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REVIEW

Impaired Macrophage Efferocytosis: Shared Mechanisms and Therapeutic Implications in Immune-Mediated Inflammatory Diseases

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Abstract: Efferocytosis, the specialized phagocytic clearance of apoptotic cells, is a fundamental mechanism for maintaining tissue homeostasis and immune tolerance. Among professional phagocytes, macrophages play a central role due to their high plasticity and tissue-resident properties. By recognizing and engulfing apoptotic cells through a repertoire of receptors and bridging molecules, macrophages prevent secondary necrosis and inflammation and actively shape the local immune microenvironment via metabolic and epigenetic reprogramming. Defective efferocytosis has been increasingly implicated in the pathogenesis of immune-mediated inflammatory diseases (IMIDs), including systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, inflammatory bowel disease, psoriasis, atopic dermatitis, and autoimmune liver diseases. Impairments in efferocytosis trigger persistent inflammation, autoantigen exposure, and tissue damage, thereby fueling chronic disease progression. Recent mechanistic studies highlight the dysregulation of TAM receptors, bridging molecules, and intracellular signaling pathways as critical determinants of efferocytosis dysfunction in IMIDs. In this review, we propose defective macrophage efferocytosis as a shared pathogenic mechanism across diverse IMIDs and integrate emerging evidence linking efferocytosis to immunometabolic and epigenetic rewiring in chronic inflammation. We further discuss therapeutic strategies targeting efferocytosis pathways and highlight key translational challenges and opportunities. By positioning efferocytosis as a central pathogenic node and a readily targetable mechanism across the spectrum of IMIDs, this review offers a conceptual framework that links fundamental mechanistic insights with clinical translation, thereby laying the groundwork for precision immunomodulatory strategies that aim to restore immune homeostasis rather than merely suppress inflammation.

Keywords: macrophage efferocytosis, immune-mediated inflammatory diseases, TAM receptors, apoptotic cell clearance, inflammation resolution

Introduction

Tissue homeostasis critically depends on the rapid and effective removal of apoptotic cells by phagocytes. It's a specialized form of phagocytosis known as efferocytosis. In a healthy human body, approximately 1×10^{10} cells undergo apoptosis daily, and their rapid clearance is essential to avoid secondary tissue damage.[1] When this process is defective, uncleared apoptotic cells undergo secondary necrosis, releasing intracellular contents that aggravate inflammation and promote further tissue injury.[2]

Efferocytosis is a fundamental cellular process predominantly executed by professional phagocytes such as macrophages and dendritic cells. In addition, several non-professional phagocytic cell types—including intestinal epithelial cells, endothelial cells, and astrocytes—also participate in the clearance of apoptotic cells.[3] In the central nervous system, microglia act as the principal resident phagocytes, maintaining neural homeostasis by removing debris from degenerating

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neurons and β-amyloid plaques, modulating neuroinflammatory responses, and preserving neuronal integrity. Dysfunction of these processes has been closely linked to the pathogenesis of neurodegenerative disorders, particularly Alzheimer's disease.[4–6] Dendritic cells (DCs) serve as essential sentinels of the innate immune system and potent antigen-presenting cells.[7] Current studies suggest that DC-mediated efferocytosis plays a critical role in tissue repairing and wound healing.[8,9]

Among both professional and non-professional phagocytes engaged in efferocytosis, macrophages occupy a central role due to their remarkable plasticity and tissue-resident characteristics. They recognize and engulf apoptotic cells through a variety of surface receptors and bridging molecules. This process induces extensive metabolic and epigenetic reprogramming in macrophages, thereby shaping the surrounding immune microenvironment.[3] Aberrant regulation of efferocytosis is increasingly recognized as a key pathogenic mechanism underlying various disorders, including cardiovascular, respiratory, and neoplastic diseases.[10–13]

Immune-mediated inflammatory diseases (IMIDs) encompass a heterogeneous group of chronic disorders characterized by dysregulated immune activation.[14] Globally, IMIDs affect approximately 10% of the population, impacting more than 670 million individuals. This broad disease spectrum spans almost a hundred distinct conditions across rheumatology, dermatology, and gastroenterology. Representative examples include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), and gouty arthritis (GA) in rheumatology; psoriasis (PsO) and atopic dermatitis (AD) in dermatology; and autoimmune liver disease (AILD) and inflammatory bowel disease (IBD) in gastroenterology. IMIDs share common inflammatory pathways and overlapping mechanisms of immune dysregulation. For instance, patients with psoriasis frequently develop psoriatic arthritis, whereas inflammatory bowel disease is frequently associated with ankylosing spondylitis or psoriasis.[15,16]

Recent studies have highlighted the important role of efferocytosis in the resolution of inflammation and the maintenance of tissue homeostasis. In diseases such as SLE, RA, and IBD, disrupted efferocytosis pathways contribute to sustained immune activation and tissue injury. Restoring efficient efferocytosis represents a promising therapeutic strategy in IMIDs. This review aims to explore the defective macrophage efferocytosis in IMIDs, focusing on its regulatory mechanisms, pathogenic roles, and emerging therapeutic targets.

