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Review

Targeting Macrophage Efferocytosis to Treat Chronic Inflammation in Cancer and Inflammaging

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ABSTRACT: Efferocytosis, the process by which phagocytes clear apoptotic cells, is fundamental for maintaining physiological homeostasis. Inflammaging as a chronic and low-grade inflammatory state characteristic of aging is recognized as a significant contributor to tumor development. As crucial innate immune cells found in various tissues, macrophages are closely involved in both inflammaging and tumor. Accumulating evidence indicates that macrophage-mediated efferocytosis is closely linked to these processes, and its disruption can initiate or accelerate disease. Therefore, it is essential to elucidate the pivotal functions of macrophage efferocytosis in inflammaging and tumor biology to develop potential therapeutic strategies. Herein, this study first aims to uncover the crosstalk between inflammaging and tumor. We then investigate the mechanisms of macrophage efferocytosis, outlining its distinct functional phases and associated metabolic adaptations. The effects of efferocytosis on macrophage functions are also discussed. Furthermore, this study summarizes the prospective therapies treating inflammaging and tumor by modulating macrophage efferocytosis. Collectively, targeting macrophage efferocytosis represents a promising strategy for treating chronic inflammation-associated diseases, including tumor and inflammaging.

Keywords: efferocytosis, macrophage, chronic inflammation-associated diseases, tumor, inflammaging

1. Introduction

Inflammaging refers to a chronic, low-degree, sterile proinflammatory state which occurs with increasing age, and chronic inflammation is widely regarded as a significant contributor to tumor development [1, 2]. Previous studies have established a strong association between chronic inflammation and tumorigenesis, for instance, inflammatory bowel disease (IBD) is a known risk factor for colorectal cancer [3, 4]. Some cytokines involved in the process of inflammaging secreted by inflammatory cells show a positive correlation with chronic disease rates in aging populations and are implicated in predisposing individuals to tumor [5, 6]. As the significant component of immune systems, macrophages are intensively engaged in chronic inflammation-associated diseases including inflammaging and tumor. However, the regulative roles of macrophages in the crosstalk of inflammaging and tumor remain to be uncovered.

Programed cell death such as apoptosis, necroptosis, and pyroptosis is crucial to the homeostasis of human body [7, 8]. This process is essential for tissue homeostasis, enabling the natural renewal of senescent cells in human body. For example, the human body clears millions of aged red blood cells daily as part of its routine physiological maintenance [9]. Senescent cells are constantly being replaced on a large scale. Despite this, human bodies function smoothly because of a remarkably efficient system that silently removes the cellular debris.

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This process, termed "efferocytosis", involves the swift engulfment of apoptotic cells by phagocytes, thereby averting the adverse consequences that uncleared apoptotic cells could impose on the surrounding normal tissues [10]. Thus, efferocytosis plays a critical role in maintaining internal environment homeostasis [11].

Efferocytosis, the process of clearing apoptotic cells, is fundamental for tissue homeostasis. Due to the universality of cell apoptosis, efferocytosis can occur in various parts of human body and is engaged in various diseases [9]. During the process of efferocytosis, tumor-associated macrophages within the tumor microenvironment (TME) could efficiently clear apoptotic tumor cells, suppress anti-tumor immunity by inducing T cell tolerance and recruiting regulatory T cells, and further promote tumor progression [12]. However, the dysfunction of efferocytosis, rather than its normal activity, is a critical driver of chronic inflammation-associated diseases. Mechanically, defective clearance leads to the accumulation of apoptotic cells, which undergo secondary necrosis. It releases intracellular contents, triggering persistent inflammation and breaking immune tolerance. This pathway is central to diseases such as atherosclerosis, where uncleared dead cells form unstable plaque necrotic cores [13]. Our study aimed to discuss the underlying mechanisms of efferocytosis, its roles in the crosstalk of inflammaging and tumor, and the potential targeting therapies involving macrophage efferocytosis.

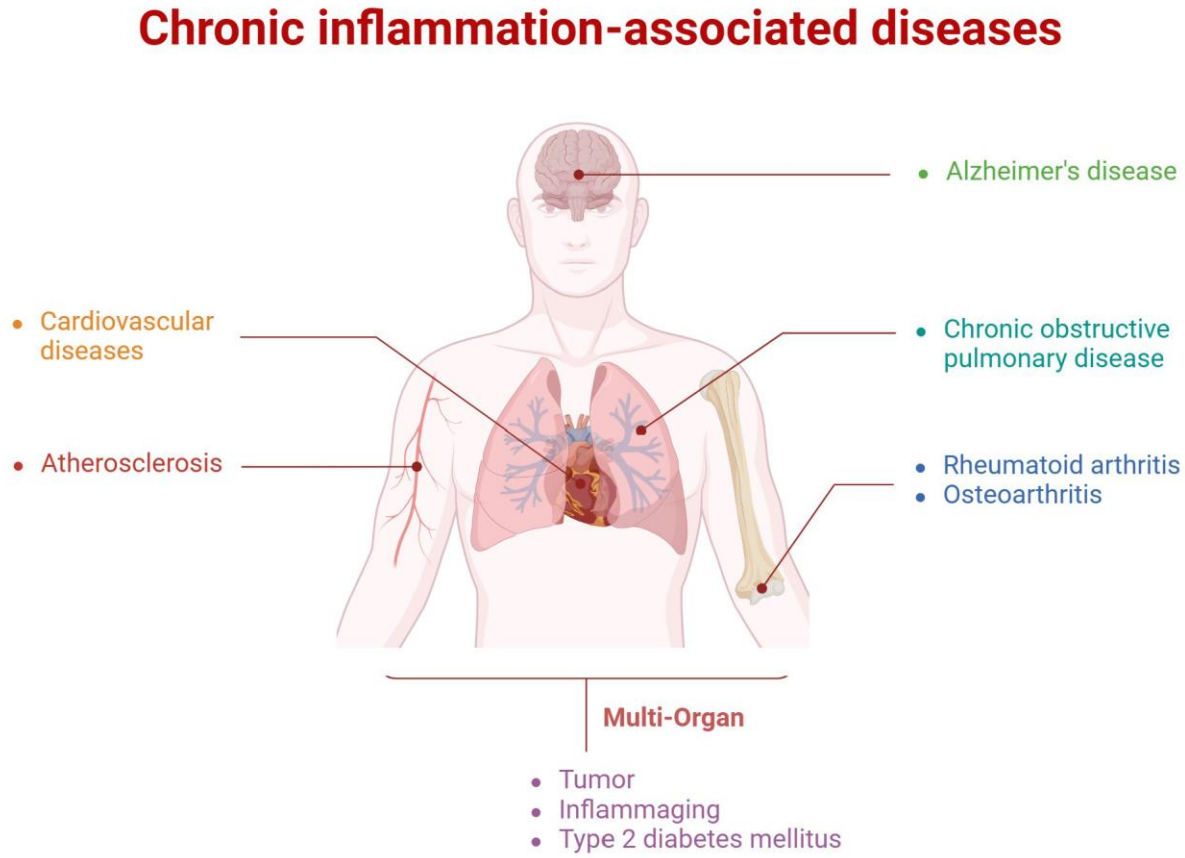

Figure 1. The types of chronic inflammation-associated diseases. Based on the affected organs and underlying mechanisms, chronic inflammation-associated diseases are primarily categorized into several classes: autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease; metabolic diseases such as cardiovascular diseases, atherosclerosis, type 2 diabetes mellitus, and non-alcoholic steatohepatitis; chronic fibrotic or degenerative diseases such as chronic obstructive pulmonary disease, Alzheimer's disease, and osteoarthritis. Other diseases such as tumors and inflammaging involve multiple mechanisms and multiple organs. This classification and highlights the shared inflammatory pathways across these diseases, which has emerged as a critical approach for managing these diverse conditions across traditional disease boundaries.

