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REVIEW

Macrophage populations and self-renewal: Changing the paradigm

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Abstract

The origin of macrophages has been considered since several decades to be a continuum from bone marrow (BM) to tissue *via* monocytes as precursors. The development of new tools such as genetic lineage tracing, parabiosis and BM chimeras changed the paradigm of macrophage origin. In steady state, most resident macrophages are of embryonic origin, whereas a monocyte origin remains prominent in pathological conditions. The findings of a proliferation of mature macrophages will oblige us to reappraise the relationship between proliferation and differentiation in macrophages. This review is based on the recent explosion of high impact articles on macrophage biology. It summarizes new data on the origin of macrophages and their self-renewal potential in steady states. While monocytes are required for intestinal macrophage development, the microglia is independent of monocyte influx and skin macrophages provide an excellent model of the balance between monocyte input and self-renewal. In addition, macrophage proliferation requires intrinsic and extrinsic factors including growth factors and cytokines. It also analyzes the impact of this new paradigm in human diseases such as athrosclerosis, cancer, infectious diseases and neurodegenerative diseases. In atherosclerosis, the finding of macrophage proliferation within the lesions will change our understanding of disease pathophysiology, this new paradigm may have therapeutical impact in the future.

Key words: Macrophages; Self-renewal; Proliferation; Homeostasis; Diseases

Core tip: The emergence of revolutionary technologies in myeloid cell research has deeply changed the paradigm of macrophage activation. It was believed that macrophage derive from myeloid precursors *via* circulating monocytes. Now, we can propose that resident macrophages are of embryonic origin in steady state whereas monocytes are recruited in pathological conditions. The second strong idea was that mature macrophages are unable to proliferate; we have strong evidence that macrophages can proliferate, which is

the basis of self-renewal. The consequences of these new concepts will lead us to reappraise the role of macrophages in pathologies.

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INTRODUCTION

Historical point of view

The initial model of macrophage differentiation was proposed by Ralph Van Furth and Zanvil Cohn[1] in 1968. Tissue macrophages arise from bone marrow (BM) progenitors *via* blood monocytes as intermediates[2]. However, this popular model is probably insufficient to describe how macrophage populations grow and mature.

The introduction of new methods including genetic lineage tracing, parabiosis and BM chimeras as well as BM transplantations in animals and myelo-ablative irradiation or chemotherapy in patients enable a reappraisal of macrophage origin dynamics[3]. We will review the diversity of macrophage populations, the contribution of the self-renewal process to macrophage dynamics and the consequences on our understanding of human pathologies.

Macrophage populations

The mononuclear phagocyte system consists of monocytes, macrophages and dendritic cells (DCs), which exhibit different morphologies, phenotypic characteristics and functions. For several years, it was believed that monocytes were released from BM into the circulation and that they were the precursors of macrophages and DCs[4].

In the past 20 years, use of specific membrane markers has allowed the discrimination of different subpopulations among mononuclear phagocytes. Hence, murine inflammatory monocytes are characterized by the high expression of LY6C, CCR2 and low level of CX_3CR1. In contrast, patrolling monocytes are characterized by the low expression of LY6C and CCR2 and high density of CX_3CR1. A similar heterogeneity has been found in humans; the most prevalent population of so-called classical monocytes expresses high levels of CD14 and is equivalent to $LY6C^{hi}$ in mice.

The level of CD14 and CD16 membrane expression enables the identification of two minor subsets of monocytes, $CD14^{hi}CD16^{lo}$ (also called intermediate monocytes) and $CD14^{lo}CD16^{hi}$ (called non-classical monocytes) respectively, which are the equivalent of $LY6C^{lo}$ monocytes in mice[5]. It has been recently found that the relative proportion of human monocyte subsets is modulated during inflammatory and infectious diseases[6,7], although the role of these different monocyte subsets in these pathologies remains to be elucidated. The situation is even more complex for tissue macrophages. Indeed, macrophages are classified according to the type of tissue: Osteoclasts in bone, alveolar macrophages in lungs, Kupffer cells in liver, intestinal macrophages in the gut, microglia in the nervous system), placenta macrophages and macrophages in secondary lymphoid organs[8,9]. These macrophages exhibit a diversity of functions from host defense to metabolism and tissue remodeling.

