Macrophage plasticity and polarization: in vivo veritas

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Diversity and plasticity are hallmarks of cells of the monocyte-macrophage lineage. In response to IFNs, Toll-like receptor engagement, or IL-4/IL-13 signaling, macrophages undergo M1 (classical) or M2 (alternative) activation, which represent extremes of a continuum in a universe of activation states. Progress has now been made in defining the signaling pathways, transcriptional networks, and epigenetic mechanisms underlying M1-M2 or M2-like polarized activation. Functional skewing of mononuclear phagocytes occurs in vivo under physiological conditions (e.g., ontogenesis and pregnancy) and in pathology (allergic and chronic inflammation, tissue repair, infection, and cancer). However, in selected preclinical and clinical conditions, coexistence of cells in different activation states and unique or mixed phenotypes have been observed, a reflection of dynamic changes and complex tissue-derived signals. The identification of mechanisms and molecules associated with macrophage plasticity and polarized activation provides a basis for macrophage-centered diagnostic and therapeutic strategies.

Introduction

Macrophages are an essential component of innate immunity and play a central role in inflammation and host defense (1). Moreover, these cells fulfill homeostatic functions beyond defense, including tissue remodeling in ontogenesis and orchestration of metabolic functions (1–3).

Cells of the monocyte-macrophage lineage are characterized by considerable diversity and plasticity. In tissues, mononuclear phagocytes respond to environmental cues (e.g., microbial products, damaged cells, activated lymphocytes) with the acquisition of distinct functional phenotypes. In response to various signals, macrophages may undergo classical M1 activation (stimulated by TLR ligands and IFN-γ) or alternative M2 activation (stimulated by IL-4/IL-13); these states mirror the Th1–Th2 polarization of T cells (2, 4).

The M1 phenotype is characterized by the expression of high levels of proinflammatory cytokines, high production of reactive nitrogen and oxygen intermediates, promotion of Th1 response, and strong microbicidal and tumoricidal activity. In contrast, M2 macrophages are considered to be involved in parasite containment and promotion of tissue remodeling and tumor progression and to have immunoregulatory functions. They are characterized by efficient phagocytic activity, high expression of scavenging molecules, the expression of mannose and galactose receptors, production of ornithine and polyamines through the arginase pathway, and an IL-12^{lo}IL-10^{hi}IL-1decoyR^{hi}IL-1RA^{hi} phenotype (1, 4). M1-M2 macrophages also are distinct in their chemokine expression profiles.

Signals including IL-10, glucocorticoid hormones, molecules released from apoptotic cells, and immune complexes also profoundly affect monocyte-macrophage function. These signals induce expression of functional phenotypes that share selected properties with M2 cells (e.g., high mannose and scavenger receptor expression), but are distinct from them, for instance, in terms of the chemokine repertoire. Operationally, we refer to these cells as M2 like (5).

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Plasticity and flexibility are key features of mononuclear phagocytes and of their activation states (2, 4, 6). The phenotype of polarized M1-M2 macrophages can, to some extent, be reversed in vitro and in vivo (7, 8). Moreover, pathology is frequently associated with dynamic changes in macrophage activation, with classically activated M1 cells implicated in initiating and sustaining inflammation and M2 or M2-like cells associated with resolution or smoldering chronic inflammation (9). It remains unclear whether the mechanism of these switches involves the recruitment of circulating precursors or the reeducation of cells in situ. However, it is now apparent that specialized or polarized T cells (Th1, Th2, Tregs) that are key orchestrators of macrophage polarized activation (2) also exhibit previously unsuspected flexibility and plasticity (10).

Here, we will focus on recent progress in understanding the molecular basis underlying macrophage polarization, including signaling pathways, transcription factors, and epigenetic regulation. Moreover, the dynamics and limitations in our understanding of polarized macrophage activation in vivo will be discussed, focusing on selected pathological conditions (for references to pathology not discussed here, see Supplemental References; supplemental material available online with this article; doi:10.1172/JCI59643DS1). Previous reviews also provide a framework for this work (1–3, 6, 11).