Macrophage Efferocytosis: Basic Principles

"Find-Me" Stage

Efferocytosis begins when apoptotic cells release "find-me" signals that attract macrophages to sites of cell death. These soluble factors bind macrophage receptors and orchestrate chemotactic migration toward apoptotic cells. Current studies have identified four major "find-me" signal–receptor pairs: sphingosine-1-phosphate (S1P) and its receptor S1PR; nucleotides ATP/UTP and their purinergic receptor P2Y2; the chemokine CX3C ligand 1 (CX3CL1) and its receptor CX3CR1; and lysophosphatidylcholine (LPC) and its receptor G2A (G protein-coupled receptor 132, GPR132). In addition, lipid-soluble vitamins and lipid metabolites released by apoptotic cells can also serve as "find-me" cues.[4] These signals are detected through pattern-recognition receptors, enabling rapid recruitment of macrophages.[17]

"Eat-Me" Stage

During the "eat-me" phase, apoptotic cells expose specific surface markers that are recognized by macrophage receptors. The two best-characterized markers are phosphatidylserine (PtdSer) and calreticulin (CRT). During apoptosis, membrane asymmetry is disrupted, resulting in the externalization of PtdSer to the outer leaflet, thereby generating a distinctive "eat-me" signal on the cell surface that facilitates recognition by macrophage receptors. PtdSer can directly engage various macrophage surface receptors including brain-specific angiogenesis inhibitor 1 (BAI1), T cell immunoglobulin and mucin domain-containing proteins (TIM-1 and TIM-4), as well as Stabilin-1 and Stabilin-2.[18–20] Several bridging molecules further facilitate apoptotic cell recognition and clearance by linking macrophage receptors to PtdSer on apoptotic cells. Notable examples include milk fat globule-epidermal growth factor 8 (MFG-E8), growth arrest-specific protein 6 (GAS6) and protein S (ProS).[21] MFG-E8 binds PtdSer through its C-terminal discoidal domains and interacts with integrins (αvβ3/β5) on macrophages via its N-terminal EGF-like domains, physically bridging the two cell types.[22]

Similarly, GAS6 and ProS act as ligands for the TAM family of receptor tyrosine kinases (Tyro3, Axl, and MerTK), linking PtdSer recognition to downstream engulfment signaling.[23] Another example is scavenger receptor class F member 1 (SCARF1), which cooperates with complement component C1q to enhance cell engulfment.[1] Collectively, these bridging molecules ensure efficient recognition and clearance of apoptotic cells, preserving tissue homeostasis. Developmental endothelial locus-1 (DEL-1) has been reported to enhance macrophage efferocytosis, thereby promoting inflammation resolution and improving insulin resistance in skeletal muscle.[24] DEL-1 functions as a non-redundant endogenous bridging molecule that binds phosphatidylserine on apoptotic cells and αvβ3 integrin on macrophages, facilitating apoptotic cell recognition and expanding the repertoire of efferocytosis regulators.[25] In addition to classical bridging molecules, DEL-1 has emerged as a non-redundant opsonin-like molecule that enhances apoptotic cell recognition and promotes inflammation resolution.

CRT functions as another major "eat-me" signal. Upon translocation to the apoptotic cell surface, CRT binds low-density lipoprotein receptor–related protein 1 (LRP1, also known as CD91) on macrophages, promoting phagocytosis. C1q can also bridge CRT on apoptotic cells to macrophages, further enhancing phagocytosis.[26–28]

To avoid inappropriate clearance, healthy cells express "don't eat me" signals. Key molecules in this category include CD24, CD47, programmed death-ligand 1 (PD-L1), and β2-microglobulin (β2M).[17] Two well-characterized examples, CD47 and CD24, are recognized by the macrophage receptors SIRPα and Siglec-10, respectively. Engagement of these pathways inhibits macrophage-mediated efferocytosis: CD47 delivers inhibitory signals through signal regulatory protein alpha (SIRPα), whereas CD24 recruits Src homology region 2 domain-containing phosphatase-1 (SHP-1) and Src homology region 2 domain-containing phosphatase-2 (SHP-2) phosphatases via Sialic acid–binding immunoglobulin-like lectin 10 (Siglec-10).[29,30] Dysregulation of this pathway can permit the persistence of harmful cells.[31]

