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Immunosenescence and macrophage functional plasticity: dysregulation of macrophage function by age-associated microenvironmental changes

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Summary

The macrophage lineage displays extreme functional and phenotypic heterogeneity which appears to due in large part to the ability of macrophages to functionally adapt to changes in their tissue microenvironment. This functional plasticity plays a critical role in their ability to respond to tissue damage and/or infection and to contribute to clearance of damaged tissue and invading microorganisms, to contribute to recruitment of the adaptive immune system, and to contribute to resolution of the wound and of the immune response. Evidence has accumulated that environmental influences, such as stromal function and imbalances in hormones and cytokines, contribute significantly to the dysfunction of the adaptive immune system. The innate immune sytem also appears to be dysfunctional in aged animals and humans. Herein, the hypothesis is presented and discussed that the observed age-associated “dysfunction” of macrophages is the result of their functional adaptation to the age-associated changes in tissue environments. The resultant loss of orchestration of the manifold functional capabilities of macrophages would undermine the efficacy of both the innate and adaptive immune systems. If the macrophages maintain functional plasticity during this dysregulation, they would be a prime target of cytokine therapy that could enhance both innate and adaptive immune systems.

Introduction

It is well documented that both the T lymphocyte and B lymphocyte compartments of the adaptive immune system deteriorate progressively with advancing age (1–6). Research is now focused on the mechanisms underlying that deterioration and on whether function can be enhanced at least transiently (1,5,7–9). The impact of advancing age on the innate immune system still remains to be resolved. The views expressed in previous reviews of the subject range from the opinion that the innate system is not significantly impacted by aging (6) to the opinion that all components of the innate system are significantly impacted (10). The following review focuses on the impact of advancing age on macrophage function. An overview of macrophage biology is presented with an emphasis on the ability of macrophages to functionally adapt to changes in microenvironmental signals. The literature on the impact of aging on macrophages is then reviewed in the context of the hypothesis that macrophage function changes with age in response to age-related changes in tissue environment. The implications of the hypothesis are that macrophage function may change with age in a tissue specific manner, that changes in macrophage function may contribute significantly to decreased clearance of microorganisms and decreased responsiveness of the adaptive immune system, and that these changes in macrophage function may be reversible, at least transiently.

Macrophage Biology: Functional Adaptability to Diverse Signaling Environments

Macrophages can produce an impressive array of cytokines, chemokines, enzymes, arachidonic acid metabolites, and reactive radicals upon activation. Many of these functions appear to antagonize or counter each other. Macrophages can clearly enhance or suppress adaptive immune responses (7,11–21). Macrophages display both pro-inflammatory and anti-inflammatory functions (22–24), produce tissue debriding metalloproteinases and inhibitors of these metalloproteinases (25–27), and produce toxic radicals that contribute to tissue cell destruction as well as cytokines that promote tissue regeneration and wound healing (23,24, 28,28–31). All of these functions are not expressed simultaneously but are thought to be regulated such that macrophages display a balanced, harmonious pattern of functions (Fig. 1).

Multiple roles of macrophages in the inflammatory response

In the classic acute inflammatory response, blood monocytes enter the damaged tissue shortly after neutrophils. Encounter with bacteria, their products, an damaged tissue results in the activation of pro-inflammatory activities, such as the production of TNFα, IL-1, and IL-6 and the secretion of metalloproteinases. As tissue debridement and clearance of bacteria proceed, the stimulus for inflammatory and effector activities at the cleared tissue sites decreases. This decrease in stimulus for inflammatory activity, coupled with the presence of many other factors such as acute phase proteins, glucocorticoids, TGFβ, IL-10, and the phagocytosis of apoptotic neutrophils, contributes to the down regulation of macrophage inflammatory/cytotoxic activities and the enhanced expression of anti-inflammatory and tissue regenerative activities (28,29,32–34). Thus, during a dynamic inflammatory response, the macrophage population will display a variety of functional patterns, depending on the balance of macrophage modulating ligands present in the tissue microenvironment (24,35).

