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Macrophages: Cells That Are More Than Just Scavengers

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ABSTRACT

Macrophages are a part of the mononuclear phagocyte system, which not only phagocytose the invading microorganisms but also as serve as antigen-presenting cells (APC) that process protein antigens to be presented to T cells. Macrophages also contribute to cell-mediated immunity and humoral immunity after they are activated by cytokines. Macrophages also serve to maintain the homeostasis of organs and systems. In addition to these immune-related and physiological functions, macrophages play a pivotal role in creating the tumour microenvironment by polarizing themselves into pro-tumour or anti-tumour phenotypes. Functions of macrophages are beyond the scope of innate immunity and immune regulation. As they contribute their role in tumour evolution, several studies documented that reprogramming the macrophages may have a therapeutic role in inflammation and tumorigenesis.

Keywords: *Emacrophages, Scavengers,Macrophage polarization, Tumourigenesis, Atherosclerosis*

INTRODUCTION

During normal homeostatic states, macrophages are transformed from blood monocytes and they are present as tissue-resident macrophages. Macrophages normally exist in different tissues namely alveolar macrophages in lung alveoli, Kupffer cells in liver sinusoids, sinus histiocytes in lymph nodes, microglia in the brain, Langerhans cells in the skin and osteoclasts in bones (Park et al., 2022). Developmental processes and physiological functionality such as angiogenesis, neuronal development, adipogenesis and ageing are

also orchestrated by macrophages (Mass et al., 2023). Macrophages act in the first step of the immune response as antigen-presenting cells (APC) during exposure to a foreign antigen in a particular tissue. They have the phagocytic property and are mainly described as scavenger cells of the immune system which remove dying or dead cells, microorganisms and other cell debris. Their actions in immune mechanisms are augmented by producing growth factors and signalling molecules to further protect the body. As the disease process begins, cell signals induce the influx of diseases-associated macrophages (M-0 macrophages) to the sites of pathologic lesions. Studies have shown that in addition to their role in immune reactions, macrophages are important for the pathogenesis of metabolic diseases such as atherosclerosis. Moreover, macrophages possess tumouricidal properties aiding the management of malignancy (Mantovani et al., 2022). Macrophages in solid tumours known as tumour-associated macrophages (TAMs) express inhibitory surface receptors that can suppress adaptive immune responses which aid in checkpoint blockade immunotherapy (Duan & Luo, 2021). This article reviewed the functions of macrophages in physiology and the process of essential functions of macrophages in various pathological aspects that will help to understand more about their potential therapeutic aspect in macrophage-related diseases.

Development of macrophages and their markers

Macrophages are components of the mononuclear phagocyte system and are derived from blood monocytes. Monocytes developed from colony-forming unit granulocytes/monocytes (CFU-G/M) which are derived from common myeloid stem cells of bone marrow called M-0 macrophages and they circulate in the blood. The functional core programme of macrophages enhances physiological adaptation important for organ homeostasis (Hussell, 2016). Ly6C or CD-16 is a marker for an inflammatory population of monocytes. Ly6Chi monocytes develop into M1 cells under low inflammatory conditions in the tissues and some of these differentiate into Ly6Clo monocytes or M2 cells (Miyake et al., 2024). Ly6C+ macrophages invade tissue by interaction with CCR2/CCL2 (MPC-1) via a VLA-1/VCAM1 and are activated by interferon-√ (IFN-√), LPS and GM-CSF. Ly6C- macrophages are also recruited to tissue and differentiate into M2 macrophages by the action of cytokines such as interleukins (IL)-4, 6 and 13, TLR ligands (Wculek et al., 2022). The process of transforming into two distinct macrophage functional phenotypes based on specific signals is called polarization.

