. 2008;**18**:745-755

[113] Tricker E, Cheng G. With a little help from my friends: Modulation of phagocytosis through TLR activation. Cell Research. 2008;**18**:711-712

[114] Tohyama Y, Yamamura H. Complement-mediated phagocytosis—The role of Syk. IUBMB Life. 2006;**58**: 304-308

[115] Helmy KY, Katschke KJ Jr, Gorgani NN, Kljavin NM, Elliott JM, Diehl L, et al. CRIg: A macrophage complement receptor required for phagocytosis of circulating pathogens. Cell. 2006;**124**: 915-927

[116] Le Cabec V, Carréno S, Moisand A, Bordier C, Maridonneau-Parini I. Complement receptor 3 (CD11b/CD18) mediates type I and type II phagocytosis during nonopsonic and opsonic phagocytosis, respectively. The Journal of Immunology. 2002;**169**:2003-2009

[117] Gorgani NN, Thathaisong U, Mukaro VRS, Poungpair O, Tirimacco A, Hii CST, et al. Regulation of CRIg expression and phagocytosis in human macrophages by arachidonate, dexamethasone, and cytokines. The American Journal of Pathology. 2011; **179**:1310-1318

[118] Hadas S, Spira M, Hanisch UK, Reichert F, Rotshenker S. Complement receptor-3 negatively regulates the phagocytosis of degenerated myelin through tyrosine kinase Syk and cofilin. Journal of Neuroinflammation. 2012;**9**: 166

[119] Galvan MD, Greenlee-Wacker MC, Bohlson SS. C1q and phagocytosis: The perfect complement to a good meal. Journal of Leukocyte Biology. 2012;**92**: 489-497

[120] Suresh R, Sutterwala F, Mosser D. Complement mediated phagocytosis

induces the activation of the NALP3 inflammasome (INC5P.331). The Journal of Immunology. 2014;**192**:-120.111

[121] Jantsch J, Binger KJ, Muller DN, Titze J. Macrophages in homeostatic immune function. Frontiers in Physiology. 2014;**5**:146

[122] Low-Marchelli JM, Ardi VC, Vizcarra EA, van Rooijen N, Quigley JP, Yang J. Twist1 induces CCL2 and recruits macrophages to promote angiogenesis. Cancer Research. 2013;**73**: 662-671

[123] Bruce AC, Kelly-Goss MR, Heuslein JL, Meisner JK, Price RJ, Peirce SM. Monocytes are recruited from venules during arteriogenesis in the murine spinotrapezius ligation model. Arteriosclerosis, Thrombosis, and Vascular Biology. 2014;**34**:2012-2022

[124] Khan B, Rangasamy S, McGuire PG, Howdieshell TR. The role of monocyte subsets in myocutaneous revascularization. The Journal of Surgical Research. 2013;**183**:963-975

[125] Avraham-Davidi I, Yona S, Grunewald M, Landsman L, Cochain C, Silvestre JS, et al. On-site education of VEGF-recruited monocytes improves their performance as angiogenic and arteriogenic accessory cells. The Journal of Experimental Medicine. 2013;**210**: 2611-2625

[126] Favre J, Terborg N, Horrevoets AJ. The diverse identity of angiogenic monocytes. European Journal of Clinical Investigation. 2013;**43**:100-107

[127] Hamm A, Veschini L, Takeda Y, Costa S, Delamarre E, Squadrito ML, et al. PHD2 regulates arteriogenic macrophages through TIE2 signalling. EMBO Molecular Medicine. 2013;**5**: 843-857

[128] Meneses AM, Wielockx B. PHD2: From hypoxia regulation to disease progression. Hypoxia (Auckl). 2016;**4**: 53-67

[129] Fang HY, Hughes R, Murdoch C, Coffelt SB, Biswas SK, Harris AL, et al. Hypoxia-inducible factors 1 and 2 are important transcriptional effectors in primary macrophages experiencing hypoxia. Blood. 2009;**114**:844-859

[130] Krausz S, Garcia S, Ambarus CA, de Launay D, Foster M, Naiman B, et al. Angiopoietin-2 promotes inflammatory activation of human macrophages and is essential for murine experimental arthritis. Annals of the Rheumatic Diseases. 2012;**71**:1402-1410

