Macrophages are central to both innate and adaptive immunity. With few exceptions, macrophages are the first cells that sense trouble and respond to disturbances in almost all tissues and organs. They sense their environment, inhibit or kill pathogens, take up apoptotic and necrotic cells, heal tissue damage, and present antigens to T cells. Although the origins (yolk sac versus monocyte-derived) and phenotypes (functions, gene expression profiles, surface markers) of macrophages vary between tissues, they have many receptors in common that are specific to one or a few molecular species. Here, we review the expression and function of almost 200 key macrophage receptors that help the macrophages sense what is going on, including pathogen-derived molecules, the state of the surrounding tissue cells, apoptotic and necrotic cell death, antibodies and immune complexes, altered self molecules, extracellular matrix components, and cytokines, including chemokines.

Keywords: macrophages, pathogens, immunity, defense, inflammation

INTRODUCTION

Macrophages are central to proper functioning of the immune system (1–4). Resting tissue macrophages make ornithine (by arginase) and promote repair, called the M2 phenotype (1, 5). Tissue macrophages arise from embryonic precursors and from blood monocytes at varying proportions (6). At the extremes are microglia cells, which are entirely embryonic-derived (7) and intestinal macrophages, which are entirely monocyte-derived (8) with other organs being populated by mixtures of both. When these tissue macrophages sense trouble (1), they express IL12 and iNOS, and become M1 macrophages (5). Macrophages express hundreds of sensor molecules to identify their surroundings (cells, extracellular matrix, and tissue), the state of the tissue (normal and healthy, apoptotic, ischemic, necrotic, altered, or otherwise distressed), metabolites [oxygen, pH, lactic acid, glucose, free fatty acids, sphingosine-1-phosphate (S1P)], lipoproteins (LDL, HDL, and their derivatives), antibodies (IgG, immune complexes), complement (C3a, C3bi, C5a), cytokines (IFN-γ, IL4, IL17), and pathogens (bacteria, viruses, fungi, parasites, and their products). Dendritic cells, another key sensor of pathogens, act in concert with the macrophages in initiating an adaptive immune response. Dendritic cells activate the adaptive immune system by antigen presentation to naïve T cells in the context of co-activating receptors. These T cells become licensed to traffic to the infected or inflamed tissue (9, 10), where they see antigen presented by macrophages (11) and differentiate (CD4: Th1, Th2, Th17, Treg, TFH and others, CD8: CTL and others). Many products of the adaptive immune
system, such as cytokines, can further activate macrophages and alter their function; for example, IFN-γ enhances M1 polarization (12) and IL-4 induces alternative activation (13), thus enhancing M2 polarization (1, 14).

This review is focused on the inputs to the macrophage and dendritic cell system: the cell surface and intracellular receptors by which these cells sense what is going on. For details of the signaling networks and effector systems downstream of these receptors, like TRAFs (15–17), NFKB (18, 19), or inflammasome assembly (20), the reader is referred to other reviews. Although there are human homologs for almost all receptors discussed here, this review is entirely based on mouse data. The innate immune system and macrophages in particular are under enormous evolutionary pressure shaped by the environment and infectious organisms that differ between mice and humans.

TISSUE INPUT AT STEADY STATE

At steady state, signals from host tissue cells result in tissue-specific gene expression profiles (21). Langerhans cells of the skin, alveolar macrophages, Kupffer cells of the liver, microglia of the CNS, osteoclasts, dendritic cells of the thymus, and other lymphoid organs all have specialized functions and phenotypes. This suggests that tissue-derived signals control the development and polarization of tissue-specific macrophage phenotypes. The first tissue cues were identified in osteoclasts (22) and peritoneal macrophages (23, 24). A key inducer of the peritoneal macrophage phenotype is retinoic acid produced by intestinal cells, which is recognized by the nuclear receptor retinoic acid receptor-β (RAR-β). Retinoic acid induces the transcription factor GATA6, which in turn controls a number of effector molecules (23, 24). Interestingly, RAR-β ligation also induces arginase-1, the defining enzyme of M2 macrophages, underscoring that resting peritoneal macrophages, like macrophages in other tissues, are in the default “healing” M2 state. A second known M2-polarizing stimulus is lactic acid, produced by hypoxic cells in cancer (25). This is consistent with the known M2 phenotype of myeloid-derived suppressor cells (26), a macrophage type found in cancers. Under homeostatic conditions, M2 polarization is maintained by TGF-β, and TGF-β receptor-1 seems to be the major factor in determining microglia phenotype (27). Under inflammatory conditions, TGF-β induces a state of deactivation that is different from M2, and promotes the resolution of inflammation. TGF-β2 is produced by resident peritoneal macrophages (28) and might play a significant role in homeostatic maintenance of surrounding tissues.

To provide a first glimpse at the expression of almost 200 “input” receptors, we compiled heat maps from published data sets on mouse peritoneal macrophages (large, small, and thioglycollate-elicited), microglia (27) (data set GSE62826), and the macrophages from lung, liver, spleen, intestinal, adipose tissue, and bone marrow (23) (data sets GSE56682, 56683, 56684) and (29) (data set GSE47049). The transcriptome data sets were accessed through the Gene Expression Omnibus site1 to examine the gene expression profiles in tissue-specific macrophages for 12 categories of receptors [apoptotic cell receptors, complement receptors, toll-like receptors (TLR), NOD-like receptors (NLR), RNA and DNA receptors, C-type lectins, scavenger receptors, selected cytokine receptors, TNF receptor superfamily members, Fc receptors, selected G-protein-coupled receptors, and integrins]. Cross-platform comparison of gene expression profiles between microarray (GSE47049, GSE56682, GSE56683, and GSE56684) and RNA-Seq (GSE62826) was done on normalized data provided by the authors on the GEO site. The normalized values from different platforms were scaled by log, transformation for comparison through generation of heat maps (30–32). In brief, MAS5.0 (Affymetrix) and quantile normalized (Illumina GUI) probe data available for the microarray platforms, i.e., GSE47049 and GSE56682/83/84 from Affymetrix Mouse Genome 430 2.0 Array and Illumina mouse expression bead chip, respectively, were annotated by R/Bioconductor packages2 and annotation files downloaded from the GEO site (GPL6105 and GPL6887). The normalized RPKM gene expression levels from the Illumina RNA-sequencing (Illumina HiSeq 2000) dataset (GSE62826) were obtained from the GEO site. Whenever a gene was represented by more than one probe set or entry, the average of the pooled expression values was used. Furthermore, the average value of the genes across the samples for a tissue from different datasets was calculated for log, transformation. Cluster 3.0 with pair-wise complete linkage was used to perform the hierarchical analysis of log, transformed expression values of around 200 genes using mean-centered gene expression vectors and visualized with the Java TreeView 10.6 (32, 33). The graphical representation of output as heat maps is presented in color scale from green to red (Z-score transformation), where red and green indicate higher and lower expression levels, respectively (Figure 1). Non-expressed genes are shown in light gray.