Molecular determinants of macrophage polarization

A network of signaling molecules, transcription factors, epigenetic mechanisms, and posttranscriptional regulators underlies the different forms of macrophage activation. Canonical IRF/STAT signaling pathways are activated by IFNs and TLR signaling to skew macrophage function toward the M1 phenotype (via STAT1) or by IL-4 and IL-13 to skew toward the M2 phenotype (via STAT6) (3). M1 macrophages upregulate IRF5, which is essential for induction of cytokines (IL-12, IL-23, TNF) involved in eliciting Th1 and Th17 responses (12). The IL-4 type I and type II receptors (1, 13) activate Stat6, which in turn activates transcription of genes typical of M2 polarization, e.g., mannose receptor (*Mrc1*), resistin-like α

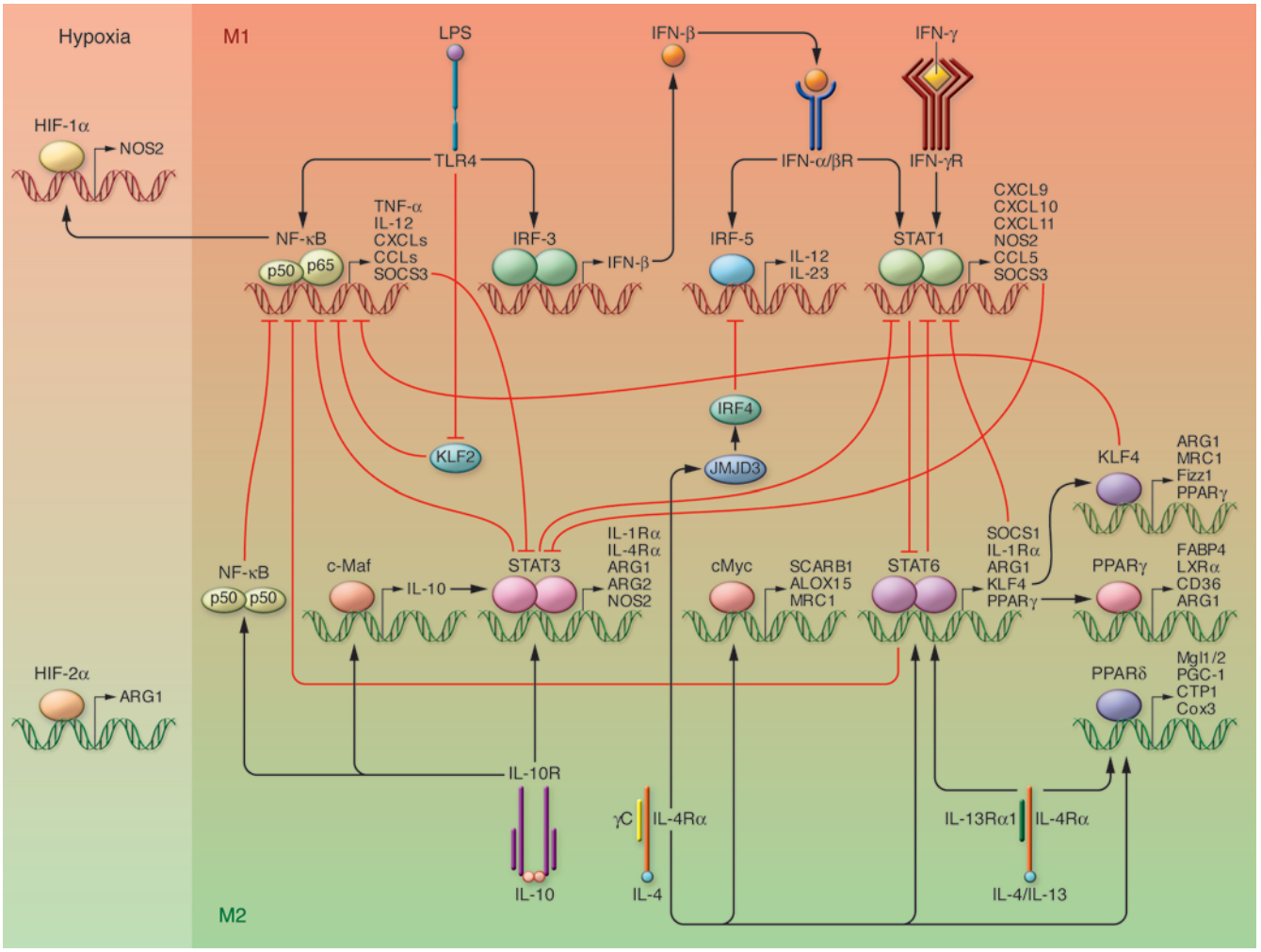

Figure 1
Mechanisms of macrophage polarization. The major pathways of macrophage polarization are outlined. The crosstalk between the M1-M2 macrophage–polarizing pathways is also indicated. The balance between activation of STAT1 and STAT3/STAT6 finely regulates macrophage polarization and activity. A predominance of NF-κB and STAT1 activation promotes M1 macrophage polarization, resulting in cytotoxic and inflammatory functions. In contrast, a predominance of STAT3 and STAT6 activation results in M2 macrophage polarization, associated with immune suppression and tumor progression. PPARγ and PPARδ control distinct aspects of M2 macrophage activation and oxidative metabolism. KLF4 and KLF2 participate in the promotion of M2 macrophage functions by cooperating with STAT6 and suppressing the NF-κB/HIF-1α–dependent transcription, respectively. IL-4–induced c-Myc activity controls a subset of M2-associated genes. IL-4 also induces the M2-polarizing Jmjd3-IRF4 axis to inhibit IRF5-mediated M1 polarization. IL-10 promotes M2 polarization through the induction of p50 NF-κB homodimer, c-Maf, and STAT3 activities.

(*Retnla*, *Fizz1*), and chitinase 3–like 3 (*Chi3l3*, *Ym1*) (14). IL-10 activates STAT3-mediated expression of genes (*Il10*, *Tgfb1*, *Mrc1*) associated with an M2-like phenotype (4, 15, 16).

STAT-mediated activation of macrophages is regulated by members of the SOCS family. IL-4 and IFN-γ, the latter in concert with TLR stimulation, upregulate SOCS1 and SOCS3, which in turn inhibit the action of STAT1 and STAT3, respectively (17, 18).