2. The crosstalk between inflammaging and tumor

Chronic inflammation-associated diseases encompass a broad spectrum of disorders driven by dysregulated immune responses and persistent activation of inflammatory signaling, leading to tissue damage and dysfunction [14, 15]. The hallmark is a self-perpetuating inflammatory state that evolves from a defense mechanism into a core pathogenic driver. As summarized in Figure 1, these conditions can be categorized by

affected organs and mechanisms into several major classes: autoimmune diseases such as rheumatoid arthritis and IBD; metabolic diseases such as cardiovascular diseases, atherosclerosis, type 2 diabetes mellitus, and non-alcoholic steatohepatitis; chronic fibrotic or degenerative diseases such as chronic obstructive pulmonary disease, Alzheimer's disease, and osteoarthritis. Other diseases such as tumors and inflammaging involve multiple mechanisms and multiple organs. Figure 1 illustrates this classification and highlights the shared inflammatory pathways across these diseases, which has emerged as a critical approach for managing these diverse conditions across traditional disease boundaries.

Inflammaging is regarded as a "fertile soil" that promotes the development of chronic diseases, including tumors. Accumulating evidence indicates that the immune system plays dual roles throughout tumorigenesis, exerting both pro- and anti-tumor effects. This is exemplified by the concept of "tumor-promoting inflammation", in which immune responses actively contribute to tumor initiation and progression. Clinically, chronic inflammation often precedes tumor formation in the same tissue, as seen in IBD and chronic hepatitis, which elevate the risk of colorectal cancer and liver cancer, respectively [16]. Persistent low-grade chronic inflammation drives the downregulation of innate immune functions, a state that compromises the organism's ability to combat both pathogens and malignant tumor cells [17]. Moreover, some cytokines associated with inflammaging, secreted by activated inflammatory cells, correlate with elevated rates of chronic diseases in the elderly and contribute to a microenvironment that favors tumor initiation [5, 6]. At the intracellular level, for example, the nuclear factor-κB (NF-κB) signaling pathway as a central regulator of inflammaging also functions as a critical oncogenic transcription factor during tumor development [18]. Collectively, these findings provide robust multi-level evidence supporting the strong association between inflammaging and tumor progression.

3. The regulative role of macrophages in inflammaging and tumor

Macrophages are central to the innate immune system, performing essential functions such as phagocytosing pathogens and clearing cellular debris to maintain tissue homeostasis [19]. Affected by different stimulators, macrophages can be polarized into different phenotypes [20] (Fig. 2A). Macrophages serve as the primary phagocytes responsible for efferocytosis. They exhibit remarkable plasticity, undergoing dynamic polarization, metabolic reprogramming, and complex interactions with other immune cells in response to specific micro-environmental stimulations. Accordingly, it is necessary to detail their critical involvement in both inflammaging and tumor biology.

Macrophages are an important and major component of TME, comprising up to 50% of the tumor mass, which are also commonly termed as tumor-associated macrophages [21]. M1 macrophages are typically pro-inflammatory and often associated with anti-tumor responses, whereas M2 macrophages are generally linked to anti-inflammatory functions and can promote tumorigenesis [22] (Fig. 2B). Efferocytosis within the TME promotes the polarization of macrophages toward a pro-tumor phenotype and enhances tumor metastasis, which is closely associated with poor clinical outcomes [23]. Macrophages promote tumor progression by generating angiogenic factors, secreting mitogenic signals, and producing matrix-degrading proteases, thereby remodeling the TME to support invasion and metastasis [24]. Tumor metastasis might be promoted by a paracrine loop involving macrophage-derived epidermal growth factor (EGF) ligands and tumor cell-derived colony-stimulating factor 1 (CSF-1), which is further stimulated by cathepsin and matrix-remodeling enzyme activity from tumor-associated macrophages [25]. DeNardo et al. also reported in the Polyoma virus middle T antigen (PyMT) model that interleukin-4 (IL-4) from CD4+ T cells reprograms tumor-associated macrophages to elevate EGF secretion, which subsequently enhances the invasiveness and metastatic capacity of malignant tumor cells [26].

Macrophages are also involved in inflammaging, playing a central role in the chronic inflammation that characterizes aging. Tissue-resident macrophages (MΦ-Ts) are crucial for tissue development, homeostasis, and wound healing. However, under the continuous stimulation of inflammation, these cells could undergo the process of inflammaging. This process is characterized by altered morphology and distribution, reduced phagocytic and autophagic activity, the expression of a senescence-associated secretory phenotype (SASP), and diminished tissue-repair capacity. Ultimately, the inflammaging of MΦ-Ts disrupts tissue homeostasis and contributes to the development of age-related diseases (ARDs) [27]. It is also discovered that senescent MΦ-Ts have an altered pattern of cytokine secretion which could cause the imbalance in pro- and anti-inflammatory factors in vivo [28]. Macrophages could interplay with other immune cells in inflammation process. In inflammaging such as rheumatoid arthritis, macrophages could make direct regulation to T cells recruitment, differentiation, and activation into rheumatoid arthritis synovium. The polarization of macrophages toward a pro-inflammatory

phenotype is a key feature of inflammaging, as observed in conditions such as rheumatoid arthritis [29].

In summary, macrophages constitute an inseparable and central component in both tumor and inflammaging. Through phenotypic plasticity and metabolic reprogramming, the macrophage subtypes orchestrate the progression of these linked processes in multiple ways.

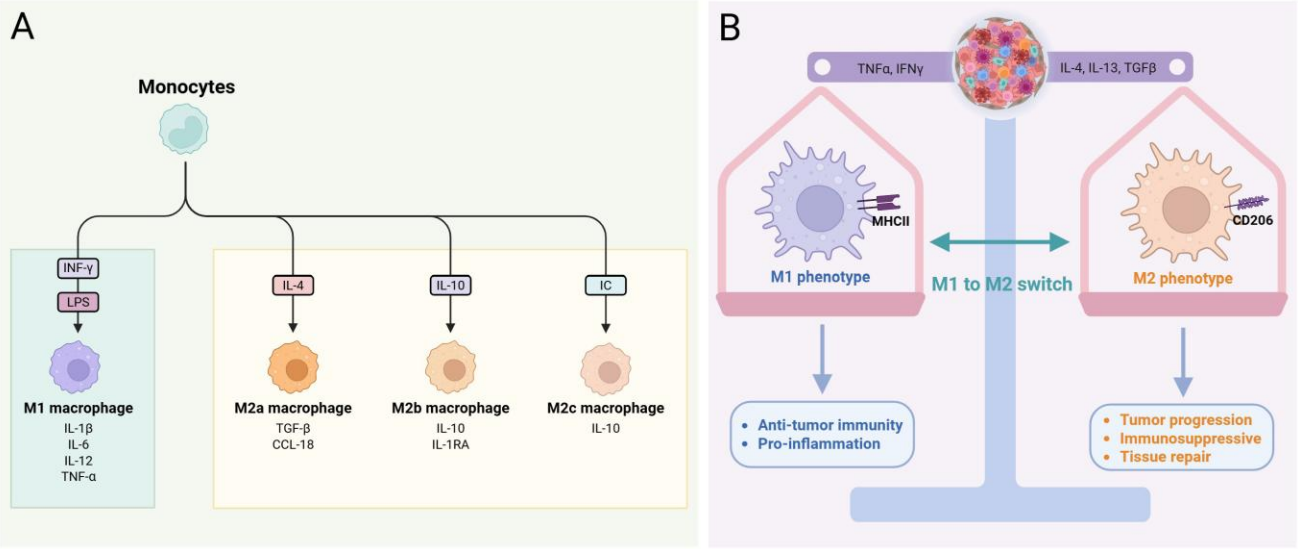

Figure 2. Macrophage polarization and the regulative roles of different macrophage subtypes in inflammaging and tumor. (A) Affected by different stimulators, macrophages can be polarized into different phenotypes. **(B)** M1 macrophages are typically pro-inflammatory and often associated with anti-tumor responses, whereas M2 macrophages are generally linked to anti-inflammatory functions and can promote tumorigenesis.

