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Perivascular macrophages in health and disease

*Antonio Lapenna[1], Michele De Palma[2] and Claire E. Lewis[1]**

[1]*Department of Oncology & Metabolism, University of Sheffield Medical School, Sheffield, UK.*

[2]*Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland.*

**e-mail: claire.lewis@sheffield.ac.uk*

Abstract | Macrophages are a heterogeneous group of cells that are capable of carrying out distinct functions in different tissues, as well as in different locations within a given tissue. Some of these tissue macrophages lie on, or close to, the outer (abluminal) surface of blood vessels and perform several crucial functions at this interface between the tissue and the blood. In steady-state tissues, these perivascular macrophages maintain tight junctions between endothelial cells and limit vessel permeability, phagocytose potential pathogens before they enter tissues from the blood and limit inappropriate inflammation. They also have a multifaceted role in important diseases such as cancer, Alzheimer disease, multiple sclerosis and type 1 diabetes. Here, we examine the important functions of perivascular macrophages in various adult tissues and describe how these functions are perturbed in a broad array of pathological conditions.

[H1] Introduction

Macrophages are present in all organs of the body, where they carry out distinct functions depending on their location and phenotype[1]. During normal vascular development, macrophages directly interact with, and modulate, the developing vasculature[2,3]. In many adult tissues, some macrophages are seen to establish close contacts with blood vessels and to have an array of functions that are important for both tissue homeostasis and pathology. Whereas in some organs such as the brain these perivascular macrophages (PVMs) can be distinguished from other tissue macrophages on the basis of both their proximity to blood vessels and their expression of certain markers[4], in other tissues such as the skin[5] PVMs have been defined largely on the basis of their location. As there is currently no general definition for PVMs, for the purposes of this Review, we define them as macrophages that either make direct contact with the abluminal surface of blood vessels (TABLES 1,2) or are located within approximately one cell thickness from it (within 15 μm of a blood vessel, as defined previously for PVMs in the dermis[5]).

The exact nature of the physical interaction between PVMs and blood vessels can vary in different tissue sites. For example, PVMs can wrap around a blood vessel with or without making direct contact with it, can be either inside or outside the basement membrane of the blood vessel and can extend their filopodia along or through the vessel wall into the blood vessel lumen (FIG. 1). The relevance of these anatomical variations to the functions of PVMs in different tissues is discussed below.

In adult steady-state tissues, PVMs often have important functions related to their perivascular position, such as the regulation of vascular permeability, the scavenging of blood-borne pathogens and the control of the movement of other leukocytes across the vasculature. Although PVMs may express some distinctive phenotypic markers in certain tissues (TABLE 1), they do not share a single, common phenotype. This is likely to result from the exposure of PVMs to a diverse array of signals in distinct tissues, as well as possible differences in their ontogeny (BOX 1).

Importantly, PVMs have recently been shown to have several essential roles in the maintenance of steady-state tissues and to contribute to the aetiology and/or progression of several pathological conditions[6–8]. In this Review, we first examine the functions, phenotype, regulation and origin of PVMs in various steady-state tissues and then contrast these properties with those of PVMs that contribute to the pathobiology of various diseased states.

[H1] Functions in steady-state adult tissues

Outlined below are the functions that are known to be carried out by PVMs in various healthy adult tissues. Some of these functions may also be carried out by most tissue-resident macrophages, whereas other functions are specific to PVMs and are associated with their proximity to the blood vessel endothelium.

[H2] Regulation of blood vessel permeability.

Pericytes, which wrap around the endothelial cells of small blood vessels, have long been known to regulate vascular permeability[9]. However, PVMs may also contribute to this important aspect of vascular homeostasis. For example, when PVMs in the stria vascularis of the cochlea are depleted, tight junctions between blood vessel endothelial cells become unstable, resulting in increased vessel permeability and, ultimately, the loss of hearing[10]. Furthermore, macrophages isolated from the cochlea can limit the permeability of monolayers of cochlear endothelial cells in vitro through the release of pigment epithelium-derived factor (PEDF), which induces endothelial cell expression of proteins involved in tight junctions, such as occludin and vascular endothelial cadherin (VE-cadherin; also known as CDH5)[10]. Furthermore, injection of a small interfering RNA that targets *Serpinf1* (which encodes PEDF) through the tympanic membrane of mice efficiently targeted PVMs in the stria vascularis and resulted in a reduction in tight junctions between endothelial cells[10], which suggests that the release of PEDF by PVMs limits vascular permeability in this tissue. Similarly, PVMs are a prominent component of the blood–brain barrier (BBB)[11] (FIG. 1a), and the permeability of monolayers of endothelial cells isolated from mouse brain is markedly reduced following their co-culture with macrophages[12]. However, it remains to be seen whether macrophage-derived PEDF also limits vessel permeability in the BBB.

PVMs have also been implicated in the regulation of blood vessel permeability in the mesentery, a double fold of the peritoneum[13]. *Csf1*$^{op/op}$ mice have a naturally occurring gene mutation that results in the lack of macrophage colony-stimulating factor 1 (CSF1), a cytokine that sustains the differentiation and viability of macrophages[14]. These CSF1-deficient mice have a reduced number of macrophages in their tissues, including PVMs around mesenteric vessels[13]. The lack of mesenteric PVMs in *Csf1*$^{op/op}$ mice was associated with vascular instability and increased permeability, a phenotype that could be reversed through the adoptive transfer of macrophages[13] that express high levels of the scavenging receptor macrophage mannose receptor 1 (MRC1; also known as CLEC13D)[15]. Mesenteric

PVMs also express high levels of arginase 1 (*Arg1*) mRNA, which, together with MRC1 expression, led the authors to describe these PVMs as having undergone alternative (M2) macrophage activation rather than classical (M1) macrophage activation. Infusion of *Csf1*$^{op/op}$ mice with macrophages lacking expression of MRC1 and *Arg1* (M1-like macrophages) did not attenuate the increased vascular permeability in *Csf1*$^{op/op}$ mice[13]. MRC1^{hi} *Arg1*-expressing macrophages could maintain endothelial cell junctions in vitro by limiting the phosphorylation of the endothelial cell adhesion molecule VE-cadherin[13], which restricts vascular permeability both in vitro and in vivo[16]. The M1–M2 classification of macrophage activation has been used widely since its inception in 2000 and assumes that M1 and M2 macrophages sit at opposing ends of a continuum of activation states[17]. However, it should be noted that this may under-represent the remarkable plasticity and diversity of tissue macrophages. Nevertheless, we have included use of this terminology when it was used by authors to describe their findings.

