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Macrophages in health and disease

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SUMMARY

The heterogeneity of tissue macrophages, in health and in disease, has become increasingly transparent over the last decade. But with the plethora of data comes a natural need for organization and the design of a conceptual framework for how we can better understand the origins and functions of different macrophages. We propose that the ontogeny of a macrophage—beyond its fundamental derivation as either embryonically or bone marrow-derived, but rather inclusive of the course of its differentiation, amidst steady-state cues, disease-associated signals, and time—constitutes a critical piece of information about its contribution to homeostasis or the progression of disease.

INTRODUCTION

Since their early description as mononuclear phagocytes in both invertebrate and vertebrate species, macrophages have become increasingly important for our understanding of human health and disease. Their fundamental attributes enable them to “clean” their surroundings by phagocytosing cellular material and regulating tissue repair and

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maintenance. Macrophages are, therefore, key tissue sentinel cells that are present across various organs throughout the body (Wynn et al., 2013). And quite remarkably, these tissue-resident macrophages (RTMs) are involved in various complex processes, including neuro-, angio-, and osteo-genesis, and even erythropoiesis, indicative of their unique ability to adapt and contribute to their place of residence. This is largely reflective of macrophages' plasticity that allows them to react to tissue-specific signals, while retaining the ability to execute core functions as tissue phagocytes (Lavin and Merad, 2013; Lavin et al., 2014; Gosselin et al., 2014; Amit et al., 2016; Cohen et al., 2018).

However, during disease, monocytes are recruited to inflamed tissues and differentiate into monocyte-derived macrophages (mo-macs) that, as we review below, are functionally and phenotypically distinct from RTMs. With developments in single-cell transcriptomics, we are able to appreciate—now, more than ever before—the diverse molecular programs used by mo-macs that underscore the cellular heterogeneity and pleiotropic functions of these phagocytes during development, health, and disease. The differences across these macrophage subsets and states highlights the significance of ontogeny (i.e., develop mental origin), and given that a number of parameters likely influence when and where ontogeny matters—such as the availability of certain cytokines, the balance of homeostatic cues and disease-associated signals, as well as biological time—much can be understood about the acquisition and application of the transcriptional programs that distinguish mo-macs from RTMs. Indeed, more work remains to be done to uncover the order in which these programs are acquired and how their induction further diversifies the split in differentiation trajectory of monocytes into RTMs at the steady state or mo-macs during disease. Still, the present review aims to highlight the compilation of studies thus far that have been done on this front. Toward that end, we begin with a summary of the unique, core functionalities of RTMs in different tissues, though we acknowledge that numerous reviews have already outlined—at far greater length and quite recently, too—the various species of RTMs and their tissue-specific activities (Lavin et al., 2015; DeNardo and Ruffell, 2019; Guilliams et al., 2020; Bleriot et al., 2021; Nobs and Kopf, 2021; Cox et al., 2021; Guilliams and Svedberg, 2021; Delfini et al., 2022; Guilliams and Scott, 2022; Zaman and Epelman, 2022; Aegerter et al., 2022). Then, in the latter sections of this review, we illustrate how they differ from the functional contributions of mo-macs to disease progression.

Tissue-resident macrophages are gatekeepers of homeostasis

Nearly all tissues are populated by self-maintaining pools of RTMs. Across different organs, long-lived RTMs execute a list of core responsibilities that serve to help facilitate homeostatic organ functions. Specifically, we highlight as examples the ability for RTMs to clear damaged cells or foreign bodies, to protect neuronal synapses and to prune undesired neuronal connections, to preserve the vasculature, and to form the first line of defense against invading pathogens (Figure 1).

Clearance of cell-associated materials and foreign bodies—Equipped with long dendrites or pseudopods and extensive endolysosomal machinery, RTMs function as sessile and observant tissue surveyors, both sensing and eliminating damaged or dying stromal or epithelial cells, with the help of an armory of phagocytic receptors. To handle the metabolic

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strain of ingesting so much, RTMs leverage sub-cellular mechanisms that are tailored to manage high-lipid content cargo without overreacting to potentially pro-inflammatory signals (e.g., downregulating Toll-like receptors) (Roberts et al., 2017). RTMs are also able to do this by modulating the extra-cellular environment, too. *In situ*-imaging of the peritoneal serosa showed that peritoneal RTMs, as part of their canonical roles in clearing damage-associated tissue lesions, expand their pseudopodia to physically enclose or "cloak" the pro-inflammatory debris and sequester them away from circulating neutrophils that might otherwise react to them and elicit unnecessary harmful inflammation (Uderhardt et al., 2019).

In the lungs, alveolar macrophages recycle excess surfactant and clear eosinophilic material from the alveolar air space (Wright, 1990; Wright and Youmans, 1995; Poelma et al., 2004; Whitsett et al., 2010). Mutations that result in the failed clearance of these substances were categorically associated with defects in surfactant homeostasis, several of which involved genes important for alveolar macrophage development (Whitsett et al., 2010). For instance, mice deficient in lipoprotein lipase or with loss-of-function mutations in granulocyte-macrophage colony-stimulating factor (GM-CSF, encoded by *Csf2*) or its receptor (GM-CSFR) harbor dysfunctional alveolar macrophages and, as a result, develop severe pulmonary alveolar proteinosis (PAP) (Greenhill and Kotton., 2009; Todd et al., 2016). Analogously, patients with GM-CSF deficits, either due to a mutation (Suzuki et al., 2008) or autoantibodies against GM-CSF (Dranoff et al., 1994; Stanley et al., 1994; Kitamura et al., 1999; Uchida et al., 2003), are also deprived of alveolar macrophages and exhibit PAP. Supplementing these patients with inhaled GM-CSF helped recover alveolar macrophages by restoring overall GM-CSF levels, prototypically provided by type II alveolar pneumocytes that form the alveolar macrophage niche (Reed et al., 1999; Wylam, 2006; Tazawa et al., 2006, 2009; Papiris et al., 2020; Gschwend et al., 2021).

Osteoclasts residing within the endosteal niche of bone also perform a similar function, as they are critical for bone resorption (i.e., dissolving excess bone) (Martin et al., 2005). These endosteal macrophages attach to sites of critical bone mass via vitronectin and other integrins and release acid phosphatases and lysosomal proteases, within a self-made acidic seal that helps break down the hydrated proteins and calcium of the bone. Osteoclasts proceed to phagocytose that debris to clear the degraded bone matrix (Lévesque et al., 2010). Mutations in the gene encoding the vacuolar ATPase that helps generate the acidic proton gradient result in osteoclast dysfunction, resulting in abnormally high bone density, a condition known as osteopetrosis (Scimeca et al., 2000; Blin-Wakkach et al., 2006). This phenotype was also observed in *Csf1* and *Csf1r* knockout mice (Marks and Lane, 1976; Wiktor-Jedrzejczak et al., 1990), as macrophage colony stimulating factor (M-CSF/CSF-1, encoded by *Csf1*) is critical for macrophage differentiation and survival. A similar phenotype was observed for patients with autosomal recessive mutations in the gene *RANKL*, indicating a central role for endosteal niche factors in the development and phagocytic functionality of resident osteoclasts (Cleiren et al., 2001; Sobacchi et al., 2007).

A third classic example of this core macrophage function is the role that different RTMs play while clearing cellular nuclei and debris during the development and subsequent clearance of other immune cells. This is seen in the hippocampus, in the kidney, and

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most frequently in the bone marrow, liver, and spleen, where bone marrow and splenic macrophages and Kupffer cells (KC) oversee the start and finish of the erythropoietic cycle, respectively (Bessis and Breton-Gorius, 1959; Sierra et al., 2010; Munro et al., 2019). Resident macrophages of the bone marrow were found to associate with the progeny of proerythro-blasts during the early stages of erythropoiesis; termed erythroblastic islands, the ejected nuclei of maturing erythrocytes were phagocytosed by these bone marrow macrophages, allowing mature reticulocytes to then enter the circulatory system (Yoffey and Yaffe, 1980; Qui et al., 1995). Later in the life cycle of erythrocytes, KC in the liver have been shown to phagocytose both dying erythrocytes and hemoglobin-containing vesicles released by aging erythrocytes (Schroit et al., 1985; Loegering et al., 1987; Willekens et al., 2005; Theurl et al., 2016). In tandem, red pulp splenic macrophages, which reside in a niche comprised of M-CSF and Wilms' tumor-1 (WT1)-expressing reticular fibroblasts (Bellomo et al., 2020), also phagocytose senescent or damaged erythrocytes and recycle the accompanying iron (Kohyama et al., 2009; Haldar et al., 2014).