Downstream of, or in parallel with, the IRF/STAT/SOCS pathway, a panel of transcription factors orchestrates polarized macrophage activation. The nuclear receptors PPARγ (19) and PPARδ (20, 21) control distinct subsets of genes associated with M2 macrophage activation and oxidative metabolism (Figure 1). Interestingly, STAT6 coordinates and synergizes with both PPARγ (22) and Krüppel-like factor 4 (KLF4), a member of a family of proteins that contribute to macrophage function (23, 24). KLF4 cooperates with Stat6 to induce M2 genes (*Arg-1*, *Mrc1*, *Fizz1*, *PPARγ*) and inhibit M1 genes (*TNFa*, *Cox-2*, *CCL5*, *iNOS*) via sequestration of coactivators required for NF-κB activation. KLF2 regulates macrophage activation by inhibiting NF-κB/HIF-1α activities (25). IL-4 also induces c-Myc activity in human macrophages (26), which controls genes of M2 activation (*Scarb1*, *Alox15*, and *Mrc1*) as well as STAT6 and PPARγ activation (26).

TLR engagement leads to NF-κB activation and production of inflammatory mediators (27) associated with M1 macrophages. However, NF-κB activation also activates a genetic program essential for resolution of inflammation (28) and for M2 polarization of tumor-associated macrophages (TAMs) (29). Moreover, induction of p50 NF-κB homodimers is essential for M2 polarization in vitro and in vivo (30). The hypoxia-inducible factors HIF-1α and HIF-2α are expressed differentially in M1- and M2-polarized macrophages (31) and regulate inducible NOS2 (M1) and arginase 1 (M2), respectively.

Epigenetic changes and noncoding RNAs also participate in directing macrophage polarization (32–34). IL-4 induces upregulation of the histone demethylase JMJD3 in mouse macrophages, which alters chromatin modifications to promote expression of M2 genes and inhibit M1 genes. miR-155 was recently identified as targeting the IL-13Rα1 subunit, thus decreasing a set of M2 genes in human macrophages (35).

Pathology

Resolution of inflammation and repair. Remodeling and repair occur dynamically during ontogenesis and inflammation, and these processes are orchestrated by macrophages.

Macrophages undergo dynamic changes during different phases of wound healing. M1-polarized macrophages mediate tissue damage and initiate inflammatory responses (1, 2). During the early stages of the repair response after wounding the skin, infiltrating macrophages have an M2 phenotype and their depletion inhibits the formation of a highly vascularized, cellular granulation tissue and of scar tissues (36). Under these conditions, the removal of apoptotic cells (efferocytosis) (37, 38) and the presence of TGF-β (39) may skew macrophage function, though demonstration of actual in vivo relevance of these findings is lacking.

