2.3 Origin of Macrophages

Hematopoiesis is the process by which lymphoid and myeloid lineage cells of the blood are formed, through a tightly regulated stepwise process involving several progenitor cells (De Kleer et al. 2014). Hematopoiesis occurs in several temporally and spatially regulated waves during the embryonic development ("primitive hematopoiesis") in the YS and culminates with the generation of HSCs in the FL before birth and in the bone marrow (BM) after birth and during adulthood ("definitive hematopoiesis"). An exhaustive description of hematopoiesis and of the ontogeny of monocytes and trMϕ is beyond the aim of this review. However, the section below will summarize the key steps of the development of mononuclear phagocytes referring to definitive/adult hematopoiesis as the main source of circulating monocytes and to primitive/definitive/fetal hematopoiesis as the main source of trMϕ.

2.3.1 Monocytes and moMϕ Development: Definitive/Adult Hematopoiesis

Lineage-committed mononuclear phagocytes, i.e., circulating monocytes and moMϕ, are generated primarily in the bone marrow from tightly regulated differentiation of HSCs to progressively more committed cell population. High levels of the transcription factor c-Myc induce the differentiation of HSCs toward more committed progenitors (Wilson et al. 2004). At the top of monocyte/macrophage development, there is the lineage-determining master regulator PU.1 that, upon activation by CSF-1 (also known as M-CSF) and IL-34 (Mossadegh-Keller et al. 2013), controls the gene expression module common to all monocytes/macrophages and is the crucial regulator of myeloid lineage commitment at the fork in the road between myeloid and lymphoid fates (McKercher et al. 1996; Nerlov and Graf 1998). The transcription factor MafB represses the activity of CSF-1 (Sarrazin et al. 2009), and its expression is reduced in myeloid-committed cells in respect to HSCs. CSF-1 not only directs lineage commitment of HSCs toward CMP (common myeloid progenitors—lymphoid potential is lost) but also of GMP (granulocyte-macrophage progenitors) toward MDP (monocyte-macrophage DC progenitors—granulocyte potential is lost). Recently, the purification of the more restricted MDP population in mouse allowed to define a precursor from which monocytes and DCs are derived, that is, the distinction between CDP (common DC progenitors), a DC-restricted precursor in the BM, and cMoP (common monocyte progenitors), a monocyte-restricted BM precursor that represents the more differentiated, committed monocyte population (Hettinger et al. 2013). cMoP give rise to both monocyte subsets Ly6C^{high} and Ly6C^{low}. A cMoP monoblast type of cell has not been identified yet in humans. Figure 2.1A summarizes the sequential steps of monocyte development.

