The Metabolic Prospective and Redox Regulation of Macrophage Polarization

Chao He and A Brent Carter

1Department of Medicine, University of Alabama at Birmingham, Alabama, USA
2Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Alabama, USA
3Birmingham VAMC, Birmingham, Alabama, USA

Received date: September 15, 2015; Accepted date: November 12, 2015; Published date: November 30, 2015

Abstract:

Macrophage plasticity is an important feature of these innate immune cells. Macrophage phenotypes are divided into two categories, the classically activated macrophages (CAM, M1 phenotype) and the alternatively activated macrophages (AAM, M2 phenotype). M1 macrophages are commonly associated with the generation of pro-inflammatory cytokines, whereas M2 macrophages are anti-inflammatory and often associated with tumor progression and fibrosis development. Macrophages produce high levels of reactive oxygen species (ROS). Recent evidence suggests ROS can potentially regulate macrophage phenotype. In addition, macrophages phenotypes are closely related to their metabolic patterns, particularly fatty acid/cholesterol metabolism. In this review, we briefly summarize recent advances in macrophage polarization with special attention to their relevance to specific disease conditions and metabolic regulation of polarization. Understanding these metabolic switches can facilitate the development of targeted therapies for various diseases.

Keywords: Macrophage; Macrophage polarization; Alternative activation; Pulmonary fibrosis; Mitochondria; Reactive oxygen species; Fatty acid oxidation

Origins of Macrophages

Macrophages are innate immune cells of the mononuclear phagocyte system that play an important role in the cross-talk between the innate and adaptive immunity [1,2]. The function of macrophages varies significantly with regard to tissue specificity, such as the alveolar macrophages, the adipose tissue macrophages, Kupffer cells in the liver, and microglia cells in the central nervous system. Based on the expression of F4/80, murine tissue macrophages can trace their origin back to two sources. Macrophages that are derived within bone marrow usually express low F4/80, whereas macrophages that originate from the embryonal yolk sac typically express high level of F4/80 and are capable of proliferating in situ, a scenario seen in the radiation-induced chimeras and the bone marrow transplant mice [3-5]. To further delineate the circulating monocyte derived macrophages, studies using specific surface markers, lymphocyte antigen 6C (Ly6C), C-C chemokine receptor type 2 (CCR2), and CX3C chemokine receptor 1 (CX3CR1), two sets of monocytes are identified: the Ly6C-high and Ly6C-low monocytes [6]. The Ly6C-high monocytes are inflammatory monocytes, which have high expression of CCR2 and a low level of CX3CR1. They are short-lived and rapidly recruited to the site of inflammation during the acute infectious process. The Ly6C-low monocytes do not express CCR2 but have high level of CX3CR1. They usually do not migrate immediately to the site of infection due to their low expression of CCR2. However, Ly6C-low monocytes are usually long-lived cells and play an important role in chronic processes, such as tumorigenesis and fibrotic remodeling.

Macrophage Polarization

Macrophage polarization is a process through which macrophages obtain different phenotypes. The phenotype of a macrophage is closely related to the microenvironment in which they reside, as macrophages are able to switch phenotypes constantly both in vivo and in vitro [7,8]. In an analogy to the T-helper-cell nomenclature, where Th1 cells are associated with the response against bacteria or viruses, and Th2 cells are associated with the response to parasitic infection and tissue remodeling, macrophages can be denoted as M1 and M2 macrophages. M1 macrophages (or classically activated macrophages, CAMs) are pro-inflammatory and have potent microbicidal and tumoricidal activity, whereas the M2 macrophages (or alternatively activated macrophages, AAMs) are involved in tumor progression and tissue remodeling, including fibrosis [9,10].

Classical macrophage activation requires priming with IFN-γ, the canonical cytokine generated by Th1 cells, and activation of the downstream transcription factors, such as signal transducer and activator of transcription 1 (STAT1), nuclear factor-kappa light-chain-enhancer of activated-B cells (NF-kB), and interferon regulatory factor 5 (IRF-5). These M1 macrophages express inflammatory genes, including TNF-α, IL-1β, and IL-6. Alternatively activated macrophages are usually activated by Th2 cytokines, IL-4 and/or IL-13. The wide range of immunosuppressive cytokines and growth factors alternatively activated macrophages produce, such IL-10, IL-1ra (IL-1 receptor antagonist), and transforming growth factor-β (TGF-β), are closely related to their ability to attenuate inflammation and promote extracellular tissue remodeling. Transcription factors involved in M2 polarization include STAT3, STAT6, IRF-4, and peroxisome proliferator-activated receptor (PPAR)-γ (Figure 1). Differential metabolism of L-arginine is characteristic of M1 and M2 macrophages. L-arginine is metabolized by iNOS to generate nitric oxide (NO) in M1.
Macrophages and by arginase-1 in M2 macrophages to augment the production of polyamines and L-proline, which are essential substrates for collagen synthesis [11,12].

