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Efferocytosis: the art of cellular clearance and novel perspectives in disease therapy

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Abstract

Efferocytosis, the process of apoptotic cell clearance, is a fundamental biological mechanism for maintaining tissue homeostasis. However, its role in disease pathogenesis is often oversimplified, neglecting a critical knowledge gap: how the single process could drive opposing pathological outcomes. This review provides a comprehensive analysis centered on the functional duality of efferocytosis. By synthesizing evidence across a spectrum of human pathologies—from atherosclerosis and neurodegeneration to cancer—we establish a core paradigm: impaired efferocytosis is a central pathogenic driver in chronic inflammatory and autoimmune diseases, leading to unresolved inflammation. Conversely, the hijacking of efferocytosis by tumors fosters an immunosuppressive microenvironment, facilitating immune evasion. This dichotomy presents a significant therapeutic conundrum, as enhancing efferocytosis benefits inflammatory conditions but exacerbates cancer. By dissecting these context-dependent mechanisms, we argue that the future of efferocytosis-based medicine hinges on developing targeted, disease-specific strategies to safely harness this powerful biological process.

Introduction

Programmed cell death (PCD) is a concept proposed by R. A. Lockshin and C. M. Williams in 1965 [1]. It refers to an actively regulated form of cellular demise mediated by a series of molecular pathways, encompassing three major forms of PCD: apoptosis, necroptosis, and pyroptosis, all of which play critical roles in both physiological and pathological processes [2]. The efficient clearance of dead and dying cells is a fundamental process for maintaining homeostasis in multicellular organisms. During mammalian embryonic development, billions of cells are eliminated through programmed death to precisely sculpt tissue architecture and ensure proper organ functionality. Moreover, cell death serves as a vital mechanism for restoring health during disease recovery phases, including tissue injury repair and infection resolution. The disassembly and recycling of cellular components represent conserved hallmarks of all dead cell clearance processes [3].

In 1972, Kerr et al. [4] coined the term "apoptosis". Distinct from necrosis, apoptosis is characterized by cytoplasmic shrinkage, chromatin condensation (pyknosis), nuclear fragmentation (karyorrhexis), and plasma membrane blebbing, ultimately leading to the formation of membrane-bound vesicles, commonly referred to as apoptotic bodies, which are efficiently engulfed by neighboring phagocytes and degraded within lysosomes [5, 6]. Apoptosis and its dysregulation underpin diverse pathophysiological processes, including cellular homeostasis, tissue remodeling, and tumorigenesis. Both apoptotic

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and non-apoptotic dying cells display and release molecular signals that guide phagocytes to coordinate subsequent engulfment and immune responses. Remarkably, although billions of adult cells undergo daily turnover, apoptotic cells (ACs) remain scarce even in tissues with high cellular renewal rates, attesting to the extraordinary efficiency of AC clearance [7]. Efferocytosis [8] refers to the process wherein professional efferocytes (macrophages and dendritic cells) or neighboring non-professional efferocytes (epithelial cells and fibroblasts) eliminate apoptotic cells undergoing PCD. This mechanism involves caspase-mediated packaging of cellular contents into apoptotic bodies, followed by phagocytic processing and recycling, thereby preventing proinflammatory leakage. Professional efferocytes exhibit exceptional capacity for sequential AC uptake, exemplified by tissue-resident macrophages maintaining homeostasis through dual pathogen/AC clearance, while immature dendritic cells initiate adaptive immunity via antigen presentation post-efferocytosis. Microglia, the CNS-resident macrophages, execute non-inflammatory dead cell removal through TAM receptor tyrosine kinase family (Tyro3/Axl/MerTK) signaling activated by Gas6 ligands, a pathway ubiquitously regulating proliferation and metabolism [9]. Non-professional efferocytes, including epithelial cells, fibroblasts, and endothelial cells, contribute to tissue-specific clearance. For instance, epithelial-fibroblast efferocytosis promotes wound healing by debris removal [10]. Specialized efferocytes operate in niche environments: Sertoli cells phagocytose apoptotic germ cells during spermatogenesis, retinal pigment epithelial (RPE) cells clear photoreceptor outer segments, and astrocytes mediate synaptic pruning [11–13]. Efferocytosis critically sustains tissue regeneration and homeostasis, serving dual roles in inflammation resolution [14] and metabolic waste disposal (e.g., lipid-laden debris in adipose tissue) [15]. Notably, this process intersects with pathogen defense mechanisms, countering intracellular infections caused by Mycobacterium tuberculosis (M. tb), Listeria monocytogenes, influenza A virus (IAV), HIV, and Leishmania spp. through shared phagocytic machinery [16]. Defective efferocytosis leads to AC accumulation, secondary necrosis, and tissue damage via inflammatory mediator release. Clinically, impaired efferocytosis in chronic diseases such as atherosclerosis promotes necrotic core expansion, which refers to the progressive accumulation of cellular debris from apoptotic cells that undergo secondary necrosis due to failed clearance, a mechanism substantiated in animal models with low-density lipoprotein receptor deficiencies [17–19].

The critical role of efferocytosis in linking cell death to tissue-level outcomes has recently propelled it to the forefront of biomedical research. Advances in molecular immunology and imaging have revealed that efferocytosis is not merely a passive housekeeping function, but an active and sophisticated signaling hub that dictates the balance between immune tolerance and inflammation. This deeper mechanistic understanding is precisely why it is now recognized as a central player in the pathogenesis of a vast array of human diseases, from cancer to neurodegeneration, making it a highly promising therapeutic target. In light of this growing importance, this review aims to provide a comprehensive overview of the field. We will first elucidate the intricate molecular mechanisms governing efferocytosis, from "Find-Me" and "Eat-Me" signals to the downstream phagocytic machinery. Subsequently, we will explore the pathophysiological implications of dysfunctional efferocytosis across multiple diseases. Finally, we will discuss current and future therapeutic strategies that seek to modulate this fundamental process for clinical benefit.

Molecular mechanisms of efferocytosis

Efferocytosis, the highly specialized process of non-inflammatory clearance of apoptotic cells (ACs), is a fundamental biological program essential for maintaining tissue homeostasis, resolving inflammation, and preventing autoimmunity. Unlike general phagocytosis, which can be a pro-inflammatory event, efferocytosis is an actively regulated, multi-stage cascade characterized by a sequence of precise molecular interactions. This process involves a complex interplay of signals released by dying cells, specialized bridging molecules, and an array of receptors on professional and non-professional efferocytes, all of which culminate in the swift and silent removal of cellular debris. The following sections detail this intricate molecular mechanism, from the initial cellular communication to the final metabolic and immunological feedback loops that define efferocytic function [8].(As summarized in Fig. 1).

The foundational signals of efferocytosis: a hierarchical system of communication

Efficient efferocytosis relies on a sophisticated system of molecular communication between the dying cell and its prospective efferocyte. This communication is governed by three distinct, yet interconnected, classes of signals that together orchestrate the efferocyte's response: "Find-Me" signals that initiate chemotaxis, "Eat-Me" signals that identify the target, and "Don't-Eat-Me" signals that prevent the engulfment of healthy cells. The coordinated action of these cues ensures that only the appropriate targets are cleared.

