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Permalink

https://escholarship.org/uc/item/9v25k83k

Journal

Annual Review of Immunology, 31(1)

ISSN

0732-0582

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Publication Date

2013-03-21

DOI

10.1146/annurev-immunol-032712-095906

Peer reviewed

INTERLEUKIN-4- AND INTERLEUKIN-13-MEDIATED ALTERNATIVELY ACTIVATED MACROPHAGES: ROLES IN HOMEOSTASIS AND DISEASE

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Abstract

The macrophage, a versatile cell type prominently involved in host defense and immunity, assumes a distinct state of alternative activation in the context of polarized type 2 immune responses such as allergic inflammation and helminth infection. This alternatively activated phenotype is induced by the canonical type 2 cytokines interleukin (IL)-4 and IL-13, which mediate expression of several characteristic markers along with a dramatic shift in macrophage metabolic pathways that influence surrounding cells and tissues. We discuss recent advances in the understanding of IL-4- and IL-13-mediated alternatively activated macrophages and type 2 immune responses; such advances have led to an expanded appreciation for functions of these cells beyond immunity, including maintenance of physiologic homeostasis and tissue repair.

INTRODUCTION

An essential element of metazoan survival is the capacity to detect and respond to foreign material encountered at barrier surfaces. This ability constitutes immunity at its most basic level, serving to rapidly and efficiently defend the host from intrusion by pathogenic invaders, although similar mechanisms can also select and retain agents that provide some host benefit (1). On a cellular level, the task of distinguishing foreign material is primarily carried out by the macrophage, an incredibly versatile cell type that has been widely conserved throughout phylogeny; macrophage-like sentinel cells that exhibit hallmark phagocytic and microbicidal functions arise even among colonies of the social amoeba *Dictyostelium discoideum* (2). Macrophages not only possess a broad array of cell surface receptors and intracellular mediators that enable recognition, engulfment, and destruction of pathogens, but they are also equipped with essential secretory molecules that serve to regulate the activities of neighboring cells. And although a century has passed since Metchnikoff first described the critical immune function of macrophages and phagocytosis in the detection and elimination of harmful microbes—observations that have since formed a fundamental tenet of modern immunology—new and diverse roles for macrophages during immune responses and various physiologic processes continue to be discovered.

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Metchnikoff's initial concept now incorporates a host of molecular detail about how macrophages recognize, phagocytose, and kill microbes. In this respect, the characterization of several germ line–encoded pattern-recognition receptors (PRRs) and subsequent intracellular signaling events induced upon PRR ligation has been instrumental in providing molecular links between the initial sensing of foreign material and the distinct cellular changes that occur in response to different classes of microbial patterns (3, 4). This paradigm is preserved throughout many phyla, constituting most invertebrate innate immunity, but also underlies the highly evolved adaptive immune system in mammals and other vertebrates. A hallmark example occurs within mammalian macrophages upon exposure to Toll-like receptor (TLR) ligands and the cytokine interferon-γ (IFN-γ), which induce a phenotype referred to as the classically activated macrophage (CAM), marked by a metabolic shift to anaerobic glycolysis, increased production of proinflammatory cytokines, and new synthesis of reactive oxygen and nitrogen species, enabling efficient killing of engulfed microbes. Elements of this system are rooted in similar macrophage-like phagocytic cells found among invertebrates, notably *Drosophila*, that exhibit striking homology with mammalian innate immune function on both genetic and cellular levels (5).

Mammals also engender a unique tissue response, encompassed by the term type 2 immunity, that diverges significantly from that associated with the CAM and is prominently associated with parasite infection and allergic disorders; however, it is also increasingly recognized to be coupled with broader mechanisms that maintain homeostasis in larger organisms (6, 7). Type 2 immunity consists of a complex orchestration of cells and cytokines involving an initial response, typically generated at mucosal barriers, which is amplified by activation and recruitment of innate and adaptive effector cells and followed by a resolution phase involving tissue repair mechanisms. Although many cell types and molecules are involved, most of these aspects are coordinated by the activities of the canonical type 2 cytokines interleukin (IL)-4 and IL-13, two closely related cytokines that play both overlapping and distinct roles in type 2 immunity. This cytokine-mediated program is required for the generation of high-affinity IgE antibodies, mucus overproduction, and smooth muscle alterations that produce the "weep and sweep" response in mammals, which mediates expulsion of large extracellular parasites but is also engaged in the context of asthma and allergic disorders for reasons that remain unclear (6--8). Chronic infection with some parasites that subvert the expulsive response leads to walled-off granulomas containing mixed macrophage- and eosinophil-rich inflammatory infiltrates, suggesting that type 2 immunity also functions as a means to suppress unrestricted inflammation, an important property in the maintenance of tissue homeostasis and host survival.

In this respect, type 2 immune responses direct phenotypic and functional changes within macrophages that are distinct from, and often oppose, the CAM phenotype. Particular alterations in endocytic and enzymatic activities shift cellular resources away from the generation of molecules associated with proinflammatory cytokine and nitric oxide (NO) production and toward the synthesis of anti-inflammatory and tissue repair factors. This distinct state, defined by exposure to IL-4 or IL-13, was first described in vitro as the alternatively activated macrophage (AAM) by Gordon and colleagues (9), who contrasted the effects of IFN-γ on macrophages with those of IL-4; these findings were subsequently recapitulated using IL-13 (10, 11). CAM and AAM have been assigned the additional terms M1 and M2, respectively, corresponding to the classic Th1 and Th2 designations, which have provided an essential framework for CD4 T cell research for decades (12). Much remains unclear, though, about how the multiple macrophage phenotypes induced by cytokines and other stimuli relate to specific transcriptional programs and/or epigenetic changes and how these factors might correspond to the heterogeneity and plasticity within the macrophage lineage, both in the steady state and during inflammatory processes

(13--15). In light of these considerations, we focus this review on the central role of the canonical type 2 cytokines IL-4 and IL-13 in mediating the alternatively activated phenotype in macrophages, emphasizing recent insights about how regulation of these cytokines can lead to differential signaling events and a profound metabolic shift that is reflected in specific tissue responses—not only in the context of type 2 immunity but also in the maintenance of homeostasis during complex physiologic processes (Figure 1).

MACROPHAGE DEVELOPMENT AND ACTIVATION

In mammals, macrophages develop from precursors that arise during multiple waves of embryonic hematopoiesis, occurring initially within extraembryonic yolk sac tissue and then subsequently in the aortic endothelium of the aorta-gonad-mesonephros region and in the placenta, fetal liver, and bone marrow (16, 17). Most adult macrophage, monocyte, and dendritic cell (DC) populations derive from bone marrow–derived myeloid precursors, which critically depend on cytokine signaling via colony-stimulating factor 1 receptor (CSF1-R) and transcription factors such as the Ets family member PU.1 (18, 19). Many tissue macrophages, however, are refractory to irradiation protocols and are poorly replaced after bone marrow transplantation, suggesting that not all adult macrophage populations derive from the bone marrow–derived hematopoietic compartment. Interestingly, recent fate-mapping studies have demonstrated that primitive yolk sac–derived myeloid precursors contribute substantially to microglial cell populations in the adult central nervous system and also, to varying degrees, to several tissue-resident macrophage populations found in kidney, lung, liver, pancreas, spleen, and skin, some of which exhibit self-renewal capability in the absence of Myb-dependent, bone marrow–derived stem cells and PU.1 (20--23). In addition, although most bone marrow–derived populations depend primarily on colony-stimulating factor 1 (CSF-1) signaling via CSF1-R for their development and survival, some self-renewing tissue macrophages, in particular microglia, require tissue-restricted signals derived exclusively from the alternate ligand of CSF1-R, IL-34 (24).