Besides these resident macrophages, macrophages can be locally recruited in response to injuries and their phenotypic and functional characteristics will depend on the type of injury. Using some phenotypic features enables the distinction of recruited macrophages from resident cells. The former exhibit a low expression of F4/80, CD64, MerTK, CD14, are mobile and short-living cells; in contrast, the latter highly express F4/80, CD64, MerTK, CD14, are long-living but can be of yolk sac (YS) or hematopoietic stem cell (HSC) origin (see below). The responses of macrophages to different stimuli have led to the concept of macrophage polarization, which allows a classification of functional macrophage subsets. A reductionist model of activation has resulted in a definition of M1 macrophages that reflects the Th1 immune response and M2 macrophages that reflects the Th2 immune response[10]. The lack of specific markers of M1 and M2 macrophages, respectively, has made the identification of these functional subsets in *in vivo* conditions difficult[11]. However, the use of high throughput methods such as microarray permitted the identification of transcriptional signatures that would require functional validation[12]. Studies of networks based on gene expression profiling have generated a resource data set to assess transcriptional regulation during macrophage activation by comparing diverse sets of agonists on a single microarray platform. Network modeling extends the current M1 *vs* M2 polarization model to a spectrum model with at least nine distinct macrophage activation programs[13]. In addition, the InnGen project has enabled the sorting of tissue macrophages from C56BL/6 mice and the analysis of their gene expression program with whole genome microarray. This approach has revealed a considerable diversity among macrophage populations, which is higher than the distance between macrophages and DCs. This diversity is illustrated by the expression of unique transcripts according to each macrophage location. As an example, this bioinformatics approach has revealed that Langerhans cells are close to BM-derived macrophages but surprisingly failed to cluster with macrophages[14]. The introduction of mass cytometry allowed a more precise analysis of murine myeloid cells. Indeed, alveolar macrophages, microglia and red-pulp macrophages are populations distinct from the other macrophages[15]. It is likely that new data will profoundly change our understanding of the relationship between the diversity of macrophage populations and their origin.

Table 1 Approaches to dissect the origins of macrophage lineages

Methods and tools	Results
Membrane markers	CX3CR1^{hi}/F4/80^{hi}/CD11b^{lo}: YS macrophages CX3CR1^{lo}/F4/80^{lo}/CD11b^{hi}: HSC macrophages
Transcription factors	MYB^{+}: HSC macrophages MYB^{-}: YS macrophages
Depletion (clodronate, Abs)	Non-specific depletion with clodronate. The CCR2$^{-/-}$ mice that are depleted from circulating monocytes exhibit normal tissue macrophage populations
Genetic fate mapping techniques: RUNX1	Early expression of RUNX1 in YS derived macrophages and identification of embryonic macrophages in adulthood (microglia, Langerhans cells)
Genetic fate mapping techniques: FLT3	Identification of a HSC stage in differentiation: + for monocytes and - for tissue macrophages
Genetic fate mapping techniques: CSF1R	Labeling of 30% YS derived macrophages in the embryo and similar persistence in adult microglia
Genetic fate mapping techniques: CX3CR1	labeling of monocytes and miocroglia
Parabiosis	Replacement of resident macrophages by chimeric monocytes
Sublethal irradiation and bone marrow transplant	Chimerism in blood monocytes without eradicating resident macrophages. Risk of inflammation and membrane leakage

YS: Yolk sac; HSC: Hematopoietic stem cell. This Table describes the methods to identify the origin of mononuclear phagocytes and the major results. It refers to recent reviews[16-18].

NEW TOOLS TO DETERMINE THE ORIGIN OF MACROPHAGES: MONOCYTES *VS* MACROPHAGES

New tools have emerged these latter years to investigate the origin, the homeostasis and the functions of mononuclear phagocytes[16,17]. We will illustrate these methodological advances with a few examples. The study of mouse embryogenesis enables a chronological dissection of macrophage origin. First, the macrophages appear in YS in which primitive hematopoiesis occurs. Then, fetal liver and BM are populated by HSCs, which represent another source of tissue macrophages[18]. This dynamic and the dual origin of tissue macrophages (YS *vs* HSC) have been reported in a growing number of important papers[18,19]. These results question the role of monocytes in tissue colonization in both homeostasis and situations of danger. Clinical features highlight the new paradigm. Many tissue macrophage populations are not affected in patients with monocytopenia due to leukemia[20] or immune deficiencies[21].