![Figure 1: General concepts of macrophage polarization and properties of M1 and M2 macrophages. INF-γ induces M1 (classical) macrophage polarization whereas IL-4 and/or IL-13 induce M2 (alternative) macrophage polarization.](image)

The origin of macrophages also plays a critical role in determining macrophage phenotype. *L. sigmodontis* infection induces M2 macrophage proliferation in situ, rather than by the recruitment and differentiation of circulating monocytes [13]. In contrast, in a LPS-induced COPD model, using MRI tracking of nanoparticles-labeled ex vivo, prepolarized bone marrow-derived macrophages, both M1 and M2 are recruited to the sites of inflammation in the lung at similar level [14].

**Macrophage polarization and human diseases**

The classically activated M1 macrophages boast the basic macrophage function as implied by the name given by Elie Metchnikoff in 1887. They are the dominant cells in acute infection, participating in bacteria/pathogen clearance and antigen presenting by their effective phagocytic ability. They also have compelling tumoricidal activity. M2 macrophages are actively involved in many processes associated with parasitic infection, immune tolerance, wound healing, and tumorigenesis. The function of M1 and M2 macrophages are detailed below with a particular focus of M2 macrophage and human diseases.

**Inflammation, infection, and sepsis:** The generation and role of alternatively activated macrophages (AAMs) has been studied extensively in helminth-related diseases [15-17]. After *N. brasiliensis* subcutaneous inoculation, their larvae travel to the lung and trigger a potent M2 polarization in alveolar macrophages [15]. Helminth infection not only initiates M2 polarization, but also is also capable of subverting the M1 polarization as shown in potent M2 polarization in alveolar macrophages [15].

**Cardiovascular diseases:** The exact mechanism of how different macrophage phenotypes influence myocardial remodeling remains largely unknown. M2 macrophages have been shown to be crucial for post-myocardial infarction remodeling as IL-13-/- mice have significant worsening outcome in an infarction model compared to wild-type mice [31]. Another study showed that mineralocorticoid receptor knockout mice displayed a dominant M2 polarization pattern, and these mice are protected against cardiac hypertrophy, fibrosis, and vascular damage caused by angiotensin II. Additionally, aldosterone can induce M1 polarization, while eplerenone, an aldosterone antagonist, inhibits M1 activation, underscoring the cardioprotective role of M2 macrophages [32].

**Pulmonary diseases:** Alternatively activated macrophages are also implicated in various pulmonary disorders, including COPD, asthma, pulmonary hypertension, and pulmonary fibrosis. Plasma Chitinase-1, a signature M2 protein, has been used to quantify disease severity in COPD patients [33]. One study shows a remarkable example of a pathogenic role of IL-13 in chronic obstructive pulmonary disease (COPD) that underscores the effect of M2 macrophages. The macrophages upregulate IL-13Rα1 expression and become alternatively activated by an autocrine or paracrine mechanism [34], which leads to COPD progression. The role of different macrophage phenotypes in pulmonary hypertension remains undetermined. It is known that fibroblast-derived IL-6 polarizes alveolar macrophages into an M1 pattern and drives the development of pulmonary hypertension in a paracrine fashion, together with activation of signature M1 transcription factors, STAT3 and HIF-1α [35]. Others have found that macrophages acquire an M2 phenotype during hypoxia, and M2 significantly elevated in monocytes treated with one dose of LPS. However, if these cells were pre-challenged with the same dose of LPS 24 h before the second dose, the level of TNF-α production was greatly reduced [21]. Peripheral blood monocytes and macrophages from these patients often display features resembling alternative activation of monocytes, including reduced production of pro-inflammatory mediators and expression of genes involved in tissue remodeling [21,22]. Similarly, peripheral monocytes collected from septic patients have higher level of T17 and Treg cell populations with elevated CD206 and CD163 expression, suggesting LPS-tolerance and M2 polarization [23].

**Wound and tissue remodeling:** Wound macrophages are known to undergo alternative activation [24]. Delayed healing occurs in mice with dysfunctional M2 macrophages or deficiency of signature M2 gene expression, such as *arg1* [25]. Arginase-1 is pertinent to fibrosis development as it metabolizes arginine to generate L-ornithine, which will be utilized by ornithine decarboxylase to generate L-proline and polyamines. While induction of arginase-1 by IL-4 and/or IL-13 is commonly believed to contribute to collagen deposition and fibrosis development [26,27], reports suggest that up-regulation of arginase-1 in macrophages actually inhibits fibrosis development as they compete with fibroblasts for arginine as the substrate for L-ornithine synthesis and by inhibiting Th2 cytokine production, particularly IL-13 [28]. Both IL-4 and IL-13 receptors have been shown to be essential for fibrosis development in *S. mansoni* granuloma formation [29]. Alternative activation of macrophages is the predominant macrophage phenotype in tissue samples from patients with chronic pancreatitis, and mice lacking IL-4Ra have less M2 macrophages and are protected from developing fibrotic changes after ceruletide injection [30]. By using an IL-4/IL-13 blocking peptide, similar anti-fibrotic effects can be achieved via inhibition of M2 polarization [30].

The origin of macrophages also plays a critical role in determining macrophage phenotype. *L. sigmodontis* infection induces M2 macrophage proliferation in situ, rather than by the recruitment and differentiation of circulating monocytes [13]. In contrast, in a LPS-induced COPD model, using MRI tracking of nanoparticles-labeled ex vivo, prepolarized bone marrow-derived macrophages, both M1 and M2 are recruited to the sites of inflammation in the lung at similar level [14].