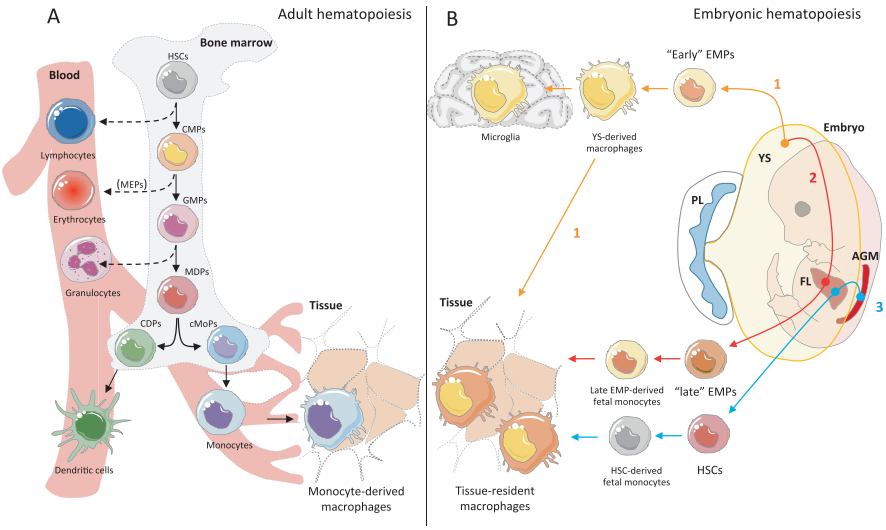

Fig. 2.1 Origin of monocyte-derived macrophages (moMϕ) and tissue-resident macrophages (trMϕ). (**A**) moMϕ are generated in the bone marrow (BM) through the tightly regulated differentiation of HSCs to progressively more committed cells up to monocytes. This hematopoiesis is defined as "definitive hematopoiesis" and occurs in fetal liver (FL) during the late phase of the embryonic development (before birth) and in BM during adulthood (after birth). Monocytes are released to the bloodstream and can be recruited into the tissue where they differentiate into macrophages. *HSCs* hematopoietic stem cells, *CMPs* common myeloid progenitors, *GMPs* granulocyte-macrophage progenitors, *MDPs* monocyte-macrophage DC progenitors, CDPs common dendritic cell progenitors, cMoPs common monocyte progenitors. (**B**) trMϕ arise from multiple sources during the embryonic development with a sequential timing: from yolk sac (YS), FL and aorta-gonads-mesonephros (AGM) regions according to three different routes. These routes are a simplification of the three main successive waves of the embryonic hematopoiesis and also of the three proposed models for macrophage ontogeny. (1) The first wave arises directly from YS, which produces "early" erythro-myeloid progenitors (EMPs) ("primitive hematopoiesis") from which YS macrophages are generated. To date, the progenitors giving rise to macrophages are poorly characterized. The first model proposes that these YS-derived macrophages represent the main precursors for the most trMϕ and not exclusively for microglia. (2) The second wave generates "late" EMPs that could migrate from YS into FL and could represent transient definitive progenitors. The second model proposes that these late EMPs represent the main precursors for most trMϕ, with the exception of microglia, through a monocytic intermediate (late EMP-derived fetal monocytes). (3) The third wave starts with the generation of immature HSCs in the AGM that colonize the FL where they establish a "definitive hematopoiesis" and maybe seed the fetal bone marrow (BM) generating HSC-derived fetal monocytes. Then, these cells will finally lead to generation of HSCs in the BM during adulthood. The third model hypothesizes that trMϕ (except microglia) arise from HSC-derived fetal monocytes, and these cells, rather than late EMPs, might generate FL monocytes. *PL* placenta

2.3.2 *trMϕ Ontogeny: Primitive/Fetal Hematopoiesis*

Until few years ago, it was believed that tissue macrophages derive entirely from circulating blood monocytes, through adult hematopoiesis. Given that there are

some tissues which require blood-borne precursors to replenish the pool of resident macrophages, such as the dermis (Tamoutounour et al. 2013), gut (Bain et al. 2014), mammary gland (Franklin et al. 2014), and heart (Epelman et al. 2014a, b), the resident macrophage pool of most tissues derives from embryonic precursors that colonize these tissues prior to birth and is maintained locally through in situ proliferation in adulthood (Gentek et al. 2014; Sieweke and Allen 2013). In the early 2000s, a series of elegant fate-mapping experiments, experiments in parabiotic mice, and genetically engineered mouse models (Tamoutounour et al. 2013; Yona et al. 2013; Bain et al. 2014; Epelman et al. 2014a, b; Ajami et al. 2007; Ginhoux et al. 2010; Guilliams et al. 2013; Hashimoto et al. 2013) demonstrated once and for all that trMϕ (e.g., microglia, LCs, alveolar macrophages, Kupffer cells) originate from early embryonic precursors prior to birth and that the extent to which they can originate from adult HSCs depends on the context and tissue (Ginhoux and Jung 2014). Assuming that trMϕ have an embryonic origin, the next step was to understand the embryonal hematopoiesis and from which precursor tissue macrophages derive. Mammalian embryonic hematopoiesis is a complex process that makes particularly challenging the goal of determining the exact ontogeny of fetal macrophages (for review, see Hoeffel and Ginhoux 2015). In the mouse, embryonic hematopoiesis is characterized by distinct waves, occurring in different districts of the embryo and in a sequential way. The first wave arises from the blood island of YS around E7–7.5 (embryonic day) and gives rise to the so-called erythro-myeloid progenitors (EMPs). This phase is termed "primitive hematopoiesis" and generates macrophages without going through a monocytic progenitor (*myb*-independent hematopoiesis) (Gomez Perdiguero and Geissmann 2013). Actually, EMPs have been renamed "early EMPs," to distinguish them from the "late EMPs" that arise from the YS hemogenic endothelium at E8–8.5. This phase represents the second wave of hematopoiesis and is characterized by the emergence of lympho-myeloid progenitors (Li et al. 2014). This wave is called "transient hematopoiesis" because it does not persist upon transplant in immune-compromised mice (Hoeffel and Ginhoux 2015; Hoeffel et al. 2015). At E8.5 the blood circulation is established, and EMPs are able to seed the FL, where they expand and generate fetal monocytes. Concomitantly with "late EMPs" at E8.5, at third wave arises from the intraembryonic hemogenic endothelium, which generates immature HSCs in the para-aortic splanchnopleura (P-Sh) region and proceeds to give rise to fetal HSCs in the aorta, gonads, and mesonephros (AGM) region at E10.5. Then, these precursors colonize both the FL, where they establish a "definitive hematopoiesis" (*myb*-dependent) (Hoeffel et al. 2015), and fetal BM, where they finally will generate adult BM HSCs. From E12.5 onward, the FL becomes the main hematopoietic organ within the embryo. While the embryonic origin of certain tissue macrophages is now accepted, the exact identity of progenitors, the exact pathway of differentiation to mature cells, and the transcription factors involved are still unknown. Three different models of the macrophage embryonic ontogeny have been proposed: (1) YS-derived macrophages represent the main precursors for most trMϕ (Gomez Perdiguero et al. 2015a), (2) "late EMPs" could represent the main precursors for most trMϕ through a monocytic intermediate

