

Chapter 2

Polarized Activation of Macrophages

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2.1 Introduction

The first line of defense against pathogens is constituted by the innate immune system. Several recent evidences also indicate innate immunity receptors as primary sensors of tissue damage and metabolic disorders (Medzhitov 2008; Verbist et al. 2013). The innate immune system comprises a cellular and a humoral arm. Mononuclear phagocytes such as macrophages belong to the cellular arm of innate immunity. These cells along with the dendritic cells play a pivotal role in initiating, orientating, and modulating many aspects of the adaptive response.

In addition to their role as innate effector cells, macrophages and neutrophils also represent a major source of humoral, fluid phase pattern recognition molecules (Bottazzi et al. 2010; Deban et al. 2010). Among them are the long pentraxin PTX3, members of the ficolin and collectin family, and serum amyloid A. Since they can be considered as functional ancestors of antibodies, the production of these soluble mediators by phagocytes bridges the gap between the cellular and the humoral arm of innate immunity (Bottazzi et al. 2010).

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Macrophages are found in almost all tissues and have important roles in immunity, tissue repair, metabolic homeostasis, and development (Biswas and Mantovani 2010, 2012; Gordon and Martinez 2010; Pollard 2009; Wynn et al. 2013). Phenotypic and functional plasticity is a key feature of macrophages (Mantovani et al. 2002, 2004; Martinez et al. 2009; Sica and Mantovani 2012; Mosser and Edwards 2008; Gordon and Taylor 2005; Biswas and Mantovani 2010). Under physiological conditions, macrophages modulate their morphological and functional aspects in response to their tissue microenvironment and give rise to distinct resident populations, such as Kupffer cells in the liver, alveolar macrophages in lungs, lamina propria macrophages in the gut, and microglia in the brain. Under pathological stimuli, such as microbes or tissue damage, macrophages activate their effector functions, namely antimicrobial and antitumoral activities. However, far from being only a transient increase in their effector functions, it is now clear that macrophage “activation” is characterized by several distinct aspects which give rise to macrophage phenotypes with distinct and specific roles (Mackaness 1969; Adams and Hamilton 1984; Evans and Alexander 1972). In this regard, the discovery of an IL-4 mediated “alternative” form of macrophage activation (Stein et al. 1992) has shed new light on the complexity of macrophage polarization. It is now widely accepted that, mirroring the Th1–Th2 paradigm and under the crucial influence of soluble mediators, namely IFN- γ or IL-4/IL-13, macrophages can be polarized toward a “classical” M1 or “alternative” M2 phenotype, respectively. However, M1 and M2 phenotypes are two extremes of a spectrum of functional states which make up the complexity of macrophage plasticity (Biswas and Mantovani 2010; Mantovani et al. 2002; Mosser and Edwards 2008; Sica and Bronte 2007; Sica and Mantovani 2012).

Here we will review the salient features of macrophage polarization as well as the underlying genetic and epigenetic mechanisms, following an overview of the new findings on macrophage origin and development.

2.2 Origin and Diversity of Macrophages

Tissue macrophages were classically viewed as terminally differentiated cells derived from circulating monocytes that originate in the bone marrow. This point of view has recently been challenged by increasing evidence that suggest tissue macrophages to originate prior to birth and maintained in the adulthood, independent of the contribution from monocytes (Wynn et al. 2013; Yona et al. 2013). In the mouse at least three distinct lineages of mononuclear phagocytes have been described: the first one derives from the yolk sac (YS) and gives rise to the tissue-resident populations of macrophages (defined as F4/80^{high}) in skin, spleen, pancreas, liver brain and lung; the second population originates from fetal liver and gives rise to Langerhans cells, with a minor contribution from YS; and the third one originates from the bone marrow and gives rise to circulating monocytes that differentiate into the F4/80⁺ macrophage population within the tissues, e.g., lamina propria macrophages

(Schulz et al. 2012; Wynn et al. 2013; Ginhoux et al. 2010; Hoeffel et al. 2012). In some organs like kidney and lung, co-existence of macrophages derived from YS as well as circulating monocytes has been proposed. In the same vein, two distinct populations of Kupffer cells (KCs) have been identified: the first one, radiosensitive, bone marrow-derived, rapidly replaced from hematopoietic precursors upon reconstitution following irradiation reconstitution and a second one, radioresistant, termed “sessile” because of the absence of rapid turnover and the missing capacity for local recruitment. Only the first KC population was found to take part into inflammatory responses (Klein et al. 2007). Interestingly in the case of lung, a recent paper demonstrated fetal monocytes to give rise to alveolar macrophages (Guilliams et al. 2013). However, further studies will be required to clarify the relative contributions of YS and fetal liver in the origin of different tissue-resident macrophages.