[131] Krock BL, Skuli N, Simon MC. Hypoxia-induced angiogenesis: Good and evil. Genes & Cancer. 2011;**2**: 1117-1133

[132] Willenborg S, Lucas T, van Loo G, Knipper JA, Krieg T, Haase I, et al. CCR2 recruits an inflammatory macrophage subpopulation critical for angiogenesis in tissue repair. Blood. 2012;**120**:613-625

[133] Sunderkotter C, Goebeler M, Schulze-Osthoff K, Bhardwaj R, Sorg C. Macrophage-derived angiogenesis factors. Pharmacology & Therapeutics. 1991;**51**:195-216

[134] Zajac E, Schweighofer B, Kupriyanova TA, Juncker-Jensen A, Minder P, Quigley JP, et al. Angiogenic capacity of M1- and M2-polarized macrophages is determined by the levels of TIMP-1 complexed with their secreted proMMP-9. Blood. 2013;**122**: 4054-4067

[135] Corliss BA, Azimi MS, Munson JM, Peirce SM, Murfee WL. Macrophages: An inflammatory link between angiogenesis and lymphangiogenesis. Microcirculation (New York, N.Y.: 1994). 2016;**23**:95-121

[136] DeFalco T, Bhattacharya I, Williams AV, Sams DM, Capel B.

Yolk-sac-derived macrophages regulate fetal testis vascularization and morphogenesis. Proceedings of the National Academy of Sciences of the United States of America. 2014;**111**: E2384-E2393

[137] Poche RA, Hsu CW, McElwee ML, Burns AR, Dickinson ME. Macrophages engulf endothelial cell membrane particles preceding pupillary membrane capillary regression. Developmental Biology. 2015;**403**:30-42

[138] Ricardo SD, van Goor H, Eddy AA. Macrophage diversity in renal injury and repair. The Journal of Clinical Investigation. 2008;**118**:3522-3530

[139] Alikhan MA, Ricardo SD. Mononuclear phagocyte system in kidney disease and repair. Nephrology (Carlton). 2013;**18**:81-91

[140] Rappolee DA, Mark D, Banda MJ, Werb Z. Wound macrophages express TGF-alpha and other growth factors in vivo: Analysis by mRNA phenotyping. Science. 1988;**241**:708-712

[141] Akhurst RJ, Hata A. Targeting the TGFbeta signalling pathway in disease. Nature Reviews. Drug Discovery. 2012; **11**:790-811

[142] Minutti CM, Modak RV, Macdonald F, Li F, Smyth DJ, Dorward DA, et al. A macrophage-pericyte axis directs tissue restoration via amphiregulin-induced transforming growth factor beta activation. Immunity. 2019;**50**:645-654.e6

[143] Zaiss DMW, Gause WC, Osborne LC, Artis D. Emerging functions of amphiregulin in orchestrating immunity, inflammation, and tissue repair. Immunity. 2015;**42**:216-226

[144] Stappenbeck TS, Miyoshi H. The role of stromal stem cells in tissue regeneration and wound repair. Science. 2009;**324**:1666-1669

[145] Wynn TA, Ramalingam TR. Mechanisms of fibrosis: Therapeutic translation for fibrotic disease. Nature Medicine. 2012;**18**:1028-1040

[146] Duffield JS, Lupher M, Thannickal VJ, Wynn TA. Host responses in tissue repair and fibrosis. Annual Review of Pathology. 2013;**8**:241-276

[147] Vernon MA, Mylonas KJ, Hughes J. Macrophages and renal fibrosis. Seminars in Nephrology. 2010;**30**: 302-317

[148] Wynn TA, Barron L. Macrophages: Master regulators of inflammation and fibrosis. Seminars in Liver Disease. 2010;**30**:245-257

[149] Pardali E, Sanchez-Duffhues G, Gomez-Puerto MC, Ten Dijke P. TGF-beta-induced endothelial-mesenchymal transition in fibrotic diseases. International Journal of Molecular Sciences. 2017;**18**(10):E2157. DOI: 10.3390/ijms18102157

[150] Vannella KM, Wynn TA. Mechanisms of organ injury and repair by macrophages. Annual Review of Physiology. 2017;**79**:593-617

[151] Lekkerkerker AN, Aarbiou J, van Es T, Janssen RA. Cellular players in lung fibrosis. Current Pharmaceutical Design. 2012;**18**:4093-4102