The issue of macrophage development and turnover is relevant, as in situ self-renewal and proliferation may define a unique property among AAM precursor populations during type 2 inflammation. This concept is supported by evidence that tissue-resident macrophages proliferate locally during helminth infection or in response to IL-4 treatment (22). The capacity for in situ self-renewal, however, does not appear to preclude overlaid contributions of blood-derived monocyte populations that assume the AAM phenotype during inflammatory responses, although monocyte subset characteristics in this regard appear to vary by experimental system (22, 25, 26). Further to this point, microglial cells can assume an IL-4-dependent AAM phenotype in vitro and during experimental autoimmune encephalomyelitis (27); however, during fungal invasion of the central nervous system only recruited monocyte-derived macrophages, not microglia, exhibit AAM markers (28). Among differentiated macrophages, self-renewal depends on suppression of the transcription factors MafB and c-Maf along with concomitant upregulation of the stem cell-inducing factors Krüppel-like factor 4 (KLF4) and c-Myc, offering potential mechanistic insights into how in situ proliferation may occur during AAM polarization (29). Notable in this regard is the finding that KLF4 is induced by IL-4 in a signal transducer and activator of transcription 6 (STAT6)-dependent manner and can directly regulate the AAM phenotype in vitro and in vivo (30). Aspects of this type of regulation may also apply to recruited monocytic AAM precursors, as bone marrow–derived macrophages deficient in Jmjd3, which is implicated in the epigenetic regulation of AAM polarization (discussed further below), show impaired cell cycle progression and decreased expression of cell cycle regulatory genes, including c-Myc and c-Myb, in response to CSF-1 signals (31). In human monocytes IL-4 treatment also induces c-Myc, which can regulate expression of a subset of AAM genes, including STAT6 (32).

PHENOTYPIC CHARACTERISTICS OF AAMS

Macrophages are inherently difficult to classify by marker analysis, due to phenotypic heterogeneity in vitro and in vivo as these cells develop, migrate, take up residence in diverse tissues, and become activated by various stimuli (13, 14). Nevertheless, AAMs have been characterized by a distinct set of cell surface receptors and intracellular factors that are induced upon exposure to IL-4/IL-13, and their in vivo functional relevance is beginning to be explored using models of genetic deficiency. Many of these factors have become variably employed as definitive markers of AAMs, but important caveats to such approaches exist: expression that is not restricted to macrophages, induction by stimuli other than IL-4/IL-13, and differences in expression between species (e.g., mouse versus human macrophages). A notable example in this regard is the signature mouse AAM marker arginase 1 (Arg1), which does not mark human AAMs (33), possibly reflecting compensation by functional isozymes or expression by other cell types. Consequently, although gene profiling studies have yielded additional markers to verify (34--37), these caveats caution against the exclusive use of any single marker in establishing the AAM phenotype; rather, a combinatorial approach should be employed in parallel with an assessment of contributions by IL-4 or IL-13 (14, 15). Some of the most prominent characteristic AAM markers are discussed below.

Arginase 1

Arg1 is a manganese metalloenzyme that catalyzes the conversion of L-arginine into L-ornithine and urea, a critical final step in the urea cycle that occurs primarily in the liver. Arg1 is also induced by IL-4/IL-13 in macrophages and functions to counterbalance inflammatory signals that generate inducible nitric oxide synthase (iNOS), which also utilizes L-arginine to produce nitric oxide and L-citrulline (38). As such, L-arginine metabolism in macrophages is a key determinant in defense against infection by both intracellular and extracellular pathogens and has emerged as a defining feature of alternative versus classical macrophage activation. Several studies support a model in which IL-4/IL-13-induced Arg1 and IFN-γ-induced iNOS compete for limiting L-arginine substrate, such that expression of either enzyme shifts the subsequent generation of metabolites, thereby suppressing the opposing pathway (39--43). Although general aspects of this paradigm are well supported, the in vivo effects of manipulating various stages in this metabolic pathway have revealed a more complex regulatory network.

A key step is Arg1-mediated production of L-ornithine, which can subsequently be decarboxylated by L-ornithine aminodecarboxylase (ODC) to produce polyamines or converted to proline by L-ornithine aminotransferase (OAT), implicating Arg1 in regulation of cell growth and collagen production, respectively. Indeed, when ODC activity was inhibited during *Schistosoma mansoni* egg–induced liver inflammation, granuloma size and fibrosis increased, presumably via increased substrate availability to OAT for proline production and collagen synthesis (43). Mice with myeloid cell–specific Arg1 deficiency, however, died at an accelerated rate in response to chronic *S. mansoni* infection, which was associated with increased type 2 cytokine production, granulomatous inflammation, and liver fibrosis (44). This is consistent with findings from acutely *S. mansoni*–infected Arg1-deficient bone marrow chimeric mice (45), suggesting that Arg1 in myeloid cells is not required for fibrotic responses in this system but instead plays a critical role in suppressing unrestrained pathologic inflammation. Further to this point, although Arg1-deficient macrophages induced expression of other AAM markers [mannose receptor (MR) and the chi-lectin Ym1] after type 2 cytokine exposure, they failed to inhibit in vitro T cell proliferation in a manner that could be restored by addition of exogenous L-arginine. This indicated that macrophage Arg1 activity depleted an essential proliferative factor, thereby providing a mechanistic basis for the exacerbated Th2 pathology observed in vivo (44). In support of these findings, high arginase activity in nonhealing *Leishmania major* lesions

impaired lesional CD4 T cell proliferation and IFN-γ production, whereas inhibition of arginase or administration of exogenous L-arginine restored T cell function and improved control of parasite replication (46), echoing earlier studies that described the T cell–suppressive effect of parasite-elicited macrophages (47).

L-arginine availability is additionally regulated by expression of cationic amino acid transporter 2 (CAT2), which is induced in concert with Arg1 and also acts to dampen T cell responses (38, 48). Absence of substrate in this setting also affects the iNOS-mediated pathway of NO production, as CAT2-deficient mice are more susceptible to infection with *Toxoplasma gondii*, in part due to impaired NO production, and CAT2-deficient mice infected with *S. mansoni* die at an accelerated rate, exhibiting exacerbated granuloma formation and fibrosis associated with increased arginase activity in fibroblasts and AAMs (49). Notably, mice deficient in CAT2 exhibit spontaneous inflammation in the lung marked by increased numbers of eosinophils, neutrophils, memory T cells, activated DCs, and alveolar macrophages that produce lower NO in response to IFN-γ and lipopolysaccharide (LPS) stimulation (50). It remains unclear, however, how steady-state lung inflammation in these mice might relate to the in vivo phenotypes induced by pathogen infection. Nevertheless, other potential regulators of L-arginine metabolism include polyamines themselves, as a recent report shows that IL-4 can induce polyamine production via Arg1-independent pathways, further modulating AAM marker levels (51). Other studies indicate that suppression of T cell proliferation by AAMs relies on cell-cell contact (52), perhaps due to a receptor-mediated process, such as ligation of the inhibitory PD-1 receptor on T cells by AAM-expressed ligands during helminth infection (53, 54).