The use of the radioelement ^{89}Sr which targets monopoiesis does not reduce tissue macrophage content in the lung and liver of mice[19]. Similarly, the depletion of circulating monocytes in CCR2$^{-/-}$ mice has a limited impact on tissue macrophage populations[19]. Using genetic fate mapping techniques based on a recombination-induced expression of reporter genes under the control of a constitutive promoter (RUNX1, CSF1R, FLT3) enables identification and tracking of different embryonic macrophage populations into adulthood (Table 1)[18]. Nevertheless, the specificity and the efficiency of these approaches, such the labeling of YS-derived macrophages with RUNX1^{CreER} or with Csf1r^{CreER}, are questionable. Although FLT3-Cre labels specifically blood monocytes, FLT3-Cre negative tissue macrophages are also observed in HSC-derived macrophages[18]. These molecular tools have provided important data and a model was recently proposed in mice: Primitive macrophages would arise from erythro-myeloid progenitors present in YS. These macrophages are the first wave of colonization of the brain and other fetal organs. A second wave would be characterized by the development of fetal monocytes in fetal liver; these latter cells would be the source of resident macrophages with the exception of the brain[22,23]. These major findings remain limited to murine models and their transposition to humans is an important scientific challenge.

MACROHAGE PROLIFERATION

If tissue macrophage renewal does not result from monocyte influx, their proliferation is necessary. The proliferation of transformed lines of macrophages is well established, but their use is limited by the loss of macrophage functions and their poor differentiation compared with mature macrophages. Michael Sieweke's group recently reviewed the self-renewal mechanisms of mature macrophages and identified extrinsic and intrinsic factors[3] (Figure 1). Among the extrinsic factors, the macrophage colony-stimulating factor (M-CSF) occupies a privileged position. The number of tissue macrophages is reduced in animals bearing mutations in M-CSF such as op/op mice and tl/tl rats and in mice deficient for M-CSF receptors (M-CSFR); the efficiency of macrophage depletion is higher in mice deficient for M-CSFR[24]. M-CSFR binds with not only M-CSF but also interleukin (IL)-34. Produced by neurons and keratinocytes, IL-34 is a good candidate for controlling the homeostasis of microglia and Langerhans cells[25] but seems more critical in the homeostasis of Langerhans cells than of microglia[26]. It is likely that the imbalance between M-CSF and IL-34 accounts for the differences in the macrophage replenishment of the skin and nervous system.

Granulocyte macrophage colony-stimulating factor (GM-CSF) is another important cytokine involved in the turnover of tissue macrophages. This has been clearly demonstrated with macrophages derived from

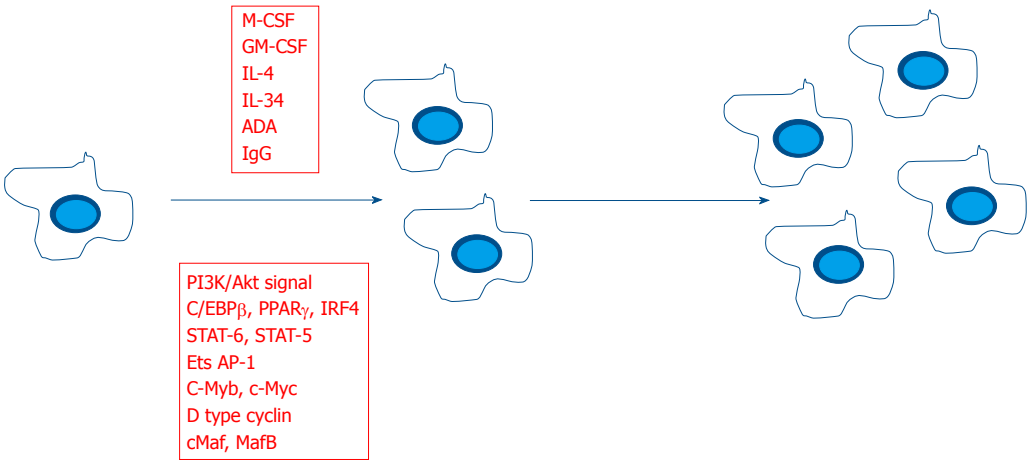

Figure 1 Extrinsic and intrinsic factors involved in macrophage proliferation. M-CSF: Macrophage colony-stimulating factor; GM-CSF: Granulocyte macrophage colony-stimulating factor; IL: Interleukin; PPARγ: Peroxisome proliferator-activated receptor γ.

fetal liver macrophages with self-renewing potential. These cells are obtained by the culture of fetal liver and grow exponentially in the presence of GM-CSF before differentiation. The removal of GM-CSF blocks their proliferation[27]. *In vivo*, the peritoneal administration of GM-CSF also induces the proliferation of peritoneal macrophages[3]. In addition, it is likely that GM-CSF is involved in the control of the alveolar macrophage population[28].

