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REVIEW ARTICLE

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Macrophage efferocytosis in health and disease

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Abstract

Creating cellular homeostasis within a defined tissue typically relates to the processes of apoptosis and efferocytosis. A great example here is cell debris that must be removed to prevent unwanted inflammatory responses and then reduce autoimmunity. In view of that, defective efferocytosis is often assumed to be responsible for the improper clearance of apoptotic cells (ACs). This predicament triggers off inflammation and even results in disease development. Any disruption of phagocytic receptors, molecules as bridging groups, or signaling routes can also inhibit macrophage efferocytosis and lead to the impaired clearance of the apoptotic body. In this line, macrophages as professional phagocytic cells take the lead in the efferocytosis process. As well, insufficiency in macrophage efferocytosis facilitates the spread of a wide variety of diseases, including neurodegenerative diseases, kidney problems, types of cancer, asthma, and the like. Establishing the functions of macrophages in this respect can be thus useful in the treatment of many diseases. Against this background, this review aimed to recapitulate the knowledge about the mechanisms related to macrophage polarization under physiological or pathological conditions, and shed light on its interaction with efferocytosis.

KEYWORDS

apoptotic cell clearance, efferocytosis, inflammation, M1/M2 polarization, macrophage polarization

1 | INTRODUCTION

Efferocytosis elucidates the process of the rapid and effective removal of undesirable (namely damaged, dysfunctional, or aged) cells by phagocytes, particularly macrophages. This process means too much for some essential functions, including organism growth, immunoregulation, and tissue homeostasis maintenance.[1] All through efferocytosis, apoptotic cells (ACs) are cleared by the immune system. The given process also occurs to remove ACs or dying cells by phagocytic ones, in particular macrophages, as they are vital for the body to function properly.[2] During the efficient efferocytosis process, dying cells are eliminated as it should be and the harmful effects of their leak to normal tissue microenvironments are avoided; otherwise, ACs can be prone to secondary necrosis, a process in which detrimental autoantigens are released into normal tissues and stimulate neurodegenerative disorders (NDDs), kidney problems, types of cancer, asthma, and so forth. AC removal by macrophages (namely efferocytosis) accordingly boosts the resolution of signaling pathways, which can be triggered via some molecules derived from the phagolysosomal degradation of ACs.[3] Through the efferocytosis

process, engulfment signals are further expressed by ACs, which should be then cleared from tissues by some signals, such as Find-Me and Eat-Me. Utilizing numerous types of phagocytic apparatus, phagocytes engulf ACs[4] (Figure 1). ACs also attract phagocytes by secreting apoptotic mediators, named the Find-Me (or Come-Get-Me) signals, as chemoattractants, viz. nucleotides and chemokines released by ACs to attract phagocytes to their location, which then assist their engulfment.[5,6] The Find-Me factors, such as chemokine (C-X3-C motif) ligand 1 (CX3CL1, or fractalkine), sphingosine-1-phosphate, and lysophosphatidylcholine (LPC), are typically secreted from ACs. Then, it is ensured that the professional phagocytosis of the cells is recruited in the vicinity of the dying cells to properly assist in efferocytosis.

LPC also helps recruit macrophages to ACs and engage G2 accumulation, a G-protein-coupled receptor on macrophages. CX3CL1 is further released by ACs under proteolysis.[5] Of note, CX3CL1 holds CX3C motif chemokine receptor 1 (CX3CR1) located on the macrophages, which causes phagocytes to migrate. Recent studies have accordingly established that ACs release nucleotides in the environment via Pannexin 1 channels. Moreover, they engage the Purinoreceptor-2 on the macrophage and acts ultimately as a short-range chemoattractant.[4] Cell apoptosis then results in the Eat-Me signal issue on the surface of cells, which make a phagocyte to phagocytose the cell. Membrane phospholipid phosphatidylserine (PtdSer) is another key signal,[7] commonly found on the inner side of the plasma membrane when apoptosis occurs, and transferred on the outer side of plasma membrane. Phagocyte receptors, such as complement receptors (CR) 3 and 4, the members of the family T-cell immunoglobulin domain and mucin domain, mannose receptor (MR), cluster of differentiation (CD)36, scavenger receptors (SRs) A and B, and integrins α5β3 and α5β5, can thus identify these signals in a direct manner.[7] One of the Eat-Me signals is calreticulin, expressed on the AC surface, which promotes engulfment by phagocytes and leads to an increase, sensed via low-density lipoprotein receptor-related protein (LRP1/CD91).[7] Some groups of intermediate molecules are also placed on the surface of macrophages, called bridging molecules, containing two receptor-binding domains (RBDs). Moreover, the phagocytosis prey-binding domain is capable of attaching onto the surface of ACs. The RBD also connects to phagocytes. The role of the bridging molecules here is that PtdSer can indirectly connect to phagocyte receptors, or allows them for direct connection to receptors on the phagocyte surface.[8]

Milk fat globule-epidermal growth factor 8 protein also refers to a bridging molecule connected on one side to PtdSer on the AC surface, and on the other side, to integrin αvβ3/αvβ5 on phagocyte receptors, thus serving as a bridge between ACs and macrophages to manage the binding phase.[8] For the duration of engulfment, ACs further express the signals, Find-Me and Eat-Me, indicating the need to remove them from tissues and engulf ACs, utilizing numerous types of phagocytic apparatus. Phagocytes dynamically change their actin cytoskeleton to help them migrate toward decay cells and the engulfment of foreign bodies.[9] Depending on the conditions, the activation state and the functions of macrophages, two phenotypes, M1 (classically) and M2 (alternatively), are activated.[10] Inflammatory parameters are also essential for macrophage polarization.