[152] Wynn TA. Cellular and molecular mechanisms of fibrosis. The Journal of Pathology. 2008;**214**:199-210

[153] Kolb M, Margetts PJ, Anthony DC, Pitossi F, Gauldie J. Transient expression of IL-1beta induces acute lung injury and chronic repair leading to pulmonary fibrosis. The Journal of Clinical Investigation. 2001;**107**: 1529-1536

[154] Wilson MS, Madala SK, Ramalingam TR, Gochuico BR, Rosas IO, Cheever AW, et al. Bleomycin and

IL-1beta-mediated pulmonary fibrosis is IL-17A dependent. The Journal of Experimental Medicine. 2010;**207**: 535-552

[155] Byrne AJ, Maher TM, Lloyd CM. Pulmonary macrophages: A new therapeutic pathway in fibrosing lung disease? Trends in Molecular Medicine. 2016;**22**:303-316

[156] Das A, Sinha M, Datta S, Abas M, Chaffee S, Sen CK, et al. Monocyte and macrophage plasticity in tissue repair and regeneration. The American Journal of Pathology. 2015;**185**:2596-2606

[157] Oishi Y, Manabe I. Macrophages in inflammation, repair and regeneration. International Immunology. 2018;**30**: 511-528

[158] Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature. 2008;**453**:314-321

[159] Varga T, Mounier R, Gogolak P, Poliska S, Chazaud B, Nagy L. Tissue LyC6-macrophages are generated in the absence of circulating LyC6-monocytes and Nur77 in a model of muscle regeneration. Journal of Immunology. 2013;**191**:5695-5701

[160] Pei L, Castrillo A, Tontonoz P. Regulation of macrophage inflammatory gene expression by the orphan nuclear receptor Nur77. Molecular Endocrinology. 2006;**20**: 786-794

[161] Wang H, Melton DW, Porter L, Sarwar ZU, McManus LM, Shireman PK. Altered macrophage phenotype transition impairs skeletal muscle regeneration. The American Journal of Pathology. 2014;**184**:1167-1184

[162] Giannakis N, Sansbury BE, Patsalos A, Hays TT, Riley CO, Han X, et al. Dynamic changes to lipid mediators support transitions among macrophage subtypes during muscle regeneration. Nature Immunology. 2019;**20**(5):626-636

[163] Arnold L, Henry A, Poron F, Baba-Amer Y, van Rooijen N, Plonquet A, et al. Inflammatory monocytes recruited after skeletal muscle injury switch into antiinflammatory macrophages to support myogenesis. The Journal of Experimental Medicine. 2007;**204**: 1057-1069

[164] Saclier M, Cuvellier S, Magnan M, Mounier R, Chazaud B. Monocyte/ macrophage interactions with myogenic precursor cells during skeletal muscle regeneration. The FEBS Journal. 2013; **280**:4118-4130

[165] Leor J, Palevski D, Amit U, Konfino T. Macrophages and regeneration: Lessons from the heart. Seminars in Cell & Developmental Biology. 2016;**58**:26-33

[166] Godwin JW, Debuque R, Salimova E, Rosenthal NA. Heart regeneration in the salamander relies on macrophage-mediated control of fibroblast activation and the extracellular landscape. npj Regenerative Medicine. 2017;**2**:22

[167] Aurora AB, Porrello ER, Tan W, Mahmoud AI, Hill JA, Bassel-Duby R, et al. Macrophages are required for neonatal heart regeneration. The Journal of Clinical Investigation. 2014;**124**: 1382-1392

[168] Petrie TA, Strand NS, Tsung-Yang C, Rabinowitz JS, Moon RT. Macrophages modulate adult zebrafish tail fin regeneration. Development. 2014;**141**:2581-2591

[169] Tsarouchas TM, Wehner D, Cavone L, Munir T, Keatinge M, Lambertus M, et al. Dynamic control of proinflammatory cytokines Il-1β and Tnf-α by macrophages is necessary for functional spinal cord regeneration in zebrafish. bioRxiv 2018:332197

[170] Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. Immunity. 2016;**44**:450-462

[171] Boulter L, Govaere O, Bird TG, Radulescu S, Ramachandran P, Pellicoro A, et al. Macrophage-derived Wnt opposes Notch signaling to specify hepatic progenitor cell fate in chronic liver disease. Nature Medicine. 2012;**18**: 572-579