RECEPTORS FOR APOPTOTIC CELLS

In many tissues, there is continuous turnover of cells, where the majority of them die by the process of caspase-dependent apoptosis. When cells undergo apoptosis, their corpses are phagocytosed by macrophages in a process referred to as efferocytosis (34–36). In addition to macrophages, epithelial cells and fibroblasts clear apoptotic cells. Apoptotic cells expose phosphatidylserine (PtdSer) on the outer leaflet of their plasma membrane, which serves as a recognition signal (Eat-me). Apoptotic cells, at the earliest stages of death, also release ATP and other molecules that serve as diffusible “find-me” signals to attract macrophages to their proximity. The find-me signals are sensed by tissue-resident macrophages via some G-protein-coupled receptors, such as P2Y2 sensing ATP and UTP released from apoptotic cells, and CX3CR1 sensing CX3CL1 released from apoptotic cells.

There are several recognition systems for PtdSer (Table 1). Routine, homeostatic uptake of apoptotic cells is inherently anti-inflammatory and helps keep the local tissue inflammation to a very minimal (or below detection) level even in tissues

1http://www.ncbi.nlm.nih.gov/geo/
2http://www.r-project.org
where there is a very high cell turnover (such as the bone marrow or thymus). This is in part achieved through the release of mediators, such as TGF-β, IL10, and prostaglandin E2 (PGE2) from macrophages that engage apoptotic cells. TGF-β and IL10 have anti-inflammatory functions. Depending on the receptor triggered (EP1-EP4), PGE2 can have pro- and anti-inflammatory functions, modulate pain sensation, and can activate mast cells (37). See Ref. (38, 39) for more details on apoptotic cell clearance. αVβ3 integrin (see Integrins) recognizes PtdSer through MFGE8. RAGE and stabilin 2 also bind PtdSer and are listed under scavenger receptors (below). Tyro3, Axl, and Mer bind PtdSer through GAS6 (gene name Gas6) or protein S (gene name Pros1). Mertk, the gene encoding Mer tyrosine kinase, distinguishes macrophages from dendritic cells and has been proposed as a universal mouse macrophage marker (40) when used in combination with other markers like F4/80, CD68, or CD11b. CD91, also known as LDL receptor-related protein LRP, is a receptor for calreticulin, which is exposed in cells undergoing ER stress and apoptosis. SIRPα (gene name Sirpa) can detect CD47 on apoptotic lymphocytes. The results presented in Figure 1A summarize the expression of genes related to apoptotic cell recognition and uptake. The clearance of apoptotic cells by phagocytes is counterbalanced by mechanisms that limit detrimental effects, such as production of reactive oxygen species. Also, efferocytic receptors, such as Mer and CD11b, can be downregulated, a process that limits further signaling and uptake of apoptotic cells.

**FIGURE 1** | Gene expression in resident tissue-specific macrophages (microglia, lung, liver, spleen, intestinal, adipose) and bone marrow-derived macrophages (BMDM) for comparison.

(Continued)
**TABLE 1 | PtdSer recognition receptors.**

| Gene name | PtdSer receptors | Function | PtdSer binding |
|-----------|-----------------|----------|----------------|
| Bai1      | BAI1            | Upstream of ELMO1-Dock180-RAC, engulfment | Direct PtdSer binding |
| Havcr1    | TIM1            | Also hepatitis A virus receptor | Direct PtdSer binding by metal ion-dependent binding site |
| Havcr2    | TIM3            | Also for antigen cross-presentation | |
| Timd4     | TIM4            | Only tethering of apoptotic cells without direct signaling to engulfment | |
| Tyro3     | Tyro3           | Tyrosine kinase receptor | Indirect PtdSer binding through Gas6 or protein S |
| Axl       | Axl             | Tyrosine kinase receptor | |
| MerTk     | Mer             | Tyrosine kinase receptor, universal mouse macrophage marker | |

**RECEPTORS FOR NECROTIC CELLS AND MODIFIED SELF**

Macrophages sense when tissue cells are distressed by events, such as ischemia (pro-angiogenic, pro-inflammatory), reperfusion (pro-inflammatory), tissue necrosis (pro-inflammatory), and altered self induced by enzymatic modification resulting in (lipo) protein citrullination (41), oxidation (42), or nitrosylation (43). Many of the receptors for altered self are among the category of cell surface molecules that are generally referred to as scavenger receptors (see below). Macrophages express many scavenger receptors that are capable of recognizing these necrotic or altered self-molecule on stressed cells within tissues.

Necrotic cells are opsonized by complement factors that are recognized through complement receptors (44, 45) (Table 2; expression in Figure 1B). The scavenger receptor RAGE (see below) also recognizes apoptotic cells and triggers pro-inflammatory mechanisms. The IL33 receptor ST2 detects IL33 released by necrotic cells. CD24 on macrophages binds HMGBl, which in turn binds necrotic cells. Mindle (Clec9) and CLEC9A are two C-type lectins (listed below) involved in the uptake of necrotic cells. TLRs (see below) can recognize the nuclear protein HMGB1, the Sin3A-Associated Protein SAP130, the heat shock protein HSP90, DNA, and urate crystals, all of which can be exposed on or released from necrotic cells.

**PATHOGEN RECEPTORS**

Pathogen sensors on macrophages can detect bacterial, viral, fungal, and parasite infections. These receptors bind pathogens directly or recognize their products. They form six main classes: TLR (17, 46), NLR (20, 47), receptors for intracellular RNA, including RIG-I like receptors (RLR) (48), receptors for intracellular DNA, including STING (49, 50), C-type lectins (51, 52), and scavenger receptors (53).
TOLL-LIKE RECEPTORS

Toll-like receptors (Table 3) are a family of homodimeric transmembrane receptors that recognize bacterial, viral, and fungal products. Some also have endogenous ligands. TLRs 1, 2, 4, 5, and 6 are expressed on the plasma membrane, whereas TLRs 3, 7, 8, and 9 are expressed in endosomes (17, 54). Most TLRs signal through the MyD88 pathway, ultimately resulting in NFκB activation, except TLR3, which signals through the intermediary TRIF resulting in type I interferon production. TLR4 signals through both MyD88 and TRIF. (Note: TLR10 is not expressed in mice).

| Gene name | Complement receptors | CD name | Function |
|-----------|----------------------|---------|----------|
| Cr1       | CR1                  | CD35    | Binds C3b and C4b, processes opsonized particles |
| Cr2       | CR2                  | CD21    | Binds C3b2, C3d. In the mouse, both CR1 and CR2 are derived from the C2 locus by alternative splicing (44) |
| Itgam     | CR3                  | CD11b   | Obligatory heterodimer, binds C3bi, denatured proteins (and many other ligands) |
| Itgb2     | CR4                  | CD11c   | Obligatory heterodimer, binds C3bi, denatured proteins |
| C5ar1     | C5ar                 | CD88    | Binds C5a, activates macrophages |
| C5ar2     | C5ar                 | CD18    | Binds C3a, C5a, and their desargamidated inactive forms |
| Cd59a     | CD59                 | CD59    | Inhibits the membrane attack complex |
| Cd48      | MCP                  | CD46    | CD48 and CD55 inactivate the C3/C5 cleaving enzymes |
| Cd55      | Decay-accelerating factor DAF | CD55 | |

NOD-LIKE RECEPTORS OR NBD-LRR CONTAINING PROTEINS

This class of pathogen receptors/sensors (20) regulates a number of key inflammatory pathways. NLRs (Table 4) contain a nucleotide-binding domain (NBD) and leucine-rich repeats (LRR). These proteins are conserved in evolution from plants to humans. NLR proteins are subdivided by their N-terminus, which can contain acid transactivation, pyrin, CARD, or BIR domains. A major pathway is the activation of the inflammasome, which is a macromolecular structure that when assembled, causes the cleavage and activation of caspase-1, and thus can produce the active species of IL1β and IL18. There are 22 known human NLRs; here, only the best-studied will be discussed. Some, but not all NLRs assemble an inflammasome. Additionally, some inflammasome-inducing NLRs also exhibit inflammasome-independent functions. The molecular mechanisms of inflammasome activation have been reviewed elsewhere (20). This review will briefly describe the key NLR molecules important for macrophage sensing with a focus on the inflammasomes.

