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Origins, Biology, and Diseases of Tissue Macrophages

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Abstract

Tissue-resident macrophages are present in most tissues with developmental, self-renewal, or functional attributes that do not easily fit into a textbook picture of a plastic and multifunctional macrophage originating from hematopoietic stem cells; nor does it fit a pro- versus anti-inflammatory paradigm. This review presents and discusses current knowledge on the developmental biology of macrophages from an evolutionary perspective focused on the function of macrophages, which may aid in study of developmental, inflammatory, tumoral, and degenerative diseases. We also propose a framework to investigate the functions of macrophages in vivo and discuss how inherited germline and somatic mutations may contribute to the roles of macrophages in diseases.

Keywords

tissue-resident macrophages; macrophage specification; tissue metabolism; genetic diseases; somatic mutations

1. INTRODUCTION

Tissue macrophages, embedded within most tissues in relatively small numbers (1–5%), are accessory cells with a central role in ensuring homeostasis during organogenesis, tissue remodeling, and metabolic adaptation (1-13). Inherited defects in macrophage-expressed genes present in young children as severe and often fatal developmental disorders that include bone deformities; neurodevelopmental delay and dementia; liver, lung, and cardiac dysfunction; and immunodeficiency (14-19). Work in murine models has nevertheless focused primarily on the contribution of macrophages to inflammatory and tumoral diseases. This is in part due to the identification of bone marrow–derived inflammatory monocytes that contribute to myeloid cells, in particular those in infected and tumoral tissues,

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and that can be confused with tissue-resident macrophages. More recent experimental work in mice has provided a developmental basis for a broader characterization of the function of tissue macrophages by defining a tissue-resident macrophage lineage genetically and developmentally distinct from inflammatory leukocytes (1, 2, 13, 20-22). This is not to say that the resident tissue macrophages are not involved in inflammation or tumors. For example, tissue macrophages are heavily implicated in recruitment of specialized cells such as neutrophils and inflammatory monocytes to tumoral tissues and sites of infection. Additionally, somatic mutations in genes from the RAS/mitogen-activated protein kinase (MAPK) pathway in tissue macrophages cause granulomas in rare myeloproliferative diseases such as histiocytoses, where patients also experience a variety of symptoms including bone-condensing or osteolytic lesions, lung and liver fibrosis, and neurodegeneration (23). In this review, we provide for the student in biology and medicine a current outline of the biology of tissue-resident macrophages and their relevance to human diseases, which may be of use for future studies and when considering therapeutic options for patients.

2. PHAGOCYTES ARE ACCESSORY CELLS PRESENT IN ALL TISSUES FROM MOST ANIMALS

2.1. Macrophages Are Conserved Across Metazoans

In the early 1880s, Elie Metchnikoff described phagocytic wandering amoeboid cells that surround and engulf foreign materials in transparent starfish larvae (24, 25). Metchnikoff was an avid comparative biologist and noted the presence of these phagocytic amoeboid cells across the phylogenetic tree ranging from starfish larvae to more complex organisms such as Xenopus. He described that during development these amoeboid cells accumulate in tissues to ingest dead or weak cells, thereby allowing tissue resorption (25). Metchnikoff saw these phagocytic cells, now referred to as macrophages, as active participants in inflammatory responses and developmental processes that reflected a host’s continued drive to maintain its integrity and homeostasis (24).

Macrophages are found in the most primitive multicellular organisms belonging to the groups protozoans (amoebae, flagellates, and ciliates), sponges (such as bath sponges), and cnidarians (e.g., jellyfish) (26-29). These organisms rely on phagocytic amoebocytes for acquisition of nutrients and recognition of foreign elements in the environment. Similar cell types are conserved through evolution and are observed in all groups from invertebrates (annelids, arthropods, mollusks, echinoderms) to vertebrates (28, 29).

2.2. The Origin of Macrophage Function

Macrophages, “big eaters,” are accessory cells found in all tissues of multicellular organisms that maintain tissue fitness and homeostasis. Initial studies by Metchnikoff and his contemporaries focused on the phagocytic activity of macrophages in the context of host defense against infections (24). However, it did not escape Metchnikoff or others that this phagocytic activity is important for a variety of other functions such as housekeeping functions, including removal of apoptotic cells and remodeling of the extracellular matrix. Cell eating is a risky behavior, as many viruses and other pathogens can gain entry to their

hosts using this mechanism (30). Thus, from an evolutionary perspective, it may not be coincidental that the roles of professional eater, housekeeper, and immune sentinel converge in macrophages. Perspectives on jobs performed by macrophages continue to expand, as studies are now beginning to highlight a more general role for macrophages in vertebrate biology, including in systemic metabolism (7-13), cold adaptation (6), tissue regeneration (4, 5), tissue maintenance, and development (1-3).

All macrophages across the phylogenetic tree share the same core function, that is, to sense environmental cues (nutrients or microbial metabolites) and phagocytose cells that are detrimental to the self (dead or unfit cells or pathogens) to remodel the environment and maintain organismal homeostasis. The origin of modern phagocytosis can be traced back to the earliest and simplest phagocytes: the unicellular microorganisms. The social amoeba Dictyostelium discoideum is the most-studied unicellular eukaryote. Phagocytosis in these amoeba arose from the needs to differentiate self from nonself (31-34) so that they can engulf bacteria, their primary nutritional source, and to remove hazardous toxins (34, 35). These simple unicellular organisms recognize and engulf bacteria and dying cells using mechanisms similar to those found in mammals (35-41) and insects (42-45), including integrin orthologs (46), lectins (35), phosphatidylserine receptors (45), and Toll/IL-1 receptor (TIR) domain–containing receptors. Interestingly, engulfment of dying D. discoideum by neighboring cells mediated through phosphatidylserine recognition is proposed to supply other members of the colony with additional nutrients (45). Similarly, in Hydra, small nurse cells internalize spent oocytes during oogenesis to supply nourishment to developing polyps, thereby allowing for redistribution of energy in a biological system.

The drive to clear dying cells and to remodel the surrounding environment to maintain homeostatic integrity is evident even in the deepest branches of the Archaea and Eubacteria phylogeny, where colonial biofilms appeared ~3.25 billion years ago as a mode of survival (47). These ancient colonies/ biofilms remove nonfunctional spent or dying cells using phagocytosis-like mechanisms to recycle nutrients and remodel the 3D architecture of the colony (48).

The drive to remove dying or unfit cells found even in the simplest prokaryotes suggests that the need to remove toxins and recycle nutrients in the context of a cellular community is paramount for survival. Such a function can also be found in phagocytes of higher eukaryotes; for example, splenic macrophages in mice recycle iron from erythrocytes (49). Therefore, perhaps it is more accurate to propose that the core function of macrophages and phagocytes may be redistribution of energy in a biological system. At a unicellular level, this translates into energy acquisition, i.e., eating, while at a multicellular level this means recycling of nutrients for use by neighboring cells (45, 49, 50) (Figure 1).

2.3. Tissue-Specific Adaptation of Macrophages

Macrophages in all tissues protrude elongated processes or dendrites beyond their cell body to create a 3D network throughout the organ to surveil their host tissue (51-53). Through evolution and adaptation to the host tissue microenvironment, macrophages have acquired tissue-specific functions. For example, macrophages of the central nervous system, microglia, have acquired machinery to mechanically prune neurons and remodel synaptic

connectivity (54-59). Splenic red-pulp and kidney macrophages, on the other hand, surveil the blood to remove spent erythrocytes (49) and small immune complexes (3), respectively. In the lungs, alveolar macrophages have adapted mechanisms to engulf and enzymatically recycle surfactant for the proper function of the lungs, where their absence causes alveolar proteinosis (60). A striking example of tissue-specific adaptation of macrophages is apparent in osteoclasts, which are multinucleated macrophages lining the bone endosteum (2, 61-63). These giant, multinucleated cells, the absence or dysfunction of which causes osteopetrosis, digest the bone matrix by acidifying their microenvironment and are required for proper bone morphogenesis and maintenance (2, 61-63), and consequently for the formation and maintenance of the hematopoietic niche in higher vertebrates (2, 63-66) (Figure 1).