Inflammation, infection, and sepsis: The generation and role of alternatively activated macrophages (AAMs) has been studied extensively in helminth-related diseases [15-17]. After *N. brasiliensis* subcutaneous inoculation, their larvae travel to the lung and trigger a potent M2 polarization in alveolar macrophages [15]. Helminth infection not only initiates M2 polarization, but also is also capable of subverting the M1 polarization as shown in [18]. In an animal model of schistosomiasis, conditional macrophage/neutrophil IL-4 receptor alpha-deficient mice (LysMCre-/-/flo) show a predominant M1 polarization and more severe infection with 100% mortality [19]. Endotoxin or lipopolysaccharide (LPS) tolerance is the reduced responsiveness to LPS stimulus after repeated exposure. It is a common scenario in patients with persistent sepsis, especially in intensive care settings [20]. TNF-α production was significantly elevated in monocytes treated with one dose of LPS. However, if these cells were pre-challenged with the same dose of LPS 24 h before the second dose, the level of TNF-α production was greatly reduced [21]. Peripheral blood monocytes and macrophages from these patients often display features resembling alternative activation of monocytes, including reduced production of pro-inflammatory mediators and expression of genes involved in tissue remodeling [21,22]. Similarly, peripheral monocytes collected from septic patients have higher level of T17 and Treg cell populations with elevated CD206 and CD163 expression, suggesting LPS-tolerance and M2 polarization [23].
Macrophages lead to the proliferation of pulmonary artery smooth muscle cells. Blocking M2 polarization can potentially attenuate the progression of pulmonary hypertension by attenuating smooth muscle cell proliferation [36]. Additionally, M2 macrophages are known to be prevalent in the lungs of patients with idiopathic pulmonary fibrosis, sarcoidosis, systemic sclerosis, asbestos-induced pulmonary fibrosis, and gamma-herpes virus-induced pulmonary fibrosis [7,37,38]. Conversely, mice with predominant M1 macrophages are protected from developing asbestos-induced pulmonary fibrosis [7,39]. Similarly, in a bleomycin-induced pulmonary fibrosis model, both fibrosis and alternative activation of macrophages are prolonged in TNF-α-/- mice. Intra-tracheal delivery of recombinant TNF-α can ameliorate established pulmonary fibrosis, partially via inducing Fas-mediated fibroblast apoptosis [40,41]. Moreover, CCL-18, a signature M2 chemokine, is known to induce lung fibroblast collagen production [42], highlighting the importance of crosstalk between macrophages and fibroblasts.

**Cancer**: Tumor-associated macrophages (TAMs) have many properties of M2 macrophages, and they contribute to tumor local invasion through secreting proteases, such as cathepsin [43]. GB111-NH₂, an inhibitor of cathepsin, decreases expression of the classic M2 genes, *fizz1* and *jmjd3*, resulting in tumor regression [44]. TAMs also promote angiogenesis and tumor growth through VEGF, leading to chemo-resistance [45,46]. M2 macrophages promote tumorigenesis by increasing signature M2 markers, such as CCL-18 [47]. IL-13, along with its receptors IL-13Ra2, induces TGF-β expression and promotes survival [49]. Exposing TAMs to the canonical Th1 cytokine, INF-γ, can reprogram TAMs to acquire M1 features and regain anti-tumor activity [50]. Similarly, targeting transcription factors crucial for TAM differentiation, such as STAT3, can also achieve tumoricidal function [51]. Molecular inhibitors targeting M2 macrophages, such as the pro-apoptotic peptide [52] and anti-VEGF antibody [53], are considered to be potential candidates for cancer treatment.

**Metabolic regulation of macrophage polarization**

**Redox status regulates macrophage polarization**: The role of oxidative stress in macrophage polarization is controversial. The development of granulomas from *S. mansoni* exposure is not impaired in IL-4-deficient mice [54,55], as other Th2 cytokines remain elevated. In addition, wound macrophages are known to undergo alternative activation despite a deficiency of Th2 cytokines in the wound environment, and the macrophage phenotype is sustained in mice lacking IL-4R. It is not clear from these studies what induced the alternative activation.

Oxidative stress has long been known to play an important role in the development and progression of pulmonary diseases. Pro-inflammatory M1 genes, such as *tnt-a*, *il-1β*, and *inos*, have all been shown to be regulated by redox proteins, including Cu,Zn-SOD [56-58]. *yml1* and *fizz1*, two signature M2 genes, are elevated in ovalbumin-challenged asthmatic mice, and their expression can be attenuated by treatment with N-acetylcysteine, a thiol-reducing agent, linking M2 polarization to oxidative stress [59]. Previous studies have shown that increases in the oxidative metabolic environment fuels alternative activation of macrophages [60], while others show that M2 macrophages generate low levels of ROS [61]. The H₂O₂ gradient, generated by dual oxidases (DUOX) in wound epithelium of zebrafish larvae, is known to be the chemo-attractants for macrophage recruitment [62]. IL-4-stimulated M2 macrophages have an enhanced mitochondrial oxygen-consumption rate [63], and inhibition of mitochondrial respiration by oligomycin dramatically increased the mRNA expression level of pro-inflammatory genes, such as *il-1β*, *tnt-a*, and *il-1β*, underscoring an important role of mitochondrial respiration in M2 polarization [64].