Importantly, although IL-4-mediated Arg1 induction in AAMs relies on STAT6 (42), Arg1 can also be induced by STAT3-dependent activation in the absence of other AAM markers after TLR stimulation or *Mycobacterium tuberculosis* infection, via signaling through the TLR adapter myeloid differentiation marker 88 (MyD88) and the transcription factor CCAAT/enhancer binding protein β (C/EBPβ) (55, 56). These studies not only reinforce the need to examine multiple markers in combination with IL-4/IL-13/STAT6 analysis in definitively establishing the AAM phenotype but also reveal a complex integration of host- and pathogen-derived signals within macrophages that converges on a critical effector pathway. Expression of Arg1 in this system can dramatically influence subsequent biological outcomes, as illustrated in an apparent immune evasion strategy employed by the intracellular pathogens *T. gondii* and *M. tuberculosis*, which act to inhibit protective NO production by engaging the STAT6-independent Arg1 pathway, effectively enhancing pathogen survival; the absence of macrophage Arg1 promotes host survival and reduced pathogen load (55, 56). Furthermore, specific strains of *T. gondii* encode rhoptry kinase ROP16, which can directly activate STAT6 to induce host Arg1 expression (57, 58); however, ROP16-deficient *T. gondii* also exhibit increased replication and dissemination in vivo, possibly resulting from increased arginine availability (59), suggesting particular strain-specific effects. Nevertheless, other pathogens, such as *Francisella tularensis*, also induce a switch from the CAM to the AAM phenotype that results in blunted pathogen killing (60), and *Helicobacter pylori* (61) and *Leishmania* (62) encode endogenous arginases that suppress host macrophage NO production in establishing an immune-suppressed niche. Notably, concurrent STAT3 activation observed in some systems may represent a point of intersection with additional cytokines, such as IL-6, GM-CSF, and IL-10, as well as suppressor of cytokine signaling (SOCS) proteins, particularly SOCS1 and SOCS3, which have also been implicated in the regulation of AAM polarization (56, 63). Exactly how these factors interconnect remains to be established, but their participation in generation of AAM markers may be recapitulated in other settings where IL-4/IL-13 is lacking.

Mannose Receptor

MR (CD206; Mrc1) is a C-type lectin receptor (CLR) expressed widely among tissue macrophages, DCs, and endothelial cells. MR can be cell surface bound or shed in soluble form and contains multiple carbohydrate recognition domains that enable binding and clearance of several serum glycoproteins (64) in addition to mediating endocytosis and potentially playing a role in antigen presentation (65). Increased expression of MR on isolated macrophages in response to treatment with IL-4/IL-13 also corresponds to increased endocytosis of mannosylated ligands by AAMs, an observation that formed a key initial determinant in the description of the alternatively activated state (9, 11). MR has been subsequently employed in many studies as a marker for the AAM phenotype, although expression tends to be broad among tissue macrophage populations and, like that of other AAM markers, can be modulated by signals other than IL-4/IL-13, such as IL-10, in the context of helminth infection (66). In addition to binding endogenous glycoproteins, MR also recognizes carbohydrate moieties on several antigenic glycoproteins associated with type 2 immune responses and thus may participate with other CLRs during innate sensitization to stimuli such as fungal particles that are rich in mannoproteins (67). In this respect, although MR-dependent binding of fungal spores can be observed in vitro (68), MR-deficient mice display normal responses to infection with *Candida albicans* (69) and *Pneumocystis carinii*, albeit with some alterations in lung pathology (70), but are more susceptible to pulmonary challenge with *Cryptococcus neoformans* (71). Notably, in MR-deficient mice, the steady-state elevation of several serum glycoproteins, particularly lysosomal hydrolases (64), could impact the in vivo phenotypes observed during fungal exposure independently from MR-mediated fungal recognition. Nevertheless, these findings and others highlight redundancy between MR and other fungal PRRs, such as dectin-1, that appear to act sequentially and exhibit fungal stage–specific binding corresponding to exposure of fungal wall carbohydrate structures (72--75). Similar findings have emerged from studies of MR in the context of parasite infection; for example, MR-deficient mice mount normal immune responses to *Leishmania* (76), and although *Trichuris muris* excretory/secretory products bind MR and induce IL-6 production by bone marrow–derived macrophages, MR-deficient mice expel *T. muris* parasites with normal kinetics (77).

Dectin-1

Dectin-1 (Clec7a) is an AAM-associated CLR that is expressed on macrophages, neutrophils, and DCs, among other cells, and is increasingly recognized as the principal PRR in mediating fungal recognition in mice (78, 79) and humans (80). In contrast to MR, dectin-1 exhibits specificity for β-glucans and contains a hemITAM in its cytoplasmic domain that transduces signals via Src and Syk family kinases to induce respiratory burst and cell type–specific transcription factor activity, mediating protection in several models of fungal infection (81). Thus, although dectin-1 expression is strongly induced by IL-4/IL-13 (82), subsequent engagement of dectin-1 results in a different signaling response than that mediated by IL-4/IL-13. Particularities in downstream activation, however, are observed in a context- and cell subtype–dependent manner, hinting that signaling events induced by fungal recognition may represent an important point of divergence from the classical and alternative paradigm. This is borne out in the pervasive induction of mixed CAM/AAM and Th1/Th2/Th17 responses in models of experimental fungal infection, in which protection has been associated with productive dectin-1-mediated signal activation and Th1/Th17-mediated responses, whereas increased fungal burdens and poorer outcomes have been associated with Th2 and AAM responses (74, 81, 83). Related to these findings perhaps, is the broader issue of plasticity within macrophage populations, which in vitro can switch expression levels of hallmark CAM or AAM markers after initial polarization, resulting in mixed marker patterns (84, 85); whether dectin-1-mediated recognition among AAMs is

pertinent to initiating such changes during the course of in vivo fungal models has not been fully explored.

Chitinases and Chi-lectins

Chitin, a biopolymer of β-1,4-*N*-acetylglucosamine and a component of many parasites and allergenic organisms such as fungi and dust mites, induces a localized innate cell infiltration characterized by eosinophils, basophils, and AAMs (25, 86). Mammals do not synthesize chitin but as a result of gene duplication events express several members of the glycosyl hydrolase family 18, including active chitinases that bind and degrade chitin as well as several homologous chi-lectins that exhibit some carbohydrate specificity but lack enzymatic activity (87, 88). Intriguingly, a close linkage observed between the human chitinase/chi-lectin gene family and major histocompatibility complex paralogon genes on chromosome 1 has led to the suggestion that recent expansion of this family is related to the acquisition of adaptive immunity (88). Both chitinases and chi-lectins, particularly AMCase (25, 89) and Ym1 (Chi3l3)/Ym2 (Chi3l4) (34, 35, 90, 91), are induced in an IL-4/IL-13- and STAT6-dependent manner in vitro and during type 2 immune responses. Copious production of the chi-lectin Ym1 leads to formation of large eosinophilic crystals in lung tissue from SHP-1-deficient viable motheaten (mev) and p47[phox]-deficient mice; similar crystals are also observed in SHIP-deficient mice, CD40L-deficient mice spontaneously infected with *P. carinii*, and mice expressing a lung-specific soluble TNFRII transgene (92--94). Ym2 has been associated with hyaline gastric and lung lesions in aging 129S4/SvJae and B6.129 strains (95). Yet, although both Ym2 and AMCase are highly upregulated in a STAT6-dependent manner during helminth infection, lung-specific transgenic expression of either AMCase or Ym2 in Balb/c mice did not result in spontaneous lung inflammation (25; T. Reese and R. Locksley, unpublished observations), indicating that these proteins do not mediate lung inflammation per se in the absence of accompanying stimuli. Another chi-lectin, breast regression protein 39 (BRP-39; Chi3l1; YKL-40 in humans), has been associated with several inflammatory disorders, including severe asthma (96), and mice lacking BRP-39 display diminished Th2 responses and AAM generation following allergen challenge (97). Thus, the recognition and degradation of chitin by mammalian chi-lectins and chitinases associated with AAMs during type 2 immune responses, when considered in the context of widespread environmental chitin derived from insects, parasites, and fungi, suggest a conserved role for this family in mediating mammalian host defense functions, perhaps representing convergence with similar chitin-recognition systems employed in plants (98).