The best-studied inflammasome is anchored by NLRP3, a receptor that does not directly recognize DAMPs or PAMPs but rather responds to cellular stress, including changes in potassium efflux, ROS production, ER stress, and unfolded protein response. The adapter GBP5 promotes NLRP3 inflammasome activation by ATP, nigericin, and bacteria, but not by crystalline agents. Several inhibitory pathways for NLRP3 activation have also been described. For example, nitric oxide can cause the S-nitrosylation...
of NLRP3 and impair assembly of the inflammasome (55–57). The G Protein signaling modulator-3 protein can associate with the LRR domain of NLRP3 and inhibit inflammasome activation. cAMP binds and inhibits NLRP3, and the neurotransmitter dopamine negatively regulates NLRP3 function via cAMP that promotes NLRP3 ubiquitination and subsequent degradation by the E3 ligase, MARCh7 (58). NLRP3 inflammasome activation depends on ASC (gene name Pycard), a common adaptor required for the activation of caspase-1 by several inflammasomes, and is comprised of a pyrin domain and a CARD domain. Linear ubiquitination via the assembly complex LUBAC is known to enhance ASC function in the activation of NLRP3-dependent inflammasome (59). The NLRP3 inflammasome also senses mitochondrial DNA. Activated caspase-1 or the related caspase-11 can induce pyroptosis (lytic cell death).

The NLRC4 inflammasome activation (60) is enhanced by ASC, and it detects bacterial proteins in the cytosolic compartment, either as markers for the activity of bacterial type III and IV secretion systems or cytosolic invasion by flagellated bacteria. NLRC4 responds to injection of three conserved bacterial proteins: flagellin, rod, and needle. Naip proteins are also members of the NLR family. Naip1, 2, 5, and 6 provide ligand specificity to the NLRC4 inflammasome. Specifically, Naip1 detects the bacterial Needle protein, Naip2 detects bacterial Rod, and Naip5 and 6 detect bacterial flagellins (61). The Naip proteins are involved in expulsion of salmonella-infected enterocytes (62).

### TABLE 4 | NOD-like receptors.

| Gene name | NLR | Pathogen or disturbance | Downstream effectors, function, and regulation |
|-----------|-----|--------------------------|-----------------------------------------------|
| Nlrp3     | NLRP3 | Cellular stress | Activates caspase-1 through ASC |
|           |       | ER stress              | Inhibited by NO from iNOS (S-nitrosylation) |
|           |       | And ATP                |                                               |
|           |       | Monosodium urate, alum |                                               |
| Nlrc4     | NLRC4 | Bacterial type III (TSSS) and IV (T4SS) secretion system, cytosolic flagellin | Activates caspase-1 to activate IL-1 and IL-18, blocks STING pathway |
| Nlrc3     | NLRC3 | HSV                     | Blocks STING pathway |
| Nlrc1a    | NLRP1A | Lethal toxin (LT) of Bacillus anthracis (mouse) |                                               |
| Nlrc1b    | NLRP1B | Muramyl dipeptide (MDP) and titanium dioxide (human) |                                               |
| Nlrc1c    | NLRP1C | Pathobiont bacteria, Bacteroides (Prevotellaceae), and TM7 microbiota |                                               |
| Nlrc6     | NLRP6 [PYPAF5] | Pathobiont bacteria, Bacteroides (Prevotellaceae), and TM7 microbiota | Blocks NrfB and MAPK pathway, activates caspase-1, inflammasome |
| Nlrc7     | NLRP7 | Mycoplasma acylated lipopeptide (acLP) | Inflammasome: hydatidiform |
| Nlrc12    | NLRP12 | Yersinia, malaria | Inflammasome function, inhibits NrfB and MAPK |
| Nlrc5     | NLRC5 | Bacteria, PAMPs, DAMPs, rhinovirus | Inflammasome function |
| Aim2      | AIM2 | Cytosolic DNA | Activates Caspase-1 through ASC |
| Pycard    | ASC | Common adaptor for inflammasome activation | Activates caspase-8 and -9 |
| Naip1     | NAIP1 | NAIPs provide ligand specificity to the | Naip1, 2, 5, and 6 provide ligand specificity to the NLRC4 inflammasome. Specifically, Naip1 detects the bacterial rod, and Naip5 and 6 detect bacterial flagellins (61). The Naip proteins are involved in expulsion of salmonella-infected enterocytes (62). |
| Naip2     | NAIP2 | NLRC4 inflammasome. |                                               |
| Naip4     | NAIP4 | |                                               |
| Naip6     | NAIP6 | |                                               |
but not several other bacteria, can cause Nlrp12-dependent inflammasome activation (73), and Plasmodium species induce a NLRP12- and NLRP3-dependent inflammasome activation (74). This dual requirement for two NLRs is also observed with NLRCS5 and NLRP3, which interact with each other in a human macrophage cell line and PBMCs in response to a host of NLRP3 activators (75). Nlr5−/− mice show deficiencies in response to NLRP3 activators, such as monosodium urate, alum, and ATP (76). However, the primary function of NLRCS5 is the regulation of class I MHC genes, thus demonstrating again the multi-faceted nature of NLRs (77).

In addition to the activation of caspase-1, a non-canonical pathway leading to caspase-11 maturation that requires NLRP3, and can be activated by some bacteria, which appears to be detrimental during endotoxic shock (78). Caspase-11 is activated by LPS from Gram-negative bacteria that invade the cytosol, and protects mice against lethal infection by Burkholderia thailandensis and Burkholderia pseudomallei. By contrast, vacuolar bacteria, such as Salmonella typhimurium are poorly detected by caspase-11. Caspase-11 is non-responsive, unless macrophages are primed by IFN-β or IFN-γ, both of which activate the transcription factor STAT1. Caspase-11 responds to cytosolic lipid A species with five or six acyl groups, but not to species with four acyl groups. This expands the role of LPS as a key microbial pattern detected by the innate immune system: extracellular and vacuolar LPS is detected through TLR4, whereas cytosolic LPS is detected through caspase-11. Interestingly, both Tlr4- and caspase-11-deficient mice are resistant to classical LPS challenge (78). The results presented in Figure 1D reveal the expression levels of NLR and related molecules.

**SENSORS FOR INTRACELLULAR RNA AND DNA**

RNA and DNA receptors recognize components of viral genomes. Herpes viruses such as herpes simplex or murine cytomegalovirus (MCMV) are double-stranded (ds)DNA viruses, where the dsDNA is recognized by STING or IFI16 (mouse gene I6204). Single-stranded (ss) viral RNA often forms stem–loop structures that can be detected by TLR7 (see Toll-Like Receptors) and RIG-I (79). ssDNA (not necessarily viral) is recognized by TLR9, especially when it is CpG-rich and not methylated.

