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Review Article

Proliferation of monocytes and macrophages in homeostasis, infection, injury, and disease

Jingbo Pang and Timothy J. Koh*

Center for Wound Healing and Tissue Regeneration, Department of Kinesiology and Nutrition, University of Illinois at Chicago, 1919 West Taylor Street, Chicago, IL 60612-7246, United States
*Corresponding author: Center for Wound Healing and Tissue Regeneration, Department of Kinesiology and Nutrition, University of Illinois at Chicago, 1919 West Taylor Street, Chicago, IL 60612-7246, United States. E-mail: tjkoh@uic.edu

Abstract

Monocytes (Mo) and macrophages (Mφ) play important roles in the function of tissues, organs, and systems of all animals during homeostasis, infection, injury, and disease. For decades, conventional wisdom has dictated that Mo and Mφ are end-stage cells that do not proliferate and that Mφ accumulation in tissues is the result of infiltration of Mo from the blood and subsequent differentiation to Mφ. However, reports from the early 1900s to the present describe evidence of Mo and Mφ proliferation in different tissues and contexts. The purpose of this review is to summarize both historical and current evidence for the contribution of Mφ proliferation to their accumulation in different tissues during homeostasis, infection, injury, and disease. Mφ proliferate in different organs and tissues, including skin, peritoneum, lung, heart, aorta, kidney, liver, pancreas, brain, spinal cord, eye, adipose tissue, and uterus, and in different species including mouse, rat, rabbit, and human. Mφ can proliferate at different stages of differentiation with infiltrating Mo-like cells proliferating in certain inflammatory contexts (e.g. skin wounding, kidney injury, bladder and liver infection) and mature resident Mφ proliferating in other inflammatory contexts (e.g. nematode infection, acetaminophen liver injury) and during homeostasis. The pathways involved in stimulating Mφ proliferation also may be context dependent, with different cytokines and transcription factors implicated in different studies. Although Mφ are known to proliferate in health, injury, and disease, much remains to be learned about the regulation of Mφ proliferation in different contexts and its impact on the homeostasis, injury, and repair of different organs and tissues.

Keywords: cell proliferation, inflammation, macrophage, monocyte

1 Introduction

Monocytes (Mo) and macrophages (Mφ) play important roles in the function of tissues, organs, and systems of all animals. Mo are generated in the bone marrow and are mobilized to play critical roles in the response to tissue injury and infection.[1,2] Tissue-resident Mφ arise from embryonic precursors as well as from bone marrow Mo, and these cells play important roles in development, tissue homeostasis, and the resolution of inflammation after injury and infection.[3,4] In contrast to these positive roles, dysregulated Mo and Mφ can cause pathology, including poor infection control, impaired wound healing, tissue fibrosis, atherosclerosis, and tumor growth.[5–9] However, much remains to be learned about the regulation of the diverse Mo and Mφ functions in homeostasis, injury, infection, and disease. Improved understanding of the regulation of these functions would lead to more specific targeting in a vast array of pathologies.

In the late 1960s, van Furth et al.[10,11] proposed the mononuclear phagocyte system (MPS) as a way to classify Mo and Mφ along with Mo precursors based on similar morphology, origin, function, and kinetics. The MPS considers Mφ as end-stage cells that are differentiated from Mo, which, in turn, are differentiated from bone marrow precursors. One inference from this model is that resident tissue Mφ are thought to be derived from blood Mo. This concept has been challenged and has recently received intense scrutiny. Over the past 15 yr, an overall consensus has developed that resident Mφ in some tissues (e.g. microglia in brain and Langerhans cells in epidermis)[12,13] are primarily derived from embryonic precursors that self-renew without input from blood Mo whereas resident Mφ in barrier tissues like the gut and dermis turn over more rapidly and are populated in adult animals by blood Mo.[14,15] In still other tissues, like lung and liver, resident Mφ are thought to be a mix of embryo-derived and Mo-derived cells.[15–17]

Another inference from the MPS model is that, whereas bone marrow Mo precursors can proliferate, Mo lack the ability to proliferate after mobilization into the blood, and consequently Mo-derived Mφ are postmitotic. Thus, the prevailing view based on the MPS model has dictated that Mφ accumulation in tissues is the result of infiltration of Mo from the blood and subsequent differentiation to Mφ, particularly during the response to injury or infection. This concept was challenged recently with the demonstration that accumulation of Mφ in response to nematode infection occurs primarily via proliferation of resident cells.[18] In fact, a review of the literature revealed reports from the early 1900s to the present describing evidence of Mφ proliferation. The purpose of this review is to summarize both historical and current evidence for the contribution of Mφ proliferation to their accumulation in different tissues in homeostasis, infection, injury, and disease. In addition, we posit future directions that we think important for better understanding of the role and regulation of Mφ proliferation in different physiological and pathological contexts.

2 Historical perspectives

2.1 Evidence against proliferation in the periphery

The conventional wisdom that peripheral Mo and Mφ do not proliferate was derived from studies that formed the basis for the MPS

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concept. In a series of studies, van Furth et al.[10,19] reported that in vivo injection of H^3-thymidine into mice under homeostatic conditions resulted in labeling of only ~3% of blood Mo and ~1% of peritoneal Mφ 1 h after H^3-thymidine injection, a time point that was likely too short for significant bone marrow Mo mobilization. At the same time, ~20% of bone marrow mononuclear cells were labeled, indicating active proliferation. Labeling of blood Mo and peritoneal Mφ increased over time and peaked 48 to 60 h after injection of H^3-thymidine, indicating that progeny of proliferating bone marrow progenitors that had been mobilized from the bone marrow likely were responsible for the increased labeling. These in vivo studies were corroborated by in vitro studies of homeostatic cells showing that no blood Mo and only ~2% of peritoneal Mφ incorporate H^3-thymidine when cultured with the nucleoside for 24 h,[10,19] whereas ~30% of bone marrow mononuclear cells were labeled in similar experiments. In follow-up studies using intraperitoneal injection of newborn calf serum in mice as a model of inflammation, although blood Mo and peritoneal Mφ increased during the inflammatory response, the percentage of labeled cells remained close to homeostatic levels.[19] These findings indicated that bone marrow Mo are the source of the increased Mo and Mφ during inflammation as well as homeostasis.

Volkman[20] performed similar experiments using intraperitoneal injection of glycogen as an inflammatory stimulus in rats and found that 1% to 2% of peritoneal Mφ incorporate H^3-thymidine 1 h after in vivo injection or 24 h after in vitro incubation. Additionally, in studies using *Salmonella* infection in rats, 0.1% to 2% of blood Mo were labeled when assessed 30 min after H^3-thymidine injection, with labeling increasing to the high end of that range 4 to 5 d after infection.[21] Volkman, van Furth, and others also performed a series of irradiation, parabiosis, and adoptive transfer experiments that implicated bone marrow Mo as the precursors to tissue Mφ, providing further evidence that proliferating bone marrow precursors are the primary source of blood Mo and ultimately tissue Mφ, in both homeostasis and inflammatory responses.

2.1.1 *Early Evidence for Proliferation.* Despite the prevailing view that blood Mo and tissue Mφ are end-stage cells that do not proliferate, even the studies that are primary underpinnings of the MPS showed a low level of H^3-thymidine incorporation, typically 1% to 3% of the population.[10,20] Evidence for proliferation of tissue Mφ was published as early as 1914 by Evans et al.,[22] when injection of Trypan blue dye into rabbits was found to be taken up by liver Kupffer cells associated with rare morphological evidence of mitosis, a process that was amplified by infection with *Mycobacterium tuberculosis*. Using different vital dyes and a rabbit ear wound chamber to visualize Mo and Mφ in vivo, Ebert and Florey[23] reported evidence that blood Mo are the primary source of wound Mφ in vivo, and morphological evidence of proliferation in the wound.