Relmα

Resistin-like molecule α [Relmα; also known as Retnla, found in inflammatory zone (FIZZ1), or hypoxia-induced mitogenic factor (HIMF)] is a member of the Relm/FIZZ family of cysteine-rich secretory proteins, initially identified in bronchoalveolar lavage fluid from allergen-challenged mice (99). Relmα is highly induced during helminth- and allergen-induced type 2 immune responses and is primarily expressed by epithelial cells, eosinophils, and AAMs (35, 91, 99--101). Analysis of helminth-infected Relmα-deficient mice by two separate groups (102, 103) has revealed an important regulatory role during type 2 inflammation, as Relmα-deficient mice displayed increased inflammation associated with increased granuloma size, liver fibrosis, and exacerbated type 2 cytokine production after *S. mansoni* infection—intriguingly echoing results from myeloid-specific Arg1-deficient mice —along with increased resistance to *Nippostrongylus brasiliensis*. The exact mechanism of regulation by Relmα in the setting of helminth infection, as well as the identity of the relevant Relmα-expressing cell type responsible for mediating the effects in vivo, remains unclear. Notably, however, additional in vitro experiments indicated that Relmα-deficient AAMs exerted direct effects on CD4 T cells, possibly through modulation of Bruton's

tyrosine kinase signaling (102). Contrasting roles for Relmα, however, have been described in other systems in which recombinant Relmα directly mediated eosinophilia, epithelial thickening, and fibrotic responses (101), whereas Relmα-deficient mice exhibited normal type 2 cytokine production, mucus production, and inflammatory responses during allergy-induced lung inflammation (100).

IL-4 AND IL-13: CANONICAL TYPE 2 CYTOKINES

AAMs arise within the context of tissues responding to the actions of the type 2 cytokines IL-4 and IL-13, which are released by various cell types and mediate effects through receptor complexes that share subunits and several downstream signaling components. The specific roles of IL-4, IL-13, and their associated receptor subunits are now becoming clearer through studies employing various mouse strains that lack specific cells, cytokines, or critical signaling components. Reporter mice, too, have allowed unprecedented spatiotemporal tracking of signature cytokine- and enzyme-expressing cells in vivo, unveiling complexities in how the appearance of these cells is tightly correlated with induction of AAMs during type 2 immune responses and associated physiologic processes.

IL-4/IL-13 Production

IL-4 and IL-13 are closely related members of the short-chain four-helix bundle cytokine family that bind shared receptor subunits but exhibit only 25% identity at the amino acid level, accounting for significant structural differences that influence receptor binding (104--109). And, although IL-4 and IL-13 can mediate similar physiologic effects, the two cytokines appear to be differentially regulated and play distinct roles during in vivo type 2 immune responses, due to additional exclusive receptor subunit binding and segregation of expression among different cellular and tissue sources. In line with these differences, recent studies employing reporter mice have indicated a partitioning of in vivo IL-4 and IL-13 production between distinct tissue sites, a concept reinforced by mice deficient in cytokines or cytokine-producing cells or lacking specific receptor subunits. These studies have ascribed nonredundant roles to IL-4, which mediates most events involved in the generation of high-affinity IgE antibodies, and IL-13, which mediates localized tissue effects such as chemokine secretion, goblet cell hyperplasia, mucus production, and smooth muscle alterations (8, 110, 111). Important species-specific differences exist, however, as human B cells induce proliferation and Ig switching in response to IL-13, whereas mouse B cells do not, owing to differential expression of IL-13-specific receptor subunits (112). During helminth infection, primary sources of IL-4 in the affected lung tissue include basophils and conventional Th2 cells, whereas T follicular helper (Tfh) cells are the main IL-4 producers in the tissue-draining lymph nodes (110, 111). Other cells, including mast cells, eosinophils, natural killer T cells, and innate lymphoid type 2 cells (ILC2; a.k.a. nuocytes, Ih2 cells, or natural helper cells), assume a constitutively poised state expressing IL-4 mRNA but do not secrete IL-4 cytokine in this context, as assessed by protein reporter mice. In contrast, tissue Th2 cells and ILC2, but not Tfh cells, are major producers of IL-13 (111, 113--115). Whether any of these cellular sources contributes IL-4/IL-13 to induce AAM development in various in vivo settings remains to be determined, but Arg1-reporter mice have revealed functional relationships between closely associated AAMs and eosinophils during innate responses to chitin administration and during maintenance of metabolic homeostasis (25, 116). Accordingly, macrophage depletion or deficiency during type 2 inflammation induced by IL-33, chitin, or helminth infection results in reduced recruitment of eosinophils (25, 117, 118). This regulation may exert reciprocal effects, as genetic deficiency of eosinophils also impairs accumulation of AAMs in white adipose tissue (WAT) (116).

Suppression of aberrant IL-4 and IL-13 production appears to be under steady-state regulation at peripheral tissue sites. Rudensky and colleagues (119) have demonstrated that

this suppression is primarily imposed by induced regulatory T (iTreg) cells, which act to restrain type 2 immune activation in the steady-state, particularly at mucosal barriers. In this model, mutation of the Foxp3 enhancer CNS1 in mice results in a lack of the normal complement of iTreg cells; these mice concurrently exhibit spontaneous airway hyperresponsiveness and type 2 immune inflammation in the lung, characterized by the increased presence of acidophilic macrophages, Arg1 and Ym1 expression, and Ym1 crystal formation, all of which correlate with the increased presence of IL-4-, IL-5-, and IL-13-producing T cells in mucosal tissues (119). The exact mechanism by which iTregs repress steady-state activation of type 2 immunity remains unclear, but this process represents an important insight into how the maintainance of immune homeostasis might be subject to multiple layers of regulation. Furthermore, several factors aside from IL-4/IL-13, particularly IL-10, IL-21R, galectin-3, and TGFβ, play relevant synergistic or inhibitory roles during the induction of AAM responses; exactly how these factors impinge upon IL-4/IL-13 and STAT6-mediated aspects also remains to be elucidated but may involve similar regulation at the cellular level or engagement of several interconnected complementary or inhibitory signaling pathway elements (93, 120--122).

IL-4/IL-13 Signaling

IL-4 or IL-13 signaling is initiated via two types of heterodimeric transmembrane receptor complexes: the type I receptor, which exclusively binds IL-4 and is comprised of IL-4Rα and γ_c subunits (the latter of which also functions as a subunit in IL-2, IL-7, IL-9, IL-15, and IL-21 receptor complexes), and the type II receptor, which binds both IL-4 and IL-13 and is comprised of IL-4Rα and IL-13Rα1 subunits. Thus, exclusive expression of type I receptor complexes on any particular cell type limits responsiveness to IL-4, as is the case for most mouse B and T cells, whereas expression of the type II receptor permits signaling in response to both IL-4 and IL-13, as occurs in many nonhematopoietic cell types. Macrophages express both type I and type II receptors and thus may initiate signaling and induction of the AAM phenotype under all three circumstances: engagement of the type I receptor by IL-4 or engagement of the type II receptor by either IL-4 or IL-13. Recent work detailing the ternary structure of each ligand-receptor binding state has revealed critical differences in affinity that influence subunit assembly as IL-4Rα is paired with γ_c versus IL-13Rα1 in the presence of ligand and also, unexpectedly, that the type II receptor varies in signaling potencies and kinetics when bound by IL-4 versus IL-13. This latter observation reflects the differences in sequential assembly of the shared subunits with consequences for the strength and duration of downstream signaling events (109). The implication of these findings is that both cytokine and receptor subunit availability influence subsequent signaling; studies demonstrating that macrophages exhibit differing signaling sensitivities depending on the presence or absence of γ_c and the exposure to either IL-4 or IL-13 provide further support (123). Also noteworthy in this respect is the potential contribution in vivo of the decoy receptor IL-13Rα2, which contains additional IL-13 binding sites that confer an affinity for IL-13 that is four orders of magnitude greater than that of IL-13Rα1 (124, 125). The in vivo relevance of this inhibitory receptor is borne out in IL-13α2-deficient mice, which display enhanced IL-13 tissue expression and suppression of NO macrophage responses (126).