[H2] Phagocytosis. PVMs are ideally positioned to detect and phagocytose potentially harmful, foreign agents as they cross the vasculature into tissues. In several mouse tissues such as the brain, retina, kidneys, cochlea, testis, pineal gland and pancreatic islets of Langerhans, macrophages have been shown to phagocytose fluorescently labelled macromolecules injected into the systemic circulation (a method that was used previously to define cells of the reticuloendothelial system). Macrophage uptake of such macromolecules in the perivascular niche has been visualized by both analysis of post-mortem tissue and, more recently, intravital imaging in live mice over time[18–25]. For example, in the kidney, PVMs are situated between the abluminal surface of endothelial cells and the basement membrane of capillaries that surround the renal tubules and Bowman capsule (FIG. 1b). These PVMs have highly motile filopodia that extend along the capillary surface and scavenge molecules such as small immune complexes that are actively transported into the renal interstitium through the endothelium[20]. PVMs were observed to move along the abluminal surface of the blood vessel endothelium in the retina, scavenging potential pathogenic substances present in the perivascular space[19] (FIG. 1c). Although perivascular myeloid cells in the islets of Langerhans in the pancreas were initially thought to be dendritic cells (DCs), they have now been shown to be macrophages[24] that project their cytoplasmic extensions into the vessel lumen to take up substances from the blood[25] (FIG. 1d). They may also be capable of phagocytosing dense core granules released by adjacent islet β-cells[26]. In the marginal zone of the spleen, highly phagocytic PVMs known as metallophilic macrophages phagocytose blood-borne pathogens such as viruses and bacteria, therefore limiting early haematogenic spread of the pathogen[27–30]. The proximity of these macrophages to T cell-rich and B cell-rich areas in the spleen may also enable PVMs to modulate adaptive immunity against invading pathogens, for example, by transferring antigens to cross-presenting CD8$^+$ DCs[31]. However, the specific elimination of metallophilic macrophages did not compromise antigen presentation and T cell responses in one study[28]. Finally, macrophages in the myocardium of the heart make contact with both endothelial cells and cardiomyocytes. The pattern of gene expression of these PVMs in mice indicates that they might have a role in the clearance of dead and dying cells[32]. It has been postulated that this phagocytic activity could be part of a broader role for these cells in the maintenance of the myocardium, as they also express genes that promote tissue repair and prevent fibrosis.

[H2] Antigen presentation. In some tissues, PVMs also seem to function as antigen-presenting cells (APCs). For example, in the pancreatic islets of Langerhans, PVMs have been shown to constitutively express β-cell antigens in situ and to be able to present them to naive T cells in ex vivo assays. In lymph nodes, PVMs adhere to the abluminal side of the endothelial cells of the subcapsular sinus and are often termed ‘subcapsular sinus macrophages’. These cells extend processes into the vascular lumen, where they capture lymph-borne agents such as viruses through various cell surface receptors. They then translocate these surface-bound substances across the sinus floor to present them to follicular B cells[33].

PVMs isolated from other tissues also seem to function as APCs ex vivo, although their ability to do this in situ has yet to be confirmed. For example, PVMs isolated from the alveolar interstitium of the lung (a thin area of parenchyma comprising the air–blood interface, in which interstitial macrophages are in close proximity to both capillaries and alveoli) present antigens and induce T cell activation ex vivo[34]. Furthermore, peritubular PVMs in the testis[35], PVMs in the pineal gland[36] and a substantial proportion of PVMs in the retina[37] express MHC class II molecules — an important feature of APCs[38]. However, more studies are required to establish whether these PVMs can process and present antigens efficiently in vivo.

[H2] Immune regulation. Importantly, some PVMs can also have immunosuppressive or anti-inflammatory properties. For example, in both the lungs and the testes, PVMs release large amounts of IL-10, an immunosuppressive cytokine that is also capable of dampening inflammation[39–41]. In the lungs, this could have beneficial effects such as reducing the migration and maturation of alveolar DCs, thereby limiting the onset of respiratory allergies to airborne agents such as pollen, dust mites and mould spores[39]. In the testes, the expression of IL-10 by PVMs, which impairs T cell activation, contributes to making this an immune-privileged organ[40,41]. This is important, as it protects developing spermatocytes — which express new antigens upon meiotic recombination — from destruction by the adaptive immune system. IL-10 is also expressed by PVMs in the myocardium; in addition, these cells express V-set and immunoglobulin domain-containing protein 4 (VSIG4), which is another negative regulator of T cell activation[32]. In the BBB, PVMs limit inflammation by restraining prostaglandin E_2 production by endothelial cells when the latter are exposed to blood-derived bacterial stimuli such as lipopolysaccharide (LPS)[42].

In the sinusoids of the spleen and lymph nodes, PVMs produce large amounts of type I interferon after encountering pathogens during sepsis, which limit excessive adaptive immune responses[43]. However, it should be noted that PVMs can also drive adaptive immune responses by capturing and transferring antigens to DCs[31]. Moreover, metallophilic as well as subcapsular macrophages in the spleen and lymph nodes are permissive to virus replication, which enables the accumulation of viral antigens for presentation to DCs and B cells[44,45]. The perisinusoidal macrophages in the spleen are also able to take up apoptotic cells and transfer self-antigens to DCs, which induces tolerance and prevents autoimmunity[46,47]. The human spleen lacks a marginal zone sinus, but the capillaries of the perifollicular zone are typically covered by a one-layered or two-layered sheath of CD169$^+$ macrophages that are considered to be the equivalent of rodent metallophilic macrophages[48].

[H2] Regulation of steroidogenesis and gamete formation. In the adult testis, PVMs are located both in the interstitium (known as interstitial PVMs) and along the seminiferous tubules (known as peritubular PVMs)[35]. Interstitial PVMs are intermingled with Leydig cells and capillaries, extend filopodia along the blood vessel walls and promote Leydig cell development and steroidogenesis[49,50]. This is thought to occur through the secretion of 25-hydroxycholesterol, a factor that induces the synthesis of testosterone by Leydig cells; the

production of 25-hydroxycholesterol is then negatively regulated by testosterone itself[49,51]. Peritubular PVMs lie on the surface of seminiferous tubules with long processes that make contact with neighbouring blood vessels, and they promote spermatogenesis by releasing factors such as CSF1 and retinoic acid[52,53]. This was inferred from a study showing that these PVMs express CSF1 and two enzymes that are essential for retinoic acid synthesis, retinal dehydrogenase 2 (RALDH2) and retinol dehydrogenase 10 (RDH10). Moreover, the density of peritubular PVMs was seen to be greater in segments of the seminiferous tubules that are enriched in undifferentiated spermatogonia[35]. These observations are supported by the finding that macrophage depletion in the mouse testis caused a marked decrease in both the total number and the proliferative activity of undifferentiated spermatogonia in seminiferous tubules[35]. However, some macrophages in the testis are associated with Leydig cells through a unique intercalated adhesion mechanism[35]. These macrophages are not associated with blood vessels per se but could still have some role in regulating the production of testosterone. Macrophage depletion removes these cells as well as PVMs, so it is difficult to distinguish the roles of these two macrophage populations in the physiology described above.

In the ovary, PVMs seem to support fertility[54], and their number and distribution vary with the oestrus cycle. For example, during ovulation, the number of macrophages (most of which are PVMs[55–57]) increases in the thecal layers of both human and mouse follicles[54–56]. Once the oocyte is released, macrophages enter the developing corpus luteum and settle along newly formed blood vessels[56,57]. These PVMs promote angiogenesis[58] and help to maintain vessel integrity in the corpus luteum[59]. This is crucial for pregnancy, as the establishment of a functional capillary network in the corpus luteum is required for progesterone production and thus successful implantation of the embryo[59].