These receptors are expressed in macrophages, epithelial cells, and other cells. The immune response starts in infected cells, where the viruses replicate in the cytoplasm. The intracellular viral RNA is detected by the RIG-I family of receptors, including RIG-I (gene name: Ddx58), MDA5 (Ifih1), and LGP2 (Dhx58). RIG-I detects many ssRNA viruses, including influenza virus, hepatitis C, Dengue, yellow fever, west Nile, and Ebola. The RIG-I family receptors require MAVS as an adapter protein and IRF3 or IRF7 as downstream transcription factors, resulting in the elaboration of IFN-α and β.

Single-stranded DNA is recognized by TLR9 (see Toll-Like Receptors). DNA-derived intracellular cyclic dinucleotides are recognized by STING (gene name, Tmemi173) (80). Humans have five common STING alleles. Listeria products are processed by cGAS (cyclic GMP AMP synthetase), which produces cGMP that in turn activates STING. STING is also involved in detecting herpes virus. Other sensors for intracellular DNA are DAI (gene name, Zbp1), Aim2 (see under NLRs), DDX41 (Ddx41), DHX9 (Dhx9), IFI16 (gene name, Ifi204), and DHX36 (Dhx36). DAI senses dsDNA. The results in Figure 1E show the mRNA expression of these DNA- and RNA-sensing receptors in various tissue-resident macrophages. Aim2 expression was only detected in bone marrow-derived macrophage (BMDM), peritoneal macrophages, and microglia.

**C-TYPE LECTIN RECEPTORS**

In general, C-type lectin receptors (Table 5) recognize multivalent carbohydrate ligands (4) that might be present on endothelial cells, epithelial cells, pathogens, and other microorganisms. C-type lectins are also involved in the uptake and clearance of dead cells (6). Macrophages express several C-type lectin receptors, which include collectins, selectins, lymphocyte lectins, and proteoglycans (4). Some are important sensors for fungal infections (81), others such as the lectins recognize host glycans (82). The C-type lectins DCIR and MICL are inhibitory, because their cytoplasmic tails contain ITIM domains. Dectin-2, Mincle, and DCAR are coupled to an ITAM-domain containing adaptor. Dectin-2 is the prototypic receptor of the Dectin-2 subfamily of C-type lectins that also contains CLECFS8, DCIR and Mincle and DCIR2, 3, and 4, DCAR, and DCARI in mice only (5). SignR3, Dectin-1, and CLEC9a also contain at least one ITAM domain. DC-Sign, SIGN-R1, Langerin, MGL, DEC-205, and the mannose receptor MR are not coupled to either ITAM or ITIM domains, but signal through adaptor proteins.

E-selectin recognizes fucosylated and sialylated ligands of the sialyl-Lewisx type. P-selectin recognizes the glycoproteins PSGL-1 on myeloid cells and TIM1 on activated T cells. L-selectin recognizes 6-sulfated carbohydrates expressed in high endothelial venules and PSGL-1. Many macrophages express P-selectin, but its function in macrophages has not been studied. Monocytes express L-selectin, but its expression is lost upon differentiation to macrophages. L-selectin is an excellent example for an adhesion molecule that is shed upon cell activation (83). Shedding of adhesion molecules, cytokine receptors, and pattern recognition receptors is an important mechanism that limits their signaling (84, 85). In some cases, the shed molecules can have signaling functions in their soluble form. The results in Figure 1F demonstrate the expression levels of C-type lectins.

**SCAVENGER RECEPTORS**

Scavenger receptors (Table 6) are cell surface receptors that typically bind multiple ligands and promote the removal of non-self or altered self targets. Both tissue-resident and monocyte-derived macrophages express a number of scavenger receptors. They often function by mechanisms that include endocytosis, phagocytosis, adhesion, and signaling that ultimately lead to the elimination of degraded or harmful substances (7). Scavenger receptors recognize non-self (mostly bacterial products) and altered (oxidized, acetylated) self. They are more involved in

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uptake and phagocytosis than activation of inflammatory effector systems. Scavenger receptors have recently been classified (53). The systematic names are SR followed by a letter (for the class) and numbers (for the members).

SR-A1, 2, and 3 and MARCO form the SR-A subfamily. Only SR-A1 has an SRCR domain and is the main macrophage receptor for HDL. MARCO is a collagen-like molecule; MARCO defects result in susceptibility to tuberculosis. The SR-B subfamily comprises SR-B1 and SR-B2 (CD36). CD36 is an important receptor for diacyl glycerides, oxidized LDL, and the malaria parasites. CD36 is important for ROS and cytokine production by macrophages. There are no mammalian members of the SR-C subfamily. SR-D is CD68 (macrosialin), an intracellular receptor of unknown function. SR-E1 is Lox1 (Loxin), which detects oxidized LDL. Dectin-1 is SR-E2. The mannose receptor MR is SR-E3 and the asialoglycoprotein receptor is SR-E4. SR-F1 is SCARF1, Ced1 in Caenorhabditis elegans, and SR-F2 is SCARF2. The only known SR-G is CXCL16, a receptor for oxidized LDL and a chemokine that binds CXCR6. SR-H1 is FEEL-1, also known as Stabilin-1 or Clever-1, SR-I is CD163, the macrophage receptor for hemoglobin–haptoglobin complexes. In bovine and ovine species, this subfamily has many more members. SR-J is RAGE, a seven-transmembrane receptor with multiple immunoglobulin domains that sees glycated proteins and advanced glycation end products. SR-L1 is also known as LRP1, and SR-L2 as LRP-2.

Some macrophage scavenger receptors are currently unclassified. Galectin-3-binding protein is a secreted product of M1 macrophages that binds galectin-3 and other cell surface ligands. CD207 (Langerin), MRC1 (CD206), CLEC7A, and CD209 (DC-SIGN) are also unclassified. CD206 is prominently expressed on M2 macrophages. C1q interacts with the Aβ protein relevant in Alzheimer’s disease. The results in Figure 1G show the expression levels of scavenger receptors.

### CYTOKINE RECEPTORS

Another class of macrophage receptors sense products of adaptive immune cells. These receptors can be considered secondary amplifiers, because they do not detect non-self or altered self, but rather amplify the macrophage response. Since most cytokines are produced by activated T cells that require antigen presentation and an ongoing immune response, the cytokine receptors on macrophages sense the nature of that ongoing immune response (Th1, Th2, Th17) (Table 7).

IFN-γ receptor is a major activator of macrophages and reinforces the M1 phenotype (12). The Ifngr1 gene encoding this receptor is highly expressed in all macrophages. Its functional antagonist is IL4 receptor. Because of their important role in inflammation, we also discuss IL1 receptors, IL17 receptors, and IL27 receptor. A major anti-inflammatory pathway is initiated by TGF-β, which has three receptors.

IL4, 5, and 13 receptors promote and reinforce the M2 phenotype (3, 86, 87), but their ligation is not required for M2 polarization; in fact, it appears that M2 is the default “healing” phenotype.