Differential signaling events occurring downstream of type I versus type II receptor engagement may also influence the induction of gene programs in AAMs. Similarly to other cytokine receptor complexes, both type I and type II receptors initiate signaling via Jak/STAT-mediated phosphorylation events but differ in particular subunit-specific adapters: namely, Jak3 associates with γ_c, whereas Jak2 or Tyk2 associates with IL-13Rα1 (127). The shared IL-4Rα chain associates with Jak1 and contains multiple tyrosine phosphorylation sites that serve as binding sites for proteins containing Src homology 2

(SH2) domains (e.g., STAT6) and phosphotyrosine-binding (PTB) domains [e.g., insulin receptor substrate (IRS) proteins]; various binding events within specific regions of the IL-4Rα chain correspond to different cellular transcriptional and growth functions (128). After initial receptor dimerization and tyrosine phosphorylation, STAT6 associates with IL-4Rα and is phosphorylated, dissociates, homodimerizes, and then translocates into the nucleus and binds to promoter elements within IL-4/IL-13-responsive genes. In macrophages, IL-4 induces γ_c-dependent tyrosine phosphorylation of IRS-2 and association with the p85 subunit of phosphatidylinositol 3-kinase (PI3K) and growth factor receptor–bound protein 2 (Grb2); these responses correlate with heightened expression of the AAM markers Arg1, Relmα, and Ym1 compared with IL-13, even in conditions of similar STAT6 phosphorylation, indicating that type I receptor engagement by IL-4 may more sensitively induce AAM polarization (129). Consistent with these findings, other groups demonstrated that IL-13Rα1 was dispensable for induction of some AAM markers but not others during allergen challenge and helminth infection (130, 131). Hence, induction of the AAM phenotype can be subject to several types of regulation solely at the level of IL-4/IL-13: availability of IL-4 and IL-13 cytokines, expression levels of both types of receptor complexes, presence or absence of IL-13Rα2, and differential engagement of signaling components downstream of each subunit.

IL-4/IL-13-induced signaling events can be further modulated by an immunoreceptor tyrosine-based inhibitory motif (ITIM) within the cytoplasmic tail of IL-4Rα, a site recognized by Src family kinases and inhibitory phophatases that are also implicated in the regulation of the AAM phenotype. Evidence for steady-state regulation of AAM polarization emerged from mice containing mutations in SH2 domain-containing inositol-5'-phosphatase (SHIP) and SH2 domain-containing protein tyrosine phosphatase 1 (SHP-1), both negative regulators of the phosphoinositide 3-kinase (PI3K)-mediated signaling pathway in hematopoietic cells. SHIP$^{-/-}$ mice have a short life span, abnormal hematopoiesis, and marked lung pathology (132), mirroring phenotypes observed in motheaten (me) or viable motheaten (mev) SHP-1-deficient states and reflecting the broad immunosuppressive activities associated with this family of signaling molecules (133--135). Peritoneal and alveolar macrophages from SHIP$^{-/-}$ mice display constitutively increased levels of Arg1 and phosphatidylinositol (3,4,5)-trisphosphate (PIP$_3$) as a result of increased PI3K activity, accompanied by lung pathology characterized by spontaneous type 2 inflammation, fibrosis, and the conspicuous presence of Ym1 eosinophilic crystals (93, 136). Although initially interpreted as an indication that SHIP was acting in a macrophage-intrinsic manner during development to repress a separate, IL-4/IL-13-independent pathway of AAM skewing (93), more recent evidence indicates that the in vivo AAM phenotype could arise from aberrant IL-4 production, perhaps by hypersensitive basophils or mast cells (137).

A similar picture has emerged in the case of SHP-1, as the severity of the spontaneous type 2 lung inflammation observed in mev mice was significantly ameliorated by concomitant loss of IL-13 or STAT6 (138). As with SHIP deficiency, the AAM phenotype in SHP-1-deficient mice may arise indirectly as a result of aberrantly activated cells that produce IL-4/IL-13 upstream of macrophage activation. In line with this, SHP-1 has also been described to play a critical role in restraining hyperresponsiveness and cytokine production in a variety of cell types, such as mast cells (139). This model gains further support from mice with combined deficiency of Src family kinases Lyn and Hck, which exhibit similarly complex hematopoietic defects along with lung AAM infiltration. This phenotype could be attenuated by expression of a membrane-bound form of SHIP in hematopoietic stem cells, and further mechanistic insights also suggest a role for increased IL-4 production by basophils (140). In contrast to these studies, however, other work indicates that IL-4-induced STAT6 transcription and expression of Ym1 and Arg1 are dependent on cell-intrinsic SHIP

degradation and the PI3K pathway in macrophages during AAM polarization (141). In addition, bone marrow–derived macrophages from mice in which the IL-4Rα ITIM, a region previously demonstrated to interact with SHP-1, SHP-2 and SHIP (142), was inactivated by mutagenesis of the tyrosine (Y709) residue into phenylalanine (F709) exhibited enhanced STAT6 phosphorylation and AAM marker expression in response to IL-13 and, to a lesser degree, IL-4 (143). Although the mechanistic details remain cloudy, these systems, along with observations made in the Foxp3 CNS1 mutant mouse, indicate a clear role for steady-state suppression of aberrant IL-4 and IL-13 signaling and/or production among various potential cellular sources, without which deleterious type 2-mediated pathology arises and proceeds unabated.

Other Factors

Several additional intracellular factors act in concert with the IL-4/IL-13–STAT6 axis to regulate the AAM phenotype. In particular, IL-4/IL-13- and STAT6-mediated signals induce the lipid-activated transcription factors peroxisome proliferator–activated receptor γ (PPARγ) and δ (PPARγ), along with PPARγ coactivator 1β (PGC1β), which mediate several aspects of AAM polarization particularly important in the context of glucose and lipid metabolism, as discussed further below (144--147). In the case of PPARγ, an interaction between STAT6 and PPARγ on promoters of PPARγ target genes appears to act as a transcriptional switch to promote DNA binding and increased gene expression in AAMs (148). These factors may act in parallel with other STAT6-inducible transcription factors such as c-Myc and KLF4, which appear to amplify STAT6-mediated signals in AAMs while, in the case of KLF4, simultaneously suppressing CAM-inducing NF-κB activation signals (30, 32). This type of signal integration is further apparent upon exposure to CAM-polarizing stimuli, as PPARγ expression in macrophages is suppressed upon LPS exposure (149); however, interestingly, macrophages induced to become LPS tolerant exhibit an AAM phenotype by a mechanism regulated by the p50 subunit of NF-κB, an observation supported by the finding that p50-deficient mice show reduced AAM responses during allergy and helminth challenge models (150).