In addition to the inflammatory, debridement, clearance and tissue regenerative activities mentioned above, macrophages also play a critical liaison role in the communication between the innate and adaptive immune systems. Macrophages can display antigen presenting activity and phenotype (13) and the inflammatory milieu created by macrophages can significantly impact the maturation of myeloid dendritic cells and thus influence the nature of the adaptive immune response that will be elicited (11,30,36). If the invading microorganisms display sufficient virulence to resist clearance by the macrophages, the inflammatory process will be prolonged. T lymphocytes, recruited by macrophage-derived chemokines, will enter the infected tissue site and, if activated, their function will influence the pattern of activities displayed by the macrophages. Thus a function-polarizing synergy can develop between T cells and macrophages wherein the functional pattern displayed by the macrophages influences the nature of the adaptive immune response and the nature of the adaptive immune response (Th1 versus Th2) influences the functional pattern displayed by the macrophages. Th1 cytokines, such as IFNγ and TNFα, promote inflammatory and cytotoxic activities of macrophages. In contrast, Th2 cytokines, such as IL-4 and IL-10, promote anti-inflammatory and/or tissue regenerative activities (22–24,31,37,38).

Macrophage functional subsets: harmonious patterns of function

Ligation of surface receptors such as CD40, TNFαR, or Toll-like receptors (TLR) on macrophages initiates signal cascades that provide a strong activating stimulus for macrophage function (32,39–49). However, which genes are expressed and the level of expression induced by receptor ligation is strongly influenced by other “modifying” signals in the environment. It was determined decades ago that IFNγ treatment of macrophages strongly upregulated the inflammatory cytokine and cytotoxic effector responses elicited by LPS stimulation (50–52). It has since been demonstrated that IFNγ does not simply amplify all macrophages functions

across the board. IFNγ selectively upregulates LPS-induced inflammatory cytokine production and iNOS and oxidase expression while down-regulating other functions, such as arginase and PGE2 and LTC4 production (23,24,31,32,53–57). Similarly, early studies on the impact of IL-4, IL-10, and/or TGFβ on macrophage activation by LPS focused on production of inflammatory cytokines or oxidative radicals and thus determined that these cytokines inhibited or "deactivated" macrophages (24,32,54,58–65). However, closer scrutiny revealed that IL-4, IL-10 and TGFβ, like IFNγ, exerted a selective effect on macrophage functions induced by LPS, down-regulating the expression of some genes but upregulating other genes (22–24,57, 66,67).

Twelve years ago, Stein *et al*. (68) published a seminal report establishing that IL-4 "…induces inflammatory macrophages to adopt an alternative activation phenotype, distinct from that induced by IFN-gamma, characterized by a high capacity for endocytic clearance of mannosylated ligands, enhanced (albeit restricted) MHC class II antigen expression, and reduced proinflammatory cytokine secretion." The concept of an alternative functional phenotype for macrophages was rapidly embraced by many immunologists. The functions which were upregulated by IL-4 soon was expanded to include increased expression of CD23 in addition to the increased expression of mannose receptor and class II MHC, increased production of select chemokines such as CCL18, CCL22, and CCL17, increased production of IL-1 receptor antagonist (IL-1Ra), and increased expression of arginase and 12,15-lipooxygenase (reviewed in ref. (23)).

Recently, Anderson *et al*. (14,15,69) described a third functional phenotype of macrophages that was clearly distinct from either classically or alternatively activated macrophages. Ligation of FcγR on macrophages prior toactivation of the macrophages with LPS resulting in enhanced IL-10 production and a dramatic decrease in IL-12 production with only moderate effects on the production of other inflammatory cytokines (22,69). Impressively, targeting antigen to FcγR on APC, either by injecting IgG complexed antigen or macrophages coated with complexes of IgG-bound antigen, resulting in strong bias toward Th2 development and away from Th1 development (14,15,70). Perhaps the most important aspect of these studies, in addition to defining unique functional pattern displayed by macrophages, is that ligation of a surface receptor, FcγR, can reverse or modulate the impact of microbial products on Th1/Th2 biasing of the adaptive immune response.