4. Mechanisms of efferocytosis

Efferocytosis refers to the programmed clearance of apoptotic cells via a precisely regulated, multi-step pathway. Disruption of this process contributes to a variety of pathological states including inflammatory, autoimmune, and neurodegenerative diseases [30]. It can be divided specifically into three stages: "smelling phase", "eating phase" and "digesting phase" (Fig. 3).

4.1. Smelling phase

The process begins with the "smelling" or "find-me" phase, during which apoptotic cells release soluble chemotactic signals that recruit phagocytes to the site of cell death [31]. The signals or mediators released by apoptotic cells is diverse, including chemokine C-X_3-C motif ligand 1 (CX3CL1) [32], sphingosine 1-phosphate (S1P) [33], lysophosphatidylcholine (LPC) [34], and nucleotides (ATP and UTP) [31]. These signals induce phagocytes to move towards a specific direction instead of random searching for apoptotic cells. Though other cells such as epithelial cells and fibroblasts can clear nearby apoptotic cells, they lose this ability in certain settings, such as the developing thymus. This necessitates the recruitment of distant professional phagocytes. The "find-me" signals fulfill this role and extend their function beyond mere recruitment; they also prime phagocytes for efficient clearance and promote anti-inflammatory responses [31, 35]. Specifically, these signals reshape the phagocyte's structure and function, driving them toward a pro-repair phenotype characterized by enhanced survival, tissue regeneration, and suppression of inflammation [9]. The directed migration of phagocytes, particularly macrophages, to inflammatory sites or tumor tissues is critical for effective tissue repair or immune regulation [36-39].

LPC is the first discovered lipid "find-me" signal. It was reported that LPC was produced by the cleavage of phosphatidylcholine by phospholipase A2 activated by Caspase-3 during apoptosis and suggested that ABCA1 is crucial for LPC release from apoptotic cells [31]. S1P is another lipid chemotactic factor that acts as a "find-me" signal in efferocytosis. It has been uncovered that sphingosine kinase 1 (SphK1) could regulate and augment the amount of excreted S1P [31, 35]. S1P can increase erythropoietin expression in macrophages. Then, the peroxisome proliferator-activated receptor-γ (PPAR-γ) pathway is activated, thereby enhancing the expression of various phagocyte receptors such as MER proto-oncogene tyrosine kinase (MerTK) and growth arrest-specific protein 6 (Gas6) [40]. However, the precise role of LPC and S1P as physiological "find-me" signals continues to be debated. The central methodological limitation lies in the fact that the effective concentrations of these lipids in vitro are orders of magnitude higher than their

physiological levels found in apoptotic supernatants. This discrepancy raises a fundamental question about whether they function as true long-range "find-me" signals in vivo [41, 42]. This inconsistency prompts a reevaluation of their proposed function. Rather than acting as long-range signals, LPC and S1P may instead serve as local mediators that regulate phagocyte responses at the site of cell death. Furthermore, their activity may be context-dependent or synergistic, potentially requiring co-signals from the apoptotic milieu that have not yet been identified. Despite widespread recognition, the essential status of LPC and S1P as "find-me" signals crucially depends on validation through in vivo studies under pathological conditions. More studies are needed to clarify whether these molecules are indispensable, auxiliary, or context-modulated components of the apoptotic cell recruitment cascade.

4.2. Eating phase

The migration of phagocytes is followed by specific recognition and phagocytosis, which is termed "eating phase". This process is marked by phagocytes binding to "eat-me" signals on apoptotic cell surface, a key step that initiates engulfment [43]. Apoptotic cells are characterized by the "eat-me" signals, which distinct them from the normal neighbored cells that have "don't-eat-me" signals on their surface [44].

Numerous "eat-me" receptors on apoptotic cell membrane have been reported so far, such as phosphatidylserine (PS), calreticulin, and annexin I [31]. Among them, the most common and widely studied "eat-me" signal is PS. In healthy cells, PS together with phosphatidylethanolamine, is located in the inner part of plasma membrane. However, when they undergo apoptosis, PS displaces to the plasma membrane external leaflet of apoptotic cells [45]. PS exposed on the surface can be directly bind with PS receptors such as the brain-specific angiogenesis inhibitor 1 (BAI1), T cell immunoglobulin mucin receptors TIM1-TIM4 (TIM family) and Stabilin 2, whereas receptors of the Tyro3/Axl/Mer (TAM) family of tyrosine kinases engage PS via soluble bridging molecules such as Gas6 and Protein S. The binding of PS and PS receptor triggers a series of tightly orchestrated steps: maturation of the nascent phagosome, fusion of the phagosome to lysosomes, pH-dependent degradation of macromolecules, efflux of solutes from phagolysosomes, and resorption of the phagosome membrane [30].

It is widely recognized that PS exposure is the most common alteration on the surface of apoptotic cells, observed in many different cells after multiple modalities of apoptosis induction [46]. However, there has been evidence proving that PS externalization does not result in consequent apoptosis [47]. Under this condition, the role of PS as "eat-me" signal seems insufficient for subsequent targeted phagocytosis. For instance, externalized PS could be also discovered on the membranes of macrophages, active B cells and T cells. Exposed PS can also be found on tumor cells or secreted microvesicles [48]. It implies that "eating phase" is not governed by a single signal; it either involves complementary "eat-me" molecules or is finely tuned by the opposing action of "don't-eat-me" signals.

The most widely studied "don't-eat-me" signal is cluster of differentiation 47 (CD47). CD47 is expressed normally in healthy cells, preventing them from being engulfed. CD47 can bind to its receptor signal-regulatory protein α (SIRPα) on macrophages and restrain myosin II conformational changes, thereby realizing the prevention of phagosome formation [49]. The downregulation of CD47 on the cell membrane can trigger efferocytosis, representing a key mechanism for eliminating aged or superfluous cells [50]. However, overexpressed CD47 on tumor cell membrane allows them to escape immune surveillance in TME through inhibition of phagocytosis [51]. In clinic, it has been reported that the expression of CD47 mRNA is negatively correlated with tumor patient survival rates. Dysregulation of CD47, therefore, affects tumor-associated efferocytosis and represents a promising therapeutic strategy [52]. Another membrane protein CD300a can also function as "don't-eat-me" signal, which is expressed on macrophage membrane. CD300a-mediated recognition of PS and phosphatidyl-ethanolamine inhibits efferocytosis preventing the engulfment step [40].