In addition to their specialized phagocytic activity in different tissues, macrophages are also an important source of tissue-specific growth factors (55). In the wounded and aging skin, for example, dermal macrophages produce IGF1 and PDGFcc to support myofibroblast proliferation and differentiation into adipocytes (67). In the brain, microglia specifically produce NGF and neurotrophin 3 to support neural outgrowth and survival (54-59), whereas eye macrophages produce NGF to initiate programmed cell death in the hyaloid vessels and the pupillary membrane and promote proper development of the eyes (68, 69). Osteoclasts, on the other hand, produce PDGFb and BMP6 to promote angiogenesis and osteoblast formation (70-72). These examples illustrate that functions of macrophages vary extensively among different tissues.

Consistent with such a broad array of essential tissue-specific functions, macrophage abnormality is an important contributor to various pathological conditions. In addition to alveolar proteinosis and osteopetrosis, one can cite microglia deficiency, associated with enlarged ventricles and alterations in neuronal density (73); lack of red-pulp splenic macrophages, associated with iron overload in the splenic red pulp (49); and maladaptation in the adipose tissue macrophages associated with obesity and type 2 diabetes (74, 75). This is not an exhaustive list, and new macrophage functions and corresponding diseases will be discovered in the future as technical advances are being made in the field of genomics. Such advances have transformed and will continue to transform the view of macrophages in physiology and pathophysiology, from specialized antimicrobial cells to a cell type with essential functions in tissue development and homeostasis. Therefore, we have found ourselves getting closer to Metchnikoff's holistic view of macrophages as essential components of metazoan biology and development than his famous paradigm of their roles in cellular immunity.

3. A SEPARATE LINEAGE OF HEMATOPOIETIC CELLS THAT COLONIZE TISSUE ANLAGE IN EMBRYOS AND PARTICIPATE IN ORGANOGENESIS

3.1. A Lineage of Macrophages Independent from Hematopoietic Stem Cells

van Furth and colleagues proposed the mononuclear phagocyte system as a developmental framework for macrophage ontogeny and differentiation (76). This framework was supported by observations of bone marrow transplantation in irradiated hosts, peritonitis models, and extensive in vitro studies (77-80). This classical, textbook model holds that

macrophages originate and renew from circulating bone marrow–derived monocytes, which extravasate into tissues, where they mature into tissue macrophages. This model, however, was not always consistent with analyses of parabiosis (81), thymidine incorporation, and bone marrow chimera experiments (79) from the 1980s and 1990s, which suggested that a proportion of myeloid cells in the brain, lung, liver, peritoneum, and spleen were dependent on local proliferation rather than monocyte recruitment. Indeed, it was shown in the late 1990s that microglia are derived from cells originating from the yolk sac (YS), whose progeny actively proliferates in situ during development (82). Using genetic fate-mapping strategies, several groups proposed a fetal origin for the majority of postnatal tissue macrophages, including microglia (21, 22, 83, 84) (Figure 2).

Specifically, our group showed that in the mouse embryo, Csf1r-expressing erythromyeloid progenitors (EMPs) arise at approximately embryonic day 8 (E8) from the yolk sac hemogenic endothelium (21, 85) independently of the transcription factor MYB and are therefore distinct genetically, temporally, and spatially from hematopoietic stem cells (HSCs). These EMPs generate circulating macrophage precursors that simultaneously colonize the whole embryo at the onset of organogenesis from E9.5, and their progeny persist as tissue-resident macrophages in adult tissues (20-22).

HSCs and bone marrow–derived progenitors also contribute to myeloid cells present within postnatal tissues in proportions that vary with the tissue considered, the age of the mice, and pathological processes (21, 22, 83, 84, 86-91). Therefore, the myeloid system of a mouse can be described as a layered system where resident tissue macrophages develop in embryos and persist in adult tissues while coexisting with HSC-derived passenger leukocytes such as monocyte-derived macrophages and dendritic cells that originate and renew from bone marrow HSCs. This model concludes that at least two distinct categories of macrophages coexist within the tissues of an adult mouse and can be distinguished by their progenitors, developmental history, function, turnover, and mechanisms of maintenance (Figure 2).

3.2. Tissue Macrophages Are Locally Maintained

Based on the original examination of macrophages during inflammation and the conception of the mononuclear phagocyte system, it was postulated that macrophages were replenished from monocytes. However, recent lineage-tracing studies of myeloid cell development have brought this view into question and have demonstrated that under homeostatic conditions tissue-resident macrophages are maintained by self-renewal without the contribution of blood monocytes (21, 83). For example, in mice, YS-derived large peritoneal macrophages maintain their population for at least four months through self-renewal independently of monocytes (92). Similarly, pancreatic islet macrophages that are in contact with blood vessels and β cells display negligible replacement by non-host-derived monocytes (93). The adventitial layer of the large arteries within the heart also contains YS-derived macrophages that retain self-renewal ability (94). Adipose tissue of mice contains macrophages of dual origins: YS-derived macrophages that are sustained by self-renewal and monocyte-derived macrophages that are continuously replaced (7, 8, 95, 96).

It is noteworthy that tissue-resident macrophages may also persist and self-maintain under nonhomeostatic conditions. In the liver, for example, Kupffer cells are depleted in response

to acetaminophen overdose, but their numbers can be restored by self-renewal without the need for blood monocytes (97). Cardiac macrophages, which are necessary for the myocardial adaptive response, similarly proliferate within the first week following pressure overload hypertrophy (98). Additionally, proliferation is also observed to repopulate tissue macrophages during influenza infection (84) or zymosan-induced peritonitis (99). Conditions of tissue stress, including uterine expansion in pregnancy (100), central nervous system injury (101), and dermatitis (102), also result in local proliferation of tissue macrophage populations. In direct juxtaposition to the aforementioned examples, intestinal mucosal macrophages are replaced entirely around the time of weaning by blood monocytes that migrate into the healthy intestinal lamina propria and contribute to the maintenance of gut homeostasis (83, 90).

3.3. Specification of Tissue Macrophages from Yolk Sac Progenitors

After EMPs arise at ~E8 from the yolk sac hemogenic endothelium in the mouse embryo (21, 85), their numbers peak in the YS between E9.5 and E10.5, and they seed the fetal liver as soon as E9.5 (85). They differentiate into erythrocytes, megakaryocytes, and myeloid cells (lymphoid cells have not been detected) (20-22). EMP-derived circulating macrophage precursors simultaneously colonize the whole embryo at the onset of organogenesis from E9.5 (20). At this time, a core macrophage transcriptional program is initiated within the progenitor of tissue-resident macrophages that drives their differentiation from EMPs into F4/80+ macrophages with characteristic differentiation trajectories specific to their tissue of residence (20). These tissue-specific transcriptional programs are determined by the preferential and progressive enrichment of tissue- specific transcriptional regulators (20). A few examples include SALL1 in the microglia (20, 103), PPARγ in the alveolar macrophages (104), SPI-C in the red-pulp macrophages (49), ID3 in the Kupffer cells (20), and GATA6 in the large peritoneal macrophages (88). Most of these factors that drive function and identity of tissue-specific macrophages have been functionally validated by knockout mice (Table 1). Deletion of these tissue-specifying transcription factors leads to tissue- specific ailments such as anemia in Spi-C-mutant mice that lack splenic red-pulp macrophages (49), alveolar proteinosis in PPARγ-deficient mice and humans that lack lung alveolar macrophages (104), and brain deformities in Sall1-mutant animals (20, 103).