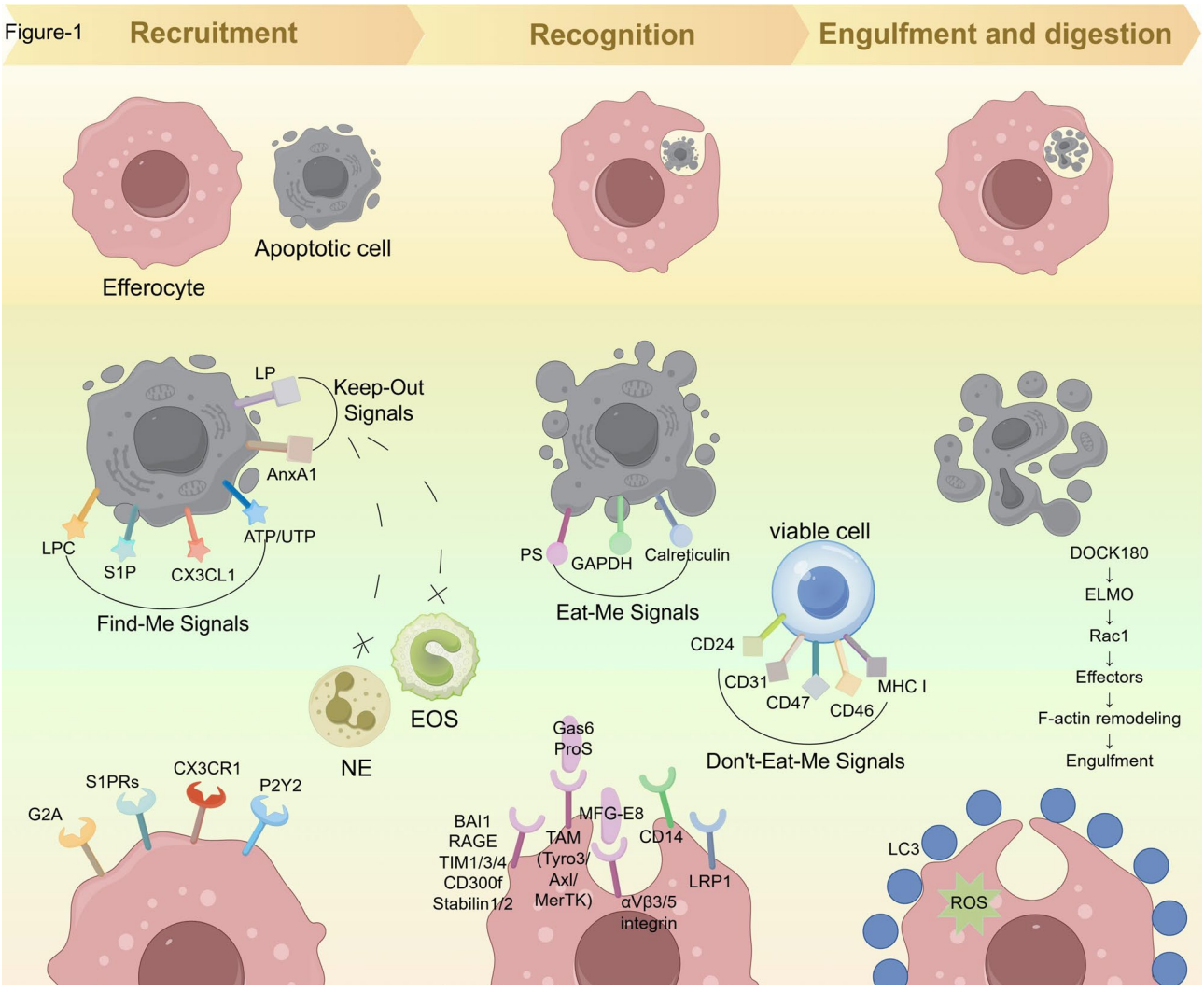

Fig. 1 Biological mechanisms of efferocytosis. The process of efferocytosis can be divided into three key steps: recruitment, recognition, and engulfment and digestion. (1) Recruitment: Apoptotic cells release a series of "Find-Me" signals, including lysophosphatidylcholine (LPC), sphingosine-1-phosphate (S1P), fractalkine (CX3CL1), adenosine triphosphate (ATP), and uridine triphosphate (UTP). These molecules attract efferocytes expressing corresponding receptors such as G2A, S1P receptors (S1PRs), CX3C chemokine receptor 1 (CX3CR1), and P2Y2. Concurrently, "Keep-Out" signals, such as Lactoferrin (LP) and Annexin A1 (AnxA1), are released to prevent the unnecessary accumulation of inflammatory cells like neutrophils (NE) and eosinophils (EOS). (2) Recognition: Efferocytes recognize "Eat-Me" signals exposed on the apoptotic cell surface. These include phosphatidylserine (PS), Glyceraldehyde-3-phosphate Dehydrogenase (GAPDH), and calreticulin. A variety of efferocytic receptors mediate this recognition. Receptors such as brain-specific angiogenesis inhibitor 1 (BAI1), receptor for advanced glycation end products (RAGE), T cell immunoglobulin and mucin domain-containing proteins (TIM1/3/4), CD300f, and Stabilin 1/2 can directly bind to PS. Other interactions are mediated by bridging molecules: Milk fat globule-EGF factor 8 (MFG-E8) bridges PS to αVβ3/5 integrins, while the TAM receptor tyrosine kinases (Tyro3/Axl/MerTK) recognize PS via Growth arrest-specific 6 (Gas6) and Protein S (ProS). Additionally, CD14 recognizes GAPDH, and low-density lipoprotein receptor-related protein 1 (LRP1) recognizes calreticulin. Meanwhile, "Don't-Eat-Me" signals on viable cells, such as CD24, CD31, CD47, CD46, and major histocompatibility complex class I (MHC I), prevent their erroneous engulfment. (3) Engulfment and Digestion: Upon recognition, an intracellular signaling cascade involving dedicator of cytokinesis 180 (DOCK180), engulfment and cell motility 1 (ELMO), and Ras-related C3 botulinum toxin substrate 1 (Rac1) is activated. This leads to F-actin remodeling and the formation of a phagocytic cup, internalizing the apoptotic cell. The subsequent LC3-associated phagocytosis (LAP) is characterized by LC3 recruitment to the phagosome membrane and the generation of reactive oxygen species (ROS), which promotes rapid phagosome maturation and lysosomal fusion, ensuring the silent and efficient clearance of the apoptotic cell

"Find-Me" signals: guiding efferocyte chemotaxis to the target

The first stage of efferocytosis is the directed migration of efferocytes towards the dying cell. This process is orchestrated by chemoattractant molecules known as "Find-Me" signals, which are released in a spatiotemporally coordinated and hierarchical manner, with early, rapid-response cues followed by more sustained, long-range attractants. Crucially, these signals not only guide recruitment but also play a broader role by enhancing

the efferocyte's clearance capacity and promoting anti-inflammatory responses [20, 21].

The immediate "call to action" is often initiated by the release of nucleotides. During apoptosis, caspase-3 and caspase-7 activation triggers the cleavage and opening of pannexin-1 (Panx1) channels, allowing the rapid efflux of adenosine triphosphate (ATP) and uridine triphosphate (UTP) from the dying cell [22]. These nucleotides serve a dual function: they establish an initial, steep concentration gradient that attracts efferocytes by activating P2Y purinergic receptors on their surfaces, and they concurrently enhance efferocyte motility and upregulate the expression of phagocytic receptors to accelerate the clearance process [22]. Simultaneously, the calcium-independent phospholipase A2 (iPLA2) generates the lipid signal lysophosphatidylcholine (LPC), which is exported via the ATP-binding cassette transporter A1 (ABCA1) [23]. LPC is then sensed by the G2A receptor expressed on various efferocytes, including macrophages [24], mast cells [25], dendritic cells [25], neutrophils [26], B lymphocytes [27], and T lymphocytes [28], stimulating their chemotactic migration towards the source [29].

This initial, rapid response is followed by the release of signals that ensure a robust and sustained recruitment. Sphingosine-1-phosphate (S1P), a lipid mediator synthesized by sphingosine kinase 1 (SPHK1), is released from apoptotic cells. It engages with a family of G protein-coupled receptors (S1PR1-5) on efferocytes, which not only directs their migration but also initiates pathways, such as those involving peroxisome proliferator-activated receptor γ (PPARγ), that enhance long-term efferocytic efficiency [30]. Concurrently, the chemokine fractalkine (CX3CL1) is released [31, 32]. This chemokine directs the migration of immune cells expressing the CX3CL1 receptor (CX3CR1). This hierarchical signaling architecture ensures that the initial burst of signals alerts nearby efferocytes, while the subsequent, sustained release of lipids and chemokines provides a persistent guidance cue for broader immune surveillance and debris removal [32–35].

"Eat-Me" signals: the universal and context-specific cues for recognition

Once efferocytes are in close proximity, a second class of molecules, the "Eat-Me" signals, serves to identify the apoptotic cell as a clearance target. These signals form a hierarchical and context-adaptive network, with a primary, universal signal complemented by a range of accessory cues [8].

The central "Eat-Me" signal is phosphatidylserine (PS). In healthy cells, PS is strictly confined to the inner leaflet of the plasma membrane by ATP-dependent phospholipid translocases, known as flippases [36, 37]. During apoptosis, a critical event is the caspase-mediated inactivation of flippases and the simultaneous activation of scramblases, such as XKR8 [36, 37]. This dual action leads to the rapid translocation of PS from the inner to the outer membrane leaflet, where it becomes exposed on the cell surface. This surface-exposed PS is the dominant and conserved signal for phagocytic recognition and clearance [38].

In addition to PS, a number of complementary signals provide a layer of specificity and refinement to the recognition process. Calreticulin, a protein chaperone in the endoplasmic reticulum, translocates to the cell surface of apoptotic cells and binds to and activates the low-density lipoprotein receptor-related protein (LRP) on efferocytes, thus facilitating recognition [39]. Thrombospondin-1 (TSP-1) also promotes the efferocytosis of apoptotic cells by enhancing efferocyte migration and uptake [39]. Furthermore, a specific isoform of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) functions as an "Eat-Me" signal on apoptotic cell surfaces by interacting with the CD14 phagocytic receptor [40]. This context-specificity is crucial in disease; for instance, ATP-binding cassette transporter A1 (ABCA1) and its close homolog ABCA7, both Alzheimer's disease risk genes, can also flip PS to the outer membrane, directly linking this clearance signal to neurodegeneration [41–44]. Similarly, in obesity, mannose-binding lectin (MBL) participates in the efferocytosis of apoptotic adipocytes [45], while miR-33 influences ABCA1 function, illustrating how efferocytic signals can be tailored to specific tissues or disease states [46, 47]. In the context of obesity-related insulin resistance, the scavenger receptors CD36 [48] and SR-A [49] also function as important "Eat-Me" signals.

"Don't-Eat-Me" signals: ensuring homeostatic selectivity

To prevent the erroneous engulfment of healthy cells that may transiently expose PS, a third class of counter-regulatory molecules, "Don't-Eat-Me" signals, must be present. These signals ensure that efferocytosis is a selective process, operating in a delicate balance with the "Eat-Me" cues. The most prominent of these signals is CD47, which is expressed on all healthy cells and binds to the signal regulatory protein α (SIRPα) receptor on efferocytes [50]. A similar interaction occurs between CD24 on healthy cells and Siglec-10 on macrophages [51].

The molecular mechanism of this inhibition is conserved and powerful. Upon ligand-receptor binding, these pathways activate intracellular phosphatases, specifically SHP-1 and SHP-2 [1]. The phosphatases then dephosphorylate myosin II, which is an integral component of the cytoskeletal machinery responsible for phagocytic engulfment. This dephosphorylation event effectively overrides any pro-phagocytic signals, ensuring that even a cell with transient PS exposure will not be engulfed if it also displays these protective

"Don't-Eat-Me" cues [50–55]. This regulatory circuit is a fundamental component of tissue homeostasis. However, it can be hijacked in pathological states like cancer and aging, where senescent cells and tumor cells can overexpress CD47 and CD24 to evade efferocyte-mediated clearance, thereby contributing to disease progression [51, 56, 57]. Other signals, such as CD31 (via homophilic interactions), CD46, and major histocompatibility complex class I molecules (recognized by their cognate receptor LILRB1), also play a similar role in preventing efferocytosis [53–55]. Additionally, lactoferrin and annexin A1 exert potent anti-migratory effects on neutrophils and eosinophils, functioning as Keep-Out signals that restrict their access to apoptotic niches [58–60].

The molecular recognition complex: bridging proteins and efferocytic receptors

The successful recognition of an apoptotic cell is often a multi-component process. A signal on the dying cell's surface must be effectively "handed off" to an efferocytic receptor. This interaction can occur directly or, more commonly, is facilitated by molecular intermediaries known as bridging proteins. These bridges act as molecular adapters, expanding the repertoire of recognition and providing a crucial link between a wide variety of "Eat-Me" signals and their cognate receptors.

The molecular bridges: adapting and facilitating recognition

Bridging molecules are secreted proteins that simultaneously bind to ligands on the apoptotic cell surface and to receptors on the efferocyte. This intermediary role is essential for linking a single "Eat-Me" signal, such as PS, to a diverse array of efferocytic receptors. A prominent example is the secreted protein milk fat globule-epidermal growth factor 8 (MFG-E8), produced by macrophages. It acts as a bridge by recognizing aminophospholipids (including PS) on apoptotic cells [61, 62]. Simultaneously, its arginine-glycine-aspartic acid (RGD) motif is recognized by members of the integrin family, such as αvβ3 and αvβ5, on the efferocyte surface [61, 62]. The homolog of MFG-E8, developmental endothelial locus-1 (DEL-1), functions in a similar manner, binding to PS on apoptotic cells and linking them to integrin αVβ3 on efferocytes [63, 64].

Another crucial family of bridging molecules includes Growth arrest-specific protein 6 (Gas6) and Protein S. These secreted proteins are the primary ligands for the TAM family of receptor tyrosine kinases—Tyro3, Axl, and MerTK [1]. Gas6 enhances the binding of PS to all three TAM receptors [65, 66]. In contrast, Protein S specifically promotes the PS interaction with Tyro3 and MerTK, but not Axl [67]. This distinction highlights the specificity that can be conferred by different bridging molecules. The diversity of molecular bridges is further highlighted by molecules such as C1q, which links apoptotic cells to the scavenger receptor SCARF1 [68]; Tubby and Tubby-like protein 1 (TULP1) and galectin-3, which both engage the central receptor MerTK [69]; and the scavenger receptor CD36, which specifically connects apoptotic neutrophils to macrophages [70].