Additionally, Mackaness[24] reported indirect evidence that resistance to *Listeria* reinfection in mice may result from proliferation of a resistant Mφ population, and Forbes and Mackaness[25] reported more direct evidence that immunization followed by reinjection of albumin in mice induced peritoneal Mφ proliferation assessed by in vitro incorporation of H^3-thymidine; >50% of Mφ incorporated H^3-thymidine after 1 h incubation when Mφ were obtained from immunized mice compared with ~1% in Mφ from naive mice. Forbes[26] also reported the endotoxin injection into mice induced proliferation of peritoneal Mφ, assessed by in vitro H^3-thymidine incorporation, which increased from <1% for control mice to 5% to 10% when Mφ were harvested 2 to 3 d after endotoxin injection and further reported that various other stimulants could induce peritoneal Mφ proliferation, including repeated puncture and mouse or rabbit serum.[27] Morphologic evidence for proliferation was also observed in Mφ from the experimental mice in all these studies. Furthermore, thioglycolate-elicited peritoneal Mφ from mice have been shown to proliferate and form colonies in liquid culture as assessed by cell counting and H^3-thymidine incorporation.[28]

Early reports also provided evidence of proliferation of liver and alveolar Mφ. North[29] reported that infection of mice with *Listeria monocytogenes* resulted in increased local proliferation of liver sinusoid Mφ peaking on day 2 after infection, with 20% of Mφ incorporating H^3-thymidine injected 30 min prior to tissue harvest. This was paralleled morphological evidence of proliferation at the same time point observed by light microscopy. Soderland and Naum[30] reported that mouse alveolar Mφ could proliferate in vitro when cultured with conditioned medium from a lung cell line, and Golde et al.[31] found that human mouse alveolar Mφ demonstrated uptake of H^3-thymidine over a 1 h period in culture, with cells from smokers demonstrating higher rates of proliferation, although these tended to be <1%.

2.2 Section summary

These older studies, although not definitive in many cases, provided evidence of Mφ proliferation in different tissues and in different contexts, contrasting with the view that these cells are nonproliferating end-stage cells. In addition, the low level of proliferation during homeostasis appeared to be increased in different models of infection, which provided early evidence that Mφ proliferation contributes to macrophage accumulation needed for host defense.

3 Mϕ proliferation during homeostasis and repopulation

3.1 Bone marrow, blood, and spleen

A number of reports have corroborated earlier findings that, during homeostasis, Mo in the bone marrow proliferate at relatively high levels, whereas Mo in peripheral blood and spleen either do not proliferate or proliferate at very low levels in mice, rats, and humans.[32–38] Studies over the past 30 yr have utilized flow cytometry and immunohistochemistry, along assessment of the cell cycle with DNA and Ki67 labeling, and DNA synthesis with BrdU or EdU labeling, to identify specific subpopulations of Mo and Mφ that proliferate in each tissue. These reports have also provided evidence that at least a subpopulation of blood Mo retain the ability to proliferate when stimulated with colony-stimulating factor 1 (CSF1),[33,36] stored human serum containing oxidized low-density lipoprotein,[36] advanced glycation end products[39] or FLT3 ligand.[37] A landmark study demonstrated that combined deficiency of the transcription factors *Maf* and *Mafb* in double knockout mice enabled Mo and Mφ derived from peripheral blood to proliferate long-term in culture with CSF1, an effect mediated by upregulation of transcription factors *Klf4* and *Myc*.[40] Similarly, a recent study demonstrated that a subpopulation of bone marrow–derived Mφ proliferate long term when cultured with CSF1, which appeared to be mediated by upregulation of the transcription factor *Klf2* and downregulation of *Mafb*.[41]

3.2 Peritoneum and lung

Abundant studies demonstrate Mφ proliferation in the peritoneum and lung; early studies used either strontium-89 or X-irradiation to deplete blood Mo and demonstrated proliferation

of local resident Mφ in the mouse via H^3-thymidine incorporation, independent of blood Mo input.[42,43] More recent studies have used flow cytometry assessment of phenotype markers to identify resident Mφ in the mouse peritoneum (e.g. F4/80^{hi} cells) along with a variety of fate mapping approaches combined with cell cycle analysis to demonstrate proliferation of these cells particularly during postnatal development but persisting into adulthood.[44,45] In an important study, a fate mapping approach was used to demonstrate that mouse peritoneal Mφ were long lived proliferating cells that were gradually replaced by bone marrow–derived Mo. The latter cells differentiated into Mφ that were phenotypically similar to embryonic Mφ but retained some differences.[45] Interestingly, replacement of embryonic Mφ occurred faster in male vs. female mice, and newly arrived cells appeared to proliferate at a higher rate than the older cells.[45] In other studies, female mice in the estrus phase or those treated with exogenous E2 (estradiol) exhibited increased proliferation of peritoneal Mφ, as shown by Ki67 labeling and BrdU incorporation,[46] indicating that sex hormones influence Mφ proliferation. Another study took advantage of observations that many resident Mφ express CD169 and used *CD169-DTR* mice to deplete these cells and study repopulation of resident Mφ in the peritoneum and lung.[47] Using *CD169-DTR* mice that were crossed with *Ccr2* knockout mice to deplete blood Mo, repopulation was demonstrated to be independent of blood Mo. Further experiments using blocking antibodies and knockout mice indicated that, during repopulation, proliferation of resident Mφ in these tissues was found to be dependent on CSF1 and CSF2.

A number of studies have focused on the mechanisms underlying self-renewal of resident Mφ particularly in the peritoneum and lung. Soucie et al.[48] used chromatin immunoprecipitation sequencing and *Maf/Mafb* double knockout bone marrow Mφ to identify enhancers associated with self-renewal and found that activated enhancers were associated with upregulation of a network of genes, directed by *Klf2* and *Myc*, and repressed by *Maf* and *Mafb*. Importantly, alveolar Mφ were shown to naturally have low levels of *Maf* and *Mafb* and have robust self-renewal capability. Single-cell analysis also showed low levels of *Maf* and *Mafb* expression in resident Mφ of the peritoneum, liver, and spleen, which are also known to have self-renewal capacity. In addition, a recent study reported that inducible depletion of interstitial lung Mφ resulted in infiltration by circulating Ly6C+ Mo in a CCR2-dependent manner, which then proliferated, as shown by EdU incorporation, cell cycle analysis, and competitive bone marrow transfer experiments using *Ccr2* knockout mice.[49] In this report, CSF1 receptor (CSF1R) signaling was found to be required for proliferation in blocking antibody experiments and MAFB was implicated in the transition from proliferation to differentiation into the resident Mφ phenotype in experiments utilizing myeloid cell specific *Mafb* knockout mice. Other studies have reported important roles for SIRT1 in self-renewal of resident Mφ in the peritoneum and lung,[50] and BACH2,[51] MTOR1,[52] VHL,[53] BHLHE40 and BHLHE41,[54] and mitochondrial metabolism[55] in homeostatic alveolar Mφ proliferation in mice.