M1 cells augment NADPH oxidase isoform 2 (NOX2), inducible nitric oxide synthase (iNOS), synaptotagmin-binding cytoplasmic RNA interacting protein (SYNCRIP), and tumour necrosis factor receptor-associated factor 6 and increases oxygen and nitrogen reactive species (Pérez and Rius-Pérez, 2022). These M1 cells are known for their properties such as pro-inflammatory, phagocytosis and cytotoxicity. M2 macrophages down-regulate NOX2, and iNOS, upregulate superoxide dismutase type 1 and counteract oxidative and nitrosative stress. These cells have immunosuppressive and tissue reparative properties (Pérez and Rius-Pérez, 2022, Wynn & Vannella, 2016). Polarization of M1 to M2 is controlled by galectin-1 (Gal-1), Gal-2 and interferon (IFN)-β resulting in the resolution of inflammation (Kane et al., 2022). In inflammation, if the M1 infiltration phase continues it will produce tissue damage so that in the later phase, M2 cells replace the injured area.

Macrophages are commonly identified by specific markers such as CD11b/Integrin alpha M, CD14, CD169, and CD68 in humans (Hume, 2015), in the forms of surface markers and intracellular markers. The formers are F4/80, CCR2, CD169, CX3CR1, CD206, CD163, Lyve1, CD9, TREM2, and MHCII and CD68, iNOS, Arg-1, and Gal-3 are intracellular (Wei et al., 2023). M1 gene markers are CD-38, G-protein

coupled receptor 18 (Gpr-18), and fomyl peptide receptor-2 (Fpr2). M2 exclusive gene markers are early growth response protein 2 (Egr2) and c-Myc (Jablonski et al., 2015) which are useful for immunotherapy.

A glance at functions of tissue macrophages

Macrophage functions are seen in early development including the maintenance of placental function in pregnancy. Macrophages function as prominent decidual immune cells which constitute 36% until the second and third trimester (Krop et al., 2023). Early decidual macrophages remove apoptotic vascular smooth muscle cells (Lash et al., 2016) and endothelial cells to remodel the maternal spiral arteries (Krop et al., 2023) and trophoblast-derived galectin-9 activates macrophages to suppress the remodelling (Li et al., 2024). In the decidua, natural killer (NK) cells and macrophages produce galectin-1 to induce apoptosis of CD3+ T cells and galectin-2 to inhibit apoptosis of Treg for immune homeostasis and regulate apoptosis (Chen et al., 2024). The normal function of immune cells at the maternal-fetal interface is important for normal uterine artery remodelling (SAR) to prevent circulatory dysfunction and preeclampsia.

In addition to involvement in placental homeostasis, macrophages perform the remodelling process in skeletal tissues. The coordination of functions between osteoblasts and osteoclasts is an essential role in the bone remodelling process to maintain bone mass. Cytokines produced by macrophages such as IFN-√, TNF-α and IL-6 promote proliferation of pre-osteoclasts and differentiation of osteoclasts (Weivoda and Bradley, 2023).

Kupffer cells (KCs) are macrophages that exist in liver sinusoids. In normal conditions, they have immunosuppressive functions engulfing the gut-derived foreign substances and apoptotic cells preventing the excessive inflammation in the liver and restoring the liver architecture. KCs also have a function in acute and chronic liver diseases In acute liver injury, KCs initiate the tissue repair response by secreting IL-10 and promote hepatocyte regeneration. They also release matrix metalloproteinases (MMPs) such as MMP12 and ADAM to induce remodelling of extracellular matrix (ECM) (Li et al., 2022). In chronic liver injury, KCs can differentiate into fibroblasts contributing to ECM deposition, and regulating haemopoietic stem cell (HSC) activity and survival via TGFB1 and EGFR signaling (Terkelsen et al., 2020).