Efferocytic receptors: sensing the signals

Efferocytes express a diverse array of surface receptors that recognize and bind to efferocytic signals, either directly or indirectly via bridging molecules. These receptors are the transducers of the efferocytic signal, initiating the intracellular cascade that leads to engulfment. The TAM receptor family, including Tyro3, Axl, and MerTK, is a critical class of receptors whose activity is dependent on bridging ligands [65]. Other prominent receptors directly bind to PS without an intermediary, including stabilins (e.g., stabilin-1 and stabilin-2) [71, 72], integrins (e.g., αVβ3 and αVβ5) [61, 62], the T cell immunoglobulin and mucin domain-containing receptors (TIMs, such as TIM1, TIM3, and TIM4) [73–75], and adhesion G protein-coupled receptor B1 (ADGRB1; also known as BAI1) [76]. Other examples include receptors for advanced glycation end products (RAGE) [77] and members of the CD300 family (CD300a, CD300b, and CD300f) [78–80]. While the TAM and TIM families are prominent, other receptors also play vital roles in efferocytosis. For instance, LRP1 recognizes apoptotic cells indirectly via calreticulin [81].

The efferocytic process: from cytoskeletal rearrangement to metabolic reprogramming

Beyond the initial stages of signaling and recognition, efferocytosis proceeds through a highly orchestrated sequence of physical and metabolic events. These downstream processes ensure the efficient internalization of the apoptotic cell and its subsequent degradation, ultimately culminating in a pro-resolving feedback loop that maintains tissue health.

Phagocytic cup formation and engulfment

Once an apoptotic cell has been recognized and bound by phagocytic receptors, an intracellular signaling cascade is activated to initiate engulfment. This process is driven by dynamic cytoskeletal rearrangements that result in the extension of pseudopods, which ultimately surround and internalize the apoptotic cell. A key signaling module involves the phagocytic adaptor protein GULP1 and the guanine nucleotide exchange factor (GEF) complex composed of engulfment and cell motility protein 1 (ELMO1) and dedicator of cytokinesis 1 (DOCK180). This complex is activated upon efferocyte-AC binding and then activates the small GTPase, Ras homolog family small GTPase 1 (Rac1). Rac1 is a master

regulator of actin remodeling, and its activation leads to the polymerization of actin filaments, which provides the mechanical force for the formation of the phagocytic cup and the subsequent internalization of the apoptotic cell [76, 82–84]. The protein thymosin β4 also plays a role in this process by interacting with the cytoplasmic domain of stabilin-2 [84, 85]. Furthermore, AC uptake triggers dynamin-related protein 1 (Drp1)-mediated mitochondrial fission, which increases Ca^{2+} release into the cytoplasm [86]. This, in turn, promotes the production of phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P3) and reactive oxygen species (ROS)—both essential for phagocytosis—thereby inducing phagolysosome assembly and acidification [87].

Phagosome maturation and catabolic degradation

Following engulfment, the newly formed intracellular vesicle containing the apoptotic cell—the phagosome—must mature to become a fully functional digestive organelle, the phagolysosome. This maturation is a stepwise process regulated by a sequential exchange of Rab GTPases. Initially, the small GTPase Rab5 is recruited to the phagosomal membrane. Rab5 mediates the fusion of the phagosome with early endosomes, which is the first step in the catabolic process [88]. Subsequently, Rab5 is replaced by Rab7, a key mediator of late endosomal and lysosomal fusion. This exchange leads to the formation of a highly acidic and enzymatic environment capable of breaking down the apoptotic cell into its constituent macromolecules for recycling [89]. Concurrently, phagosome maturation requires Rab17, which transports ruptured efferocytic cargo to recycling endosomes for subsequent efferocytosis, thereby inhibiting their trafficking to antigen-loading compartments [90]. Additionally, a specialized form of autophagy known as LC3-associated phagocytosis (LAP) accelerates this maturation process, resulting in faster and more efficient degradation of apoptotic cells [87].

The pro-resolving metabolic feedback loop

The efferocytic process does not end with the digestion of the apoptotic cell; rather, it actively drives a crucial pro-resolution feedback loop that maintains tissue homeostasis and prevents inflammation. This mechanism is directly coupled to the metabolic fate of the engulfed cellular debris. As the lipid-rich apoptotic cells are catabolized within the phagolysosome, their degradation products, including fatty acids, are released into the efferocyte's cytoplasm.

These liberated lipids act as ligands for a family of master regulators [91–93]: the nuclear receptors Liver X receptor-α (LXRα) and peroxisome proliferator-activated receptors (PPARγ and PPARδ). The activation of these receptors by efferocytic-derived metabolites triggers a coordinated, dual-pronged response that is central to inflammation resolution. This activation potently stimulates the efferocyte to secrete key anti-inflammatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), which actively suppress the inflammatory cascade and prevent tissue damage caused by secondary necrosis [94]. Simultaneously, LXRα and PPARγ act as transcription factors to bolster the entire efferocytic apparatus, upregulating the synthesis of critical components such as phagocytic receptors (e.g., Tyro3, Axl, and MerTK), bridging molecules (e.g., MFG-E8 and Gas6), and the cytoskeletal regulator Rac1. Thus, this single metabolic trigger orchestrates both the quenching of inflammation and the enhancement of the cell clearance capacity required for sustained tissue homeostasis [95–98].

This positive feedback loop is a core principle of efferocytic function. The act of clearing an apoptotic cell directly leads to a state where the efferocyte is better equipped to clear subsequent cells and simultaneously suppresses the inflammatory response. This self-reinforcing, homeostatic program reveals that efferocytosis is far more than a simple waste disposal mechanism; it is a central, metabolically driven process that actively promotes the resolution of inflammation and prevents the transition to chronic inflammatory disease [91, 94].

Role of efferocytosis in diseases

(The diverse associations between defective efferocytosis and various human diseases discussed in this section are summarized in Table 1).

Cancer

Efferocytosis within the tumor microenvironment (TME) plays a complex, multifaceted role that often promotes tumor progression by fostering an immunosuppressive landscape. While a fundamental homeostatic process, it can be co-opted by malignant cells to facilitate immune evasion and growth, making it a critical area of interest in oncology. The consequences of efferocytosis in cancer are highly context-dependent, varying with tumor type, location, and the specific phagocytic cells involved [99, 100].

Immunosuppressive mechanisms in the tumor microenvironment

In the TME, the substantial burden of apoptotic tumor cells, often resulting from chemotherapy, radiotherapy, or natural turnover, is primarily cleared by tumor-associated macrophages (TAMs). This process, however, triggers a pro-tumorigenic cascade instead of a normal, silent clearance. The ingestion of apoptotic cells activates key transcription factors like PPARγ in TAMs, which promotes fatty acid oxidation and drives their polarization toward an M2-like, immunosuppressive phenotype that

Table 1 Association between defective efferocytosis and various diseases

Disease	Defects in Efferocytosis	Molecules/Receptors	Potential Therapeutic Targets
Cancer			
Various Tumors	Hijacked efferocytosis fosters an immunosuppressive microenvironment, promoting tumor growth and immune evasion.	PPARγ, MerTK, Axl, PD-L1, NLRP3	MerTK inhibitors, CD47 blockade, combination immunotherapies
Cardiovascular Diseases			
Atherosclerosis/MI	Impaired clearance leads to necrotic core formation in plaques; inefficient removal of dead cardiomyocytes post-MI.	MerTK, LRP1, ADAM17	Inhibiting MerTK cleavage, LXR agonists, VEGFA
Neurodegenerative Diseases			
AD, PD, HD, ALS	Failure of "silent" clearance by microglia, leading to chronic neuroinflammation and debris accumulation (e.g., Aβ, α-SYN).	TREM2, TAM family, mHTT, SOD1	TREM2 agonists, modulation of microglial phenotype
Respiratory Diseases			
COPD, Asthma, ARDS	Defective alveolar macrophage function, leading to persistent inflammation, especially in non-eosinophilic asthma.	RhoA, Rac1, S1P	Glucocorticoids, macrolide antibiotics, S1P signaling modulators
Urinary/Reproductive System			
AKI to CKD Transition	Failure to clear massive apoptotic burden in kidneys, driving transition from acute injury to chronic fibrosis.	MerTK, KIM-1/TIM-1	TYRO3 agonists, enhancing local renal clearance capacity
Autoimmune Diseases			
SLE, RA, T1D, SS	Systemic clearance failure exposes autoantigens, breaking self-tolerance and driving chronic inflammation.	TAM family, TIM family, Gas6	Enhancing TAM signaling, glucocorticoids
Aging			
Aging and inflammaging	Progressive decline in macrophage clearance efficiency, contributing to chronic low-grade inflammation.	MerTK, ADAM17, SASP	Resolvin D1, senolytic therapies
Hepatic & Metabolic Diseases			
NAFLD, Obesity	Defective clearance of hepatocytes and adipocytes, leading to lipotoxicity and insulin resistance.	MFG-E8, NLRP3, PPARγ	NLRP3 blockade, PUFA supplementation

Abbreviations: *AD* Alzheimer's disease, *AKI* Acute kidney injury, *ALS* Amyotrophic lateral sclerosis, *Aβ* Amyloid-beta, *CKD* Chronic kidney disease, *COPD* Chronic obstructive pulmonary disease, *HD* Huntington's disease, *KIM-1* Kidney injury molecule-1, *LRP1* LDL receptor-related protein 1, *MerTK* MER tyrosine kinase, *MFG-E8* Milk fat globule-EGF factor 8, *MI* Myocardial infarction, *mHTT* Mutant huntingtin, *NAFLD* Non-alcoholic fatty liver disease, *NLRP3* NOD-like receptor family pyrin domain containing 3, *PD* Parkinson's disease, *PD-L1* Programmed death-ligand 1, *PPARγ* Peroxisome proliferator-activated receptor γ, *PUFA* Polyunsaturated fatty acid, *RA* Rheumatoid arthritis, *SASP* Senescence-associated secretory phenotype, *SLE* Systemic lupus erythematosus, *SOD1* Superoxide dismutase 1, *SS* Sjögren's syndrome, *T1D* Type 1 diabetes, *TAM* Tyro3, Axl, MerTK, *TIM-1* T-cell immunoglobulin and mucin domain-containing 1, *TREM2* Triggering receptor expressed on myeloid cells 2, *VEGFA* Vascular endothelial growth factor A

supports tumor growth [101]. Furthermore, efferocytosis by dendritic cells (DCs) suppresses their maturation and impairs their capacity to process and present tumor antigens, thereby failing to activate an effective anti-tumor T cell response [102, 103]. Preclinical studies have consistently shown that this efferocytosis-driven signaling suppresses T cell expansion and induces a state of functional exhaustion, critically undermining the host's anti-tumor immunity. This immunosuppressive shift is mediated by a complex secretome. The efferocytic clearance of apoptotic neutrophils, for instance, stimulates the secretion of anti-inflammatory cytokines like TGF-β and IL-10, as well as prostaglandin E2 (PGE2), while reducing the release of pro-inflammatory mediators [104, 105]. Paradoxically, in some contexts, efferocytosis can also activate pro-tumorigenic inflammatory pathways. Preclinical models have shown that the engulfment of dying tumor cells can directly activate the NLRP3 inflammasome in efferocytes, leading to IL-1β secretion that promotes tumor growth in vivo [106]. This highlights the dual nature of efferocytosis, where it can either suppress anti-tumor immunity or actively fuel pro-tumor inflammation depending on the context.

Beyond immune cells, other stromal cells in the TME also participate in this process. For example, studies have shown that metabolically reprogrammed, ADAM12-depleted mesenchymal stem cells (MSCs) can enhance macrophage efferocytosis and M2 polarization by overexpressing genes such as Gas6, Lgals3, and Csf1. This MSC-driven process, in turn, induces pathological angiogenesis and further deepens the immunosuppressive state of the TME [107]. (The core immunosuppressive signaling pathways are illustrated in Fig. 2).