Safeguarding the neuronal net—Early studies have shown that macrophages interact with neurons in the central and peripheral nervous systems (CNS and PNS). But it is only within the past decade that we have recognized the dynamic crosstalk between these cell types that is essential for the health of the nervous system at-large (Prinz and Priller, 2014; Colonna and Butovsky, 2017). In the CNS, microglia constitute the major type of RTMs; work from our groups and others helped show that microglia arise from primitive macrophages in the yolk sac that invade the brain parenchyma and persist from early development through adulthood (Ginhoux et al., 2010; Ajami et al., 2011; Kierdorf et al., 2013; Hoeffel et al., 2015). Studies dating back as early as the 1980s used silver carbonate staining to show that microglia are important for phagocytosing dying neurons (Morgese et al., 1983; Nimmerjahn et al., 2005). Recent work indicates that microglia play more extensive roles in managing neuronal health. For instance, microglia join the neurovascular unit (NVU) to modulate blood flow and nutrient supply to neurons and other glial cells (Arnold and Betsholtz, 2013; Jolivel et al., 2015; Lou et al., 2016; Stankovic et al., 2016; Zarb et al., 2021; Delaney et al., 2021; Császar et al., 2022). Importantly, the presence and functionality of these brain RTMs from early stages of brain development have been linked to synaptic plasticity, learning, and memory (Thion et al., 2018), while in the periphery, recovery of compromised nerves has been shown to be dependent on the presence of nerve-associated macrophages, specifically those in the epineurium (epineurial macrophages) and endoneurium (endoneurial macrophages) (Mueller et al., 2001; Müller et al., 2008, 2010; Kolter et al., 2020). Orthogonal lineage-tracing experiments using *Cx3cr1*$^{\text{CreERT2}}$:*Rosa26*-YFP and *Cxcr4*$^{\text{CreERT2}}$:*Rosa26*-tdTomato mice showed that nerve-associated macrophages are indeed derived from embryonic precursors (De Schepper et al., 2018; Ydens et al., 2020).

Additional work has shown that this relationship is not strictly unidirectional; in fact, both CNS and PNS neurons promote macrophage survival by producing growth factors like M-CSF or IL-34, a cytokine that shares the same receptor with M-CSF (Greter et al., 2012; Wang et al., 2012; Muller et al., 2014; Kana et al., 2019). In response to neurotoxic insults, macrophages protect their neuronal allies, too; muscularis macrophages

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that associate with enteric neurons limit neuronal death during intestinal infections by responding to β_2-adrenergic signals and engaging an arginase-1/polyamine axis (Matheis et al., 2020; Ahrends et al., 2021), highlighting that this two-way street is indeed a fundamental symbiosis for the maintenance of the PNS.

Preservation of vascular integrity—Experiments with mice that lack M-CSF also showed that angiogenesis and lymphangiogenesis are impaired, indicating a central role for macrophage in a functioning vasculature (Kubota et al., 2009). Seminal lineage-tracing studies subsequently showed that these perivascular and cardiac macrophages are RTMs that locally self-renew and collaborate to help preserve cardiac function and vascular tone in peripheral tissues (Epelman et al., 2014; Lavine et al., 2014; Lapenna et al., 2018; Chakarov et al., 2019). During the postnatal phases of development, for example, cardiac RTM not only stimulate angiogenesis and proliferation of cardiomyocytes, but they also sustain the electrical conductivity and metabolic health of the heart by eliminating cardiac-derived exophers of junk mitochondria via the phagocytic receptor MerTK (Hulsmans et al., 2017; Nicolás-Ávila et al., 2020). In the periphery, perivascular macrophages (PVMs) chaperone anastomoses downstream of induced tip cells (Fantin et al., 2010; Cattin et al., 2015; Graney et al., 2020; Vagesjö et al., 2021), regulate permeability (Hickey and Kimura, 1988; Zhang et al., 2012; He et al., 2016), phagocytose blood-borne materials, and contribute to the proteome of the tissues that the vessels supply (Serrats et al., 2010; Pinto et al., 2012). Upon CSF-1R blockade, mice exhibit significant edema (i.e., enhanced fluid retention in tissues), associated with an increase in matrix metal-loproteinases, changes to the integrin-mediated adhesion strength of vessels, and enhanced deposits of hyaluronan and proteoglycan (Evans et al., 2019; Bissinger et al., 2021), emphasizing further the role of PVMs in the preservation of vascular function.

Mounting the first line of defense against pathogens—Lastly, but also perhaps most importantly, RTMs of various tissues act as the first line of defense against pathogens, representing the most effective and frequently leveraged form of cellular innate immunity. Along the skin and internal mucosal surfaces, this function is essential, as they are the most vulnerable to breach by microbes. The lungs, for instance, are patrolled by alveolar macrophages that migrate along the air-liquid-air interface to capture and contain bacteria or virally infected cells (Neupane et al., 2020). This ability is dependent on the availability of pro-differentiation factors, such as GM-CSF and its activation of the transcription factor PU.1. When deprived of this signal, mice with impaired or absent alveolar macrophages fail to eliminate *Streptococcus pneumoniae* during active pneumonia (LeVine et al., 1999; Deady et al., 2014), *Mycobacterium tuberculosis* (Gonzalez-Juarrero et al., 2005), *Pseudomonas* (Ballinger et al., 2006), *Pneumocystis* (Paine et al., 2000), and other viral agents. Salvaging alveolar macrophages with exogenous GM-CSF, however, enabled mice to respond appropriately to subsequent secondary challenges. For instance, following recovery from a non-fatal influenza infection, mice given supplemental GM-CSF were better able to clear secondary *S. pneumoniae* infections than control mice, indicating specific protection conferred by promoting differentiation of lung-infiltrating monocytes into alveolar macrophages during the recovery phase (Umstead et al., 2020). Ultimately, the timely function of RTMs serves to avert pathogenic, systemic inflammation, without

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completely compromising the innate immune response to infections. As discussed above, one method that RTMs employ is physically concealing the local sites of inflammatory response and preventing them from injudiciously recruiting an armada of inflammatory monocytes and neutrophils (Uderhardt et al., 2019). In doing so, RTMs deter what might result in unnecessary tissue destruction.

That is not to say that RTMs themselves are shielded from the inflammation caused by infections. Acute inflammation can result in the death and destruction of RTMs in a variety of scenarios; for example, alveolar macrophages may either succumb to direct infection and become necrotic or undergo an epithelioid transition as part of the granulomatous response to advanced tuberculosis (Cooper et al., 2009; Pagán et al., 2022; Cronan et al., 2016, 2021). In the liver, KC also undergo regulated necrosis during *Listeria* infection to elicit a microbicidal inflammatory response (Bleriot et al., 2015; Ginhoux et al., 2017). These instances of RTM death can prompt the recruitment of monocytes to fill RTM niches; and if the quality of RTM niches is still preserved (i.e., homeostatic cues remain available and the cellular sources of these cues are still present and not too damaged), the supply of new RTMs will help control the infection and appropriately engage tissue repair pathways. Below, we elaborate further why we suspect monocyte-derived RTMs are needed to preserve tissues at the steady state, in addition to effectively redirecting inflamed tissues toward resolution.

Monocyte-derived RTMs reinforce embryonically derived phagocytes in protecting tissue homeostasis

Some organs, such as the brain, will generally function with just the native pool of embryonically derived RTMs throughout a lifetime, granted that no major perturbations force RTM loss. In other tissues such as the heart, pancreas, or gut, though, genetic fate-mapping models have shown that some RTMs may also originate from circulating monocytes in response to specific cues in certain tissues, and often the proportion of monocyte-derived RTMs increases with time (Figure 2) (Bain et al., 2013, 2014). For instance, at the steady state, turnover of tissue cells associated with “natural” perturbations that do not necessarily elicit pathognomonic inflammation (e.g., aging, shifts in the microbiome) necessitates certain RTMs to be maintained by the circulating monocytes that extravasate from the vasculature (Cummings et al., 2016)). Such need for peripheral input may be driven by the inability for embryonic RTMs to keep up with the tissues’ demand for phagocytes (Barker et al., 2010), due to either a limited self-renewal capacity, their inability to access and colonize newly forming niches, or an excessive rate of tissue cell turnover. The latter is less probable, as the epidermis and lungs experience a higher rate of epithelial cell turnover than do the pancreas or heart, yet embryonically derived RTMs dominate these tissues. Therefore, other parameters likely dictate this balance between demand and supply. For example, monocyte differentiation into RTMs likely require prolonged periods of cellular interactions with the tissue microenvironment (Scott et al., 2016; Chakarov et al., 2019; Bleriot et al., 2020), so monocyte differentiation may heavily depend on biological time and the continued maintenance of niche integrity (Liu et al., 2019).