In summary, it can be seen that PVMs carry out a range of homeostatic and protective functions under steady-state conditions to maintain tissue integrity. However, they can also have highly specialized, tissue-specific functions, such as filtering the blood in the kidneys, regulating hormone production in the testes and stimulating angiogenesis in the corpus luteum.

[H1] Functions in diseased tissues

Here, we outline the important roles of PVMs in several pathological processes, where they seem to be able to either promote or limit disease progression.

[H2] Malignant tumours.

A subset of tumour-associated macrophages (TAMs) lies close to blood vessels in mouse and human tumours (FIG. 2a); these macrophages were initially characterized by their expression of angiopoietin 1 receptor (TIE2)[60]. The selective elimination of these TIE2$^+$ PVMs in mouse tumours showed that they are important for tumour angiogenesis and growth[60–62]. Furthermore, their numbers positively correlate with microvessel density in both renal and hepatocellular human carcinomas, which suggests that they also promote angiogenesis in human tumours[63,64]. When isolated from mouse mammary tumours, these PVMs were found to express higher levels of pro-angiogenic and M2-like genes than their TIE2$^-$ (non-perivascular) counterparts[65].

Angiopoietin 2 (ANGPT2), which is often upregulated by tumour endothelial cells, triggers the phosphorylation of TIE2 in macrophages and promotes their upregulation of various pro-angiogenic factors, such as the enzymes thymidine phosphorylase and cathepsin B. ANGPT2 is also chemotactic for TIE2$^+$ monocytes and macrophages and stimulates their accumulation around blood vessels in mouse tumours[60,66–68]. Therefore, it is tempting to speculate that exposure of TIE2$^+$ PVMs to ANGPT2 in malignant tumours regulates the vascular-promoting activities of these cells. Interestingly, TIE2$^+$ PVMs, similarly to TIE2$^+$ TAMs[61,62,65,69], facilitate the sprouting[70], branching[3] and anastomosis[71] of blood vessels during vascular development in mouse embryos. ANGPT2 also stimulates the immunosuppressive functions of TIE2$^+$ PVMs by upregulating their expression of IL-10, which suppresses T cell proliferation ex vivo[67], and of CC-chemokine ligand 17 (CCL17), which recruits regulatory T (T_{reg}) cells[67]. Other mechanisms regulating the phenotype and functions of TIE2$^+$ TAMs include those mediated by CSF1 and invariant natural killer T (iNKT) cells. Perivascular TIE2$^+$ TAMs express higher levels of the CSF1 receptor (*Csf1r*) than do TIE2$^-$ TAMs[65], and CSF1 has been shown to upregulate the expression of both TIE2 and vascular endothelial growth factor A (VEGFA) by TIE2$^+$ TAMs[72,73]. Furthermore, a recent study has shown that the presence of TIE2$^+$ PVMs in mouse prostate tumours is, at least partly, regulated by tumour-infiltrating iNKT cells, as the latter promote the selective killing of TIE2$^+$ macrophages to inhibit tumour angiogenesis and growth[74].

High-resolution, intravital imaging of blood vessels in mouse mammary tumours has shown that cancer cells often undergo intravasation at sites of close association between TIE2$^+$ PVMs and endothelial cells. The escape of cancer cells into the circulation at these sites in primary tumours leads to the formation of metastases at distant sites, such as the lungs. The PVM–endothelial cell–cancer cell clusters have been termed tumour microenvironments of metastasis (TMEMs)[75]. Increased intravasation occurs at these sites as a result of increased vascular permeability induced by both increased expression of VEGFA by TIE2$^+$ PVMs and a decreased number of VE-cadherin-based junctional complexes in endothelial cells[75]. Furthermore, a recent study has shown that CD163$^+$ TAMs expressing high levels of insulin-like growth factor 1 (*Igf1*), a growth and survival factor that is also upregulated by TIE2$^+$ TAMs[65], stimulate metastasis in primary mouse mammary tumours[76]. The above findings accord well with the observation that high TMEM density — which presumably reflects a high density of PVMs — in human breast carcinomas correlates with increased risk of distant metastasis[77].

PVMs are also present in metastatic mouse and human tumours[78–80]. MRC1$^+$ PVMs have been reported in both lung metastases of a mouse breast cancer (4T1) model and human bone metastases from patients with advanced breast cancer[80]. Moreover, PVMs occur at sites of tumour cell extravasation in lung metastases in a mouse breast cancer (MMTV-PyMT) model. Interestingly, these metastases were inhibited when the recruitment of CC-chemokine receptor 2 (CCR2)$^+$ inflammatory monocytes to the lungs was prevented using a CCL2-specific antibody or following the conditional knockdown of VEGFA expression by these cells[78,79].

Finally, PVMs have been implicated in tumour resistance to some antivascular agents, such as the vascular-disrupting agent combretastatin-A4-phosphate[81]. PVMs also contribute to the relapse of mouse tumours after chemotherapy and irradiation[80,82,83]. This effect probably involves CXC-chemokine ligand 12 (CXCL12)-driven recruitment of TIE2$^+$MRC1$^+$CXCR4$^+$ PVMs to the tumour from the circulation after the cessation of therapy[80,82,83], which then stimulate tumour revascularization and regrowth[83].

[H2] Diseases of the central nervous system.

PVMs have been implicated in various pathological conditions of the central nervous system (CNS). Their role in these diseases has been identified using clodronate-containing liposomes (CCLs), which, when injected directly into the cerebral ventricles, are phagocytosed by PVMs but not microglia, leading to PVM depletion[84]. The accumulation of amyloid-β (Aβ) peptide in and around cerebral blood vessels is a hallmark feature of both Alzheimer disease and cerebral amyloid angiopathy. In a transgenic mouse model of such amyloid accumulation, CCL-mediated elimination of PVMs increased Aβ deposition around cerebral

blood vessels, although it should be noted that meningeal macrophages (which were also depleted in this study) may have contributed to this phenomenon[85]. Interestingly, when chitin was injected into the cerebrospinal fluid of the brain ventricles to selectively stimulate brain PVMs to acquire a phenotype resembling M2-like activation[86], the clearance of vascular amyloid was increased[85]. This role for PVMs in amyloid clearance is supported by another study, which used a transgenic mouse model of cerebral amyloid accumulation to show that PVMs accumulate around areas of amyloid deposition and upregulate their expression of scavenger receptor class B member 1 (SRB1)[87]. When mice in this model were crossed with a transgenic mouse line lacking SRB1, amyloid deposition in the brain was increased, which suggests that SRB1 expression by PVMs mediates their ability to clear amyloid[87].