IL-4 shares with M-CSF the ability to polarize macrophages towards a M2 phenotype and is associated with the self-renewal of macrophages. IL-4 is probably sufficient to induce the proliferative expansion of macrophages in serous cavities, the liver, spleen and lungs[29]. The administration of IL-4 in mice causes macrophage proliferation and their accumulation in the liver, spleen and BM[30,31]. In contrast, IL-4 is unable to induce the proliferation of macrophages *in vitro*, suggesting that IL-4 acts in concert with other cytokines. Finally, among the extrinsic factors involved in the self-renewal of mature macrophages, one can evoke adenosine deaminases, known for their role in the regulation of adenosine levels which are associated with monocyte-to-macrophage differentiation and macrophage proliferation[32].

The intrinsic factors playing a role in the self-renewal of macrophages include the signaling pathways of IL-4, IL-34, M-CSF and GM-CSF. In addition, transcription factors such as c-Myb and c-Myc, known for their role in cell proliferation, play a role in monocyte differentiation. Although their ectopic expression in mature macrophages re-initiates the cell cycle[3], they are not involved in the proliferation of mature macrophages[33]. The transcriptional factor Gata6 is specifically expressed by self-renewing peritoneal macrophages but not by monocytes recently recruited into the peritoneum after challenge. Gata6 deficiency impairs peritoneal macrophage renewal during steady state and in response to inflammatory challenge compromising the resolution of inflammation. Gata6 targets genes involved in cell proliferation since their expression is altered in macrophages from Gata6-deficient mice[34]. Other transcription factors regulate macrophage proliferation *via* their cooperation. The cooperation of cMyc and Klf4 and MafB and cMaf seems necessary for macrophage self-renewal as described for stem cells[3]. Hence it has been reported that macrophages isolated from MafB- and cMaf-double deficient mice divide indefinitely; the self-renewal depends on cMyc and Klf4[19]. Taken together, these results suggest that other tissue-specific mechanisms may be identified in the future to account for the expansion of mature macrophages.

HOMEOSTASIS

Different strategies based on the proliferation of YS- or HSC-derived cells or monocyte influx are used by macrophages to maintain their population in peripheral tissues (Figure 2). It has been clearly shown that monocytes are involved in the control of homeostasis[35,36]. Experiments using Cre-loxP-based fate mapping methods or parabiotic mice with mice lacking or not CCR2 have shown that circulating monocytes have a minimal contribution to the maintenance of tissue macrophages in the absence of injury[37,38]. Nevertheless, the sites in contact with microorganisms such as the intestine, skin and spleen are specialized areas in which monocyte input is necessary to maintain macrophage population. Exposure to commensal microorganisms is likely to cause a low grade inflammation also called "primed homeostasis", which is reminiscent of the recruitment of classical monocytes in fully inflammatory conditions[39]. This seducing hypothesis accounts in part for the homeostatic maintenance of macrophage populations such as intestinal macrophages. In mice, the colons of newborns contain macrophages of embryonic origin (F4/80^{hi}CD11b^{lo}) and hematopoietic origin (F4/80^{lo}CD11b^{hi}); the embryonic population of macrophages is prominent after birth and dramatically decreases thereafter[40]. Although macrophages in adult mice retain the ability to divide locally, this ability is not sufficient to account for maintaining macrophage populations in the intestine.