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In the brain, for instance, a number of soluble factors preserve microglial identity. These include M-CSF and IL-34 from neurons or glial cells (Greter et al., 2012; Wang et al., 2012; Kana et al., 2019), and resident microglia continue to rely on these maintenance cues to perform (e.g., rapidly accumulate around sources of foreign or damaging materials via clonal microgliosis) (Ladeby et al., 2005; Ajami et al., 2007). Another molecule, IL-3 and IL-33 from astrocytes, promotes microglial motility and encourages microglial clustering in healthy mice and around plaques in diseased mice (Vainchtein et al., 2018; McAlpine et al., 2021). Accordingly, deletion of astrocyte-derived IL-3 or microglial IL-3 receptor exacerbates plaque disease, whereas exogenous IL-3 infusion alleviates plaque burden and improves cognitive function (McAlpine et al., 2021). The decline of these signals and the accumulation of insoluble debris results in microglial dysfunction. The autophagy protein Beclin-1, for instance, regulates phagocytosis, and its expression in microglia is reduced in Alzheimer's disease (AD), thus impairing phagocytosis of cellular debris by these cells (Lucin et al., 2013). Excessive myelin degradation overwhelms dysfunctional microglia and leads to the formation of insoluble, lipofuscin-like lysosomal bodies that further hinder their homeostatic activity (Safaiyan et al., 2016). With time, the functional exhaustion and the subsequent attrition of microglia is compensated for by a repopulation of the niche by microglial-like cells. Over the years, different studies have sought to probe the ontogeny of these cells but have yielded mixed reports. Chemical depletion of microglia using a diphtheria toxin model indicated a replenishment of the microglial niche by infiltrating monocytes (Lund et al., 2018). In contrast, fate-mapping in CCR2 and CX3CR1 reporter mice crossed to an AD model of plaque formation indicated a near exclusive repopulation of the microglial pool by resident phagocytes (Reed-Geaghan et al., 2020). But after accounting for the presence of RTMs in the different brain border regions (Masuda et al., 2022), more advanced fate-mapping models collectively point to the more modern consensus that niche-reconstituting cells in the brain are, in fact, likely comprised of both a subset of locally proliferating microglia and monocyte-derived RTMs (Bruttger et al., 2015; Askew et al., 2017) that remain transcriptionally, epigenetically, and functionally distinct from one another (Shemer et al., 2018, Silvin et al., 2022).

In the lungs, nerve-associated ($CX3CR1^{+}MHCII^{hi}$) and perivascular ($LYVE\text{-}1^{+}$) macrophages were found to be derived from embryonic progenitors but are slowly replaced by monocyte-derived cells in adults (Lim et al., 2018; Chakarov et al., 2019); these subsets of macrophages in these specific subtissular locations were identified in other tissues (Chakarov et al., 2019), suggesting that their global presence may reflect a safety feature associated with replenishing the local supply of tissue macrophages with monocyte-derived RTMs, as these cells reinforce the structural integrity and maintenance of the nervous innervation and vascularization of tissues that are so important for their health.

Macrophage ontogeny is more than just a one-time label of developmental origin

Given these insights into embryonic and monocyte-derived RTMs, we preface the following text on mo-macs with a commentary on issues of vernacular that we suspect may disrupt the community, especially because one could argue that the ontogeny of RTMs fails to matter functionally at the steady state (van de Laar et al., 2016). But, in fact, whether embryonic and monocyte-derived RTMs react to disease signals differently is not well known, and

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perhaps even more importantly, the ontogeny of tissue macrophages has only recently gained traction as an important metadatum and has received correspondingly little attention, particularly in disease contexts. Studies thus far, though, suggest that ontogeny does indeed matter (as we review below). Accordingly, characterization of the molecular programs used by these ontogenically distinct macrophages and how they contribute to disease pathogenesis lacks precision. So, these insights caution the potential shortcomings of underestimating our interpretation and use of macrophage ontogeny as it currently stands—strictly based on whether a macrophage, in general, is embryonically derived or bone marrow-derived—and instead emphasize the need to investigate the cues that influence monocyte-to-macrophage differentiation.

For macrophages, timely tissue cues are everything—Taking on this challenge requires a nuanced perspective on how embryonic and monocyte-derived RTMs can both feed tissue-residing reservoirs, while monocyte-derived cells recruited during disease fail to fully recapitulate the phenotypes of their RTM counterparts. Toward this end, we define homeostatic differentiation as the steady-state process of imprinting tissue-specific traits into either fetal precursors or adult monocytes that intend on becoming homeostatic RTMs. This contrasts with non-homeostatic differentiation during disease, whereby disease-associated signals drown out the homeostatic ones and skew the maturation of monocyte-derived cells toward dysregulated, often inflammatory, states. This paradigm is seemingly binary, in that both homeostatic and non-homeostatic differentiation are not likely to necessarily occur simultaneously within a single tissue, albeit our expanding understanding of the heterogeneity of distinctive topological areas within a given tissue section (e.g., cancerous tissue versus adjacent, non-involved tissue) would suggest that both types of differentiation could concurrently be permitted for recruited monocytes (Shaw et al., 2018). But by and large, what this may indicate is that timing is integral: the point at which homeostatic differentiation becomes improbable and signals that drive non-homeostatic differentiation begin to overwhelm macrophage niches may determine the degree to which specific disease-associated molecular programs are engaged by mo-macs and affect disease course.

Defining these threshold time points for each organ remains a major quest in macrophage biology. Kinetic profiling of monocyte and macrophage populations *in vivo* and characterizing them at the molecular level *in silico* are two potential approaches to the problem (Bleriot et al., 2020). For instance, liver-resident KC that survey the hepatic sinusoids at the steady state, if depleted, are replaced by monocytes that fill emptied KC niches and take on KC features (Scott et al., 2016). These monocyte-derived KC downregulate monocytic markers (e.g., Ly6C) and quickly acquire general macrophage markers (e.g., F4/80, CD64) within two days of KC depletion in a diphtheria toxin receptor model. Interestingly, though, KC markers like CLEC4F or TIMD4 were expressed weeks after engraftment, indicating that homeostatic differentiation may take more time than previously thought. Understanding how to preserve homeostatic tissue cues over this duration of time to ensure homeostatic differentiation, in the face of disease or inflammation-associated signals that might otherwise disrupt them, is a critical aim. Thus, our characterization of mo-macs in diseased tissues as “pathogenic drivers of disease” speaks to a timely need to expand our interpretation and use of cell ontogeny as more

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than just a notation of developmental origin or age or tissue type. This adjustment in our frame of reference will be essential for achieving our broader goal of identifying (1) disease-associated signals that fuel non-homeostatic differentiation and (2) the downstream cellular networks regulated by mo-macs to develop clinically relevant therapies.

Disease-associated signals recruit monocyte-derived cells into tissues

Canonical pro-inflammatory cytokines, such as IL-6 and IL-8, are secreted by stressed stromal cells (e.g., fibroblasts), epithelial cells, and activated immune cells. In tandem, other "red-light" signals, including canonical alarmin cytokines like IL-33, damage-associated and pathogen-associated molecular patterns (DAMPs and PAMPs) amplify the cascades that result in enhanced myelopoiesis and excess recruitment of inflammatory monocytes into tissues.

Alarmins, such as IL-33 and thymic stromal lymphopoietin (TSLP), are also released from the intracellular storage of damaged endothelial, epithelial, and fibroblastic cells, and in most instances, promote a reparative type II immune response (Liew et al., 2016; Cayrol and Girard, 2018; Andersson et al., 2018). Monocytes and mo-macs share the IL-33 receptor and respond to local alarmin signals. In the lungs, IL-33 has been shown to regulate the self-renewal of mo-macs that resemble resident alveolar macrophages during the resolutive phases of influenza infection (Dagher et al., 2020). In the spleen, in the context of erythrocyte damage, *Il33*$^{-/-}$ and *Il1rl1*$^{-/-}$ (IL-33 receptor-deficient) mice exhibit a profound decrease in both the abundance of red pulp macrophages and their erythrophagocytic potential, highlighting once more the importance of alarmin signals in the generation and function of mo-macs during disease (Lu et al., 2020).