However, as well as this protective role in scavenging amyloid, brain PVMs can also accelerate the neurovascular dysfunction that occurs in areas of the brain in which amyloid deposits occur. This is because amyloid-mediated activation of CD36 stimulates PVMs to release reactive oxygen species (ROS), leading to increased cerebrovascular oxidative stress[88]. Similarly, brain PVMs have a role in the neurocognitive alterations that are related to hypertension, as depletion of PVMs in mouse models of chronic hypertension reduces vascular oxidative stress and rescues cognitive function[89]. Studies of bone marrow chimeric mice have shown that the cognitive dysfunction is mediated by the activation of type 1 angiotensin II receptors on PVMs by angiotensin II, which is known to increase blood pressure by stimulating the contraction of vascular smooth muscle cells. The PVM activation results in the generation of NADPH oxidase 2 (NOX2; also known as CYBB)-dependent ROS[89], which promote vascular dysfunction.

Brain PVMs also have a role in protecting the brain during bacterial meningitis. They do so by facilitating the influx of neutrophils into the brain to counteract invading bacteria. This was shown in a rat model of streptococcal meningitis, in which CCL-mediated depletion of brain PVMs reduced the influx of neutrophils across the BBB into the brain, increased bacterial load in the cerebrospinal fluid and increased symptoms associated with infection[90]. Paradoxically, the elimination of PVMs was accompanied by increased levels of CXCL2, which is a chemotactic factor for neutrophils, as well as leukocyte adhesion molecules in endothelial cells. These apparently contradictory results show that, in the absence of PVMs, compensatory mechanisms occur that may support neutrophil influx. However, the role of PVMs in protection from, versus facilitation of, infection may vary with the type of pathogen, as CCL-mediated depletion of brain PVMs increased the survival of mice with vesicular stomatitis virus-induced encephalitis[91]. Similarly, brain PVMs have been implicated in the pathogenesis of encephalitis associated with HIV-1 infection, as these PVMs seem to host a viral reservoir in the brain[92,93]. In rhesus macaques infected with a simian immunodeficiency virus (SIV), both SIV RNA and the viral glycoprotein 120 (gp120) were abundant in PVMs but were barely detectable in $CD163^{-}$ microglia in the brain parenchyma[92,93]. Moreover, $CD163^{+}$ PVMs in encephalitic lesions express the proliferation marker Ki-67 when infected with HIV or SIV[94], which indicates that these cells may proliferate under such conditions, thereby increasing the cellular reservoir of the virus. Interestingly, these studies suggest that brain PVMs, similarly to peri-sinusoidal PVMs in the spleen and lymph nodes, can function as a reservoir for viruses.

Brain PVMs may also have a role in the progression of multiple sclerosis. These cells are typically $CD163^{+}HLA\text{-}DR^{+}$ (REF.[95]) and have been found to accumulate around blood vessels in areas of demyelination in the CNS of patients with multiple sclerosis. They present peptides derived from myelin basic protein on the MHC class II molecule HLA-DR[96], which could lead to an autoimmune reaction to myelin and thereby accelerate disease progression. This potential role for PVMs is also supported by studies of rats with experimental autoimmune encephalomyelitis, a commonly used model of multiple sclerosis, in which the number of PVMs in the brain is increased; the selective elimination of PVMs in this model reduces the progression of the disease[97]. In another study, it was reported that in rat models, PVMs strongly upregulate expression of CCL2 and CCL3, which suggests that these chemokines maypromote monocyte recruitment to the brain during multiple sclerosis[98].

Finally, PVMs have been implicated in protecting the brain from the deleterious effects on glucose uptake and from cognitive impairment in mice fed a high-fat diet[99]. Normally, glucose transporter type 1, erythrocyte/brain (GLUT1; also known as SLC2A1) shuttles glucose across endothelial cells of the BBB into the brain. This process was reduced in mice fed a high-fat diet, triggering a compensatory increase of VEGFA expression by PVMs in the BBB, which in turn restored GLUT1 expression and cerebral glucose metabolism. When VEGFA expression by PVMs was ablated, GLUT1 expression remained low in the BBB and the integrity of the BBB was compromised, leading to cognitive impairment of the mice. Thus, PVMs in the BBB might have a role in limiting neurodegeneration in obesity.

[H2] Inflammatory conditions. PVMs may also promote rather than dampen inflammation. This can be beneficial under some conditions but when uncontrolled can lead to chronic inflammation and contribute to disease progression.

During experimentally induced inflammation of the retina in rabbits, PVMs increase their expression of MHC class II molecules and accumulate in the injured area[100]. PVMs also show increased motility and accumulation when the blood–retinal barrier is experimentally disrupted in mice; retinal PVMs move into the injured area along blood vessels from non-disrupted areas[19]. In both cases, PVMs attempt to limit the effects of the injury or inflammation by phagocytosing dead and dying cells or by limiting the extravasation of blood-derived materials[19,100]. Alternatively, in chronic inflammation of the uvea (experimental autoimmune uveitis) in rats, retinal PVMs support retinitis by releasing pro-inflammatory cytokines such as IL-1β and tumour necrosis factor[101].

In a mouse model of LPS-induced otitis, PVMs are activated, and this correlates with the vascular leakage of the intrastrial fluid–blood barrier and hearing loss[102]. Furthermore, in a model of acoustic trauma, PVMs detach from capillary walls and decrease their release of PEDF, which in turn increases vascular permeability in the cochlea[103] (FIG. 2b). Finally, the contribution of cochlear PVMs to age-related hearing loss (presbycusis) was inferred from the observation that these cells are reduced in number — and have less physical contact with endothelial cells — in aged mice[104].

The deposition of immune complexes in the renal interstitium contributes to autoimmune diseases of the kidneys. Recently, a combination of tissue immunostaining and intravital imaging showed that renal PVMs lying between the endothelium and the basement membrane of glomerular and peritubular capillaries take up, via Fcγ receptor IV (FcγRIV), immune complexes delivered into the interstitium from the blood by *trans*-endothelial transport. This then triggers the onset of inflammation[20] (FIG. 2c).

There are also studies in mice showing that $CD4^{hi}$ PVMs in the dermis of the skin can promote inflammation by supporting the *trans*-endothelial migration of neutrophils in dermal postcapillary venules[105], which is a key event in the inflammatory response against pathogens. In *DPE*–GFP mice, which express green fluorescent protein (GFP) under the control of the *Cd4* enhancer and promoter, infection with *Staphylococcus aureus* promotes neutrophil extravasation specifically through postcapillary dermal venules surrounded by clusters of GFP^{+} PVMs that express neutrophil chemoattractants[105]. Interestingly, GFP^{+} PVMs could be lysed by a toxin, Hle, produced by *S. aureus*. When mice were infected with Hle-deficient bacteria, PVMs were not lysed, resulting in increased neutrophil extravasation[105]. Therefore, bacterial products such as Hle can protect bacteria from host defences[106] by ablating skin PVMs, which results in

the reduced recruitment of neutrophils.