**TABLE 5 | C-type lectins.**

| Gene name | C-type lectin | CD | Binds ligands from | Function |
|-----------|---------------|----|--------------------|----------|
| Ly75      | DEC-205       | CD205 | HIV, *V. parahaemolyticus*, *E. coli*, endogenous | Uptake of pathogens and apoptotic cells |
| Clec10a   | Mgl1          | CD301a | Streptococcus, Lactobacilli, apoptotic cells: Sialoadhesin | Uptake of pathogens and apoptotic cells |
| Clec9a    | DNGR-1        | F-actin | α-mannose and glycolipids from *Mycobacterium tuberculosis*, *Candida albicans* | Uptake of necrotic cells |
| Clec4e    | Mincl          | α-mannose and glycosylated lipids from *Mycobacterium tuberculosis*, *Candida albicans* | Necrotic cell uptake; couples through FcγR1, activates NFκB |
| Clec7a    | BGR           | CD369 | Beta-1,3-linked and beta-1,6-linked glucans from fungi and plants | |
| Clec4a1   | DCIR1         | Unknown | | Down regulated by cell activation |
| Clec12a   | MICL           | CD371 | | |
| Clec4n    | Dectin-2-like | | | |
| Clec4b1   | DCAR           | | | |
| Clec4d    | MCL, MPCL     | CD368 | | |
| Clec4e3   | DCTR3         | | | |
| Clec4e4   | DCTR2         | Bisecting N-acetylgalactosamine | Associates with Fc receptor γ chain |
| Clec4k    | Langerin      | CD207 | Measles virus | Endocytotic, signals through Syk |
| Cd209a    | DC-SIGN       | CD209 | Microbial polysaccharides, sialylated antibody | Possible role in Th17 response |
| Cd209b    | SIGNR1, CLEC4m | CD209b | Oligomannose | Interacts with C1q |
| Cd209d    | SIGNR3        | CD209d | Leishmania, mycobacterial saccharides | Required for lymphangiogenesis, separates lymphatics from blood vessels |
| Clec7b    | Clec2         | High on platelets | | |
| Seld      | L-selectin    | CD62L | High endothelial venules, PSGL-1 | Rolling of Ly6C+ monocytes |
| Selp      | P-selectin    | CD62P | PSGL-1, TIM1 | Endothelial cells: rolling; macrophages: unknown |
| Sere      | E-selectin    | CD62E | PSGL-1, CD44, CD43, others | Largely restricted to endothelium |
of macrophages (5). IL13 receptor α1 chain is expressed in all macrophages, but the α2 chain is missing from peritoneal macrophages. IL5 receptor is expressed at very low levels on these cells.

TGF-β receptors strongly promote M2 polarization. TGF-β is made by many tissue cells, especially epithelial cells, and seems to signal to the macrophage that the tissue cells are in good health and not infected. Tgfb1 is highly expressed in all macrophages, with highest levels in microglia. The same is true for Tgfb2, but with highest levels in adipose tissue macrophages. Tgfb3 is expressed in all macrophages except microglia and BMDM. Overabundance of TGF-β can lead to excessive collagen formation resulting in fibrosis. Macrophages have receptors for cytokines of the IL17 family. The results in Figure 1L indicate that the IL17 receptor A is expressed in all macrophages, and being highest in microglia. Il17rb, c, d, and e are expressed at low levels. IL1 receptors 1 and 2 are expressed at high levels in all macrophages.

**TABLE 6 Scavenger receptors.**

| Gene name | Systematic name | Other names | Ligands and function |
|-----------|----------------|-------------|----------------------|
| Msr1      | SR-A1          | SCARA1      | Heat shock proteins, acLDL, oxLDL |
|           |                | MSR1        | Bacteria, yeast, amyloid, hepatitis C virus |
| Scara3    | SR-A3          | SCARA3      | Protection from ROS |
| Colec12   | SR-A4          | SCARA4      | Modified LDL |
|           |                | SRCL, COLEC12 | Endocytic receptor for lipoproteins |
| Scara5    | SR-A5          | SCARA5      | Binds bacteria |
| Marco     | SR-A6          | MARCO       | Bacterial clearance from lung and blood |
| Scarb1    | SR-B1          | SCARB1      | HDL |
| Cad68     | SR-D1          | Macrosialin | Controversial: may bind oxidized lipoproteins, apoptotic cells, but inconsistent data |
| Olr1      | SR-E1          | LOX-1       | oxLDL, CRP |
| Clec7a    | SR-E2          | Dectin-1    | Bacterial, fungal, and plant carbohydrates β-glucans interacts with TLR2 |
| Scarf1    | SR-F1          | SCARF1      | Calreticulin, fungal and heat shock proteins, cross-presentation of antigens on MHC-I. Binds oxLDL. Apoptotic cell clearance |
| Scarf2    | SR-F2          | SREC-II     | |
| Megf10    | SR-F3          | MEGF10      | Amyloid-β |
| Cxcl16    | SR-G1          | RS-PD16X    | oxLDL, phagocytosis of bacteria, chemotaxis through CXCR6 |
| Stab1     | SR-H1          | Stabilin-1  | Lymphocyte adhesion, transmigration, angiogenesis, apoptotic cell clearance, and intracellular trafficking |
|           |                | FEEL-1      | |
|           |                | CLEVER-1    | |
| Stab2     | SR-H2          | Stabilin-2  | Binds PS, interacts with GULP and thymosin-β4 to initiate uptake of apoptotic cells |
|           |                | FEEL-2      | |
| Cd163     | SR-I1          | CD163       | Hemoglobin-haptoglobin, anti-inflammatory signaling, secretion of cytokines IL-6 and IL-10 |
| Ager      | SR-J1          | RAGE        | Advanced glycation end products, high mobility group protein box 1, S-100, oxidative stress, pro-inflammatory |
| Lgals3bp  | Galectin-3     | GAL3BP      | Binds galectin-1 and 3, anti-inflammatory, produced by M1 macrophages |

**TNF RECEPTOR SUPERFAMILY**

The TNF receptor superfamily (Tnfsf) (88–91) bind soluble and cell surface-expressed TNF superfamily members that have diverse biological functions (Table 8). These can range from molecules that induce caspase activation and apoptosis and regulate cell death (Fas, TNFRI, TRAILR) to those that activate NFkB and MAPK pathways and are pro-inflammatory (e.g., TNFRII, RANK, CD40, BAFFR, OX40) inducing a multitude of effects, such as promoting division, survival, cytokine production, chemokine production, and upregulation of other receptors in varied protein families. The summarized expression values in Figure 11 reveal that the Tnfsf receptors are of specific interest here, because many of them show highly differential expression among tissue macrophages, suggesting that different macrophage subsets have different abilities to see Tnfsf ligands.

Many of the Tnfsf members are well known for controlling responses of T and B cells, dendritic cells, NK, and NKT cells,
as well as inflammatory activity in structural cells, such as fibroblasts, epithelial cells, and osteoclasts. This has resulted in clinical targeting of many of the molecules for autoimmune and inflammatory diseases (89), and approved drugs in blockers of TNF and LTβ to TNFR1 and TNFRII for RA, psoriasis, Crohn’s disease, and others; blockers of RANKL binding to RANK for osteoporosis; and blockers of BAFF binding to its receptors BAFFR, TACI, and BCMA for SLE.