While other DAMPs like hyaluronan and nucleic acids or PAMPs like LPS during bacterial infections contribute to the gradient of chemotactic agents that would also recruit and mold the monocyte-derived cells that infiltrate tissues (Zindel and Kubes, 2020), other non-conventional gradients may also act as trails for inflammatory blood monocytes to follow. Metabolites, for instance, can facilitate the recruitment of these cells. Early studies of atherosclerosis identified a role for oxidized cholesterol (oxysterol), not just ligands for CCR2, in the recruitment of inflammatory blood monocytes to plaque lesions and the subsequent pathogenesis of vascular disease (Staprans et al., 2000; Bensinger et al., 2008; Moore and Tabas, 2011; Calkin and Tontonoz, 2012; York and Bensinger, 2013). Similar mechanisms involving chemotactic oxysterols had also been described for dyslipidemia, neurodegenerative disease (Gamba et al., 2019; Varma et al., 2021; Griffiths et al., 2021) and cancer (Villablanca et al., 2010; Raccosta et al., 2013), all of which have also been shown to be associated with an accumulation of dysfunctional mo-macs, as we review more extensively below. At the steady state, oxysterols are present at low levels and typically modulate innate lymphoid cells and dendritic cells (DCs) in secondary and tertiary lymphoid structures via the G-protein coupled receptor (GPR183) (also known as Epstein Barr virus-induced GPCR, or EBI2) (Gatto et al., 2013; Emgård et al., 2018; Wyss et al., 2019). But in certain diseases, oxysterol levels have been shown to rise; in cancer, for instance, tumors themselves generate oxysterols. Then, oxysterol sensing subsequently recruits GPR183^{+} inflammatory blood monocyte-derived cells into damaged tissues. Typically, soluble DAMPs

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first induce oxysterol production by mo-macs via the enzyme cholesterol 25-hydroxylase (encoded by the gene *CH25H*) in both humans and in mice (Dang et al., 2017). This local release is also accompanied by a transient upregulation of GPR183, and the autocrine loop promotes the migratory capacity of these cells by mobilizing intracellular calcium (Hannedouche et al., 2011; Preuss et al., 2014; Rutkowska et al., 2016). It is also fed by oxysterol gradients generated by distal sites of damage, thus promoting trafficking of inflammatory blood monocyte-derived cells into injured tissues.

Decay of RTM niches and the occupation of damaged tissues by mo-macs drives disease progression

During severe, and often chronic disease, RTMs fail to meet the challenge presented by the successive, uncloaked inflammation that leads to tissue barrier activation and damage and likely their own death, as well. Likely, the sustained damage to tissues during disease results in a loss of tissue cells that are responsible for providing the steady-state cues that preserve RTM niches (Lavin et al., 2014; Okabe and Medzhitov, 2014; Amit et al., 2016). In combination with injury-associated signals, including alarmins and pro-inflammatory cytokines (Maus et al., 2006; Bosurgi et al., 2017; Minutti et al., 2017), recruited monocytes rapidly undergo non-homeostatic differentiation into mo-macs (Liu et al., 2019), with major transcriptomic changes upon exposure to the flux of disease-associated signals, oxidative species, and inflammatory byproducts (Desalegn and Pabst, 2019). Whether this event occurs in multiple waves, whether the lifespan of mo-macs changes during disease versus during resolution, and precisely when recruited mo-macs will go on to help repopulate RTMs during disease resolution are unclear. However, what is seemingly conserved across various tissues in multiple disease conditions is the observation that the broader collection of these mo-macs shapes disease (Figure 3), wherein the molecular programs that these cells engage mold the immune landscape of the local microenvironment.

We propose that this pattern of RTM depletion and repopulation by mo-macs is pathognomonic for disease and discuss this below. Understanding how these mo-macs modulate the inflammatory response to the drivers of disease will likely depend on our ability to (1) parse the transcriptomic programs that uniquely identify specific subsets of mo-macs (Figure 4) and to (2) uncouple the components that drive excessive inflammation from those that prematurely solicit an immunosuppressive wound healing or tissue-repair response. Although we assuredly fall short of reviewing all available studies, the intent of the following is to highlight recent bodies of work that provide robust evidence suggesting a unique role for mo-macs in disease onset or progression and contrasting them with their RTM counterparts that have failed to fulfill their duties in clearing tissue debris, surveilling the microenvironment, and curbing excess inflammation.

Respiratory disease—The recruitment of inflammatory blood monocyte-derived cells into diseased tissues and their differentiation into mo-macs that influence disease progression can be most easily exemplified from within the COVID-19 literature. Initial characterizations of myeloid cells in the peripheral blood and in bronchoalveolar lavage samples of COVID-19 patients showed a significant expansion of immature monocytes and neutrophilia, indicative of emergency myelopoiesis in the bone marrow (Schulte-Schrepping

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et al., 2020; Silvin et al., 2020; Wilk et al., 2020; Grant et al., 2021; Chen et al., 2022). Detailed analyses of these cell subtypes highlighted an inflammatory phenotype, marked by the elevated expression of calprotectin and other S100 family molecules, like S100A12, occupying the lungs of SARS-CoV-2-positive patients.

Subsequent studies that more closely dissected the composition of the macrophage subset within the immune landscape of SARS-CoV-2-infected lungs demonstrated that resident alveolar macrophages are severely depleted in patients with severe disease, even more so than those with mild to moderate disease. Instead, the lungs of patients with poorer clinical outcomes were heavily infiltrated by mo-macs that failed to recapitulate the antigen presentation capacity and homeostatic wound healing properties of their RTM predecessors (Chen et al., 2022). And strikingly, convalescent patients showed a rebound of alveolar macrophages and a decline of these putatively pathogenic mo-macs in the lungs (Chen et al., 2022). Accordingly, clinical efforts to rescue resident alveolar macrophages in patients with COVID-19 with inhaled GM-CSF yielded improvement in oxygenation, highlighting the therapeutic potential of salvaging lost RTMs to counterbalance the deleterious role of dysfunctional mo-macs during disease (Bosteels et al., 2021). Beyond COVID-19, it is likely that restoring the altered balance between RTMs and inflammatory mo-macs may help treat other critical lung illnesses, representing an important and unmet clinical need. For example, in chronic lung diseases such as pulmonary fibrosis, the same imbalance between alveolar macrophages and mo-macs is also evident (Watanabe et al., 2021). Additional transcriptomic profiling characterized major differences between alveolar macrophages and mo-macs over the course of fibrosis, such as the expression of profibrotic genes by mo-macs (Misharin et al., 2017).

Intestinal disease—Early genome-wide association studies demonstrated that the dysregulation of innate immunity in genetically prone individuals drives the development of inflammatory bowel disease (IBD) and related intestinal conditions, including ileal Crohn disease (CD) and ulcerative colitis (UC) (Jostins et al., 2012). A number of genomic loci have been identified as sites of risk variants, including *NOD2* (nucleotide-binding oligomerization domain protein 2), *SLAMF8* (SLAM family member 8), and *ATG16L1* (autophagy related 16-like protein 1). These and other IBD risk loci are strongly enriched for promoters that regulate mo-mac differentiation and have implicated these cells in the development of IBD in both pediatric and adult patients (de Lange et al., 2017; Huang et al., 2019).

The pool of resident intestinal macrophages constitutes the largest subset of myeloid cells in the intestinal tract. Recent efforts to profile myeloid cells in IBD patients suggest that dysregulation of the intestinal macrophage pool may underscore disease progression; CD patients, for example, have been found to harbor anti-GM-CSF autoantibodies that recognize post-translational glycosylation on GM-CSF, detectable even years before diagnosis (Mortha et al., 2022). Additionally, the mucosa of IBD patients are highly enriched with immature inflammatory monocytes that produce IL-23, TNF-α, IL-6, and OSM (West et al., 2017), supporting the potential pro-disease roles that recruited blood monocyte-derived cells play in IBD (Kamada et al., 2008; Ogino et al., 2013; Bernardo et al., 2018). This particular observation has been validated in multiple models of colonic inflammation (Duerr et al.,

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2006; Yen et al., 2006; Martin et al., 2019). But, most recently, single-cell profiling of immune cells in the inflamed and non-involved mucosa of CD patients revealed that depletion of circulating monocytes, which likely reflects their excessive recruitment at the injury site, alongside the enrichment for a cellular module, comprised of inflammatory mo-macs—transcriptionally distinct from their resident intestinal macrophage counterparts—associated with resistance to anti-TNF therapy (Martin et al., 2019). Expressing high levels of *CXCL2*, *CXCL3*, *CXCL8*, and *SOD2*, these mo-macs likely respond to pro-inflammatory IL-1 family cytokines, chemokines like *CCL2* and *CCL7*, and alarmins (Martin et al., 2019; Waddell et al., 2021; Friedrich et al., 2021). More in-depth functional studies will likely help uncover how these mo-macs, in fact, drive IBD pathogenesis, and how we can modulate their phenotype toward a resolutive, anti-inflammatory state, since depleting them entirely may compromise the proper replenishment of resident intestinal macrophages, too. Designing the appropriate strategies to test these cells functionally will heavily depend on our ability to parse the molecular programs that define mo-mac states, as we will want to preserve any potentially beneficial properties of these mo-macs, while suppressing their harmful effects.