Phagocytic Stage

Following receptor engagement, macrophages activate Rho family small GTPases, particularly Rac1 and RhoA, to drive actin cytoskeletal remodeling. This remodeling drives plasma membrane invagination and localized protrusions that form the phagocytic cup, ultimately leading to engulfment of apoptotic cells. Rac1 activation occurs through two main signaling routes. The first is initiated by TAM receptors or integrins, which promote the assembly of the engulfment and cell motility protein 1 (ELMO) –dedicator of cytokinesis 180 (DOCK180) complex with the adaptor protein CrkII and BAI1, recruiting DOCK180 to the membrane and triggering Rac1 activation.[18] The second involves CD91, which recruits the adaptor protein engulfment adapter protein (GULP), leading to Rac1-dependent actin polymerization and phagosome formation.[19,32]

Digestion Stage

The final stage of efferocytosis involves degradation of the internalized apoptotic material. After engulfment, phagosomes mature through fusion with lysosomes to form phagolysosomes. These lysosomes are enriched with hydrolytic enzymes capable of efficiently degrading the engulfed apoptotic material and its components. Phagolysosome maturation also promotes the release of anti-inflammatory mediators such as IL-10 and TGF-β.[33,34] As degradation proceeds, macrophages activate metabolic and autophagic programs to process nucleic acids, proteins, and lipids, thereby restoring cellular equilibrium.[35] The internalized cell is then degraded in phagolysosomes, a process enhanced by LC3-associated phagocytosis (LAP), promoting anti-inflammatory mediator release[21,36,37] (Figure 1).

Beyond these immediate metabolic and transcriptional changes, macrophage efferocytosis capacity is also shaped by long-term epigenetic and metabolic reprogramming, a phenomenon termed trained immunity.[38] Emerging evidence highlights a complex, bidirectional interplay between trained immunity and efferocytosis. Stimuli such as β-glucan or oxidized low-density lipoprotein (oxLDL)–induced trained immunity can differentially modulate macrophage efferocytosis capacity. β-glucan–induced trained immunity enhances alveolar macrophage efferocytosis and protects against bleomycin-induced lung injury, a process associated with histone modifications and increased production of the pro-resolving mediator resolvin D1 (RvD1).[39] Lung-resident alveolar macrophages pre-exposed to bacterial endotoxin or *Pseudomonas aeruginosa* displayed increased efferocytosis capacity and upregulated MERTK expression, promoting a pro-resolving phenotype that limited inflammatory lung injury in vivo.[40] In contrast, in the tumor microenvironment,

