Functions of CD169 positive macrophages in human diseases (Review)

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Abstract. CD169$^+$ macrophages are a unique type of macrophage subset that differ from M1 and M2 macrophages. CD169$^+$ macrophages are present in multiple tissues and organs throughout the body and are primarily expressed in secondary lymphoid organs. These cells are primarily divided across three locations in secondary lymphoid organs: The metallophilic marginal zone of the spleen, the subcapsular sinus and the medulla of the lymph nodes. Due to their unique location distribution *in vivo* and the presence of the CD169 molecule on their surfaces, CD169$^+$ macrophages are reported to serve important roles in several processes, such as phagocytosis, antigen presentation, immune tolerance, viral infection and inflammatory responses. At the same time, it has been reported that CD169$^+$ macrophages may also serve an important role in anti-tumour immunity. The present review focuses on the research progress surrounding the function of CD169$^+$ macrophages in a variety of diseases, such as viral infection, autoimmune diseases and tumours.

Contents

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1. Introduction

Macrophages are distributed throughout the body in various tissues and organs and show a high degree of heterogeneity and diversity (1). Several specific markers expressed on macrophage surfaces have been used to identify different subsets, such as F4/80, CD68, SRA-1 and CD169 (2). CD169$^+$ macrophages are a unique subset of macrophages distributed across multiple tissues and organs of the human body. The results in the NCBI database showed that the CD169 molecules were expressed in 27 different tissues of the human body, such as the spleen, lymph node, small intestine, liver, lung, heart, kidney, colon, bone marrow and placenta, with a particularly high expression in the placenta, spleen, lymph nodes, lungs and bone marrow. The expression of CD169 also changes in these organs when the organ becomes diseased (Fig. 1) (3). Studies on CD169$^+$ macrophages show its unique roles in certain diseases. CD169$^+$ macrophages exhibit a unique location distribution, primarily in the secondary lymphoid organs where the blood and lymph enter and leave, and express the unique CD169 molecule on their surface (2). Unlike M1 and M2 macrophages, CD169$^+$ macrophages can interact directly with T cells, B cells and dendritic cells (DC) through CD169 molecules to participate in immune regulation (4).

The discovery of CD169$^+$ macrophages can be traced back to 1986, when Crocker found a macrophage in the centre of the bone marrow hematopoietic island in mice that expressed a nonphagocytic, sialic acid-dependent sheep erythrocyte receptor, which was later termed Sn, sialic acid binding immunoglobulin-like agglutinin (Siglec)-1 or CD169 (5). Several studies have shown significant changes in the number of CD169$^+$ macrophages in pathological tissues, lymph nodes and peripheral blood under conditions of disease, such as cancer and autoimmune diseases (6-8). This suggests that CD169$^+$ macrophages are involved in the regulation of multiple immune responses and can serve as a potential molecular marker for predicting disease progression.

In the past 30 years, CD169$^+$ macrophages have been studied in various fields. However, to date, there are still several aspects of their biology to be explored, including their differentiation and development, signal transduction pathways and modes of activation. With the successful development of mice with CD169 gene deletion and its application in various