In a peritoneal model of inflammation, resolution phase macrophages expressed a unique mixed M1-M2 phenotype, and cAMP was essential to restrain M1 activation (40). In humans, chronic venous ulcers (CVU) represent a failure to resolve a chronic inflammatory condition (41). Correlative analysis in patients and a mouse model suggested that in CVU the infiltrating macrophages fail to switch from an M1 to an M2 phenotype (41). Notably, iron metabolism is differentially regulated in polarized macrophages (42). In CVU, the iron overload in macrophages sustained their M1 activation, leading to ROS-mediated DNA damage, fibroblast cellular senescence, and defective tissue repair (41). It is tempting to speculate that similar mechanisms may underlie M2 functions in patients with severe burns, where hemorrhage and tissue damage, along with the high release of iron by M2 macrophages (42), may result in high iron tissue levels (43).

Dynamic changes in the phenotype of recruited mononuclear phagocytes have been observed in models of ischemic heart disease (44), suggesting that this is a general feature of the natural history of repair processes. In a murine model of hind limb ischemia, haplodeficiency of the oxygen sensor prolyl-hydroxylase PHD2 induced the canonical NF-κB pathway in macrophages, which promoted their M2 polarization and proarteriogenic phenotype (45). This observation may suggest a functional link between oxygen deprivation, as occurring in wounds and tumors, and progressive induction of proarteriogenic M2 macrophages. Thus, although the macrophage phenotype in resolution need not be a phenocopy of in vitro–generated M2 cells, preclinical and clinical evidence support the long-held view of a key role of polarized macrophages in tissue repair.

In a model of retinal neuropathy, mononuclear phagocyte infiltration generates a neuroprotective microenvironment promoting retinal progenitor cell survival (46). The interplay of polarized macrophages with stem and progenitor cells is likely a key component of their role in repair and remodeling, although the actual tissue-protective significance of polarized macrophages in degenerative diseases and their involvement with stem and progenitor cells remain to be determined (see Supplemental References).

Macrophage activation has been found in autoimmune and inflammatory diseases and in particular in lupus nephritis (47). In a murine model of SLE, proinflammatory activation of macrophages was sustained by Notch signaling (48). Conversely, the acute phase protein serum amyloid P (SAP) skewed macrophages toward an antiinflammatory M2-like phenotype, thus alleviating lupus nephritis (49). In RA, a major source of M1 cytokines (TNF-α, IL-1β, IL-12p70) (50) in the joints are the synovial macrophages, whose number correlate with the inflammatory disease activity (51). On this basis, PPARδ and PPARγ are considered potential disease-modifying drugs for RA (52, 53). In a murine model of experimental colitis, recruitment of CCL11-expressing $Ly6C^{hi}CCR2^{+}$ inflammatory monocytes into the colon correlates with eosinophil infiltration and histopathology (54).

Infection

Bacteria. M1 macrophages are generally considered responsible for resistance against intracellular pathogens and characterize infection with *Listeria monocytogenes* (55), *Salmonella typhi*, and *Salmonella typhimurium* (56), as well as the early phases of infection with *Mycobacterium tuberculosis* (57), *Mycobacterium ulcerans*, and *Mycobacterium avium* (58, 59). Uncontrolled M1 inflammation associated with acute infections with *E. coli* or *Streptococcus* sp. causes gastroenteritis, urinary tract infections, neonatal meningitis, and sepsis (60). The M1-M2 switch observed during the transition from acute to chronic infection may provide protection against overwhelming uncontrolled inflammation; however, a phenotype switch can also favor pathogens that have evolved strategies to interfere with M1-associated killing (58, 61–64).

Chronic inflammation and granuloma formation are characterized by the presence of macrophages with an epithelial morphology and by macrophage homotypic fusion with the formation of multinucleated giant cells (MNG) (65). IL-4–mediated upregulation of E-cadherin, which engages in intercellular homotypic adhesion, is likely to underlie MNG formation. STAT6 drives expression of E-cadherin and DC transmembrane protein (DC-STAMP; ref. 66) during MNG generation. The actual function and role of MNG remain elusive.

Parasites. In experimental and human parasite infections, macrophages generally undergo a dynamic switch toward M2 polarization (61, 67). The early and late phases of *Taenia crassiceps* infection are characterized by Th1-driven M1 and Th2-driven IL-4–mediated M2 polarization of macrophages, respectively (11, 68). A similar M1-M2 switch has been reported during *Schistosoma mansoni* and *Trypanosoma congolense* infection (69). In the chronic stage of *T. crassiceps* infection, the p50 NF-κB subunit (see above) promotes protective M2 macrophage polarization associated with decreased parasite burden (30).