Colony stimulating factor-1 (CSF-1) and its receptor (CSF-1R) is a major cytokine regulating the differentiation of macrophages (Chitu and Stanley 2006; Hamilton and Achuthan 2013). Accordingly, genetic ablation of CSF-1 or its receptor, CSF-1R results in the loss of macrophages in many tissues, such as skin, brain, bone, testis, and ovary. However compared to the CSF-1 deficiency, genetic ablation of CSF-1R resulted in a more severe phenotype, characterized by a complete lack of microglia, suggesting a role for another ligand of the CSF-1R (Erblich et al. 2011). This was identified as IL-34 (Wang et al. 2012; Lin et al. 2008; Wei et al. 2010). Indeed, genetic ablation of IL-34 had resulted in loss of microglia and Langerhans cells (Wang et al. 2012). A recent study on the transcriptional factors responsible for macrophage differentiation revealed an interesting dichotomy with YS-derived murine tissue-resident macrophages (such as microglia) to be dependent on CSF-1R and the transcription factor PU.1 but not Myb, while the bone marrow-derived macrophages being dependent Myb (Schulz et al. 2012). Other factors like GM-CSF has been shown to be critical to differentiation of alveolar macrophages (Guilliams et al. 2013) and the compensatory role of VEGF in osteoclast development (Niida et al. 1999).

In contrast to the steady-state differentiation of macrophages as described above, under pathological situation like inflammation, blood monocytes are a key source of inflammatory macrophages and inflammatory DCs. However, in murine models of Type 2 inflammation, macrophage accumulation was found to be maintained by local self-renewal, independently of replacement by circulating monocytes or other putative precursors (Jenkins et al. 2011; Liddiard et al. 2011; Davies et al. 2011). Interestingly, in the liver, KCs have also been suggested to be maintained by local proliferation, following hepatectomy (Widmann and Fahimi 1975). However, further studies are necessary to ascertain the relative role of monocyte-derived and local expansion of macrophages in other tissue compartments upon pathological settings. Lastly, considering the emerging differences between murine and human macrophages differ a lot from each other (Martinez et al. 2013), it will be interesting to explore the existence of multiple origins and the functional significance of distinct lineages of macrophages in human settings.

2.3 Macrophage Activation and Polarization

The concept of plasticity of mononuclear phagocytes became more complex when an alternative form of macrophage activation induced by IL-4 was found (Stein et al. 1992). Indeed, the Th1 cytokine, IFN- γ alone or together with microbial stimuli (e.g., LPS) or inflammatory cytokines (e.g., TNF and GM-CSF) was the first soluble mediator found to activate classical effector functions of macrophages (Fig. 2.1). IL-4 and IL-13 were subsequently found to be responsible for an “alternative” (M2) form of macrophage activation (Gordon 2003) (Fig. 2.1). The term M1 and M2 was initially proposed to describe macrophage populations that showed distinct nitrogen metabolism pathways (Nitric oxide versus arginine) upon LPS or IFN γ stimulation, depending on whether they were derived from Th1 mice strains (e.g., C57/BL6) or Th2 mice strains (e.g., Balb/c) (Mills et al. 2000). This concept was extended and further developed by Mantovani and colleagues to propose a general scheme for macrophage polarization, wherein M1 state represented the classically activated macrophages, whereas the M2 state included the alternatively activated macrophages (Mantovani et al. 2002). It is now known that other mediators besides IL-4 and IL-13 can also drive M2 polarization. For example, IL-33, a cytokine of the IL-1 family (Hazlett et al. 2010; Kurowska-Stolarska et al. 2009), amplifies IL-13-induced polarization of alveolar macrophages to an M2 phenotype which is responsible for lung eosinophilia and inflammation (Kurowska-Stolarska et al. 2009). Similarly, IL-21 is another Th2-associated cytokine that is shown to promote M2 activation of macrophages (Pesce et al. 2006). CSF-1 and IL-34 have also been suggested to polarize macrophages to a M2 phenotype (Foucher et al. 2013; Martinez et al. 2006). Indeed, a study of the LPS response of GM-CSF and CSF-1 derived bone marrow macrophages showed the former to induce more IL-12 and IL-23 resembling an M1 state while the latter induced more of IL-10 but no IL-12/23, suggesting a M2 polarization (Fleetwood et al. 2007). Activin A was found to be one of the molecules responsible for the M1 polarization of GM-CSF-derived macrophages (Sierra-Filardi et al. 2011).