Hepatic disease—In the human body, the liver is most heavily burdened with metabolism-related demands, and the tissue-resident pool of KC are crucial for fulfilling these demands. And like other RTMs, KC maintenance and functionality are dependent on their topological orientation in hepatic sinusoids and on the availability of homeostatic signals such as M-CSF. Interactions with neighboring stromal cells, such as endothelial cells and fibroblasts, also contribute to KC maintenance (Bonnardel et al., 2019; Guilliams et al., 2022), but the accumulation of oxidative stressors and lipotoxic substances induce hepatocyte death, steatosis, and fibrosis, resulting in the decay of KC niches and the progression of liver damage toward more advanced stages of cirrhosis (Nakagawa et al., 2014; Grohmann et al., 2018; Sun et al., 2020). Homeostatic cues, such as the crosstalk between hepatic stellate cells and KCs via BMP9/BMP10-ALK1, has been shown to be important for inducing liver X receptor (LXR) signaling in KC to promote the expression of lineage-determining factors in tissue-infiltrating monocytes that fill vacant KC niches (Sakai et al., 2019; Bonnardel et al., 2019; Guilliams et al., 2022; Zhao et al., 2022). Notably, however, these mo-macs generated after an injury to the liver still failed to fully recapitulate the phenotype of *bona fide* embryonic RTMs, resulting in an impaired response to the subsequent lipotoxic burden of non-alcoholic steatohepatitis (Tran et al., 2020).

Different markers have been identified to distinguish these disease-associated mo-macs from KC, such as osteopontin (*Spp1*) (Remmerie et al., 2020). These recruited mo-macs have commonly been referred to as hepatic lipid-associated macrophages (LAMs), as they are typically enriched with lipid droplets within the cytosolic space (Morgan et al., 2021) and resemble the lipid-laden phagocytes that are enriched in the adipose tissues of obese individuals (Jaitin et al., 2019; Worthmann and Heeren, 2020; Chen et al., 2021). Analogous populations of mo-macs, also expressing *TREM2* and other genes involved in lipid metabolism, were enriched in cirrhotic livers (Ramachandran et al., 2019), indicating a potentially unique role in progressive liver disease. Interestingly, in contrast to the orientation of steady-state KC, these TREM2^{+} macrophages are located peri-centrally in

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zones of steatosis, suggesting that inflammatory blood monocytes are not directly recruited to vacant KC niches, but are rather pulled to distinct locations in obese livers (Guilliams et al., 2022), likely reflecting key functional differences between RTMs and mo-macs that still need to be unraveled.

Neurodegenerative disease

Multiple sclerosis.: Infiltration of the CNS by inflammatory monocytes has been linked to multiple diseases of neuro-inflammation, such as multiple sclerosis (MS). In the experimental autoimmune encephalomyelitis model of MS, infiltrating monocytes triggered disease progression (Ajami et al., 2011). The injury to oligodendrocytes and gray matter astrocytes resulted in IL-33 release, prompting a recruitment of monocytes to the CNS (Gadani et al., 2015). Local GM-CSF promoted an inflammatory response in infiltrating monocytes that resulted in tissue damage in EAE mice. Deleting the CSF2 receptor in circulating monocytes phenocopied EAE resistance observed in complete *Csf2rb*-deficient mice (Croxford et al., 2015). Using single-cell transcriptomics, a specific subset of CXCL10-expressing monocytes was identified as the pathogenic subset of monocyte-derived cells in the spinal cord that drives EAE progression (Giladi et al., 2020). Interestingly, inflammatory monocytes from the bone marrow, but not this subset of $CXCL10^{+}$ monocytes, were recruited into inflamed tissues, where they relied on licensing by IFN-ɣ and GM-CSF to differentiate into phagocytic mo-macs of the inflamed CNS (Amorim et al., 2022).

Alzheimer's disease.: Similar phenomena of RTM dysfunction and replacement by inflammatory mo-macs have been observed for neurodegenerative diseases, such as AD, too. Foundational studies on the disease primarily involved whole-genome profiling of patients and murine models of AD, and identified at-risk genomic loci that are uniquely active in microglia (Lambert et al., 2013; Wightman et al., 2021). Loss-of-function mutations in *TREM2*, for instance, confer significant susceptibility for developing AD. Genome-wide survival analysis also showed that a single nucleotide polymorphism (SNP) in the locus of *SPI1*, encoding the myeloid transcription factor PU.1, also associates with AD risk, implicating a now widely explored role for dysfunctional microglial innate immunity in disease pathogenesis (Guerreiro et al., 2013; Sims et al., 2017; Huang et al., 2017). TREM2 itself recognizes multiple molecules and signals via the DAP12 adaptor protein (Daws et al., 2003; Cannon et al., 2012). Accordingly, screening of the proteomic metabolome in AD-afflicted brains highlighted a link between microglial dysfunction and lipid dysregulation (Loewendorf et al., 2015).

Broader immune profiling of myeloid cells in the CNS of AD patients and mice has shown that the composition of the immune landscape is more heterogeneous and complex than just the phenotypic decline of resident microglia. The use of single-cell omics enabled the identification of a unique microglial signature that defines a subset of microglia, termed disease-associated microglia (DAM), that (1) are uniquely enriched in *Trem2* and other molecules involved in lipid metabolism, and (2) are associated with limiting neurodegeneration in AD-transgenic mice (Keren-Shaul et al., 2017; Zhou et al., 2020). These findings indicate that a portion of surviving microglia engage molecular programs that aim to compensate for the loss of ulterior microglial functions that underscore AD

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pathology. Enrichment of DAM in AD brains is associated with reduced disease burden, and therapeutically activating TREM2 attenuated AD in mice (Wang et al., 2020).

However, more recent works have shown that inflammatory mo-macs actually contribute significantly to the pool of TREM2-engaging DAM-like phagocytes during AD pathogenesis, representing a shift in our understanding of DAMs as an embryonically derived population of microglia. These disease-inflammatory mo-macs (DIMs) express comparable levels of TREM2 and were a primary source of TNF-α in diseased brains of AD patients and mice (Silvin et al., 2022). Interestingly, these phagocytes were preferentially organized in the hippocampus, amygdala, and frontal cortex of murine AD brains, whereas DIMs were principally located in the leptomeninges of AD patients. Collectively, though, these findings underscore the clinical efficacy demonstrated for Enbrel/etanercept, an anti-TNF antibody from rheumatoid arthritis trials, in managing AD (Butchart et al., 2015; Chou et al., 2016). And though reducing excess inflammation is likely therapeutic for reducing damage done to native microglial niches and the surrounding glia, parsing the molecular programs that uniquely identify the mo-macs will help us be more precise about what targets actually modulate the cell-intrinsic phenotype of this compartment, representing a more directed strategy that addresses the root of pathogenic inflammation in AD.

Cardiovascular disease—The vasculature is patrolled and protected by circulating monocytes and perivascular macrophages. The preservation of the cardiovascular system is, therefore, dependent on the proper function of these phagocytes. But, in atherosclerotic disease, inflammatory monocytes become more abundant in unobstructed vessels and will go on to accumulate within early plaques (Swirski et al., 2006, 2007; Tacke et al., 2007). Notably, kinetic studies of monocyte ingress and egress from injured myocardial tissue indicated rapid monocyte to mo-mac turnover (Kircher et al., 2008; Leuschner et al., 2012). Intravital imaging showed that the development of layers of inflammatory mo-macs underscores the growth of atherosclerotic plaques, with the luminal layers representing newly arrived inflammatory monocytes, and the deepest layers occupied mo-macs that destabilize the endothelial floor of advanced plaques (Williams et al., 2018). Single-cell RNA-sequencing (scRNA-seq) of these cells in atherosclerotic plaques revealed that the mo-macs express TREM2, resembling the lipid-laden macrophages found in AD lesions (Cochain et al., 2018; Depuydt et al., 2020). Accordingly, the loss of chemokine receptors such as CCR2 and CX3CR1 on monocytes alleviated plaque burden (Saederup et al., 2008; Combadiere et al., 2008). In line with these observations, inhibiting monocyte migration and suppressing monocyte differentiation into mo-macs also reduced plaques in *Apoe*-deficient mice (Potteaux et al., 2011; Cao et al., 2015). These observations clearly demonstrate a central role for inflammatory mo-macs in the progression of vascular disease.