[172] Chen CC, Wang L, Plikus MV, Jiang TX, Murray PJ, Ramos R, et al. Organ-level quorum sensing directs regeneration in hair stem cell populations. Cell. 2015;**161**:277-290

[173] Nagata S, Hanayama R, Kawane K. Autoimmunity and the clearance of dead cells. Cell. 2010;**140**:619-630

[174] Nagata S. Autoimmune diseases caused by defects in clearing dead cells and nuclei expelled from erythroid precursors. Immunological Reviews. 2007;**220**:237-250

[175] Janko C, Schorn C, Grossmayer GE, Frey B, Herrmann M, Gaipl US, et al. Inflammatory clearance of apoptotic remnants in systemic lupus erythematosus (SLE). Autoimmunity Reviews. 2008;**8**:9-12

[176] Kawane K, Ohtani M, Miwa K, Kizawa T, Kanbara Y, Yoshioka Y, et al. Chronic polyarthritis caused by mammalian DNA that escapes from degradation in macrophages. Nature. 2006;**443**:998-1002

[177] Rawji KS, Yong VW. The benefits and detriments of macrophages/ microglia in models of multiple sclerosis. Clinical & Developmental Immunology. 2013;**2013**:948976

[178] Abourbeh G, Theze B, Maroy R, Dubois A, Brulon V, Fontyn Y, et al. Imaging microglial/macrophage activation in spinal cords of experimental autoimmune encephalomyelitis rats by positron emission tomography using the mitochondrial 18 kDa translocator protein radioligand [(1)(8)F]DPA-714. The Journal of Neuroscience. 2012;**32**: 5728-5736

[179] Dogan RN, Long N, Forde E, Dennis K, Kohm AP, Miller SD, et al. CCL22 regulates experimental autoimmune encephalomyelitis by controlling inflammatory macrophage accumulation and effector function. Journal of Leukocyte Biology. 2011;**89**: 93-104

[180] Jiang Z, Jiang JX, Zhang GX. Macrophages: A double-edged sword in experimental autoimmune encephalomyelitis. Immunology Letters. 2014;**160**:17-22

[181] Yin J, Valin KL, Dixon ML, Leavenworth JW. The role of microglia and macrophages in CNS homeostasis, autoimmunity, and cancer. Journal of Immunology Research. 2017;**2017**:12

[182] Wallet MA, Wallet SM, Guiulfo G, Sleasman JW, Goodenow MM. IFNgamma primes macrophages for inflammatory activation by high molecular weight hyaluronan. Cellular Immunology. 2010;**262**:84-88

[183] Krausgruber T, Blazek K, Smallie T, Alzabin S, Lockstone H, Sahgal N, et al. IRF5 promotes inflammatory macrophage polarization and TH1-TH17 responses. Nature Immunology. 2011; **12**:231-238

[184] Schmidt A, Zhang XM, Joshi RN, Iqbal S, Wahlund C, Gabrielsson S, et al. Human macrophages induce CD4(+) Foxp3(+) regulatory T cells via binding and re-release of TGF-beta. Immunology and Cell Biology. 2016;**94**:747-762

[185] Laria A, Lurati A, Marrazza M, Mazzocchi D, Re KA, Scarpellini M. The macrophages in rheumatic diseases. Journal of Inflammation Research. 2016; **9**:1-11

[186] Greenwell-Wild T, Moutsopoulos NM, Gliozzi M, Kapsogeorgou E, Rangel

Z, Munson PJ, et al. Chitinases in the salivary glands and circulation of patients with Sjogren's syndrome: Macrophage harbingers of disease severity. Arthritis and Rheumatism. 2011;**63**:3103-3115

[187] Mustafa W, Zhu J, Deng G, Diab A, Link H, Frithiof L, et al. Augmented levels of macrophage and Th1 cell-related cytokine mRNA in submandibular glands of MRL/lpr mice with autoimmune sialoadenitis. Clinical and Experimental Immunology. 1998; **112**:389-396

[188] Jun HS, Yoon CS, Zbytnuik L, van Rooijen N, Yoon JW. The role of macrophages in T cell-mediated autoimmune diabetes in nonobese diabetic mice. The Journal of Experimental Medicine. 1999;**189**: 347-358