**Figure 2**: Redox regulation of macrophage polarization. Superoxide generated by either membrane-bound NADPH oxidase or mitochondrial electron transfer chain (ETC) will be converted to H₂O₂ by superoxide dismutase, which will inhibit M1 polarization and activate M2 polarization via STAT6. Revised from [7]. Data linking ROS to macrophage activation are emerging, but the exact role of ROS still requires further investigation. The loss of NADPH in a type I diabetes mouse model, superoxide-deficient bone marrow-derived macrophages had a marked reduction in proinflammatory M1 gene expression and showed increased M2 polarization, together with STAT6 activation [65]. Deficiency of nuclear-encoded protein NADH: ubiquinone oxidoreductase iron-sulfur protein 4 (Ndufs4), a critical component of mitochondrial complex I, is known to be related to impairment of oxidative phosphorylation [66]. Global Ndufs4 loss causes systemic inflammation with a predominant M1 polarization [67]. At the same time, a metabolic shift from fatty acid oxidation (FAO) to glycolysis was observed in Ndufs4-/- pups. Moreover, Ndufs4-/- bone marrow macrophages have significantly higher superoxide levels, which can be attenuated by MitoTEMPO to further decrease pro-inflammatory gene expression. Conversely, circulating M2 macrophages accelerate the pathological progression of amyotrophic lateral sclerosis (ALS), a disease characterized with aberrant Cu,Zn-SOD function and excessive H₂O₂ production [68]. Over-expression of Cu,Zn-SOD, the redox protein that catalyzes the generation of H₂O₂, polarizes macrophages to an M2 phenotype via activation of STAT6 with a cysteine residue (Cys258) serving as the redox switch [7]. Moreover, Cu,Zn-SOD-mediated macrophage polarization can be altered by modulating H₂O₂ generation. As previously mentioned, differential metabolism of L-arginine is characteristic of M1 and M2 macrophages. Overexpression of Cu,Zn-SOD leads to a reduction of *inos* gene expression and NO synthesis, while arginase-1 expression and urea generation is enhanced.

---

**Citation**: He C, Carter AB (2015) The Metabolic Perspective and Redox Regulation of Macrophage Polarization. J Clin Cell Immunol 6: 371. doi: 10.4172/2155-9899.1000371
[7] (Figure 2). Acute chlorine gas exposure leads to oxidation of surfactant protein and augmentation of M2 genes, such as arg1,Fizz1, and ym1 [69]. Another study showed that alveolar macrophages exposed to ozone have elevated levels of both M1 and M2 genes [70]. Interestingly, one study has compared macrophage phenotype in two Nox2-deficient mouse models, gp91phox-/- and p47phox-/- mice [71]. Mice deficient in p47phox-/- have a significant increase of M2 gene expression upon IL-4 stimulation and are protected from Listeria monocytogenes infection compared with gp91phox-/- mice [71]. Explanations for the differences include that macrophage polarization is driven by specific reactive oxygen species (H2O2 vs O2•-), the different origin of ROS (membrane-bound NADPH oxidase, particularly Nox2 versus mitochondria), or the different tissue and intracellular distribution of NADPH oxidases or SODs.

Redox regulation in macrophage polarization is closely related to hypoxic conditions and hypoxia-inducible factors (HIFs) activation. In murine macrophages, the expression of hypoxia-inducible factors HIF-1α and HIF-2α appears to be dependent on respective inducers. M1-promoting factors induce the expression of HIF-1α, whereas IL-4 primarily induces HIF-2α that regulates M2 polarization [72]. HIF-1α-/-macrophages exhibit diminished production of TNF-α and IL-6 in response to LPS/IFN-γ stimulation in a model of tumor spheroids [73].

Oxidative stress, particular the mitochondrial redox signal, is known to cause endoplasmic reticulum (ER) stress due to the proximal distance between mitochondria and ER [74]. Asbestos-treated macrophages, which show M2 polarization, have elevated ER stress with elevated level of binding immunoglobulin protein (BIP) and C/EBP homologous protein (CHOP) [75]. Induction of ER stress induces macrophage polarization from the M1 into the M2 phenotype leading to increased cholesterol deposition and enhanced foam cell formation [76]. MCP-1-induced protein (MCPIP), induced by either STAT6 or KLF-4, inhibits NF-kB in murine macrophages and instigates M2 polarization via induction of ER stress [77]. BIP and CHOP levels are elevated in THP-1 monocytes treated with ER-stress inducers, tunicamycin or thapsigargin, and the THP-1 cells undergo M2 polarization via the PPAR-γ pathway. Interestingly, M2 polarization could be reversed by treating with ER stress inhibitor 4-phenylbutyrate (PBA), emphasizing a potential therapeutic target [78].