3.3 Brain and skin

Microglia in the brain and Langerhans cells in the skin are generally thought to be sustained by self-renewal under most conditions in adult animals.[12,13] Using a multicolor fate mapping mouse model, combined with EdU/BrdU labeling, microglia self-renewal was found to be a random process during homeostasis with renewal rates showing regional differences in the brain.[56] Interestingly, microglia proliferation correlated with proliferation of other cells in the same region, and proliferation was increased after facial nerve axotomy in a clonal manner. In another study, *CX3CR1-DTR* mice were used to deplete microglia, and repopulation of these cells occurred via proliferation of local resident cells assessed by BrdU labeling, mediated at least in part by interleukin-1 receptor 1 (IL1R1) signaling in experiments using an IL1R antagonist.[57] These findings were supported by a subsequent report that utilized an CSF1 receptor antagonist to deplete microglia, along with different fate mapping approaches and EdU labeling to show that microglia were replenished via self-renewal. Another investigation demonstrated that administration of CSF1 locally to the brain in vivo or to cultured cells induced proliferation of microglia, as shown by Ki67 labeling and BrdU incorporation.[58]

In skin, using an inducible multicolor fate mapping approach and EdU labeling, Langerhans cells were found to be self-renewing cells that could be observed in proliferative clusters even in steady state, and such proliferation was increased following tape stripping.[59] In other studies, self-renewal of Langerhans cells has been reported to rely on signaling via IL34 in experiments using *Il34* knockout mice[60] and the phosphoinositide-dependent kinase 1 target kinases, and ribosomal S6 kinases 1 and 2 also in knockout mouse experiments.[61]

3.4 Other tissues

Mφ proliferation has also been demonstrated in a variety of other tissues. In the heart, various fate mapping approaches in mice along with Ki67 and BrdU labeling have been used to demonstrate that cardiac Mφ are initially proliferating embryonic cells that are gradually replaced by bone marrow–derived Mo as the animals age.[62,63] The low level of proliferation of cardiac Mφ during homeostasis was increased by prior depletion or angiotensin II administration.[62] In contrast, the proportion of embryonic yolk sac–derived Mφ was reported to increase with age in the mouse kidney, using fate-mapping approaches along with parabiosis and Ki67 labeling.[64] This increase was due to local proliferation and potentially recruitment of circulating yolk sac–derived progenitors, an intriguing possibility. In the liver, specific depletion of Kupffer cells using *Clec4f-DTR* mice resulted in repopulation by blood Mo. These Mo-derived Kupffer cells gained many of the characteristics of embryonic cell–derived Kupffer cells, including the ability to proliferate, as assessed using a protected bone marrow chimera approach and Ki67 labeling.[65] Proliferation of adipose tissue Mφ has also been observed in mice using BrdU labeling, and in vitro experiments have implicated a neuropeptide FF-induced increase in *Ndrg2* expression and decreased expression of proliferation inhibitors, including *Ifi200* family members and *Mafb* in this process.[66] Finally, local proliferation assessed by BrdU incorporation was found to contribute to the accumulation of both Mφ and dendritic cells in the mouse uterus during pregnancy.[67]

3.5 Section summary

Local proliferation of Mφ contributes to their maintenance during homeostasis, and to their repopulation after depletion, and there is evidence that both embryonically derived and adult bone marrow–derived cells possess this capacity. Initial work implicates the transcription factors MAF and MAFB, as well as the growth factor CSF1, as potential common mechanisms driving Mφ proliferation in different tissues. However, further study is needed to elucidate cell-intrinsic and cell-extrinsic mechanisms contributing to Mφ

proliferation that are common to all tissues as well as mechanisms that may differ between tissues (Fig. 1).

4 Mϕ proliferation during infection

4.1 Peritoneum and lung

Both infiltrating Mo-derived and resident Mφ have been shown to proliferate at a higher rate after injection in different tissues, and such proliferative responses have been most extensively studied in peritoneum and lung. In addition to their findings on peritoneal Mφ proliferation during postnatal development, Davies et al.[44,68] reported that zymosan, which is found in the yeast *Saccharomyces cerevisiae*, increased proliferation of adult mouse peritoneal Mφ as assessed by Ki67 labeling and cell cycle analysis. Injection of zymosan increased proliferation of both bone marrow–derived and tissue-resident Mφ, differentiated by levels of F4/80 and Ly6B expression, and proliferation appeared to depend on CSF1 but not on IL4 in blocking antibody experiments.[68] A later study demonstrated that infiltrating bone marrow–derived Mφ can persist long term in the peritoneal cavity but do not completely phenocopy tissue-resident Mφ, including a higher capacity for proliferation of the newly arrived cells as indicated by Ki67 labeling.[69] Furthermore, infection with the helminth *Heligmosomoides polygyrus* results in proliferation of large peritoneal macrophages, assessed by cell cycle analysis and BrdU incorporation, which appears to be dependent on the transcription factor BHLHE40, as demonstrated in experiments with *Bhlhe40* knockout mice.[70] BHLHE40 also appeared to mediate the proliferative response to an IL4 agonist, potentially via negative regulation of *Maf* and *Mafb* and positive regulation of cell cycle genes.

Infection with the nematode *Litomosoides sigmodontis* was shown to increase proliferation of resident Mφ in the lung of C57Bl/6 mice, and infection with *H. polygyrus bakeri* was shown to increase proliferation of resident Mφ in the peritoneum of BALB/c mice, and these responses were blocked in *Il4* knockout mice and myeloid-specific *IL4ra* knockout mice.[18,71] In addition, administration of an IL4 agonist could induce proliferation of resident peritoneal and lung Mφ, and of inflammatory peritoneal Mφ induced by thioglycolate, further implicating IL4 as a mediator of Mφ proliferation. Other experiments showed that proliferation of resident alveolar Mφ was associated with resistance to infection with *L. sigmodontis* in C57Bl/6 mice, whereas BALB/c mice did not exhibit robust resident Mφ expansion but instead demonstrated accumulation of infiltrating Mφ associated with susceptibility to infection.[72] In these latter studies, tissue-resident and infiltrating Mφ were differentiated by surface levels of F4/80 and Ly6C, along with GATA6 and CD102.

Following influenza virus infection, alveolar Mφ were initially reduced and their repopulation appeared to be due, at least in part, to local proliferation as assessed by Ki67 labeling.[73] In these studies, a β-catenin-HIF1A signaling pathway appeared to mediate an inflammatory Mφ phenotype and inhibited their proliferation and repopulation capacity. Another study by the same group showed that influenza infection decreased expression of *Tfam* and causes mitochondrial damage, which may lead to impaired self-renewal and increased susceptibility to severe infection.[74]

4.2 Liver

An early clue that liver Kupffer cells may proliferate in response to infection came from a study showing that glucan administration induced proliferation of liver Mφ as assessed by H^3-thymidine incorporation, despite induction of monocytopenia via strontium-89.[75] In addition, consistent with early studies by North et al,[29] a more recent study showed that *L. monocytogenes* infection induced proliferation of liver Mφ as assessed by Ki67 labeling.[76] In this latter study, lineage tracing studies using CX3CR1 and MaFIA reporter mice along with *Ccr2* knockout mice demonstrated that the proliferating Mφ were Mo-derived cells and further experiments demonstrated that CSF1, IL4, and IL33 are involved in this proliferative response. Another study demonstrated that infection with *Schistosoma mansoni* resulted in depletion of resident liver Mφ and replacement with Mo-derived cells using congenic bone marrow lineage tracing experiments.[77] During this process, proliferation of Ly6Chi Mo-like cells appeared to contribute to the repopulation of liver Mφ, as assessed by EdU labeling, whereas proliferation of more mature Mφ was negligible.

4.3 Bone marrow and blood

Systemic infection with *L. monocytogenes* induced proliferation of bone marrow cells that were Ly6Chi, and either CD11b+ or CD11b–, as assessed by BrdU incorporation.[78] These cells likely represent a mix of Mo progenitors and Mo, and *Listeria*-induced proliferation appeared to be dependent on toll receptor signaling. In studies on the fungus *Cryptococcus neoformans*, Fc-mediated phagocytosis of live or heat-killed fungus, or even polystyrene beads, by the J774 Mφ-like cell line, bone marrow–derived Mφ, or peritoneal Mφ, resulted in proliferation of these cells as assessed by cell cycle analysis and BrdU incorporation.[79] This process did not appear to require ingestion, because it was also induced by incubating cells on IgG1-coated plates. In a study on the mechanisms of HIV infection, in vitro proliferation of human blood Mo was increased by stimulation with CSF2, as assessed by H^3-thymidine incorporation.[80] Interestingly, such proliferation was required for productive HIV infection.