(Hoeffel et al. 2015), (3) fetal HSCs are the main precursors of FL monocytes, and adult macrophages (with the exception of microglia and partially LCs) arise from these definitive fetal HSCs (Sheng et al. 2015a). Which of the three hypotheses is valid remains still a matter of heated and constructive debate (Sheng et al. 2015b; Gomez Perdiguero et al. 2015b). For an exhaustive description of the three models and for an overview of the experiments on the ontogeny of macrophages, we refer the reader to the recent wonderful review by Ginhoux and Guilliams (Ginhoux and Guilliams 2016). Figure 2.1B summarizes the sequential steps of macrophage development.

2.4 trMϕ Versus moMϕ

According to the above evidence, we will consider trMϕ predominantly as macrophages derived from embryonic hematopoiesis that have colonized different tissues before birth and moMϕ as the mononuclear phagocyte population originating through definitive hematopoiesis after birth. This different origin has contributed not only to a primary distinction in terms of ontogeny but also to a secondary one in terms of functions. Generally, a conventional view implies that at steady-state the embryonic-derived trMϕ serve to maintain tissue homeostasis via surveillance of local tissue microenvironment. On the other hand, during inflammation (due to infection, disease, or trauma), it is generally accepted that circulating monocytes are predominantly recruited in the tissue, where they mediate various effector functions and differentiate into macrophages (moMϕ). To date it is not fully understood how much these two populations differ from each other and in their contribution to the initiation and resolution of the inflammatory response. Likewise, it is not known how much their functions differ due to diverse development origin ("nature") or how much overlap due to influence of the environmental cues ("nurture"). The next sections will address these issues.

2.4.1 In Situ Macrophage Expansion/Proliferation Versus Monocyte Recruitment

In healthy tissues and in steady-state conditions, trMϕ are maintained by self-renewal with a variable contribution by circulating monocytes (Yona et al. 2013; Hashimoto et al. 2013; Gomez Perdiguero et al. 2015a, b). It has been observed that in situ proliferation versus peripheral BM-derived monocyte recruitment for the maintenance of the tissue macrophages can change based on the tissue. Thus, on the one hand, we observed that the brain microglia have the potential for efficient self-renewal without the contribution of BM-derived precursors (Bruttger et al. 2015), and the same happens for resident macrophages in the liver, epidermis, lung,