The research literature actually contains many demonstrations of unique functional phenotypes of macrophages. Considering that IFNγ, IL-4, and FcRγR ligation all selectively alter the response pattern induced by LPS stimulation of macrophages, then the functional phenotype induced by LPS stimulation in the absence of those co-stimulants need be considered the fourth (or first?) unique functional phenotype displayed by macrophages. Engulfment of apoptotic neutrophils enhances production of TGFβ and VEGF while reducing LPS-induced production of TNFα, IL-12, and IL-10 (29,33,34). Ligation of the different TLR results in distinctly different patterns of gene expression (48), which yields several more unique patterns of function. Cross-talk between TLR further modifies the signaling cascade, such that ligation of multiple TLR may result in distinctive patterns of gene expression (71). Do IL-4 and IFNγ promote the same alternative and classical functional phenotypes when ligation of TLR other than TLR4 are the activating stimulus? This question has yet to be explored and the answer is likely to reveal additional functional patterns within the repertoire of macrophages.

Gene array analyses have indicated that LPS activation of macrophages induces the expression of more than 250 genes (72–74). One of these studies reported that IL-10 repressed expression of 62 of these genes and enhanced expression of 15 others (72). Another research group reported a gene array study that indicated that the pattern of gene expression elicited by IL-4, IL-10, and TGFβ were distinctly unique (73). A third group has demonstrated that the pattern

of gene expression induced by LPS stimulus alone is unique in 4 different strains of mice tested (74). This latter observation is not surprising. Up to this point, the biological response modifiers of macrophage functional phenotypes has been relatively restricted to a few cytokines and TLR. In fact there a many, many physiological factors that significantly impact macrophage function and thus the functional phenotypes displayed upon activation. To mention a few, macrophage function is significantly modified by glucocorticoids and catecholamines (75–78), complement and Fc receptors (22,47,79–87), TLR and nucleotide-binding oligomerization domain (Nod) proteins (48,49,71,88–90), peroxisome proliferator activated receptors (PPAR) (91–93) and fatty acid binding proteins (FABP) (94,95), integrins (43,96–99), arachidonic acid metabolites (100–102), histamine (103,104), insulin (105,105,106), and uptake of apoptotic cells (29,33,34). The general effects of these agents on macrophages are summarized in Table 1. The point that needs to be made here is that given the large number of activating receptors on macrophages (CD40-family, TLR family, Nod family, etc.), the even larger array of physiological factors that influence the functional phenotype displayed by the activated macrophages, and the evidence for crosstalk between both the activating receptors and the signal modifying physiological factors, it is evident that the number of unique functional patterns or phenotypes macrophages are capable of displaying could be huge.

Macrophage subsets: differentiation or differential regulation?