4.4 Other tissues

Consistent with the idea that proliferation of Mo-like cells may contribute to Mφ accumulation during the response to infection, intravenous administration of interferon-γ to rats induced intravascular proliferation of ED1+ Mo as assessed by pulsed BrdU incorporation.[81] In addition, infection of the brain of macaques with simian immunodeficiency virus results proliferation of infected perivascular CD68+ Mφ assessed by Ki67 and BrdU labeling.[82] Finally, urinary tract infection in mice with *Escherichia coli* induced proliferation of Ly6C+ F4/80+ cells in the bladder, and these cells were shown to be recruited from blood via congenic bone marrow transfer experiments.[83] Proliferation of these cells was found to depend on IL6 *trans*-signaling via administration of soluble gp130.

4.5 Section summary

Bacterial, viral, fungal, and helminth infection all result in proliferation of Mφ in peripheral tissues. Accumulated evidence indicates that both Mo-derived and/or resident Mφ can proliferate, potentially depending on the specific pathogen and tissue involved. Proliferation of these cells can be induced by various factors, including CSF1, IL4, IL6, and the hypoxia inducible factor 1 subunit alpha pathway, but further study is needed to determine mechanisms that are common to different types of infection, and which are pathogen and/or tissue dependent (Fig. 2).

5 Mϕ proliferation during tissue injury and repair

5.1 Skin

Different types of tissue injury also result in increased proliferation of both infiltrating Mo-derived and resident Mφ. In skin, epidermal and dermal Mφ both proliferate following injury in different species. Langerhans cells in the epidermis are thought to be embryo-derived self-renewing cells during homeostasis, but after immune injury induced by allogeneic hematopoietic stem cell transplantation, donor Mo replace damaged Langerhans cells in the epidermis.[84] These Mo-derived Langerhans cells undergo sequential differentiation and proliferation that matches that of embryonic-derived cells as assessed by Ki67 labeling. In addition, ultraviolet irradiation of human skin resulted in expansion of a dermal Mφ population that expressed CD11b, CD36, and HLA-DR but not CD1 and cell cycle analysis indicated a high proportion of these cells in the proliferative S/G2/M phases of the cell cycle.[85] Similarly, in vitro stimulation of human skin explants with substance *P* increased the population of dermal CD68+ cells but this increase was not associated with increased proliferation of CD68+ cells, assessed by Ki67 labeling.[86] Instead, substance *P* stimulation increased a population of Ki67+ CD34+ in proximity to CD68+ cells and the authors suggested the former cells may be the source of increased dermal CD68+ cells.

Until recently, the accumulation of Mφ following skin injury was thought to result solely from infiltration of blood Mo that differentiate into Mφ. Using an excisional wound model, our laboratory demonstrated that wounding increased Mo-like Ly6C+ F4/80lo cells in the proliferative S/G2/M phases of the cell cycle, peaking at ~25% of these cells on day 6 postinjury.[35] Blood Mo did not show evidence of proliferation, nor did more mature Ly6C-F4/80+ cells in wounds, indicating that environmental factors may induce proliferation in a maturation stage–dependent manner. Importantly, impaired wound healing in diabetic mice was associated with increase proliferation and accumulation of Ly6C+ F4/80lo cells in wounds.[34] Although proliferation of Ly6C+ Mφ was reminiscent of the response to urinary tract infection,[83] proliferation was not altered in *Il6* knockout mice in our studies. Instead, studies utilizing administration of recombinant CCL2 and adoptive transfer with CCR2 knockout Mo indicated that CCL2/CCR2 signaling induces proliferation of Ly6C+ Mφ. Thus CCL2 may contribute to persistent accumulation of Ly6C+ Mφ in wounds of diabetic mice by inducing both infiltration and proliferation.[34] Interestingly, CCL2 also stimulated proliferation of cultured microglia, indicating that this phenomenon may not be restricted to skin wound Mφ.[87]

5.2 Kidney

Mφ proliferation has also been demonstrated in a number of different models of kidney injury in mouse, rat and humans. Robust local proliferation of ED1+ Mφ, identified by double labeling with proliferating cell nuclear antigen (PCNA), were observed within a kidney allograft undergoing acute rejection.[88] ED1+ cells are typically considered to be proinflammatory Mo-like Mφ, similar to Ly6C+ Mφ in mice. In this study, the immunosuppressant drug deoxyspergualin inhibited Mφ proliferation in the graft. Local proliferation of ED1+ Mφ was also observed in a rat model of glomerulonephritis induced by anti-glomerular basement membrane antibody.[89] In this study, proliferation was assessed by PCNA labeling and confirmed by BrdU labeling, was restricted to ED1+ ED2– ED3– Mo-like cells, and was confined to areas of severe damage. Local proliferation of Mφ was also observed in regions of damage after partial nephrectomy in rats (ED1+ PCNA+ cells;[90]), and in human glomerulonephritis (CD68+ PCNA+ cells;[91]).

Local Mφ proliferation assessed by PCNA labeling has been correlated with CSF1 expression in both rat models of kidney damage and in human glomerulonephritis.[92,93] Furthermore, in a mouse model of unilateral ureteric obstruction, an anti-CSF1R blocking antibody largely prevented the proliferation of Mac-1+ cells, assessed by PCNA and BrdU labeling, and blocked the accumulation of these cells.[94] These latter studies implicate CSF1R and CSF2R signaling in the local proliferation of Mφ following kidney injury. Recent studies have also reported local proliferation of Mφ in models of chronic ischemia assessed by pulsed BrdU labeling[95] and ischemia/reperfusion assessed by PCNA labeling,[96] with periostin implicated as an inducer of proliferation following ischemia/reperfusion.

5.3 Other tissues

In the liver, Kupffer cells identified as $CD11b^{hi}$ $MHCII^{hi}CD64^{hi}$ $F4/80^{hi}$ $CX3CR1^{neg/lo}$ Mφ were reduced following acetaminophen-induced injury in mice and repopulated by self-renewal as demonstrated by BrdU and Ki67 labeling.[97] Monocyte adoptive transfer and CCR2 knockout mice were used to demonstrate lack of monocyte input into repopulating Kupffer cells and CSF1 administration did not affect Kupffer cells proliferation. In the pancreas, duct ligation in the rat resulted in proliferation of both Mo-like ED1+ cells and Mφ-like ED2+ cells as assessed by BrdU pulse labeling.[98] Proliferation was robust, peaking on day 2 postligation at 20% to 30% of the parent population. Pancreatic duct ligation in mice also induced local Mφ proliferation peaking on day 3 postligation at 10% to 30% of the parent population as assessed by BrdU pulse labeling and Ki67 labeling.[99] Proliferation was enhanced in CCR2 knockout mice, indicating a compensatory effect for lack of Mo input to damaged pancreas and inhibited by a CSF1R blocking antibody, indicating that CSF1 promotes Mφ proliferation in this model.

5.4 Section summary

Contrary to conventional wisdom, Mφ proliferation contributes to accumulation of these cells following immune, chemical, and physical injury to skin, liver, kidney, and pancreas. In some cases, infiltrating Mo-like cells show robust proliferative capacity that may exceed the proliferative capacity of resident cells. The factors inducing Mφ proliferation following tissue injury include CSF1, CCL2, and substance *P*, but further study is needed to better understand mechanisms that are generalizable over different types of injury in different tissues and mechanisms that may be context dependent (Fig. 3).