**Metabolism of fatty acid/cholesterol regulates macrophage polarization:** Prior data show that M2 polarization is dependent on fatty acid oxidation (FAO), whereas M1 macrophages rely on aerobic glycolysis [79]. The differences between the two metabolic pathways involve a switch in the expression of 6-phosphofructo-2-kinase/fructose-2,6-bisphostase (PFK2). M1 macrophages display a high expression of glycolytic enzymes and glycolysis-related metabolites. This shift toward aerobic glycolysis, known as the Warburg effect in cancer biology, rapidly provides immune cells with ATP and metabolic intermediates. In contrast, M2 macrophages have increased expression of genes encoding molecules in FAO and oxidative phosphorylation pathways [63]. Blocking oxidative metabolism not only selectively abrogates the ability of cells to undergo alternative activation but also potentiates the expression of M1 genes. Conversely, overexpressing PGC-1β, a key transcriptional proponent of oxidative metabolism, potentiates alternative activation and prevents classical activation by augmenting FAO [60] (Figure 3). Compared with M1 macrophages, which exert their functions over short time periods, M2 macrophages are engaged in long-term cellular activities, and the relative efficiency of FAO versus that of glycolysis is well suited to meet the metabolic requirements of their roles [80]. M2 macrophages have been shown to have longer survival compared to their M1 counterparts [63], and FAO is known to support cellular longevity [81].

![Figure 3: Metabolic regulation of macrophage polarization. M1 macrophages have increased uptake of glucose and augmented glycolysis, whereas M2 macrophages have increased uptake of lipid and augmented fatty acid oxidation. Specific cytokines and transcription factors regulate these pathways. Activation of PFK2 leads to M1 polarization while over-expressing PGC-1β leads to M2 polarization.](image)

The isoprenoid pathway, which is essential for cholesterol metabolism, is a new target of modulating macrophage function. The use of statins has been associated with interstitial lung abnormalities in smoking individuals, a condition known to have a predominance of M2 macrophages [82]. Statins have potent anti-inflammatory properties and are known to orchestrate the immune response toward alternative activation via regulating isoprenoid biosynthesis [83]. The inhibition of farnesyltransferase, geranylgeranyltransferase 1, and geranylgeranyltransferase II decreases cell survival, migration, and proliferation in many cancers [84]. Activation of Rac1 by geranylgeranylation in alveolar macrophages promotes characteristics of M2 macrophages and associates with the development of oxidative stress and pulmonary fibrosis. Digeranyl bisphosphonate (DGBP), which impairs geranylgeranylation of Rho GTPases by inhibiting geranylgeranyl diphosphate synthase, reduces mitochondrial oxidative stress and abrogates progression of pulmonary fibrosis by inhibiting Rac1 activation and its mitochondrial translocation [85].

Both the Akt pathway and the isoprenoid pathway are important in maintaining cell survival. Akt regulates apoptosis by modulating isoprenoid pathway. Akt-deficient macrophages (Akt-/-) have a significant increase of apoptosis. Akt overexpressing macrophages have a distinct M2 polarization pattern and promote fibrotic development. Conversely, Akt+/+ mice are protected from developing pulmonary fibrosis [86]. Statins activate Akt and, as previously mentioned, the use of statins has been associated with interstitial lung abnormalities in smoking individuals [82,87]. Surface scavenger receptors, which are crucial for internalization of extracellular oxidized lipid particles, are capable of regulating macrophage polarization. CD36 is known to be important for triacylglycerol substrate uptake and sequential oxidative phosphorylation, which leads to M2 polarization [63]. Another surface scavenger receptor, MARCO (macrophage receptor with collagenous...
structure) has been shown to increase mitochondrial oxidative stress and regulates macrophage polarization. Over-expression of wild-type MACRO leads to increased M2 gene expression, while knockdown of MARCO reduces M2 gene expression. Moreover, MACRO+ mice are protected from developing asbestos-induced pulmonary fibrosis. Inhibition of the scavenger receptor by fucoidan reduces mitochondrial H₂O₂ production, which inhibits macrophage M2 polarization [88]. Similarly, MARCO can limit inflammatory response as MACRO-deficient mice show an early-enhanced development of inflammation in response to influenza infection [89]. CD163, a scavenger receptor for the hemoglobin-haptoglobin complex, is expressed at high level by M2 macrophages in patients with idiopathic pulmonary fibrosis [90].

Conclusion

Macrophage polarization is a dynamic process that our immune system utilizes to maintain an immunological homeostasis. Various factors influence polarization and further investigation for metabolic regulation in shaping the macrophage differential profile is warranted. In this review, we briefly summarize recent advances in macrophage polarization with special attention to their relevance to specific disease conditions and metabolic regulation of polarization. Understanding these metabolic switches can facilitate the development of targeted therapies for various diseases related to the distinct macrophage subtype.

Acknowledgement

This publication was supported in part by National Institute of Health Grants 2R01ES015981-08 and by a Merit Review from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Biological Laboratory Research and Development BX001135-04.