In addition, among the various activation states that characterize the macrophage complexity is an “M2-like” state, which shares some but not all the functional aspects of M2 cells (Biswas and Mantovani 2010) (Fig. 2.1). Various stimuli, such as immunoglobulin complexes, glucocorticoids, transforming growth factor- β (TGF- β), and IL-10, give rise to M2-like functional phenotypes that exhibit properties similar to IL-4- or IL-13-activated macrophages (e.g., high expression of mannose receptor, IL-10, and angiogenic factors) (Mantovani et al. 2004). In addition, many *in vivo* conditions were found to be characterized by the appearance of M2-like macrophages, such as in the placenta and embryo, helminth or *Listeria* infection, obesity, and cancer (Auffray et al. 2007; Gustafsson et al. 2008; Odegaard et al. 2007; Rae et al. 2007; Raes et al. 2005).

From the functional point of view, M1 cells play a pivotal role in polarized Th1 responses and mediate resistance against intracellular parasites and tumors. In fact, these cells produce high levels of IL-12 and IL-23, as well as effector molecules

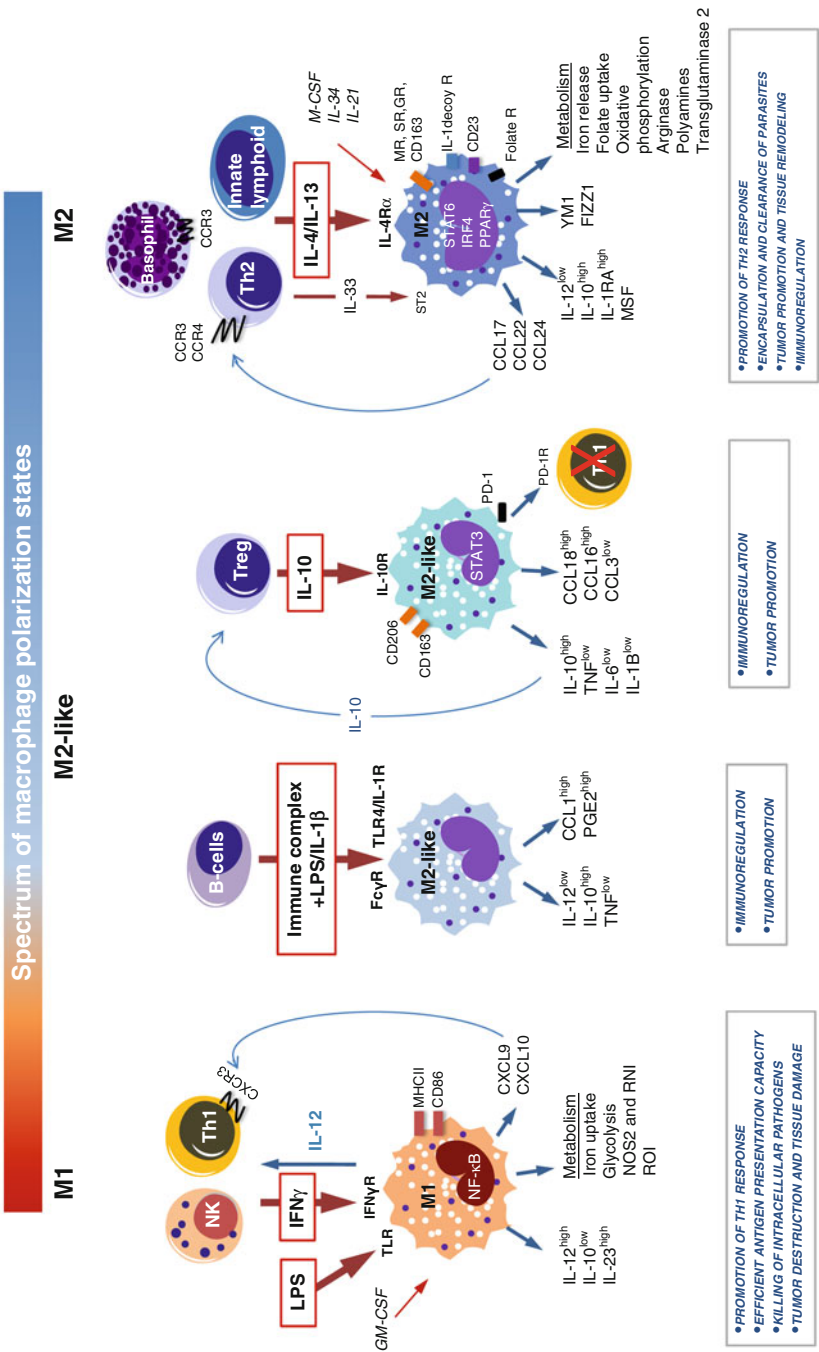


Fig. 2.1 Polarized activation of macrophages. Figures showed the salient features of the M1, M2, and M2-like polarized macrophages. For each polarization state, key genes, metabolic features, transcription factors, and functional properties associated with it are indicated. The principal stimuli responsible for each polarizing state are indicated by the *red box* (color figure online). Other polarizing stimuli are shown in *italics*. Crosstalk between polarized macrophage and lymphocyte subsets is also shown. Figure is adapted from Biswas and Mantovani (2010)