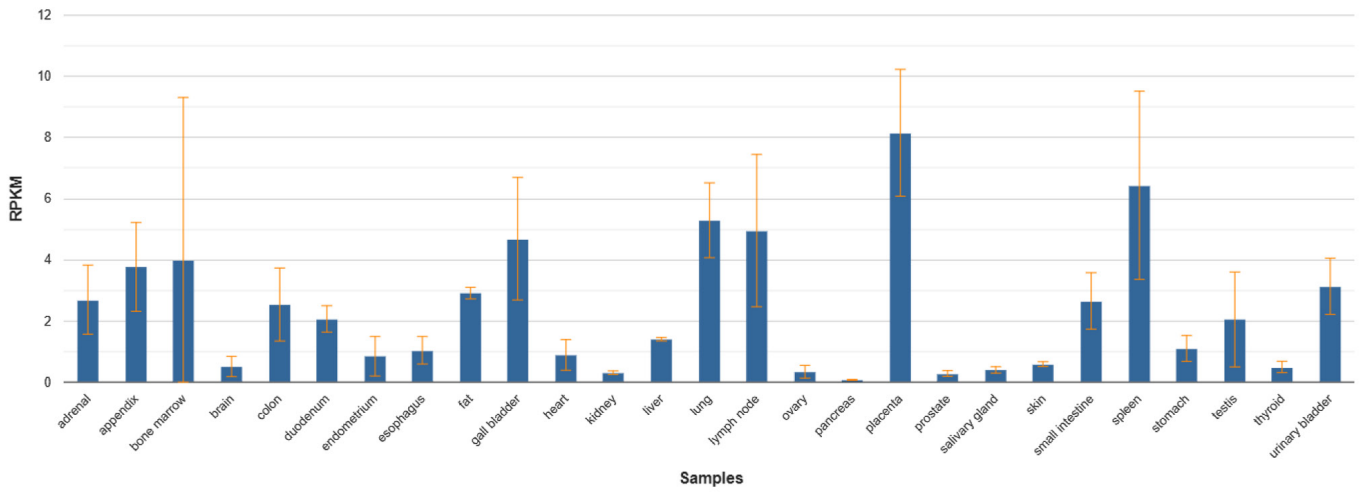

Figure 1. Expression of CD169 molecules in human tissues. RNA sequencing was performed on tissue samples from 95 human individuals representing 27 different tissues in order to determine tissue-specificity of the CD169 genes (3).

disease models, the roles of CD169$^+$ macrophages in immune regulation are gradually being elucidated.

2. Biological function of the CD169 molecule

CD169, is a member of the Siglec family (9). It is primarily expressed on the surface of specific macrophage subsets and its precursor monocytes, as well as on some DCs or T lymphocytes (10). The CD169 molecule consists of 17 Ig-like domains, including an N-terminal V-set domain and 16 C2-set domains, which are highly conserved in humans and mice (11). CD169 is involved in cell-to-cell adhesion and cell-pathogen interactions (12). The CD169 molecule endows CD169$^+$ macrophages with their unique functions. Cells expressing CD169 have high affinity for α2-3-glycosyltransferase and glucosidase, and communicate with other immune cells by recognizing and binding other cell surface polysaccharides, such as CD43 on T cells (13). CD169$^+$ macrophages in the marginal zone of the spleen recognize phosphatidylserine on the surface of apoptotic cells, present apoptotic cell antigens and recruit regulatory T cells (Tregs) to exhibit their role in immune tolerance (14). Furthermore, the recruitment of Tregs may negatively regulate the immune responses and inhibit autoimmune diseases (15-18). The CD169 molecule has been used as molecular marker in several autoimmune diseases to predict patient outcomes, such as Grave's diseases (19,20). CD169 molecules in the marginal zone of the spleen are also key components participating in virus defence in the host, where it can bind to ganglioside GM3 on the surface of HIV-1 particles, capture viral particles and mediate viral infection (21). As an adhesion molecule, CD169 is a facilitator of the recognition and internalization of sialic acid decorated apoptotic bodies and exosomes derived from tumours. It can potentially contribute to both the attenuation as well as the facilitation of anti-tumour immunity (22). CD169 in lymph nodes, for example, are involved in immunomodulation with MUC-1 binding on the surface of breast cancer tumour cells (23). Moreover, CD169$^+$ macrophages capture B cell-derived exosomes in the spleen and lymph nodes through their surface a2,3-linked sialic acids (24).