It has been general opinion for several decades that the macrophage lineage contains several developmentally distinct sublineages, the most frequently used examples being tissue-specific macrophages such as Kupffer cells and microglial cells (107–109). Whether the alternatively and classically activated macrophage subsets described above also represent developmentally stable subsets (e.g., distinct sublineages) has been implied but has not been formally established. It is clear that chronic infections result in the accumulation of macrophages with distinctive functional characteristics dependent on whether a Th1 or Th2 immune response has been elicited (23,110–114). Thus schistosome and nematode infections that elicit a strong Th2 response also result in infiltrates of macrophages which display some of the characteristics of “alternatively activated” macrophages, such as expression of arginase (110–112). In contrast, toxoplasma and mycobacterial infections, which elicit strong Th1 responses, result in the accumulation of macrophages displaying classical inflammatory and cytotoxic activities (23, 113,114). The macrophages which are associated with metastatic tumors usually display an anti-inflammatory, pro-angiogenic functional phenotype (21,115). Do these represent distinct developmentally stable subsets of macrophages or do they represent differential regulation of macrophage function by the different diseased environments? In support of the hypothesis that they represent distinct myeloid sublineages, a number of experiments suggest that clonal variation may exist in myeloid precursors and that responsiveness to select stimuli is acquired and lost during developmental progression of monoblasts to monocytes (116–119). Different strains of mice, even with congenital absence of lymphocytes, display distinct macrophage functional patterns which some investigators have catalogued into “type 1” and “type2” subsets (31). The development of “type 1” and “type 2” macrophages in the absence of lymphocytes has been used as an argument against differential regulation as being the basis for macrophage functional bias. However, gene array analysis has revealed that macrophages from the 3 strains of mice studied (intact, not lymphocyte deficient) display unique functional patterns which only partially overlap with each other (74). In addition, lymphocyte derived cytokines are not the only factors that influence macrophage function. They represent only one of the twelve modulating factors listed in Table 1. Therefore, it can be argued that the different pattern of functional response to a given stimulus by macrophages from mice of different genetic backgrounds may be the result of congenital differences in the basal level of expression of, or responsiveness to, one or more of the modulating agents listed in Table 1 (e.g., congenital basal level of insulin-like growth factor, insulin, histamine, stress hormones, etc.).

In support of a role for differential regulation in the functional heterogeneity of macrophages are the observations that the functional pattern displayed by macrophages is very plastic and mutable. The functional pattern displayed by macrophages treated with IL-4 depends on whether the macrophages were treated with IL-4 prior to or concurrently with the activating signal. Thus, prior treatment with IL-4 results in elevated TNFα and reduced IL-10 production upon LPS stimulation whereas the opposite result is obtained if IL-4 treatment is concurrent with LPS stimulation (66,120). We have shown the same temporal impact applies to the effects of treatment of macrophages with IL-10 or with IFNγ (Stout *et al*., submitted for publication). More directly to the point, a variety of macrophage populations, including peritoneal macrophages, bone marrow derived macrophages, splenic macrophages, and transformed macrophage lines, can be sequentially converted from one functional phenotype to a second phenotype to a third phenotype by sequentially altering the *in vitro* cytokine environment (Stout *et al*., submitted for publication). This is not without precedent *in vivo*. It appears that the "suppressor" macrophage subset which accumulates in tumor bearing mice can be targeted by cytokine therapy and induced to display inflammatory function [3567, Watkins and Stout, unpublished data]. Tissues macrophages which are considered specialized sublineages of macrophages, such as alveolar macrophages, Kupffer cells and microglia, can change their functional pattern, as evidenced by the response to infectious or inflammatory insult (107–109,121). Microglia display a unique ramified morphology in the brain and support neuronal survival by producing cytokines such as brain-derived neurotrophic factor and TGFβ (109, 121). *In vitro* or during inflammatory responses in the brain, microglia lose their characteristic morphology and become migratory macrophages producing oxidative radicals and inflammatory cytokines (108,122). Even myeloid dendritic cells have been shown, *in vitro* and *in vivo*, to change into a surface and functional phenotype more characteristic of macrophages, including nitric oxide production and loss of expression of their defining membrane protein, CD11c (13,16,17). Whether these specialized macrophage subsets are differentially regulated in a reversible fashion or represent differentiated sublineages with a limited degree of functional plasticity has not been established. The level of functional adaptivity or plasticity displayed by the macrophage lineage(s) needs to be directly and formally tested. Whether the different functional patterns displayed by macrophages represent development of stable subsets or reversible differential regulation impacts our perception of the mechanics of both acute and chronic inflammation. During the progression of acute inflammation, are precursors for the inflammatory subset recruited first, followed later by recruitment of precursors for the functional subset that promotes healing or are common precursors recruited that, during the course of the response, shift their function from inflammatory/cytotoxic to wound resolution in response to changes in the tissue environment (Fig. 2)? Are the macrophage subsets which accumulate in chronic responses, such as occurs with cancer or nematode infections, stably differentiated or can their function be changed by appropriate alteration of the signaling environment? The answers to these questions will formulate how we address therapeutic intervention in reducing inflammatory dysfunction in the elderly.