4.3. Digestion phase

The digestion phase following internalization presents dual challenges. First, phagocytes must process apoptotic corpses that often exceed them in number and size, which demands careful management of cellular volume and surface area. The ingested cargo comprising membranes, lipids, proteins, and nucleic acids imposes a significant metabolic burden, requiring its efficient recycling into metabolic pathways or excretion. Second, phagocytes must neutralize potentially harmful contents within the corpses. Simultaneously, they must execute this degradation while functionally shifting toward an anti-inflammatory, pro-repair phenotype, which is a unique and coordinated challenge central to efferocytosis [9, 53]. Beyond its degradative role, digestion phase also involves the production of anti-inflammatory mediators. During efferocytosis, phagocytes release a range of such mediators, including prostaglandin E2 (PGE2), transforming growth factor-β (TGF-β), interleukin-10 (IL-10), and lactate. Accordingly, the digestion of

apoptotic cargo induces metabolic reprogramming within the phagocyte, which actively leads to the suppression of pro-inflammatory signaling [54]. However, disability of digestion phase or production of anti-inflammatory mediators is an important factor leading to chronic inflammation-associated diseases such as atherosclerosis [55].

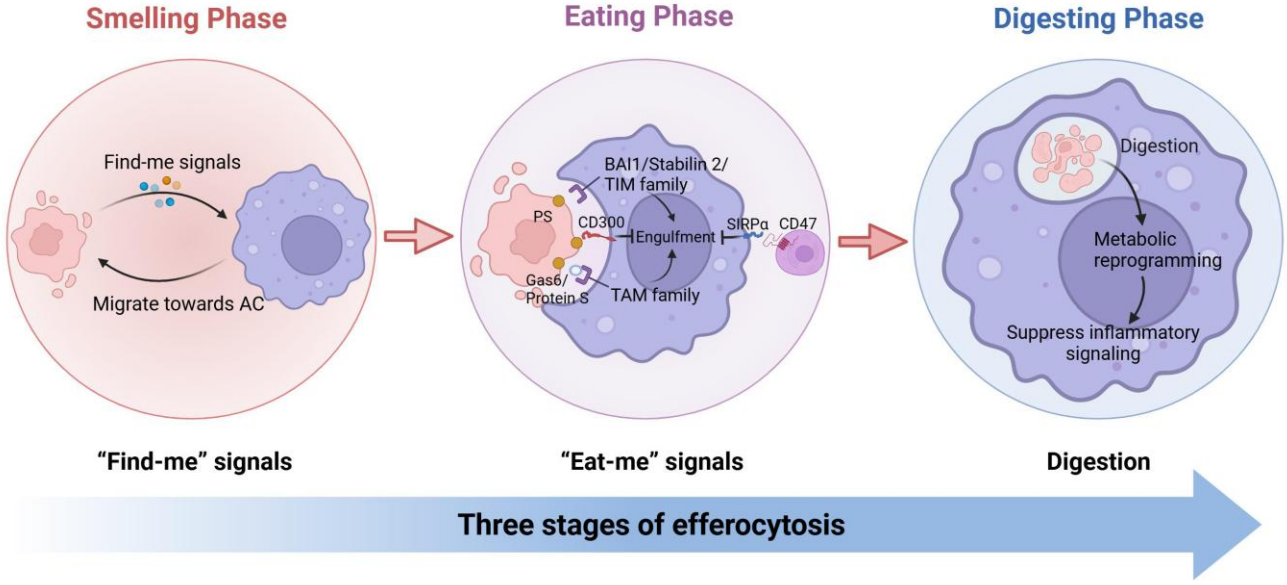

Figure 3. Mechanisms of macrophage efferocytosis with three stages of "smelling phase", "eating phase", and "digesting phase". First, the smelling phase: apoptotic cells (AC) release "find-me" signals (e.g., lysophosphatidylcholine) to recruit phagocytes. Second, the eating phase: phagocytes recognize "eat-me" signals such as phosphatidylserine (PS) on the apoptotic cell surface via specific receptors (e.g., TIM, BAI1), leading to engulfment. Finally, the digestive phase: the ingested cell is degraded within phagolysosomes, and the phagocyte initiates anti-inflammatory signaling.

5. The role of efferocytosis in the function of macrophages

The phagocytic process by which macrophages engulf and degrade apoptotic cells is termed efferocytosis, a crucial component of macrophage functionality. Macrophage efferocytosis could be regulated in adjustment to macrophage metabolic activities (Fig. 4). For instance, maresin conjugates in tissue regeneration (MCTRs) promote the initial internalization of apoptotic cells (AC), a process dependent on Rac1 signaling and glycolytic metabolism [52]. Furthermore, following AC engulfment, the autophagy-related protein LC3 can be recruited to the phagosomal membrane to form a LAPosome, in a process known as LC3-associated phagocytosis (LAP). LAP enhances phagosome-lysosome fusion, thereby accelerating the degradation of engulfed material [56]. Glycolysis is particularly significant in this context, as it supplies the necessary energy for efferocytosis. Current evidence highlights its dual role: it promotes initial AC uptake and supports lactate-fuelled, continual efferocytosis, while efferocytosis itself can reciprocally induce aerobic glycolysis [57, 58]. Importantly, efferocytosis is not merely a terminal function but actively reprograms macrophage activity. Nucleotides released from the phagolysosomal hydrolysis of AC-DNA can activate the mTORC2 pathway and upregulate Myc expression, leading to efferocytosis-induced macrophage proliferation (EIMP). A similar proliferative response can be triggered via MerTK binding to AC and subsequent extracellular regulated protein kinases (ERK1/2) activation [59]. In summary, intracellular metabolism (e.g., generating LC3 or MCTRs) critically regulates efferocytosis. In turn, efferocytosis profoundly influences fundamental macrophage activities, such as proliferative capacity, establishing a dynamic bidirectional relationship. Therefore, efferocytosis is a central regulatory axis in tissue homeostasis, based on a dynamic, bidirectional relationship: macrophage function directs clearance activity and is fundamentally reshaped by it.

6. The function and targeting therapies of efferocytosis in tumor

6.1. The function of efferocytosis in tumor

Accumulating evidence supports the significant impact of efferocytosis on tumor development [60]. In contrast to its physiological role in the clearance of apoptotic cells to prevent secondary necrosis, efferocytosis within the TME

can be detrimental. This is because the clearance process is accompanied with pro-tumor immunosuppression [40]. Efferocytosis prevents the release of proinflammatory damage-associated molecular patterns (DAMPs) from secondary necrotic corpses. Concurrently, it alters cytokine production within the TME, shifting it from a potentially immunostimulatory profile to an immunosuppressive one [52]. Efferocytosis induces an M2 macrophage phenotype that suppresses antigen presentation and T cell expansion; it also upregulates macrophage aerobic glycolysis. This metabolic reprogramming also favors tumor progression, as a glucose-deficient TME cannot support the metabolic demands of efficient anti-tumor T cell function [49]. Based on these mechanisms, efferocytosis can facilitate tumor growth and promote tumor immune escape [61]. However, it is important to note that the benefits of blocking efferocytosis for tumor patients should not be assumed. Defective efferocytosis could cause secondary necrosis after tumor cells apoptosis, which is also detrimental to the host [62].