3. Development and phenotype of CD169$^+$ macrophages

CD169$^+$ macrophages are primarily reported to be present in three locations in the secondary lymphoid organs: The metallophilic marginal zone (MZM) of the spleen, the subcapsular sinus and the medulla of the lymph nodes (2). Mouse lymph node subcapsular sinus macrophages (SSMs) express CD169$^+$CD11b$^+$F4/80$^-$CD11C^{lo} and medulla sinus macrophages (MSMs) express CD169$^+$F4/80$^+$. These two groups of macrophages are derived from CD11b$^+$ cell precursors in embryonic or adult mice and rely on lymph node mesenchymal and endothelial stromal cells to form a niche environment through the RANK-RANKL cytokine axis (25). MZM macrophages in the spleen express CD169$^+$CD11b$^+$ F4/80$^-$CD11C^{lo} and CD169$^+$ macrophages in the intestine are present far from the epithelial boundary, being primarily distributed in the colonic lamina propria, around the crypt, expressing CD115$^+$CD169$^+$CD11b$^+$ F4/80^{lo}CD11C^{lo} (26). The surface markers of CD169$^+$ macrophages in the colon lamina propria are similar to those in the spleen, but they differ widely with regard to differentiation. CD169$^+$ macrophages express low levels of F4/80, indicating that they are not derived from yolk sac precursors (26). CD169$^+$ macrophages in the colon lamina propria may originate partly from self-renewal of tissue resident macrophages and partly from blood stem cell supplementation (26).

Similar to most macrophages, the development of CD169$^+$ macrophages is regulated by CSF-1. CD169 expression was not detected in CSF-1 gene knockout mice, and injection of CSF-1 rescued the expression of CD169. In addition, interfering with the CSF-1 signalling pathway in the spleen of mice could quickly inhibit the generation of this cell (27,28). The development of CD169$^+$ macrophages also depends on lymphotoxin (LT)-α and LT-β secreted by B cells, and the deletion of B cells or LT can affect cell development directly (29,30). In the colon however, the development of CD169$^+$ macrophages is dependent on vitamin A, rather than LT (26). Colonic CD169$^+$ macrophages display different phenotypes, which is dependent on Maf expression levels in various phases of inflammation (31). Moreover, CD169 expression in the peripheral blood can be induced by type I interferon (IFN) *in vitro*, and both type I IFN levels and

Table I. Macrophage populations in mouse secondary lymphoid organs and the colon.

Organ	Area	Macrophage population	Makers
Spleen	Red pulp	Red pulp MΦ	F4/80, MR, CD68
	Marginal zone	MZM MΦ	CD169, CR-L, CD11b
		Outer MZ MΦ	SR-A, Macro, SIGNR-1
	White pulp	White pulp MΦ	CD68, CR-L
Lymph nodes	SS	SS MΦ	CD169, CR-L, CD11b
	Medulla	Med MΦ	CD169, SIGN-R1, Macro, SR-A, F4/80, MR
	Cortex		CD68
Colon	Lamina propria	Lamina propria $CD169^+$ MΦ	CD115, CD169, CD11b

MΦ, macrophages; SS, subcapsular sinus; R-L, ligand for the cysteine-rich domain of MR.

the expression of CD169 is increased in animal models and patients with autoimmune diseases (Table I) (32-36).

4. Roles of $CD169^+$ macrophages in bone marrow

$CD169^+$ macrophages were initially found in the mouse bone marrow, located in the centre of the 'erythroid hematopoietic island' (5,37,38). This cell subset expresses several molecules($CD169^+VCAM\text{-}1^+ER\text{-}HR3^+CD11b^+F4/80^+Ly\text{-}6G^+$) (39). $CD169^+$ macrophages scavenge apoptotic cells and efflux nuclei produced during erythroid haematopoiesis by binding to sialose complexes on the surface of erythroid cells, maintaining the function and integrity of haematopoietic islands (40). Through the combination of CD169 and sialic acid complexes on the surface of erythroid cells, the apoptotic cells and the effluxed nuclei produced in erythroid haematopoiesis are eliminated (41). $CD169^+$ macrophages also circulate iron in the blood, providing the nutritional microenvironment required for haematopoiesis (41). Postponed haematopoietic recovery was observed in a mice model of haemolytic anaemia induced by hydrazinobenzene, when monocyte clearance and $CD169^+$ macrophage clearance were caused by disodium chloride phosphate liposomes (42). At the same time, $CD169^+$ macrophages promoted late erythrocyte maturation in the study of a mouse model of polycythaemia (43). These results suggested that $CD169^+$ macrophages are essential in the development and maturation of erythrocytes and may provide a new avenue for the treatment of iron deficiency anaemia, erythrocyte regeneration disorder and polycythaemia (43). In studies of $CD169^+$ macrophages in the bone marrow of mice, it was also found that the absence of $CD169^+$ macrophages could lead to bone injury and inhibit bone repair, indicating that $CD169^+$ macrophages may be helpful in maintaining bone homeostasis and bone regeneration (44). $CD169^+$ macrophages also exist in the human bone marrow, and its distribution is similar to that in mice; however, the study of its roles in bone marrow are still limited, and their roles have not been fully elucidated.