3.4. Development, Life Span, and Maintenance of Tissue Macrophages in Humans

There is a paucity of information on the development and life span of tissue-resident macrophages in humans. Even though the use of genetic fate-mapping tools in animal models cited above can result in conflicting interpretations and has generated controversy, it is even more difficult to determine with confidence the ontogeny of human tissue-resident macrophage subsets. It is nevertheless proposed that human microglia are formed without meaningful contribution from circulating hematopoietic progenitors and renewed by local proliferation, at an estimated median rate of 28% per year based on modeling data from 14C microglial birth dating (105). Additionally, a single-cell analysis of human embryos suggests that human macrophage development mirrors that of the mouse macrophage (106). In accordance, the human embryo YS generates CX3CR1+ macrophages, similarly to its mouse counterpart (107-109), and human pluripotent stem cells can differentiate in vitro into macrophages in a MYB-independent manner, resembling the developmental program of the

murine YS-derived macrophages (110). These MYB-independent macrophage progenitors can further differentiate into tissue-resident macrophages once they are exposed to tissue-specific signals (111).

3.5. Transcriptional and Epigenetic Control of Macrophage Specification

Gene expression in macrophages is determined by distinct transcriptional modules that are controlled by hierarchically arranged transcriptional regulators (112-114). At the top of the hierarchy are the lineage-determining master regulators, such as PU.1 and CEBPβ, which control the gene-expression modules common to all macrophages. PU.1, in particular, occupies and engages macrophage-specific gene enhancers, making them accessible to other transcriptional regulators (115). For example, peritoneal macrophages and microglia have PU.1 bound to enhancer regions of genes transcribed in a tissue-specific manner (114). The next level of hierarchy is controlled by transcription factors that are induced by tissue-specific signals. The three known examples that fit tissue-identity signals are TGF-β in the brain, retinoic acid in the omentum, and desmosterol in the liver (88, 116, 117). Neither TGF-β nor retinoic acid is unique to any particular organ, which would suggest that tissue-specifying factors are most likely a combination of signals received in a particular order. For example, in the case of Kupffer cells, a delta-like ligand (DLL4) is required to promote expression of liver X receptor alpha (LXRα) in Kupffer cell progenitors, which is necessary for response to desmosterol and the subsequent specification of these cells (117). In absence of all the signals, cell specification is blocked (117) (Table 1). When and in which order these cells are exposed to the tissue-specifying factor may also play a role in how macrophage specification takes place. This might explain how a small number of signaling pathways generate diverse cell types during development and might account for the difficulty in recapitulating differentiation programs in vitro.

Analyses of enhancer landscapes have revealed that some enhancer-like regions in various tissue-resident macrophage populations are shared and that PU.1 is required for the development of macrophages in almost all tissues. The enhancer of Spi1, which controls the expression of PU.1, has H3K4me2 and H3K27ac marks in all macrophage populations (118). In contrast, there are epigenetic variations in macrophage populations in different tissues. For example, the Rarb gene, induced by retinoic acid, is labeled by H3K4me2 in all macrophage populations, but H3K27ac is present only in the peritoneal macrophage population, suggesting enhancers may have a broader primed potential but be activated only in precise tissue-specific and lineage-specific contexts (114).

Of note, phagocytes in all metazoans as well as echinoderms and hydras display nearly complete sets of homologs for vertebrate transcription regulators of myelopoiesis (e.g., PU.1/SPI-B/SPI- C/ETS) as well as key molecular players for macrophage functions, such as pathogen recognition and uptake, including Toll-like receptors (TLRs; >210 genes), Nod-like receptors (NLRs; >200 genes), and scavenger receptors (>1,000 genes) (119).

3.6. To What Extent Are Macrophage Specification and Maintenance Controlled by the Microenvironment?

As we begin to suspect that the specification of macrophages is a developmental process, and that their maintenance is supported at least in part by local proliferation, an alternative to the *à la demande* model of production of tissue macrophages from a pool of circulating progenitors is needed. The numbers, phenotypes, and specific functions of resident macrophages in individual tissues appear developmentally and genetically hardwired by evolution. At the same time, macrophage tissue identity requires an intact tissue microenvironment. When removed from their tissue contexts and cultured in vitro, microglia and peritoneal macrophages rapidly lose their tissue-specific gene and enhancer signatures while maintaining a core macrophage identity (114, 120). Cultured macrophages could then be partially restored or reprogrammed by the addition of tissue-specific signals, TGF-β and retinoic acid for microglia and peritoneal macrophages, respectively (114). In microglia, the transcription factor SALL1 controls a brain-specific gene program (e.g., Sall1, Tmem119, P2ry12, Hexb) that is lost in vitro but regained when cultured cells are transplanted back into brain tissue (121).

During development, it is possible that migratory progenitor cells find a local combination of signaling molecules within each tissue to undergo terminal differentiation and specification, therefore giving rise to specialized tissue-resident macrophages with unique functions restricted to the host tissue. This model parallels the development of many other cells, such as the neural crest cells that in response to signaling molecules such as BMP, FGF, Wnt, and Hedgehog family members differentiate into various cell types, including chondrocytes, sensory neurons, and melanocytes (122). This developmental paradigm does not require precursors to be prespecified for the generation of tissue-resident macrophages with phenotypic characteristics matching their tissue of residence. Three known examples that seem to follow this developmental model are the differentiation of microglia, peritoneal macrophages, and liver Kupffer cells in response to local production of TGF-β in the brain, retinoic acid in the omentum, and desmosterol in the liver (88, 116, 117).

Nevertheless, the response of macrophage progenitors to a specific tissue factor is in fact predetermined by their developmental history. Retinoic acid induces expression of the transcription factor GATA6 only in precursors of peritoneal macrophages and not in progenitors of bone mar- row macrophages (88). Similarly, monocytes may give rise to Kupffer-like cells in the liver, but they lack the machinery necessary for uptake and recycling of erythrocytes (117). Thus, despite phenotypic similarities between monocyte-derived macrophages and YS-derived macrophages, there may be critical functional disparities. One might speculate further that the development of resident macrophages could be achieved by predetermined YS-derived macrophage progenitors, or even earlier, by predetermined mesodermal progenitors, so that only a subset of EMPs can give rise to a given type of tissue macrophage, e.g., microglia in the brain in response to TGF-β. Future studies that would improve our understanding of macrophage specification would likely have consequences on the design of therapies directed at regeneration or depletion of macrophages in a tissue-specific manner.

4. MACROPHAGES CONTRIBUTE TO TISSUE MAINTENANCE AND THE DYNAMIC ORGANIZATION OF TISSUES

4.1. Macrophages Control Dynamic Reorganization of Tissues

Macrophages are found in all tissues and protrude elongated processes or dendrites beyond their cell body throughout each organ to constantly surveil their host tissue for changes in nutrient availability, extracellular matrix organization, and cellular composition. The universal presence of macrophages in all tissues allows for an orchestrated response to local and systemic stimuli, therefore organizing tissue responses while maintaining optimal organismal functions

Macrophages play diverse homeostatic roles and maintain their host tissues by scavenging cellular debris, apoptotic cells, and invading pathogens and by clearing senescent cells (123-125). For example, splenic red-pulp macrophages phagocytose approximately 2 × 1011 spent erythrocytes each day, thereby contributing to recycling of heme (49). In the lungs, alveolar macrophages remove and recycle spent surfactant for the proper function of the lungs (126-128). Macrophages also scavenge apoptotic cells in an immunologically silent way (129-136), in a phosphatidylserine-dependent manner through tyrosine kinase receptors TYRO3, AXL, and MER (137-142). It is thought that removal of apoptotic cells by macrophages prevents the release of antigenic macromolecules into the tissue milieu. In support of this hypothesis, deficiencies associated with components of efferocytosis are accompanied by the aberrant presence of nucleic acids and autoimmune disease (132, 136, 143-147). However, it is worth noting that engulfment of apoptotic or unfit cells by phagocytes predates any inclination toward autoimmunity. For example, cnidarians have dedicated phagocytes that remove apoptotic cells despite a lack of an adaptive immune system in these animals. Additionally, in hydras, small nurse cells are internalized by surrounding phagocytes during oogenesis (148). Similarly, during the development of the fruiting body, the social amoeba D. discoideum may engulf apoptotic cells (45). In these examples, engulfment of the apoptotic or spent cells is a presumed attempt to recycle nutrients for the survival of the animal. Thus, efferocytosis in vertebrates may have as of yet unknown roles in recycling of nutrients and cellular macromolecules in addition to preventing autoimmunity. Indeed, experiments in vitro using radiolabeled cells have shown that macrophages can recycle nucleotides and release them to the environment so that they can be used by other cells (76).