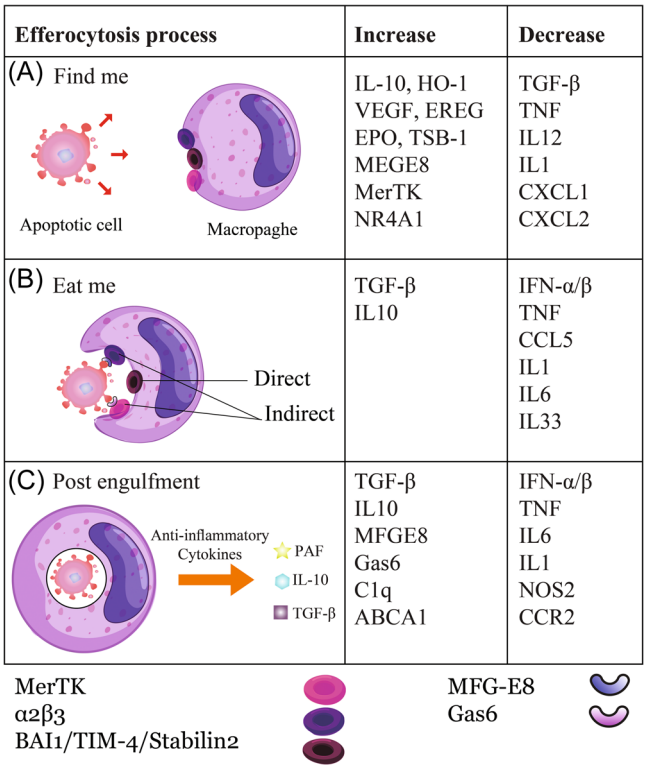

FIGURE 1 Efferocytosis is a multistep process involving: (A) Find me, (B) Eat me, and (C) Engulfment. (A) "Find-me" stage: Find-me signals (such as low levels of nucleotides ATP and UTP, lysophosphatidylcholine, sphingosine 1-phosphate, and fractalkine) released by apoptotic cells (ACs) help to attract phagocytes such as macrophages. (B) "Eat-me" stage: Phagocytic receptors of macrophages recognize and bind to the "Eat me" signal molecules of ACs. This binding is directly or indirectly through bridging molecules secreted from macrophages, such as MFG-E8 and growth arrest-specific 6 (Gas6). (C) Post engulfment stage: Forming "a phagocytic cup" completes the endocytosis of ACs and finally macrophages digest and degrade apoptotic cell debris.

Significance statement

- Efferocytosis occurs to remove apoptotic cells by phagocytic ones, in particular macrophages.
- Any insufficiency in macrophage efferocytosis facilitates the spread of a wide variety of diseases, including autoimmune disorders, neurodegenerative diseases, kidney problems, types of cancer, asthma, and the like.
- Recent research has established that macrophage polarization can affect the efferocytosis process.
- A better understanding of macrophage polarization and its cytokines in many diseases can help design treatments to improve patient outcomes.

Macrophage activation with pro-inflammatory cytokine, including interleukin-12 (IL-12), pathogen-associated molecular patterns, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), like lipopolysaccharide (LPS), accordingly polarize M1 macrophages.[11] Among the M1 macrophage activities, the release of TNF-α, IL-6, and IL-1, inflammatory responses in the upregulation of type-1 T helper (Th1) cell responses, and tumoricidal activities can be mentioned. Generally, macrophage polarization leans toward an M1 phenotype to defend against intracellular pathogens and the upregulation of antitumor action. Besides, M2 macrophages are considered as anti-inflammatory ones with great contents of IL-10 and low contents of pro-inflammatory cytokines, which contribute to some processes such as wound-healing and dampening inflammation. In view of this, pathogens and debris are eliminated by inflammatory M1 macrophages and neutrophils in the early-stage wound-healing. During the efferocytosis process, apoptotic neutrophils are then phagocytized by inflammatory M1 macrophages.[11]

According to their functions, M2 macrophages have more diversity compared with the M1 ones, found in some subclasses of M2a, M2b, M2c, and M2d, which produce various growth factors, cytokines, and chemokines.[10] Despite the numerous functions of macrophages in some diseases associated with efferocytosis, the molecular mechanism of macrophage polarization is still not fully understood. The current knowledge of the mechanisms involved in macrophage polarization under physiological or pathological conditions and its interactions with efferocytosis are thus summarized in this review.

2 | EFFEROCYTOSIS AND MACROPHAGE POLARIZATION

Apoptosis and the efficient removal of dead cells are among the important processes in multicellular organisms to maintain homeostasis. Cells often take part in their demise through a programmed cascade of signaling events (also known as regulated cell death),[11] where damaged or aged cells die and then replaced with new ones derived from stem cells under the vast majority of physiological and pathological conditions.[12] Billions of cells are accordingly destroyed on a daily basis to shape new structures in mammals throughout their embryonic and developmental stages.[13,14] Numerous cells also die as a result of pathogenic processes, such as tissue injury and infection. Excessive damage, such as heat, mechanical compression, or osmotic pressure, may further produce necrosis, spill intracellular contents into the surrounding environment, and activate inflammatory response pathways that can wipe out healthy cells. The elimination of cellular corpses is thus critical for homeostasis and diseases. Whenever dead cells are ingested by phagocytes through efferocytosis,[15] pro- or anti-inflammatory signals may be sent by regulating the activity of macrophages after efferocytosis in response to various types of cell death. Macrophages comparably have impressive diversity in the immune system, with a critical role in homeostasis maintenance. They further absorb and digest microbes, foreign agents, as well as cancerous and dead cells through phagocytosis. Of note, phagocytic cells are often found in nearly all human body tissues.[16,17] Recently, it has been proven that macrophages have acquired diving-related phenotypes in terms of functionality versus many environmental signs, such as activated lymphocytes, microbial products, and cells damaged by phenotypic polarization. This adaptability helps the body to respond appropriately to infections or signaling chemicals, produced by activated lymphocytes or damaged tissues.[18] Polarization is accordingly the term recruited to explain the variability of macrophage phenotypes.[19] It is further used to categorize macrophages into three distinct subtypes, namely naive (M; sometimes referred to as Mφ), which quickly differentiates into the two other macrophages of M1 and M2 (Table 1).