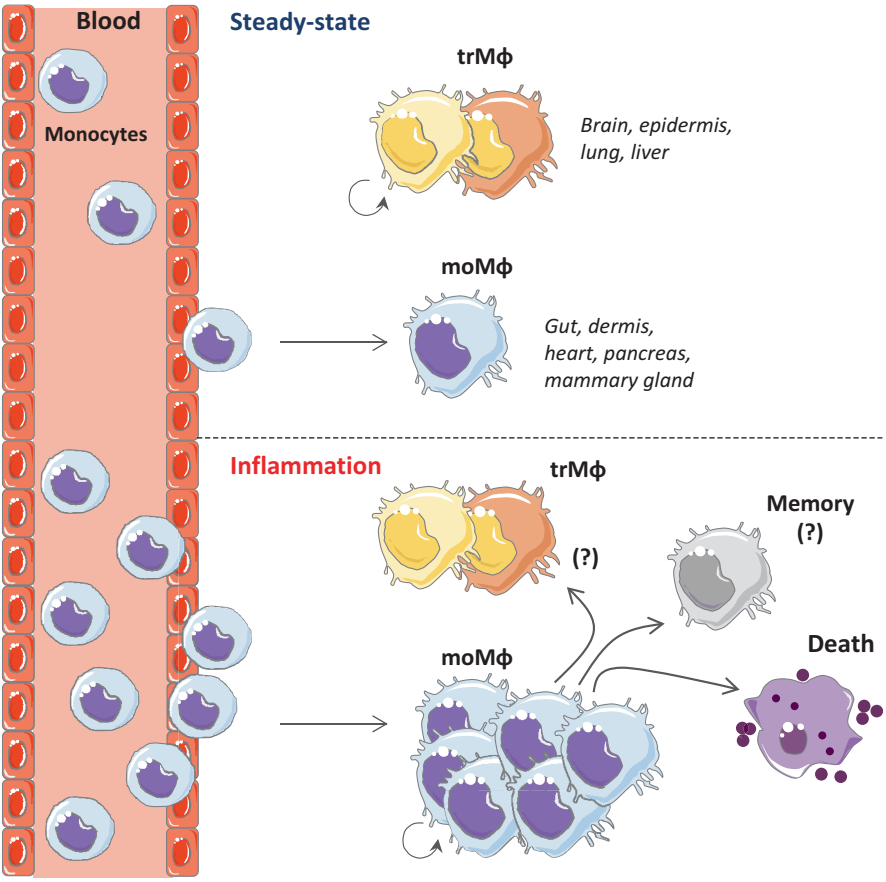

Fig. 2.2 Fate of monocyte-derived macrophages (moMϕ) in steady state and inflammation. In the steady state, tissue-resident macrophages (trMϕ) derived from embryonic progenitors populate various tissues (i.e., the brain, epidermis, lung, liver) and maintain their mass by self-renewing proliferation. In the tissues with high rate of cell turnover (i.e., the gut, dermis, heart, pancreas, mammary glands), trMϕ can originate from bone marrow (BM)-derived circulating monocytes. During inflammation, a large number of BM-derived circulating monocytes enter all tissues where they differentiate into macrophage-like cells (moMϕ), which might proliferate. The main fates of moMϕ are highlighted: (1) they die during the effector phase of the inflammatory reaction, (2) they become part of the trMϕ, and (3) they preserve the "memory" of the inflammatory challenge

pancreas, and splenic red pulp (Hashimoto et al. 2013; Chorro et al. 2009; Calderon et al. 2015). On the other hand, a crucial role for adult monocytes in replenishing the resident macrophage pool has been identified in the gut (Bain et al. 2014), dermis (Jenkins et al. 2011), heart (Epelman et al. 2014a, b; Molawi et al. 2014), and recently in the peritoneum (Bain et al. 2016).

During inflammatory conditions (upon infection, damage, or pathology), a large influx of BM-derived monocytes occurs, which differentiate into macrophage-like cells (moMϕ), and this differentiation occurs in parallel with the expansion of trMϕ

within the tissue. The fate of these moMϕ is not known. For instance, it is not clear if they mostly die (as it has been postulated) or if some of them survive becoming memory macrophages (Italiani and Boraschi 2014) (see Fig. 2.2).

Currently, the most relevant question is whether moMϕ are able to do self-maintenance in the tissue, i.e., the extent by which they survive and populate the inflamed tissue after recruitment, thereby contributing to replenishing trMϕ after the resolution of inflammation. Recent studies revealed that BM-derived monocytes display limited expression of proliferation genes as compared to FL monocytes and YS macrophages (Hoeffel et al. 2015; van de Laar et al. 2016) and often fail to stably persist in a tissue once inflammation resolves (Ajami et al. 2007; Hashimoto et al. 2013). Thus, they can be considered as "passenger myeloid cells" with respect to "resident counterparts of embryonic origin" (Gomez Perdiguero and Geissmann 2016). However, new evidence, obtained by using neonatal Csf2rb$^{-/-}$ mice with empty alveolar macrophage niche and a model of diphtheria toxin-mediated depletion of liver-resident Kupffer cells, demonstrates that the BM origin per se does not preclude the development of self-maintaining trMϕ (van de Laar et al. 2016, Scott et al. 2016).