In addition to exercising phagocytic activity, macrophages actively sculpt their immediate microenvironment by modifying the extracellular matrix and the cellular composition of the tissues. For example, osteoclasts resorb bones and remodel the collagen matrix via production of cathepsin K to create and maintain the hematopoietic niche (2, 65, 66). Tissue macrophages also take part in mounting an appropriate response to tissue trauma (149). Abnormalities in tissue homeostasis associated with organ damage or wounding are often accompanied by dramatic reorganization and morphological changes in macrophages (150-154). In these cases macrophages produce coagulation factors to promote clotting (155, 156), secrete matrix metalloproteases to remodel the host tissue (157), and recruit immune cells to disinfect the damaged organ (3).

Macrophages may also alter the composition of their host tissue by releasing trophic factors necessary for proliferation, differentiation, and maintenance of new cells (55, 67, 158). In the brain, microglia secrete IGF1 to promote survival of layer V cortical neurons during postnatal development (159). Microglia secrete other growth factors, including NGF, neurotrophin 3, basic fibroblast growth factor, and platelet-derived growth factor, which are necessary to support neuronal outgrowth and astrocyte proliferation (54-59). Interestingly, other brain cells, such as brain astrocytes, are known to express CSF1, therefore creating a hypothetical cellular circuitry between microglia and astrocytes. These cellular circuitries may form higher-order connections between cells in such a way that changes in the activity of macrophages, e.g., tissue damage, nutritional changes, or infections, may translate into local alterations in cellular composition in the vicinity of the affected macrophage. These cellular circuitries may be viewed as a method to orchestrate tissue responses to an environmental insult. Alternatively, such circuitries might generate positive feedback loops that lead to derailment of tissue function, such as fibrosis.

Many functions of macrophages remain enigmatic due to the pleiotropic roles of these cells within tissues. For example, mice deficient in CSF1R, a receptor necessary for macrophage survival and proliferation, are physically smaller (58, 59, 160-163). It is not clear whether this phenotype is simply due to skeletal abnormalities or whether it in fact reflects a function of macrophages in determining body size or tissue size in response to environmental factors, e.g., nutrients. Tissue macrophages are also important in development of the mammary gland (164), pancreatic β cells (165), lymphatic vasculature (166), and the vascular network (167) as well as in branching morphogenesis of the lung (168, 169), submandibular gland (170), and kidney (171, 172). Similarly, macrophages are required for full limb regeneration in adult salamanders (4) and for regeneration of digit tips in mice; however, these functions remain mechanistically puzzling.

4.2. Macrophages Control Metabolic Adaptation in Tissues

Due to their proximity to the vasculature, macrophages continuously sample the circulation and their microenvironment via macropinocytosis, phagocytosis, and scavenger-receptor-mediated pathways. This leads to accumulation of various metabolites in macrophages, where they can be processed and sensed (173). Macrophages have thus been suggested as ideal metabolic sensors. Indeed, initial studies of macrophages in tissues suggested that their activation and accumulation during inflammation are associated with metabolic ailments such as insulin resistance, hyperglycemia, and altered fatty acid synthesis (11, 12, 174-177). Therefore, macrophages or their mediators were first hypothesized to signal selective energy mobilization needed to combat host invasion and tissue trauma (174). However, it was not until the early 1980s that it was experimentally demonstrated that macrophages can directly alter metabolism in target cells such as adipocytes by controlling insulin response and fatty acid metabolism (176). In the following decades, it has been shown that macrophages are involved in control of lipid storage and glucose homeostasis at tissue and organismal levels (8, 12, 174, 178-183).

It is necessary to mention that the aforementioned studies primarily focused on the role of inflammatory monocytes or monocyte-derived macrophages in metabolism rather than

the role of tissue macrophages. Studies on heterogeneity of macrophages in the adipose tissue by our group and others have revealed that YS-derived tissue macrophages and HSC-derived Ccr2-dependent macrophages coexist within the adipose tissues of mice, where they are characterized by distinct cellular dynamics and functions (95, 184). Whereas tissue macrophages are maintained locally and promote lipid storage in adipose tissues (10, 13, 160, 185) in part via regulated local production of PDGFcc (184), HSC-derived, Ccr2-dependent macrophages are recruited in increasing numbers in response to overfeeding and are implicated in adipose tissue inflammation and adipocyte death (12, 13, 177, 186-189). Outside the adipose tissue, HSC-derived, Ccr2-dependent macrophages, through production of mediators such as TNF, promote ectopic lipid accumulation and insulin resistance in the liver and muscle (12, 160, 174-177, 190-192). Interestingly, a population of adipose tissue macrophages that express markers reminiscent of YS-derived tissue macrophages in mice is also found in humans, suggesting a potential developmental heterogeneity comparable to that in mice (193).

Macrophages respond to dietary changes in various organisms, including Drosophila, zebrafish, rodents, and humans (9, 194). What could be the nutritional sensors in macrophages that monitor changes in metabolites? Nuclear receptors, a large family of ligand-activated transcription factors (195, 196), are promising candidates for this function. They sense alteration in lipophilic hormones, vitamins, and dietary lipids (197). Nuclear receptors include members such as peroxisome-proliferator-activated receptors (PPARs) and LXRs, which are expressed in many tissue macrophage populations (20, 117, 198).

Several studies have demonstrated the role of macrophage nuclear receptors PPARγ and LXR in control of glucose and lipid metabolism (199-205). For example, PPARγ activation leads to increased cholesterol efflux away from atherosclerotic lesions and toward transport to the liver (199). In contrast, disruption of PPARγ in myeloid cells impairs insulin response and glucose homeostasis in the skeletal muscle and liver (200). PPARγ exerts its metabolic functions in macrophages in part directly or indirectly through LXR (201-205). Other PPAR members are also implicated in macrophage biology. For example, macrophages sense very-low-density lipoprotein via activation of PPARδ, which upregulates genes necessary for lipid storage, such as Perilipin. Altogether, these studies indicate that PPAR and LXR activity in macrophages may control lipid metabolism and glucose metabolism, therefore providing a link between lipid sensing in macrophages and metabolic adaptation in tissues.

4.3. Macrophages in Infection and Tumoral Response

Macrophages are ubiquitous in all organs, where they constitute 1–5% of most tissues. It is thus proposed that tissue macrophages are sentinels, surveying their surroundings for signs of infection and tissue abnormalities such as tumor growth. Very mild stress or infection might be handled locally by tissue macrophages; however, more extensive insults require recruitment of neutrophils and inflammatory monocytes by tissue macrophages (206, 207). Upon entering tissues, neutrophils and inflammatory monocytes proceed to disinfect the tissue and engulf the microbial agents. Tissue macrophages also produce inflammatory cytokines such as TNF-α, IL-1, and IL-6 during infections to activate the endothelium and induce the acute phase response to facilitate removal of pathogens (208). Phagocytosis

is an inherently risky behavior, as many viruses and other pathogens can gain entry into phagocytes such as tissue macrophages (30). Indeed, resident macrophages are invaded by pathogens such as Mycobacterium tuberculosis and HIV (209, 210). It is therefore noteworthy to that although tissue macrophages are considered to initiate immune responses to pathogens in most tissues, they may also act as reservoirs for various pathogens.