The recurrent association of M2 polarization with parasite infections does not necessarily imply a generalized relevance in pathogenesis. For instance, lineage-selective ablation of the IL-4α chain causes a dramatic increase in susceptibility to *S. mansoni*, but has no discernible effect on *Nippostrongylus* infection (70).

Viral infections. Polarized activation of macrophages has been associated with virus infection (e.g., HIV, Kaposi sarcoma–associated herpes virus, and others; see Supplemental References), and this polarization may be important in containing and limiting tissue damage. In particular, during severe respiratory syncytial virus–induced (RSV-induced) bronchiolitis, IL-4Rα/STAT6-dependent M2 macrophage differentiation reduces inflammation and epithelial damage in lungs (71).

Table 1
Prototypic therapeutic strategies targeting macrophage polarization

Function	Therapeutic agent	Disease
Recruitment	Anti–CSF-1 (Ab and antisense-ODN)	Breast cancer
	Anti-CCL2 (Ab)	Breast, prostate cancer
	CCL2 inhibitor (bindarit)	Melanoma and vascular pathology
	fms-tyrosine kinase inhibitors	Acute myeloid leukemia and bone metastasis
Depletion	Trabectedin	Liposarcoma
Switch to M1	IFN-γ	Atopic dermatitis; ovarian cancer
	TLR9 agonist (CpG-ODN)	Asthma
	CpG-ODN + anti–IL-10	Breast cancer
	Anti-CD40 (agonist)	Pancreatic cancer
	STAT3 inhibitors	Breast cancer; melanoma
	STAT6 inhibitors	Breast cancer; *T. crassiceps* (e.s.)
	p50 NF-κB inhibitors	*T. congolense*; fibrosarcoma, melanoma
	IKKβ inhibitors	Ovarian cancer
	Imidazoquinolines (TLR7/8 agonists)	SCC, cutaneous B cell lymphomas
	Zoledronic acid	Breast cancer
Inhibition of M1 pathways	CD40 (antagonist)	Atherosclerosis
Inhibition of M2 pathways	IL-33 (antagonist)	Airway inflammation
Induction of M2 pathways	PPARγ agonists (thiazolidinediones)	Diabetes; atherosclerosis
	Nonthiazolidinedione tyrosine-based PPARγ ligand (GW7845)	Atherosclerosis
	Statin	Glomerulonephritis

ODN, oligodeoxyribonucleotides; IKKβ, IKKβ subunit of IκB kinase (IKK); e.s., early stage of infection. For an extensive reference list, see Supplemental References.

Allergy

Allergy is driven by Th2 cells and products and is associated with M2 polarization of macrophages (72, 73). IL-4–inducible chemokines acting on CCR4 (e.g., CCL22) have also been reported to promote skewing of macrophage function (74). Evidence now indicates that chitin- and arginase-dependent M2 pathways play an active role in pathogenesis (75, 76). Asthma is associated with tissue remodeling, including collagen deposition and goblet cell hyperplasia. IL-4–driven M2 polarization is likely to play a key role as an orchestrator of these processes (77).

Allergy represents a paradigm for IL-4/IL-13–driven type 2 inflammation. However, there is evidence that the inflammasome/IL-1/Th17 pathway can also drive allergic inflammation (78, 79). Moreover, a Th1-associated cytokine, IL-18, has also been implicated in allergic inflammation (80). It is therefore perhaps not surprising that mixed phenotype macrophages have been observed (81).

Cancer

Cancer-related inflammation is characterized by the recruitment of cells of the monocyte-macrophage lineage to tumor tissues (2, 82, 83), which also condition the premetastatic niche, to favor secondary localization of cancer. Classically activated M1-polarized macrophages have the potential to exhibit antitumor activity and to elicit tumor tissue disruption (4). At least in some models of carcinogenesis in the mouse, progression is associated with a phenotype switch from M1 to M2 (84). Th1-driven macrophage activation was found to mediate elimination of senescent hepatocytes, which drive subsequent carcinogenesis (85). It is therefore likely that classically activated M1 macrophages contribute to the T cell–mediated elimination and equilibrium phases during tumor progression (86).