(e.g., reactive nitrogen and oxygen intermediates, RNI, ROI) and inflammatory cytokines (IL-1 β , TNF, IL-6), but low levels of the immunoregulatory cytokine IL-10. On the contrary, the various forms of M2 macrophages generally express high levels of IL-10, low levels of IL-12 and IL-23, and display variable capacity to produce inflammatory cytokines. M2 cells are generally characterized by high expression of scavenger, mannose, and galactose-type receptors as well as Arginase-1, which is responsible for the production of ornithine and polyamines. M2 cells also express low levels of IL-1 β and caspase 1, high levels of IL-1ra and decoy type II receptors (Dinarello 2005). In terms of function, M2 cells are mainly involved in polarized Th2 responses, such as parasite clearance (Noel et al. 2004). In addition, these cells along with M2-like macrophages display immunoregulatory properties, promote tissue remodeling, angiogenesis, and tumor progression (Wynn 2004; Mantovani et al. 2013; Biswas and Mantovani 2010).

Chemokine production and chemokine receptor expression are also differentially represented by M1- and M2-polarized macrophages. M1 macrophages express typical Th1 cell-attracting chemokines such as CXCL9 and CXCL10, while M2 macrophages express the chemokines CCL17, CCL22 and CCL24 (Mantovani 2008; Martinez et al. 2006; Medzhitov and Horng 2009). Chemokines themselves can also influence macrophage polarization such as CCL2 promoting an M2-like phenotype while CXCL4 inducing a unique macrophage phenotype with a mixture of both M1 and M2 characteristics (Gleissner et al. 2010; Roca et al. 2009). Finally, cellular metabolism of iron, folate, and glucose is also differentially regulated between M1- and M2-polarized macrophages (Puig-Kroger et al. 2009; Recalcati et al. 2010; Rodriguez-Prados et al. 2010; Biswas and Mantovani 2012) (Fig. 2.1). In this regard, the expression of the protein metabolism enzyme, Transglutaminase 2 has been found to be a conserved M2 characteristics in human and mouse macrophages (Martinez et al. 2013). Finally, consistent with concept of polarization, the functional phenotypes expressed by macrophages in vivo or ex vivo in pathological conditions such as parasite infections, allergic reactions, and tumors reflect many aspects of polarized M1 and M2 macrophages [for review, (Sica and Mantovani 2012)]. However, macrophages with overlapping M1–M2 characteristics and shifts in their polarization states in course of pathological setting have also been noted suggesting the plasticity of these cells (Biswas and Mantovani 2010).

2.4 Transcriptional Regulation of Macrophage Polarization

Over the last few years, considerable progress has been made in toward characterizing the transcription factors, epigenetic mechanisms, and post-transcriptional events regulating macrophage polarization (Natoli and Lawrence); Also see Chapter 26 by Natoli and colleagues. IFN- γ was the first cytokine identified to induce M1 polarization (Nathan et al. 1983). Binding of IFN- γ to its receptor induces JAK 1/2-mediated phosphorylation and dimerization of Signal transducer and activator of transcription 1 (STAT1) (Shuai et al. 1993), which in turn engages responsive

elements in the promoters of M1 phenotype related genes such as iNOS, IL-12, and CXCL10 (Darnell et al. 1994). STATs are also involved in LPS-mediated M1 polarization through TLR4 activation. In response to LPS, the TRIF-dependent TLR4 pathway triggers IFN Regulatory Factor 3 (IRF3) activation which induces the expression of IFN- β . IFN- β in turn through the IFNAR triggers STAT1 and STAT2 phosphorylation. The STAT1/STAT2 heterodimer also recruits IFN-Recognition Factor 9 (IRF9) as part of a complex that binds the IFN-response gene elements (Stark et al. 1998). Another member of the IRF family, namely IRF5, whose stability is regulated through the interaction with the COP9 signalosome (Korczeniewska and Barnes 2012), was found to be activated in M1 macrophages. IRF5 activation in M1 cells regulates the expression of IL-12, IL-23, and TNF, thereby controlling Th1 and Th17 responses (Krausgruber et al. 2011). Expression of M1 macrophage-associated genes is also promoted by the Notch-RBP-J axis, which induces the synthesis of IRF8 by selectively augmenting IRAK2-dependent signaling via TLR4 (Xu et al. 2012). JNK activation is also required for pro-inflammatory macrophage activation and lack of JNK in macrophages protected mice against insulin resistance (Han et al. 2013).