Macrophages can also respond to sterile abnormalities of tissues, such as tumor growth. In fact, macrophages constitute the dominant myeloid cell population in most solid tumors in both human and mouse malignancies; however, the details regarding macrophage origin and function in different tumor types are still being defined. For the most part, it is presumed that tumor-associated macrophages originate from circulating monocyte precursors (reviewed in 211, 212). Originally, it was believed that monocyte-derived macrophages were present in high numbers at the tumor site to engulf and remove the growing tumor. However, despite high levels of infiltration, monocyte- derived macrophages are unable to stimulate an effective anti-tumor response and are instead generally associated with poor patient prognosis (211-213), with colorectal cancer as the exception to this trend (213). Surprisingly, little is known about the role of resident macrophages in the context of tumor growth. Studies of Kupffer cells, liver-resident macrophages, indicate that tissue macrophages may engulf tumor cells to reject growing tumors (214, 215). However, studies of microglia and pancreatic tissue macrophages suggest that tissue macrophages may promote tumor growth (216-218). These studies highlight the paucity of information on the seemingly complex role of tissue-resident macrophages in tumor growth and development.

5. GENETIC DISEASES OF MACROPHAGES

5.1. Inherited Macrophage Diseases

The essential roles of macrophages in tissue development and homeostasis are demonstrated by the presence of germline mutations in genes critical to macrophage function, such as mutations in the gene for CSF1R (Table 2). Such mutations are often associated with severe phenotypes and multiple-organ involvement, with the brain and bones most frequently affected. A good example of this is adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) (14). This is a rare disease characterized by behavioral changes, cognitive decline, motor impairments, and dementia. The damage affects the white matter, and the pathological hallmarks include demyelination, axonal loss, and the presence of axonal spheroids (15-18). The symptoms begin in the fourth or fifth decade of life and result in death, usually within ten years. ALSP is inherited in an autosomal dominant pattern, and it is caused by mutations in CSF1R. Most of the reported mutations are missense and located in the intracellular kinase domain of the tyrosine kinase receptor. Some of these mutations are suggested to be loss-of-function, due to disruption of the kinase domain (17). In the brain, CSF1R is expressed primarily by microglia, where due to the role of the CSF1R/CSF1 axis in the development, proliferation, and survival of macrophages, deficient microglia function is suspected to cause ALSP. Mouse models of CSF1R haploinsufficiency have shown features of ALSP accompanied by regional microgliosis (219), while zebra fish models of haploinsufficiency show a reduced density of microglia cells (220), which correlates with observations of pediatric onset of the disease and some adult patients.

Whether the disease is triggered by an abnormality in microglia cell number or is due to a malfunction of microglia remains unclear.

More recently, it has been reported that homozygous mutations in CSF1R can cause pediatric brain phenotypes distinct from those of adult ALSP, with a near complete absence of microglia (19). Two cases were reported with different mutations and phenotypes, one with a missense mutation and the other with a splice variant mutation. The latter presented with severe brain abnormalities, including ventriculomegaly, and increased bone density, and the patient died at one year of age. This suggests a key role for tissue macrophages in both brain and bone development. This is supported by mouse models of homozygous deletion of Csf1r, where lack of Csf1r expression results in brain and bone developmental abnormalities such as reduced neuron density, enlarged brain ventriculus, hydrocephaly, and osteopetrosis (2, 19, 73, 163, 220-222).

Another important macrophage-expressed gene that has been associated with both neurodegenerative and bone disorders is the gene for triggering receptors expressed on myeloid cells 2 (TREM2) (223). TREM2 is expressed in various tissue macrophages, including microglia and osteoclasts. Upon ligand binding, it signals through an adaptor protein, DAP12 or DAP10 (DNAX- activating protein of 12 kDa or 10 kDa), which recruits the kinase SYK. This leads to the activation of a cascade of signaling events, e.g., the phosphatidylinositol 3-kinase (PI3K) and MAPK pathways. Mutations in TREM2 and DAP12 (the majority homozygotic) are the cause of Nasu- Hakola disease, also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, which is recessively inherited and characterized by a fast-progressing presenile dementia and bone cysts that lead to fractures (224). Neurological symptoms typically begin in the third or fourth decade of life and lead to death rapidly. Postmortem examinations of the brains of these patients show demyelinating lesions, neuronal loss, astrogliosis, and accumulation of free fatty acids, mainly in the white matter of the frontotemporal lobe and basal ganglia. Mice deficient in DAP12 or TREM2 develop osteopetrosis and hypomyelinosis, mainly in the thalamus, and have reduced numbers of microglia. Of note, Trem2-deficient mice do not develop bone lesions, obvious neurological phenotypes, or clear histological changes associated with Nasu-Hakola disease. However, when treated with copper chelator cuprizone, which triggers demyelination, Trem2- deficient mice do not show signs of remyelination and have an accumulation of myelin debris and axonal dystrophy reminiscent of Nasu-Hakola disease (225). Genome-wide association studies (GWAS) have shown that heterozygous variants of TREM2 (and some homozygous variants with Nasu-Hakola disease) are associated with a two to four times greater predisposition to Alzheimer disease (AD) (226-228) and have also been detected in patients with frontotemporal dementia, suggesting a role of microglia in sporadic neurodegenerative diseases (226; reviewed in 229).

Due to the role of macrophages in the clearance of apoptotic cells and debris, they are thought to be the main cell type affected in lysosomal storage diseases (LSDs). LSDs are a heterogeneous group of over 70 genetic disorders that present mainly in children, but also in adults, and are characterized by mutations in lysosomal proteins, including hydrolases, transporters, and membrane proteins, among others. More than 1,000 genes have been

reported to be involved in these diseases, resulting in enormous genetic diversity and thus extremely heterogeneous presentations (230). Many patients present with developmental problems and neurological phenotypes that include ataxia and seizures as well as behavioral changes and intellectual disabilities. Other tissues such as bone, liver, and lung tissues are occasionally involved. Lysosomal dysfunction of macrophages interferes with the catabolism and recycling of molecules, leading to their accumulation in the cell and thus triggering cellular damage and organ dysfunction. Foamy macrophages are commonly observed in damaged tissues in different types of LSDs, including Gaucher disease. One of the most frequent LSDs, with a birth prevalence of 2 per 100,000 during the period 1970–1996, Gaucher disease is caused by mutations in hydrolase β-glucocerebrosidase. Of note, GWASs have found associations between mutations in lysosomal storage disease genes with Parkinson disease and Lewy body disease (231-233). In support of a macrophage origin of LSDs, enzyme replacement via bone marrow transplantation and engraftment of hematopoietic cells has been an effective therapeutic strategy in the CNS (234).

AD is the most frequent cause of progressive dementia. Its prevalence increases with age, with an estimated prevalence in the population of 10% after 65 years and 30% after 85 years in 2020 (325, 236). The role of germline genetic variation in AD risk has been studied intensely. The risk of AD for carriers of one germline copy of the ε4 allele of the apolipoprotein E gene (APOE4) (237, 238), expressed by macrophages, is three times greater, and two copies increase AD risk by a factor of approximately ten. Large-scale GWASs have discovered hundreds of single-nucleotide variations associated with the risk of neurological and psychiatric disorders. The vast majority of these disease-risk genetic variants are located in noncoding regions of the genome (239). In addition to mutations in genes, noncoding DNA variations implicate microglia in AD. GWASs have identified approximately 50 genetic variants that moderately increase the risk of AD, including variations in macrophage-expressed TREM2 (226, 228), CD33, and the MS4A gene family (240). Two-thirds of the germline AD-risk single-nucleotide variations are located within or near genes expressed in macrophages (120, 240). A recent study that mapped brain-cell-type-specific enhancers showed a strong enrichment of sporadic AD-associated variants within microglial gene enhancers as com- pared to enhancers that control genes specific to other glia or neurons (120). These data support a long-held hypothesis that microglia may play an important role in the pathogenesis of AD (241, 242).