5. Role of $CD169^+$ macrophages in antigen presentation

In the lymph nodes and spleen, $CD169^+$ macrophages are associated with the regions of organs exposed to body fluids, close to the T and B lymphocyte regions, which is consistent with their role in antigen processing (45). However, the effect of $CD169^+$ macrophages in different parts of the body varies slightly. SSMs have poor endocytotic properties compared with MSMs, expressing only low levels of lysosomal enzymes with limited degradative ability (46). Thus, SSMs are not intended to degrade antigens but present these antigens to homologous or nonhomologous B cells along immunological synapses extending into the follicles. SSMs can even enter follicles under inflammatory conditions. The antigen recognition of B cells homologous to SSMs results in the activation of B cells and migration to T-B cell boundaries for assistance from Th cells (47). $CD169^+$ macrophages present antigens to B cells via two means: $CD169^+$ macrophages present antigens directly to homologous B cells or $CD169^+$ macrophages acquire immune complexes that are delivered to follicular DCs in follicles to retain the native antigens, ensuring long-term presentation to B cells (48,49). SSMs also secrete a large number of cytokines whilst presenting antigens, particularly type I IFN, increasing the cascade reaction produced by cytokines, leading to the influx of DCs, neutrophils and NK cells (50). MSMs are exposed to the medullary cords and flow out of the medullary cords of the lymph nodes before being excreted through the efferent lymphatic vessels. MSMs can phagocytose and present microbial antigens, but there is little evidence that they produce proinflammatory cytokines (2). Under certain conditions, $CD169^+$ macrophages, particularly SSMs, cross-present to $CD8^+$ T cells. The cross-presentation of $CD8^+$ T cells by $CD169^+$ macrophages is performed via two methods: $CD169^+$ macrophages transfer antigens to the spleen $CD8a^+$ DCs and then to $CD8^+$ T cells or $CD169^+$ macrophages directly present antigens to $CD8^+$ T cells (13,51). In addition, $CD169^+$ macrophages may also present lipid antigens to promote the activation of invariant natural killer T (iNKT) cells by expressing the MHC class of molecules, and iNKT cells further activate DC, NK, B and T cells by secreting cytokines (Table II) (52-54).

6. Functions of $CD169^+$ macrophages in immune tolerance

Ravishankar *et al* (14) confirmed that $CD169^+$ macrophages also participate in the immune tolerance induced by apoptotic cell clearance. Apoptotic cells are important sources of autoantigens;

Table II. Development and functions of CD169$^+$ macrophages.

Organ	Development	Area	Functions
Lymph nodes	LT-α and LT-β	SS	Low phagocytic, present antigens, secrete cytokines
		Medulla	Engulf and present microbial antigens
Spleen	LT-α and LT-β	Marginal zone	Engulf and present viruses and apoptotic cell antigens, antiviral effects, immune tolerance
Colon	Vitamin A	Lamina propria	Present antigens, secrete CCL8, recruit monocytes, promote inflammation

LT: lymphotoxin; SS: subcapsular sinus.

their normal clearance process may induce immune tolerance, and abnormal accumulation of autoantibodies can lead to the occurrence of autoimmune diseases (55-58). A previous report showed that CD169$^+$ macrophages have a strong capacity to phagocytose apoptotic cells, by which immune homeostasis is maintained (59). Splenic CD169$^+$ macrophages can bind to α2,3- and α2,6-sialic acid on the surface of blood-derived apoptotic cells, thereby presenting apoptotic cell-associated antigens (60). Antigens are transmitted to CD8a$^+$ DCs in the spleen and then activates CD8$^+$ T cells in response to apoptotic cell-associated antigens (61,62). CD169$^+$ macrophages secrete CCL22 whilst presenting antigens and in-turn recruit Tregs through the CCL22-CCR4 axis, increasing the number of Tregs and inducing immune tolerance (63). However, injection of apoptotic cells into CD169-null mice resulted in an increase in autoantibodies, such as IgG and IgM and an increase in serum inflammatory factors (14). Nevertheless, the role of CD169$^+$ macrophages in immune tolerance induced by other pathways remains unclear.