In macrophages, there appears to be strongly divergent expression among tissue macrophages (Figure 11). Tnfsf1a (TNFR1), Tnfsf1b (TNFR2), Tnfsf11a (RANK), and Tnfsf13 (LTβR) are highly expressed by most tissue macrophages. Tnfsf5 (CD40), Tnfsf12a (Fn14), Tnfsf14 (HEM), Tnfsf21 (DR6) are also highly expressed in some macrophage populations, but variably expressed in others at moderate levels. TNFR2 is largely pro-inflammatory, whereas TNFR1 can display both pro-inflammatory and anti-inflammatory (apoptosis-inducing) activities. Since TNF is a product of macrophages, various reports have suggested both positive and negative effects of TNF on macrophages correlating with these functions of its receptors (92–96). The outcome of TNFR signaling in macrophages may be heavily influenced by the location of the cells and the inflammatory environment in which they are responding. CD40, RANK, and LTβR are stimulatory receptors for antigen-presenting cells, particularly dendritic cells and B cells. CD40 is best known in this regard, but RANK and LTβR can display overlapping and synergistic activities. They have been less studied in macrophages, but parallel activities in promoting survival, differentiation, and inflammatory cytokine production, as well as upregulating co-stimulatory ligands that promote T cell activation, are consequences of engaging these receptors (97, 98). However, some studies of LTβR signaling on macrophages have suggested a regulatory activity in limiting TLR signaling (99). HVEM shares binding to the ligand LIGHT with LTβR. Signaling from either HVEM or LTβR can promote migration of macrophages (98, 100) and can induce inflammatory mediators, such as TNF, IL8, MMPs, and TGF-β (101, 102). Fn14 has been implicated in driving inflammation and remodeling activities in several tissues. TWEAK, the ligand for Fn14, can be made by macrophages (103) and TWEAK can also exert pro-inflammatory activity in macrophages via Fn14, promoting production of molecules, such as IL6, IL8, MCP-1, MMPs, and HMGB1, and driving macrophage migration into inflamed sites (104–107).

The receptors for BAFF and APRIL are best known as regulators of B cell survival or differentiation and also control T cell activity in some cases. Tnfsf13c (BAFFR) that only binds BAFF was low in all macrophages, but Tnfsf13b (TACI) and Tnfsf17 (BCMA) that bind BAFF and APRIL were high in intestinal, adipose, and peritoneal macrophages and adipose macrophages and microglia, respectively. BAFF can be made by macrophages in soluble and membrane form, and membrane BAFF may (reverse) signal to promote inflammatory mediators (108), but the roles of the receptors are not well understood. Recent studies suggest that TACI or BCMA signals can also promote pro-inflammatory cytokines/mediators (109). TACI activity may also suppress differentiation of macrophages into the M2 phenotype, allowing enhanced clearance of intracellular organisms (110).

Tnfsf9 (4-1BB), Tnfsf25 (DR3), Tnfsf4 (OX40), Tnfsf18 (GITR), Tnfsf8 (CD80), and Tnfsf7 (CD27) showed low levels of transcript expression in most tissue macrophages, as did the decoy receptor for RANK (Tnfsf11b – OPG). 4-1BB, DR3, OX40, GITR, CD80, and CD27 are best known as regulators of conventional T cells as well as Treg cells, NK, or NKT cells. Most have rarely been found on the surface of macrophages, although several studies have seen DR3 and GITR on macrophages/foam cells associated with atherosclerotic plaques, or in joints associated with RA (111–114). Signaling through these receptors, probably via NFκB, may aid production of pro-inflammatory molecules, such as TNF or MMPs. The ligands for 4-1BB, DR3, OX40, GITR, and CD27 can be expressed by many macrophages after they are activated, and can aid the antigen-presenting capacity of macrophages by providing co-stimulatory signals to their receptors on T cells. Certain TNF family ligands, like 4-1BBL, TL1A (ligand for DR3), and GITRL can also signal into macrophages or monocytes (reverse signaling) to modulate their survival, production of cytokines or molecules, such as PGE2, COX-2, and iNOS, and in some cases migration (115–119). In the case of 4-1BBL, it can also associate with TLRs on macrophages independently of binding its receptor and enhance TLR signaling (120, 121).

Tnfsf27 (EDA2R) was low/absent in most macrophages, not surprising given its role outside the immune system in formation of tissues, such as sweat glands. Tnfsf19 (TROY) is primarily expressed in the nervous system and has been suggested to regulate axon regeneration, but may also contribute to hair follicle formation. TROY was also low in most tissue macrophages and BMDMs. One prior report had suggested that it could be

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**TABLE 7 | Cytokine receptors on macrophages.**

| Gene name | Common name | CD | Ligands and function |
|-----------|-------------|----|---------------------|
| lhrgr1    | IFN-γ R     |    | IFN-γ: forces M1 polarization |
| 8tr1      | IL-1 R1     | CD121a | IL-1α and β, pro-inflammatory |
| 8tr2      | IL-1 R2     | CD121b | IL-1α and β, pro-inflammatory |
| 84ra      | IL-4 R      | CD124 | IL-4: forces M2 polarization |
| 8lra      | IL-5 R      | CD125 | IL-5: forces M2 polarization |
| 8lora     | IL-10 Rα    | CD210 | IL-10: strongly anti-inflammatory, suppresses antigen presentation (135) |
| 8lorb     | IL-10 Rβ    |    |                     |
| 8lraa     | IL-13 R     | CD213a | IL-13: forces M2 polarization |
| 8loraa    | IL-13 R     | CD213b | IL-13: forces M2 polarization |
| 8lraa     | IL-17 Rα    | CD217 | IL-17α: activates macrophages Basophil function, asthma |
| 8lrb      | IL-17 Rβ    |    | Needed for IL-17α-induced CXC chemokine expression Anti-inflammatory |
| 8lrc      | IL-17 Rγ    |    |                     |
| 8lrd      | IL-17 RΔD   |    | Receptor for IL-17C: immunity to intestinal pathogens IL-27: regulates Th1 and Treg |
| 8ler      | IL-17 RΔE   |    |                     |
| 827ra     | IL-27 Rα    |    | IL-27: upregulates Th1 and Treg inflammatory activity in structural cells, such as fibroblasts, epithelial cells, and osteoclasts. This has resulted in clinical targeting of many of the molecules for autoimmune and inflammatory diseases (89), and approved drugs in blockers of TNF and LTβ to TNFR1 and TNFRII for RA, psoriasis, Crohn’s disease, and others; blockers of RANKL binding to RANK for osteoporosis; and blockers of BAFF binding to its receptors BAFFR, TACI, and BCMA for SLE.

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expressed in microglia in MS patients (122) but this has not been confirmed.

The death receptors Tnfrsf10b (TRAILR2) and Tnfrsf6 (Fas), and the mouse decoy receptors for TRAIL (Tnfrsf22 and 23 – mDcTRAILR1 and R2) showed low levels of expression in most macrophages, except for Fas in peritoneal macrophages and mDcTRAILR1 in BMDM, lung, liver, and peritoneal cells. Fas is likely to promote apoptosis of macrophages in some cases to limit autoimmunity or inflammation (123, 124), but it can be pro-inflammatory by augmenting caspase-dependent production of IL1 and IL18 or other activities (125–127). It is not known when production of the TRAIL decoy receptor by macrophages could be important for limiting TRAILR activity. Tnfrsf21 (DR6) is another death receptor that has been reported to regulate neuronal death and may also limit T and B cell activation, but whether it has other functions is not clear. It was highly expressed in microglia, peritoneal, spleen, and lung macrophages and BMDM (Figure 11).