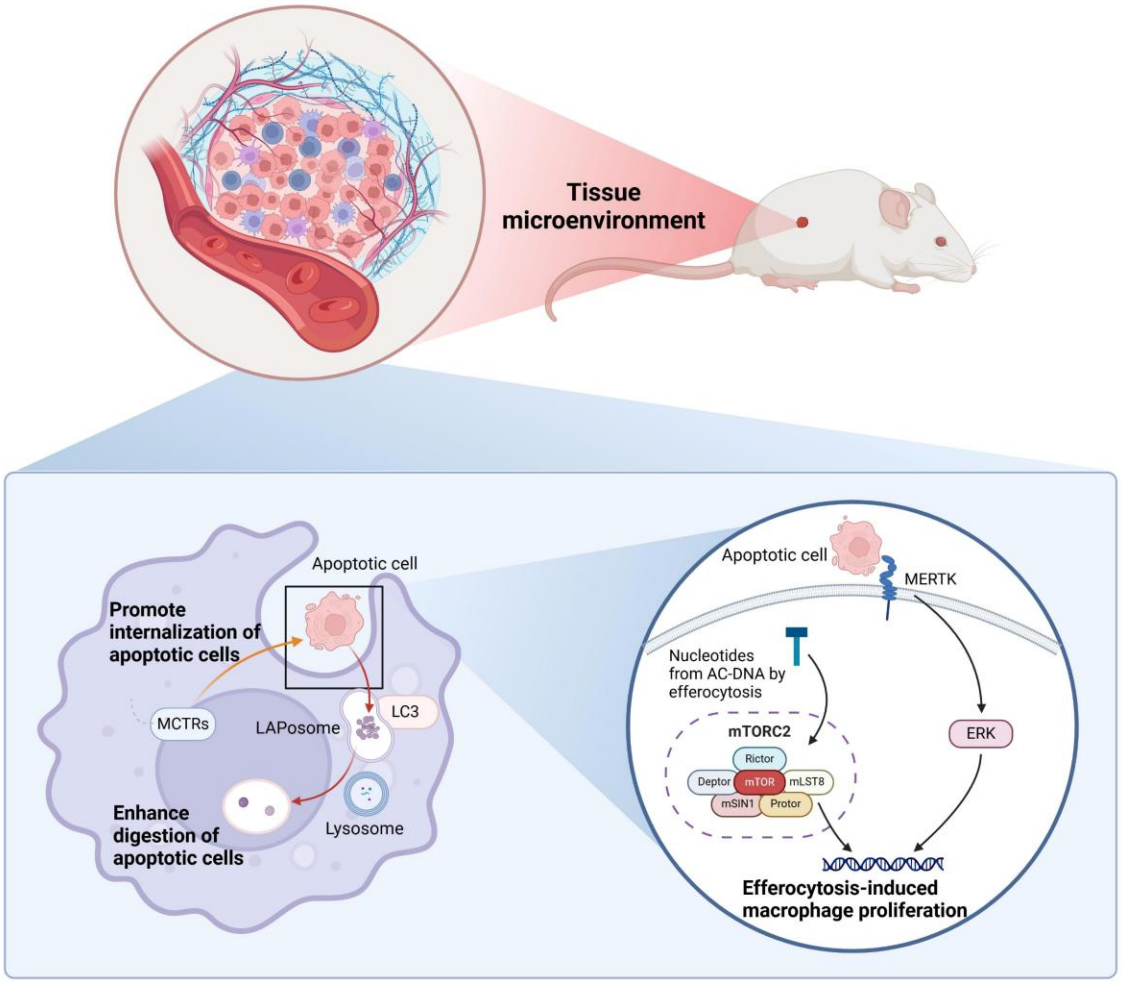

Figure 4. The regulative roles of efferocytosis in the function of macrophages in tissue microenvironment. Efferocytosis acts as a core regulatory mechanism that not only clears apoptotic cells (AC) but also actively reprograms the macrophage itself in tissue microenvironment. By inducing metabolic shifts like aerobic glycolysis and triggering pathways such as LC3-associated phagocytosis (LAP), efferocytosis enhances the degradative capacity of macrophages. Crucially, it also provides feedback signals that promote efferocytosis-induced macrophage proliferation (EIMP) via pathways like mTORC2.

6.2. The efferocytosis targeting therapies in tumor

Macrophages constitute a central cellular component of the TME and are the primary effectors of the engulfment phase in efferocytosis. Therefore, modulating their function represents a promising therapeutic strategy for tumor. Macrophage-targeted therapies are generally designed to achieve one or more of the following

objectives: (a) depleting tumor-associated macrophages, (b) inhibiting the recruitment of circulating monocytes into the TME, or (c) reprogramming tumor-associated macrophages [63]. For example, macrophage phagocytic function and phenotypic polarization are closely linked to lysosomal pH. Chloroquine (CQ) as a lysosomotropic alkalinizing agent could accumulate within lysosomes and elevates their pH. This disruption of the acidic lysosomal environment can reprogram tumor-associated macrophages [64, 65].

Table 1. Tyro3/Axl/Mer (TAM) targeting monoclonal antibodies

mAbs	Species	Targets
hTryo-3-ECD	Human	Tyro3
hTyro3-Ig	Human	Tyro3
hTyro3-ECD-Fc	Human	Tyro3
DAXL-88	Human and Mouse	Axl
BA3011	Human	Axl
YW327.6S2	Human	Axl
20G7-D9	Human	Axl
RGX-019	Human	MerTK
Murine-RGX-019	Mouse	MerTK
Mer590	Human	MerTK

A key focus in efferocytosis-targeted anti-tumor therapy involves modulating the interaction between PS as the main "eat-me" signal and its receptors. Activation of Tyro3/Axl/Mer (TAM) receptors shifts macrophages towards M2 phenotype, which enhances immuno-suppressive cytokine secretion and promotes tumor development [66]. Therefore, inhibiting PS receptors of the TAM family is an attracting therapeutic strategy, including monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs) and small molecule inhibitors (SMIs) [48]. Table 1 shows the concrete information of TAM mAbs. For example, UNC2025 is a small molecule inhibitor to MerTK, decreasing its kinase activity by preventing its phosphorylation [67]. Researchers developed a versatile nanosystem composed of UNC2025 and the bacterial outer membrane vesicles (OMVs). OMVs loaded with the inhibitor demonstrate potent efferocytosis suppression and elicit robust systemic anti-tumor immunity [68]. The Gas6/Axl axis is expressed not only in efferocytotic cells but also in various normal and tumor cells, where it is known to promote tumor growth, metastasis, and invasion. Axl inhibition offers a dual therapeutic benefit by directly suppressing tumor progression and simultaneously modulating efferocytosis. This has been demonstrated by SMIs such as TP-0903, BGB324, and DP3975, as well as by clinically approved anti-tumor agents including crizotinib and gilteritinib, which achieve their efficacy through Axl blockade [69].

In addition to targeting PS receptors, direct inhibition of PS itself represents a viable therapeutic strategy. Researchers have developed mAbs that specifically bind to PS externally exposed on endothelial cells in tumor. Furthermore, these PS mAbs have been shown to promote macrophage polarization [48]. Notably, bavituximab (PGN401), a human-mouse chimeric monoclonal antibody against PS, has demonstrated promising efficacy in phase II clinical trials for certain tumors [70].

The "don't eat me" signal in the eating phase of efferocytosis constitutes another promising therapeutic target. Specifically, disrupting the CD47-SIRPα axis can enhance the anti-tumor capability of macrophages [71, 72]. Agents such as anti-CD47 antibodies, anti-SIRPα antibodies, and the 4N1K peptide block CD47-SIRPα axis, thereby enhancing the phagocytic elimination of tumor cells by macrophages [73]. However, a significant clinical challenge associated with this approach, particularly with anti-CD47 antibodies, is the risk of inducing anemia due to the unintended opsonization and clearance of erythrocytes, which also express CD47 [35]. Furthermore, the digestion phase of efferocytosis is also recognized as a critical regulatory node influencing tumor progression. Digestion of apoptotic cargo generates tolerogenic signals that help tumors evade immune surveillance. LAP can resolve inflammation and promote wound healing by finalizing the intracellular digestion process of efferocytosis, which is a booster for immune suppression and tumor growth. Therefore, researchers have proposed that targeting LAP in the TME represents a feasible therapeutic strategy, for example by inhibiting LC3 recruitment or blocking cytokines involved in LAP initiation, such as TGF-β [56].