At later stages of progression in mice and humans, TAMs generally have an M2-like phenotype with low IL-12 expression, high IL-10 expression, and low tumoricidal activity and promotion of tissue remodeling and angiogenesis. TAM infiltration is generally associated with poor prognosis, as shown in Hodgkin disease, glioma, cholangiocarcinoma, and breast carcinoma (87, 88). However, TAMs with various functional states can coexist in the same tumor (2, 89). Various pathways orchestrate the protumor function of myelomonocytic cells, including tumor-derived and host-derived signals (2). Lymphocytes are key orchestrators of TAM function (2), but pathways differ in tumors originating in different organs. For instance, skewing of macrophage function was found to be mediated by IL-4–producing Th2 cells in skin (90, 91) and by antibody-producing B cells in breast carcinogenesis (92, 93). B1 cells can promote cancer progression in the skin (5), and fibroblasts can also contribute to circuits driving macrophage polarization and tumor promotion (94).

Tumor cell products, including extracellular matrix components, IL-10, CSF-1, and chemokines (CCL2, CCL18, CCL17, and CXCL4), set macrophages in an M2-like, cancer-promoting mode (82, 95–97). TAMs can also interact with and promote the tumorigenicity of cancer stem cells (CSCs) via production of the milk-fat globule-epidermal growth factor–VIII (MFG-E8) by activation of the STAT3 and sonic hedgehog pathways (98).

The identification of the various cellular and molecular pathways that participate in inflammation in different human cancers will be required to translate our understanding of cancer-related inflammation to meaningful therapeutic advances.

Obesity and metabolism

Obesity-associated insulin resistance, diabetes, and metabolic syndrome are sustained by chronic subclinical inflammation (99). Adipose tissue macrophages (ATMs) are a major component