7. Roles of CD169$^+$ macrophages in autoimmune diseases

Macrophages usually maintain immune homeostasis by phagocytosis of foreign particles and production of anti-inflammatory factors, such as IL-10 (64). CD169$^+$ macrophages do not exhibit changes in mice lacking MyD88-mediated Toll receptor signalling, and in mice in which bacterial flora have been eradicated, despite the high levels of bacterial flora in the colon and the importance of TLR signalling in mucosal homeostasis (26,65). However, several studies have shown that activated CD169$^+$ macrophages are involved in inflammatory responses during several autoimmune diseases. In the colon, CD169$^+$ macrophages are reported to promote colitis progression in a dextran sulfate sodium (DSS)-induced IBD model (66,67). The symptoms of colitis in DSS-induced mice were significantly alleviated in CD169$^+$ macrophage-deficient CD169-DTR mice. Our previous study showed that the numbers of CD169$^+$ macrophages in the mesenteric lymph nodes (mLN) and abdominal cavity were higher in DSS-induced colitis mice than in the WT mice, with higher expression of mLN inflammatory cytokines, such as IL-17 and IL-6 (68). At the same time, the expression levels of the chemokine CCL22 decreased, together with decreased CCR4-expressing Treg cells, which are critical factors for maintaining homeostasis (63). A further study revealed that CD169$^+$ macrophages respond to microbial antigens and produce CCL8 to recruit inflammatory monocytes that exacerbate inflammation during colitis (68). Moreover, the decrease in CD169$^+$ macrophages in cyanidin 3-O-glucoside-treated colitis suggests that this subset could be a potential biomarker and therapeutic target (69).

Studies on human multiple sclerosis have shown that CD169$^+$ macrophages are abundantly present in MS patients, and have been used as selective markers for microglia and macrophages which are activated early in MS lesions (70). Treatment with CD169 neutralizing antibody in patients with rheumatoid arthritis significantly inhibited inflammation (71). The increased number of CD169$^+$ macrophages in damaged tissues in a mouse experimental autoimmune encephalomyelitis (EAE) models and in human-derived IRBP peptide-induced experimental autoimmune uveoretinitis similarly inhibited Treg proliferation by binding sialic acid residues on the surface of Tregs (72). The depletion of CD169$^+$ macrophages increases the numbers of Tregs and decreases the numbers of effector T (Teff) cells, and the severity of the disease is significantly reduced (72). In addition, CD169$^+$ macrophages in the kidney regulate ICAM-1 expression and infiltration of inflammatory cells by interacting with endothelial cells (73).

8. Antiviral effects of CD169$^+$ macrophages

In the past decade, the marginal zone of the mouse spleen has been shown to serve a very important role in host defence against pathogen infections, such as viruses (74,75). CD169$^+$ macrophages are reported to be the primary cell type infected during viral infection, and they can capture viral particles in the blood, absorb antigens, such as immune complexes and viruses, and then present them in a complete form to follicular B cells, inducing germinal centre B cellular responses (30,76,77). CD169$^+$ macrophages transfer antigens to CD8a$^+$ DCs using the CD169 molecule, which preferentially participate in cell contact, eventually inducing an effective CD8$^+$ T cell response (51). Moreover, CD169$^+$ macrophages have been shown to enforce viral replication, resulting in the delivery of a large number of viral antigens, and the amplification of T and B lymphocyte responses (29,78). Type I IFN induced macrophages express CD169 molecules both *in vivo* and *in vitro* (50). CD169$^+$ macrophages can also mediate antiviral activity by secreting type I IFN during viral infection. Since CD169$^+$ macrophages simultaneously express programmed death ligands (PD-L1), the expression of IFN-I can upregulate the expression of PD-L1, which may result in CD8$^+$ T cell exhaustion. The exhaustion of CD8$^+$ T cells is