To sum up, efferocytosis in the TME transfers from a physiological clearance mechanism into a driver of tumor progression. By clearing apoptotic tumor cells, it induces macrophage polarization toward an immunosuppressive phenotype and upregulates aerobic glycolysis, collectively fostering an environment that suppresses T cell function while promoting tumor growth and metastasis. Consequently, targeting key steps in this process such as the "eat-me" signal PS and its receptors, the "don't-eat-me" signal CD47, and downstream LAP has emerged as a promising therapeutic strategy in tumor (Table 2).

6.3. Clinical translation and future perspectives about targeting efferocytosis in tumor

The translation of macrophage efferocytosis-targeting strategies into clinical applications requires a paradigm shift from broad inhibition to context-dependent precision modulation. The dual role of efferocytosis, as a janitorial process that can either suppress or provoke immunity,

dictates that its therapeutic manipulation is not universally applicable but must be guided by a clear decision framework. Future efforts should focus on defining the specific tumor-immune contexts that predict benefit from either inhibition or enhancement of macrophage efferocytosis. Key determinants will likely include the composition of the tumor microenvironment (e.g., "immune-desert" vs. "immune-inflamed" phenotypes), the dominant cellular source of apoptotic material (e.g., dying tumor cells vs. infiltrating lymphocytes), and the stage of therapy (e.g., post-chemotherapy vs. during immunotherapy). The clinical framework are summarized as Table 3.

Table 2. Macrophage efferocytosis-associated therapeutic strategies for tumors.

Strategies	**Targeting macrophage polarization**	**Targeting key molecules in efferocytosis process**			
Phases	**Induced M1 polarization**	**Smelling phase**	**Eating phase**	**Digestion phase**	
Drugs	Chloroquine	None	Inhibiting PS receptors of TAM family: mAbs	Eliminating tolerogenic signals released by apoptotic cells	Prevention of LC3 recruitment
			Inhibiting PS receptors of TAM family: ADCs		
			Inhibiting PS receptors of TAM family: SMIs: crizotinib, BGB324, UNC2025 with OMVs		Blockage of cytokines involved in LAP initiation
			Inhibiting PS: mAbs: bavituximab		
			anti-CD47 antibodies, anti-SIRPα antibodies and 4N1K peptides		

Abbreviation: PS, phosphatidylserine; TAM, Tyro3/Axl/Mer; mAbs, monoclonal antibodies; ADCs, antibody-drug conjugates; SMIs, small molecule inhibitors; OMVs, outer membrane vesicles; LAP, LC3-associated phagocytosis.

A critical next step is the identification of predictive biomarkers to stratify patients. For instance, tumors exhibiting high expression of "don't-eat-me" signals such as CD47 might be primary candidates for blockade strategies, while those with evidence of defective clearance but high "eat-me" signal exposure might benefit from phagocytic enhancement. Furthermore, rational combination therapies must be designed based on mechanistic synergy; for example, coupling efferocytosis inhibitors with immunogenic cell death-inducing agents to convert immunologically silent apoptosis into potent inflammation.

To sum up, the success of this approach hinges on moving beyond the standard narrative to develop and validate testable, integrated models that map decision points and generate explicit hypotheses. This will enable the design of clinical trials that select patients based on biological rationale, transforming a compelling mechanistic target into a viable and precise therapeutic strategy.

7. The function and targeting therapies of efferocytosis in inflammaging

7.1. Possible mechanisms of inflammaging

Inflammaging is a chronic, age-related inflammatory state marked by three key features: reduced resilience to stressors, persistently elevated inflammatory cytokines, and low-grade immune dysfunction [74]. The chronic activation of macrophages serves as a central mechanism through which inflammation spreads and establishes a pervasive state over time. Inflammaging has been closely linked to a spectrum of ARDs. These include cardiovascular and metabolic conditions (e.g., type 2 diabetes mellitus), neurodegenerative disorders (e.g., Alzheimer's disease), specific organ pathologies (e.g., chronic obstructive pulmonary disease, retinal and macular degeneration), and tumor [75]. However, the underlying mechanisms of inflammaging still remain unclear.

The development of inflammaging can be attributed to several complementary theoretical frameworks. Chronic stress activates a maladaptive immune-stress-inflammation network, shifting a protective response into a persistent inflammatory state [76]. Oxidative stress drives inflammaging through reactive oxygen species (ROS)-generated damage and the activation of toll like receptors (TLR) and NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome pathways [77, 78]. According to the cytokine theory, a systemic increase in factors such as IL-6 and tumor necrosis factor-α (TNF-α), derived from both innate and adaptive immune cells, establishes a high background of inflammation in aging [76, 77]. Meanwhile, the autophagy theory attributes inflammaging to the accumulation of cellular debris due to impaired autophagy, which in turn triggers inflammatory signaling [77]. It is acknowledged that these theories contribute to explaining the sterile inflammatory state in inflammaging. However, the detailed mechanistic pathways are not yet

fully defined. Focusing on ARDs, immune cells such as macrophages play a pivotal role in inflammaging environment. Therefore, targeting efferocytosis of macrophages is helpful in treating inflammaging.

Table 3. Clinical framework about macrophage efferocytosis-targeting strategies for tumors.

Key Determinant	Specific Context	Recommended Strategy	Rationale & Key Considerations
Tumor Microenvironment (TME) Composition	Immune-Desert Phenotype	Favor enhancing efferocytosis combined with immunotherapies	In immune-desert tumors, efferocytosis must be redirected from silent clearance to an immunogenic alarm, promoting antigen-presenting cell involvement for T-cell priming. This strategy requires combination with immune-stimulating agents to overcome the inherent barriers of T-cell recruitment and activation
	Immune-Inflamed Phenotype	Favor inhibiting efferocytosis	In immune-inflamed tumors, where active immune infiltration exists, inhibiting efferocytosis can prolong the exposure of apoptotic cells. This increases their progression to secondary necrosis, releasing more DAMPs to amplify inflammatory and immune activation through a positive feedback loop
Dominant Source of Apoptotic Material	Dying Tumor Cells	Favor cautiously enhancing efferocytosis	The goal is to enhance efferocytosis to maximize tumor antigen cross-presentation, thereby eliciting or expanding an anti-tumor immune response. This strategy aims to exploit the "antigen reservoir" generated by treatments such as chemotherapy or radiotherapy
	Infiltrating Lymphocytes	Favor inhibiting efferocytosis	The strategy is to inhibit efferocytosis in order to protect the already infiltrated (albeit potentially dysfunctional) anti-tumor T cells from premature clearance. It is critical for their functional recovery via immunotherapy, as excessive clearance could otherwise exacerbate immunosuppression
Stage of Therapy	Post-Chemotherapy/Radiotherapy	Favor enhancing efferocytosis	This phase produces a large amount of immunogenic cell death, creating a critical window to leverage efferocytosis for antigen presentation. This can convert the localized cytotoxic effect into a broad, systemic immune response, ideally in sequence or combination with immunotherapy
	During Immunotherapy	Strategy depends on TME context and treatment goal: (a) In inflamed TME, consider inhibition to boost inflammation. (b) In desert TME, may require enhancement to initiate immunity, alongside other therapies	Requires a delicate balance. While inhibition may enhance inflammation and synergize with treatment, enhancement could help initiate responses to neoantigens or clear suppressive cells. Dynamic monitoring of immune response is crucial

7.2. The efferocytosis targeting therapies in diseases about inflammaging

Targeting defective efferocytosis presents a promising therapeutic strategy for inflammaging-associated diseases [79]. By restoring efficient apoptotic cell clearance, the interventions aim to break the vicious cycle of chronic inflammation, potentially alleviating conditions like atherosclerosis, arthritis, and metabolic disorders, and so on (Table 4).