Epigenetic changes may also impinge upon the IL-4/IL-13-mediated AAM program. For instance, IL-4 signals induce STAT6 binding to the promoter of the chromatin-remodeling factor Jmjd3, which was shown to demethylate histone H3 at lysine 27 and thereby regulate expression of AAM marker genes such as Arg1, Ym1, and Relmα (151). Because Jmjd3 deficiency in mice results in perinatal lethality, Akira and colleagues (31) generated chimeric mice using Jmjd3-deficient fetal liver cells; these mice displayed normal responses to CAM-inducing stimuli, but the induction of AAMs was impaired in response to intraperitoneal chitin administration, M-CSF exposure, and helminth infection. Curiously, however, IL-4-induced AAM marker expression among bone marrow–derived macrophages from these mice was preserved, in contrast to the prior study (151), which demonstrated using siRNA knockdown of Jmjd3 that IL-4 induction of AAM genes acted via a Jmjd3-dependent mechanism. Further, impaired IL-4 and IL-13 production and lymph node T cell defects were observed during *N. brasiliensis* infection in Jmjd3-deficient chimeric mice, which, when coupled with the observation that Jmjd3-deficient macrophages showed impaired proliferation in response to M-CSF (31), suggest broader and more fundamental effects of Jmjd3 deficiency apart from AAM marker induction. Indeed, Jmjd3 is also induced in response to LPS and inflammatory cytokines to bind and regulate polycomb group target gene activity in macrophages (152). Nevertheless, the additional demonstration that the gene encoding the transcription factor interferon regulatory factor 4 (*Irf4*) is the Jmjd3 target gene responsible for controlling AAM marker expression (31) is of potential relevance in light of other recent studies showing that, in contrast to AAM polarization, CAM polarization can be directed by IRF5 (153) or IRF8 via the Notch1–RBP-J axis (154).

PHYSIOLOGIC FUNCTIONS OF AAMS

Although IL-4 and IL-13 production and AAM development have generally been studied in the context of type 2 immunity to helminthes or allergic airways disease, a crucial role for AAMs in metabolic homeostasis is also emerging, in concert with the increasing appreciation of a role for hematopoietic cells in this and other physiologic processes; these roles may ultimately have roots in basic mechanisms of tissue maintenance and repair (Figure 2). In vivo functional studies are limited, however, and tools to selectively deplete AAMs or AAM products are hampered by reagents that lack complete specificity for macrophages or display incomplete penetrance among macrophage populations.

Helminth Infection

Several helminths elicit highly polarized type 2 immune responses, marked by induction of IL-4 and IL-13, which direct IgE antibody and mucus overproduction, eosinophilia, and smooth muscle and fibroblast alterations along with AAM development. AAMs have been described to play important roles in modulating various pathologic features of helminth infection, including suppression of T cell responses, modulation of fibrosis, and formation of multinucleated giant cells found within parasite-induced granulomas. Brombacher and colleagues (155) described a vital function for AAMs after acute *S. mansoni* infection, in which myeloid-restricted IL-4Rα deficiency resulted in early mortality, phenocopying results from mice with global IL-4Rα deficiency. In contrast to global IL-4Rα deficiency, however, myeloid-restricted IL-4Rα-deficient mice retained robust eosinophilic granuloma formation and fibrosis, along with antigen-specific Th2 responses (155). Similar effects of myeloid cell–restricted Arg1 deficiency during *S. mansoni* infection indicate that AAM-derived Arg1 is a key mediator in this process, acting to restrain both unrestricted Th2-mediated fibrotic pathology and intestinal damage associated with increased Th1/Th17 cytokines, NOS-2 levels, and endotoxemia (44, 45). These effects appear to vary among helminths, however, as myeloid-specific IL-4Rα-deficient mice exhibited normal cytokine and antibody production, parasite clearance, and mucous goblet cell numbers in response to *N. brasiliensis* infection (155), and Arg1 blockade or deficiency in hematopoietic and endothelial cell lineages had little effect on responses to acute and chronic infection with *T. muris* (156). Macrophage depletion, however, impaired eosinophil recruitment and tissue repair processes during *N. brasiliensis* infection (117, 157) and abrogated memory responses to the gastrointestinal helminth *Heligmosomoides*; further, chemical inhibition of Arg1 in this system attenuated expulsion of *Heligmosomoides* (158). Thus, roles for AAMs during parasite infection depend on the infection model, along with the particulars of AAM depletion, perhaps resulting from inadequate drivers of deletion in these mouse models or compensatory factors aside from IL-4/IL-13—particularly IL-10, which can also mediate important AAM functions. For example, IL-10-induced expression of selenoprotein P contributes to lowered pathogenicity and associated susceptibility in a model of African trypanosomiasis (121).

Asthma and Allergic Inflammation

Type 2 immune responses are also prominently associated with asthma and allergic inflammation, in which many features of helminth infection, such as elevated IgE, eosinophilia, mucus production, and smooth muscle hypercontractility, are recapitulated in a manner dependent on IL-4/IL-13 and STAT6. Animal models of allergic airways disease have yielded a consistent view of distinct yet overlapping roles for IL-4 and IL-13 in mediating most aspects of associated pathology (8). For instance, hallmarks of human asthma such as airway hyperreactivity (AHR; increased sensitivity to bronchoconstricting agents), eosinophilia, and mucus overproduction can be reproduced in rodents by transgenic overexpression or exogenous administration of IL-13, whereas these effects are inhibited by

IL-13 neutralization or IL-13Rα1 deficiency, albeit somewhat variably, in the context of allergen-induced airway inflammation (130, 131, 159--161). Although IL-4 mediates similar effects, IL-13 in this context appears to act directly on smooth muscle cells and epithelial cells expressing IL-4Rα and STAT6, rather than on hematopoietic cells. For instance, transgenic expression of hSTAT6 in CC10-expressing epithelial cells restores IL-13-induced mucus overproduction and AHR in STAT6-deficient mice (162). In contrast, AHR develops normally in allergen-challenged mice lacking IL-4Rα on epithelial cells expressing Clara cell secretory protein (163), indicating the involvement of other IL-13 targets such as airway smooth muscle cells. Accordingly, mice engineered to express IL-4Rα exclusively on smooth muscle cells show normal induction of IL-13-mediated AHR, but this restricted expression is sufficient but not necessary to induce AHR in response to cytokine or allergen inhalation (164). These findings extend to human studies, in which treatment with an IL-13-neutralizing antibody led to improved lung function in asthmatic adult populations, particularly in patients exhibiting a Th2-high phenotype marked by elevated blood eosinophils, serum IgE, and periostin (165).

Prominent expression of IL-4/IL-13 also leads to AAM development in several allergen-driven models, much like in helminth infection, although a functional role for AAMs in mediating pathology in these settings is less clear. For example, myeloid deficiency of IL-4Rα in mice reduced Ym1, Arg1, and Relmα AAM marker expression during ovalbumin (Ova)- or house dust mite extract–induced allergic inflammation, but this reduction resulted in minor alterations to other parameters, such as AHR, antibody and cytokine production, mucus hypersecretion, eosinophil levels, and collagen deposition (166). These findings were mirrored by a similarly limited impact of Relmα deficiency in the context of allergy-induced lung inflammation (100). A separate study, however, showed that AAMs contribute to eosinophil recruitment in an Ova-driven allergy model, as demonstrated by the ability in mice of adoptively transferred bone marrow–derived macrophages to acquire AAM markers and enhance lung eosinophil recruitment, in contrast to IL-4Rα-deficient macrophages (167). In support of this finding, IL-33 administration, which induces AAM development via an IL-13-dependent mechanism in the lung, also mediated eosinophil recruitment in a macrophage-dependent manner (118). Thus, it seems likely that the involvement of AAMs in allergy-driven models may depend critically on the nature of the stimulus and exposure regimen, as extracellular parasite infection is often accompanied by a significant tissue injury component that may be lacking in most allergen-driven model systems.