While M1-promoting signals activate STAT1, IL-4 and IL-13 skew macrophages toward the M2 phenotype via STAT6 (Sica and Bronte 2007). Indeed, binding of IL4 or IL13 to their receptors promote the phosphorylation and dimerization of STAT6, which in turn recruits IRF4 and triggers the transcription of M2-associated genes, such as mannose receptor (*Mrc1*), resistin-like α (*Retnla*, *Fizz1*), chitinase 3-like 3 (*Chi3l3*, *Ym1*) (Gordon and Martinez 2010; Junttila et al. 2008) (Pauleau et al. 2004) as well as the inhibition of many inflammatory genes (Ohmori and Hamilton 1998). Another member of the same family, STAT3 is the main transcription factor regulated by IL-10 and induces the expression of several genes related to the M2-like phenotype (*Il10*, *Tgfb1*, *Mrc1*) (Lang et al. 2002; Gordon 2003; Mantovani et al. 2002). Moreover, among the M2-promoting transcription factors, STAT5 also finds a place due to its activation in response to IL-3 (Kuroda et al. 2009).

Members of the suppressor of cytokine signaling (SOCS) family block JAK/STAT pathway by negative feedback in macrophages. In fact, IL-4 and IL-13 up-regulate SOCS 1 and 2, thus inhibiting STAT1 pathway and interfering with M1 polarization. On the contrary, IFN- γ in concert with TLR stimulation, up-regulates SOCS3, which in turn inhibits STAT3, resulting in the dampening of M2 polarization (Spence et al. 2013; Whyte et al. 2011). A SOCS3-dependent pathway has also been found to be involved in RBP-J-mediated Notch signaling regulating macrophage polarization (Wang et al. 2010b).

IL-4-STAT6 pathway modulates various transcription factors promoting M2 polarization of macrophages. For instance, the nuclear receptor peroxisome proliferator-activated- γ (PPAR γ) is constitutively expressed at low levels in macrophages but once induced by IL4-STAT6, it inhibits STAT, NF- κ B, and AP-1, thus inhibiting M1 response (Odegaard et al. 2007; Ricote et al. 1998; Szanto et al. 2010). PPAR γ activity similarly promotes a M2 phenotype in tissues and its expression is also induced by IL4-STAT6 pathway (Odegaard et al. 2008; Kang et al. 2008). Of relevance, STAT6 synergizes with Krüppel-like factor 4 (KLF4)

(Liao et al. 2011; Cao et al. 2010). Indeed, IL4 induces STAT6 phosphorylation to promote KLF4 gene expression. KLF4 in turn synergizes with STAT6 to promote M2 gene expression (*Arg-1*, *Mrc1*, *Fizz1*, *PPAR γ*) and inhibits M1 genes (*TNF α* , *Cox-2*, *CCL5*, *iNOS*) preventing NF- κ B activation through the sequestration of the necessary co-activators. Thus, KLF4 functions as a point of no return in M1 versus M2 polarization: in the absence of KLF4 M1 polarization is facilitated and M2 polarization is impaired (Liao et al. 2011). In parallel to KLF4, KLF2 impairs macrophage activation by inhibiting the NF- κ B/HIF-1 α functions, even though the lack of KLF2 is not associated to defects in M2 marker expression (Mahabeleshwar et al. 2011).

Downstream of IL-4 signaling, human macrophages also activate c-Myc, which modulates the expression of genes associated with M2 activation (*Scarb1*, *Alox15*, and *Mrc1*), as well as STAT6 and PPAR γ activation (Pello et al. 2012b). Accordingly, in an in vivo model, the myeloid-specific c-Myc deletion resulted in a delayed maturation of tumor-associated macrophages (TAMs) and a reduction of their pro-tumoral functions (reduced expression of VEGF, MMP9, and HIF1 α) that was associated with impaired tissue remodeling, angiogenesis, and reduced tumor growth (Pello et al. 2012a).