a double-edged sword. In studies of lymphocytic choroidal meningitis virus infection *in vivo*, the persistent expression of IFN-I resulted in increased IL-10 and PD-L1 levels (79). IFN-I produced by CD169$^+$ macrophages during chronic infection inhibits activation of the immune response to secondary infection (80). However, the absence of CD169$^+$ macrophages results in inadequate production of IFN-I, reducing antiviral activity and persistence of the virus in the human body. Deletion of CD169$^+$ macrophages also limits IFN-1 dependent PD-L1 expression. Without PD-L1, viral replication is enhanced, and the virus persists. At the same time, CD8$^+$ T cell depletion is inhibited. Thus, in a mouse model, PD-L1 deletion resulted in the development of severe immunopathology and they died quickly following infection (79).

Similarly, mice infected with respiratory syncytial virus (RSV) also showed that the number of CD169$^+$ macrophages localized in the alveoli increased significantly (81). CD169-diphtheria toxin receptor (DTR) mice revealed that the secretion of IFN-β, IL-6 and TNF-α decreased when CD169$^+$ macrophages were absent, whereas CD169$^+$ macrophage deletion reduced the aggregation of effector CD8$^+$ T cells to the lungs following RSV mucosal infection. Overall, regulating the number of CD169$^+$ macrophages to enhance the immune response to RSV infection may be a novel therapeutic strategy (82).

Some studies of retroviral HIV revealed that the expression of CD169 induced by IFN-I could promote cis-infection in bone marrow cells and target HIV to DC-mediated trans-infection pathways (82-86). Siglec-1 on the surface of CD169$^+$ macrophages can recognize gangliosides in the lipid membrane of the virus, capture HIV particles, and further transmit the viral signal to DCs, leading to the infection of CD4$^+$ T cells and reducing the antiviral effect of IFN-I (87,88). Moreover, Siglec-1 induces the formation of a virus-containing compartment and enhances macrophage-to-T cell transmission of HIV-1 (83). Siglec-1 expression on pre-DCs amongst blood DCs promotes attachment and fusion of viral particles and mediates the replication-independent transfer of HIV-1 to activated primary T lymphocytes (20). Whether CD169$^+$ macrophages serve an antiviral role or promote viral replication during viral infection is dependent on the genetic characteristics of the virus and the location of CD169$^+$ macrophages. Altogether, the roles and mechanisms of CD169$^+$ macrophages in humans infected with viruses still requires further study.

9. Anti-tumour roles of CD169$^+$ macrophages

The production of cytotoxic T lymphocytes (CTLs) in tumour targeting CTLs is considered to be key in inducing antitumour immunity (89,90). A previous study reported that CTLs and NK cells were activated by the subcutaneous injection of apoptotic tumour cells and they exhibited anti-tumour immunity effects (91). Antigen-presenting cells are critical for the activation of CTLs by capturing tumour cell-related antigens, which are primarily released from apoptotic tumour cells (92). CD169$^+$ macrophages in lymph nodes and spleen were reported to present apoptotic tumour antigens. Additionally, intravenous injection of apoptotic tumour cells may be different from those obtained by subcutaneous injection of apoptotic tumour cells (93). Furthermore, tumour antigen-specific CD8$^+$ T cell activation and subsequent anti-tumour immune function in CD169$^+$ macrophage-deficient mice was severely impaired (13,59).