Similarly, microglia are macrophages of the brain parenchyma. Microglia not only protect from pathogens but also maintain homeostasis. Microglia express high mitochondrial oxidative phosphorylation (OXPHOS)–related genes to adjust brain glucose levels by switching to the use of glutamine as the main fuel to meet the energy demands (Bernier et al., 2020). As components of the neurovascular unit (NVU), they regulate cerebral blood flow (CBF) by producing vasoactive mediators such as IL-1β, TNF-α, NO, PGE2, or ROS (Zhao et al., 2018). P2Y12R-positive microglia regulate CBF response by signalling somatosensory pathways (Császár. et al., 2022). Survival of microglia is supported in the nervous system by central and peripheral neurons through growth factors like MCSF and IL-34 (Kana et al., 2019).

Macrophages act to maintain the metabolic homeostasis of humans (Sreejit et al., 2020). Alveolar macrophages regulate the lipid catabolism and clearance of pulmonary surfactant proteins. Dysfunction of activated macrophages caused by disruption of signals of granulocyte-macrophage colony-stimulating factor (GM-CSF) leads to pulmonary alveolar proteinosis (Nakamura et al., 2013).

Aging and macrophage functions

Macrophages play an essential function in ageing when they have adaptive changes. Age-related changes are seen in their effector functions. Long-lived macrophages are integrated into a programme of high self-

renewing capacity to change their behaviour to react to micro-environmental signals (Mass, 2023). Short-lived macrophages are replenished by monocytes and these ontogenetically distinct macrophages can have different effector functions for tissue structure changes and stiffness of extracellular matrix in ageing (Selman & Pardo, 2021, Zahalka et al., 2022). Events of mild inflammation induced by lipopolysaccharides enhance long-lived macrophages to be reinforced with proinflammatory and reparative abilities (Zahalka et al., 2022).

There is a decrease in secretion or altered function of tumour necrosis factor (TNF), IL-6 and IL-1β in aged macrophages in pro-inflammatory settings (Hirano, 2021) and phagocytic and chemotactic functions of macrophages regulated by transcription factors MYC and USF-1 decline with ageing (Moss et al., 2024). This immunosenescence affects the progression of age-related diseases such as tumours and the repair process after injury.

Macrophages in tumour microenvironment

The tumour microenvironment (TME) is a complex ecosystem surrounding the tumour and it consists of a matrix, tumour cells, stroma, carcinoma-associated fibroblasts, endothelial undergoing mesenchymal transition, network of blood vessels, and immune cells (Yang et al., 2023). Macrophages are most abundant and play a key role in tumour immunity and tumourigenesis.

Hypoxic TME controls the infiltration of tumour-associated macrophages (TAMs) in cervical and hepatocellular carcinomas (Fernández-Palanca et al., 2023). TAMs undergo polarization to M1-macrophages under the influence of interferon (IFN), TNF, LPS and other growth factors like GM-CSF (Cencini et al., 2021). Increased expression of neuropilins (nrp) which are receptors for mononuclear phagocyte chemotaxis and co-receptors for epidermal growth factor (EGF), are seen in tumour hypoxic areas with associated increased infiltration of M2 macrophages (Chen, 2019). nrp-2 expression is associated with increased angiogenesis and infiltration of macrophages in tumours (Fernández-Palanca et al., 2023). TME infused with M-CSF, IL-4, IL-10, and IL-13 polarizes the macrophages into M2 macrophages with protumour and inflammatory effects (Hwang et al., 2020). TAMs readapt metabolic needs to favour tumour support and immune evasion. Such metabolic changes are acidosis, hypoxia and dysregulated lipid metabolism contributing to tumour survival and aggressiveness (Bian et al., 2021). Dendritic cells in TME present the tumour antigen to T cells and achieve T cell-mediated immunity. After metabolic adaptation, dendritic cells uptake lipid droplets through Msr1 receptors resulting in in defective translocation of major histocompatibility complex (MHC) to the cell surface thus impairing the antigen presentation and anti-tumour immunity (Jiang et al., 2018).