Skin PVMs are also important for the induction of DC clustering around postcapillary venules — an area where effector T cells extravasate into inflamed skin during inflammation[107]. Indeed, PVMs could have a role in the induction of skin allergies, as a mouse model of contact hypersensitivity showed that PVMs attract DCs around postcapillary venules through the release of CXCL2 in response to IL-1α produced by activated keratinocytes. This DC clustering was abrogated by inhibition of either IL-1 receptor (IL-1R) or CXC-chemokine receptor 2 (CXCR2)[108]. Therefore, skin PVMs facilitate DC–T cell interactions and, in turn, promote adaptive immune responses.

A recent study has suggested that PVMs in the lung interstitium have an important role in the pathogenesis of lung fibrosis[109]. In a mouse model of lung fibrosis, intratracheal injection of bleomycin to induce lung injury increased the number of vascular endothelial growth factor receptor 1 (VEGFR1)-expressing PVMs present around pulmonary capillaries. These cells then stimulated WNT–β-catenin-dependent upregulation of the Notch ligand Jagged 1 in neighbouring endothelial cells, which, in turn, stimulated Notch signalling in perivascular fibroblasts to promote lung fibrosis (FIG. 2d). However, it is not clear whether these pro-fibrotic PVMs in the lungs derive from monocytes recruited from the circulation or lung-resident PVMs. Also, it remains to be seen whether PVMs have a similar role in regulating fibrotic reactions in other tissues[110].

[H2] Type 1 diabetes. Type 1 diabetes is an autoimmune disease characterized by the infiltration of pancreatic islets by immune cells, resulting in T cell-mediated destruction of insulin-producing β-cells. Intravital imaging of islets in the non-obese diabetic (NOD) mouse model of type 1 diabetes has led to speculation regarding a possible role for PVMs in the pathogenesis of this disease. For example, there is close interaction between PVMs and T cells in the pancreatic islets[111], and at the onset of pancreatic autoimmunity, both $CD4^+$ and $CD8^+$ T cells make close contacts with islet PVMs. Thus, the PVMs may support diabetogenesis by presenting islet-derived antigens to T cells (as they are able to do so ex vivo). Indeed, the pancreatic islets of *Nox1*$^{-/-}$ mice — which lack NADPH oxidase 1 (NOX1)-derived superoxide (which is important for the pro-inflammatory, M1-like activation status of islet PVMs[112,113]) — contain PVMs that are less pro-inflammatory, as assessed by their gene expression profile[113]. This contrasts with NOD mice expressing normal levels of NOX1, which have M1-like islet PVMs expressing high levels of pro-inflammatory genes. NOX1-proficient NOD mice develop diabetes more rapidly than NOD mice lacking NOX1 (REF.[114]). Moreover, when NOX1-deficient NOD mice are infected with the diabetogenic agent coxsackie virus B3, they remain resistant to virus-induced autoimmune diabetes, and their islet PVMs fail to induce a strong pro-inflammatory response while retaining the ability to clear virus[113]. It is possible, therefore, that certain viral infections may be linked to the onset of type 1 diabetes[115] and that this process involves the activation of pro-inflammatory islet PVMs, which, in turn, promote autoimmunity.

In summary, PVMs have been implicated in a wide variety of disease conditions. Whereas in malignant tumours, multiple sclerosis, HIV infection and type 1 diabetes, PVMs seem to promote disease progression, in Alzheimer disease and bacterial meningitis, they can be protective and limit, but not prevent, the onset of tissue pathology.

[H1] Concluding remarks

As outlined above, PVMs carry out several important functions at the interface between tissues and the blood, including limiting vascular permeability to maintain tissue integrity, sensing and clearing potential blood-borne pathogens rapidly as they enter tissues and limiting inflammation and autoimmunity. The study of these cells is a rapidly expanding field, and a picture is emerging of the factors in the perivascular niche that regulate their functions in both steady-state and diseased tissues. Endothelial cell-derived cytokines such as ANGPT2, CXCL12 and CSF1 have been shown to support the proliferation, differentiation and retention of PVMs in some tissues, and extracellular vesicles can also transfer signalling molecules and genetic information between these two cell types[2,8,116].

By contrast, little is known about how pericytes interact with PVMs in the vascular niche or the extent to which this interaction regulates the maintenance and functions of either cell type. Both PVMs and pericytes seem to contribute to the control of vascular permeability, raising the intriguing question of whether their contribution to this process differs between tissues or even in different areas of the same tissue. Another unanswered question concerns whether the functions of PVMs vary with their position within the vascular tree (for example, capillaries versus venules) of a given tissue or organ. We also know little about whether PVMs interact with intravascular macrophages, such as Kupffer cells in the liver, when both are in contact with the same blood vessel. Although intravascular macrophages have some functional similarities with PVMs, they also carry out distinct and specialized tasks (BOX 2), some of which may depend on their exposure to the constituents of the blood, the sheer stress of being under flow and/or differences in their ontogeny.

In certain diseased tissues, the selective depletion or re-education of PVMs, such as those driving angiogenesis and metastasis in tumours, triggering inflammation in the kidneys or functioning as a viral reservoir in the brain, could provide therapeutic benefit. However, targeting PVMs selectively is currently challenging, as PVMs share many cell surface receptors (TABLES 1,2), transcriptional programmes and signalling pathways with other macrophage populations[117]. For example, some studies have attempted to selectively target PVMs in the mouse brain using CCLs. However, this approach probably depletes both meningeal macrophages and PVMs[5,90,91]. Interestingly, a recent study has shown that PVMs can derive from other macrophages in the same tissue, highlighting the interrelationship between motile TAMs and sessile PVMs in mouse mammary tumours[118]. Monocyte-derived TAMs were seen to be attracted to blood vessels in response to CXCL12 expressed by perivascular fibroblasts. Upon reaching the perivascular niche, these motile TAMs then became sessile PVMs. This exciting new finding argues in favour of the notion that PVMs may sometimes represent a ‘snapshot’ of a highly dynamic process. It remains to be seen whether PVMs in healthy tissues can also derive from monocyte-derived macrophages elsewhere in the same tissue or organ. Although there is evidence for PVMs in the myocardium being derived from circulating monocytes[119] (BOX 1), this may not be ubiquitous, as other studies have shown that PVMs in the healthy brain, pancreas and testis are derived from the local proliferation of yolk sac-derived progenitors[69,120,121] (BOX 1). However, this does not exclude the possibility that self-renewing, yolk sac-derived macrophages can migrate into the perivascular niche under some conditions. Other studies have tried to separate PVMs from non-PVM macrophages in the mouse cortex on the basis of CD45 expression. However, use of fluorescence-activated cell sorting (FACS) to separate $CD45^{hi}$ macrophages (mainly PVMs) from $CD45^{low}$ microglia resulted in enrichment for rather than isolation of pure PVMs[120]. A recent study took a different approach to isolate various types of perivascular cell situated along blood vessels in the healthy mouse cortex. This involved first isolating the brain vasculature, enzymatically dispersing the cells attached to these vessels and then analysing their gene expression through single cell RNA sequencing[122].