[189] Lee KU, Amano K, Yoon JW. Evidence for initial involvement of macrophage in development of insulitis in NOD mice. Diabetes. 1988;**37**:989-991

[190] Navegantes KC, de Souza Gomes R, Pereira PAT, Czaikoski PG, Azevedo CHM, Monteiro MC. Immune modulation of some autoimmune diseases: The critical role of macrophages and neutrophils in the innate and adaptive immunity. Journal of Translational Medicine. 2017;**15**:36-36

[191] Kopelman PG. Obesity as a medical problem. Nature. 2000;**404**:635-643

[192] Hotamisligil GS, Erbay E. Nutrient sensing and inflammation in metabolic diseases. Nature Reviews. Immunology. 2008;**8**:923-934

[193] Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. The Journal of Clinical Investigation. 2003;**112**: 1821-1830

[194] Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;**542**:177-185

[195] Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E, et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. Journal of Lipid Research. 2005;**46**: 2347-2355

[196] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. The Journal of Clinical Investigation. 2003;**112**:1796-1808

[197] Castoldi A, Naffah de Souza C, Câmara NOS, Moraes-Vieira PM. The macrophage switch in obesity development. Frontiers in Immunology. 2016;**6**:637-637

[198] Lauterbach MAR, Wunderlich FT. Macrophage function in obesity-induced inflammation and insulin resistance. Pflugers Archiv: European Journal of Physiology. 2017;**469**:385-396

[199] Chawla A, Nguyen KD, Goh YPS. Macrophage-mediated inflammation in metabolic disease. Nature Reviews Immunology. 2011;**11**:738

[200] Konner AC, Bruning JC. Toll-like receptors: Linking inflammation to metabolism. Trends in Endocrinology and Metabolism. 2011;**22**:16-23

[201] Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. The Journal of Clinical Investigation. 2006;**116**: 3015-3025

[202] Rocha DM, Caldas AP, Oliveira LL, Bressan J, Hermsdorff HH. Saturated fatty acids trigger TLR4-mediated inflammatory response. Atherosclerosis. 2016;**244**:211-215

[203] Saberi M, Woods NB, de Luca C, Schenk S, Lu JC, Bandyopadhyay G, et al. Hematopoietic cell-specific deletion of toll-like receptor 4 ameliorates hepatic and adipose tissue insulin resistance in high-fat-fed mice. Cell Metabolism. 2009;**10**:419-429

[204] Pal D, Dasgupta S, Kundu R, Maitra S, Das G, Mukhopadhyay S, et al. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. Nature Medicine. 2012;**18**:1279-1285

[205] Shen X, Yang L, Yan S, Zheng H, Liang L, Cai X, et al. Fetuin A promotes lipotoxicity in beta cells through the TLR4 signaling pathway and the role of pioglitazone in anti-lipotoxicity. Molecular and Cellular Endocrinology. 2015;**412**:1-11

[206] Fujisaka S, Usui I, Nawaz A, Takikawa A, Kado T, Igarashi Y, et al. M2 macrophages in metabolism. Diabetology International. 2016;**7**: 342-351

[207] Braune J, Weyer U, Hobusch C, Mauer J, Brüning JC, Bechmann I, et al. IL-6 regulates M2 polarization and local proliferation of adipose tissue macrophages in obesity. The Journal of Immunology. 2017;**198**:2927-2934

[208] Zheng C, Yang Q, Xu C, Shou P, Cao J, Jiang M, et al. CD11b regulates obesity-induced insulin resistance via limiting alternative activation and proliferation of adipose tissue macrophages. Proceedings of the National Academy of Sciences. 2015;**112**: E7239-E7248

[209] Pirzgalska RM, Domingos AI. Macrophages in obesity. Cellular Immunology. 2018;**330**:183-187

[210] Herold S, Mayer K, Lohmeyer J. Acute lung injury: How macrophages orchestrate resolution of inflammation and tissue repair. Frontiers in Immunology. 2011;**2**:65

[211] Aggarwal NR, King LS, D'Alessio FR. Diverse macrophage populations mediate acute lung inflammation and resolution. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2014;**306**:L709-L725

[212] Ariel A, Maridonneau-Parini I, Rovere-Querini P, Levine JS, Mühl H. Macrophages in inflammation and its resolution. Frontiers in Immunology. 2012;**3**:324-324