Immunosenescence in the macrophage lineage

The inflammatory response in aged rodents and humans

Although chronic inflammatory pathologies are common in the elderly (123–129), the inflammatory response appears to lack normal orchestration, which reduces its overall efficacy in the context of infectious disease and wound healing. Reports on the impact of advanced age on the recruitment of monocytes into excisional wound sites vary from observations of no significant effect to observations of long delays in attainment of peak monocyte numbers (10,130–132). Chemotactic activity decreases with advanced age, as does macrophage production of chemokines such as MIP-1α/β and MIP-2 (131,133). Phagocytosis and clearance of infectious organisms is also reduced with advanced age (131,134–137). Expression of class

II MHC and antigen presentation by macrophages have been reported to be reduced in aged rodents and humans (138–142). The production of fibroblast growth factor (FGF-2), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), epithelial growth factor (EGF), and transforming growth factor-beta (TGFβ-3) are reduced and/or delayed, as is the expression of their corresponding receptors (132,143). The result is a delay and/or deficiency in re-epithelialization, collagen deposition, and angiogenesis in excisional wounds of the elderly. All of these deficiencies in the inflammatory response are not due solely to deficiencies in macrophage inflammatory function. The tissue itself contributes to the disharmonious response. The expression of cell adhesion molecules on the vascular endothelium is decreased in the elderly (130) and responsiveness (receptor expression) to VEGF and EGF is reduced (143,144). Thus the communication between the tissue cells and the innate immune system appears to be impaired. Given the functional adaptibility of macrophages and their dependency on environmental (tissue-derived) signals to orchestrate the progression of their functional response, this disruption of communication likely contributes significantly to the observed functional “deficiencies” in macrophages participating in inflammatory responses in the elderly.

The impact of aging on macrophage function

Although inflammatory cytokines such as IL-6 are elevated in the plasma of aged animals and humans (123,145), the production of inflammatory cytokines by peritoneal macrophages from mice and rats decreases with age. Stimulation of macrophages from aged rodents with LPS results in significantly lower production of IL-1 (146,147), TNFα (10,147–149), and IL-6 (10,148), as well as lower production of chemokines such as MIP-1α and MIP-1β (131) compared to macrophages from young rodents. The production of oxidative radicals also appears to decline with age. The expression of iNOS and production of nitric oxide is reduced in macrophages from aged rodents (10,150–156). Similarly the generation of reactive oxygen intermediates (oxidative burst) is lower in peritoneal macrophages from aged rodents compared to young rodents (10,151,155–158). There is some controversy concerning the basis for the decline in production of inflammatory cytokines and oxidative radicals in response to LPS stimulation. Renshaw *et al.* (159) reported that the expression of TLR on macrophages was reduced with advancing age and that this was the basis for the reduced cytokine production upon stimulation with LPS. Boehmer *et al.* (148) reported that TLR expression was not impacted by advanced age and that the basis for the reduced cytokine production was impaired intracellular signaling, specifically a reduction in LPS-induced phosphorylation of the p38 and JNK mitogen activated protein kinases (MAPK). One point that need be held to the forefront is that the overall responsiveness of macrophages to LPS stimulation is not reduced. The influence of aging appears to be selective. Macrophages from aged mice have increased levels of cyclooxygenase-2 (COX-2) and produce elevated levels of PGE2 upon stimulation with LPS (160,161). LPS induction of IL-10 production also appears to be elevated in macrophages from aged rodents and humans (162,163). It thus appears that aging selectively impacts LPS-induced signaling cascades such that some functions are depressed and others are elevated. Another example of a signaling deficiency that appears in advanced age is responsiveness to IFNγ. Although expression of the receptor for IFNγ appears to be normal (156), IFNγ-induced phosphorylation of MAPK and STAT-1 is reduced in aged rodents (156,164). Part of this deficiency is due to IFNγ-independent decrease to total STAT-1 protein in macrophages from aged rodents (164). The basis of this reduced STAT-1 level in macrophages from aged rodents has not been resolved.