**Fc RECEPTORS**

Fc receptors (Table 9) are receptors for immunoglobulins, which are products of plasma cells, and immune complexes. There are receptors for IgG (FcγRI, II, and III) (128, 129) and IgE (Fcε receptor). They vary in their affinity (high to low) and in their downstream signaling effects (activating and inhibitory). Fc receptors are very highly expressed and are of key importance for clearing antibody-opsonized pathogens and antibody-opsonized necrotic cells. In the mouse, most Fc receptors signal through a common adaptor protein called Fc receptor γ chain or CD23.

The results in Figure 1J summarize the expression of Fc receptors in tissue macrophages. Fcgr1, the gene encoding the CD64 Fc

| Gene name | Systematic name | Other names | Ligands and function |
|-----------|-----------------|-------------|----------------------|
| Tnfrsf1a  | Tnfrsf1a        | TNFR1       | TNF, soluble lymphokinx α: pro- and anti-inflammatory (apoptosis) many cell types |
| Tnfrsf1b  | Tnfrsf1b        | TNFR2       | TNF, soluble lymphokinx α: pro-inflammatory many cells; T cell activation |
| Ltb       | Tnfrsf3         | LTβR        | Membrane lymphokinx β and LIGHT; pro-inflammatory for APC and tissue cells; lymph node development |
| Tnfrsf4   | Tnfrsf4         | OX40, CD134 | OX40L (=CD252): T and NK activation/differentiation |
| Cd40      | Tnfrsf5         | CD40        | CD40L (=CD154): immunoglobulin class switching, APC activation |
| Fas       | Tnfrsf6         | Fas         | FasL (=CD178): apoptosis/cell death |
| Cd27      | Tnfrsf7         | CD27        | CD70: T and B cell activation; antibody production |
| Tnfrsf8   | Tnfrsf8         | CD30        | CD30L (=CD153): T and B cell activation |
| Tnfrsf9   | Tnfrsf9         | 4-1BB, CD137| 4-1BB: T and NK activation/differentiation |
| Tnfrsf10b | Tnfrsf10b       | TRAIL R2    | TRAIL (=CD253): apoptosis in tumor cells and T cells |
| Tnfrsf11a | Tnfrsf11a       | RANK        | RANKL (=CD254): osteoclast and lymph node development; activation of APC. Blockers of RANKL (antibody: denosumab) binding to RANK are used clinically to treat osteoporosis |
| Tnfrsf11b | Tnfrsf11b       | OPG         | Decoy receptor for RANK: modulates osteoclastogenesis |
| Tnfrsf12a | Tnfrsf12a       | Fn14        | TWEAK: tissue inflammation |
| Tnfrsf13b | Tnfrsf13b       | TACI        | APRIL (= CD256) and BAFF (= CD257): B cell activation/differentiation |
| Tnfrsf13c | Tnfrsf13c       | BAFFR       | BAFF (= CD257); B cell differentiation/survival. Blockers of BAFF (antibody: belimumab) binding to its receptors BAFFR, TACI, and BCMA are used clinically to treat systemic lupus. |
| Tnfrsf14  | Tnfrsf14        | HVEM        | LIGHT (= CD258): T cell activation; pro-inflammatory tissue cells and APC; BTLA: T cell inhibition |
| Tnfrsf17  | Tnfrsf17        | BCMA        | APRIL (= CD256) and BAFF (= CD257): B cell activation/differentiation |
| Tnfrsf18  | Tnfrsf18        | GITR        | GITRL: T and B cell activation |
| Tnfrsf19  | Tnfrsf19        | TROY        | Nogo coreceptor: axon regeneration? Unknown: hair follicle development? |
| Tnfrsf21  | Tnfrsf21        | DR6         | Amyloid precursor protein: neuron death? Unknown: T cell inhibition/death |
| Tnfrsf22  | Tnfrsf22 and 23 | mDcTRAILR2 and mDcTRAILR1 | Decoy receptors for TRAIL only expressed in mice: neutralize TRAIL activity |
| Tnfrsf23  | Tnfrsf23        | DR3         | TL1A: T cell activation/differentiation |
| Eda2r     | Tnfrsf27        | XEDAR       | EDA: control of hair follicle, sweat gland, teeth development |

**TABLE 8 | TNF receptor superfamily.**
γ receptor, is specific for macrophages and has been proposed as a universal mouse macrophage marker (40).

CHEMOKINE RECEPTORS AND OTHER GPCRs

Macrophages and dendritic cells are important sources of many inflammatory chemokines including CCL1, 2, 3, 4, and 5. However, they also express chemokine receptors (Table 10) and, thus, respond to their chemokine environment. The major chemokine receptors on macrophages are CCR2, CCR5, and CX3CR1 (130, 131). CCR2 binds CCL2 and related chemokines of the MCP subfamily and is responsible for release of monocytes from the bone marrow and their trafficking to inflamed tissues. CCR1 and 2 are expressed in all tissue macrophages, but very low in microglia. CCR5 is a receptor for CCL5 and attracts monocytes to the vascular wall. It is expressed in all macrophages, highest in microglia. CX3CR1 is a receptor for CX3CL1 (fractalkine) and promotes macrophage survival. It is expressed in all macrophages, highest in microglia and intestinal macrophages.

OTHER GPCRs

Other GPCRs (Table 10) include four adenosine receptors, Adora 1, 2a, 2b, and 3. Adenosine is a ubiquitous metabolite found in the extracellular space, and macrophages can respond to adenosine through these receptors. ATP is released by apoptotic cells through a pannexin-dependent mechanism, and ATP and ADP are important metabolites influencing macrophages through P2Y receptors. Sphingosine-1-phosphate is produced by platelets and other blood cells and is sensed by macrophages through S1P receptors S1P1-4 (Figure 1K).

The adenosine receptor A2A (Adora2a) is expressed at low levels in all tissue macrophages except microglia. This receptor downregulates inflammatory responses. A2B (Adora2b) is also expressed at low levels, but much higher in adipose tissue macrophages. This is considered a pro-inflammatory receptor.

P2Y1 (P2y1) is an ADP receptor with low expression in all macrophages except microglia, where it does not appear to be expressed. By contrast, the ADP receptor P2Y12 (P2ry12) shows low expression in all macrophages but very high expression in microglia. P2Y12 on platelets is a target for anti-thrombotic treatment. P2Y2 is a receptor for UTP and ATP, which is released from apoptotic cells via pannexin (PANX1) (132).

The sphingosine-1-phosphate receptor encoded by S1pr1 is expressed by all tissue macrophages. S1pr2 is also broadly expressed, with highest levels in BMDM and bone marrow macrophages. S1pr3 and S1pr4 are expressed at low levels. Expression of these GPCRs is shown in Figure 1K.