Role in specific tumor types

The functional consequences of efferocytosis are highly dependent on the cancer type, with preclinical and clinical data revealing its diverse roles across various malignancies.

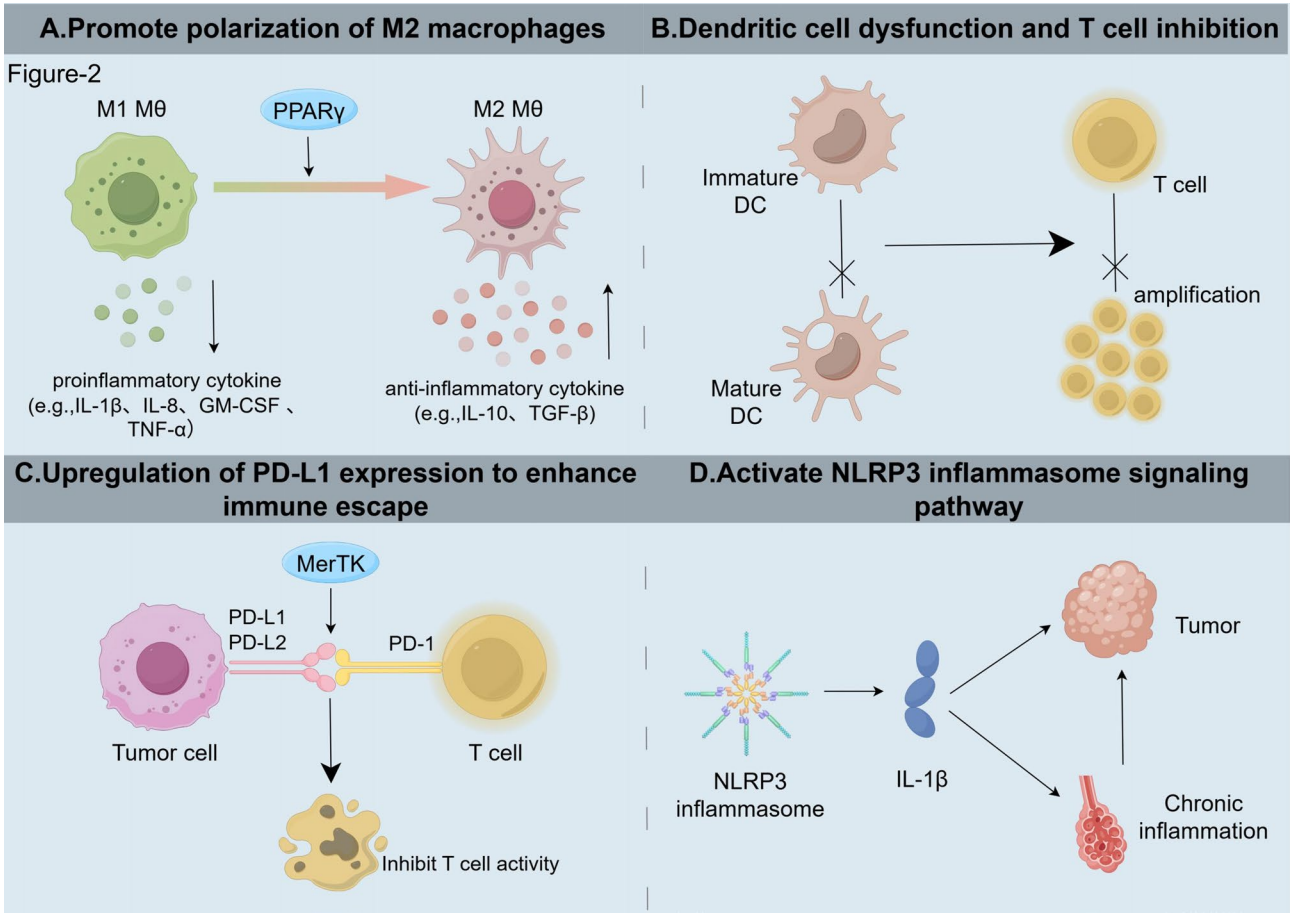

Fig. 2 Immunosuppressive signaling pathways through which efferocytosis promotes tumor progression. **A** Promotes M2 Macrophage Polarization. Efferocytosis activates PPARγ, a key transcription factor for mitochondrial-dependent fatty acid oxidation (FAO), driving tumor-associated macrophages (TAMs) toward an anti-inflammatory, pro-angiogenic M2 phenotype. This process increases the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β while reducing pro-inflammatory cytokines like IL-1β, IL-8, GM-CSF, and TNF-α, thereby creating an immunosuppressive microenvironment conducive to tumor growth. **B** Impairs Dendritic Cell Function and T Cell Activity. Dendritic cells (DCs) that have phagocytosed apoptotic cells fail to mature properly, impairing their ability to stimulate autologous T cell proliferation and hindering effective antigen presentation. Consequently, T cell expansion is suppressed, leading to exhaustion and weakening the body's antitumor immunity. **C** Upregulates PD-L1 Expression to Enhance Immune Evasion. Through MerTK activation, efferocytosis increases the expression of PD-L1 and PD-L2 on cancer cells. These molecules bind to the PD-1 receptor on T cells, inhibiting T cell activity and enabling tumor cells to evade immune recognition and attack. **D** Activates NLRP3 Inflammasome Signaling. In the tumor microenvironment, efferocytosis of dying tumor cells triggers NLRP3-dependent inflammasome signaling, driving IL-1β secretion. This further promotes tumor growth and may induce chronic inflammatory responses that support tumor progression. These four key mechanisms illustrate how efferocytosis reshapes the immunosuppressive tumor microenvironment through multiple pathways, playing a pivotal role in tumor immune evasion and progression

In prostate cancer bone metastasis, efferocytosis displays a striking pro-tumorigenic role. Preclinical research has revealed that when bone marrow macrophages clear apoptotic prostate cancer cells, they do not adopt an anti-inflammatory state. Instead, the process activates STAT3 and stabilizes Hypoxia-Inducible Factor-1α (HIF-1α), leading to the secretion of pro-inflammatory and pro-tumorigenic factors like Macrophage Migration Inhibitory Factor (MIF) and the chemokine CXCL5. This establishes a vicious cycle where cell death actively fuels the growth of surviving cancer cells. Beyond macrophages, efferocytosis by epithelial cells is also critical [108]. Clinical models of prostate regression following androgen deprivation show that massive apoptosis is managed by neighboring epithelial cells, which alter their metabolism and gene expression to support tissue remodeling, a process that can be subverted during the development of castration-resistant disease [109].

In pancreatic ductal adenocarcinoma (PDAC), efferocytosis is a key mechanism facilitating liver metastasis. Preclinical studies show that the colonization of the hepatic metastatic niche is associated with low-grade tissue injury. The subsequent efferocytosis of dead parenchymal cells by macrophages reprograms them toward an immunosuppressive phenotype, which is essential for metastatic outgrowth. Mechanistically, this reprogramming requires the expression of progranulin in macrophages, which controls lysosomal function and leads to

the upregulation of arginase 1, a hallmark of immunosuppressive macrophages [100].

In Acute Myeloid Leukemia (AML), the efferocytosis-related Axl/Gas6 signaling axis is a key driver of malignancy. Clinical data show that high expression of Axl and its ligand Gas6 correlates with poor prognosis in AML patients [110, 111]. Preclinical studies confirm that Gas6-mediated Axl activation promotes oncogenic transformation by engaging downstream PI3K/AKT and MAPK signaling pathways and by interacting with other receptors like FLT3 to accelerate leukemia cell migration and invasion [110, 112].

Table 2 Functional roles of efferocytosis-related pathways in specific cancers

Cancer Type	Key Molecule/ Pathway	Pro-Tumorigenic Role/Consequence	References
Prostate Cancer (Bone Metastasis)	STAT3/HIF-1α activation	Induces secretion of pro-tumorigenic factors (e.g., MIF, CXCL5), creating a cycle where cell death fuels tumor growth.	[108]
Pancreatic Cancer (PDAC)	Progranulin in macrophages	Reprograms macrophages toward an immunosuppressive phenotype, which is essential for metastatic outgrowth in the liver.	[100]
Acute Myeloid Leukemia (AML)	Axl/Gas6 signaling axis	Drives oncogenic transformation and accelerates leukemia cell migration and invasion via PI3K/AKT and MAPK pathways.	[110–112]
Osteosarcoma	MerTK	Enhances PD-L1 expression on tumor cells, directly linking efferocytosis to an immune checkpoint pathway and promoting immune escape.	[103]
Renal Cell Carcinoma	TIMD4	Acts as a prognostic risk factor; its silencing inhibits cancer cell proliferation and invasion in preclinical models.	[99]
Breast Cancer	Thymosin α–1	Reverses M2 polarization of tumor-associated macrophages (TAMs) during efferocytosis, enhancing chemotherapy efficacy.	[113]

AML Acute Myeloid Leukemia, *Gas6* Growth arrest-specific 6, *HIF-1α* Hypoxia-Inducible Factor-1α, *MerTK* Tyrosine-protein kinase Mer, *MIF* Macrophage Migration Inhibitory Factor, *PDAC* Pancreatic ductal adenocarcinoma, *PD-L1* Programmed death-ligand 1, *STAT3* Signal transducer and activator of transcription 3, *TIMD4* T-cell immunoglobulin and mucin domain-containing 4, *TAMs* Tumor-Associated Macrophages

In preclinical models of osteosarcoma, MerTK-mediated efferocytosis was found to directly enhance PD-L1 expression on tumor cells. This provides a direct link between the clearance of apoptotic cells and the activation of an immune checkpoint pathway, contributing to immune escape and tumor progression [103].

In renal cell carcinoma, the efferocytosis core gene TIMD4 has been identified as a prognostic risk factor. Preclinical in vitro and in vivo experiments have confirmed that silencing TIMD4 can effectively inhibit the proliferation and invasion of renal cancer cells, highlighting it as a potential therapeutic target [99].

In a preclinical breast cancer model, the immunomodulator Thymosin α–1 was shown to reverse the M2 polarization of TAMs that occurs during efferocytosis, thereby enhancing the efficacy of chemotherapy. This demonstrates that the pathological consequences of efferocytosis in the TME can be therapeutically reversed [113]. (Table 2 provides a summary of the key pro-tumorigenic mechanisms driven by efferocytosis-related pathways in the cancers discussed).

Cardiovascular diseases

In the pathogenesis of atherosclerosis, dysfunctional efferocytosis is a central driver of plaque progression, necrotic core formation, and clinical instability [114].

Vascular wall macrophages and foam cell formation

In the early stages of atherosclerosis, monocytes are recruited to the arterial intima, where they differentiate into macrophages. These macrophages avidly engulf modified lipoproteins, transforming into lipid-laden "foam cells," a histological hallmark of the disease. As the lesion progresses, these foam cells, along with vascular smooth muscle cells, undergo apoptosis [115]. While initially cleared efficiently, the efferocytic capacity of macrophages becomes severely overwhelmed and impaired in advanced plaques. This defect leads to the accumulation of uncleared apoptotic cells, which undergo secondary necrosis, releasing their pro-inflammatory and thrombogenic contents and driving the formation of the unstable necrotic core that precedes plaque rupture [116–118].