In human lymph nodes, CD169$^+$ macrophages are primarily located in the paracortical area and in the medullary sinus, and express CD68 (6). Infiltration of these cells into local lymph nodes drains in patients with endometrial cancer, melanoma, colon cancer, bladder cancer, oesophageal cancer and diffuse large B cell lymphoma is associated with clinical staging, overall survival and clinical prognosis (94-99). A high density of CD169$^+$ macrophages is indicative of a long survival period and a good clinical prognosis in patients with tumours. The density of CD169$^+$ sinus macrophages correlates positively with CD8$^+$ T cell or CD57$^+$ NK cell infiltration in tumour tissues. The number of both CD8$^+$ T cells and CD57$^+$ NK cells in tumour nests and tumour stroma increased significantly when CD169$^+$ regional lymph nodes (RLN) sinus macrophages were abundantly present (96). CD169$^+$ sinus macrophages exhibit direct contact with CD8$^+$ T cells that express CD43, a major ligand of CD169, but whether interactions occur between CD169$^+$ sinus macrophages and CD57$^+$ NK cells in RLN has remained unclear (100). In a study of human head and neck squamous cell carcinoma, it was found that RLN metastasis was related to the density of CD169$^+$ macrophages in the subcapsular sinus of the draining lymph nodes. The number of CD169$^+$ macrophages in patients with lymphatic metastasis is lower than that in patients with lymphatic non-metastasis (101). These results suggest that the density of CD169$^+$ macrophages may be used as a potential indicator for evaluating and detecting the clinical prognosis of malignant tumours.

In addition to CD169$^+$ macrophages in lymph nodes, a large number of tumour-associated macrophages (TAMs) exist in the tumour microenvironment. TAMs are primarily composed of M2 type macrophages with immunosuppressive phenotypes. Regulation between different macrophages in the tumour microenvironment determines the progression of tumour development. For example, the predominant M2-polarized macrophages in bladder cancer can promote tumour angiogenesis and invasion, and they are associated with tumour grade (102). Two types of macrophage subsets, CD204$^+$ macrophages and CD169$^+$ macrophages, were labelled using specific labelling of different subsets of tumour-infiltrating macrophages (27). CD204, also known as scavenger receptor A, is a phagocytic pattern recognition receptor that is primarily expressed in the medullary cells and is involved in the balance of functions, such as lipid metabolism and phagocytosis (103). It has been shown that the tumour microenvironment can upregulate the expression of CD204 on macrophages, whereas autocrine transforming growth factor β, which is produced by tumour-exposed macrophages, is involved in the downregulation of CD169 expression on these cells. In addition, a high density of tumour infiltrating CD204$^+$ macrophages has been shown to be associated with a poor prognosis in patients with different types of cancer (104). Current clinical studies have found that the number of CD169$^+$ macrophages in tumour-infiltrating macrophages in patients with liver cancer and urothelial cell carcinoma of the bladder is lower than that in the non-tumour tissues, but the opposite results have been observed in patients with gastric cancer (105).