INTEGRINS

Macrophages use integrins (Table 11), αβ heterodimers that bind to extracellular matrix molecules (ECM) and other cells (133, 134). Since integrins, once bound to ligand, promote outside-in signaling, integrin engagement is an important input into macrophage biology. Almost all integrin subunits are expressed at some level in various tissue macrophages. Many integrin α subunits pair with β1, which is expressed in all macrophages (Itgb1). Itga1, Itga11, Itga2, Itga2b, Itga3, and Itga7 are expressed at low levels. Itga4 pairs with Itgb1 forming VLA-4, an integrin known to be involved in monocyte recruitment to tissues. Itga4 expression varies widely between tissue macrophages, with highest expression levels seen in large and small peritoneal macrophages. Itga5 pairs with Itgb1 to form a fibronectin receptor that is expressed at moderate levels in all tissue macrophages, highest in thioglycollate-elicited peritoneal

| Table 9 | Fc receptors. |
|---|---|---|---|
| Gene name | FcR | CD | Function |
| Fcgr1 | FcγRI | CD64 | High affinity IgG binding |
| Fcgr2b | FcγRIIb | CD32 | Low affinity IgG R, immune complexes |
| Fcgr3 | FcγRIII | CD16 | Low affinity IgG R, immune complexes |
| Fcgr4 | FcγRIII-2 | CD16-2 | Low affinity IgG R, immune complexes |
| Fcere1a | FcεR | High affinity IgE receptor |
| Fcere1g | Fc γ chain | CD23 | Adaptor for most Fc receptors |
| Fcere2a | FcεR2 | CD23a | Low affinity IgE receptor |
| Ms4a2 | FcεR1 | |

| Table 10 | GPCRs expressed on macrophages. |
|---|---|---|---|---|
| Gene name | GPCR | CD, other | Function |
| Ccr1 | CCR1 | CD191 | Pro-inflammatory |
| Ccr2 | CCR2 | CD192 | Recruits monocytes |
| Ccr5 | CCR5 | CD195 | Arrest, integrin activation, recruits monocytes |
| Ccr7 | CCR7 | CD197 | Directs macrophages and dendritic cells to lymphatics and lymph nodes, also involved in lymphocyte homing and development |
| Cx3cr1 | CX3CR1 | | Fractalkine R: Macrophage survival |
| Adora1 | Adenosine A1 | | Pro-inflammatory, sleep-inducing |
| Adora2a | Adenosine A2a | | Anti-inflammatory, Istradefylline is an A2A antagonist approved for Parkinson’s disease |
| Adora2b | Adenosine A2b | | |
| Adora3 | Adenosine A3 | | |
| P2y1 | ATP R 1 | | ATP and ADP receptor |
| P2y2 | ATP R 2 | | Apoptotic cell recognition |
| P2y12 | ATP R 12 | | ATP and ADP receptor |
| S1pr1 | S1P1 | CD363 | Regulates lymphocyte trafficking |
| S1pr2 | S1P2 | EDG5 | |
| S1pr3 | S1P3 | EDG3 | |
| S1pr4 | S1P4 | EDG6 | |
**TABLE 11 | Integrins.**

| Gene Name | Integrin | CD, other | Function |
|-----------|----------|-----------|----------|
| Itgb1     | β1 integrins | CD29 | Pairs with α1–11 |
| Itga1     | α1β1 | CD49a | Collagen receptor |
| Itga2     | α2β1 | CD49c | Type 4 collagen receptor |
| Itga4     | α4β1 | CD49d | VLA-4 |
| Itga5     | α5β1 | CD49e | Bind fibronectin, pro-inflammatory signal |
| Itga6     | α6β1 | CD49f | VLA-6 |
| Itga7     | α7β1 | | Muscle development |
| Itga8     | α8β1 | | Extracellular matrix assembly? |
| Itga9     | α9β1 | | Fertilization of egg |
| Itga10    | α10β1 | | Collagen binding |
| Itga11    | α11β1 | | Collagen binding |
| Itgb2     | β2 integrins | CD18 | Pairs with αL, αM, αX, αd |
| Itgal     | αLβ2 | CD11a/CD18 | Adhesion to ICAM-1, 2, and 3 |
| Itgam     | αMβ2 | CD11b/CD18 | LFA-1 |
| Itgax     | αXβ2 | CD11c/CD18 | Mac-1 |
| Itgcd     | αDβ2 | CD11d/CD18 | Binds C3bi, ICAM-1, denatured proteins |
| Itgbd     | β3 integrins | CD61 | |
| Itgad     | αDβ3 | CD61 | |
| Itgab     | αLβ3 | CD41/CD61 | High on platelets, binds fibrinogen |
| Itgay     | αVβ3 | CD51/CD61 | Major receptor for vitronectin, uptake of apoptotic cells |
| Itgbc     | αVβ6 | CD51 | Involved in TGFß activation (136) |
| Itgbe     | αVβ7 | CD51 | |
| Itgbf     | β7 integrins | Ly69 | Intestinal specific |
| Itgaf     | α4β7 | CD49d | Binds MacCAM-1 |
| Itgai     | αEβ7 | CD103 | Binds to E-cadherin |

The integrin subunits Itgal, Itgam, Itgax, and Itgad all pair with Itgb2 and are leukocyte specific. These β2 integrins are highly expressed in all macrophages, with highest mRNA levels in thioglycollate-elicited peritoneal macrophages. Itgal (LFA-1) is expressed at modest levels in most macrophages but not in microglia. Itgam (Mac-1), also known as complement receptor-3, is expressed at intermediate levels in most macrophages but very high in peritoneal and BMDM. Itgax (CD11c) is widely used as a dendritic cell marker, but this integrin is also expressed in all macrophages, most highly in thioglycollate-elicited peritoneal macrophages. Itgad (CD11d) is expressed at very low levels except for spleen macrophages, where it is very high.

Itgab pairs with Itgb3 to form the vitronectin receptor αVβ3, also known as leukocyte response integrin. Both subunits are expressed across all macrophages. Itgacan also pair with Itgb6 to form αVβ6 integrin, which is involved in TGF-β processing and fibrosis. Itgae and Itgad pair with Itgb7, a receptor family generally found more in intestinal tissues. Indeed, Itgb7 expression is highest in peritoneal and intestinal macrophages. Itgae is highly specialized and binds to E-cadherin. Its expression is low except in intestinal macrophages, where it is very high (Figure 1H). The collagen receptor α2β1 integrin was not expressed in any of the macrophages studied here.

**CONCLUDING REMARKS**

This review provides a broad overview of receptors used by macrophages to sense their environment, including apoptotic and necrotic cells, pathogens, carbohydrates, modified self molecules, cytokines, chemokines, and other soluble molecules and extracellular matrix components. Some of these macrophage receptors are broadly expressed in all tissue macrophages studied, while others are highly restricted. This suggests that certain macrophages are well equipped for certain functions (listed in the tables) and others are “blind” to certain challenges or inputs. Recent reviews on each of the 12 classes of receptors are cited in the respective subsections for more detailed information. The remarkable heterogeneity in expression of macrophage receptors suggests highly specialized functions of resting tissue macrophages in lung, liver, spleen, intestine, fat tissue, the peritoneal cavity, and the brain (microglia).

This review is limited to mRNA expression data, and it is unknown how these expression patterns correlate with protein levels. In macrophages, the correlation between mRNA and protein levels is modest. Also, we consider the 12 receptor classes individually, but they may cooperate or even compete for ligand recognition, which would affect macrophage function. There could be more than one “danger” that affects a tissue, such as infection with multiple pathogens or viral infection and apoptotic cells. How tissue macrophages respond to such complex inputs remains to be studied. We did not analyze infiltrating monocyte-derived macrophages here, which can be a dominant population in inflammatory diseases, infections, autoimmune diseases, and cancer.

**AUTHOR CONTRIBUTIONS**

KL wrote the paper. AP constructed the heat maps and input to the tables. MC wrote and edited the TNFSF part. KR edited the apoptotic cell uptake part. JT wrote and edited the NLR and RLR part.

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