The critical roles of MerTK and LRP1 in plaque formation

This pathological clearance deficit is underpinned by the dysfunction of a network of key phagocytic receptors on macrophages, with a convergence of preclinical and clinical evidence highlighting the central roles of MerTK and LRP1. The impairment of these receptors creates a "clearance crisis" that directly fuels plaque instability.

MerTK, a primary efferocytosis receptor, is crucial for maintaining plaque homeostasis, but its function is progressively compromised within the inflammatory milieu of the lesion. Preclinical studies in atheroprone mouse

models, such as Ldlr-/- mice transplanted with Mertk-/- bone marrow, have definitively shown that loss of myeloid MerTK function leads to larger necrotic cores and an accumulation of uncleared apoptotic cells. This dysfunction is actively driven by the plaque environment itself; pro-inflammatory stimuli promote the proteolytic cleavage of MerTK by metalloproteinases like ADAM17, generating a soluble decoy receptor that further cripples the clearance machinery [119]. This process is tightly linked to anti-inflammatory signaling, as efficient efferocytosis via MerTK upregulates IL-10 production, a response often mediated by the activation of PPARγ and LXRα [120]. Furthermore, the synthesis of putrescine via ornithine decarboxylase (ODC) also promotes IL-10 expression through the MerTK-MAPK ERK1/2 pathway, highlighting a metabolic link to inflammation resolution [121]. In addition, efferocytosis induces PGE2 production via the CD36/ERK/COX2 pathway, which in turn promotes TGF-β synthesis, further contributing to the resolution of atherosclerotic lesions [122].

Compounding this issue is the impairment of another critical phagocytic receptor, the Low-Density Lipoprotein Receptor-Related Protein 1 (LRP1). Preclinical studies using myeloid-specific LRP1 knockout mice have demonstrated that its deficiency similarly increases plaque size, macrophage apoptosis, and necrotic core formation by disrupting efferocytosis and downregulating essential cell survival signals. Other metabolic regulators are also involved; for example, myeloid cell-specific deletion of the enzyme PKM2 was found to enhance macrophage efferocytosis and facilitate the regression of aortic lesions [123]. Together, the synergistic failure of these clearance pathways transforms the plaque into a site of unresolved inflammation [124]. In stark contrast to its detrimental role when dysfunctional in chronic atherosclerosis, efferocytosis plays an acute, protective role in the context of myocardial infarction (MI). Following an ischemic event, the rapid and efficient MerTK-dependent clearance of apoptotic cardiomyocytes by macrophages is essential for resolving inflammation and promoting cardiac repair [125–128], partly by increasing the secretion of pro-angiogenic factors like VEGFA to improve functional recovery post-MI [125, 126].

Neurodegenerative diseases

The central nervous system (CNS) is an immune-privileged environment where homeostasis is critically dependent on non-inflammatory, or "silent," immune surveillance to prevent neuronal damage. This task is primarily performed by microglia, the resident macrophages of the CNS. Through efferocytosis, microglia clear apoptotic neurons, cellular debris, and dysfunctional synapses. A failure in this silent clearance mechanism leads to chronic neuroinflammation, a pathological hallmark of many neurodegenerative diseases [129, 130].

Alzheimer's disease: microglia, TREM2, and Aβ clearance

In Alzheimer's Disease (AD), the function of microglial efferocytosis is central to disease progression. The strong genetic link between rare, loss-of-function variants in the Triggering Receptor Expressed on Myeloid cells 2 (TREM2) gene and a significantly increased risk of AD provides conclusive evidence that the immune response actively contributes to pathogenesis [131, 132]. TREM2 is a key microglial receptor that recognizes lipids on apoptotic neurons and damaged myelin, enabling microglia to form a protective barrier around amyloid-beta (Aβ) plaques. Consequently, preclinical studies in AD mouse models confirm that loss of TREM2 function impairs this critical barrier, leading to a cascade of pathological events: it not only hinders the clearance of myelin debris but also disrupts microglial cholesterol metabolism. This dual defect results in reduced Aβ plaque compaction, ultimately causing more severe axonal and neuronal damage in the surrounding tissue [133–135].

Alongside TREM2, the TAM family of receptors, particularly MerTK and Axl, constitutes another essential system for the microglial response to AD pathology. Preclinical studies in AD mouse models show that MerTK and Axl expression is specifically induced in microglia that are physically associated with Aβ plaques. Genetic ablation of both MerTK and Axl in these models renders microglia unable to properly detect, organize, or phagocytose Aβ plaques, demonstrating that the TAM system is an indispensable mediator of this response. While MerTK is also involved in the immunologically silent clearance of protein aggregates like α-synuclein in other neurodegenerative diseases, its role in AD is complex. Intriguingly, preclinical evidence suggests that TAM-driven microglial phagocytosis of Aβ promotes the compaction of diffuse amyloid into dense-core plaques. This suggests a potential protective mechanism where microglia, via MerTK and Axl, sequester neurotoxic Aβ species into less harmful, inert deposits. Together, these findings indicate that both the TREM2 and TAM receptor systems are critical for orchestrating the "silent" microglial clearance programs necessary to contain AD pathology [136].

Interestingly, the process of synaptic pruning during brain development is guided by the same classes of signals used for apoptotic cell clearance, including fractalkine (CX3CL1), PS, C1q, and CD47. This suggests that dysfunction in microglial synaptic efferocytosis may lead to abnormal elimination of healthy synapses or failure to clear dysfunctional ones, contributing to the synaptic loss seen in early AD [137–139]. Furthermore, human genetics studies have solidified this link, showing that

AD risk-increasing variants are often loss-of-function in genes promoting efferocytosis (e.g., TREM2 R47H), while risk-lowering variants can be gain-of-function in such genes (e.g., PLCG2 P522R), directly implicating the efficiency of microglial clearance in AD susceptibility [140].

Roles in Parkinson's, Huntington's, and amyotrophic lateral sclerosis

Dysfunctional efferocytosis is also implicated in other neurodegenerative disorders.

Parkinson's disease (PD), the second most common age-related neurodegenerative disease after AD, involves the conversion of monomeric α-synuclein (α-SYN) into mature amyloid fibrils, driving continuous microglial polarization toward a proinflammatory phenotype and altering microglial efferocytosis [141]. Consequently, α-SYN mutations can disrupt microglial phenotypes and lead to abnormal phagocytic function.

Huntington's disease (HD), a rare late-onset neurodegenerative disorder, is caused by autosomal dominant CAG trinucleotide repeat expansions in the huntingtin (HTT) gene, leading to cognitive and motor impairments [142]. CD206, TGF-β, Arg1, VEGF, and Ym1—common markers of M2-like microglia typically involved in efferocytosis of dying cells—can rescue neurons expressing mutant huntingtin (mHTT) [143]. However, studies report coexistence of TGF-β and VEGF with M1 markers in brain tissues of HD patients, suggesting either reduced numbers of phagocytic microglia or phagocytic dysfunction induced by mHTT expression in microglia within HD patient brain tissues [144, 145].

Amyotrophic lateral sclerosis (ALS), the most common fatal neurodegenerative disorder of the adult motor system and the third most prevalent neurodegenerative disease, is characterized by rapidly progressive paralysis and death from respiratory failure within 2–3 years of symptom onset [146]. Autopsy analyses of ALS cases reveal increased macrophage numbers in motor neuron-depleted regions and activated microglia clustering around damaged motor neurons. While microglia can sense disruptions in the brain and spinal cord and respond via phagocytosis, the efferocytosis process in the ALS spinal cord may be impaired, with non-apoptotic and apoptotic motor neurons potentially targeted by microglia [147–149]. Findings also indicate that M2 microglia exhibit neuroprotective effects by producing neurotrophic factors—glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF)—but shift to a neurotoxic M1 phenotype in the presence of pathological Cu/Zn superoxide dismutase 1 (SOD1) aggregates [150]. (Fig. 3 provides a schematic overview of the shared and disease-specific mechanisms underlying defective efferocytosis in these neurodegenerative conditions).

Respiratory diseases

In the lungs, alveolar macrophages are the primary guardians of homeostasis. Defective efferocytosis is a key contributor to the persistent inflammation seen in several chronic respiratory conditions [151].

Clearance defects in COPD and asthma

In Chronic Obstructive Pulmonary Disease (COPD), particularly in patients with a history of smoking, the efferocytic function of alveolar macrophages is significantly impaired. This defect is considered a primary reason for the accumulation of apoptotic cells, sustained inflammation, and progressive tissue destruction [152]. Preclinical models show that cigarette smoke exposure directly inhibits macrophage function by disrupting the balance of cytoskeletal regulators like RhoA and Rac1 [153–155].

In asthma, efferocytosis impairment appears to be specific to certain disease subtypes. Clinical studies comparing patient samples have found that macrophages from individuals with non-eosinophilic asthma exhibit a significantly reduced capacity to clear apoptotic epithelial cells compared to those with eosinophilic asthma [156, 157]. This finding provides a mechanistic explanation for the persistent airway neutrophilia and relative corticosteroid insensitivity that characterize this asthma subtype.

Acute respiratory distress syndrome (ARDS) and pulmonary fibrosis

In Acute Respiratory Distress Syndrome (ARDS), a condition involving widespread lung inflammation and cell death, the efferocytic system can be completely overwhelmed [158]. In severe viral infections like COVID-19, the massive number of apoptotic cells, combined with a direct impairment of macrophage function by the pathogen and associated cytokine storm, leads to clearance failure. Mechanistically, SARS-CoV-2 infection is thought to impair efferocytosis by disrupting the release of S1P, a key mediator, and by promoting IL-6 secretion, which induces further lymphocyte apoptosis, thus creating a vicious cycle of apoptotic cell overload and clearance deficiency [159, 160]. This results in secondary necrosis, the release of DAMPs, and a feed-forward loop of hyperinflammation [161–163]. When this acute inflammation fails to resolve, it can transition to idiopathic pulmonary fibrosis, a chronic condition where defective efferocytosis, driven in part by impaired MerTK signaling, contributes to persistent inflammation and scarring [164, 165].

Urinary/reproductive system

Efferocytosis is an essential process for maintaining tissue integrity and immune privilege across the urinary and reproductive systems. Its efficiency is a critical determinant of outcomes ranging from normal organ function to the progression of acute and chronic diseases.