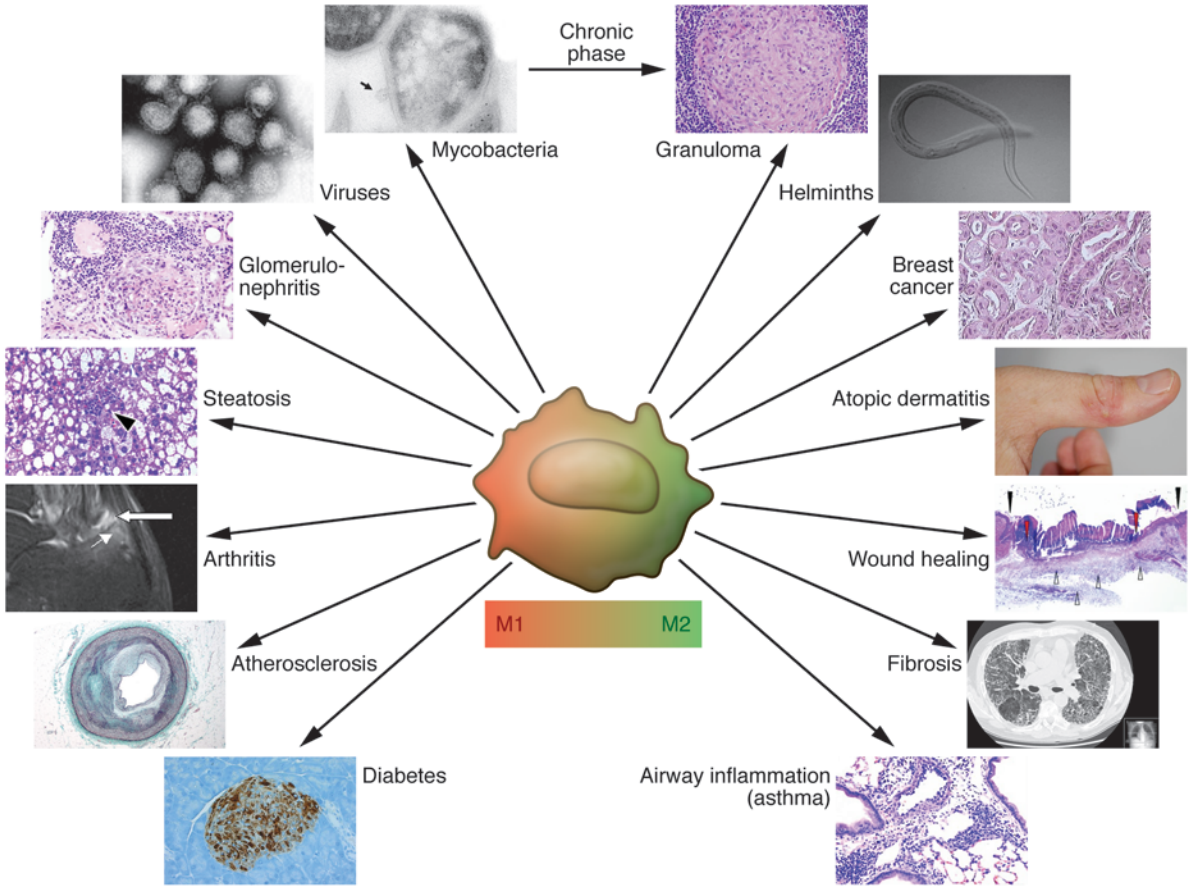

Figure 2
Schematic representation of macrophage plasticity and polarization in pathology. Dynamic changes occur over time with evolution of pathology: for instance, a switch from M1 to M2 macrophage polarization characterizes the transition from early to chronic phases of infection. Moreover, mixed phenotypes or populations with different phenotypes can coexist. For pathologies not discussed in the text, see Supplemental References. Images adapted from refs. 141–144.

of adipose tissue and are important players in obesity-associated pathology. In obese subjects and mice, adipocytes release mediators such as CCL2, TNF, or free fatty acids, which promote the recruitment and activation of ATMs (100–102). In turn, ATM-produced inflammatory cytokines (e.g., TNF, IL-6, IL-1β) counteract the insulin-sensitizing action of adiponectin and leptin, leading to insulin resistance. ATM infiltration correlates with the degree of obesity (101–103). ATM accumulation is orchestrated by selected chemokines and their receptors (e.g., CCL2/CCR2 or CCL5/CCR5) (101, 103, 104) and by the macrophage-derived apoptosis inhibitor of macrophages (AIM) (105).

ATMs from obese mice and humans are polarized toward an M1 phenotype, with upregulation of TNF and iNOS. In contrast "lean" ATMs express high levels of M2 genes, including IL-10, Ym1, and Arginase 1 (106, 107). Weight loss is associated with a shift back to an M2-like phenotype. However, evidence indicates that the ATM population in obese patients is diverse, with a minor $F4/80^+CD11b^+CD11c^-$, $IL\text{-}10^{hi}$, M2-like population coexisting with M1 cells (106). Moreover, analysis of $CD11c^+$ ATMs from obese mice revealed a mixed profile of several M1-M2 gene transcripts (108). Weight loss is associated with an increase in $F4/80^+CD11c^-CD301^+$ M2-like macrophages, which promote lipolysis (109).

Progress has been made in defining the molecular pathways that account for polarization of ATMs (19, 20, 24, 110, 111) in obesity. Mice with macrophage-selective genetic inactivation of PPARγ, PPARδ, and KLF4 show inhibition of obesity-induced insulin resistance (19, 20, 24, 106, 110), although these results may be strain specific (112). The adipose tissue of obese subjects shows a marked reduction in KLF4 levels. Nguyen et al. have recently demonstrated that adaptation to lower temperatures (thermogenesis) is associated with polarization of brown adipose tissue (BAT) and white adipose tissue (WAT) macrophages to the alternative state (M2), with increased expression of thermogenic genes (*Ppargc1* and *Ucp1*) (113). In response to cold, IL-4–driven M2 macrophages release noradrenaline in BAT and WAT, which coordinates fatty acid mobilization and energy expenditure (113). Although further work is needed to dissect the diversity and dynamics of ATMs, M2-like cells in nonobese individuals are likely involved in maintaining adipose tissue homeostasis, preventing inflammation, and promoting insulin sensitivity. In contrast, M1-like ATMs drive obesity-associated inflammation and insulin resistance (107). The role of macrophages in obesity and associated disorders underlines a homeostatic function of macrophages in metabolism as cells capable of reorienting their own metabolic activity and as orchestrators of general metabolism.

Therapeutic targets in polarized inflammation

Specific macrophage-targeted therapies are now taking the first steps into the clinical arena (Table 1). In addition, therapeutic approaches not originally designed as macrophage oriented or specific have been found to affect macrophage activation and polarization. These off-target examples provide insights and lessons for the development of more specifically directed approaches.