References

1. Guilliams M, De Kleer I, Henri S, Post S, Vanhoutte L, et al. (2013) Alveolar macrophages develop from fetal monocytes that differentiate into long-lived cells in the first week of life via GM-CSF. J Exp Med 210: 1977-1992.
2. Hume DA, Ross IL, Himes SR, Sasmono RT, Wells CA, et al. (2002) The mononuclear phagocyte system revisited. J Leukoc Biol 72: 621-627.
3. Schulz C, Gomez Perdiguerio E, Chorro L, Szabo-Rogers H, Cagnard N, et al. (2012) A lineage of myeloid cells independent of Myb and hematopoietic stem cells. Science 336: 86-90.
4. Schmidt A, Sucke J, Fuchs-Moll G, Freitag P, Hirschburger M, et al. (2009) Alveolar macrophages: evidence from radiation chimera studies. J Leukoc Biol 86: 186-194.
5. Tarling JD, Lin HS, Hsu S (1987) Self-renewal of pulmonary alveolar macrophages: evidence from radiation chimera studies. J Leukoc Biol 42: 443-446.
6. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, et al. (2004) The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 25: 677-686.
7. He C, Ryan AJ, Murthy S, Carter AB (2013) Accelerated development of pulmonary fibrosis via Cu,Zn-superoxide dismutase-induced alternative activation of macrophages. J Biol Chem 288: 20745-20757.
8. Guiducci C, Vicari AP, Sangalletti S, Trinchieri G, Colombo MP (2005) Redirecting in vivo elicited tumor infiltrating macrophages and dendritic cells towards tumor rejection. Cancer Res 65: 3437-3446.
9. Lucas T, Waismann A, Ranjan R, Roes J, Krieg T, et al. (2010) Differential roles of macrophages in diverse phases of skin repair. J Immunol 184: 3964-3977.
10. Zaynagetdinov R, Sherrill TP, Polosukhin VV, Han W, Ausborn JA, et al. (2011) A critical role for macrophages in promotion of urethane-induced lung carcinogenesis. J Immunol 187: 5703-5711.
11. Modoléll M, Corraliza JM, Link F, Soler G, Eichmann K (1995) Reciprocal regulation of the nitric oxide synthase/arginase balance in mouse bone marrow-derived macrophages by TH1 and TH2 cytokines. Eur J Immunol 25: 1101-1104.
12. Munder M, Eichmann K, Morán JM, Centeno F, Soler G, et al. (1999) Th1/Th2-regulated expression of arginase isoforms in murine macrophages and dendritic cells. J Immunol 163: 3771-3777.
13. Jenkins SJ, Ruckerl D, Cook PC, Jones LH, Finkelman FD, et al. (2011) Local macrophage proliferation, rather than recruitment from the blood, is a signature of TH2 inflammation. Science 332: 1284-1288.
14. Al Faraj A, Sultana Shaik A, Pureza MA, Alnafae M, Halwani R (2014) Preferential macrophage recruitment and polarization in LPS-induced animal model for COPD: noninvasive tracking using MRI. PLoS One 9: e90829.
15. Chen F, Liu Z, Wu W, Rozo C, Bowridge S, et al. (2012) An essential role for TH2-type responses in limiting acute tissue damage during experimental helminth infection. Nat Med 18: 260-266.
16. Chuah C, Jones MK, Burke ML, McManus DP, Gobert GN (2014) Cellular and chemokine-mediated regulation in schistosome-induced hepatic pathology. Trends Parasitol 30: 141-150.
17. Salgame P, Yap GS, Gause WC (2013) Effect of helminth-induced immunity on infections with microbial pathogens. Nat Immunol 14: 1118-1126.
18. Shirey KA, Cole LE, Keegan AD, Vogel SN (2008) Francisella tularensis live vaccine strain induces macrophage alternative activation as a survival mechanism. J Immunol 181: 4159-4167.
19. Herbert DR, Hölscher C, Mohrs M, Arendse B, Schwengmann A, et al. (2004) Alternative macrophage activation is essential for survival during schistosomiasis and downmodulates T helper 1 responses and immunopathology. Immunity 20: 623-635.
20. Cavallion JM, Adib-Conquy M (2006) Bench-to-bedside review: endotoxin tolerance as a model of leukocyte reprograming in sepsis. Crit Care 10: 233.
21. Pena OM, Pistolic J, Raj D, Fjell CD, Hancock RE (2011) Endotoxin tolerance represents a distinctive state of alternative polarization (M2) in human mononuclear cells. J Immunol 186: 7243-7254.
22. Adib-Conquy M, Muriel A, Schlegel D, Schwengmann A, et al. (2006) Up-regulation of MyD88 and SIGIRR, molecules inhibiting Toll-like receptor signaling, in monocytes from septic patients. Crit Care Med 34: 2377-2385.
23. Brunialti MK, Santos MC, Rigato O, Machado FR, Silva E, et al. (2012) Increased percentages of T helper cells producing IL-17 and monocytes expressing markers of alternative activation in patients with sepsis. PLoS One 7: e37393.
24. Daley JM, Brancato SK, Thomay AA, Reichner JS, Albina JE (2010) The phenotype of murine wound macrophages. J Leukoc Biol 87: 59-67.
25. Wynn TA, Ramalingam TR (2012) Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nat Med 18: 1028-1040.
26. Hesse M, Modolell M, La Flamme AC, Schito M, Fuentes JM, et al. (2001) Differential regulation of nitric oxide synthase-2 and arginase-1 by type 1/2 cytokines in vivo: granulomatous pathology is shaped by the pattern of L-arginine metabolism. J Immunol 167: 6533-6544.
27. Wynn TA, Barron L (2010) Macrophages: master regulators of inflammation and fibrosis. Semin Liver Dis 30: 245-257.
28. Pesce JT, Ramalingam TR, Mentink-Kane MM, Wilson MS, El Kasi KM, et al. (2009) Arginase-1-expressing macrophages suppress Th2 cytokine-driven inflammation and fibrosis. PLoS Pathog 5: e1000371.
29. Jankovic D, Kullberg MC, Noben-Trauth N, Caspar P, Ward JM, et al. (1999) Schistosoma-infected IL-4 receptor knockout (KO) mice, in
contrast to IL-4 KO mice, fail to develop granulomatous pathology while maintaining the same lymphopoeitic expression profile. J Immunol 163: 337-342.