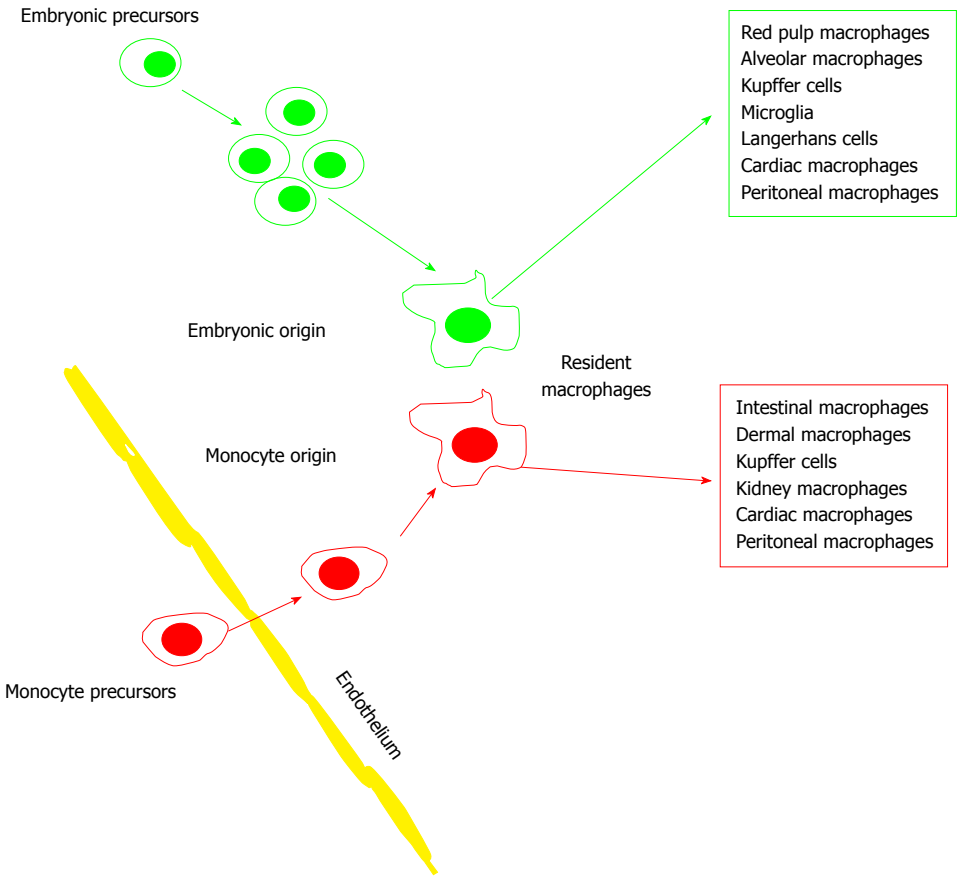

Figure 2 Macrophage origin and homeostasis.

Different studies based on CX_3CR1^{+GFP} mice, the irreversible expression of YPC by $CSF1R^+$ and parabiotic mice demonstrated that intestinal macrophages require constant replenishment through CCR2-dependent recruitment of $LY6C^{hi}$ monocytes[41]. It has also been demonstrated that the constant replenishment of intestine macrophages is related to the microbiota.

Indeed, the administration of broad-spectrum antibiotics for 2 wk in conventional mice results in a small reduction of $LY6C^{hi}$ MHC^+ macrophages but not in the number of $LY6C^{lo}$ MHC^+ mature macrophages in the colon. Hence, homeostasis of resident intestinal macrophages requires both the microbiota and the CCR2-dependent recruitment of inflammatory macrophages.

In contrast, the microglia cells are monocyte-independent. They are localized in the central nervous system and exhibit different morphologies according to the type of activation[42,43]. After birth, the massive expansion of microglia cells that is observed is related to the *in situ* cell proliferation induced by M-CSF and IL-4, but not to monocyte input[44]. The microglia deletion results in decreased synaptic formation and learning[18]. Alveolar macrophages are derived from fetal monocytes that colonize the lungs shortly after birth in a process dependent on GM-CSF and peroxisome proliferator-activated receptor (PPAR)-γ. Another example of macrophages that do not result from monocyte influx is provided by alveolar macrophages. They do not differentiate from blood monocytes because CD163-DTR-mediated depletion results in repopulation by *in situ* proliferation[37,45]. However, when alveolar macrophages are depleted by a genotoxic injury such as a lethal irradiation, recruited monocytes can repopulate the alveolar macrophage niche[18]. Hence, alveolar macrophages do not require monocyte recruitment but can accommodate such requirement when required.