Altogether, these observations make a compelling case that normal macrophage functions are essential to keep tissues free of a large variety of developmental and degenerative diseases.

5.2. Somatic Mosaicism in the Macrophage Lineage

The aforementioned macrophage-associated diseases are characterized by germline mutations (mainly loss-of-function) (Table 2). Much less in known about the contribution of postzygotic mutations in macrophages to disease. The involvement of somatic mutations in the clonal evolution of cancer is well known. However, due to progress in sequencing technologies, a high burden of somatic mutations, including driver mutations, in normal (nontumoral) tissues has been revealed, suggesting associations between these somatic

mutations and developmental disorders and other noncancerous diseases (243-249). Because macrophages arise early during embryonic development and self-renew locally, cells carrying somatic mutations that confer a proliferative/survival advantage likely accumulate as the organism ages, similar to what has been reported for other cell types (e.g., epithelial cells), although the somatic mosaicism of macrophages had not been investigated.

Only one group of disorders, i.e., histiocytoses, can be attributed to the presence of somatic activating mutations in macrophages. Histiocytoses are a rare and heterogeneous group of clonal myeloid disorders that are characterized by granulomatous lesions and a broad spectrum of clinical manifestations and outcomes that can affect both children and adults. Granulomatous lesions contain neoplastic macrophages—also called histiocytes—with abnormal differentiation, proliferation, and functions. These lesions can involve one or multiple organs, such as skin, bone, lymph gland, liver, lung, and brain. The most frequent histiocytoses are Langerhans cell histiocytosis and juvenile xanthogranuloma, which predominantly affect young children, and Erdheim-Chester disease, which is mostly observed in adults (250-252). The clonality of histiocytes was first demonstrated in 1994, and several teams in the last five years have identified recurrent RAS-MEK-ERK or PI3K pathway somatic mutations in a large proportion of histiocytosis patients (252-257). The most frequent mutation is BRAF V600E, which is identified in about 50% of cases.

We tested the hypothesis that the BRAF V600E mutation introduced into tissue-resident macrophages of mice would produce a histiocytosis-like disease. Indeed, we found that expression of BRAF V600E in a mosaic manner in EMPs in mouse embryos causes accumulation of excess macrophage clones within several tissues, including microglia in the brain, when the mice are adults. Strikingly, these mice develop a progressive and lethal neurodegenerative disease that closely resembles what is observed in some histiocytosis patients who develop neurodegenerative disease (23, 258-260). BRAF V600E microglia clones accumulate preferentially in the hindbrain and form small aggregates in the white matter. They have a distinct transcriptional profile associated with neuronal toxicity and are associated with activated astrocytes, deposition of amyloid precursor protein, neuronal degeneration, myelin loss, and ultimately neuron death and neurobehavioral symptoms (23).

These findings lead to a more broadly hypothetical scenario where somatic mutations, in particular driver mutations that would enable the outgrowth of pathogenic microglial clones, could be associated with other neurological disorders. As found in histiocytosis, mutations in MAPK in microglia could also contribute to pathogenesis in sporadic neurodegenerative diseases like AD, where there is no clear heritable cause and microglial involvement is implicated (120, 240), as well as multiple sclerosis (Figure 3).

5.3. Targeting Macrophages Therapeutically

Because of their role in the immune response of normal and tumoral tissues, macrophages have been explored as a therapeutic target in cancer and inflammation, as previously reviewed (261-263). A number of the resulting agents have been repurposed to modulate tissue-resident macrophages. For example, a small-molecule inhibitor of CSF1R (PLX5622), which depletes macrophages regardless of their developmental origin, has been used to eliminate microglia, showing efficacy in reducing plaque formation in a mouse model of

inherited AD (264). Further supporting a reactive role for microglia in neurodegeneration, microglial depletion following traumatic brain injury reduces chronic neuroinflammation and associated neurodegeneration, as well as the related motor and cognitive deficits in mice (265). Our team has shown that use of the BRAF inhibitor (PLX4270), the CSF1R inhibitor (PLX5622), and particularly their combination significantly delays the disease course of BRAF V600E–mutant-microglia-driven neurodegeneration (23). Conversely, a monoclonal antibody that stimulates the TREM2 receptor improves the pathology of AD in a mouse model harboring a defective human TREM2 variant (R47H) (266). Many additional examples of therapeutic targeting of macrophages cannot be adequately reviewed here. Furthermore, the sometimes-conflicting effects of macrophage modulation on attenuation or promotion of disease highlight the need to further study macrophage biology. In light of the distinct functions of tissue-resident versus bone marrow–derived macrophages, and the essential roles resident macrophages play in tissue function, the therapeutic depletion of macrophages may be expected to have adverse consequences and should be implemented thoughtfully. Ideally, genes and pathways altered as a result of mosaicism in macrophages should be explored using next-generation sequencing and targeted in the setting of human diseases to increase the specificity of treatments.

6. CONCLUDING REMARKS

In the last few decades, many studies have provided insights into the life history of macrophages and have revealed that two separate lineages of macrophages coexist in animals: long-lived, locally maintained resident macrophages that develop during embryogenesis and passenger myeloid cells that originate and replenish continuously from bone marrow HSCs. This distinction is relevant to functions and diseases of macrophages. With regard to macrophage function, it is now understood that the developmental lineage dictates macrophage function rather than the environment. Elegant studies in liver Kupffer cells, for example, demonstrate that although monocytes may take a Kupffer-like phenotype, they will not become Kupffer cells, as they lack the machinery to recycle erythrocytes (117). Regarding macrophage diseases, studies in mice have demonstrated that mutations in the RAS/MAPK pathway in resident macrophages may cause rare diseases known as histiocytoses, whereas the same mutations in inflammatory monocytes/macrophages result in leukemia (23). It is paramount, however, to note that despite many studies on the roles of tissue-resident macrophages, little is known about their functions in most tissues. In addition, it is not clear how mutations in macrophage-associated genes affect macrophage function or tissue integrity. It is integral to the field of macrophage biology to reevaluate the functions of macrophages in different tissues in the context of their developmental history to better understand organ development and tissue remolding, and to cultivate new and effective macrophage-directed therapies.

Exciting studies in the last decade have revealed a high burden of somatic mutations, including driver mutations, in normal (nontumoral) tissues and suggested a potential association between these somatic mutations and developmental disorders and other noncancerous diseases (243-249). Because macrophages arise early during embryonic development, are long-lived, and self-renew locally, they likely accumulate somatic mutations as the organism ages, similar to what has been reported for other cells within

tissues. As driver somatic mutations can result in the accumulation of mutant cells as a function of time, it is tempting to postulate that increasing mutational burden in the resident macrophages of aged individuals may contribute to the age-related decline in macrophage function. In addition, deep sequencing of somatic mosaicism may be utilized as an endogenous bar-coding system, which should allow for lineage mapping of human macrophages in various tissues.

Future works investigating the life history and the respective contribution of lineage-specific programs and local tissue signals will improve our understanding of macrophage functions and elucidate novel ways to modulate their functions in vivo.