6 Mϕ proliferation during disease

6.1 Adipose tissue

Mφ proliferation has been observed in a variety of disease states, including metabolic disease in both humans and rodents. Adipose tissue exhibits increased Mφ accumulation in obese humans, in genetically obese mice and in mice fed a high-fat diet (HFD), and this accumulation is due at least in part to local proliferation. Proliferating Mφ were localized to crown-like structures assessed by Ki67 labeling in both obese mouse and human adipose tissue and such proliferation increased over time in mice fed a HFD.[100] Using bone marrow transfer experiments in which adipose tissue was shielded from irradiation, bone marrow–derived Mo were found to contribute little to adipose tissue Mφ

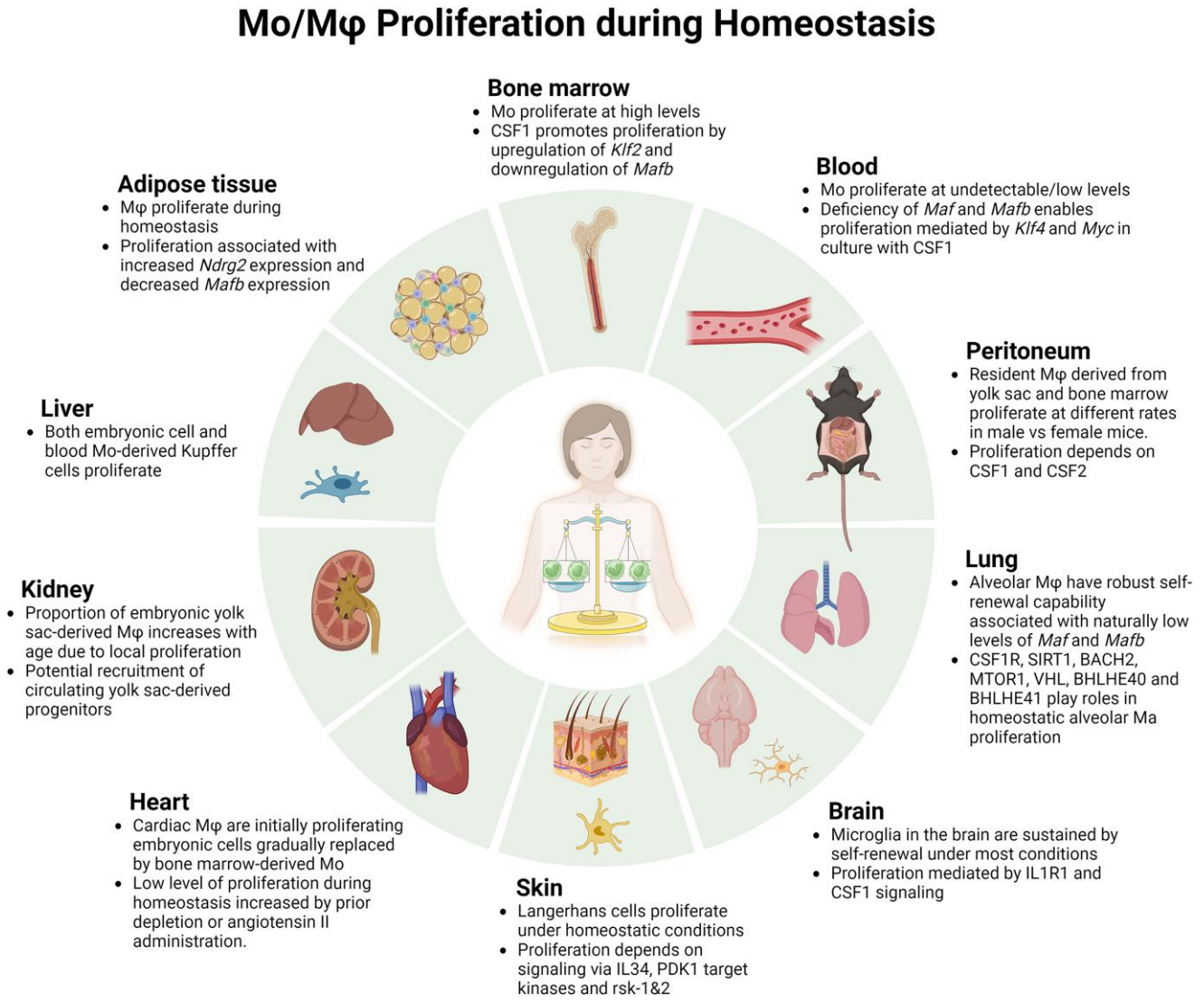

Fig. 1. Mo/Mφ proliferation during homeostasis. Local proliferation of Mo/Mφ contributes to their maintenance during homeostasis, and to their repopulation after depletion, including embryonically derived and adult bone marrow–derived cells.

accumulation early (8 wk) in the accumulation of fat mass in HFD mice, but their contribution increased at later time points (12 wk).[101] Proliferation of both the resident and newly arrived cells, assessed by Ki67 and EdU labeling, contributed to adipose tissue Mφ accumulation throughout the time course of obesity, and IL4/STAT6 signaling appeared to contribute to this phenomenon. Another study demonstrated that adipose tissue Mφ proliferation in both genetically obese *ob/ob* and HFD mice, assessed by Ki67 and EdU labeling, was associated with an increase in CCL2, that CCL2 treatment increased Mφ proliferation in adipose tissue explants, and that local Mφ proliferation was reduced in CCL2 knockout mice.[102] Osteopontin is also increased in adipose tissue of HFD mice and enhances survival and proliferation of bone marrow–derived Mφ in culture; importantly, adipose tissue Mφ proliferation induced by HFD obesity was blocked in osteopontin knockout mice.[103] Interestingly, chronic cold exposure also resulted in proliferation of adipose tissue Mφ assessed by EdU labeling, a process associated with adaptive thermogenesis.[104] Chronic cold also increased adiponectin expression, which appeared to be required for adipose tissue F4/80+ CD206+ Mφ proliferation as such proliferation was eliminated in adiponectin knockout mice. Thus, a number of pathways appear to trigger adipose tissue Mφ proliferation under different pathophysiological conditions.

6.2 Liver

Feeding mice a diet deficient in methionine and choline is a model of nonalcoholic steatohepatitis (NASH), and is associated with infiltration of Mo, whereas numbers of resident Kupffer cells do not appear to be altered.[105,106] Parabiosis and bone marrow transfer experiments with CCR2 knockout mice were used to demonstrate that Mo-derived cells partially replace resident Kupffer cells during development of NASH, and are more proinflammatory, although both resident and Mo-derived cells show similar levels of proliferation as assessed by Ki67 labeling.[106] Another study demonstrated similar levels of proliferation of resident and Mo-derived Kupffer cells in mice recovering from NASH, when they were switched back to a normal diet.[105] Furthermore, heme oxygenase 1 (Hmox1) deficiency in humans is a lethal disease characterized by severe anemia, and Hmox1 knockout mice recapitulate this disease phenotype. Wild-type bone marrow–derived Mφ infused into Hmox1 knockout mice engrafted into the