In other tissues such as mouse tumours, earlier studies have used *Tie2*–GFP reporter mice to isolate $TIE2^+$ PVMs[68]. As PVMs in

some tissues express high levels of MRC1 (TABLES 1,2), it may be possible to use fluorescently labelled high-molecular-mass dextran to isolate these cells (or to target them with dextran-coated nanoparticles), as this form of dextran is selectively ingested by MRC1$^+$ PVMs in mouse mammary tumours[123]. However, the use of dextran to label PVMs may be restricted to diseased tissues with increased vessel permeability such as malignant tumours, where passage of dextran across the vasculature into the perivascular space is assured.

As mentioned previously, some studies have shown that PVMs in certain tissues express markers that are consistent with an M2-like phenotype, although mixed M1–M2 phenotypes predominate in most of the tissues and organs that have been examined (TABLES 1,2). This is of interest because recent experimental data suggest that, in order to limit vascular permeability, PVMs need to be M2-skewed[13]. However, there is now considerable evidence that PVMs in tumours are largely M2-skewed[68] and that they promote, rather than limit, vascular permeability[75]. This means that the effects of PVMs on vascular permeability may depend upon their local environment. Inhibitors of CSF1R have been found to induce facial or peri-orbital oedema in a substantial proportion of patients[124]. Notably, CSF1R inhibitors deplete macrophages from several organs[125], so oedema formation may be explained by the loss of vascular integrity and the increased permeability at certain as-yet-undetermined sites[126]. Deciphering the key factors that regulate the development and function of PVMs in either normal tissues or tumours might help to develop drugs that selectively target pro-tumoural PVMs while sparing PVM populations that are likely to maintain vascular integrity in normal organs.

We still have much to learn about the biology of PVMs. Increasing use of high-resolution imaging techniques and precision tools for gene and protein analysis at the single cell level will, hopefully, generate new insights into the functions of these cells and highlight targets for therapeutic intervention.

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A.L. and C.E.L. conceived the topic. All authors provided intellectual input and contributed to writing, reviewing and editing the article.

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Box 1 | Ontogeny of perivascular macrophages

As is the case for other tissue-resident macrophage populations, the exact origin(s) of perivascular macrophages (PVMs) in most tissues are still poorly understood. However, this has been described in more detail for several tissues.

[b1] Brain

Initial studies using bone marrow transplantation (BMT) seemed to show that PVMs in the healthy adult mouse brain originate from precursors in the bone marrow[127]. However, more recent fate-mapping studies have shown that brain PVMs actually originate from yolk sac-derived, erythromyeloid progenitors that are seeded in brain tissue during early embryogenesis[120]. This apparent discrepancy between the studies may be due to the fact that BMT following whole-body irradiation can lead to the atypical recruitment of monocytes into the central nervous system[128].

[b1] Heart

There are two subsets of PVMs in the myocardium — a more abundant subset derived from embryonic yolk sac progenitors that self-renew during adulthood and a smaller subset derived from haematopoietic stem cell-derived precursors in the fetal liver. The latter subset depends on circulating monocytes for maintenance[119]. These results were obtained from parallel in vivo cell tracking, parabiosis, bone marrow transplants and fate-mapping studies[119]. Moreover, following the disruption of homeostasis, monocyte-derived macrophages were not only recruited to the myocardium but also permanently replaced the embryonically derived, resident macrophage populations[119].

[b1] Endocrine pancreas

PVMs in pancreatic islets seem to be derived mainly from yolk sac precursors that self-renew throughout adult life. After myeloablation and BMT, bone marrow-derived precursors were seen to be able to replace pancreatic islet PVMs, but parabiosis studies showed that most islet PVMs are long lived, self-replicating cells and cannot be replaced by blood monocytes under steady state (only after irradiation and/or myeloablation)[121].

[b1] Testis

In the testis, interstitial PVMs derive from yolk sac progenitors, whereas peritubular PVMs are exclusively constituted postnatally from bone marrow-derived progenitors[69]. In adults, the total number of PVMs in the testis is maintained by self-renewal, and these PVMs can only partially be replenished by circulating monocytes[69].

[b1] Tumours

Although the origin of angiopoietin 1 receptor $(TIE2)^+$ PVMs in tumours has not been fully defined, some have suggested that they derive from $Ly6C^{low}CX_3CR1^{hi}CCR2^{low}$ monocytes, which have a similar phenotype[62,67]. A minor subset of human monocytes (<25%) expresses TIE2 and could, therefore, be a circulating pool of potential precursors for $TIE2^+$ PVMs[61,62,66]. However, in a mouse model of pancreatic ductal adenocarcinoma, tumour-associated macrophages (TAMs) have recently been shown to be derived from both circulating monocytes and yolk sac-derived macrophages[129]. PVMs were not looked at per se in this study, so it is not known whether they fall into one or both TAM subsets in this type of tumour.

Box 2 | Comparison of the main functions of perivascular and intravascular macrophages in the liver, spleen and lymph nodes under steady-state conditions

[b1] Functions of perivascular macrophages

- Regulation of vascular permeability[13]
- Phagocytosis of pathogens and other potentially harmful blood-borne agents[18–23,25,27–30]
- Antigen presentation[11,24,26,29,33,34,36,37]
- Maintenance of immune tolerance in some tissues through local immunosuppression and participation in tissue–blood barrier functions[18,19,21,40,42]
- Limiting inappropriate inflammation[32,39,40,42,46,47], with the exception of perivascular macrophages in pancreatic islets, which express pro-inflammatory genes (TABLE 1)

[b1] Functions of intravascular macrophages

- Phagocytosis of pathogens and other potentially harmful blood-borne agents, in the case of Kupffer cells* (liver), red pulp macrophages (spleen) and medullary macrophages in the lymph nodes[29,30,130]
- Destruction of aged platelets and erythrocytes (a process known as haemocatheresis) and the recycling of iron, in the case of Kupffer cells and red pulp macrophages[27,30,131]
- Antigen presentation, in the case of Kupffer cells[132]
- Uptake and metabolism of lipids, in the case of Kupffer cells[133]

*Kupffer cells sometimes extend their filopodia through the perivascular space of Disse. However, because their cell bodies are always on the luminal side of the liver sinusoids, they are intravascular macrophages[134].

Fig. 1 | **Interactions between perivascular macrophages and blood vessels in steady-state tissues.** Transmission electron microscopy has been used to provide unequivocal evidence of the various sites that are occupied by macrophages in the perivascular niche in the following tissues. **a** | In the brain, perivascular macrophages (PVMs) lie under the basement membrane alongside pericytes. **b** | In the kidneys, PVMs also lie under the basement membrane on the abluminal side of endothelial cells and extend long filopodia along the vessel length. **c** | In the retina, PVMs lie on the outer surface of the basement membrane, where they scavenge along the outside of the retinal vessels. They often contain autofluorescent inclusions. **d** | In the pancreatic islets of Langerhans, PVMs make contact with endothelial cells and often extend protrusions into the vessel lumen. In other tissues (not shown), PVMs make contact with, or are found in close proximity to, the abluminal surface of blood vessels (for example, in the dermis of the skin, PVMs are usually found within 15 μm of vessels), but the specific nature of their interaction with the endothelium (in other words, whether they reside below the basement membrane or on its abluminal surface) has yet to be determined by ultrastructural studies.