Another indication that age-associated factors are differentially, and possibly indirectly, impacting macrophage function is that aging impacts macrophages in different tissues differently. The degree to which production of inflammatory cytokines and oxidative radicals are impacted by aging vary when macrophages from bone marrow, spleen, alveoli, and

peritoneum are compared (74,147,165–168). This suggests that part of the deficiency observed in macrophages from aged animals and humans might be caused by changes in the tissue environment. It is known that the stromal environments of bone marrow, spleen, lymph nodes and thymus change with age, resulting in reduced hematopoiesis, thymopoiesis, and peripheral homeostasis (1–5,169–176). Although myeloid dendritic cells in aged rodents and humans appear to be poorly immunogenic (8,10,141,142), fully functional myeloid dendritic cells can be generated *in vitro* from blood monocytes from aged donors (177). Macrophages generated *in vitro* from bone marrow cells from aged mice respond identically to macrophages generated from bone marrow from young mice, indicating that there is no age-associated intrinsic defect in the lineage (178). The function of many of the myeloid and lymphoid cells in aged animals can be at least transiently improved by a variety of treatments. IL-7 provides a burst of thymopoietic activity (5). Inflammatory cytokine therapy seems to improve antigen presentation and T cell responses in aged mice (7). Treatment of macrophages from aged donors with IFNγ (56) or with insulin-like growth factor (IGF) (179) significantly improves their inflammatory and effector responses to LPS stimulation. Our group has recently demonstrated that functional balance can be restored in macrophages from aged mice by removing them from the aged environment (Matta *et al.*, manuscript in preparation).

Concluding Remarks

Given the above discussion of the evidence supporting the exquisite functional adaptability of macrophages to environmental changes, the evidence that aging impacts tissue environments, and that age-related changes in macrophage function may be reversible rather than intrinsic, it is suggested that targeting the regulatory factors of the aged environment might restore, at least transiently, the inflammatory and proimmunogenic function of macrophages in the elderly. The problem is that the age-associated factors altering macrophage function are unidentified and may be very numerous (Table 1). Oxidative stress is hypothesized to alter transcription factors (e.g., NFkB) an nuclear receptors (e.g., PPAR's) and thus alter the ability of macrophages to respond to inflammatory stimuli (180). Anti-oxidants do seem to improve macrophage inflammatory function (161,181,182). Neuroendocrine factors and stress hormones have also been hypothesized to contribute to the immunosenescence and decreased macrophage function (123,183). One approach being used in cancer therapy may also have applicability in age-associated inflammatory deficiencies and that is to target macrophages with cytokines that promote the desired macrophage function (21). The disruption of macrophage functional homeostasis that appears with aging may seem excessively complex. But one fact made clear by Haynes *et al.* (7), who reported that administration of inflammatory cytokines of the innate immune system enhanced the adaptive immune response of aged mice, is that restoration of the functional balance of macrophages in the elderly will not only improve innate responses but, as a result, improve the function of the adaptive immune system, as well. Given the critical need for improvement of vaccine efficacy and control of infectious disease in the elderly, more research emphasis on the impact of aging on the macrophages and macrophage-derived dendritic cells is clearly needed.

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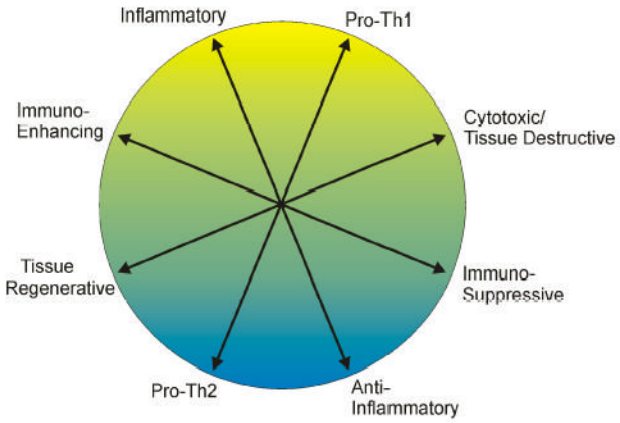

Figure 1. Macrophages display a harmonious balance of functions.