3 | MACROPHAGE-RELATED EFFEROCYTOSIS

3.1 | Naïve macrophages (Mφ)

Monocytes and Mφ are extensively found as circulatory forms.[20] The Mφ macrophages are also named in relation to their location in organs and tissues; for instance, alveolar macrophages in the lungs, Kupffer cells in the liver, and microglial cells in the brain.[21] ACs and pathogenic materials can be further cleared by the Mφ macrophages through phagocytosis, as well as those that take part in the processes of tissue regeneration and wound-healing.[22] Reportedly, the Mφ cells are known as heterogeneous ones. In addition, signaling molecules generated by injured tissues or activated lymphocytes respond through the Mφ cells.[23] Therefore, the Mφ cells are classified based on local microenvironment cytokines into two phenotypes, viz., M1 macrophages (viz., inflammatory mediators), which act as resident macrophages and produce major pro-inflammatory cytokines, and M2 macrophages (i.e., anti-inflammatory mediators), assumed to be responsible for the synthesis of anti-inflammatory cytokines and the ingestion of pathogenic agents to assist in the inflammation resolution.[24] Macrophage polarization is accordingly the term employed to describe the phenomena of different M1/M2 phenotypes.[25]

3.2 | M1 macrophages (pro-inflammatory mediators)

The activation of classically activated macrophages, or M1-polarized ones, occurs via IFN-γ, bacterial LPS, and granulocyte-macrophage colony stimulation factor (GM-CSF), which are implicated in the response of Th1 to infection.[26,27] IFN- γ not only plays an essential role in the induction of classical macrophage but also regulates the macrophage genes that encode cytokine receptors, cell adhesion agents, and cell activation indicators.[28] The M1 macrophage activation has been further stimulated by LPS through the Toll-like receptor (TLR). M1-polarized macrophages have additionally

TABLE 1 M1 and M2 polarization.

M1	M2
Classically activated macrophages	Alternatively activated macrophages
Activated by: • Th1 • IFN-γ • LPS	Activated by: • IL-4
Contribute to: • Pro-inflammatory responses • Produce IL-6, IL-12, TNF-α, CXCL1-3, CXCL-5, CXCL8-10.	Play a role in: • Anti-inflammatory responses • Repair damaged tissues
↓CD206, TGF-β, IL-10, anti-inflammatory cytokines	↓CD86, pro-inflammatory cytokines
↑CD16, CD32, CD80, CD86, pro-inflammatory cytokines, IL-1, IL-6, Il-12, IL-23, IL-6, TNF-α	↑Arg-1, CD206, IL-10, TGF-β, dectin-1, DC-SIGN, MR, SR-A and B-1, CD163, CCR2, CXCR1, CXCR2, chemokines CCL17, CCL22
Typical characteristics of M1: • ↑ Antigen presentation • ↑ NO and ROI production	Typical characteristics of M2: • Ornithine and polyamine production through the arginase pathway

Abbreviations: Arg-1, arginase-1; CCL, C-C motif chemokine ligand; CCR2, C-C chemokine receptor type 2; CD, cluster of differentiation; CXCR, C-X-C motif chemokine receptor; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin; IFN-γ, interferon-γ; IL, interleukin; LPS, lipopolysaccharide; MR, mannose receptor; NO, nitric oxide; ROI, reactive oxygen intermediate; SR-A, scavenger receptor A; TGF-β, transforming growth factor-β; Th1, type-1 T helper; TNF-α, tumor necrosis factor-α.

expressed high levels of CD86, pro-inflammatory cytokines, such as IL-1/-6/-10/-12/-23 and TNF-α, but CD206, transforming growth factor-β (TGF-β) and anti-inflammatory cytokines have been decreased.[29] By producing tumoricidal and microbicidal substances, such as reactive oxygen intermediates (ROIs) or nitric oxide (NO), M1 macrophages accordingly protect hosts from intracellular bacteria and viruses in the process of tumors or acute infections.[30] However, M1 macrophages sometimes give rise to chronic inflammation, and damage the health of host.[31] Much research has correspondingly demonstrated that M1 macrophage is the dominant type in colorectal carcinomas and even associated with a drop in metastasis and higher survival rates.[32]

3.3 | M2 macrophages (anti-inflammatory mediators)

Although M2 macrophages are essential for tissue remodeling, they typically act in sustained inflammations.[33] The M2-type responses are also known as the resting phenotypes, which are being extremely intensified via IL-4/-10/-13, and are observed under healing-type conditions.[34] M2 macrophages cause the overexpression of dendritic cell (DC)-specific intercellular adhesion molecule-3 grabbing non-integrin, dectin-1, SR-A and B-1, MR, CD163, C-C chemokine receptor type 2, and C-X-C motif chemokine receptor (CXCR) 1/2. Rather than the production of ROI or NO, M2 macrophages use the arginase pathway to synthesize ornithine and polyamines.[35] Such macrophages also produce anti-inflammatory cytokines, such as IL-10 and low expression levels of IL-12, and further M2 phenotypic indicators, such as Ym1 (belonging to the family of chitinase) and resistin-like molecule α (FIZZ1) (present in inflammatory area 1, Retnla) are identified.[36,37] Moreover, M2 macrophages have functions in metazoan parasite inhibition, Th2 response stimulation, tissue regeneration, tumor growth, and immunological tolerance.[38] Such macrophages are found as the subtypes of M2a, M2b, M2c, and M2d in accordance with the stimuli and transcriptional alterations. The overexpression of IL-10 and the downregulation of IL-12 are accordingly among the frequent features of this subpopulation, and arginase-1 (Arg-1) generation has been introduced as a pivotal sign.[8] The Arg-1 overexpression can thus decrease L-arginine (Arg), thereby disturbing the proliferation of T cells and the production of IFN-g. Higher amounts of Arg-1 have further raised competitions with inducible NO synthase for L-Arg and reduced NO formation.[39] Additionally, MR (CD206) and chemokines C-C motif chemokine ligand (CCL) 17 and 22 expression levels are elevated in M2 macrophages that are crucial for tissue healing, angiogenesis, and metabolism. Infections with fungi and helminths may further trigger M2a polarization, which is associated with Th2 cell immune response.[40] Eosinophils, basophils, macrophages, and Th2 cells also generate IL-4, which are important to encapsulate parasites.[30] Of

note, M2b macrophages are triggered by immune complexes, including TLR or IL-1 receptor ligands, so immunological responses are regulated.[31] The production and antigen presentation (namely major histocompatibility complex [MHC] II and CD86) are both increased, but the IL-12 level is decreased. IL-10 and TGF-β further activate M2c macrophages, which play a role in tissue remodeling and extracellular matrix creation. Adhesion, dissemination, apoptosis, and phagocytosis in these macrophages are also affected by glucocorticoids. Both IL-6 and adenosine are then stimulated and polarized into M2d.[41] However, M2 macrophages assist in the growth of tumors by encouraging migration, angiogenesis, and invasion[17,42] (Figure 2).