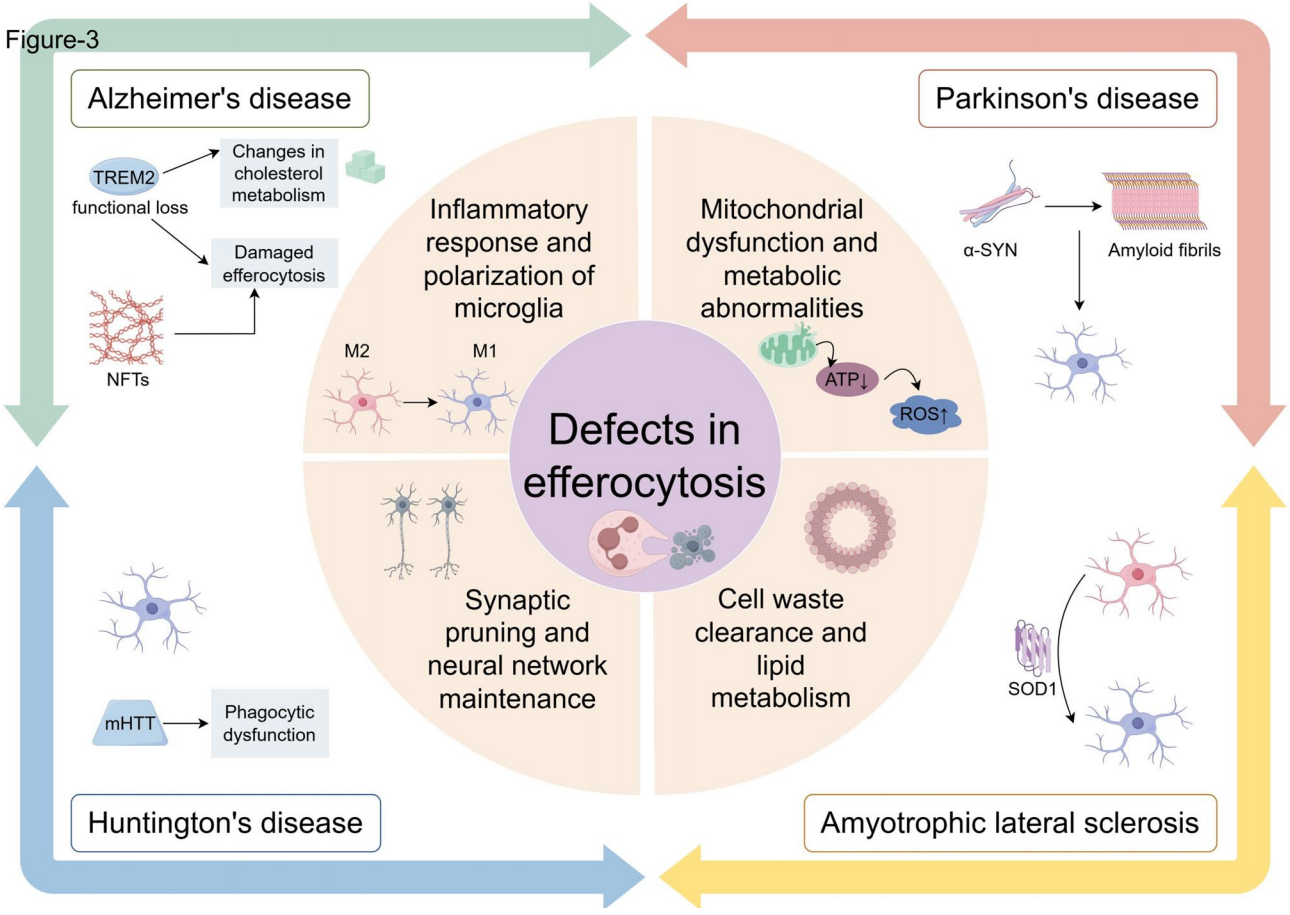

Fig. 3 Shared mechanisms and disease-specific pathways of neurodegenerative diseases caused by defective efferocytosis. The central circle, composed of four sectors, illustrates the shared mechanisms by which defective efferocytosis contributes to neurodegenerative diseases, encompassing four key aspects: Top-left: Inflammatory Response and Microglial Polarization. When efferocytosis is impaired, macrophages exhibit reduced differentiation into anti-inflammatory M2 phenotypes and increased pro-inflammatory M1 polarization. This leads to the accumulation of uncleared injured neurons and apoptotic debris, fostering a chronic inflammatory microenvironment that exacerbates neurodegeneration. Top-right: Mitochondrial Dysfunction and Metabolic Abnormalities. Mitochondrial dynamics are closely linked to immunometabolism and efferocytosis, influencing neuronal energy metabolism and survival. Mitochondrial dysfunction reduces intracellular ATP levels and increases reactive oxygen species (ROS), further aggravating neuronal damage. Bottom-left: Synaptic Pruning and Neural Network Maintenance. Proper synaptic pruning is essential for maintaining healthy brain connectivity. Microglia-mediated efferocytosis includes critical synaptic pruning functions. Dysfunctional synaptic efferocytosis may result in either excessive elimination of healthy synapses or failure to clear aged/unnecessary synapses, ultimately leading to synaptic loss and altered neural circuitry. Bottom-right: Cellular Waste Clearance and Lipid Metabolism. Defective efferocytosis causes excessive fatty acid accumulation, triggering oxidative stress and lipid peroxidation, which contribute to cell death/apoptosis, inflammation, and lipotoxic damage. Efferocytosis plays a particularly vital role in clearing myelin debris and cholesterol-rich cellular remnants. Surrounding the central circle are four neurodegenerative diseases, each with distinct mechanisms: Alzheimer's Disease (Top-left, green sector): Loss-of-function mutations in TREM2 impair its binding to phosphatidylserine (PS) on apoptotic cells, disrupting efferocytosis of myelin debris and altering microglial cholesterol metabolism. This reduces plaque compaction and increases peri-plaque neuronal damage, accelerating AD progression. Additionally, Aβ plaques and tau neurofibrillary tangles hinder efferocytosis efficiency, further compromising microglial function. Parkinson's Disease (Top-right, red sector): Conversion of α-synuclein (α-SYN) monomers into mature amyloid fibrils drives microglial polarization toward the pro-inflammatory M1 phenotype, diminishing their efferocytic capacity. This exacerbates neuroinflammation and neuronal death. Huntington's Disease (Bottom-left, blue sector): In HD patient brains, co-expression of TGF-β and VEGF with M1 markers suggests reduced phagocytic microglia or phagocytic dysfunction caused by mutant huntingtin (mHTT). Amyotrophic Lateral Sclerosis (Bottom-right, yellow sector): Under pathological conditions (e.g., Cu/Zn superoxide dismutase 1 (SOD1) aggregates), M2 microglia shift toward a neurotoxic M1 phenotype, weakening neuroprotection and promoting neuroinflammation and neuronal loss

The essential role in renal homeostasis and acute kidney injury (AKI)

In the healthy adult kidney, a quiescent organ with low cell turnover, a basal level of apoptosis occurs to remove senescent or damaged cells. This clearance is performed silently and efficiently by two main cell types: kidney-resident macrophages (KTRMs), which are strategically positioned to survey the renal interstitium, and proximal tubule epithelial cells (PTECs), which act as non-professional efferocytes for their immediate neighbors. This homeostatic process, which relies on receptors

like MerTK, prevents the release of immunogenic intracellular contents and maintains renal immune tolerance [166, 167].

In Acute Kidney Injury (AKI), which can be caused by insults like ischemia-reperfusion or nephrotoxins, the pathology is characterized by massive and rapid apoptosis of tubular epithelial cells [168]. This sudden apoptotic burden overwhelms the kidney's baseline clearance capacity. The renal immune response involves an initial influx of pro-inflammatory (M1-like) macrophages to clear necrotic debris. However, the key to successful recovery lies in the subsequent transition of these macrophages to an anti-inflammatory, pro-repair (M2-like) phenotype. This crucial switch is driven by efferocytosis [169]. Preclinical studies in mouse models of nephritis have demonstrated that genetic deletion of MerTK leads to a dramatic exacerbation of kidney damage, with increased apoptotic cell accumulation and uncontrolled inflammation, confirming its critical protective role [170–172]. Concurrently, surviving PTECs upregulate Kidney Injury Molecule-1 (KIM-1/TIM-1), a receptor for phosphatidylserine, transforming them into highly efficient efferocytes that are essential for limiting local inflammation and preventing tubular obstruction [173].

From AKI to chronic kidney disease (CKD): the consequence of clearance failure

If the apoptotic load in severe AKI surpasses the kidney's enhanced clearance capacity, efferocytosis fails. This is a critical tipping point in the transition from AKI to Chronic Kidney Disease (CKD) [168, 174]. Uncleared apoptotic cells undergo secondary necrosis, releasing DAMPs that transform a resolving acute inflammation into a self-perpetuating chronic inflammatory state. This environment is a primary driver of renal fibrosis, promoting the activation of myofibroblasts and the excessive deposition of extracellular matrix, mediated by pro-fibrotic cytokines like TGF-β [175–178]. In established CKD, such as diabetic kidney disease, macrophage efferocytosis is also found to be intrinsically defective, creating a vicious cycle of impaired clearance, chronic inflammation, and progressive fibrosis [179, 180].

Autoimmune diseases

Patients with autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 diabetes (T1D), and multiple sclerosis (MS) [181], exhibit elevated levels of apoptotic cells. This accumulation is partly attributable to increased apoptosis in tissue-resident or immune cells, such as glomerular cells, epidermal keratinocytes, and T cells [182]. Defective efferocytosis delays the clearance of apoptotic cells, which may undergo secondary necrosis, releasing intracellular contents that stimulate inflammatory and immunogenic responses and potentially contribute to the initiation or exacerbation of autoimmunity [183].

Animal studies further support a causal role for efferocytosis defects in autoimmune pathogenesis. TAM triple-knockout mice (MerTK^-/-, Axl^-/-, Tyro3^-/-) develop an SLE-like multi-autoimmune syndrome, characterized by elevated autoantibody titers, uncontrolled B and T cell proliferation, and lymphocyte accumulation [184]. Similarly, loss-of-function models of TIM4 [185], TIM-1 [186], SCARF1 [68], and CD300f [80] exhibit SLE-like phenotypes, underscoring the critical role of apoptotic cell clearance in maintaining self-tolerance.

In RA, inflammatory lesions are enriched with uncleared apoptotic cells, highlighting a link between impaired efferocytosis and disease pathology. In murine models, deficiency of Axl and MerTK exacerbates arthritis, whereas overexpression of their ligands, Protein S (ProS1) and Gas6, mitigates disease severity via receptor activation [187].

Type 1 diabetes, a T cell–mediated autoimmune disorder characterized by insulin deficiency and hyperglycemia, involves inefficient clearance of apoptotic pancreatic cells, which may exacerbate inflammation and necrosis, accelerating the release of autoantigens [170]. Impaired efferocytosis also contributes to delayed wound healing in T1D patients, as apoptotic cell accumulation at injury sites sustains inflammation and hinders tissue repair [188].

Sjögren's syndrome (SS), a chronic autoimmune disease presenting with xerostomia and keratoconjunctivitis sicca, is similarly associated with apoptotic cell accumulation and a type I interferon signature in both patients and animal models. Defective TAM-mediated efferocytosis and impaired suppression of interferon responses have been reported in SS [189]. Clinically, plasma Gas6 concentrations are reduced in SS patients, suggesting Gas6 as a potential independent risk factor [190], and decreased Tyro3 and Axl expression has also been observed, indicating that impaired apoptotic cell clearance may influence disease activity and inflammation [191].

Aging and inflammaging

The aging process is characterized by a chronic, low-grade, sterile inflammation termed "inflammaging," which is driven, in large part, by a progressive decline in efferocytosis efficiency [192].