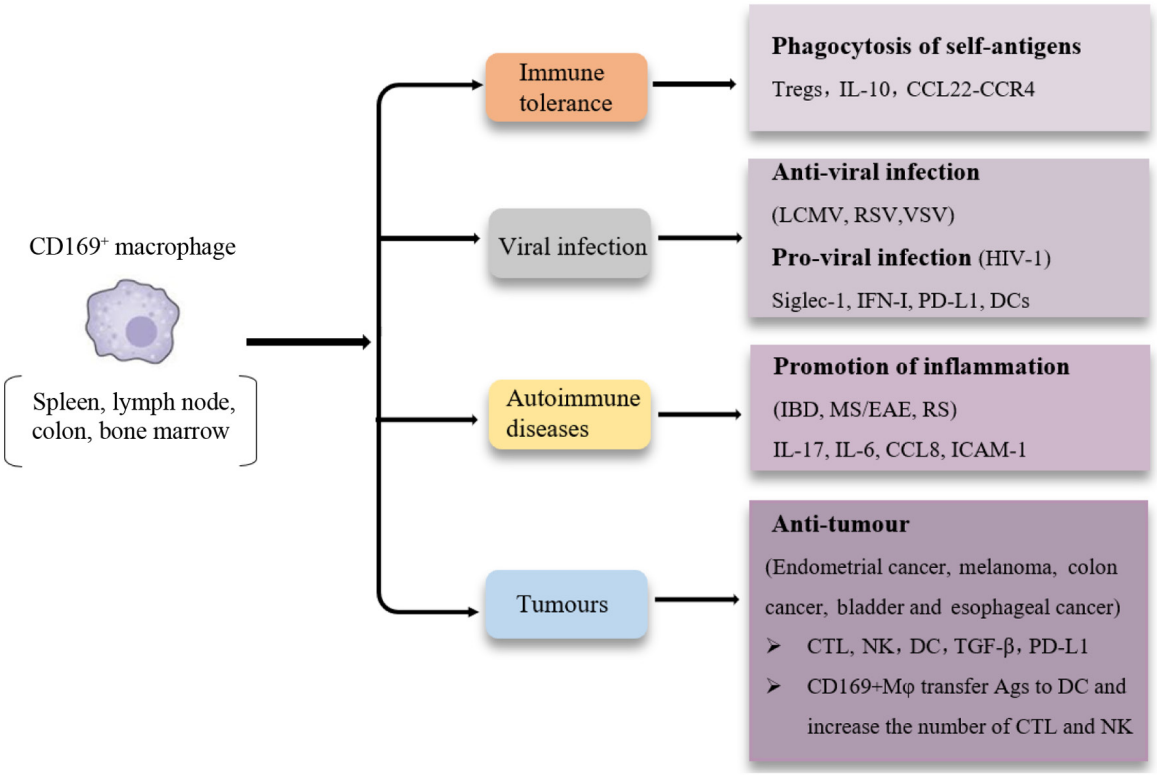

Figure 2. Summary of tissue CD169+ macrophages in various diseases. CD169+ macrophages in the spleen, lymph nodes, bone marrow and intestines have been reported in various biological processes and diseases, including immune tolerance, autoimmune diseases, virus infection and tumours.

10. Conclusion

CD169+ macrophages are widely distributed *in vivo* and have a variety of functions (Fig. 2). The role of CD169+ macrophages in immune regulation and several human diseases has been widely reported, and these cells can be used as an effective indicator to monitor disease progression and assess prognosis, and may also serve as novel targets for the treatment of several diseases. However, studies on CD169+ macrophages in numerous diseases are not substantial enough to accurately determine their role and value, and identifying the signalling pathways and critical cytokines associated with CD169+ macrophages mediated pathways still need to be determined.

The developmental sources of CD169+ macrophages in different tissues and organs should also be determined. Self-renewal of tissue-resident CD169+ macrophages may have different functions to monocyte-derived CD169+ macrophages. To determine cell fate mapping of CD169+ macrophages and identify their developmental precursors in the intestine and other tissues and organs may assist in improving our understanding of the sources which allow for development of CD169+ macrophages. Moreover, CD169+ macrophages are different from M1 and M2 macrophages, as the CD169+ can simultaneously express markers of M1/M2-type macrophages. CD169+ macrophages serve different roles in different tumours and this may be related to their location in tissues. PD-L1 expression on the surface of these CD169+ is upregulated during viral infections, but whether this also affects cell exhaustion and activation of tumour-infiltrating CD8+ T cells remains unknown. These cells in different microenvironments in different diseases may be regulated by different signals, thus polarizing these cells towards different states (106).

Although the roles of CD169+ macrophages in cancer studies have received more attention regarding their potential use as a therapeutic target, the current body of clinical and experimental studies have failed to provide suitable evidence of their application clinically. Contrary to previous studies, a recent article in mouse breast cancer suggested that CD169+ macrophages in breast tumours inhibited the antitumour effects of CD8+ T cells by mediating the upregulation of PD-L1 expression via the JAK2 signalling pathways under the influence of tumour cells (107). Hence, further studies are required to reveal the complex roles and mechanisms of CD169+ macrophages in different tumour environments. Additional studies are required to identify effective methods for sorting CD169+ macrophages for *in vitro* analysis and transcriptome sequencing of CD169+ macrophages to understand the signalling pathways and key cytokines involved in their regulation, and this may assist in improving our understanding of the mechanisms of CD169+ macrophages in different diseases.

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Authors' contributions

YL, YX and CHQ wrote the manuscript. CHQ edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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