4 | EFFECT OF MACROPHAGE EFFEROCYTOSIS ON HEALTH AND DISEASE

Every day about 0.4% out of 37.2 trillion cells in the human body die.[43] In tissue cells, turnover increases, whereas ACs are scarce, indicating that the efficiency and capacity of AC clearance have been extremely elevated. The elimination of ACs is accordingly described as efferocytosis, in the form of a critical process for maintaining tissue homeostasis during normal physiological circumstances and restoration after illness.[3,44] At some stage in many nonresolving, acute inflammations caused by defective efferocytosis, dead cells are also accumulated.[45] Secondarily, necrotic cells trigger autoimmune disorders, necrosis, and inflammatory responses.[46,47] Therefore, a significant field of biomedical science is devoted to elucidating such processes, including how efferocytosis occurs effectively in normal physiological conditions and how it becomes defective in diseases.

4.1 | NDDs

To remove dead cells and cellular debris, the central nervous system (CNS) contains phagocytic cells, termed microglia, which are similar to macrophages in terms of phenotypes.[48,49] However, other CNS cells, including neuronal progenitor cells such as oligodendrocytes and astrocytes, may also act as efferocytosis regulators. The CNS accordingly needs effective efferocytosis for homeostasis, but efferocytosis is critical for rearranging neuronal circuits and initiating

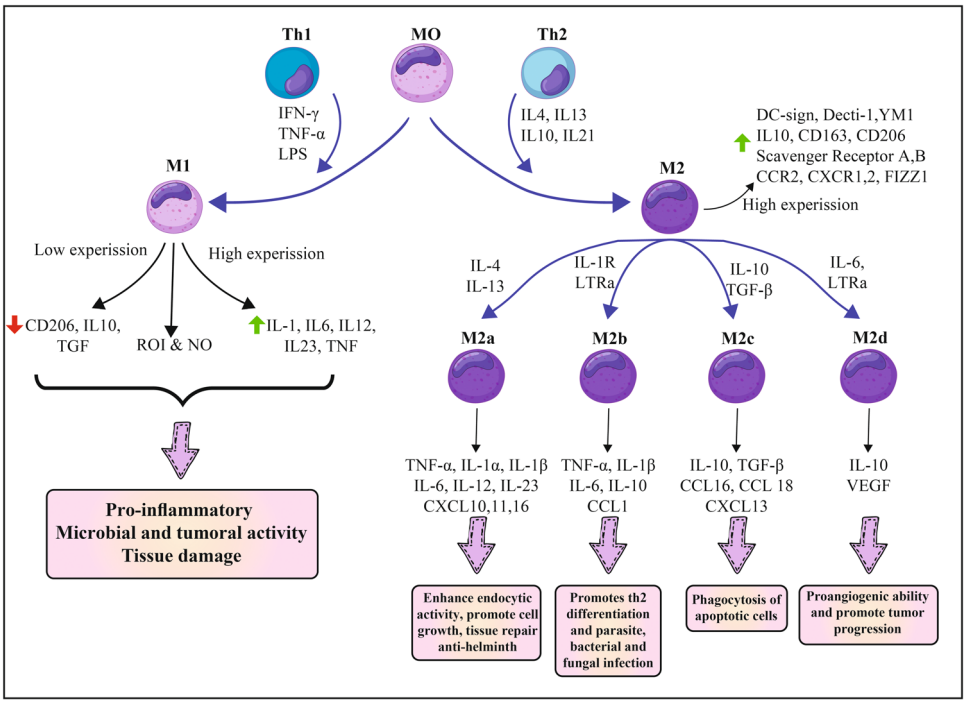

FIGURE 2 M1 and M2 polarization of macrophages. Pro-inflammatory M1 polarization and anti-inflammatory M2 polarization of macrophages. Interferon-γ, tumor necrosis factor (TNF), and lipopolysaccharide (LPS) are the major stimulators of M1 polarization, M1 activation is associated with high expression levels of interleukin (IL)-1, 6, 12, 23, and TNF, but low levels of CD206, IL-10, and transforming growth factor-β (TGF-β). Besides, M1 pro-inflammation plays a role in microbial and tumoral activity and tissue damage. In contrast, IL-4, 13, 10, and 21 are inducers of M2 polarization. High expression levels of dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin (DC-SIGN), CD163, YM1, CD206, C-C chemokine receptor type 2 (CCR2), C-X-C motif chemokine receptor 1, 2 (CXCR1, 2), FIZZ1, and Scavenger receptor A, B are considered as significant feature of M2 activation. M2 macrophages fall into four subtypes: M2a, M2b, M2c, and M2d. M2a is simulated by IL-3, 13, which is associated with enhanced endocytic activity, cell growth promotion, tissue repair, and anti-helminth. M2b is triggered by IL-1R and LTRa, which promotes Th2 differentiation and parasite, bacterial, and fungal infection. M2c is activated by IL-10 and TGF-β, which is involved in phagocytosis of apoptotic cells. IL-6 and LTRa both are stimulated polarization into M2d that has proangiogenic ability and promote tumor progression.

regenerative responses after damage. As a result, some NDDs are related to defective efferocytosis.[50]

4.2 | Alzheimer's disease (AD)