NF- κ B is a key transcriptional regulator of both M1 and M2 polarization (also see Chapter 21 by Lawrence). LPS and TLR-induced NF- κ B activation play a pivotal role in the expression of many inflammatory genes and orchestration of M1 polarization (Bonizzi and Karin 2004). Indeed, many M1 genes present a NF- κ B binding site in their promoter region, including iNOS, CCL2, COX2, and CCL5 (Huang et al. 2009). In contrast, NF- κ B activation also triggers a genetic program necessary for resolution of inflammation and M2 skewing of tumor-associated macrophages (Lawrence and Gilroy 2007; Hagemann et al. 2008). In this regard, nuclear accumulation of p50 NF- κ B homodimers was observed in both TAMs and LPS-tolerant macrophages, suggesting a role of this transcriptional repressor in promoting M2 phenotype and impairing M1 polarization (Porta et al. 2009; Saccani et al. 2006). Thus, depending on the temporal framework, the stimuli involved and the relative amounts of different NF- κ B homo- or heterodimers, this master transcription factor can drive macrophage polarization to distinct and contrasting outcomes. The nuclear receptor NR4A1 (Nur77) which is expressed in macrophages and within atherosclerotic lesions was recently found to inhibit the activation of the p65 NF- κ B in macrophages, thus acting as a negative regulator of M1 polarization (Hanna et al. 2012).

Hypoxia Inducible Factors (HIFs) play important roles in macrophage polarization. HIF-1 α and HIF-2 α were found to be differentially expressed in M1- versus M2-polarized macrophages (Takeda et al. 2010). Moreover, Th1 cytokines promote HIF-1 α activity via NF- κ B and mediate transcription of iNOS (M1-associated gene); Th2 cytokines promote HIF-2 α activation, which limits nitric oxide production by inducing arginase 1 (M2 associated gene) (Takeda et al. 2010). Earlier study with myeloid cell-specific HIF1 α knockout also indicated its contribution to the inflammatory and bactericidal response of macrophages (Cramer et al. 2003). However, myeloid cell-specific HIF2 α knockout has revealed its dominant role in macrophage inflammatory response to M1 stimuli and macrophage migration into

tumors (Imtiyaz et al. 2010). Further studies considering the temporal interaction of the HIF isoforms may shed further light on their differential contribution in macrophage activation and polarization.

2.5 Epigenetic Regulation of Macrophage Polarization

Epigenetic changes define modifications in DNA that do not alter the genetic sequence but regulate the expression of encoded information in a context-specific way. They usually occurs post-translationally and comprises modifications of histones, such as methylation, acetylation, and phosphorylation, that set the “histone code,” aimed at controlling the “availability” of chromatin for selected transcription factors, thus regulating the final rate of the expression of a target gene (Ivashkiv 2012). Recent evidence suggests that macrophage polarization may be controlled by different chromatin states of relevant gene loci (Medzhitov and Horng 2009; Smale 2010; Natoli et al. 2011). As a general point of view, the gene loci involved in macrophage polarization may present three transcriptional states: (a) a repressed state, characterized by “repressive” histone marks, namely trimethylation of histone 3 lysine 9 (H3K9me3), lysine 27 (H3K27me3), and lysine 79 (H3K79me3); (b) an intermediate transcriptional state, characterized by the simultaneous presence of activating (H3K4me3, H3K9,14-Ac) and repressing histone marks (H3K9me3 and H3K27me3); and (c) an active transcriptional state, characterized by open chromatin configuration and active histone marks, such as trimethylation of histone 3 lysine 4 (H3K4me3) (Medzhitov and Horng 2009; Wei et al. 2009; Barski et al. 2007).

Epigenetic remodeling modulates macrophage activation, differentiation, and polarization. As an example, a reduced global DNA methylation is associated with myeloid commitment from hematopoietic stem cells, in comparison with that occurring during lymphoid commitment (Takeuchi and Akira 2011). During macrophage differentiation, some pivotal transcription factors such as PU.1 and CCAAT/enhancer binding protein (C/EBP) α may directly bind and open the regulatory regions of several M1 genes induced in response to TLR ligands (e.g., TNF, IL-1 β , IL-6, IL-12p40, CXCL10) (Ghisletti et al. 2010; Jin et al. 2011). During M1 macrophage polarization, IFN γ -induced STAT1 activation mediates chromatin opening (Chen and Ivashkiv 2010). In resting macrophages, inflammatory gene transcription is “silenced” by repressive elements, such as repressors (e.g., BCL6) or receptors that sequester activating factors (histone deacetylases and demethylases). TLR activation results in dissociation of repressors from relevant gene loci and in activation of demethylases, such as Jumonji JMJD3, JMJD2d, PHF2, and AOF1, that eliminate negative histone marks, thus making chromatin accessible to the transcription machinery (De Santa et al. 2009; Stender et al. 2012; Zhu et al. 2012). Among these enzymes, TLR engagement induces the expression of the H3K27 demethylases JMJD3 that is involved in fine-tuning the expression of a set of genes skewing macrophages toward M1 polarization (De Santa et al. 2009). However, *in vivo* evidence showed that JMJD3 is dispensable for M1 polarization, but is fundamental for M2 macrophage polarization to

helminth infection, through the induction of IRF4, required for M2 polarization, as mentioned before (Sato et al. 2010). Noteworthy, M2 polarization in response to IL-4 seems to be independent of JMJD3, suggesting that macrophage polarization in one direction in response to distinct stimuli may follow distinct ways (Sato et al. 2010). IL-4-induced M2 polarization is counteracted by HDAC3, which deacetylates enhancers of IL-4 responsive genes (Mullican et al. 2011).