Macrophages can be used as a diagnostic marker as well as prognostic predictors (Bied, 2023). Tumour cells secrete cytokines such as CCL2 and CXCL12 to transform M1 into M2. A high M1/M2 ratio is associated with ovarian cancer survival (Zheng et al., 2014). CD68 can be used as a pan macrophage marker and CD163 is used to identify M-2 in the solid tumours (Svensson et al., 2022). Leukaemia cells can polarize M-1 macrophages and help in tumour immunity by phagocytosis and mediating cytolysis of tumour cells (Mantovani et al., 2022). M-2 macrophages are involved in growth and metastasis. TAM towards a pro-tumour type and M2 TAM can determine disease progression and drug resistance (Cencini, 2021).

In a primary tumour, TAMs favour tumourigenesis by creating a pro-tumoral immune environment. It occurs by inactivating cytotoxic T cells through PD-L1 expression and producing cytokines to create

an inflammatory milieu. M2 macrophages favour tumour growth by the production of tumour cell proliferating growth factors such as EGF and FGF and angiogenetic factors VEGF, PDDGF, TGFβ, MMPs, and CXCL8. TAM favours distant metastasis by increased epithelial-mesenchymal transition (EMT) and extracellular matrix remodelling by releasing factors such as matrix metalloproteinase, CCL18, TGFβ, MMPs, and TNFα, which ultimately causes metastasis and secondary tumour formation (Bied et al., 2023).

TAMs can negatively affect the functions of NK cells, dendritic cells and cytotoxic T cells. They promote immunosuppression by actively playing a role in the recruitment of Treg cells in the TME (Basak et al., 2023). TAMs also secrete cytokine and growth factors to induce T cells to release immune inhibitory checkpoint protein to form immunosuppressive TME to accept seedlings of circulating tumour cells (Lin et al., 2019). TREM2+ m0-macs are considered to be both pathogenic and protective potential. TREM2 deficiency is associated with the growth of murine HCC, suggesting that the TREM2 program is linked with pathogenic and protective potential (Esparza-Baquer et al., 2021). Various signals in TME activated the recruited macrophages to exhibit important steps in tumour initiation, metastasis, tumour surveillance and angiogenesis.

Tumour angiogenesis is essential for tumour growth and survival. Angiogenesis is induced by hypoxia-inducible factor (HIF) and HIF expression is significant in TAMs. Knockout of the HIF-1α gene enhances M2 polarization and attenuates their pro-angiogenic responses (Werno et al., 2010). Hypoxic stress in TME M2 polarization induces tumour angiogenesis by producing angiogenic factors such as VEGF-A, EGF, IL-1 beta, IL-8, CCL2 and CXCL12 (Hughes et al., 2015). TAM-induced matrix metalloproteinase (MMPs) from macrophages degrades the basement membrane and the extracellular matrix favours metastasis (Niland et al., 2022). Researchers target TAMs in the treatment of cancer which are based on inhibition and genetic manipulation of TAMs (Mantovani et al., 2022).

Macrophages and atherosclerosis

Atherosclerosis is caused by the accumulation of lipids in the vascular wall. Tissue-resident and monocyte-derived macrophages contribute to the formation and regression of atheromas. Monocytes infiltrate the subendothelium and transform themselves into macrophages. Macrophages as APCs present oxidized LDL (ox-LDL) to T cells to accelerate the inflammation. In normal steady states, Ly6Clo monocytes protect the endothelium and arterial vasculature by engulfing lipid particles, cellular debris and necrotic cells. Their numbers increased in hyperlipidemic and atherosclerotic conditions. Ly6Clo monocyte activity is partly stimulated by CCR5 and their signalling and lifespan are controlled by Lck/yes tyrosine kinases (Miyake et al., 2024).