7.2.1. Atherosclerosis

Atherosclerosis initiates with endothelial dysfunction, followed by low-density lipoprotein (LDL) infiltration and monocyte recruitment. These monocytes mature into macrophages under the influence of macrophage colony-stimulating factor (M-CSF) and ingest modified lipids to become foam cells. This process ultimately leads to the formation of a necrotic core and a fibrous cap, constituting the advanced atherosclerotic plaque [80, 81]. Substantial evidence indicates that atherosclerosis is linked to the retention of apoptotic cells and insufficient efferocytosis. As atherosclerosis progresses, apoptosis in macrophages becomes more severe, further impairing their ability to clear accumulated apoptotic cells. In advanced stages, efferocytosis is also compromised due to the dysfunction of key receptors mediating the process, such as MerTK, LDL receptor related protein 1 (LRP1), CD36, and scavenger receptor class B type 1 (SR-B1) [73].

Enhancing the efferocytosis of macrophages represents a key strategy to inhibit the progression of

atherosclerosis. Interventions targeting different stages of this process have shown therapeutic potential: (a) Direct targeting of efferocytosis receptors: TIM4 and MerTK are important receptors for "eat-me" signals. Promoting TIM4 function or enhancing MerTK expression and synthesis can effectively improve efferocytosis and limit the formation of the inflammatory necrotic core within plaques [82-84]. (b) Modulation of related signaling pathways: orally administered p38 MAPK inhibitors can restore efferocytosis function in aged individuals [85]. SIRT1 promotes efferocytosis by inducing macrophage autophagy and represents a potential therapeutic target [86]. (c) Blocking inhibitory signals: antibodies targeting the "don't-eat-me" signal CD47 have shown anti-atherosclerotic effects in some studies, although results are conflicting, as its absence may exacerbate lesions by over-activating lymphocytes [87, 88]. Inhibiting CD147 with emmprin improves plaque formation and reduce lipid accumulation [89]. In summary, the multi-targeted regulation of efferocytosis offers several promising novel avenues for the treatment of atherosclerosis.

Table 4. Macrophage efferocytosis-associated therapeutic strategies for inflammaging.

Inflammaging	Targeting macrophage polarization	Targeting key molecules in efferocytosis process			
	Induced M2 polarization	Smelling phase	Eating phase	Digestion phase	
Atherosclerosis	None	None	Promoting TIM-4 expression: orally active p38 inhibitor	Targeting anti-efferocytosis CDs	anti-CD147 antibody: HAb18
			Enhancing MerTK synthesis or blocking its cleavage		anti-CD47 antibody
Type 2 diabetes mellitus	None	None	Enhancing MerTK synthesis or blocking its cleavage	Promoting miR-126: nanoparticles or REDV peptide-modified chitosan containing miR-126	
Osteoarthritis	SIRT1 activator	None	IA injection of Gas6	None	
	Opsonized nanoparticle (IgG/Bb@BRPL)	None			
	Conventional medicines: triamcinolone, dexamethasone, celecoxib	None			
Rheumatoid arthritis	None	Injecting ACs or AC-derived factors: S1P-PS-MMV@SPD		None	

Abbreviation: MerTK, MER proto-oncogene tyrosine kinase; CD, cluster of differentiation; Bb, berberine; Gas6, growth arrest-specific protein 6; IA, intra-articular; AC, apoptotic cell; S1P, sphingosine 1-phosphate; PS, phosphatidylserine; MMV, macrophage membrane-derived vesicle.

7.2.2. Type 2 diabetes mellitus

Type 2 diabetes mellitus, a condition marked by chronic low-grade inflammation, presents a persistent therapeutic challenge due to its requirement for effective anti-inflammatory management. Emerging evidence positions the enhancement of efferocytosis as a promising novel strategy [90]. MiR-126 level was observed suppressed in diabetic mice, resulting in subsequent efferocytosis deficiency [91]. This evidence highlights a promising intervention aimed at restoring efferocytosis: utilizing targeted nanoparticles or REDV peptide-modified chitosan to deliver miR-126 directly to sites of pathological apoptotic accumulation, like diabetic wounds [9]. Targeting efferocytosis may alleviate several diabetic complications. Inhibiting SLC7A11, an amino acid transporter that negatively regulates efferocytosis, improves the capacity of dendritic cells and accelerates diabetic wound healing [92]. As for diabetic microangiopathy, overexpression of miR-126 can rescue impaired efferocytosis, promoting the clearance of apoptotic cardiomyocytes and facilitating the repair of damaged cardiomyocytes [90].

7.2.3. Osteoarthritis

Osteoarthritis is a chronic musculoskeletal disorder strongly associated with advancing age. The understanding of osteoarthritis pathogenesis now extends beyond cartilage to include tissues such as the synovium, bone, and adipose tissue. These act as pro-inflammatory drivers that promote cartilage injury [93, 94]. These findings highlight the influence of inflammaging on both the development and progression of osteoarthritis [95].
In traditional treatment, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are broadly applied in osteoarthritis, which can achieve pain relief but fail to ameliorate joint situation. Targeting efferocytosis and

macrophage polarization represents a promising therapeutic approach for osteoarthritis. Melatonin and the SIRT1 activator SRT2104 could promote M2 macrophage polarization and enhance efferocytosis via the SIRT1 pathway [96, 97]. The opsonized nanoparticles (IgG/Bb@BRPL), mainly consisting of immunoglobulin IgG and anti-inflammatory agent berberine (Bb), are selectively internalized by macrophages, thereby reducing inflammation and cartilage damage [98]. Conventional agents such as triamcinolone, dexamethasone, celecoxib, and metformin also facilitate efferocytosis by shifting macrophages toward the M2 phenotype [99]. It is notable that M1 macrophage in synovium reduces Gas6 release, causing efferocytosis impairment of synovial apoptotic cells and subsequent increased inflammatory factors and immune response. Therefore, intra-articular (IA) injection of Gas6 could be a novel therapy by restoring macrophage efferocytosis and clearing accumulated apoptotic cells in osteoarthritis [100].

7.2.4. Rheumatoid arthritis

Rheumatoid arthritis is a systemic autoimmune disease characterized by synovitis and damage of both cartilage and bone in synovial joints [101]. Clinically, disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and sulfasalazine, form the cornerstone of therapy [102], alongside biologic agents that target inflammatory cytokines such as IL-6 [103]. Augmenting efferocytosis presents a novel therapeutic avenue. One strategy involves administering apoptotic cells or their derivatives; for example, intravenous injection of apoptotic thymocytes or PS-containing liposomes (apoptotic cells-derived factor) can reprogram macrophages, reducing IL-1β and elevating IL-10 to alleviate arthritis [104]. A more advanced approach utilizes engineered efferocytosis-mimicking nanovesicles (EMNVs). One design (S1P-PS-MMV@SPD) incorporates the "find-me" signal S1P and the "eat-me" signal PS on a macrophage membrane vesicle, loaded with the apoptotic metabolite spermidine. These EMNVs home to inflamed joints upon intravenous injection, dampening inflammation and attenuating the progression of rheumatoid arthritis [105].