Age-associated decline in clearance efficiency and MerTK cleavage

With age, macrophages exhibit reduced efferocytic capacity. A key molecular mechanism identified in preclinical models is the increased proteolytic cleavage of the MerTK receptor by metalloproteinases like ADAM17.

This shedding process, which generates a non-functional soluble receptor, is exacerbated by the pro-inflammatory environment created by senescent cells [193].

The impact of cellular senescence and the SASP

Cellular senescence, a state of irreversible growth arrest, contributes to this decline. Senescent cells accumulate with age and actively resist clearance by upregulating "Don't-Eat-Me" signals like CD47. Furthermore, they release a complex mixture of pro-inflammatory factors known as the Senescence-Associated Secretory Phenotype (SASP) [194]. The SASP not only promotes a chronic inflammatory state but also directly impairs the function of neighboring macrophages, further suppressing their ability to clear apoptotic cells and creating a vicious cycle that fuels inflammaging [56]. Beyond receptor shedding, aging also impacts intracellular machinery and other immune cells. For instance, aging reduces the activity of dynamin-related protein 1 (Drp1), disrupting mitochondrial fission and impairing the macrophage's ability to perform continuous efferocytosis [195]. Aged macrophages also exhibit reduced expression of the transcription factor Klf4 [196]. In neutrophils, aging impairs their chemotaxis and migration, partly due to sustained activation of the PI3K pathway, further compromising the overall efficiency of the inflammatory response and clearance process [197, 198].

Hepatic and other metabolic diseases

Defects in efferocytosis may contribute to several liver diseases, including alcoholic liver disease, fatty liver, and primary biliary cholangitis [3, 199, 200]. In patients with alcoholic liver disease, alcohol and its metabolites increase liver inflammation and steatosis [199]. Research [200] has shown that alcohol inhibits MFG-E8 gene expression and impairs efferocytosis, leading to hepatocyte necrosis. During apoptotic cell efferocytosis, efferocytes enhance cholesterol efflux activity to maintain lipid homeostasis. Engagement of PS receptors activates PPARγ/δ and LXR, regulators of cellular lipid homeostasis, and upregulates phagocytic receptors such as the TAM family to accommodate phagocytosis-induced cholesterol increases [91, 201]. Excessive fatty acid accumulation due to efferocytosis defects triggers oxidative stress and lipid peroxidation, resulting in hepatocyte death/apoptosis, inflammation, hepatic steatosis, and even lipotoxic hepatocyte injury. Gas6 and MerTK protect primary mouse hepatocytes in culture from lipotoxicity via protein kinase B (AKT)/signal transducer and activator of transcription 3 (STAT3) signaling [202]. Enhanced oxidative stress responses and ROS expression in fatty liver tissue exacerbate non-alcoholic fatty liver disease (NAFLD) [203]. MerTK protects primary macrophages from oxidative stress-induced apoptosis [204]. Significantly upregulated NLR family, pyrin domain-containing 3 (NLRP3) inflammasomes greatly exacerbate NAFLD [205].

Defective efferocytosis in the adipose tissue of individuals with obesity underpins the chronic, low-grade inflammation and insulin resistance characteristic of the disorder. This failure to clear dead adipocytes is not just a consequence but a driver of pathology. Mechanistically, a key defect observed in obese mouse models is an altered macrophage membrane composition—specifically, an increased ratio of saturated to unsaturated fatty acids. This lipid imbalance directly impairs the efferocytic process, a defect that can be rectified by supplementation with polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) [206].

Applications of efferocytosis in disease treatment

The modulation of efferocytosis, the process of apoptotic cell clearance, offers a powerful therapeutic paradigm for a wide spectrum of conditions, ranging from inflammatory diseases to malignant tumors. Core strategies can be categorized into enhancing endogenous clearance functions, blocking inhibitory signaling pathways, and leveraging the effects of existing drugs. However, the dual role of efferocytosis in both maintaining tissue homeostasis and potentially promoting tumor immune evasion necessitates that all therapeutic interventions be based on a profound understanding of the disease context to achieve precise regulation [10].

Enhancing cellular clearance functions

This approach aims to augment the intrinsic capacity of efferocytes to clear apoptotic cells, representing a highly promising therapeutic direction for diseases driven by unresolved inflammation or the accumulation of apoptotic cells, such as atherosclerosis, acute kidney injury (AKI), autoimmune disorders, and neurodegenerative diseases. (An overview of diseases caused by impaired efferocytosis and their corresponding therapeutic strategies, organized by physiological system, is presented in Fig. 4).

Targeting TAM receptors and associated pathways

The TAM (Tyro3, Axl, MerTK) family of receptor tyrosine kinases is critical regulators of the "silent" clearance of cells [207, 208]. Preclinical studies have demonstrated that a selective TYRO3 agonist confers renal protection by attenuating podocyte injury [209]. In hepatic diseases, administration of the TAM ligand Gas6 can protect against fulminant hepatic failure [210], while MerTK + macrophages have been identified as a liver-protective population capable of suppressing tissue-destructive reactions post-injury [211]. Galectin-3 has also been shown to promote efferocytosis via MerTK [212]. In the

Figure-4

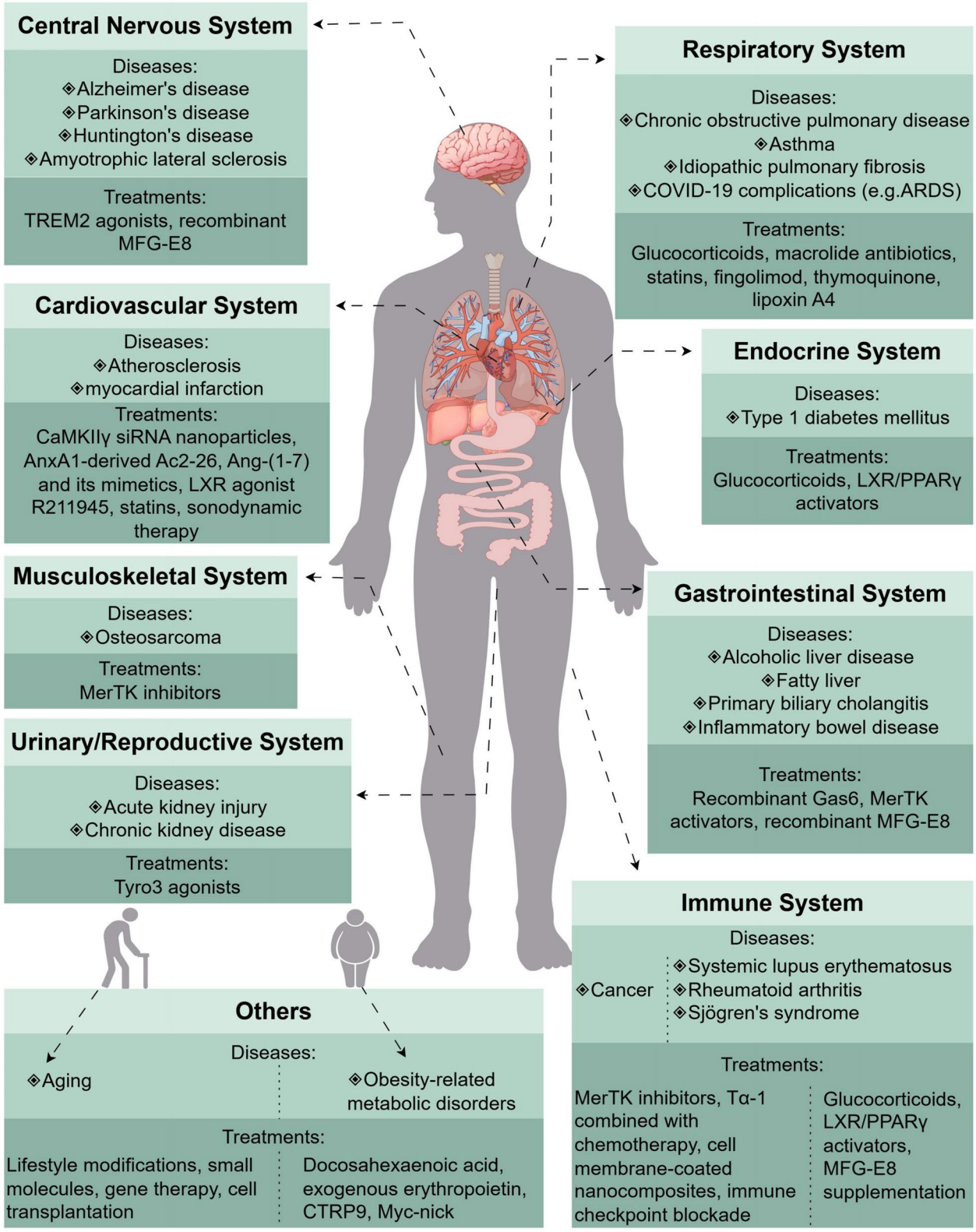

Fig. 4 Diseases caused by impaired efferocytosis and corresponding treatments classified by the nine major human body systems. Light green indicates the system name, green represents diseases caused by impaired efferocytosis in that system, and dark green indicates the corresponding treatment methods

exploration of treatments for inflammatory bowel disease (IBD), Axl and MerTK are likewise considered potential therapeutic targets [213].

However, the function of TAM receptors is highly context-dependent, a reality that dictates their therapeutic potential. Axl activation, for instance, can be pro-inflammatory under certain conditions [214]. More critically, the role of TAM receptors like MerTK undergoes a fundamental reversal in the tumor microenvironment, where its high expression often correlates with poor patient prognosis. This is because cancer cells hijack MerTK-driven efferocytosis to create an immune-evasive shield. Specifically, tumors exploit this pathway to upregulate immunosuppressive molecules like PD-L1, a mechanism powerfully reinforced by the apoptotic cells themselves, which also trigger increased surface expression of both PD-L1 and PD-L2 on cancer cells via MerTK activation [215, 216]. Given its central role in orchestrating this dual-fronted immunosuppression, inhibiting MerTK has become a key anti-tumor strategy, one that effectively restores the infiltration and proliferation of anti-tumor CD8 + T cells [217].

Application of specialized pro-resolving mediators (SPMs)

Specialized pro-resolving mediators (SPMs), including resolvins, protectins, and lipoxins, are endogenous lipid molecules that actively orchestrate the resolution of inflammation without causing systemic immunosuppression [218]. A key mechanism of their action is the potentiation of macrophage efferocytosis [219–221]. In models of lung injury and colitis, the administration of SPMs has been shown to accelerate inflammation resolution and tissue repair [222, 223]. In cardiovascular disease, Annexin A1 (AnxA1) and its derivatives can promote the production of the anti-inflammatory cytokine IL-10 to ameliorate atherosclerosis and can foster neovascularization and myocardial repair following myocardial infarction [224, 225]. Lipoxin A4 is considered a potential therapeutic option for severe pulmonary inflammation, such as in acute respiratory distress syndrome (ARDS) [226]. Furthermore, aging is often associated with a decline in efferocytic capacity, partly due to increased cleavage of the MerTK receptor [227, 228]; resolvin D1 has been demonstrated to inhibit this process, thereby improving age-related efferocytosis defects [229].