Chemokine induces Ly6C+/ Ly6Chi macrophages to M1 polarization in the plaque shoulder. These M1cells which have pro-inflammatory, phagocytic and cytotoxic properties are responsible for matrix degradation and necrotic core formation (Lin et al., 2021). They phagocytose lipids including low-density lipoproteins (LDL) complexes to clear the inciting stimuli (Theofilis et al., 2023). M1 cells have increased expression of lipid–processing genes and also interact with other immune cells in the progression of atherosclerosis and sustained inflammation.
Ly6C- /Ly6Clo monocytes which normally patrol the endothelium stability differentiate into M2 subtypes when induced by IL-4, IL-13, toll-like receptor (TLR) agonists and other soluble factors in the later phase at the core of atheroma. They maintain the tissue homeostasis and resolution of inflammation by inhibiting pro-inflammatory cytokines and inducing secretion of anti-inflammatory cytokines such as IL-10 and IL-12 (Theofilis et al., 2023). M2 cells promote angiogenesis

and fibroblast formation and aid in tissue repair at the site of atheroma. Inflammatory macrophages with up-regulated inflammatory genes are key contributors to atherosclerosis. As Gal-1 and Gal-2 induce reprogramming from pro-inflammatory into anti-inflammatory types, treatment with anti-Gal nanobodies reduces atherosclerotic burden (Kane et al., 2022). The diversity of macrophages accumulation in atheromatous plaque and their metabolic characterization determine the type of atheromatous plaques. Stable plaques characterized by slow growth can give rise to progressive stenosis of arteries with low embolic sequelae. Unstable plaques have higher risks of thromboembolic manifestations.

Macrophages and infections

Macrophages are key members of the immune system against infection. They detect the infective agents and engulf and kill them. They present antigens to T and B lymphocytes after recruiting them by secreting cytokines and chemokines to assist the immune reaction. Macrophages possess specific pattern recognition receptors to detect pathogen-associated molecular patterns (PAMPs). After being detected, pathogens are engulfed and fused with lysosomes, phagosomes mature and pathogens are degraded (Pandey et al., 2022). Intracellular microorganisms such as Mycobacterium can survive inside macrophages as latent state and reactivate when the host immune systems weakened (WHO, 2015). Macrophage proteins such as Slc11a1 mediate resistance to certain intracellular microorganisms by promoting the transport of Fe+2 into phagosome and iron-mediated toxicity to the microbes (Blanc-Potard and Groisma, 2020) and polymorphism of protein results in susceptibility to microbes (Liu et al., 2017). Pathogen-induced macrophage intracellular microenvironment affects the nutrients and growth factors required for bacterial intracellular survival. Micronutrients are required for the regulation of virulence factors for example, magnesium for PhoP/PhoQ two-component system in Salmonella, iron for Shiga toxin in Shigella, and calcium for Yersinia. Macrophages undergo polarization and secrete cytokine towards pro or anti-inflammatory actions in the presence of infection by Staphylococcus aureus. Bacteria may be killed by intracellular or extracellular mechanisms. Alternatively, bacteria may escape antimicrobial killing and survive intracellularly by ROS and RNS, phagosome acidification, nutrient restriction and release of degradative enzymes (Pidwill et al., 2021). Reactive oxygen species (ROS) are molecules with oxidizing properties and they are produced as a result of cell metabolism. ROS induce oxidative stress in bacteria and kills them by breaking the DNA strands or modification of lipids and proteins (Vaishampayan and Grohmann, 2021). Some bacteria adapt themselves by developing genes required for anti-oxidant defence. For example, S aureus survives the killing by their enzyme property of superoxide dismutase A (SodA) and superoxide dismutase M (SodM) which can dysfunctional the superoxide radicals (Pidwell et al., 2021). Reactive nitrogen species (RNS) are nitrogenous products such as nitric oxide (NO) produced by nitric oxide synthase (NOS). Formation of inducible NOS (iNOS) occurs mainly in macrophage phagolysosomes when macrophages are stimulated by immune reactions. RNS impairs microbial growth by inhibiting bacterial respiration and DNA replications (Fang and Vázquez-Torres, 2019). Successful microorganism develops virulence-associated genes to survive nutrient restriction and phagolysosome toxicity (Pandey et al, 2022). The ability of Salmonella typhimurium to survive inside macrophages needs the two-component virulence regulatory system, PhoP/PhoQ which consists of sensor PhoQ and regulator PhoP. These genes regulate the magnesium concentration in the salmonella-containing vacuoles inside macrophages thus promoting the virulence of bacteria in low magnesium concentration. Mildly acidic pH in macrophages also activates the PhoP/PhoQ system and increases bacterial virulence