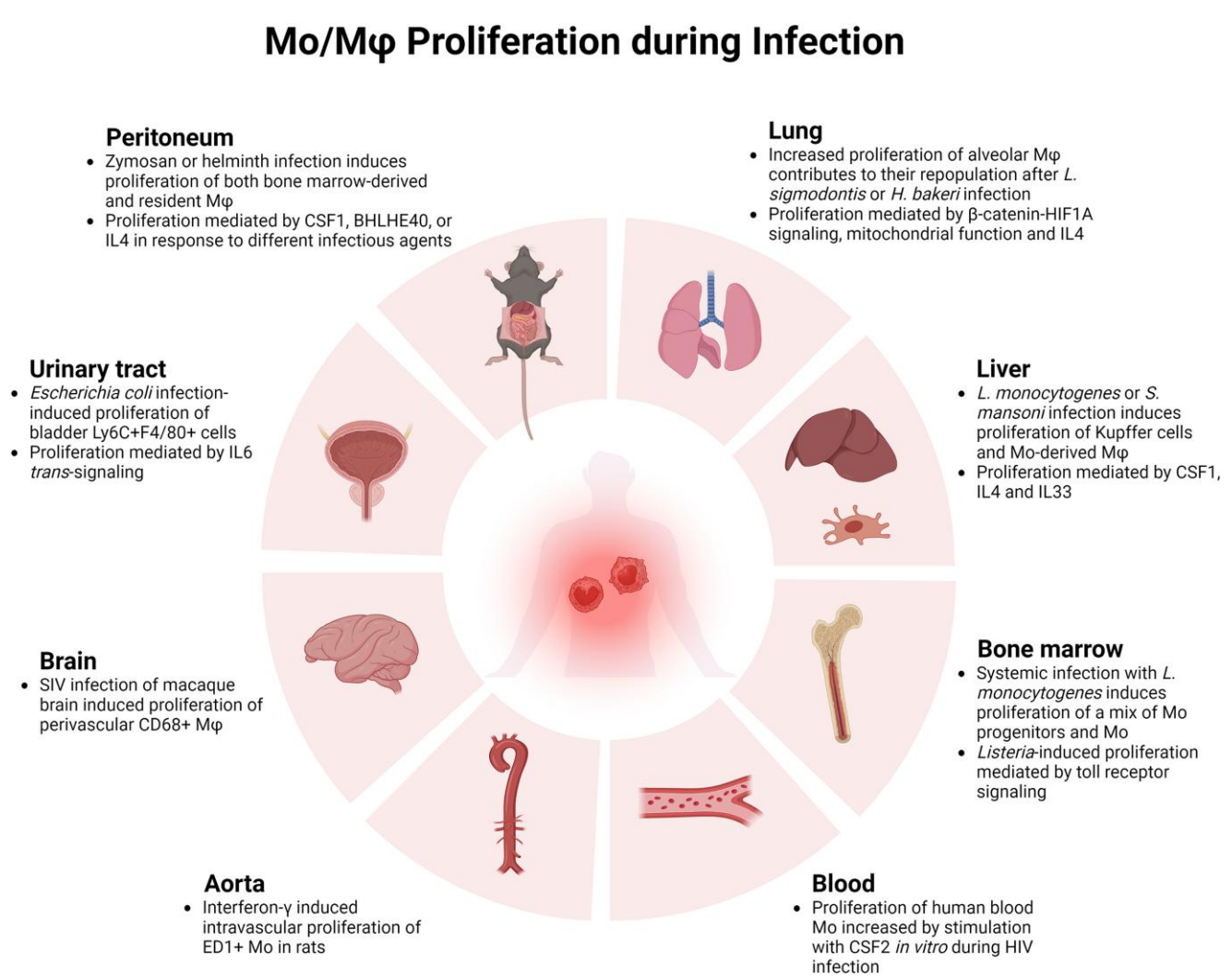

Fig. 2. Mo/Mφ proliferation during infection. Infection with various pathogens results in proliferation of Mo-derived and/or resident Mφ potentially depending on the specific pathogen and tissue involved. *H. bakeri* = *Heligmosomoides polygyrus bakeri*; HIF1A = hypoxia inducible factor 1 subunit alpha; *L. monocytogenes* = *Listeria monocytogenes*; *L. sigmodontis* = *Litomosoides sigmodontis*; SIV = simian immunodeficiency virus.

liver and proliferated as assessed by BrdU labeling, rescuing these mice from disease.[107] In human hepatocellular cancer, tumor Mφ proliferation assessed by Ki67 labeling was positively correlated with Mφ accumulation and poor prognosis.[108] In this study, tumor Mφ proliferation appeared to be stimulated by adenosine signaling. Finally, in the lupus prone mouse strain MRL lpr/lpr, liver Mφ are increased compared with control mice.[109] The increased Mφ population was associated with increased proliferative potential of non-parenchymal cells, which included Mo, Mφ and potentially precursor cells, assessed by CSF2-induced H^3-thymidine incorporation in vitro. In short, liver Mφ proliferation appears to be involved in a variety of diseases.

6.3 Aorta and heart

Early studies provided evidence for local Mφ proliferation in atherosclerotic plaques of mice, rabbits, and humans using H^3-thymidine or BrdU incorporation, or PCNA labeling along with immunohistochemical detection of Mφ markers in histological sections.[110–112] Using a BrdU labeling strategy in *Apoe* knockout mice fed a high-cholesterol diet, Mφ turnover was found to be surprisingly rapid, and local proliferation contributed to this turnover as assessed by cell cycle analysis, Ki67, and phosphohistone H3 labeling along with adoptive transfer and parabiosis experiments.[113] Mφ proliferation appeared to depend on the lesion microenvironment, and scavenger receptor A was implicated in the process in competitive bone marrow transfer experiments. CSF1 has also been shown to promote Mφ proliferation in atherosclerotic lesions in mice treated with *Ldlr* antisense oligonucleotides and fed a high-cholesterol diet.[114] Proliferation of Mac-3+ and CD68+ Mφ was reduced in lesions of *Csf1*+/− mice as well in smooth muscle cell– and endothelial cell–specific *Csf1* knockout mice as assessed by labeling with Ki67 or BrdU, indicating that these cells were important sources of CSF1 in lesions.

In the mouse heart, doxorubicin-induced cardiomyopathy was associated with accumulation of Mφ that were derived from blood Mo, as shown by parabiosis and lineage tracing experiments, whereas resident Mφ were depleted.[115] Both the newly arrived and resident Mφ proliferated in the heart, with resident cells proliferating at a higher rate, induced in part by a scavenger receptor A1-c-Myc axis, contributing to the recovery of resident Mφ during recovery from myopathy. In addition, in a mouse model of hypertension-induced cardiac growth, Mo-derived cells transiently accumulated early followed by later accumulation of resident Mφ