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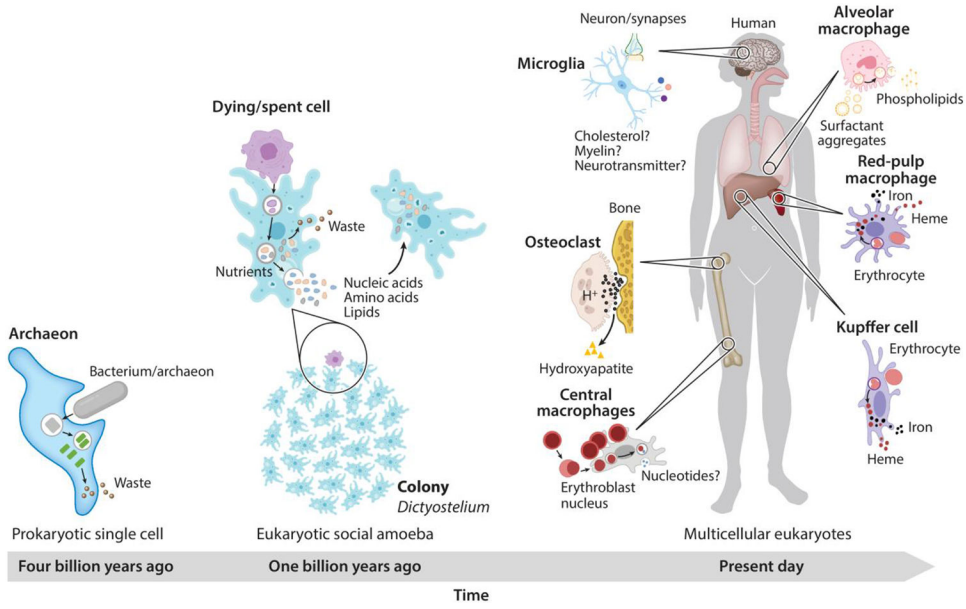

Figure 1.

Evolution of phagocyte function. Phagocytes across the phylogenetic tree sense environmental cues and phagocytose cells or foreign material in an attempt to redistribute energy and remodel their environment. This core function of phagocytes is evident in the deepest branches of the Archaea phylogeny, where these ancient phagocytes are proposed to engulf other unicellular organisms to obtain nutrients. As unicellular organisms evolved and began to form colonies, phagocytes acquired specialized functions in recycling of nutrients from dead/spent cells for consumption by healthy members of the colony. At the onset of multicellularity, phagocytes gained more complexity and obtained tissue-specific functions, including recycling of heme, nucleotides, surfactants, and bones as well as remodeling of the extracellular matrix. Figure adapted from images created with BioRender.com.

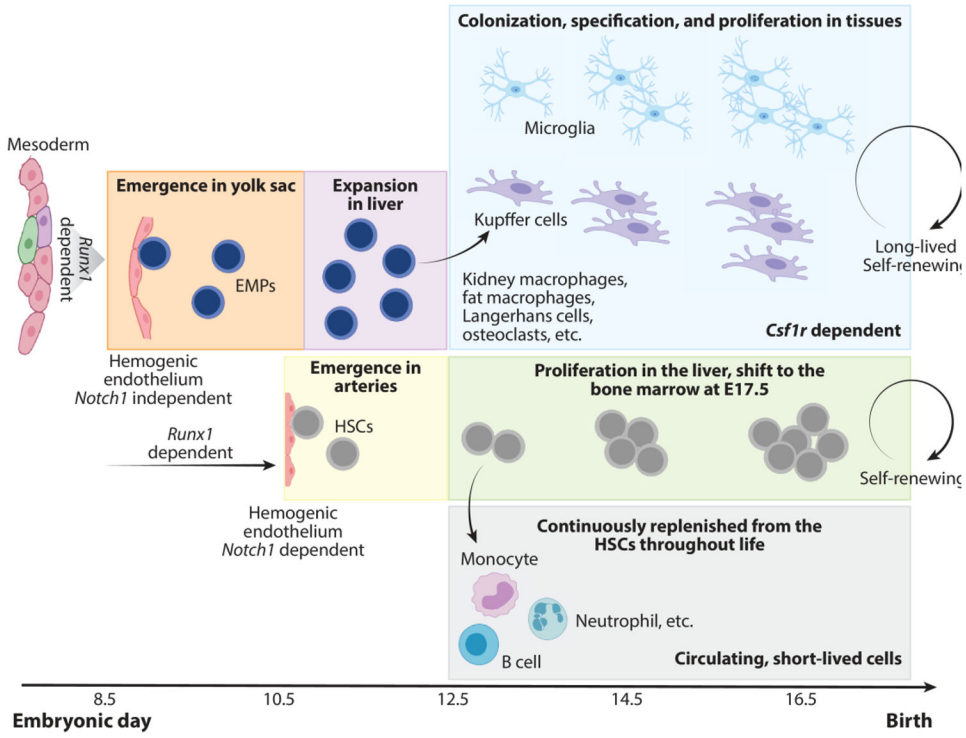

Figure 2.

Macrophage development and specification. Intra- and extraembryonic hemogenic endothelium develops from the mesoderm but gives rise to two developmentally distinct lineages of hematopoietic cells. EMPs emerge in the yolk sac around E8.5 and represent the first wave of definitive hematopoiesis. They migrate to the fetal liver and give rise to fetal erythrocytes and myeloid cells, including fetal macrophages, the precursors of the postnatal resident macrophages (only macrophages are depicted here). EMP-derived macrophages develop in the absence of MYB and persist in postnatal tissues as resident macrophages. Within the embryo proper, the hemogenic endothelium of large arteries gives rise to HSCs at E10.5 as the second wave of the definitive hematopoiesis. HSCs migrate first to the fetal liver, and at E17.5, to the bone marrow, where they persist and self-renew. HSCs continuously give rise to adult-type red blood cells, lymphoid cells, and myeloid cells such as granulocyte, monocyte, and dendritic cell subsets. Abbreviations: E8.5, embryonic day 8.5; EMP, erythromyeloid progenitor; HSC, hematopoietic stem cell. Figure adapted from images created with BioRender.com.

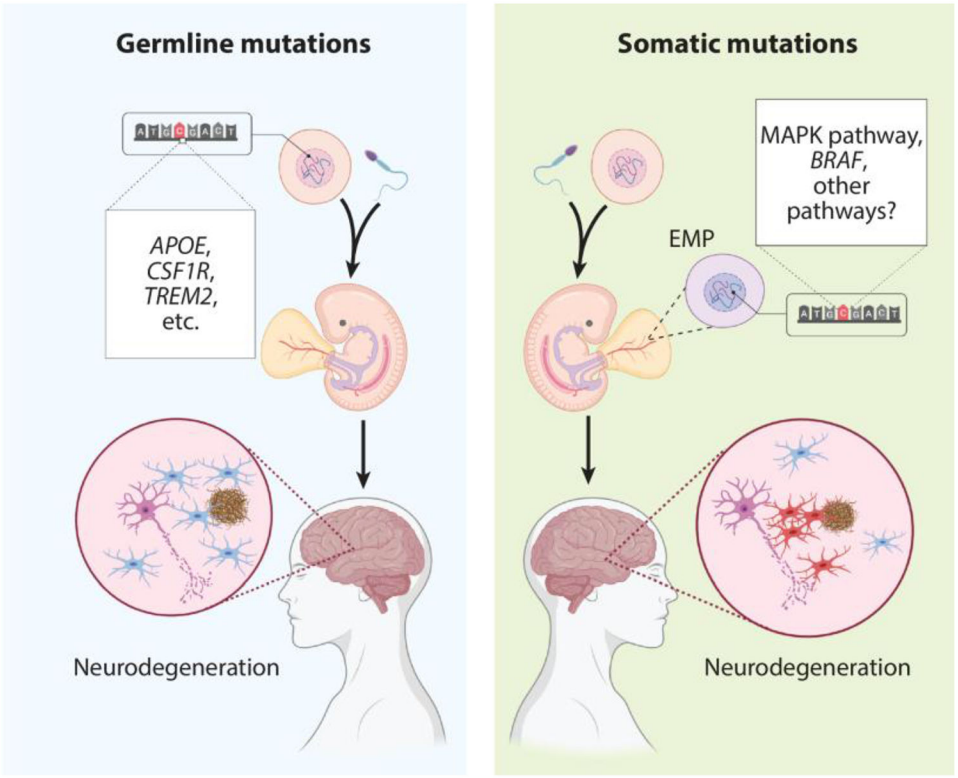

Figure 3.