(Choi and Groisman, 2016). Nutritional immunity refers to how host factors restrict bacterial growth by changing the nutritional status in the microenvironment of host cells and bacteria. Acidification of macrophage phagosomes is important in killing engulfed bacteria since bacterial growth is reduced at pH4.5 (Bore et al., 2007). Methicillin-resistant S aureus (MRSA) overcomes the killing by Kupffer cells of the liver survives intracellularly and spreads through circulation. Liposomal formulation of vancomycin targets the source of reservoirs of bacteria without attacking liver toxicity and dissemination to other organs (Surewaard et al., 2016).

Macrophage and immune disorders

Macrophages Macrophage activation syndrome (MAS) is an acute and severe inflammatory syndrome triggered by various factors such as infections, immune disorders, malignancy and drugs. It is also known as secondary haemophagocytic lymphohistiocytosis which is a potentially harmful immune disorder. MAS is usually associated with the expression of markers namely increased levels of cytokines such as IL-1, IL-6, TNF-α, INF-γ, high levels of ferritin and complicated by multiple organ failure (Wynn, 2022). In the bone marrow, activation of macrophages leads to secondary haemophagocytic lymphohistiocytosis which results in phagocytosis of haemopoietic cells including red cells, lymphocytes and other haemopoietic precursors and enlarged extramedullary haemopoietic organs such as liver and spleen (Nguyen et al., 2022).

Macrophages are major cells in the development of type IV hypersensitivity reaction which is useful for immune reaction against intracellular microorganisms such as mycobacteria, fungi parasite infections and other granulomatous inflammations. Macrophages act as APCs that present antigens to CD4+ T cells, in association with class II MHC molecules. Macrophages also produce cytokines namely interleukin (IL)- 12, a critical cytokine, for induction of TH1 lymphocyte response leading to production of other cytokines such as tumour necrosis factor (TNF) and interferon (IFN) -√ which induce further differentiation of TH1cells to augment the delayed hypersensitivity. Due to their property to function as APCs in both transplanted grafts and recipients, macrophages induce local delayed hypersensitivity reactions on kidney allografts leading to the destruction of histocompatible grafts (Lackner et al., 2023).

The age-related functional decline of macrophages may represent a starting innate immune functional decline associated with ageing and age-related diseases (Moss et al., 2024). Identifying downstream targets of macrophage functionality in ageing is a future therapy for geriatric diseases. Modern genome editing technologies mediate the alteration, addition and ablation of genes (Dunbar et al., 2018). Genetic alteration in macrophage genes is associated with bone mass abnormality. Clusters of inflammatory macrophages expressing CD209, CCl4, IL-1B, CD14 and MMP9 are expanded in patients with inflammatory bowel disease. ETS2 signalling through MEK1/2 inhibition affects cytokines such as TNF and IL-23 which can be used as targets for inflammation-related diseases. This pathway is also related to IL-1β which is linked to therapy resistance cases (Stankey et al., 2024).

Based on the knowledge of the polarization of macrophages into M1 and M2 phenotypes and their distinctive functions in inflammatory and tumourigenesis, the macrophage-based therapeutic approach is a hopeful future for anticancer therapy. Anti-cancer therapy possibly uses depletion of TAMs by inhibitors of colony-stimulating factor-1 receptor (CSF 1R) (Cassetta & Pollard, 2018) and targeting TAM is a future novel approach. Gene therapy targeting to modulate the macrophage function through the nucleic acid modification is a future hope for precision cancer Medicine. Nucleic acid therapeutics

such as plasmid DNA (pDNA), messenger RNA (mRNA), small hairpin RNA (shRNA) and microRNA (miRNA) are delivered through gene delivery vectors (Dunbar, 2018) to alter their TAM's phenotypes or expression of receptors or release of cytokines and chemokines (Huang et al., 2023). DNA nanoparticles combined with peptides or hyaluronic acids repolarize the macrophages to reverse tumour immunoresistance (He et al., 2018).