Other pro-clearance targets and applications

Beyond the aforementioned targets, modulating other pathways related to efferocytosis has also shown therapeutic potential in various diseases. In the field of neurodegenerative diseases, one strategy for Alzheimer's disease (AD) involves targeting the TREM2 receptor on microglia, using agonists to activate its signaling pathway to enhance protective functions, including efferocytosis [230]. The bridging protein MFG-E8 has also shown promise, not only for protecting midbrain dopaminergic neurons in models of Parkinson's disease (PD) [231] but also for inhibiting Aβ-induced microglial inflammation in AD models by suppressing MAPK and NF-κB signaling [232].

In metabolic diseases such as obesity, modulating macrophage function is crucial. For instance, docosahexaenoic acid (DHA) and exogenous erythropoietin can enhance the efferocytic capacity of macrophages by activating the PPAR-γ pathway [233]. Furthermore, C-1q/TNF-related protein 9 (CTRP9) enhances efferocytosis via MAPK/Drp1-mediated mitochondrial fission [234], while the oncogene fragment Myc-nick has been shown to increase efferocytosis in M2 macrophages [235].

In cardiovascular disease, several novel strategies are emerging. Silencing CaMKIIγ, which inhibits MerTK expression, has been shown to promote efferocytosis and induce regression of atherosclerosis in preclinical models [236]. Additionally, the angiotensin-(1–7) mimic AVE0991 has demonstrated anti-atherosclerotic effects by stimulating macrophage efferocytosis [237]. Targeted delivery of LXR agonists can also accelerate inflammation resolution and enhance plaque stability [238]. In the context of myocardial infarction, engineered neutrophil apoptotic bodies (eNABs) have been constructed to mimic natural apoptosis, successfully stimulating an anti-inflammatory macrophage phenotype and improving cardiac function in vivo [239].

Therapeutic enhancement of efferocytosis is also relevant in other inflammatory conditions. In experimental colitis, where MFG-E8 expression is reduced, intrarectal administration of recombinant MFG-E8 was shown to ameliorate the disease [240]. Similarly, MFG-E8 has demonstrated potential therapeutic effects in promoting the healing of diabetic wounds by correcting clearance defects and resolving inflammation [241].

Efferocytosis is also important in infectious diseases. For example, in Mycobacterium tuberculosis (M.tb) infection, the efferocytosis of apoptotic neutrophils by macrophages has been shown to enhance the clearance of the bacteria [242].

Blocking "Don't-Eat-Me" signals

The core of this strategy lies in disengaging the molecular "brakes" that inhibit efferocytosis, most typically by targeting the CD47-SIRPα axis, thereby unmasking harmful cells for clearance by the immune system [243]. In oncology, many tumor cells overexpress the CD47 "Don't-Eat-Me" signal to evade efferocytosis by macrophages [244]. Therapeutic antibodies that block the CD47-SIRPα interaction have achieved initial success in clinical trials for

hematological malignancies such as acute myeloid leukemia (AML) [245–247]. Beyond oncology, CD47 blockade shows significant potential in mitigating ischemia-reperfusion injury in organ transplantation [248–251]. Additionally, sonodynamic therapy has been shown to treat atherosclerosis by downregulating CD47, effectively reducing lesion size and local inflammation [252, 253]. A significant limitation of CD47-targeted therapy is the potential for resistance, which can arise through mechanisms such as the upregulation of alternative phagocytic checkpoints or increased CD47 expression on tumor cells [254]. Furthermore, because CD47 is ubiquitously expressed on healthy tissues, on-target toxicities like anemia and thrombocytopenia are notable concerns [243]. A further challenge is the lack of validated biomarkers to predict patient response to these therapies [255].

The efferocytosis-modulating effects of existing drugs

Several clinically established drugs have been found to exert part of their therapeutic efficacy through the modulation of efferocytosis pathways, providing a rationale for drug repurposing. As a cornerstone of anti-inflammatory therapy, glucocorticoids enhance efferocytosis by upregulating key molecules such as MerTK, Annexin A1, LXR, and PPARγ; this is one of the core mechanisms underlying their efficacy in treating autoimmune and inflammatory conditions [213] like systemic lupus erythematosus (SLE) [256–259] and asthma [260]. Supporting this pathway as a therapeutic target, preclinical evidence from mouse models of inflammatory arthritis demonstrates that direct activation of LXR/PPARγ exerts therapeutic effects [261, 262]. Furthermore, macrolide antibiotics such as azithromycin possess immunomodulatory properties and can promote efferocytosis in alveolar macrophages, which may contribute to their clinical benefits in respiratory diseases like chronic obstructive pulmonary disease (COPD) [263, 264]. The macrolide telithromycin has also shown significant benefits in improving lung function in patients with moderate-to-severe asthma [264]. Similarly, statins, in addition to their lipid-lowering effects, directly enhance macrophage efferocytosis within atherosclerotic plaques, thereby promoting plaque stabilization [265]. This mechanism may also be relevant to their beneficial effects in reducing asthma-related hospitalizations and mitigating inflammation in COVID-19 via the RhoA pathway [266–268]. In the context of COVID-19, agents like fingolimod and thymoquinone, which regulate S1P signaling, have also been proposed as treatment options to improve impaired efferocytosis [269, 270]. Finally, traditional Chinese medicines such as Guanxinkang have been confirmed to alleviate atherosclerosis by improving efferocytosis through the MAPK signaling pathway [271].

Combination strategies and the challenge of therapeutic duality

In the future, efferocytosis-based therapies will likely rely on sophisticated combination approaches that fully account for the dual nature of the process. In oncology, combining efferocytosis modulation with other treatments (e.g., chemotherapy, immune checkpoint inhibitors) is a highly promising direction. For instance, combining Thymosin α–1 (Tα–1) with chemotherapy can reverse the immunosuppressive M2 polarization of macrophages following efferocytosis, thereby enhancing the anti-tumor T cell response [113]. Novel nanotechnologies are also being developed to leverage this principle. For example, a cell membrane-coated nanocomposite can block PS exposure on dying tumor cells, inhibiting efferocytosis and promoting immunostimulatory secondary necrosis, which in turn activates the cGAS/STING pathway and robust anti-tumor immunity [272]. Another innovative approach uses a bacterial outer membrane vesicle (OMV)-based nanosystem to deliver a MerTK inhibitor; this strategy not only induces secondary necrosis but also allows the OMVs to act as an adjuvant, forming an in situ cancer vaccine that triggers a powerful tumor-specific immune response [273].

However, all therapies targeting efferocytosis must confront the central challenge of its therapeutic duality in different disease contexts. Enhancing efferocytosis is beneficial in sterile inflammatory conditions but can be co-opted by cancer cells to promote immunosuppression and growth. Conversely, inhibiting efferocytosis is an effective anti-cancer strategy to promote immunogenic cell death but carries the risk of inducing autoimmunity or exacerbating inflammation in other tissues. Therefore, successful clinical translation will depend heavily on the development of highly specific strategies, such as cell-targeted drug delivery or agents activated only within a specific disease microenvironment, to maximize therapeutic benefits while minimizing potential risks [272, 273].

Conclusion and future directions

Conclusion: a unifying role for dysfunctional efferocytosis in disease

Efferocytosis is far more than a simple cellular disposal mechanism; it is a fundamental biological program whose integrity is a critical determinant of tissue health and disease. As this review has detailed, a clear pattern emerges across a wide range of pathologies: diseases of chronic inflammation and autoimmunity are often defined by impaired efferocytosis, whereas cancer pathogenesis frequently involves the hijacking of efferocytosis.

In sterile inflammatory conditions such as atherosclerosis, neurodegenerative diseases, and autoimmune disorders, a central pathogenic axis is the failure of efferocytes to efficiently clear apoptotic cells [274, 275]. This

clearance deficit leads to an accumulation of secondarily necrotic cells, unleashing pro-inflammatory mediators that perpetuate a vicious cycle of tissue damage and unresolved inflammation. A recurring molecular theme is the dysfunction of key receptors, particularly MerTK, whose proteolytic cleavage and subsequent inactivation is a shared feature in both atherosclerosis and the age-related decline in clearance capacity ("inflammaging") [18, 192]. Similarly, the genetic linkage of receptors like TREM2 to Alzheimer's disease underscores that a breakdown in silent clearance by microglia is not merely a consequence but a driver of pathology [276, 277]. Conversely, in the tumor microenvironment (TME), the efferocytic machinery is co-opted to foster immune evasion and tumor progression. Rather than being impaired, efferocytosis by tumor-associated macrophages (TAMs) and dendritic cells is exploited to induce an immunosuppressive, M2-like phenotype, driven by metabolic reprogramming and the secretion of anti-inflammatory cytokines like TGF-β and IL-10. Receptors such as MerTK and Axl, which are protective in inflammatory contexts, become pro-tumorigenic by facilitating silent clearance that prevents the activation of anti-tumor T cell responses and can directly drive the expression of immune checkpoints like PD-L1 [278]. This functional switch highlights the profound context-dependency of efferocytosis.

Future directions: addressing key challenges and opportunities

The therapeutic potential of modulating efferocytosis is immense, but its clinical translation hinges on addressing several key questions and overcoming current limitations.

First, efferocytosis exhibits strong tissue- and cell-type specificity. Professional efferocytes such as macrophages cooperate with non-professional efferocytes including epithelial and fibroblasts, yet their division of labor differs across organs. Evidence from lung injury models highlights that non-professional efferocytes play indispensable roles in debris clearance and tissue repair, underscoring the need to map the organ- and cell-specific efferocytic network before designing targeted interventions [279, 280].

Second, clinical translation is hampered by the lack of robust in vivo monitoring tools and validated biomarkers. The current review emphasizes major gaps in tracking how apoptotic cargo is processed and translated into pro- or anti-inflammatory signals, which limits patient stratification and response assessment [8]. Meanwhile, probes targeting PS—including PET tracers and PS-binding peptides/antibodies—have shown promise for non-invasive efferocytosis imaging in preclinical and early clinical studies, but sensitivity and specificity remain to be optimized for clinical decision-making [281–286].

Looking ahead, resolving the "therapeutic duality" of efferocytosis will require precision and localization rather than systemic modulation. Emerging strategies such as cell membrane–engineered nanoparticles that deliver MerTK agonists have already been shown to enhance efferocytosis and reduce plaque burden in diabetic ApoE−/− mice, offering proof-of-concept for disease-focused interventions [287]. Ultimately, future progress will depend on integrating tissue-specific insights, validated biomarkers, and targeted delivery platforms into a biomarker-guided precision medicine framework, so that efferocytosis can be safely harnessed to resolve inflammation without inadvertently promoting tumor progression [8].

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Authors' contributions
Gege Li collected the data, performed the primary analysis, and drafted the manuscript. The others assisted with sample collection and manuscript revision. Shuangtao Zhao conceived and supervised this study. All authors declare that they do not have a financial conflict of interest. All authors have seen and approved its content and contributed significantly to the work. And all authors declare that this manuscript (any part of it) was not published or submitted to any other journal. Additionally, all authors prefer our figures appear in color and agree to pay for full color reproduction for figures within the main manuscript if the article is published.

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Data availability
All data was collected from PubMed dataset. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This project was approved by the institutional review committee.

Consent for publication
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