The skin, which has been well studied in mice in recent years, provides an excellent model of the role of the balance between monocyte input and self-renewal. It contains two major macrophage populations, Langerhans cells in the epidermidis and dermal macrophages. The Langerhans cells originate from YS-derived myeloid precursors and monocytes from fetal liver. They undergo an extensive proliferation after birth and a low rate of *in situ* proliferation that is sufficient to maintain their number in adulthood without further monocyte input. Dermal macrophages probably have a complex origin; they contain a pool of established prenatal macrophages and one postnatal pool derived from blood monocytes expressing high levels of CCR2 and LY6C. The dermal macrophages are clearly distinct from Langerhans cells and other dermal DCs[46].

Recent studies concern cardiac macrophages in which depletion experiments enable the description of repopulation strategies. There is evidence that

combined mechanisms are required. In steady state, the majority of cardiac macrophages are of embryonic origin and repopulation after depletion is supported by circulating monocytes[18]. All these findings have been based on murine models and their extrapolation to homeostasis of human macrophages will require original methodological approaches.

MACROPHAGE IN DISEASES

It is well known that macrophages are necessary to fight against microbial pathogens or tumor cells, but they may also contribute to inflammatory and autoimmune diseases and the development of metastasis. While there is evidence that the self-renewal of tissue macrophages seems sufficient to maintain resident cells in steady state, pathological situations require exogenous contribution. Different models of response to injury have provided essential information. The most usual model consists of the injection of microbial or toxic agents inside the mouse peritoneal cavity in which resident macrophages are of embryonic origin. The initial response consists of the recruitment of blood monocytes. During the phase of resolution of inflammation, recruited monocytes mature into macrophages[38]. In a murine model of acute liver injury induced by N-acetyl-p-aminophenol, the number of resident Kupffer cells first decreases and then starts to increase without requiring LY6C^{hi} monocytes during the resolution phase. In the necroinflammatory phase, LY6C^{hi} monocytes are recruited in a CCR2-dependent manner. In addition, the transcriptional signatures of self-renewed Kupffer cells and recruited monocytes are clearly distinct[38]. In patients, some examples illustrate the fact that monocyte influx does not explain the response to inflammatory challenge. For instance, the macrophages present in ocular adnexae are polarized and express markers of proliferative activity[47]. During the acute inflammatory response in which inflammatory macrophages are recruited, tissue macrophages proliferate intensively, suggesting a combination of mechanisms to restore homeostasis after an aggression[48]. We will briefly describe macrophage renewal in some clinical situations.

Atherosclerosis

Atherosclerosis is characterized by the accumulation of macrophages in atheromatous plaques; they ingest lipids and produce a panel of inflammatory mediators leading to an amplification loop. It has been shown at least in mouse models that lesional macrophages arise predominantly from circulating LY6C^{hi} monocytes[49]. The introduction of cholesterol in the diet induces an influx of monocytes in atheromatous plaques after two weeks with a difference between monocyte subsets: monocytes expressing LY6C are more efficiently recruited than monocytes which do not express LY6C and it is believed that the latter cells may promote vascular stability and play an atheroprotective role[50]. Recent papers suggest that the accumulation of macrophages in atheromatous lesions is not the only consequence of monocyte input. Hence, macrophage proliferation in atheromatous lesions has been reported in humans, rabbits and mice[50-52]. In apolipoprotein E-deficient mice (ApoE$^{-/-}$) with a high-cholesterol diet, a rapid turnover of macrophages is observed within the lesions. The monocyte depletion does not affect the turnover of lesion aortic macrophages. In addition, using parabiosis reveals that monocyte recruitment cannot fully account for lesional macrophage accumulation in established atherosclerosis but it cannot be excluded monocyte circulating precursor is involved[50,53]. Using an adoptive transfer methodology in ApoE$^{-/-}$ mice under a high-cholesterol diet shows that proliferating aortic macrophages derive from non-proliferating circulating monocytes. The contribution of recruited monocytes seems to be prominent in early lesions, but it is likely that less than 20% of macrophages in established atheromatous lesions are due to monocyte influx, with local proliferation of macrophages accounting for the largest part of lesional macrophages[50]. Recently, the expression of type 1 scavenger receptor class A (Msr1) on lesional macrophages has been reported and seems to be correlated with macrophage proliferation. Hence, lesional macrophages from Msr1$^{-/-}$ mice proliferate poorly compared with wild type macrophages and are less abundant[53].