Recruitment is a key determinant sustaining macrophage numbers at sites of inflammation and immunity. Monocyte attractants include members of the chemokine superfamily, CCL2/MCP-1 in particular, and growth factors interacting with tyrosine kinase receptors CSF-1 and VEGF (83, 114, 115). CSF-1 receptor (c-fms) kinase inhibitors have been generated, and these molecules exhibit antiangiogenic and antimetastatic activity in acute myeloid leukemia and melanoma models (116, 117). Chemokines and CSF-1 are more than monocyte attractants; they also promote M2-like skewing of macrophage function (97, 118, 119). Antibodies directed against CCL2/CCR2 have proven active in prostate and breast cancer (83, 120). A CCL2 inhibitor (bindarit) has proven active in preclinical models of cancer and vascular pathology, resulting in inhibition of monocyte recruitment (121); this agent is now undergoing evaluation for clinical use. Anti–CSF-1 antibodies and antisense oligonucleotides suppress macrophage infiltration and xenograft mammary tumor growth in mice (122–124). VEGF inhibitors can decrease macrophage recruitment, and this effect may contribute to their antiangiogenic activity (125). In contrast, in response to neoadjuvant chemotherapy, altered composition in the immune microenvironment was found in breast cancer patients, with increased percentage of infiltrating myeloid cells (126).

Recent results suggest that in situ, proliferation is a key determinant of macrophage accumulation during inflammation in the peritoneum and lungs (127, 128). In the latter, IL-4 was found to sustain macrophage proliferation. If proliferation is indeed a major general mechanism sustaining macrophage accumulation, this may suggest novel approaches to reduce macrophage numbers in situ and a different perspective for anti–CSF-1/CSF-1R strategies. However, determining the actual significance of macrophage proliferation in humans, in particular in Th2-mediated inflammation, is a major stumbling block in this perspective.

Reorienting and reshaping deranged macrophage polarization is the holy grail of macrophage therapeutic targeting (129). Polarized phenotypes are reversible in vitro and in vivo (29, 130–132). In proof of concept and in a large clinical study in ovarian cancer patients, IFN-γ was found to activate TAM tumoricidal activity, inducing a phenotype switch with unequivocal evidence of clinical responses (133). In a model of pancreatic ductal adenocarcinoma, CD40 agonist antibodies promoted a remarkable antitumor effect and induced high expression of M1 markers (MHC class II and CD86) in macrophages (132).

Modulation of macrophage function is an off-target effect for a number of diverse therapeutic agents. PPARγ agonists (thiazolidinediones) have long been used in the treatment of diabetes. The evidence linking PPARγ to M2 polarization and hence to the homeostatic role of ATMs sheds fresh new light on their mode of action. Preclinical evidence suggests that PPARγ promotes M2-like polarization and homeostatic metabolic function in ATMs and that alteration of this function is a key pathogenic feature in diabetes (134–136). Other therapeutic strategies that have been reported to affect macrophage polarization include zoledronic acid (an agent used for preventing recurrence of breast cancer bone metastasis), statins (137), trabectedin (138) and TLR ligands (e.g., imiquimod and CpG) (see also Supplemental References).

Concluding remarks

Progress has been made in defining the molecular networks underlying polarized activation of macrophages. Molecular determinants of M1 versus M2 polarization include members of the PPAR, KLF, IRF, STAT, NF-κB, and HIF families. Regulation of skewing also involves epigenetic modifications with involvement of histone methylation and acetylation. miRNAs have emerged as regulators of phagocyte activation and function (34, 139), but their role in macrophage polarization needs to be further defined.

Functional polarization has now been observed in vivo under physiological and pathological conditions. The former include embryogenesis and pregnancy and normal maintenance of selected tissues, such as testis and adipose. The latter include chronic inflammation and tissue repair, metabolic and vascular disorders, infection, and cancer. There is now evidence that macrophages are a key component of all of these processes (Figure 2).

Under condition such as parasite infections, allergy, and many cancers, the functional phenotypes of macrophages in vivo mirror those of canonical M1-M2 or M2-like polarized states as defined in vitro. However, in a number of pathological conditions, such as neurodegenerative disorders (140), this is not the case, and macrophage populations express mixed or unique phenotypes. The contribution of coexisting cells with different phenotypes, the impact of dynamic changes during disease evolution, and the molecular networks orchestrating these mixed phenotypes need to be carefully dissected on a case-by-case basis. Indeed, this macrophage plasticity calls for in-depth analysis in different pathological conditions.

Therapeutic macrophage targeting is in its infancy. Selected clinically approved therapeutic strategies, such as use of PPARγ inhibitors, statins, zolendronic acid, and preventive activities such as weight loss may have an impact on the functional status of macrophages; however, the extent to which their effect on macrophages explains their clinical efficacy remains to be defined. The identification of mechanisms and molecules associated with macrophage plasticity and polarized activation provides a basis for macrophage-centered diagnostic and therapeutic strategies.

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