Neoplastic disease—Although tumor-associated macrophages (TAMs) have become more seriously studied within the recent decade, few have gone on to specify functional roles for the different subtypes of TAMs that are present in tumor lesions. Over the past few years, a series of seminal studies have demonstrated how ontogenically distinct macrophages play distinct roles in tumor progression and in modulating anti-tumor immunity. Single-cell technologies have given a snapshot of these properties to better appreciate (1) the

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heterogeneity of RTMs and mo-macs in tumor tissues, (2) their localization in the tumor topography, and (3) the molecular programs that are conserved among tumor-enriched mo-macs across multiple cancer types. The results from these efforts have shown that the roles of RTMs and mo-macs recruited in response to inflammation and tumor-derived cues are often stage-specific and spatially restricted.

Recent results have revealed that both RTMs and mo-macs populate tumor lesions and engage different molecular programs. In both lung and pancreatic adenocarcinoma lesions, RTMs were shown to play a role in tumor inception (Zhu et al., 2017; Casanova-Acebes et al., 2021; Baer et al., 2022); whereas in non-small cell lung cancer (NSCLC), alveolar macrophages facilitate epithelial-mesenchymal transition in tumor cells and activate regulatory T cells and fibroblasts, all of which promote tumor progression and invasiveness (Casanova-Acebes et al., 2021). Interestingly, though, these RTMs are reorganized to the periphery of tumors and are replaced by a massive accumulation of mo-macs (Loyher et al., 2018; Casanova-Acebes et al., 2021). The tumor-infiltrating pool of mo-macs has been profiled in a variety of cancers (Cheng et al., 2021; Mulder et al., 2021; Nalio Ramos et al., 2022), and subsets of them have been shown to universally engage the lipid-associated *TREM2* molecular program (Lavin et al., 2017; Molgora et al., 2020; Katzenelenbogen et al., 2020; Binnewies et al., 2021; Leader et al., 2021). Interestingly, analogous programs have been shown to be present in chronically inflamed lesions and AD, as discussed earlier.

Another mo-mac program that is seemingly common in tumor lesions involves the expression of *SPP1*, encoding the glycoprotein osteopontin (Mulder et al., 2021; Leader et al., 2021). In a large cohort of 35 NSCLC patients, *SPP1*$^{+}$ mo-macs were found to closely associate with CXCL13-expressing T cells and IgG plasma cells, the sum of which were termed the “lung cancer immune activation module” or LCAM (Leader et al., 2021). Strikingly, the enrichment for LCAM positively correlated with a number of prognostic clinical metadata, including tumor mutational burden, presence of driver mutations, and response to immune checkpoint blockade (Leader et al., 2021). Such findings motivate the need for an understanding of the precise functional roles that these tumor-infiltrating mo-macs play to determine how to best target them, whether it be through modulating their phenotype or depleting them. This task becomes especially integral for the development of new myeloid-targeting therapies. In subcutaneous murine models of sarcoma and colon carcinoma, TREM2 deficiency or therapeutic antibody-based blockade of TREM2 restricted tumor growth and synergized with PD-L1 blockade in a CD8 T cell-dependent manner (Molgora et al., 2020; Katzenelenbogen et al., 2020), indicating a pathogenic role for TREM2-expressing mo-macs in tumor progression.

However, growing evidence suggests that the pro-tumorigenic contributions of TREM2 may be tissue specific. For instance, in the liver, while TREM2^{+} mo-macs accumulated with progressive stages of liver injury (i.e., steatosis, cirrhosis, to advanced hepatocellular carcinoma [HCC]) (Ramachandran et al., 2019; Sharma et al., 2020), TREM2 deficiency enhanced tumor growth in mice with HCC, suggesting that the *TREM2* program is a tissue-dependent molecular network with both pathogenic and protective potential (Perugorria et al., 2019; Esparza-Baquer et al., 2021). Also in HCC, with additional reports suggesting that other mo-mac programs are, in fact, similar to those used by early macrophages during

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fetal development, questions concerning the fetal-like programming of tumor-infiltrating mo-macs and their functional purpose during tumorigenesis are also highly intriguing (Sharma et al., 2020). Overall, although mo-macs associate with progressive disease in cancer, the exact functions of the molecular programs that they engage must be probed individually to determine their utility as therapeutic targets.

Concluding remarks

The onset of disease often instigates inflammation that results in cell stress and death of exposed cell types, including RTMs, in the affected microenvironment. In tandem, the recruitment of circulating monocytes likely refills available and vacant RTM niches, as previously defined (Guilliams et al., 2020; Guilliams and Svedberg, 2021), with the likely goal of fulfilling the unmet needs of the damaged tissue, such as the clearance of pathogens and the removal of damaged cells. But unlike the macrophages that seeded the tissue in its developmental stages during embryo-genesis, these mo-macs encounter a much more distinct milieu, reacting to inflammatory and disease-specific cues that skew their differentiation and prompt the expression of distinct repertoires of molecular programs that may further drive disease, as we have discussed. Therefore, it seems the recruitment of mo-macs comes at a price: their maturation in the context of a dysregulated or damaged tissue microenvironment results in the non-homeostatic differentiation of tissue-infiltrating monocytes into mo-macs that enter cell states that may impair tissue healing and instead promote damage and fibrosis. Accordingly, these observations emphasize the importance of refining our use of macrophage ontogeny and developmental pathways, taking into account both the kinetics of monocyte recruitment and differentiation and how that affects their ability to possibly revert to “unconventional” monocyte-derived RTMs upon disease resolution (Figure 5).

With the publication of new data on macrophage heterogeneity and function at the steady state and during disease, it remains essential for the field to approach two principal questions: (1) how the molecular diversity of cell states is modulated by the balance of homeostatic tissue signals and disease-associated alarmins, and (2) how it is influenced by the persistence, disappearance, dysregulation, and neo-formation of subtissular niches. Harnessing our findings to these questions will be crucial for our study of disease, where we actually find the greatest diversity of macrophage cell states, some of which are conserved across tissues (Mulder et al., 2021). And it will be equally important to synthesize our understanding of how both niche-based education of embryonic or monocyte-derived RTMs, and the lack thereof for mo-macs occupying disease-afflicted niches, can be modulated to select for disease-resolving programs. The identification of conserved mo-mac programs across disease states and across multiple tissues, most popularly the TREM2 program, speaks to the broader translational potential in studying these programs, as they might reveal candidate targets that may be ideal for therapeutic modulation. This approach to studying macrophage biology requires a more informed and evolved take on ontogeny, one that accounts for the functional distinction between homeostatic RTMs and mo-macs generated in response to disease signals. Doing so would present the opportunity to be more precise with how we target pathogenic macrophage programs in a tissue-specific manner. In addition to genetic fate-mapping models, such as the *Ms4a3*^{Cre} model (Liu et

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al., 2019) or the binary-transgenic system (Kim et al., 2021), other classic methods that reveal ontogeny can be helpful, including parabiosis or bone marrow transplants. This task does also require information about (1) intrinsic properties of tissues (i.e., handling of metabolic burden, stromal cell composition, etc.), (2) the homeostatic duties of RTMs that are relegated to them at the steady state, and (3) whether mo-macs recruited in response to injury appropriately meet the demands of those responsibilities. The sum of all these factors will likely dictate whether certain programs—even if they are engaged by mo-macs across multiple tissues—play protective or pathogenic roles in disease.

Therefore, several pressing questions remain. The first is concerned with where embryonic and monocyte-derived RTMs localize in tissues, i.e., whether monocyte-derived RTMs fully migrate to and occupy the exact same niches as their embryonic counterparts, and what their respective contributions are to homeostasis. And in the contexts of disease-related injury, it remains important for us to determine whether being monocyte-derived imprints certain epigenetic memories into monocyte-derived RTMs that prompt them to react differently to injurious cues or damage to their niche long after acquiring RTM phenotypes. One possibility is that soluble disease-associated signals influence the education and phenotype of myeloid progenitor cells in the bone marrow during disease inception, resulting in the epigenetic imprinting of monocyte-derived cells that distinguish them from epigenetic hallmarks of RTMs (Netea et al., 2016). Alternatively, mo-macs may be imprinted locally at tissue sites of disease, though the likelihood of this option is likely to be more dependent on the lifespan of mo-macs in different disease contexts and tissues, which still requires more work to be done, as previously mentioned. Both scenarios would also require us to better understand how disease-associated cues may impact monocyte phenotypes before they even enter the circulation, whereby education within the marrow influences the activity of monocytes once they begin to migrate (Askenase et al., 2015).