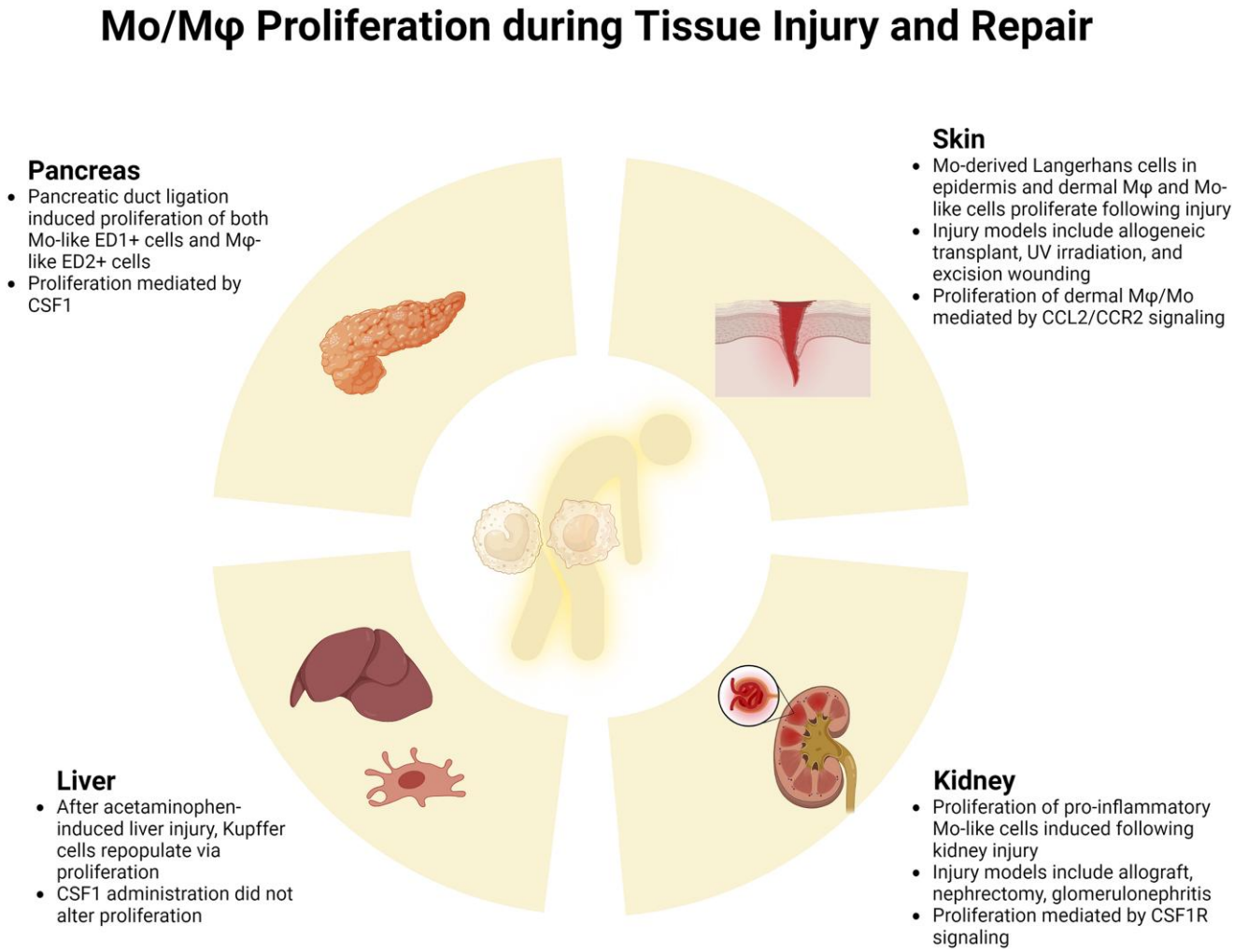

Fig. 3. Mo/Mφ proliferation during tissue injury and repair. Mφ proliferation contributes to their accumulation following injury to skin, liver, kidney, and pancreas. In many cases, infiltrating Mo-like cells show robust proliferative capacity. UV = ultraviolet.

as shown by *Cx3cr1* fate mapping.[116] Accumulation of TimD4^{hi} subsets of resident Mφ was associated with proliferation as assessed by BrdU incorporation. In short, Mφ proliferation contributes to both adaptive and pathophysiological processes in the cardiovascular system.

6.4 Lung

Alveolar Mφ from patients with chronic lung inflammatory disease, including smokers, idiopathic pulmonary fibrosis, and sarcoidosis, showed increased proliferation in vitro compared with Mφ from healthy control subjects, as assessed by H^3-thymidine incorporation.[117] These findings were confirmed by flow cytometric cell cycle analysis and morphological evidence of mitosis. In addition, chronic exposure of mice to particulate matter resulted in a time-dependent accumulation of bone marrow–derived Mo into the alveolar Mφ population, as shown by shielded bone marrow transfer experiments.[118] The accumulation of bone marrow–derived Mφ was associated with reduced proliferation of resident alveolar Mφ as assessed by BrdU incorporation and a chronic inflammatory phenotype. Furthermore, in mice exposed to cigarette smoke, increased alveolar Mφ proliferation assessed by EdU incorporation was associated with reduced prostaglandin E2 levels.[119] This study also demonstrated that reduced alveolar Mφ numbers in aged mice was associated with increased prostaglandin E2 levels. In vitro, prostaglandin E2 inhibited CSF2-induced expansion of alveolar Mφ, suggesting that this eicosanoid limits proliferation.

6.5 Other tissues

In the skin, Langerhans cells undergo robust proliferation during mouse development, as assessed by Ki67 labeling, with much lower levels of proliferation during homeostasis in the adult.[120] Langerhans cell proliferation in the adult mouse is dramatically increased by local treatment with a vitamin D3 analog, which induces inflammation resembling atopic dermatitis; increased Langerhans cell proliferation was also seen in skin human atopic dermatitis patients.[120] In a mouse model of autoimmune encephalomyelitis, proliferation of resident Mφ subsets, assessed by lineage tracing and Ki67 labeling, was observed in the spinal cord, which contributed to their accumulation alongside infiltration of Mo and their differentiation into Mφ .[121] In the MRL-Fas^{lpr} lupus mouse model, IL34 appears to contribute to lupus nephritis by increasing Mφ accumulation in the kidney, via increased production of bone marrow Mo and by local Mφ proliferation, assessed by Ki67 labeling.[122] In a mouse model of rheumatoid arthritis, injection of CSF1 or CSF2 increased local proliferation of Mφ assessed by BrdU labeling and exacerbated pathology.[123] Local proliferation of Mφ has also been reported at the vitreous-retinal interface of the