Fig. 2 | **Role of perivascular macrophages in diseased tissues. a** | In malignant tumours, angiopoietin 1 receptor $(TIE2)^+$ perivascular macrophages (PVMs) stimulate several tumour-promoting processes in response to cytokines that are present in the perivascular niche such as angiopoietin 2 (ANGPT2) (which binds TIE2), macrophage colony-stimulating factor 1 (CSF1) (which binds CSF1 receptor (CSF1R)) and CXC-chemokine ligand 12 (CXCL12) (which

binds CXC-chemokine receptor 4 (CXCR4)). **b** | In acoustic trauma, PVMs detach from capillaries and decrease their release of pigment epithelium-derived factor (PEDF). This results in decreased stability of tight junctions between blood vessel endothelial cells and increased vascular permeability, which compromises the integrity of the labyrinth–blood barrier in the cochlea and can lead to hearing loss. **c** | In renal inflammation, PVMs in the kidneys ingest circulating immune complexes — which are taken up from the blood by endothelial cells — through Fcγ receptor IV (FcγRIV). This induces inflammation, including the recruitment of monocytes and neutrophils into the renal interstitium. **d** | After lung injury (here, induced experimentally by bleomycin injection), vascular endothelial growth factor receptor 1 (VEGFR1)$^+$ PVMs in the perivascular niche release WNT3A, which induces a β-catenin-mediated signalling pathway in blood vessel endothelial cells that upregulates their expression of Jagged 1. This triggers (through Notch signalling) the production and release of collagen from perivascular fibroblasts and promotes fibrosis. PEDFR, PEDF receptor.

Table 1 | Features of perivascular macrophages in steady-state adult tissues (mouse and human)

Healthy adult tissue	Species	Phenotype	Activation markers expressed	Gene expre
Brain	Mouse	$CD45^{hi}CD11b^{+}Ly6C^{low}CX_3CR1^{low}AIF1^{-}F4/80^{+}$	$CD163^{+}LYVE1^{+}MRC1^{+}MHCII^{hi}CD80^{+}CD86^{+}CD40^{+}$	*Cd36*, *Mrc1*, *Slc40a1*, *F1*
	Human	$CD45^{low}CD68^{+}$	$CD163^{+}HLAII^{+}MRC1^{+}CD209^{+}CD40^{+}CD86^{+}CD80^{-}$	ND
Retina	Mouse	$CD45^{hi}AIF1^{-}F4/80^{+}$	$SRA1^{+}MHCII^{hi}$	ND
	Human	$CD45^{+}S22^{+}$	$HLAII^{hi}$	ND
Cochlea	Mouse	$F4/80^{+}CD68^{+}$	$SRA1^{+}SRB1^{+}$	ND
Kidney	Mouse	$F4/80^{hi}CX_3CR1^{+}CD11c^{+}$	$MHCII^{+}CD86^{+}$	ND
Lung	Mouse	$F4/80^{+}CD11b^{hi}CD11c^{low}CD64^{hi}$	$MHCII^{+}MRC1^{+}$	ND
	Human	$CD68^{+}CD11b^{+}CD11c^{low}$	$HLAII^{+}MRC1^{+}$	ND
Myocardium	Mouse	$CD45^{+}CD11b^{+}F4/80^{+}CD14^{+}$	$MHCII^{+}CD86^{+}$	*Cx3cr1*, *Mrc*, *Mgl1*, *Mgl2*, *C3ar1*, *Igf1*, *Il1b*, *Il6*, *Il1*, *Cxcl3* and *V*
Skin	Mouse	$CD45^{+}CD11b^{hi}F4/80^{+}CD68^{+}CD64^{+}CD169^{+}ABCA1^{+}$	$MHCII^{+}$	*Csfr1*, *Cd4* a
	Human	$CD11b^{+}CD68^{+}F13A^{+}$	$LYVE1^{+}CD163^{+}MRC1^{+}HLAII^{+}$	ND
Pancreas	Mouse	$CD45^{+}CD11b^{+}CD11c^{+}CD64^{+}CD68^{+}F4/80^{+}$	$MHCII^{+}$	*Il1b* and *Tnf*

Pineal gland		Mouse	$CD68^+$	$MHCII^+$	ND
		Rat	$CD68^+$	$MHCII^+$	ND
Testis	Interstitium	Mouse	$CD11b^+AIF1^+F4/80^+CSF1R^+$	$MHCII^-$	*Ym1*, *Arg1*, *Marco*
	Peritubular space	Mouse	$CD11b^+AIF1^+F4/80^+CSF1R^{low}$	$MHCII^+$	*Ym1*, *Arg1*,
Ovary		Mouse	$CD11b^+F4/80^+$	$MHCII^+$	ND
		Human	$CD68^+$	$MHCII^+$	ND
Spleen	Marginal zone macrophages	Mouse	$CD68^+F4/80^-$	$MARCO^+CD209b^+Dectin2^+TIM4^+$	ND
	Metallophilic macrophages	Mouse	$CD68^+F4/80^-$	$CD169^+CR\text{-}L^+$	ND
		Human	$CD68^+$	$CD169^+$	ND
Lymph node (subcapsular sinus macrophages)		Mouse	$CD68^+F4/80^-$	$CD169^+CR\text{-}L^+$	ND

ABCA1, ATP-binding cassette subfamily A member 1; AIF1, allograft inflammatory factor 1; *Arg1*, arginase 1; *C1q*, complement component 1q; *C3*, complement component 3; *C3ar1*, complement component 3a receptor 1; CR-L, ligand for cysteine-rich domain of mannose receptor; CSF1R, macrophage colony-stimulating factor 1 receptor; CX_3CR1, CX_3-chemokine receptor 1; *Cxcl*, CXC-chemokine ligand; Dectin2, dendritic cell-associated C-type lectin 2 (also known as CLEC6A); F13A, coagulation factor XIII A; *Fizz1*, resistin-like-α (also known as *Retnla*); HLAII, HLA class II; *Hpgd*, hydroxyprostaglandin dehydrogenase 15; *Igf1*, insulin-like growth factor 1; Ly6C, lymphocyte antigen 6C; LYVE1, lymphatic vessel endothelial hyaluronic acid receptor 1; MARCO, macrophage receptor with collagenous structure; *Mgl1*, macrophage galactose-type C-type lectin 1 (also known as *Clec10a*); MHCII, MHC class II; *Mmp13*, matrix metalloproteinase 13; MRC1, macrophage mannose receptor 1; ND, not determined; *Nrp1*, neuropilin 1; PVM, perivascular macrophage; *Slc40a1*, solute carrier family 40 (iron-regulated transporter), member 1; *Spic*, Spi-C transcription factor (Spi-1/PU.1 related); SRA1, scavenger receptor class A member 1; TIM4, T cell immunoglobulin mucin receptor 4 (also known as TIMD4); *Tlr4*, Toll-like receptor 4; *Tnf*, tumour necrosis factor; *Trem2*, triggering receptor expressed on myeloid cells 2; *Vsig4*, V-set and immunoglobulin domain-containing protein 4; *Ym1*, chitinase-like 3 (also known as *Chil3*).