The persistence of lesional macrophages also reflects defective cell death. Hence, the lack of macrophage death at early stages of atherosclerosis increases macrophage burden and seems to reduce the progression of the disease in later stages[50,54].

Myocardial infarction is a complication of atherosclerosis and the heart lesion is characterized by an inflammatory response mediated by recruited neutrophils and monocytes, and the proliferation of local cardiac macrophages[55].The expansion of local macrophages is long lasting until healing and these macrophages display heterogeneity of activation states from M1 to reparative M2 macrophages. Healing requires cardiac macrophages whatever their origin (monocyte recruitment *vs* local proliferation) as assessed by numerous studies including clinical studies[56,57].

Recently, it has been reported that Osmr$^{-/-}$ (oncostatin M receptor) mice undergoing myocardial infarction exhibit a reduced number of myeloid cells expressing F4/80 and CD11b. In addition, Osm induces the expression of REG3β, which is a potent chemoattractant for macrophages. In REG3$^{-/-}$ mice with myocardial infarction, the macrophage burden is decreased, suggesting that the macrophages within infarcted lesions are of monocytic origin. Again, the functional activity of lesional macrophages is time dependent. Indeed, the monocytes recruited early within infarcted lesions lead to M1 macrophages whereas macrophages found during tissue remodeling are of M2 type, but these two macrophage functional subsets are controlled by REG3[58]. The inflammatory reaction seems to be similar

in the brain after a stroke. It is likely that the perivascular macrophages replenished by circulating monocytes, in contrast to microglia, drive the recruitment of inflammatory cells in lesions of cerebral tissue. In contrast, microglia may play a role in post-ischemic inflammation and also in tissue repair[59]. Finally, another feature of atherosclerosis is its association with obesity in which macrophages accumulate in adipose tissue and it has been recently reported that local macrophage proliferation is related to obesity-associated adipose tissue inflammation[60].

Cancer

The abundance of tumor-associated macrophages (TAMs) in solid tumors is often correlated with the prognosis of the tumors[9,61]. TAMs are usually of M2 type and may be considered to be repairing the cancer lesions, but the acquisition of tumorigenic properties may involve a complex dialogue between macrophages, tumor cells and stromal cells[62]. The pool of TAMs results from circulating monocytes. Monocyte recruitment depends on the tumor microenvironment and occurs mainly in hypoxic regions of the tumors[63], as demonstrated by different murine tumor models. For instance, in lung adenocarcinoma, two populations of TAMs designated MHCII^{lo} and MHCII^{hi} are present and derive from LY6C^{hi} monocytes[64]. In addition, the spleen is a reservoir for TAM precursors in a CCR2-dependent way[65]. Besides the monocyte origin of TAMs, there is growing evidence that they may also result from a self-renewal process of *in situ* macrophages. It has been reported that TAMs proliferate in human breast carcinomas[66]. Fully differentiated macrophages and not blood-borne precursors drive TAM accumulation in a mouse model of spontaneous mammary carcinogenesis[67]. The situation seems more complex in gliomas in which microglia and TAMs derived from monocytes are present within and around the tumor cells.

Although they exhibit a M2 phenotype under the influence of glioma cells, their origin remains to be determined[43]. It has also been shown that cancer can promote extra-medullary monocytopoiesis in spleen red pulp. In murine lung adenocarcinoma, angiotensin is directly involved in the self-renewal of HSCs and macrophage progenitors; the blockade of its production restrains the number of TAMs[68]. In cancer, the recruitment of monocytes seems to be prominent but understanding of the nature of the dialogue between macrophages and tumoral cells is only in the early stages.

Infectious diseases

The recruitment of monocytes and their maturation in macrophages is essential for defense against microbial pathogens[5]. Indeed, monocytes enter sites of infection and draining lymph nodes to promote adaptive immunity. For instance, the recruitment of inflammatory monocytes in the lungs in response to *Mycobacterium tuberculosis* is necessary to T-cell activation and tuberculosis control[69]. In several infectious diseases, CCR2-mediated monocyte mobilization plays a prominent role. The recruitment of monocytes mediated by CCR2 is required for the control of *Legionella pneumophila* infection in mice[70]. The protective role of LY6C^{hi}monocytes *via* the CCR2 pathway has been reported in infections with *Plasmodium chabaudi* and *Cryptococcus neoformans*[5]. Most of these inflammatory monocytes mature in tissue lesions and granulomas into macrophages and DCs, and exhibit a M1 profile[71]. Cytomegalovirus (CMV) infection is known to reprogram monocytes towards a M1 phenotype[72]. In a mouse model of congenital CMV infection, the virus is responsible for neurological lesions, disruption of the self-renewal of neural stem/progenitor cells and increased number of activated macrophages (meningeal macrophages and parenchyma microglia) in infection foci. The increased macrophage infiltration may be due to the recruitment of macrophage precursors[73].