Tissue Damage and Repair

Parasite migration through host tissues causes extensive tissue destruction that simultaneously invokes repair processes, which are characterized by deposition of collagen and other extracellular matrix proteins and by increased mucus production and smooth muscle effects directed at generating the mechanical force needed to expel large foreign entities. Engagement of these processes suggests that type 2 immunity may have evolved from a more generalized innate response to tissue injury (7). Tissue repair and regeneration processes, such as those triggered during virus-induced lung inflammation, invoke close collaboration among the stem cell compartment, innate lymphoid cells, and AAMs (168). The kinetics and magnitude of AAM induction during innate and adaptive immune responses indicate that early innate sources of IL-4/IL-13 stimulate an immediate basal AAM polarization that is reinforced and potentiated by subsequent Th2 cell–derived IL-4/IL-13. For example, recent work confirming earlier observations (169, 170) indicates that normal wound healing responses are critically dependent on macrophages present during the first several days following sterile tissue damage such as surgical trauma. These early time points are concurrent with the IL-4Rα1-dependent innate induction of AAM markers among macrophages, a response that wanes over subsequent days unless accompanied by an

adaptive Th2 response induced by antigenic stimulation (170--172). In the case of parasite infection, this later engagement by the adaptive immune system serves to amplify early innate responses and is required for normal expulsion of many parasites, such as *N. brasiliensis*. As such, worsening of hemorrhage and inflammation were seen when macrophages were depleted during the early stages of *N. brasiliensis* migration through the lung (157), corroborating results from the surgical injury model. Myeloid KLF4 deficiency, which led to impaired AAM polarization, also resulted in significantly delayed wound healing in a mouse skin injury model (30). Repair processes after injury critically involve additional factors, such as IL-10 and TGF-β1 signaling, but, as in other type 2-mediated processes, how they interact with IL-4/IL-13 remains undefined.

The induction of multinucleated giant cells in response to granulomatous diseases or foreign bodies, such as surgical implants, that cannot be otherwise phagocytosed may involve AAMs in a manner resembling osteoclast function in bone degradation, although in vivo data are lacking. In vitro, IL-4 or IL-13 can trigger formation of multinucleated cells and induction of fusogenic molecules, depending on the macrophage source, adherence to particular substrates, and membrane and cytoskeletal rearrangements. Several molecules have been implicated in regulating the fusogenic state, including surface receptors E-cadherin and DC-STAMP (173). Intriguingly, recent evidence implicates microRNAs as exerting transcriptional control over macrophage fusion and DC-STAMP induction by IL-4, particularly through miR-7a-1, which negatively regulates fusion by directly targeting DC-STAMP mRNA, providing a mechanistic basis for feedback suppression that may be involved in the differential induction of this phenotype within various settings (174). Additionally, microRNAs may control other aspects of AAMs, as miR-155 targets IL-13Rα1 in human macrophages to modulate AAM gene expression (175).

Metabolism and Homeostasis

Initial appreciation that a significant inflammatory component present in obese WAT may contribute to the pathogenesis of insulin resistance, diabetes, and metabolic syndrome gave way to more recent findings that, upon transition from a lean to an obese state in mice, WAT macrophages switch phenotypes from AAM to CAM (145, 176). Subsequently, the maintenance of AAMs in WAT was found to be dependent on macrophage-intrinsic PPARγ and IL-4/IL-13–STAT6 signals, likely derived from WAT-associated eosinophils; reduction of either cell type in vivo resulted in diet-induced metabolic dysregulation characterized by insulin resistance and glucose intolerance (116, 145). In addition, impaired AAM polarization due to myeloid KLF4 deficiency promoted insulin resistance (30). Other PPARs contribute to metabolic homeostasis, as similar metabolic effects and AAM marker impairment were also observed in the absence of PPARδ (146, 147); however, metabolic dysregulation was not observed in chimeric mice reconstituted with PPARγ-, PPARδ-, or doubly deficient bone marrow (177), perhaps reflecting different genetic backgrounds of the mice used in these studies. Notable, too, is a recent report indicating that synthetic PPARγ agonists may target cells other than macrophages, such as adipose tissue Tregs, which play a role in thiazolidinedione-mediated restoration of insulin sensitivity in obese mice (178). Nevertheless, IL-4 mediates dramatic changes in macrophages that are relevant to metabolism on both a cellular and a tissue level, including activation and maintenance of PPARγ, PPARδ, and PGC1β. These factors antagonize the program of anaerobic glycolysis induced within CAMs by hypoxia-inducible transcription factor (HIF)-1α and instead promote a program of aerobic metabolism characterized by β-oxidation of fatty acids. This program enables long-term alternative activation and sustainment of macrophages, which may be relevant not only to the homeostatic maintenance of metabolic parameters but also during prolonged type 2 immune responses typified by chronic helminth infection (179).

The endogenous regulators of this immunometabolic unit remain undefined, but points of integration with several other physiologic systems suggest a default state that can be perturbed by various stressors. For example, exposure to cold temperatures can induce an IL-4-mediated AAM response in adipose tissue macrophages, which directly produce norepinephrine in mediating an adaptive thermogenic program in both WAT and brown adipose tissue, indicating that type 2 immune cells operate in parallel with the nervous system to integrate physiologic stress signals (180). Also, the appearance of AAMs or macrophages exhibiting AAM markers in several tissues such as bone (181), skeletal muscle (182), mammary gland (183), and testes (184) suggests potential involvement of type 2 immune cells in the regulation of several other physiologic processes, but these possibilities also remain largely unexplored. The notably mixed CAM/AAM population and angiogenic response to hypoxic environments in the context of tumors, for example, may reflect metabolic energy flux that occurs within macrophages and that can also contribute to general tissue homeostasis. Glucose metabolism, which is controlled by several kinases acting via the pentose phosphate pathway of glycolysis, may thus be a critical branch point during induction of AAM/CAM phenotypes. A recent study implicated the carbohydrate kinase-like protein CARKL as a key rheostat in macrophage metabolism, acting to maintain oxygen consumption in AAMs, whose metabolic profile resembled nonpolarized macrophages; CAMs, in contrast, downregulated CARKL to increase glycolysis and decrease oxygen consumption rate. CARKL also downregulated SOCS3 expression in CAMs, resulting in enhanced STAT3 phosphorylation (185) and thereby representing an intriguing link between metabolic flux and modulation of cytokine signaling within macrophages.

SUMMARY AND NEW DIRECTIONS

The critical role of macrophages in host defense has been reinforced by a century of research since Metchnikoff's initial description. New appreciation for the spectrum of phenotypes that these cells can assume within a wide range of cellular milieus invoked by homeostatic and inflammatory physiologic conditions has extended their functions into previously unexplored realms. Thus, an important area for future work will be the careful characterization of how these various phenotypic states are influenced and how they function in vivo, taking into consideration recent findings detailing the development and differentiation of distinct macrophage populations. Differential exposure to IL-4 versus IL-13 and receptor type expression may contribute substantially to heterogeneous responses even among AAMs, but the in vivo relevance of this remains to be established. Also, the induction and modulation of AAM markers by stimuli or cytokines other than IL-4/IL-13, such as IL-10 and TGF-β, suggest that specific aspects of AAMs are preserved in a redundant fashion. How these states of activation relate to or modify AAMs, in the context of IL-4/IL-13 or otherwise, is also unclear but may be important in the context of tissue responses that exhibit a complement of macrophages with mixed CAM/AAM phenotypic markers, such as tumor-associated macrophages or myeloid-derived suppressor cells.