Under polarized conditions, microglia show both toxicity and protective function during AD. The related data have so far indicated that the induction of moderate microglia relieves the pathological consequences of AD and amyloid-β (Aβ) has been diminished through tissue healing and phagocytosis. However, excessive neuroinflammation produces pro-inflammatory cytokines/chemokines and NO, thereby aggravating neuronal damage and causing AD progression.[51] The extravagant activation of M1 microglia has been further demonstrated to exacerbate pathogenic damage in AD through a wide variety of mechanisms. First, M1 microglia stimulate the TNF-α and IL-1 generation, and macrophage inflammatory protein-1, which augment neuronal impairment, deposition,[52,53] and cholinergic neuronal damage.[54,55] Second, neurofibrillary tangles (NFTs) are surrounded by the aggregation of activated microglia all through early and late phases of AD.[56,57] The M1 microglia-released inflammatory cytokines, including IL-1, IL-6, and CX3CL1, are also capable of modulating the function and structure of τ, and increase τ hyperphosphorylation and NFT production.[58] Additionally, the chronic activation of M1 microglia results in the production of some neurotoxic chemicals as AD progresses, including pyridinedicarboxylic acid and amines, which cause neuronal excitotoxicity.[59,60] Furthermore, growing evidence indicates that the Aβ phagocytosis in microglia has been substantially impeded throughout AD due to the lowered expression of certain proteins in microglia/macrophages (MM), such as SR-A, insulin-degrading enzyme, and the receptor for advanced glycation end-products (RAGEs).[61] SRs also include scavenger receptor class A member 1, CD36, and RAGEs, as a family of proteins conserved evolutionarily, which are produced on microglia and function as Aβ receptors. Other pro-inflammatory cytokines, such as IFN-γ and TNF-α, mediated by M1 microglia, then impede the absorption of Aβ and hinder the breakdown in the internalized Aβ degradation.[62,63] Pro-inflammatory M1 microglia do not seem to eliminate Aβ; conversely, M2 microglia are found to be potent phagocytes. The decreased inhibitory activity of Aβ has been further cited as the primary explanation for the progression of pathology in numerous sporadic AD patients.[64] Activated microglia also guard against Aβ deposition in the early stages of AD, just before the senile plaque development, through phagocytosis and Aβ-degrading enzyme release.[65] In the early-stage AD, simply before senile plaque formation, protective impacts are further exerted by activated microglia in Aβ deposition through phagocytosis and Aβ-degrading enzyme release. Numerous investigations have accordingly demonstrated that neuroinflammation and microglia are activated by Aβ in the CNS, and then misfolding and aggregated Aβ protein are phagocytosed and removed via activated microglia.[66,67] The M2 activation by IL-4 and IL-10 cytokines also remarkably leads to the LPS-stimulated inhibition of Aβ phagocytosis.[68] Exposure to IL-4, which is a potent M2 polarization promoter, has further facilitated internalized Aβ degradation through lysosomes and phagosomes.[69]

Recent findings have shown that various subtypes of M2 microglia have their own unique roles. M2a microglia generated by IL-4 accordingly have considerable Aβ inhibitory activities, but M2c microglia created by IL-10, TGF-β, and glucocorticoids may be critical for tissue repair.[70] Furthermore, latest research has established that M2 microglial products inhibit the interneuronal transfer of Aβ and reduce the Aβ distribution in the AD brain.[71] Moreover, M2 microglia significantly lower neuroinflammatory responses and prevent τ hyperphosphorylation that improve pathogenic damage in AD.[72] M2 microglia have also had neuroprotective impacts by secreting anti-inflammatory cytokines, including TGF-β and IL-10, and releasing neurotrophic substances, like nerve growth facto.[73] Thus, M2 microglia have a strong inhibitory effect on the induction of neuronal toxins, which facilitate tissue repair and the regeneration.[74,75]

4.3 | Asthma

Macrophages contribute to asthmatic inflammation in many ways, such as changes in the production of anti-inflammatory cytokine/chemokine (MM), and the inflammasome stimulation and cellular dysfunction, such as impaired phagocytosis. There are also numerous M1 and M2 macrophages in the lung tissue of asthmatic people.[76,77] In mice, blocking the polarization sequentially had led to greater eosinophilic or neutrophilic inflammatory responses.[78] Given that both IL-4 and IL-13 are the effective promoters of M2 macrophage polarization, M2 cells are the predominant ones in allergic asthma.[79] Moreover, increasing evidence indicates that IL-33 is a powerful inducer of M2 macrophages. Above all, IL-33 that is secreted from airway epithelial cells in response to antigen stimulation has the ability to alter the M2 macrophage polarization by suppression of tumorigenicity 2 (ST2). Intriguingly, ST2 has binding sites for the additional cytokines, IL-4/-5/-13, as well as chemokines, CCL-17/-18/-24.[80,81]

In addition, eosinophils, innate lymphoid cell type 2 (ILC2), CD4+CD25+ regulatory T cell (Treg), and mesenchymal stem cells (MSCs) are pivotal regulatory cells in promoting the M2 macrophage polarization.[82,83] Recent studies have further found that M2 macrophages play a direct role in allergic airway responses and asthma pathogenesis.[84] They have thus discovered considerably enhanced M2 macrophages in bronchoalveolar lavage fluids from individuals with asthma, along with elevated expression levels of both MRC1 and MHC class II. According to these data, M2 macrophages can significantly contribute to asthma and pharmacologic treatments targeting M2 formation and performance may be a viable strategy in asthma treatment, synergistic with current asthma therapies.[85]

4.4 | Kidney problems

During damage and repair, macrophage phenotypes are altered. After damage, inflammation, repair/regeneration, and fibrosis are thus the stages of injury resolution. At various stages, different macrophage phenotypes coexist and certain phenotypes predominate. Following