Besides the prominent mechanism related to monocyte influx, M2-polarized macrophages are associated with the self-renewal of macrophages in tissues in some parasitic infections. In experimental filariasis, *Litomosoides sigmodontis* worms are killed in the pleural cavity in resistant C57BL/6 mice; the depletion of blood monocytes does not prevent the expansion of macrophages in the pleural cavity of infected mice. The expansion of resident macrophages can be mimicked by the administration of IL-4[30]. Nevertheless, M2 macrophages in the intestinal tract of nematode-infected mice are largely monocyte-derived and the macrophages of lamina propria from these mice are able to proliferate, thus demonstrating the complexity of macrophage origin in helminth infections[29]. It will be important to determine if the self-renewal of macrophages is only a property of helminthiasis infections and what the role of this property of human infectious diseases is.

Neurodegenerative diseases

The pathogenesis of neurodegenerative diseases is critically associated with the neuroinflammation that involves several cell types including microglia. The blood-brain barrier slows down the traffic of monocytes from the blood to the central nervous system and has to be integrated to understand neuroinflammation. Parabiosis and BM transplant studies in mice have revealed the infiltration of monocytes in experimental autoimmune encephalomyelitis and that this infiltration is related to the progression of the disease and the breakdown of the blood-brain barrier. The recruited monocytes are eliminated over time whereas microglia cells expand locally through proliferation in a persistent manner[36,74]. While monocyte-derived macrophages may be responsible for demyelination, microglia maybe involved in clearance of cellular debris[17]. Alzheimer disease is characterized by the deposition of amyloid-β

into parenchyma, the formation of neurofibrillary tangles and neuroinflammation.

Although there is no overall change in microglia cell numbers in the late stages of Alzheimer disease, the chronic stimulation of microglia may result in microglia loss and further replenishment within the brain in the early stages of the disease through the proliferation of tissue-resident microglia[75]. IL-34 induces the proliferation of microglia which results in the clearance of soluble oligomeric amyloid-β; co-cultivating primary neurons with microglia in the presence of IL-34 attenuates the neurotoxicity of amyloid-β. The protective effect of IL-34 has been observed in a mouse model of Alzheimer disease in which IL-34 is administered in intra-cerebral ventricles[76]. Alternatively, macrophages of BM origin may also contribute to Alzheimer disease pathogenesis. It has been proposed that self-renewing microglia produce chemoattractants that may also attract myeloid cells to neuroinflammation sites[42]. Other studies have reported that CCR2-expressing macrophages are the preferential population recruited to amyloid-β deposits and CCR2 deficiency is associated with impaired amyloid-β clearance[77]. Finally, Huntington disease is due to the expansion of the trinucleotide CAG in the gene encoding huntingtin, which is associated with microglial activation. A proliferation of microglia seems to be critical in the pathogenesis of the disease. Indeed, experiments based on cultures of microglia and brain slices have revealed the activation of microglia and their proliferation in the vicinity of degenerating neurons expressing mutated huntingtin[78].

CONCLUSION

The introduction of new molecular tools has greatly modified our vision of the origin of macrophages. The role of circulating monocytes in replenishing macrophage populations seems to be limited in steady state conditions even if they play an important role in pathological conditions. The demonstration of mature macrophages' ability to proliferate has profoundly changed our vision that this proliferation reflects macrophage immaturity. The proliferation of macrophages seems to be associated with macrophage polarization in pathological conditions. These new results open fascinating perspectives in different pathologies. The interference with the recruitment of monocytes with therapeutic monoclonal antibodies is already a means to modify the microenvironment of tumors for instance, but this strategy may be a source of potential complications including infectious complications. Better knowledge of the origin of macrophages in lesions may lead to the reprogramming of macrophages to enhance their beneficial functional properties without promoting deleterious effects.

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