Ultimately, it will be crucial for us to identify reliable markers that distinguish the subsets of RTMs and the disease-driven pool of mo-macs. And with that information, we can better characterize the lifespan of mo-macs that are recruited during disease and determine how that may inform our insight into their functional contribution and relevance to different stages of disease progression. For instance, we could imagine that initial waves of monocyte-derived cells involve an elevated phagocytic activity and lipidic remodeling of the microenvironment, with latter waves bringing in monocytes that attempt to synthesize resolutive cues and promote tissue repair (Kratofil et al., 2022), which may or may not actually be beneficial to the tissue at that particular point in time, depending on the context. Alternatively, the converse may be true; earlier waves of monocyte-derived cells that manage to properly differentiate and resolve disease could inculcate an environment that is advantageous for responding to secondary insults (Machiels et al., 2017; Aegerter et al., 2020). Therefore, a growing body of literature has begun revealing a host-protective function of mo-macs, but as previously stated, when and why these properties manifest remain crucial pieces of information that must be elucidated.

An expanded understanding of this kind of dynamic would then be additive to characterizing the kinetic heterogeneity of monocyte-derived cells that are recruited early versus later in the course of the disease. It would help guide therapeutic intervention at different stages of

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diseases, especially if mo-macs from the more recent waves of recruitment might be more susceptible to homeostatic cues and be more “easily convinced” to reform RTM niches to their pre-disease state; in sum, they would probably benefit more from that extra therapeutic push needed to be beneficial for disease resolution than older mo-macs that might be more difficult to reprogram. Accordingly, both descriptive profiling and functional studies are needed to appreciate the value and utility of this type of macrophage heterogeneity to the fullest extent. In doing so, we will be armed with a clearer and practical understanding of how myeloid programs can be targeted therapeutically in a tissue-specific and disease-specific manner.

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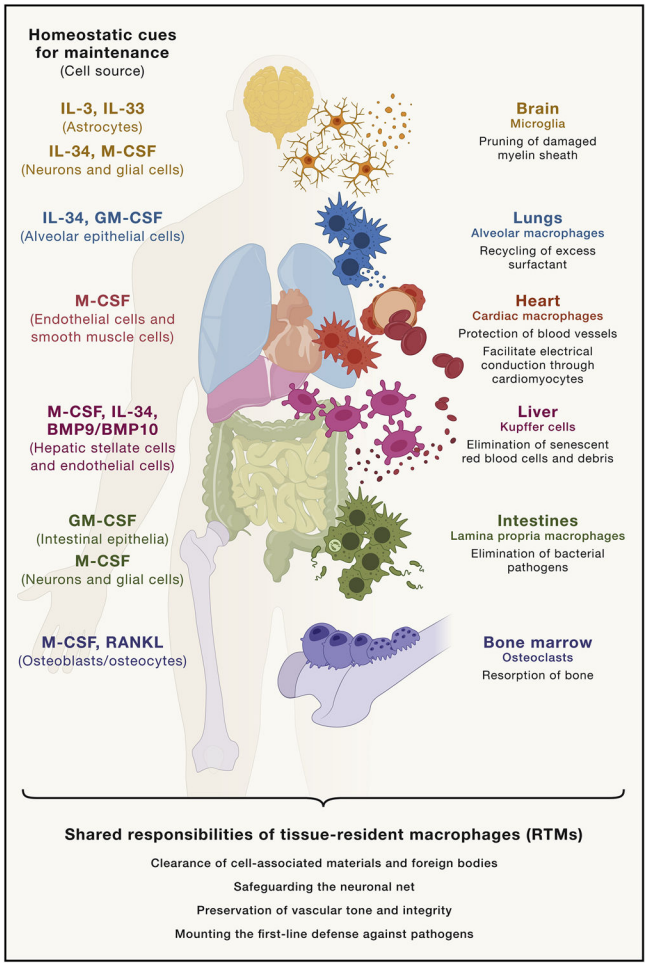

Figure 1. Fundamental responsibilities of tissue-resident macrophages across tissues

RTMs represent the primary entourage of tissue sentinel phagocytes that help maintain the tissues they inhabit. For example, osteoclasts of the bone eliminate excess bone mass, whereas other macrophages residing within the marrow and splenic macrophages facilitate the generation and elimination of new and dying red blood cells. Whether it be in the CNS, where microglia cooperatively function within neurovascular units, or in the periphery, where perivascular and cardiac macrophages support vascular integrity, RTMs help preserve the vasculature in different tissues. Microglia are also integral for the pruning of neuronal synapses, which also requires them to phagocytose any debris originating from degraded myelin. Alveolar macrophages, like other RTMs in mucosal surfaces, form the immediate innate defense to pathogens.

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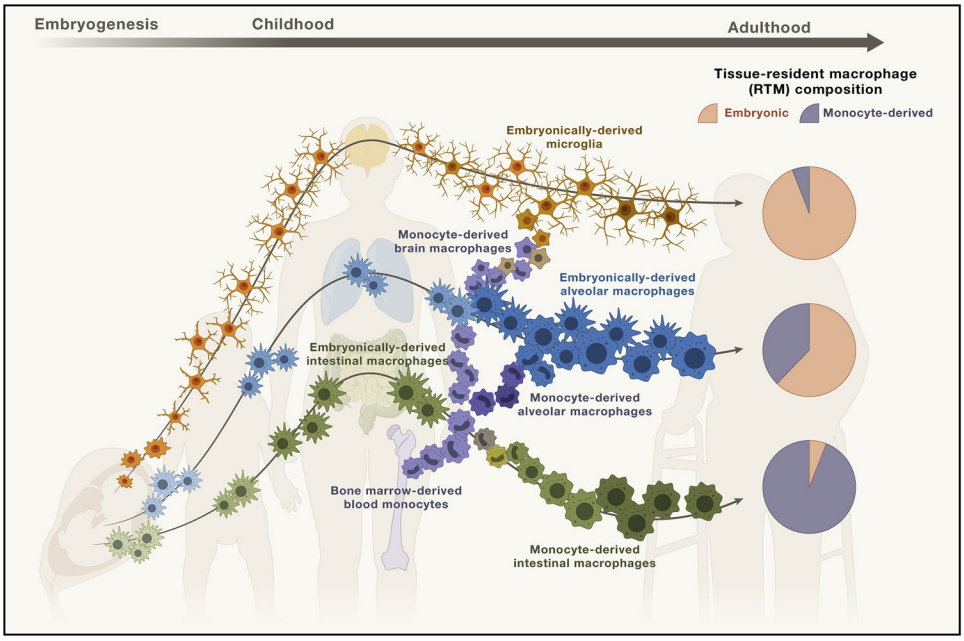

Figure 2. Composition of different tissue-resident macrophage populations at the steady state

Depending on the tissue, the ontological composition of the tissue-resident macrophage (RTM) compartment varies, and here, we depict the generation and development of these RTM populations during fetal development and post-birth, based on the accepted paradigm that all RTM are embryonically derived phagocytes.

Microglia continue to self-maintain in the brain through interactions with glial cells, like astrocytes, and persist through age with minimal input from peripheral monocytes that infrequently pass the blood-brain barrier to infiltrate the brain parenchyma at the steady state.

Alveolar macrophages in the lungs are also capable of preserving their pool of embryonically derived cells during homeostasis, but unlike the brain-resident microglia, tissue-infiltrating monocytes make up an increasing proportion of alveolar macrophages over the course of aging. Therefore, a notable fraction of alveolar macrophages can be derived from monocytes.

Intestinal lamina propria macrophages are one such exception of RTMs that are largely comprised of monocyte-derived RTMs. The remarkable turnover of macrophages in the gut require input from blood monocytes.