Germline and somatic causes of neurodegeneration. Germline mutations present in the gametes of either or both parents will be passed down to all cells of the offspring and can be detected by DNA sequencing of any tissue. A number of coding and noncoding variants affecting genes uniquely expressed in macrophages have been found to be enriched in patients with inherited forms of neurodegenerative diseases (Table 2). On the other hand, somatic mutations arise spontaneously throughout development and adulthood and will be passed down only to direct cellular progeny through differentiation and cell division. DNA mutations thus arising within EMPs or their downstream progeny will lead to mutant clones within the tissue-resident macrophage lineage. These mutations are not likely to be detected by whole-tissue genomic sequencing and require enrichment of macrophage populations prior to DNA sequencing. In particular, somatic driver mutations in genes resulting in the aberrant activation of the MAPK pathway are causative of histiocytosis. Abbreviations: EMP, erythromyeloid progenitor; MAPK, mitogen-activated protein kinase. Figure adapted from images created with BioRender.com.

Table 1

Transcription factors and niche signals involved in control of macrophage specification

Organ/tissue	Tissue-resident macrophage/cell	Niche signals	Transcription factors	Homeostatic functions	Citations
Core program embryo	Premacrophage	CSF1	PU.1, ZEB2, cMAF, BATF3, PPARγ, IRF8	Differentiate into tissue-resident macrophages	20, 161
Brain	Microglia	TGF-β, IL-34, SCFAs	SALL1, SALL3, MEIS3, SMAD2/3, MEF2C	Synaptic prun- ing, learning- dependent synapse formation	20, 113, 114, 267
Liver	Kupffer cell	Desmosterol, DLL4	ID1, ID3, LXRα, SPI-C, NR1H3, IRF7	Erythrocyte clearance, portal circulation clearance, bilirubin metabolism	20, 113, 117
Bone	Osteoclast	RANKL, OPG, TGF-β	NFATC1, SMAD2/3, RXR	Bone resorption, ECM remodeling	2, 63, 64, 268, 269
	Bone marrow macrophage	Sterols	SPI-C, LXRα	Regulate HSC niche, erythropoiesis	127, 268, 270
Kidney	Kidney macrophage		IRF9, NFAT, AHR	Sample the circulation and remove macromolecular immune complexes	3, 20
Skin	Langerhans cell	TGF-β, IL-34	RUNX3, ID2, AHR	Skin tolerance/immunity	20, 271-273
Peritoneum	Peritoneal macrophage	Retinoic acid, omental factors	GATA6, CEBPβ	Maintain IgA production	88, 114, 274
Spleen	Red-pulp macrophage	Heme	BACH1, SPI-C	Erythrocyte clearance, iron recycling	49, 269
	Metallophilic and marginal zone macrophage	Oxysterols, marginal zone factors	LXRα	Sample circulation, maintain marginal zone B cells	113, 275
Lung	Alveolar macrophage	CSF2, TGF-β	PPARγ, BACH2, CEBPβ, KLF4, ATF5	Surfactant clearance	20, 276, 277
Intestine	Intestinal macrophage	TGF-β, NOTCH	RUNX3, HES1, DTX4	Gut tolerance/immunity	113

Abbreviations: ECM, extracellular matrix; HSC, hematopoietic stem cell; SCFA, short-chain fatty acid.

Table 2

Examples of human diseases associated with allelic variants expressed in macrophages

Disease	Genes	Variants	Phenotipic outcome	Possible therapeutic strategies	References
Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), also known as POLD and HDLS (OMIM: 221820)	CSF1R	Suspected loss-of-function, autosomal dominant. Most of the reported mutations are missense and located in the intracellular kinase domain of the tyrosine kinase receptor	Behavioral changes, cognitive decline, motor impairments, and dementia. The damage affects the white matter, and the pathological hallmarks include demyelination, axonal loss, and the presence of axonal spheroids. The symptoms begin in the fourth or fifth decade of life and result in death, usually within ten years. Altered cellularity of microglia, regional microgliosis, or reduction	None currently available	1, 14-19
Pediatric-onset leukoencephalopathy (OMIM: 618476)	CSF1R	Suspected loss-of-function, autosomal recessive. Two cases reported with different mutations and phenotypes, one with a missense mutation and the other with a splice variant mutation	Absence of microglia. One case with severe brain abnormalities, including ventriculomegaly and increased bone density, and the patient died at one year of age. This suggests a key role for tissue macrophages in both brain and bone tissue development. This is supported by mouse models of homozygous deletion of CSF1R, where lack of this gene results in brain developmental abnormalities and bone phenotypes	None currently available	2, 19, 73, 163, 220-222
Nasu-Hakola disease, also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (OMIM: 221770, 618193)	TREM2, DAP12	Loss-of-function, autosomal recessive	Progressive presenile dementia associated with recurrent bone fractures due to polycystic osseous lesions of the lower and upper extremities. Postmortem examinations of the brains of these patients show demyelinating lesions, neuronal loss, astrogliosis, and the accumulation of free fatty acids, mainly in the white matter of the frontotemporal lobe and basal ganglia.	There is no curative treatment for the disease. Management is supportive. Antiepileptic drugs are prescribed to prevent seizures. Regular orthopedic and neurologic surveillance is recommended	224-228
Lysosomal storage diseases (230) (OMIM: 230800, 268800)	GBAa, GLA, GLB1, HEXA, HEXB, LAMP2, SMPD1a, CTSDa, SLC17A5a, ASAH1a (for a complete list and associated diseases, see Reference 230)	Most inherited forms are loss-of-function, autosomal recessive	Diverse manifestations	Chaperone therapy, enzyme replacement therapy, hematopoietic stem cell therapy, small-molecule therapy, substrate reduction therapy	230-234
Histiocytosis: Langerhans cell histiocytosis (OMIM:	BRAF, NRAS, MAP3K, PICK1,	Somatic mutation, in general gain-of-function, in genes of	Rare diseases characterized by granulomatous lesions containing neoplastic	Chemotherapy, radiotherapy,MAPK pathway inhibition	23, 250-252, 258-260, 278

Disease	Genes	Variants	Phenotipic outcome	Possible therapeutic strategies	References
604856), juvenile xanthogranuloma, Erdheim-Chester disease	PIK3R2, PIK3CA, PICK3CD	the MAPK pathway. BRAF V600E in ~50% of cases	macrophages, also called histiocytes. Lesions can involve one or multiple organs, such as skin, bone, liver, lung, and brain. Lagerhans cell histiocytosis and juvenile xanthogranuloma predominantly affect young children, and Erdheim-Chester disease is mostly observed in adults		
Osteopetrosis (OMIM: 259710, 166600, 259700, 259720, 259730, 607634, 611490, 611497, 612301)	TCRG1, OSTM1, CLCN7, SNX10, TNFRSF11a, IKBKG. See also TREM2, CSF1R above	Loss-of-function, autosomal recessive: TCRG1, OSTM1, CLCN7, SNX10, TNFRSF11a,,X-linked: IKBKG Autosomal dominant: CLCN7	Osteopetrosis is a rare, inherited disorder that affects bone formation and hematopoietic cell development. It can be caused by defects in osteoclast formation or function, as listed here, or by defects in osteoblast functions	Bone marrow transplantation	2, 19, 62, 162, 163, 221, 223, 279-283
Alzheimer disease (OMIM: 615080, 104310, 104300, 611073, 606187)	APOE, TREM2, CD33, MS4A gene family	Allelic variants identified in association studies, e.g., APOE, TREM2, CD33	Progressive dementia, activated microglia	None currently available	226, 228, 237, 238, 266

Abbreviation: MAPK, mitogen-activated protein kinase. aGene is also a risk factor for Parkinson disease.