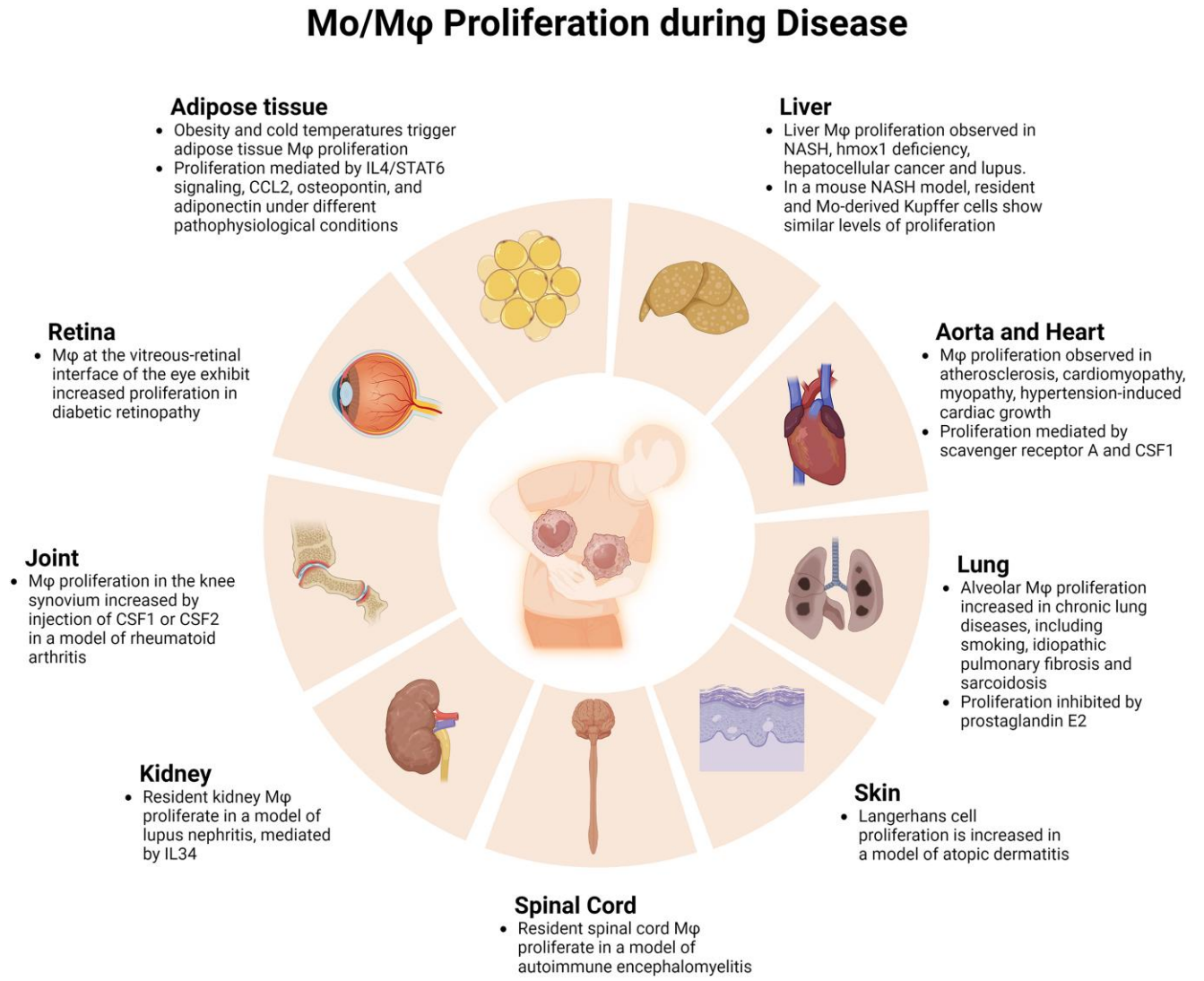

Fig. 4. Mo/Mφ proliferation during disease. Local Mφ proliferation contributes to the inflammatory response in a variety of tissues and diseases.

eye in diabetic retinopathy in mice and humans, assessed by BrdU and Ki67 labeling.[124]

6.6 Section summary

Local Mφ proliferation of both Mo-derived and resident Mφ contribute to the inflammatory response and pathogenesis in a variety of diseases, including metabolic disease, chronic inflammatory/immune disease, cancer, and cardiovascular disease. A number of factors have been reported to induce Mφ proliferation in these diseases, including CSF1, CSF2, IL4, IL34, CCL2, adiponectin, and prostaglandin E2. However, additional research is needed to elucidate the mechanisms that contribute to Mφ proliferation in each disease state and whether targeting these mechanisms can ameliorate disease pathology (Fig. 4).

7 Summary and future directions

In summary, numerous studies have shown that Mφ can proliferate during homeostasis as well as during the response to infection, injury, and disease. Mφ proliferate in different organs and tissues, including skin, peritoneum, lung, heart, aorta, kidney, liver, pancreas, brain, spinal cord, eye, adipose tissue, and uterus, and in different species including mouse, rat, rabbit, and human. Mφ can proliferate at different stages of differentiation with infiltrating Mo-like cells proliferating in certain inflammatory contexts (e.g. skin wounding, kidney injury, bladder infection) and mature resident Mφ proliferating in other inflammatory contexts (e.g. helminth infection, fungal infection, and metabolic disease) and during homeostasis. The pathways involved in stimulating Mφ proliferation also appear to be context dependent, with IL-1, IL4, IL6, IL34, CSF1, CSF2, CCL2, SIRT1, mTOR, VHL, osteopontin, PGE2, Flt3 ligand, oxidized low-density lipoprotein, and transcription factors MAF, MAFB, KLF2, KLF4, MYC, BACH2, BHLHE 40, and BHLHE41 implicated in different studies. Although much has been learned about the role and regulation of Mφ proliferation in health, injury, and disease, further research is needed on both generalizable and context-dependent mechanisms involved and the impact of Mφ proliferation on the homeostasis, injury, and repair of different organs and tissues.

7.1 Regulation of Mφ proliferation

An intriguing observation is that Mo proliferate in bone marrow, but do not proliferate after their mobilization to peripheral blood, and then can proliferate again after recruitment to sites of

inflammation during the response to infection, injury, and disease. Evidence suggests that the microenvironment plays a role in stimulating Mo and Mφ proliferation, and different factors have been implicated in triggering proliferation, including IL1, IL4, IL6, IL34, CSF1, CSF2, and CCL2, but a comprehensive understanding of the cell-intrinsic and cell-extrinsic pathways that regulate Mo and Mφ proliferation in the bone marrow, in the blood, and at sites of inflammation remains to be elucidated. In addition, whether Mo and Mφ preferentially proliferate in specific locations or niches of different tissues remains to be determined. The transcription factors MAF and MAFB are likely to be involved as a number of studies have demonstrated that these transcription factors are part of a pathway that blocks Mo and Mφ proliferation, and that downregulation of these factors permits proliferation.[40,48,49,70]

In addition, the self-renewal capacity of Mφ has been reported to be influenced by sex, with higher levels of peritoneal Mφ proliferation in male vs female mice that appears to be driven by the local environment.[45] These findings appear to contrast with findings that both administration of exogenous estradiol and the endogenous hormone surge in female mice increase proliferation of peritoneal Mφ .[46] Thus, the pathways that influence sexual dimorphism in Mφ proliferation remain to be elucidated, and the impact of sex differences in Mφ proliferation on the inflammatory response during infection, injury, and disease should be a fruitful area of future study.

7.2 Impact on function

The studies reviewed have provided evidence for proliferation of infiltrating Mo-derived Mφ as well as tissue-resident Mφ that appear to be context dependent. Mo-derived Mφ and tissue-resident Mφ appear to retain somewhat different phenotypes even when exposed to the same environment, with Mo-derived cells tending to have proinflammatory roles and resident cells tending to contribute to resolution and repair at least in some contexts.[1,3,12,125,126] Thus, differential proliferation may be a mechanism by which the function of the total Mφ population is regulated. This idea could be extended to subsets within the Mo-derived Mφ and tissue-resident Mφ populations if subsets of these cells have different capacities to proliferate. Recent studies have identified heterogeneity of blood Mo that could affect their function after infiltration into tissues and subsequent differentiation, supporting the idea that both cell-intrinsic and cell-extrinsic factors play a role in regulating the function of Mφ .[127,128] Further study is needed to determine whether subsets of Mo-derived Mφ and tissue-resident Mφ proliferate differently in different contexts, and if so, to determine the impact on the function of Mφ in those contexts.

7.3 Need for human studies

Most studies on Mφ proliferation have been performed in rodents, particularly mice, whereas fewer studies have been performed in humans or on human cells. Most human studies have used peripheral blood Mo stimulated in culture, or other cells that are relatively easy to obtain, including alveolar or adipose tissue Mφ. A few studies have capitalized on the ability to obtain cells from diseased organs, including heart, kidney, liver, and intestine. Other interesting studies have taken advantage of the accessibility of skin and the utility of skin allografts to study the ability of resident Langerhans cells and dermal Mφ to proliferate in the graft, the ability of infiltrating host Mo to replace these resident cells, and the respective roles of host and donor cells in the function of the graft.[129–131] Barriers to human studies include logistical and technical difficulties in obtaining cells in a form suitable for identifying cells and cell subsets and assessing proliferation, as well as difficulties in performing mechanistic studies especially in vivo. However, the need for such studies is emphasized by differences observed in mouse vs human immune systems[132]; there is need both for studies that translate findings from mouse studies and for those that make context-specific observations in humans that can be mechanistically tested in mice.

Further work in these areas will improve our understanding of the role of Mo and Mφ proliferation in physiological and pathological conditions in various organs and tissues, how proliferation is regulated, and how proliferation can be targeted to improve outcomes of a number of different disorders and diseases.

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Author contributions

J.P. helped write the manuscript and made the figures. T.J.K. helped write the manuscript.

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