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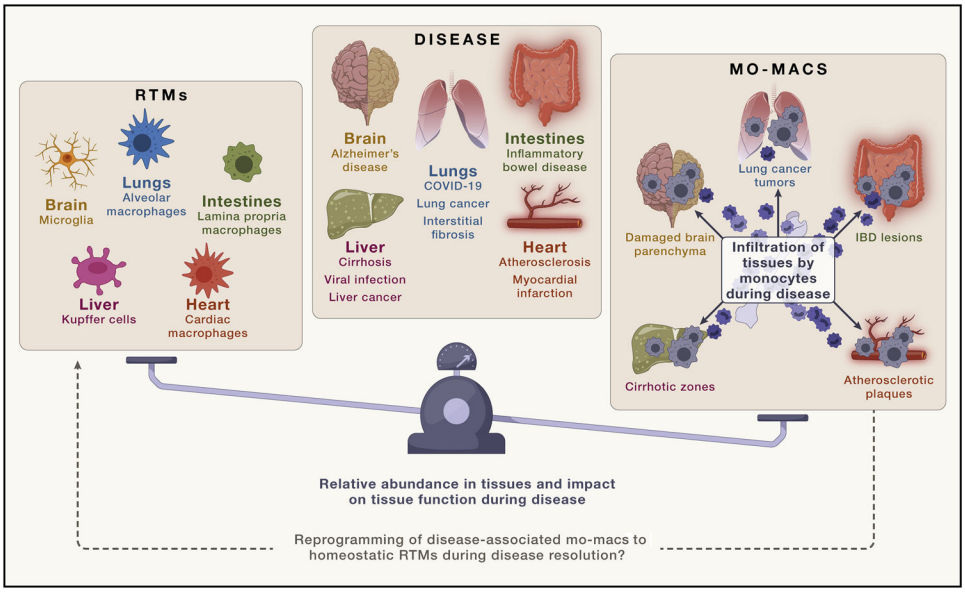

Figure 3. The dynamic of ontogenically distinct RTMs at homeostasis and disease-associated mo-macs during disease

At the steady state, tissue-resident macrophages (RTMs) can be comprised of either embryonically derived RTMs or monocyte-derived RTMs, depending on the tissue. Yet, regardless of their development, the two groups are generally phenotypically indistinguishable from one another. However, during disease, injury-associated signals and disease-specific cues prompt the recruitment of blood monocytes and instigate their inflammatory differentiation into disease-associated monocyte-derived macrophages (mo-macs). Although a growing body of work illustrates their more significant contributions to disease and the functionality of tissues during that time, whether these macrophages, at the resolutive phases of disease, simply die off or revert to the *bona fide* RTM phenotype upon recovery of homeostatic tissue signals is not entirely clear.

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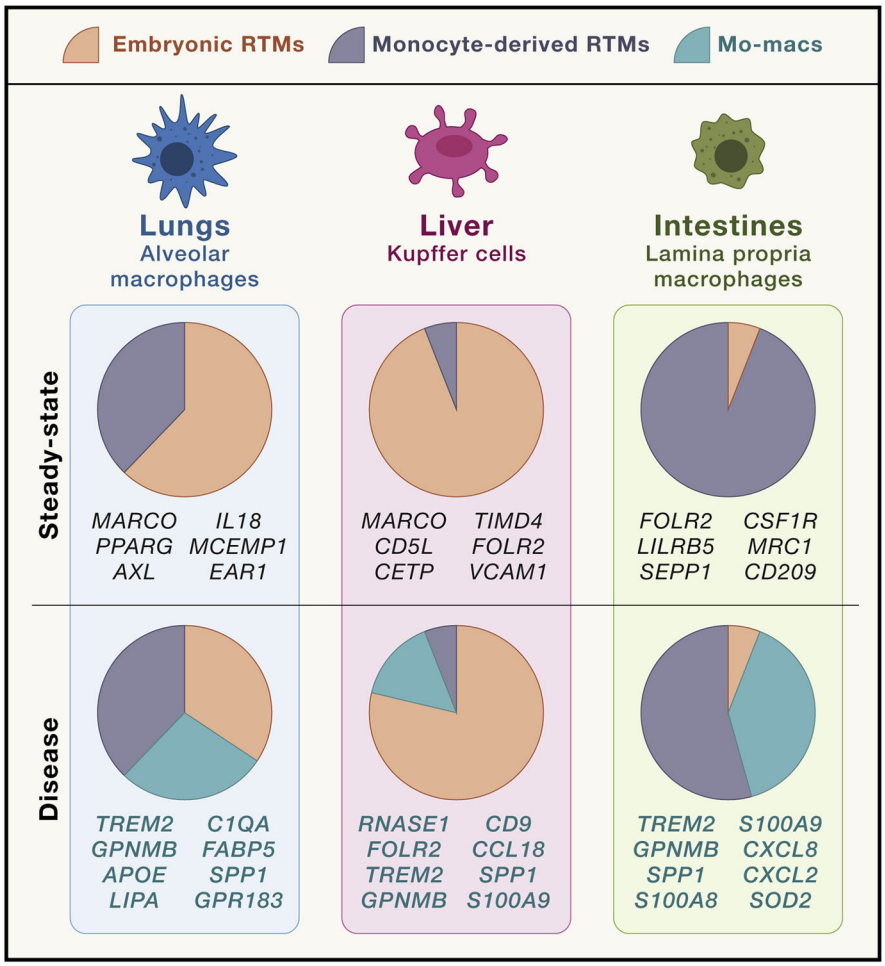

Figure 4. Transcriptional differences that distinguish disease-associated mo-macs from RTMs

The recruitment of monocyte-derived macrophages (mo-macs) during disease reflects a wide variety of inputs, including the lack of steady-state tissue cues that encourage homeostatic differentiation of monocytes into monocyte-derived tissue-resident macrophages (RTMs) and the presence of disease-specific alarmins. As such, their transcriptomic signature distinguishes them from their tissue-resident counterparts, and what remains to be studied more extensively are the functional contributions of these molecular programs to disease progression.

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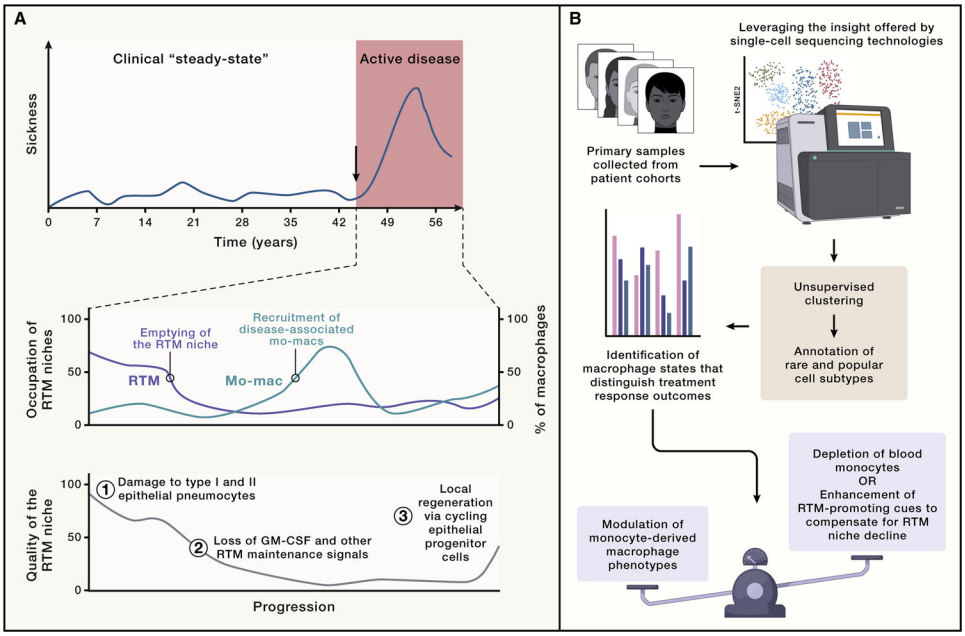

Figure 5. Overview of the dynamic among RTMs and disease-associated mo-macs in tissues and leveraging it for translational science

(A) Delineating the occupational dynamic of tissues by tissue-resident macrophages (RTMs) (blue) and monocyte-derived macrophages (mo-macs) generated during disease (red) will not only elucidate how their functional differences drive disease in humans but also at what points during disease would response to certain therapies be most appreciated. (B) In order to do so, insight must be driven by precise, scientific questions with translational potential. The advent and continued use of single-cell technologies enable the scientific community to do that, though other methods of highly rigorous profiling efforts could do the same. Broadly, considering the uncertainty of whether mo-macs at disease resolution help revive the local pool of RTMs and the fact that cell states among mo-macs are wide-ranging and diverse, modulating their phenotype—as opposed to trying to deplete them entirely or outcompete them by attempting to forcibly expand surviving RTMs during disease—will be the more practical outlook on new therapeutic designs.