30. Xue J, Sharma V, Hsieh MH, Chawla A, Murali R, et al. (2015) Alternatively activated macrophages promote pancreatic fibrosis in chronic pancreatitis. Nat Commun 6: 7158.

31. Hofmann U, Knorr S, Vogel B, Weirather J, Frey A, et al. (2014) Interleukin-13 deficiency aggravates healing and remodelling in male mice after experimental myocardial infarction. Circulation. Heart failure 7: 822-830.

32. Usher MG, Duan SZ, Ivaschenko CY, Frieler RA, Berger S, et al. (2010) Myeloid metalloproteinase-1 controls macrophage polarization and cardiovascular hypertrophy and remodeling in mice. J Clin Invest 120: 3350-3364.

33. Prasse A, Kollert F, Pechkovsky DV, Toews GB, Jungraithmayr W, Kollert F, et al. (2010) A vicious circle of alveolar macrophages and fibroblasts in mice by targeting Stat3 signaling in the hematopoietic system elicits multicomponent antimurine tumor immunity. Nat Med 16: 1314-1321.

34. El Kasmi KC, Pugliese SC, Riddle SR, Poth JM, Anderson AL, et al. (2006) Tumor necrosis factor-alpha accelerates the resolution of established fibrosis in mice by targeting chitinase-like proteins and FIZZ1 in lung tissue and bronchoalveolar lavage fluid. J Proteome Res 8: 1631-1638.

35. Chen J, Yao Y, Gong C, Yu F, Su S, et al. (2011) CCL18 from tumor-associated macrophages promotes breast cancer metastasis via PITPNM3. Cancer Cell 19: 541-555.

36. Jin Z, Wei W, Yang M, Du Y, Wan Y (2014) Mitochondrial complex I activity suppresses inflammation and enhances bone resorption by shifting macrophage-osteoclast polarization. Cell Metab 20: 483-498.

37. Pelegrin P, Surprenant A (2009) Dynamics of macrophage polarization during tumor evasion of immune surveillance. Cancer Cell 8: 822-830.

38. Padgett LE, Burg AR, Lei W, Tse HM (2015) Loss of NADPH oxidase-deficiency: a tissue-scale model for the role of mitochondria in aging. Nature 459: 996-999.

39. Huanga Y, Yuanb E, Kamoausa W, Ancukiewicza M, et al. (2012) Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proc Natl Acad Sci U S A 109: 15919-15924.

40. Pechkovsky DV, Prasse A, Frankel SK, Cosgrove SC, Riddle SR, Poth JM, Anderson AL, et al. (2006) Schistosoma mansoni Inhibiting Stat3 and IFNgamma and IL-4 knockout mice: analysis of local and regional cytokine and chemokine networks. J Immunol 179: 3565-3573.

41. Thomas DA, Massagué J (2005) TGF-beta directly targets cytotoxic T cell functions during tumor evasion of immune surveillance. Cancer Cell 8: 369-380.

42. Fichtner-Feigl S, Terabe M, Kitani A, Young CA, Fuss I, et al. (2008) Restoration of tumor immunosurveillance via targeting of interleukin-13 receptor-alpha 2. Cancer Res 68: 3467-3475.

43. Kortylewski M, Kujawski M, Wang T, Wei S, Zhang S, et al. (2005) Inhibiting Stat3 signaling in the hematopoietic system elicits multidimensional antitumor immunity. Nat Med 11: 1314-1321.

44. James KN, Wang M, Kang X, Boontheung P, Li N, et al. (2009) Oxidative metabolism and PGC-1beta attenuate macrophage-mediated zebrafish. Nature 459: 996-999.

45. Meissner F, Molawi K, Zychlinsky A (2008) Superoxide dismutase 1 regulates caspase-1 and endotoxic shock. Nat Immunol 9: 866-872.

46. Zha X, Wang T, Wei W, Yang M, Du Y, Wan Y (2014) Mitochondrial complex I activity suppresses inflammation and enhances bone resorption by shifting macrophage-osteoclast polarization. Cell Metab 20: 483-498.
68. Vaknin I, Kunis G, Miller O, Butovskiy O, Bukhshan S, et al. (2011) Excess progression of chronic myeloid leukemia while inhibiting experimental autoimmune encephalomyelitis. PloS one 6:e26921.