Histone methylation is also controlled by oxygen availability. In macrophages, hypoxia impairs Jumonji histone demethylases activity, thus favoring the prevalence of repressive marks, (H3K9me2/me3), and the consequent inhibition of transcription of chemokine (Ccl2) and chemokine receptor (Ccr1 and Ccr5) genes (Tausendschon et al. 2011).

Epigenetic regulation consists of a further level of modulation of cellular functions and phenotypes. Thus, proteins that interact with post-translationally modified histones may represent an intriguing molecular target for new therapeutic strategies. To this regard, the bromodomain and extracellular domain (BET) family proteins recognize acetylated histones, thus promoting transcription by RNA polymerase II (Jang et al. 2005; Yang et al. 2005). A synthetic compound (I-BET) which inhibit the interaction between BET proteins and acetylated histones has been found to repress the expression of genes involved in M1 polarization in LPS-activated macrophages, thus providing a new potential tool against lipopolysaccharide-induced endotoxic shock and bacteria-induced sepsis (Nicodeme et al. 2010). Compounds that inhibit JMJD3 and related demethylases were found to reduce the LPS-induced inflammatory cytokines production by human primary macrophages (Kruidenier et al. 2012).

Glucocorticoids (GCs) are one of the most potent anti-inflammatory drugs that interact with homodimeric nuclear receptors (GRs), which regulate transcription of target genes by binding to glucocorticoid response elements (GREs) (Glass and Saijo 2010). It was recently found that following TLR4 engagement by LPS in macrophages, GR cistrome is dramatically remodeled to an expanded inflammatory cistrome, that includes both GR-induced and -repressed genes (Uhlenhaut et al. 2013). Interestingly, negative GR enhancers selectively use the co-repressor GRIP1, interfere with the IRF3 activity, and present reduced histone acetylation, thus suggesting a role for the epigenetic regulation and chromatin status in driving the transcriptional effect on GR controlled target genes, beyond the GR itself (Uhlenhaut et al. 2013).

2.6 MicroRNA Regulation of Macrophage Activation and Polarization

Micro RNA (miRNAs) are small (20–22 nucleotides) non-coding RNAs which bind to the 3' untranslated regions (UTRs) of target genes, thus repressing mRNA translation and/or inducing degradation of target gene transcripts, resulting in the inhibition of the target gene expression (Bartel 2009). A huge number of miRNAs have been identified and each miRNA may control several mRNA transcripts: this

post-transcriptional mechanism of gene expression regulation is emerging as a major player in modulating a number of biological processes.

An intense experimental effort has been made in identifying miRNAs that are differentially expressed in polarized macrophages and recent evidence describe a role for these non-coding sequences in regulating the differential gene expression profiles in macrophages during inflammation and tumorigenesis (Also see Chapter 28 by Locati et al.). In particular, both in human and murine monocytes and macrophages, TLRs signaling has been associated to the regulation of miRNAs, thus activating multiple targeting strategies that modulate expression of key molecules and fine-tune pro- and anti-inflammatory processes. The best characterized pro-inflammatory miRNA is miR-155, which is strongly induced by LPS or Type I interferons in both mouse and human monocytes and macrophages (O'Connell et al. 2007). The well-established pro-inflammatory function of this molecule is due to its ability in increasing the TNF transcript stability (Bala et al. 2011), promoting antiviral immunity through SOCS1 down-regulation (Wang et al. 2010a), and favoring atherosclerosis by targeting BCL6 (Nazari-Jahanigh et al. 2012). In contrast, miR-146a, the first miRNA shown to be induced by TLRs activation in macrophages, can itself regulate TLR signaling pathway by targeting key signaling molecules such as IRAK-1 and TRAF6 (Taganov et al. 2006), thus acting as negative regulator of inflammation (Jurkin et al. 2010) and in endotoxin tolerance (Nahid et al. 2009). TLRs engagement induces others miRNAs, namely, miR-9 (Bazzoni et al. 2009), miR-21 (Sheedy et al. 2010), and miR-147 (Liu et al. 2009), all of which have been demonstrated to operate a feedback control of the NF- κ B-dependent response, by directly fine-tuning the expression of key members of the NF- κ B family (miR-9) or down-regulating the translation of the pro-inflammatory tumor suppressor, programmed cell death 4—PDCD4, an inhibitor of IL-10 production (miR-21). MiR-125a/b play a dual role in the control of inflammatory circuitries, as they reduce the TNF transcript stability (Tili et al. 2007), but at the same time, also sustain inflammation enhancing NF- κ B signaling by targeting the NF- κ B negative regulator, TNF α Induced Protein 3 (TNFAIP3, A20) (Kim et al. 2012), and IRF4, thus resulting in an enhanced macrophage activation (Chaudhuri et al. 2011).