Table 2 | Features of perivascular macrophages in diseased adult tissues (mouse and human)

Diseased tissue	Species	Phenotype	Activation markers expressed	Gene exp
Malignant tumours	Mouse	$CD45^+CD11b^+F4/80^+TIE2^+VEGFA^+$	$MRC1^+$	*Tie2*, *Csfr* *Cd163*, *Sto* *Msr2*, *Tlr2* *Il10*, *Icam* *Cxcr4*, *Cc* *Cxcl11*, *Cx* *Vegfb*, *Pgf* *Ctsb*
	Human	$CD45^+CD11b^+CD11c^+CD14^+CD16^+CD33^+CD115^+CCR2^-$ $CCR5^+CD62L^-TIE2^+$	$CXCR4^+MRC1^+$	*TIE2* and

Neurocognitive alterations related to hypertension (brain)	Mouse	$CD45^{hi}CD11b^{+}AIF1^{-}$	$MRC1^{+}LYVE1^{+}$	ND
Multiple sclerosis (brain)	Human	$CD45^{+}CD68^{+}$	$CD163^{hi}HLAII^{+}MRC1^{+}CD209^{+}CD40^{+}CD86^{+}CD80^{+}$	ND
Experimental autoimmune encephalomyelitis (brain)	Rat	$CD68^{+}$	$CD163^{+}$ $MHCII^{+}$ $CD40^{+}$ $CD80^{+}$ $CD86^{+}$ $IL\text{-}1\beta^{+}$	ND
SIV encephalitis (brain)	Macaque	ND	$CD163^{+}$ $Ki\text{-}63^{+}$	ND
HIV encephalitis (brain)	Human	$CD45^{+}$ $CD14^{+}$	$CD163^{+}$	ND
Alzheimer disease (brain)	Mouse	ND	$CD163^{+}$ $MRC1^{+}$	ND
Experimental retinitis (retina)	Rat	ND	$MHCII^{+}$ $IL\text{-}1\beta^{+}$ TNF^{+}	ND
	Rabbit	$CD18^{+}$	$MHCII^{hi}$	ND
Renal inflammation	Mouse	$F4/80^{hi}$ CX_3CR1^{+} $CD11c^{+}$	$MHCII^{hi}$ $CD86^{hi}$ TNF^{+}	*Il1b*, *Il6*, *T*
Skin inflammation	Mouse	$CD45^{+}$ $CD11b^{hi}$ $F4/80^{+}$ $CD68^{+}$ $CD64^{+}$ $CD34^{+}$ $CD169^{+}$ $ABCA1^{+}$	$MHCII^{+}$	*Cd4*, *Tlr4*, and *Cxcl2*
Lung fibrosis	Mouse	$CD11b^{+}$ $F4/80^{+}$	ND	ND
Otitis (cochlea)	Mouse	$F4/80^{+}$	ND	ND
Type 1 diabetes (pancreas)	Mouse	$CD11b^{+}$ $F4/80^{+}$	ND	ND

ABCA1, ATP-binding cassette subfamily A member 1; AIF1, allograft inflammatory factor 1; *Arg1*, arginase 1; *Ccl*, CC-chemokine ligand; CCR, CC-chemokine receptor; *Cox2*, cyclooxygenase 2; *Csf1r*, macrophage colony-stimulating factor 1 receptor; *Ctsb*, cathepsin B; CX_3CR1, CX_3-chemokine receptor 1; *Cxcl*, CXC-chemokine ligand; CXCR4, CXC-chemokine receptor 4; HLAII, HLA class II; *Icam1*, intercellular adhesion molecule 1; *Igf1*, insulin-like growth factor 1; LYVE1, lymphatic vessel endothelial hyaluronic acid receptor 1; MHCII, MHC class II; *Mmp9*, matrix metalloproteinase 9; MRC1, macrophage mannose receptor 1; *Msr1*, macrophage scavenger receptor 1; ND, not determined; *Nrp1*, neuropilin 1; *Pdgfb*, platelet-derived growth factor B; *Pgf*, placental growth factor; SIV, simian immunodeficiency virus; *Stab1*, stabilin 1; TIE2, angiopoietin 1 receptor; *Tlr*, Toll-like receptor; TNF, tumour necrosis factor; VEGFA, vascular endothelial growth factor A; *Vegfb*, vascular endothelial growth factor B; *VEGFR2*, vascular endothelial growth factor receptor 2 (also known as *KDR*).

Glossary

Stria vascularis

A highly vascularized area in the lateral wall of the cochlea (a sensory organ of the inner ear) that produces endolymph and is responsible for generating the endocochlear potential that is required for the transduction of sound.

Blood–brain barrier

(BBB). A tightly regulated, protective, vascular interface that separates the peripheral blood and central nervous system.

Alternative (M2) macrophage activation

Activation to a group of polarized, anti-inflammatory phenotypes (M2a, M2b and M2c) that is induced by type 2 cytokines such as IL-4 and IL-13 (M2a), immune complexes and Toll-like receptor or IL-1 receptor ligands (M2b), and IL-10 and glucocorticoids (M2c).

Classical (M1) macrophage activation

Activation to a polarized, pro-inflammatory and antimicrobial phenotype that is induced by the type 1 cytokine interferon-γ, various microbial molecules (such as lipopolysaccharide) or other inflammatory cytokines (such as tumour necrosis factor and granulocyte–macrophage colony-stimulating factor).

Islets of Langerhans

Regions of the pancreas that contain the hormone-producing cells.

Reticuloendothelial system
A network of cells sharing a common function, namely, phagocytosis.

Bowman capsule
A cup-like sac at the beginning of the tubular component of a nephron in the mammalian kidney that encloses a cluster of microscopic blood vessels known as the glomerulus and filters the blood to form urine.

Dense core granules
Subcellular organelles in the β-cells of the pancreatic islets that store and release various peptide hormones, including insulin.

Subcapsular sinus
The space between the capsule and the cortex of a lymph node that enables the free movement of lymphatic fluid.

Sinusoids
Capillaries with a fenestrated, discontinuous endothelium.

Seminiferous tubules
Structures in the testis that contain epithelium enveloping and supporting germ cells that are undergoing progressive differentiation and development into mature spermatozoa.

Leydig cells
Cells in the connective tissue between the seminiferous tubules that produce testosterone.

Corpus luteum
A temporary, hormone-secreting structure that develops in an ovary after an ovum has been discharged at ovulation.

Intravasation
Movement of cells through a basement membrane into a blood or lymphatic vessel.

Clodronate-containing liposomes
(CCLs). Synthesized liposomes containing the bisphosphonate clodronate, which kills macrophages when taken up by them.

Cerebral amyloid angiopathy
A condition in which β-amyloid is deposited around the small-sized and mid-sized arteries (and, sometimes, the veins) of the cerebral cortex.

Experimental autoimmune uveitis
A mouse or rat model of inflammation in the uveal component of the eye caused by an autoimmune reaction to self antigens.