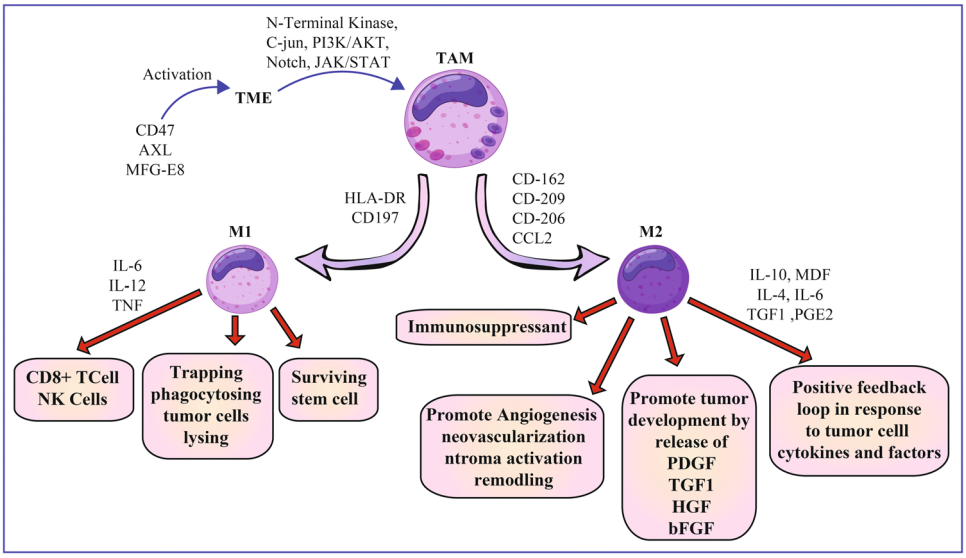

FIGURE 3 Immune cells in tumor immune microenvironment (TME) are activated by efferocytosis markers such as CD47, Axl, and MFG-E8. Tumor associated macrophages (TAMs) are engaged in both innate and adaptive immune responses, and are a common form of cell in the TME. Numerous important signaling pathways such as C-Jun N-terminal kinase (JNK), PI3K/Akt, Janus tyrosine kinase-signal transducer and activator of transcription (JAK/STAT), and Notch are contributed to TAM polarization. In response to a variety of stimuli, TAM may be split into M1 and M2 macrophages. Macrophages with the M1 phenotype have the innate ability to entrap, phagocytose, lyse tumor cells, surviving stem cells, whereas M2 macrophages play a role in angiogenesis, tumor development, immune suppressant, and neovascularization.

an acute kidney injury (AKI), neutrophils and natural killer cells (NKCs) are the initial cells recruited to the damaged kidney tissue. Later, inflammatory monocytes are drawn to this tissue.[86,87] Numerous pro-inflammatory mediators, such as IFN-γ generated by NKCs, neutrophils, and Th1 cells, also help polarize monocytes into M1 phenotype. This is characterized by the prevalence of M1 macrophage, which exacerbates inflammation.[88] Thereafter, regulatory T Tregs and Th2 cells are employed, and release IL-4 and IL-10, thereby polarizing macrophages toward M2.[89] At this stage, M2 macrophages predominate and help in inflammation clearance and tissue regeneration.[88]

The rise in M2 macrophage during the healing phase has been thus far validated in many AKI animal studies, such as sepsis-mediated AKI, ischemia reperfusion injury (IRI), diphtheria toxin-mediated AKI, and rhabdomyolysis-associated AKI.[90] Based on strong evidence, the repair process is inhibited by the depletion of macrophages, which points to the potential protective function of M2 macrophages. In kidney IRI, tubular cell proliferation and recovery further decrease by macrophage depletion within the repair stage.[91] In patients with lupus nephritis, macrophage depletion in the process of healing also intensifies the damage.[92] The repair process is thus controlled by M2 macrophages.[93] Of note, such macrophages are recognized by CX3CR1 upregulation, which promotes their migration to the damaged areas of the kidney.[94] Furthermore, M1 macrophages have the ability to alter phenotypically and become M2 ones both in vivo and in vitro.[95] In situations where Th2 inflammation dominates, and M2 macrophages have the main performance, the immune responses are controlled by local expansion rather than bone marrow recruitment.[96] Among the AKI models, the local proliferation of M2 macrophages has been to date discovered as a method of repair following diphtheria toxin-induced AKI, whereas in IRI, M2 macrophage population has been increased by the recruitment of monocytes.[97]

4.5 | Cancer

Numerous efferocytosis-related markers, including CD47, Axl, PtdSer, MFG-E8, MER proto-oncogene, tyrosine kinase (MerTK), IL-10, growth arrest-specific 6, and TGF-β, are associated with cancer development and greatly regulate immune cells in tumor immune microenvironment (TME)[98,99] (Figure 3).

Previous studies have further shown that, cytokine storms have been simulated by chemotherapy and irradiation in tumor stroma, thereby releasing tumor-inducing cytokines, such as IL-6 and TNF-α, and inducing macrophages to produce pro-inflammatory indicators via ascites tumor cells (ATCs).[100,101] Antitumor immunity caused by the remnants of dead and dying tumor cells can also alter the microenvironment to enhance tumor spread.[102] It is noteworthy that the immunosuppressive influence of cytokines in the process of efferocytosis may upregulate cytokines, boost TME, increase cancer metastasis, and raise the evasion of antitumor immunity.[103] It has been further demonstrated that cell death frequently occurs throughout the progression of solid tumors, which may persist even in the face of cytotoxic treatments. Thus, efferocytosis is an immunosuppressive mechanism for clearing dead or dying cells from TME.[104] The efferocytosis-mediated immunosuppressive phenotype in tumors also ensues via a coordinated sequence of signaling events,

like that from many sections of the tumor milieu.[105] The phagocytic engulfment effects of ACs also modulate cytokines, influence immune inhibitory level, and ensure that inflammation is not induced and tissues are not damaged.[106] In addition, efferocytosis with its effects on the phenotype of antigen-presenting macrophages and DCs, promotes a tolerogenic microenvironment, thereby declining antigen cross-presentation to T cells, T-cell clonal expansion, and development of antigen-dependent antitumor immunity.[106] Cytokines are also connected to wound-healing and immune suppression. In this regard, efferocytosis may stimulate the secretion of cytokines involved in wound-healing and immunosuppression, such as IL-4, IL-10, IL-13, and TGF-β, but inhibit the production of pro-inflammatory cytokines, such as IL-12 and IFN-γ.[107]