69. Massa CB, Scott P, Abramova E, Gardner C, Laskin DL, et al. (2014) Acute chlorine gas exposure produces transient inflammation and a progressive alteration in surfactant composition with accompanying mechanical dysfunction. Toxicol Appl Pharmacol 278: 53-64.

70. Sunil VR, Patel-Vayas K, Shen J, Laskin JD, Laskin DL (2012) Classical and alternative macrophage activation in the lung following ozone-induced oxidative stress. Toxicol Appl Pharmacol 263: 195-202.

71. Yi L, Liu Q, Orandle MS, Sadiq-Ali S, Koontz SM, et al. (2012) p47(phox) directs murine macrophage cell fate decisions. Am J Pathol 180: 1049-1058.

72. Takeda N, O'Dea EL, Doedens A, Kim JW, Weidemann A, et al. (2010) Differential activation and antagonistic function of HIF-α isoforms in macrophages are essential for NO homeostasis. Genes Dev 24: 491-501.

73. Werno C, Menrad H, Weigert A, Dehne N, Goerdt S, et al. (2010) Knockout of HIF-α1 in tumor-associated macrophages enhances M2 polarization and attenuates their pro-angiogenic responses. Carcinogenesis 3: 1863-1872.

74. Kornmann B, Currie E, Collins SR, Schuldiner M, Nunnari J, et al. (2009) An ER-mitochondria tethering complex revealed by a synthetic biology screen. Science 325: 477-481.

75. Ryan AJ, Larson-Casey JL, He C, Murthy S, Carter AB (2014) Asbestos-induced disruption of calcium homeostasis induces endoplasmic reticulum stress in macrophages. J Biol Chem 289: 33391-33403.

76. Oh J, Riek AE, Weng S, Petty M, Kim D, et al. (2012) Endoplasmic reticulum stress controls M2 macrophage differentiation and foam cell formation. J Biol Chem 287: 11629-11641.

77. Kapoor N, Niu J, Saad Y, Kumar S, Sirakova T, et al. (2015) Transcription factors STAT6 and KLF4 implement macrophage polarization via the dual catalytic powers of MCP1. J Immunol 194: 6011-6023.

78. Xiu F, Catapano M, Diao L, Stanojcic M, Jeschke MG (2015) Prolonged Endoplasmic Reticulum-Stressed Hepatocytes Drive an Alternative Macrophage Polarization. Shock 44: 44-51.

79. Rodríguez-Prados JC, Trávés PG, Cuenca J, Rico D, Aragonés J, et al. (2010) Substrate fate in activated macrophages: a comparison between innate, classic, and alternative activation. J Immunol 185: 605-614.

80. Odegaard JJ, Chawla A (2011) Alternative macrophage activation and metabolism. Annu Rev Pathol 6: 275-297.

81. van der Windt GJ, Everts B, Chang CH, Curtis JD, Freitas TC, et al. (2012) Mitochondrial respiratory capacity is a critical regulator of CD8+ T cell memory development. Immunity 36: 68-78.

82. Xu JF, Washko GR, Nakahira K, Hatabu H, Patel AS, et al. (2012) Statins and pulmonary fibrosis: the potential role of NLRP3 inflammasome activation. Am J Respir Crit Care Med 185: 547-556.

83. Youssif S, Stüve O, Patarroyo JC, Ruiz P, Radosевич J-L, et al. (2002) The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature 420: 78-84.

84. Jiang K, Coppola D, Crespo NC, Nicosia SV, Hamilton AD, et al. (2000) The phosphoinositide 3-OH kinase/AKT2 pathway as a critical target for farnesyltransferase inhibitor-induced apoptosis. Mol Cell Biol 20: 139-148.

85. Osborn-Heaford HL, Murthy S, Gu L, Larson-Casey JL, Ryan AJ, et al. (2015) Targeting the isoprenoid pathway to abrogate progression of pulmonary fibrosis. Free Radic Biol Med 86: 47-56.

86. Larson-Casey JL, Murthy S, Ryan AJ, Carter AB (2014) Modulation of the mevalonate pathway by akt regulates macrophage survival and development of pulmonary fibrosis. J Biol Chem 289: 36204-36219.

87. Kureishi Y, Luo Z, Shiojima I, Bialik A, Fulton D, et al. (2000) The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normcholesterolemic animals. Nat Med 6: 1004-1010.

88. Murthy S, Larson-Casey JL, Ryan AJ, He C, Kobzik L, et al. (2015) Alternative activation of macrophages and pulmonary fibrosis are modulated by scavenger receptor, macrophage receptor with collagenous structure. FASEB J 29: 3527-3536.

89. Ghosh S, Gregory D, Smith A, Kobzik L (2011) MARCO regulates early inflammatory responses against influenza: a useful macrophage function with adverse outcome. Am J Respir Cell Mol Biol 45: 1036-1044.

90. Gibbons MA, MacKinnon AC, Ramachandran P, Dhalwal K, Duffin R, et al. (2011) Ly6Chi monocytes direct alternatively activated profibrotic macrophage regulation of lung fibrosis. Am J Respir Crit Care Med 184: 569-581.