Conversely, in the lung and brain, BM-derived monocytes do not seem to substantially contribute to the resident macrophage population after the resolution of infection or injury (Hashimoto et al. 2013; Ajami et al. 2011). In the epidermis, a small subset of moMϕ has been observed that may be remnant of monocytes recruited upon tissue damage (Sere et al. 2012), despite LCs also demonstrate a local proliferation (Chorro et al. 2009). In the liver, the nature of the damage determines the contribution of moMϕ to the pool of Kupffer cell. Upon bacterial infection, moMϕ repopulate trMϕ (Blériot et al. 2015), whereas upon paracetamol-induced injury, Kupffer cells proliferate and expand in the liver (Zigmond et al. 2014). Upon viral infection, Kupffer cells have a beneficial antiviral effect in the early phase after infection but seem to suppress the antiviral immunity during chronic infection. Moreover, it is difficult to distinguish the contribution of Kupffer cells versus infiltrating monocytes/macrophages because of the lack of distinctive phenotypical markers (Ju and Tacke 2016). Likewise, local proliferation of the resident macrophage population has been observed in atopic dermatitis (Chorro et al. 2009), while a contribution from moMϕ has been observed in ultraviolet irradiation-induced skin damage (Ginhoux et al. 2006). It has been observed that not only trMϕ but also BM-derived moMϕ proliferate in the zymosan-induced inflammatory reaction in the mouse peritoneal cavity (Davies et al. 2013). This proliferation depends on CSF-1 but is independent of IL-4, suggesting that the in vivo proliferation of trMϕ mediated by IL-4 upon nematode infection (Jenkins et al. 2011; Jenkins et al. 2013) may be restricted to type 2 inflammatory reactions. Recently, multiple fate-mapping approaches demonstrated that arterial macrophages arise from CX3CR1^{+} embryonic precursors and postnatally from BM-derived monocytes. Arterial macrophages are maintained by self-renewal and local proliferation, without a substantial contribution from blood monocytes in adulthood and after severe depletion during polymicrobial sepsis (Ensan et al. 2016). On the other hand, moMϕ are able to proliferate during pancreatic injury

(Van Gassen et al. 2015) and during hemolysis and erythrocyte damage in the red pulp spleen (Haldar et al. 2014). Monocytes contribute to the resident macrophage population also during inflammation due to pathological conditions such as atherosclerosis (Tacke et al. 2007) (where an important local proliferation of trMϕ is also observed - Robbins et al. 2013), cardiac inflammation (Epelman et al. 2014b), or aged heart (Molawi et al. 2014), in spinal cord injury (Shechter et al. 2009) but not in brain injury and neurodegeneration (Ajami et al. 2007).

2.4.2 Are moMϕ and trMϕ Phenotypically Distinguishable?

Upon inflammation, monocytes may infiltrate the tissue and differentiate into macrophages (moMϕ). This raises the crucial questions how to distinguish them from trMϕ, how much they are similar or differ in terms of gene expression/phenotype and in terms of their function in the inflammatory reaction, and the role of the environment in modulating their functional programming. These aspects are still not fully established. Using a genotoxic irradiation model, in which embryonic (host)- and postnatal (donor)-derived macrophages coexist in the tissue, and comparing the transcriptome between embryonic macrophages and BM moMϕ, more than 90% identity of gene expression has been observed in the lung, peritoneal cavity, and liver (Lavin et al. 2014; Scott et al. 2016; Gibbings et al. 2015; Beattie et al. 2016), although a few phenotypic markers (such as MARCO or Tim4) have been identified that could be used to phenotypically separate the two types of macrophages (Gibbings et al. 2015; Beattie et al. 2016). These findings highlight that the environment largely dictates the transcriptional programming of macrophages. However, by using the same model of macrophages depletion coupled with genotoxic irradiation, it was shown that the monocyte-derived microglia possess more than 2000 genes differentially expressed as compared to embryonic microglia (Bruttger et al. 2015).

2.4.3 Are moMϕ and trMϕ Functionally Interchangeable?

We will briefly review the functional contribution of trMϕ versus moMϕ during local inflammatory events, with a focus in the brain, gut, lung, and liver (Table 2.1). For the role of resident versus incoming macrophages in heart diseases (including stoke/ischemic damage) and chronic inflammatory conditions such as rheumatoid arthritis and cancer, we refer the reader to recent excellent reviews (Udalova et al. 2016; Lahmar et al. 2016; Mirò-Mur et al. 2016).