As such, the definition of the AAM phenotype as a signature of IL-4 or IL-13 activation remains useful to guide interrogation of relevant cell types or particular microenvironmental cues that thus induce AAM markers in contexts other than highly polarized type 2 immune responses such as helminth infection or allergic inflammation. The complex roles and regulation of IL-4 and IL-13 are now becoming clearer as new tools allowing in vivo functional analysis have revealed an element of innate activation, originally inferred from the tissue repair and immunosuppressive processes induced by parasites, that appears to be relevant in maintaining tissue homeostasis. New appreciation of the dramatic metabolic changes occurring upon macrophage activation that shift amino acid, oxygen, and glucose processing on a cellular level has led to a greater understanding of the connections between immune cells and broader physiologic tissue responses. In addition, as the critical producers

of IL-4/IL-13 are parsed in various experimental systems, attention has focused on the initiation of type 2 immunity upstream of canonical IL-4/IL-13 production, where newly identified innate cells and epithelial cytokines have been implicated. In particular, IL-25, IL-33, and TSLP appear to play critical roles in priming type 2 immunity and activating ILC2, a rare population of innate effector lymphoid cells found in multiple tissues that is poised to rapidly produce IL-5 and IL-13 in response to these cytokines (6). Whether these cells contribute to the development of AAMs remains to be established, but their involvement in the innate production of type 2 cytokines and the recruitment of other cells competent for cytokine production is intriguing and raises broader questions about how they fit into the initiation of polarized type 2 immunity and other physiologic processes that invoke similar innate responses. Finally, although AAMs have been described in several physiologic settings, their functions have remained elusive due to a lack of adequate in vivo tools. Novel mouse strains exhibiting genetic deficiencies of various cytokines and cytokine receptor subunits, along with deleter and reporter mice, have been greatly informative, but caveats exist, including deletion efficiency, lineage specificity, marker analysis, and particulars of the mouse model systems employed. Thus, a systems approach using careful in vivo evaluation must guide future research aimed at elucidating AAM function within the larger context of type 2 immune biology.

Acknowledgments

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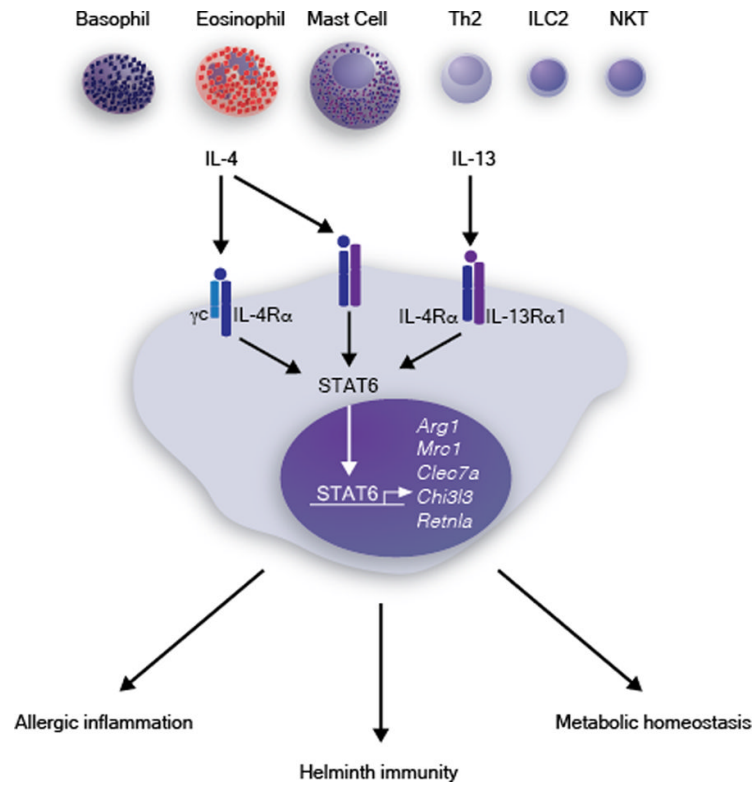
FIGURE 1. Alternatively activated macrophages in disease and homeostasis
Various cell types involved in type 2 immune responses or maintenance of metabolic homeostasis are capable of producing the canonical type 2 cytokines IL-4 and IL-13. These cytokines induce the alternatively activated phenotype in macrophages, which is characterized by the expression of a distinct set of genes (examples shown for mouse macrophages). Alternatively activated macrophages are induced in tissues associated with type 2 immune responses such as those that occur with allergic inflammation and helminth infection as well as in adipose tissue during maintenance of metabolic homeostasis. Abbreviations: ILC2, innate lymphoid type 2 cell; NKT, natural killer T cell; STAT6, signal transducer and activator of transcription 6; Th2, type 2 helper T cell.
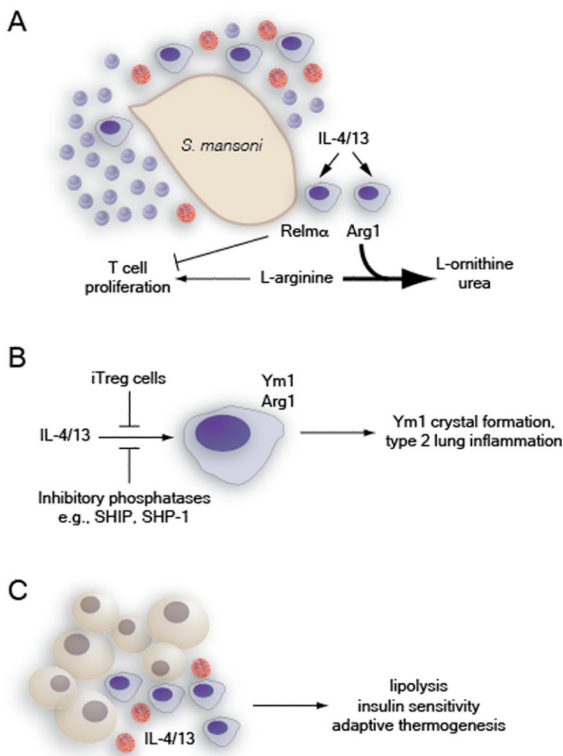
FIGURE 2. Functional aspects of alternatively activated macrophages (AAMs) during immunity and homeostasis

(a) IL-4 and/or IL-13 produced in the context of Schistosoma mansoni–induced granuloma formation in the liver induces AAMs. In mouse tissues, arginase 1 (Arg1) is produced by AAMs and mediates T cell suppression by catabolizing available L-arginine into L-ornithine and urea, thereby depleting an essential T cell proliferative factor. Relmα is also produced by AAMs and mediates T cell suppressive effects. (b) IL-4/IL-13 production and/or receptor signaling is suppressed in the steady state by induced T regulatory (iTreg) cells and inhibitory phosphatases such as SHIP and SHP-1. In their absence, the AAM phenotype is spontaneously induced, resulting in excessive expression in vivo of Arg1 and Ym1, which leads to Ym1 crystal formation and type 2 inflammation in the lungs. (c) Adipose tissue in lean animals contains eosinophils and AAMs, which mediate maintenance of metabolic homeostasis via lipolysis, insulin sensitivity, and stress-induced thermogenesis; in obese animals, AAMs are replaced by classically activated macrophages and these effects are diminished.