8. Conclusion and prospect

Efferocytosis is essential for maintaining physiological homeostasis and resolving inflammation. Its dysregulation contributes to the pathogenesis of various diseases, including tumor, atherosclerosis, osteoarthritis, and rheumatoid arthritis. Building upon an understanding of its orchestrated steps, numerous therapeutic strategies targeting efferocytosis have been proposed, with some advancing toward clinical application (Table 2 and Table 4). In tumor, a range of regimens have been developed, primarily focusing on intervening in the "eat-me" signals using mAbs, ADCs, and SMIs. For instance, mAbs against TAM family receptors such as UNC2025 have demonstrated efficacy. For atherosclerosis, anti-CD147 antibodies exhibit potential in attenuating lipid accumulation within plaques. In osteoarthritis, melatonin appears to slow disease progression by activating the SIRT1 pathway, which in turn influences efferocytosis and promotes a shift in macrophage phenotype toward tissue repair. Despite these advances, significant challenges remain. Key mechanisms of efferocytosis remain to be fully elucidated, thereby hindering the rational design of precise therapeutics. For example, while CD47 blockade was expected to alleviate atherosclerosis, CD47 deficiency in mice paradoxically exacerbated tissue damage due to increased lymphocyte activation [88]. Although specialized pro-resolving mediators (SPMs) such as resolvins naturally enhance efferocytosis with a favorable safety profile, their clinical translation has yet to be reported. Therefore, future efforts must focus on elucidating their precise mechanisms and advancing them through clinical trials to validate their therapeutic potential.

To sum up, this study uncovered the crosstalk between inflammaging and tumor and stated the role of efferocytosis in the function of macrophages. Furthermore, the prospective therapies targeting inflammaging and tumor based on efferocytosis have been proposed and concluded (Fig. 5). Age-related decline in macrophage efferocytosis efficiency leads to the accumulation of apoptotic cells, which undergo secondary necrosis. This releases and sustains a low-grade, pro-inflammatory cytokines to induce chronic inflammation. However, long-term chronic inflammation could cause cancerous changes in tissues. Efferocytosis in the tumor microenvironment transfers from a physiological clearance mechanism into a driver of tumor progression. By clearing apoptotic tumor cells, it induces macrophage polarization toward an immunosuppressive M2 phenotype, collectively fostering an environment that suppresses T cell function while leading to tumor progression. In chronic inflammation, targeting efferocytosis therapy are supposed to activate macrophage efferocytosis, thereby accelerating the clearance of apoptotic cells. As for tumors, targeting efferocytosis therapy could promote the anti-tumor immunity by inhibiting macrophage efferocytosis (Fig. 5). Taken together, targeting efferocytosis of macrophages is a promising strategy for the treatments of chronic inflammation-associated diseases including inflammaging and tumor.

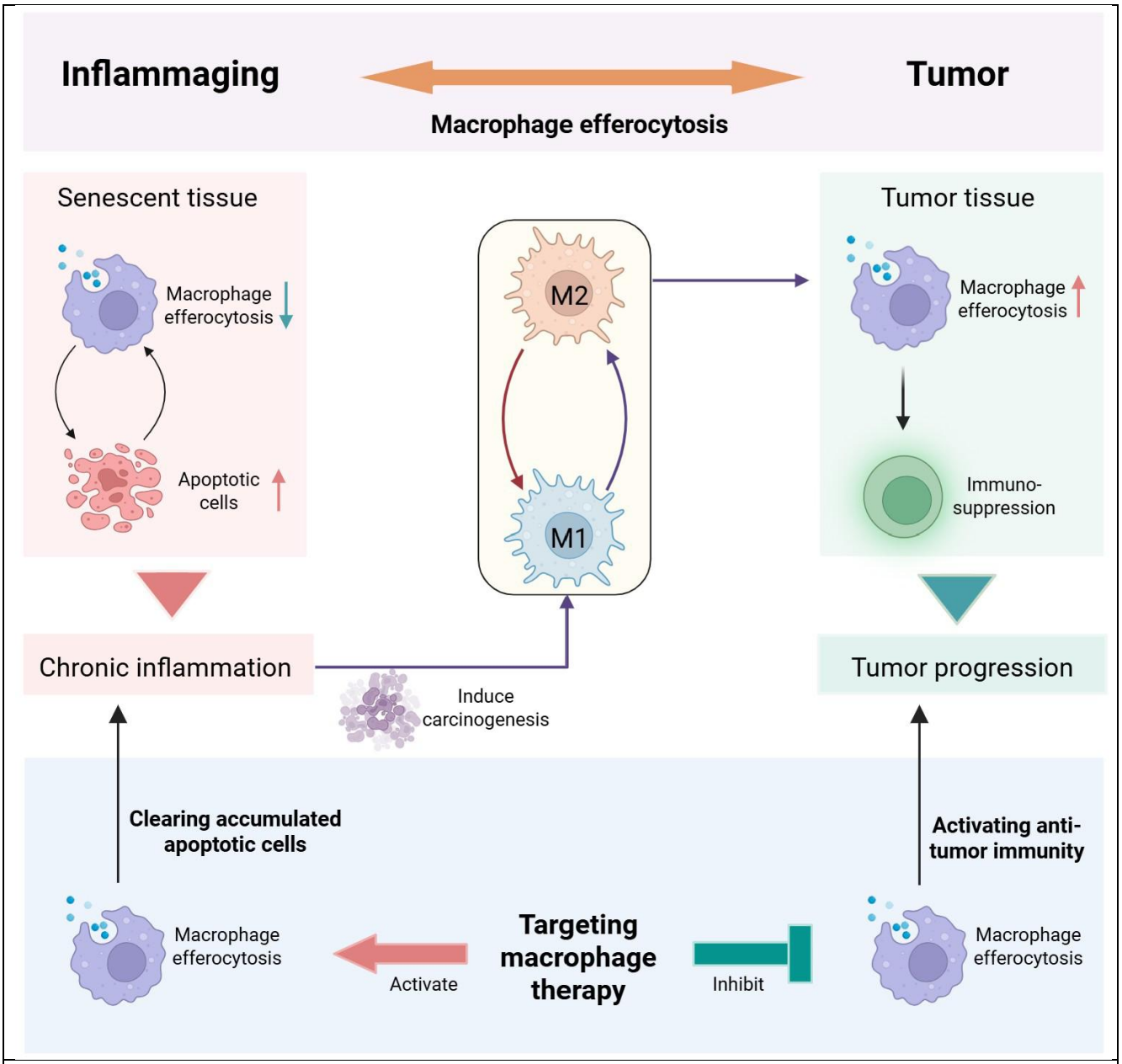

Figure 5. The framework for macrophage efferocytosis in the crosstalk between inflammaging and tumor. Age-related decline in macrophage efferocytosis leads to the accumulation of apoptotic cells, which undergo secondary necrosis and sustain low-grade pro-inflammatory cytokine release, driving chronic inflammation. Prolonged inflammation could promote tissue carcinogenesis. In the tumor microenvironment, efferocytosis shifts from a homeostatic clearance mechanism to a driver of tumor progression. By clearing apoptotic tumor cells, it promotes macrophage polarization toward an immunosuppressive M2 phenotype, collectively suppressing T cell function and accelerating tumor progression. Therefore, therapeutic strategies differ: in chronic inflammation, enhancing efferocytosis could accelerate apoptotic cell clearance, whereas in tumor, inhibiting efferocytosis could restore anti-tumor immunity.

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Author Contribution

Huang X and Qu B: investigation, supervision, writing-original draft. Chen M: investigation, methodology. Zhang W: conceptualization, funding, writing review & editing. All authors have approved the final version of the manuscript.

Competing Interest

The authors have declared no conflict of interest regarding the publication of the manuscript.

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