The macrophage phenotypes found inside tumor tissues also exhibit both innate and adaptive immunity. Due to their function in cancer formation, tumor associated macrophages (TAMs) are the common cells in TME and can be even a desirable target for cancer treatments.[108] Both M1 and M2 macrophages also function in the inflammatory response caused by tumors and M2 can cause angiogenesis, stromal induction, as well as neovascularization and regeneration, thus favorably affecting cancer development and adversely influencing patient prognosis.[109,110] Theoretically, TAM are divided into functional subtypes, most notably into M1 phenotypic macrophages via T1 (IFN- γ, TNF-α, and LPS) and M2 macrophages by T2 (IL-4, IL-10, TGF-β1, and PGE2) cytokines and immunocomplexes in response to diverse stimuli.[111] M1 macrophages also show the presence of CD197 and MHC II cell surface receptor (Human Leukocyte Antigen DR), and M2 macrophages have high expression levels of CD209, CD163, CCL2, and CD206.[112] The underlying processes of TAM polarization have been further related to numerous signaling routes, such as C-Jun N-terminal kinase, protein kinase B (PKB/Akt) pathway, the Notch signaling, and the Janus tyrosine kinase-signal transducer and activator of transcription signaling route.[113] M1 phenotype macrophages are intrinsically capable of trapping, phagocytosing, and lysing tumor cells.[114] Furthermore, other leukocytes cytotoxic actions have been promoted by increased tumor antigen presentation capabilities of M1. For example, CD8+ T cells and NKCs have been boosted by immunostimulatory cytokines (viz., IL-6, IL-12, and TNF) from M1 macrophages.[115] Consequently, tumor cell apoptosis has been promoted at this stage. Although tumor stem cells contain low immunogenic antigens, they can significantly proliferate and differentiate. Taking into account heterogeneity and tumor-intrinsic ways of immune evasion, tumor stem cells may further employ M1 macrophages as a natural filter to prevent resection and subsequent survival.[116,117]

According to immunoediting, and in opposition to M1 phenotype, numerous macrophages are altered to the M2 phenotype after interacting with tumor cells, which shows their immunosuppression potential (Figures 2 and 3). In contrast, M2 can serve as an immunosuppressor tumor nest. The pro-inflammatory capacity of M2 phenotype macrophages significantly reduce, owing to their poor ability to present tumor antigen[118] and the release of suppressive elements, such as IL-12.[119] The M2 macrophages may be further programmed to promote tumor development via secreting growth factors, such as platelet-derived growth factor, TGFβ1, hepatocyte growth factor, and basic fibroblast growth factor,[120] generating a positive feedback-loop on the basis of tumor cell factors and cytokines (namely IL-4/-6/-10, PGE2, MDF, and TGF1)[121] (Figure 3). In reality, all macrophages play a critical role in tumor growth at the initial tumor nest and during tumor metastasis progression. Thus, tumor growth might be predicted as a series of immunological clearance, equilibrium, and escape phases based on the M1/M2 ratio and immunoediting.[122]

4.6 | Other diseases

Natural monosaccharide (L-fucose) can be further utilized by fucosyltransferases to regulate polarization and macrophage function without adverse side effects.[123] Since M1 and M2 macrophages require diverse bioenergetics, different macrophage phenotypes are often required to maintain the nutritional condition of tissues. Based on aerobic glycolysis, M1 macrophages produce ATP and increase glucose and glutamine consumption, but they prevent oxidative metabolism. By interrupting the tricarboxylic acid (TCA) cycle, M1 macrophages also enhance the accumulation of citrate and succinate, which are beneficial for the formation of antimicrobial molecular fatty acids and itaconic acid.[124,125]

Additionally, M2 macrophages are largely employed to maintain TCA cycling and induce fatty acid oxidation, as a prototype for ATP synthesis.[126] Glutaminase-derived α-ketoglutarate (αKG) is also known as an anti-inflammatory molecule that plays a major role in regulating macrophage polarization.[127] The pro-inflammatory response of M1 macrophages is further disturbed by inhibiting nuclear factor-κB (NF-κB) pathway through αKG. Overall, the NF-κB signaling pathway may be employed to regulate macrophage polarization.[128]

5 | TREATMENTS

5.1 | AD

As reported, pathogenic damage in AD patients is alleviated by the inhibitors of extra neuroinflammation. According to in vitro investigations, nonselective COX inhibitors may selectively reduce the levels of the highly amyloidogenic Aβ1-42 peptides. In the murine models of AD, Aβ plaque deposition had been also reduced by nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) in the rat brain.[129] A prospective article had further indicated the protective effect of long-term NSAID use for AD, but not vascular dementia.[130] Some other inflammatory regulators, such as phosphordiesterases,[131] histone deacetylase,[132] and NADPH oxidase also have neuroprotective activities in AD.[133] Anti-inflammatory medications, such as naproxen, could also delay cognitive decline in slow decliners, but accelerate it in rapid ones.[134] Additionally, increasing data have

suggested that the regulators of microglial phenotypes might be a potent strategy for AD therapy.

5.2 | Asthma

In a recent study on mice, alveolar macrophage efferocytosis had caused the remission of allergic airway inflammatory responses, so AC clearance might be a promising treatment method. As this is based on the MerTK process, increasing Mer activity may be a novel strategy for targeting efferocytosis. Similarly, the macrophage efferocytosis of ACs have been promoted by angiotensin-(1–7) in mice with induced asthma.[135] Hence, eosinophil counts, NF-kB phosphorylation, airway remodeling, and collagen deposition are reduced, but apoptotic eosinophils are increased, leading to inflammation resolution and homeostasis restoration. Additionally, efferocytosis has been simulated by treatment through galectin-3.[136] Based on galectin-3 therapy, efferocytosis by monocyte-derived macrophages has elevated in asthmatic patients. Notably, however, this effect has been only on non-eosinophilic asthmatics not on eosinophilic ones with regard to asthma phenotype classification. Accordingly, *Escherichia coli* phagocytosis via alveolar macrophage induced by ovalbumin had been improved by the inhalation of hydrogen gas in asthmatic mouse models, and then airway hyperresponsiveness and inflammatory responses had been alleviated, potentially due to its antioxidant influences and triggering nuclear factor erythroid 2-related factor two.[137] Asthma therapy accordingly focuses on reducing inflammation as a primary objective. Corticosteroids, for instance, have anti-inflammatory impacts on macrophages through blocking IL-1b as well as increasing IL-10.[76] Recently, a few more studies have indicated that protostemonine and emodin have reduced the inflammatory effects of macrophages on asthma. In a mouse model, they reduced asthmatic inflammation induced by dust mites, ragweed, and aspergillus, and inhibited the polarization of activated macrophages.[139]