Recent fate-mapping studies have established that microglia are of embryonic origin (Ginhoux et al. 2010), persist in the brain during adulthood and in the healthy organism, and are maintained independently on BM-derived monocytes by a limited self-renewal capacity (Ginhoux et al. 2013). However, moMϕ are

Table 2.1 The main functions of trMϕ versus moMϕ in some tissues of the body

	trMϕ	moMϕ
Brain	• Monocyte recruitment • Inflammation	• Inflammation
Gut	• Maintenance of tolerogenic microenvironment	• Inflammation • Macrophage replenishment
Lung	• Immune-suppression	• Inflammation • Macrophage replenishment
Liver	• Maintenance of tolerogenic microenvironment • Protection against infections	• Inflammation • Fibrosis

massively recruited in the brain during an inflammatory event, although they do not contribute to replenishing microglia once homeostasis is restored (Ajami et al. 2011). Recently, the advantages and disadvantages of the various microglial ablation models and the origin of the "new" repopulating microglia have been discussed and reviewed (Waisman et al. 2015). At present, it is difficult to discriminate resident microglia from infiltrating myeloid cells using currently known markers and current tools (Greter et al. 2015). However, it is evident that both microglia and moMϕ play an important role in brain pathologies, as observed in experimental autoimmune encephalomyelitis (EAE), the mouse model of multiple sclerosis (Shemer and Jung 2015; Wlodarczyk et al. 2015). While infiltrating monocytes are harmful and critical in the effector phase of the disease, are highly phagocytic and inflammatory, are associated with nodes of Ranvier, and initiate demyelination, on the other side microglia remain rather inert during the early stage of EAE development, demonstrating globally suppressed cellular metabolism, but it is able to clear debris and its activation precedes the massive monocyte infiltration (Yamasaki et al. 2014). Indeed, microglia secrete numerous chemokines believed to play a role in EAE induction as responsible of the massive monocyte recruitment (Jiang et al. 2014). Therefore, an inhibition of microglia could slow down disease progression (Shemer and Jung 2015).

In the intestine, the situation is opposite, as this tissue is practically devoid of embryonic macrophages. The gut contains the largest pool of functionally specialized macrophages in the body (Gordon et al. 2014), which are essential for the tight crosstalk with microbiota, ensuring a symbiotic relationship and tolerogenic environment. Continual exposure to environmental challenge warrants constant replenishment by blood monocytes. Experiments with fate-mapping and parabiotic mouse models have demonstrated that embryonic precursors populate the intestinal mucosa during neonatal period, but they do not persist in the intestine of adult mice, and they are constantly replaced by circulating monocytes ($Ly6C^{high}$ in mice and $CD14^{++}$ in humans), which differentiate in situ into mature anti-inflammatory macrophages (Bain et al. 2014), favoring the constant need for epithelial renewal (and tissue remodeling). For this reason, in the gut, the distinction is not between trMϕ and moMϕ but rather between moMϕ (which are the resident tissue macrophages) and newly recruited monocytes. Under steady-state conditions, monocytes recruited from the blood differentiate locally into anti-inflammatory moMϕ. They

are positioned immediately beneath the epithelial barrier, where they contribute to its integrity. These macrophages are able to survey the tissue sensing and sampling the luminal content by extending processes between epithelial cells, and they produce IL-10 that facilitates the expansion of regulatory T cells. In the mouse, Ly6C^{high} monocytes are recruited during inflammation and mount an inflammatory reaction, while the resident moMϕ retain their anti-inflammatory signature. All these events are described in detail elsewhere (Gordon et al. 2014).