Macrophages are capable of displaying many different functional activities, many of which are antagonistic. It is hypothesized that modulating influences such as cytokines, stress hormones, and other factors coordinate the level of expression of each function as well as the balance between the functions.

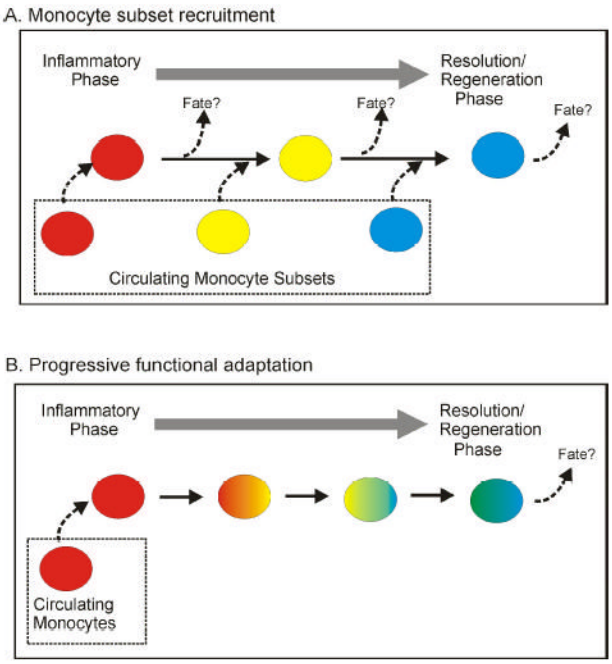

Figure 2. Macrophages can functionally adapt to their tissue environment.

It is not clear to what degree the functional heterogeneity of macrophages results from differentiation into sublineages or results from differential regulation by microenvironmental signals in the tissue. It is hypothesized that in many cases, including inflammation and development of at least some tissue histiocyte characteristics, macrophages can progress through a series of functional patterns, adapting to progressive changes that occur in damaged or infected tissue.

Table 1

Ligands and receptors selectively modulating function patterns expressed by macrophages

Ligand/Receptor	Functional Impact	References
TLR & Nod	Selectively stimulate distinct patterns of macrophage function	48,49,71,88–90
TNFα-R family	Selectively stimulate distinct functional patterns, emphasizing inflammatory function	39,40,46,184–188
Cytokines	Each cytokine appears to have a unique influence on macrophage function	22–24,31,37,57,67,72–74
Complement	Ligation of complement receptors enhances inflammatory function of macrophages	79,80,87,189
Fc receptors	Ligation of different FcR reduce or enhance inflammatory function of macrophages	22,47,82–84,86,87, 189,190
Integrins	Enhance pro-inflammatory activities and macrophage emigration	43,96,97,191
Arachidonic Acid metabolites	Selectively decrease inflammatory cytokine production by macrophages	100–102
Stress hormones (glucocorticoids and catecholamines)	Differentially inhibit inflammatory cytokines and NO release and enhance IL-10 production	75–78
PPAR	Selectively inhibit pro-inflammatory functions of macrophages	91–93
FABP (aP2)	Selectively enhance pro-inflammatory activities	94,95
Histamine	Selectively inhibits production of some inflammatory cytokines and enhances production of IL-10	103,104
Insulin	Augments alternative activation of macrophages by IL-4	105,106
IGF	Enhances inflammatory cytokine production	192
Apoptotic Cells	Engulfment differentially down-regulates some inflammatory functions and differentially upregulates some anti-inflammatory functions and pro-wound resolution activities	29,33,34