Additionally, it has been established that allergic airway inflammation in mice has been alleviated by blocking resistin-like molecule-an and arginase-1-producing M2 macrophages through muscarinic M3 receptor antagonist tiotropium, demonstrating the critical role of M2 macrophage polarization in pathogenesis.[138] Likewise, RAW 264.7 macrophages have been treated by anti-inflammatory drugs, suggesting that the expression levels of CD86 (M1-associated) and CD206 (M2-associated) decreased, so active status was declined, and pro-inflammatory cytokines were slightly released.[139] One other study in mice lung macrophages also found that the recruitment of inflammatory cells and the expression levels of chitinase-like protein three (YM1) and resistin-like molecule-α would decrease if sirtuin-2 could be inhibited pharmacologically, which were associated with M2 polarization.[140] Targeting the NLR family pyrin domain containing 3 (NLRP3) inflammasome is another effective asthma therapy. In mice with severe asthma, airway hyperresponsiveness and inflammation are prevented by inhibitory drug, CRID3, via blocking the NLRP3 inflammasome, accompanied by reduction in the expression levels of IL-1b, Th2 cytokines, and chemokines related to macrophages, neutrophils, and eosinophils.[141]

5.3 | Kidney problems

To acquire an M2 phenotype for the treatment of renal disorders, macrophages may be altered ex vivo or in vivo. Recent studies have thus indicated that macrophages in spleen triggered via IL-4/-13 had been administered to mice with severe combined immunodeficiency with adriamycin nephropathy (AN). Consequently, M macrophages (IL-4) had improved renal damage and IL-10/TGF-β-modified macrophages in the spleen had been protected versus AN.[142,143]

A main problem regarding such modified M2 macrophages as a therapy is that their phenotype may transition to M1 throughout the progression under in vivo conditions. The macrophage source also influences the phenotypic persistence. Unlike M macrophages in spleen (IL-4), those in the bone marrow (IL-4) go through phenotype shift to inflammatory one and fail to protect against AN.[144] Furthermore, the M macrophages from mice peritoneum (IL-4), experiencing peritoneal dialysis, could maintain their M2 phenotype and protect against AN in vivo.[145] IL-10/TGF-β-induced macrophages have been further effective in decreasing renal injury compared with IL-4/IL-13-mediated macrophages, probably due to their capacity to promote Tregs.[146] Recently, scientists have been investigating whether it is possible to treat solid tumors using chimeric antigen receptor macrophages.[147] Currently, further attention has been drawn to the use of MSCs, which have positive effects on some AKI models due to their inherent reparative characteristics. Moreover, they have exerted their beneficial impacts on M2 phenotype through polarizing macrophages. Numerous sources of MSCs, including MSCs derived from the bone marrow, stromal cells from serum-starved adipose, and mesenchymal stromal cells stemmed from the umbilical cord have been accordingly explored.[148] It has been shown that all promote M2 polarization in a wide variety of renal injury models and reduce damage.[149] Additionally, ILC2s have been recognized as a new subset of innate immune cells, as they are activated by IL-33 or IL-25, and have renoprotective effects induced by M2 macrophage polarization.[150] M-CSF mainly targets tissue-resident macrophages instead of bone marrow-derived monocytes, and then modulates macrophage proliferation and turnover.[151]

Thiazolidinedione, zoledronic acid, and trabectedin, as the examples of medicines regarding M2 polarization, have not still been tested in renal injuries.[152]

5.4 | Cancer

In fact, radiotherapy mainly aims to destroy tumor cells and reduce tumor size. Cytotoxic treatment also directly impacts tumor cells as a determinant whether radiotherapy would succeed or not. The therapeutic outcomes also depend on the next inherent and adaptive immunity, which can choose local radiation-resistant tumor cells.

Moreover, the elimination of dead or dying tumor cells through phagocytes of the innate immunity is another critical factor. Adaptive immune responses have been thus simulated, suppressed, and skewed by mature DCs and macrophages, capable of engulfing, processing, and presenting antigens of ATCs to the adaptive immune system.[153,154] Conventional cancer therapies are extremely based on chemotherapy and radiotherapy. Such techniques aim to directly destroy tumor cells, however, as stated earlier, their success rate is dependent on intrinsic and adaptive antitumor immune responses.[155] Within the process of such treatments, signaling between DCs and TLR-4 and the respective adaptor myeloid differentiation primary response 88 are required to process and cross-present the ATC-related antigen effectively. In a recent work on individuals with breast cancer, TLR4 loss-of-function allele had recurred rapidly after radiation or chemotherapy. TLR-4 and high-mobility group box 1 have been further demonstrated to be critical in initiating immune responses against dying tumor cells, induced by chemotherapy and radiation, possibly through modifying the potential of DC process and displaying tumor-mediated antigens under in vivo conditions.[156,157]

6 | CONCLUSION

Efferocytosis is vital for cell homeostasis in tissues and proper cell debris clearance seems essential for preventing unnecessary inflammatory responses. If phagocytes, such as macrophages, do not quickly remove ACs, owning to disintegrated cell membranes, they transform into secondary necrotic cells. Upon releasing cell contents and DNA from necrotic cells into the environment, these cells can thus promote an inflammatory response. Macrophages, as the professional phagocytes, accordingly play a leading role in proper efferocytosis. Owing to their phagocytic activity and capability for expressing mediators and cytokines, macrophages also establish inflammatory responses. Interpreting signs from the environment, they further control early pro-inflammatory reactions to pathogens and tissue damage, and then express anti-inflammatory cytokines and lipids to actively block the inflammatory response and homeostasis restoration of tissues. The precise regulation of polarization in macrophages under pathological and physiological conditions is thus of great importance during proper efferocytosis. Any insufficiency in macrophage efferocytosis thus facilitates the spread of a wide variety of diseases, including autoimmune disorders, NDDs, kidney problems, types of cancer, asthma, and the like. Macrophage polarization also means the production of macrophages with special phenotypes versus micro-environmental actions. M1/M2 macrophages are also two main and opposite subtypes. Accordingly, M1 macrophage can begin and maintain inflammation, express pro-inflammatory cytokines, trigger endothelial cells, and recruit other immune cells toward the inflammation site. M2 macrophage can further cause the resolution of inflammation. Detailed information about efferocytosis, in particular, the relationship between M1/M2 macrophage polarization and efferocytosis, can accordingly render promising curative approaches, and even potent targeted or combinatorial therapies.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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