The role of macrophages is also essential in the lung, constantly exposed to airborne irritants and microbes. About 90% of the pulmonary macrophage population is represented by alveolar macrophages, located in the alveolar spaces. Alveolar macrophages originate from fetal liver monocytes (Thomas et al. 1976), and in steady state, they are sustained by self-renewal through local proliferation (Tarling et al. 1987). In inflammatory conditions, the repopulation of alveolar macrophages is context specific. In fact, it has been observed that during lethal irradiation, they are replenished by BM monocytes (Duan et al. 2012), while upon inoculation with influenza virus, they are replenished by self-renewal proliferation (Hashimoto et al. 2013) and, upon LPS stimulation, by both incoming monocytes and self-renewal (Upham et al. 1995). Alveolar macrophages seem to have an immunosuppressive function, as they can suppress antigen-induced cell proliferation (Holt et al. 1993) and downregulate antigen presentation by lung DCs (Careau and Bissonnette 2004). Also, alveolar macrophages seem to be protective against airway hyperresponsiveness (Guilliams et al. 2013), and, although exhibiting microbicidal and tumoricidal activities, they are less responsive than macrophages resident in other lung compartments (Hoidal et al. 1981). In the case of inflammatory diseases, such as COPD, monocytes are recruited in the lung, but their contribution to the alveolar macrophage pool remains to be determined (Vlahos and Bozinovski 2014). Using hyperreactivity mouse models with house dust mite and OVA, it has been demonstrated that alveolar macrophages dampen, whereas circulating monocytes promote, early events in allergic lung inflammation (Zaslona et al. 2014).

The liver trMϕ, Kupffer cells, represent the hematopoietic cell population among non-parenchymal cells within the liver. They arise from YS during fetal development (Schulz et al. 2012) and self-renew their population number at steady state throughout adult life with minimal contribution of blood monocytes (Hashimoto et al. 2013). Kupffer cells mainly support the tolerogenic milieu within the liver (Thomson and Knolle 2010), but their presence ensures the protection of the liver during infections (Lee et al. 2010). Recently, it has been observed that Kupffer cell death is a key signal orchestrating type 1 microbicidal inflammation and type 2-mediated liver repair upon infection (Blériot et al. 2015). Indeed, infection by *Listeria monocytogenes* induces the early necroptotic death of Kupffer cells, which is followed by monocyte recruitment and an antibacterial type 1 inflammatory response. Kupffer cell death also triggers a type 2 response that involves the hepatocyte-derived alarmin IL-33 and IL-4. This leads to the alternative activation of the moMϕ recruited to the liver, which replace ablated Kupffer cells and restore liver homeostasis (Blériot et al. 2015). Both Kupffer cells and moMϕ are involved in liver fibrosis, a common endpoint of many chronic liver diseases such as viral

hepatitis, primary biliary cirrhosis, alcoholic and NASH, or autoimmune liver disorder (Eckert et al. 2015). Generally, Kupffer cells are involved in the initiation and moMϕ in the progression phase of the fibrosis through the production of inflammatory cytokines. During disease progression, Ly6C^{hi} cells seem to develop into Ly6C^{lo} restorative macrophages, able to express MMPs and phagocytosis-related genes. These cells, if the harmful agent is eliminated, lead to resolution and can restore normal tissue architecture (Eckert et al. 2015). Otherwise, with the persistence of the initiating agent, they are responsible of anomalous repairing activity, thereby inducing fibrosis.

2.5 Conclusions

The current knowledge on the origin and role of trMϕ suggests that these cells, either coming from YS/FL precursors before birth or from blood monocytes in adulthood, have a central role in defining and maintaining tissue architecture, function, and homeostasis. The specific role of these cells obviously changes from tissue to tissue, as it is shaped (by the tissue microenvironment) to support the specific tissue requirements. It appears that the origin of these cells makes little difference in the eventual role they have within a tissue, as this is dictated by the tissue itself. Likewise, it is in most cases difficult to distinguish phenotypically, within the trMϕ, between moMϕ and YS-derived cells.

In inflammatory/disease conditions, tissue macrophages mostly act as alarmins, which do not directly exert a potent reaction against the dangerous event but that recall the specialized effector cells, the monocytes, from the blood to the affected tissue. The fate of these inflammatory monocytes, once entering the tissue to eliminate the danger, is not clear. While most of them probably die during the inflammatory reaction, it is possible that some of them survive and persist in the tissue, taking part to the phase of resolution of inflammation and tissue reconstruction/remodeling. Alternatively, or in parallel, it is possible that moMϕ, which enter the inflamed tissue from blood in successive waves, may become highly inflammatory effector cells in the initial phases of inflammation, and "healing" cells in the final phases, being differently polarized by the different tissue microenvironmental conditions. Eventually, it is possible that some of these moMϕ become part of the tissue-resident macrophage pool and develop the capacity of self-renewal. If these macrophages, should they really exist, preserve the "memory" of the past experience, or how this memory influences their response to subsequent dangerous events, i.e., how memory can influence macrophage polarization, is one of the most exciting questions in macrophage biology.

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