Together with clinical and morphological parameters, measuring baseline TAM content in malignancies may be useful for the prediction of disease prognosis and identifying high-risk groups in leukaemia, lymphoma and myeloma patients (Cencini et al., 2021). The use of CD163 as a marker for TAM was proposed as a useful marker for predictor of clinical outcome in classical Hodgkin lymphoma patients in general and advanced-stage groups (Klein et al., 2014, Nam et al., 2014). Dysregulation of the metabolic system can bring up polarization of anti-tumour M1 and pro-tumour M2 phenotypic changes in the immune milieu of TME. Reprogramming of immunometabolism in macrophage polarization can be applied in the modification of tumour environment (Leon, 2020) and inflammatory lesions (O'Neill et al., 2016).

Immunotherapy is a major choice of treatment in non-small cell lung cancer (NSCLC). The evolution of tumour cell mutation with resultant increased tumour mutational burden is a major concern in the failure of response to immunotherapy. Lung cancer activation module (LCAMhi), a cellular module which consists of SPP1+ macrophages and other immune cells, is enriched in NSCLC lesions. Baseline data of abundant LCAMhi score is closely related to NSCLC clinical response to immunotherapy proven in patients with high TMB (Leader et al., 2021). TAMs possess receptors with collagenous structure (MARCO). In therapy using the antibodies to block these receptors, TAMs can be changed into pro-inflammatory effectors with a resultant anti-tumour immune response (Georgoudaki et al., 2016). Cytokine and chemokines are produced in TME to both recruit and polarize tumour-promoting myeloid cells and anti-tumour and immunostimulating functions. Trials use mechanisms that inhibit these cytokines to control the regulators of myeloid cell functions. Macrophages can be candidate cell therapy with chimeric antigen receptor effector cells (Mantovani et al., 2022). Chemokine with receptor-ligand CCL-5 and vascular endothelial growth factor (VEGF) regulate the macrophage recruitment in tumour TME. Monoclonal antibodies or receptor antagonists can reduce the tumour growth rate and macrophage density in TME (Beltraminelli & De Palma, 2020). As TAMs uptake lipids through MARCO, studies showed that genetic modification and inhibition of MARCO results in reduced lipid accumulation in TAMs and redirect TAMs towards an anti-tumour profile (Masetti et al., 2022). Genetic deletion of CD36 stops lipid scavenging by TAMs and renders anti-tumour efficacy in haematological malignancies (Su et al., 2020). As dysregulated lipid metabolism of TAMs promotes tumour survival and progression, targeting therapy at changing lipid metabolism in TAMs is also a hopeful approach in cancer therapy (Ren et al., 2024).

CONCLUSION

TUnderstanding through past knowledge of macrophages is they are part of the mononuclear phagocyte system which functions as scavengers in inflammation. Moreover, macrophages also have their roles in the induction of cell-mediated immune responses by processing antigens and presenting peptide fragments to T cells. They also serve as effector cells in immune responses such as delayed hypersensitivity reactions. After being activated by T cell-released cytokines, macrophages are enhanced to perform the killing of microbes and tumour cells. Recent and upcoming advances suggest there are many more functions of macrophages other than scavenger functions. Based on the

knowledge of macrophage biodiversity and immune functions, scientists try to modify macrophages to use them as candidates for treating inflammation-related diseases as well as malignant diseases as a modality of immunotherapy and markers for predicting prognosis.

CONFLICT INTEREST

The authors do not have any conflict of interest.

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