Considering their purpose in modulating TLR-mediated cell activation, anti-inflammatory stimuli may also act through miRNA induction or repression. To this regard, IL-10 has recently been shown to directly induce miR-187 in TLR4-activated monocytes: miR-187 directly targets TNF mRNA and indirectly decreases IL-6 and IL-12p40 expression, through the down-modulation of I κ B ζ , a positive transcriptional regulator of these two cytokines (Rossato et al. 2012). In addition, our group recently identified miR-146b as a second IL-10-dependent miRNA and demonstrated its ability in dampening the production of inflammatory mediators by multiple targeting of components of the TLR signaling pathway (Curtale et al. 2013).

A clear role of miRNAs is emerging in macrophage polarization. To this regard, miR-125 and miR-29b interfere with M2 activation by targeting IRF4 and sustain M1 activation via targeting the NF- κ B negative regulator A20, respectively (Chaudhuri et al. 2011; Graff et al. 2012). In the same direction, miR-155 targets

the IL-13 receptor α chain, thus interfering with M2 polarization, and C/EBP β , a major transcription factor controlling the expression of M2 markers such as Arg1 and Chi3l3 (He et al. 2009), thus resulting in macrophage skewing toward the M1 phenotype.

In contrast, two intronic miRNAs are co-regulated together with their host M2 genes and thus their expression increases in response to alternative activation. MiR-378 is hosted in the first intron of the PPAR γ gene and acts as a negative regulator as it targets the IL-4 signal transducer Akt1 (Ruckerl et al. 2012). MiR-511 is hosted in the fifth intron of the mannose receptor 1 gene (also known as CD206): it is highly expressed in M2 macrophages and TAMs and is shown to down-regulate the pro-tumoral genetic program of TAMs, inhibiting tumor growth (Squadrito et al. 2012). Quite recently, miRNA let-7c has been found to be involved in promoting murine M2 polarization, by targeting the negative regulator of TLR4-mediated inflammatory response C/EBP- δ and by regulating bactericidal and phagocytic activities of murine macrophages (Banerjee et al. 2013). Conversely, murine *in vitro* and *in vivo* evidence indicate that miR-19a-3p inhibits the M2 phenotype of macrophages, by targeting the protooncogene Fra-1, thus repressing its downstream genes VEGF, STAT3, and pSTAT3. As a result, miR-19a-3p was found to inhibit *in vivo* breast cancer progression and metastasis (Yang et al. 2013). Finally, a recent report identified a set of miRNAs specifically expressed in distinct subsets of M2 and M1 human monocyte-derived macrophages and showed their influence on cytokine profile (Graff et al. 2012). However, seven of the eight identified miRNAs were passenger strands, that usually are not included in the silencing complex, but are quickly degraded (Bartel 2004): the real functional significance for these miRNAs in macrophage polarization needs to be further clarified.

2.7 Concluding Remarks

Plasticity is a well-known characteristic of the monocyte–macrophage lineage. Within the tissue microenvironment, the complex integration of tissue-specific signals, microbial factors, and soluble mediators determines genetic re-programming, phenotypic changes, and differential activation of these cells. The pathologic consequences of macrophage polarization imply that specific targeting of polarized macrophage subsets (or activation states) can be considered as the final goal for therapeutic intervention. It is emerging that the therapeutic effect of some current drugs that were not specifically designed to target macrophages, such as PPAR γ inhibitors, statins, zoledronic acid, and glucocorticoid hormones, are likely to act by targeting cells of the monocyte–macrophage lineage [for discussion see (Sica and Mantovani 2012)]. For instance, the clinically approved anticancer agent Trabectedin has recently been found to be effective because of its major effect in inducing depletion of TAMs (Germano et al. 2013). Further investigations of mechanisms and molecules involved in polarized activation of macrophages may

facilitate the finding of novel diagnostic and therapeutic tools aimed at modulating the multi-faced functions of mononuclear phagocytes.

While this book was in production, new transcriptomic studies on macrophages revealed a spectrum model of macrophage activation states extending the current M1 versus M2-polarization model (Xu et al. 2014). Simultaneously, an effort has been made by the community to suggest an uniform nomenclature for macrophage activation (Murray et al. 2014)

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