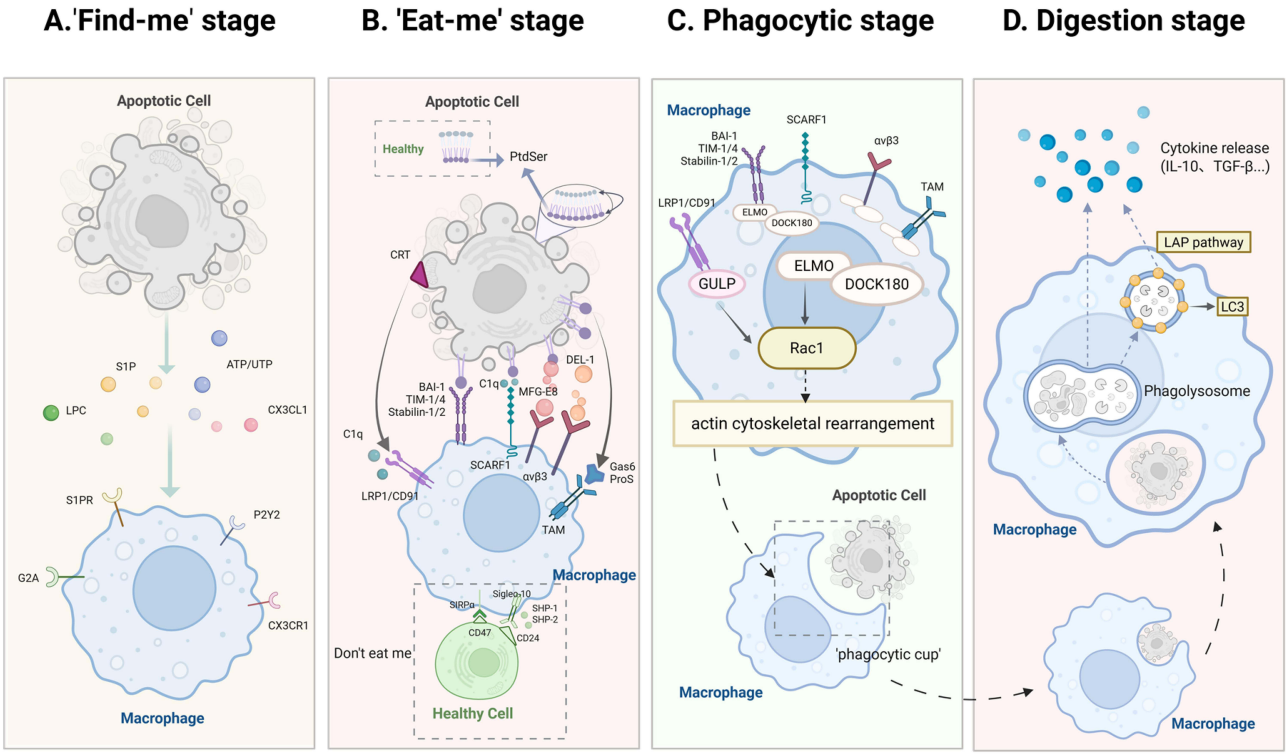

Figure 1 Four stages of macrophage efferocytosis. Efferocytosis proceeds through four stages. (**A**) Apoptotic cells release "find-me" signals to recruit macrophages. (**B**) Exposure of "eat-me" signals such as PtdSer and CRT enables recognition by macrophage receptors and bridging molecules. (**C**) Engulfment of apoptotic cells is mediated by cytoskeletal remodeling. (**D**) Internalized apoptotic cargo is degraded within phagolysosomes or via LAP, leading to anti-inflammatory responses and restoration of tissue homeostasis.

Abbreviations: BAI1, brain-specific angiogenesis inhibitor 1; β2M, β2-microglobulin; CRT, calreticulin; CX3CL1, the chemokine CX3C ligand 1; Del-1, developmental endothelial locus-1; DOCK180, dedicator of cytokinesis 180; ELMO, engulfment and cell motility protein 1; GAS6, growth arrest-specific protein 6; GULP, the adaptor protein engulfment adapter protein; G2A, G protein-coupled receptor 132, GPR132; LAP, LC3-associated phagocytosis; LPC, lysophosphatidylcholine; LRP1/CD91, low-density lipoprotein receptor-related protein 1; MFG-E8, milk fat globule-epidermal growth factor 8; PD-L1, programmed death-ligand 1; ProS, protein S; PtdSer, phosphatidylserine; Rac1, Ras-related C3 botulinum toxin substrate 1; SCARF1, Scavenger receptor class F member 1; SHP-1/2, Src homology region 2 domain-containing phosphatase-1/2; SIRPα, signal regulatory protein alpha; Siglec-10, sialic acid–binding immunoglobulin-like lectin 10; S1p, sphingosine-1-phosphate; TAM, Tyro3, Axl, and MerTK; TIM-1/4, T cell immunoglobulin and mucin domain-containing proteins-1/4.

trained macrophages exhibit reduced efferocytosis of apoptotic cancer cells, accompanied by downregulation of efferocytosis-related genes and decreased IL-1β production.[41] These findings support the notion that trained immunity can program macrophages toward long-lasting tissue-protective and pro-resolving states in some contexts, but may conversely impair apoptotic cell clearance and resolution in others, highlighting the context-dependent nature of this regulatory mechanism.

Defective Efferocytosis in Immune-Mediated Inflammatory Diseases

Defective efferocytosis has emerged as a critical driver in the pathogenesis and progression of IMIDs. The following sections outline the pathological consequences of efferocytosis dysfunction in representative IMIDs (Figure 2).

Systemic Lupus Erythematosus

SLE is a chronic autoimmune disease marked by immune dysregulation, autoantibody production, and inflammation affecting multiple organs. In SLE, apoptotic cell generation markedly exceeds macrophage clearance capacity, leading to their accumulation in tissues. Uncleared apoptotic cells release nuclear antigens that form immune complexes with autoantibodies, which subsequently deposit in target organs and cause characteristic lesions.[42] Histopathological analyses consistently demonstrate abundant apoptotic debris in both lesional sites and the bone marrow of SLE patients, accompanied by aberrant autoantibody production.[43–45]

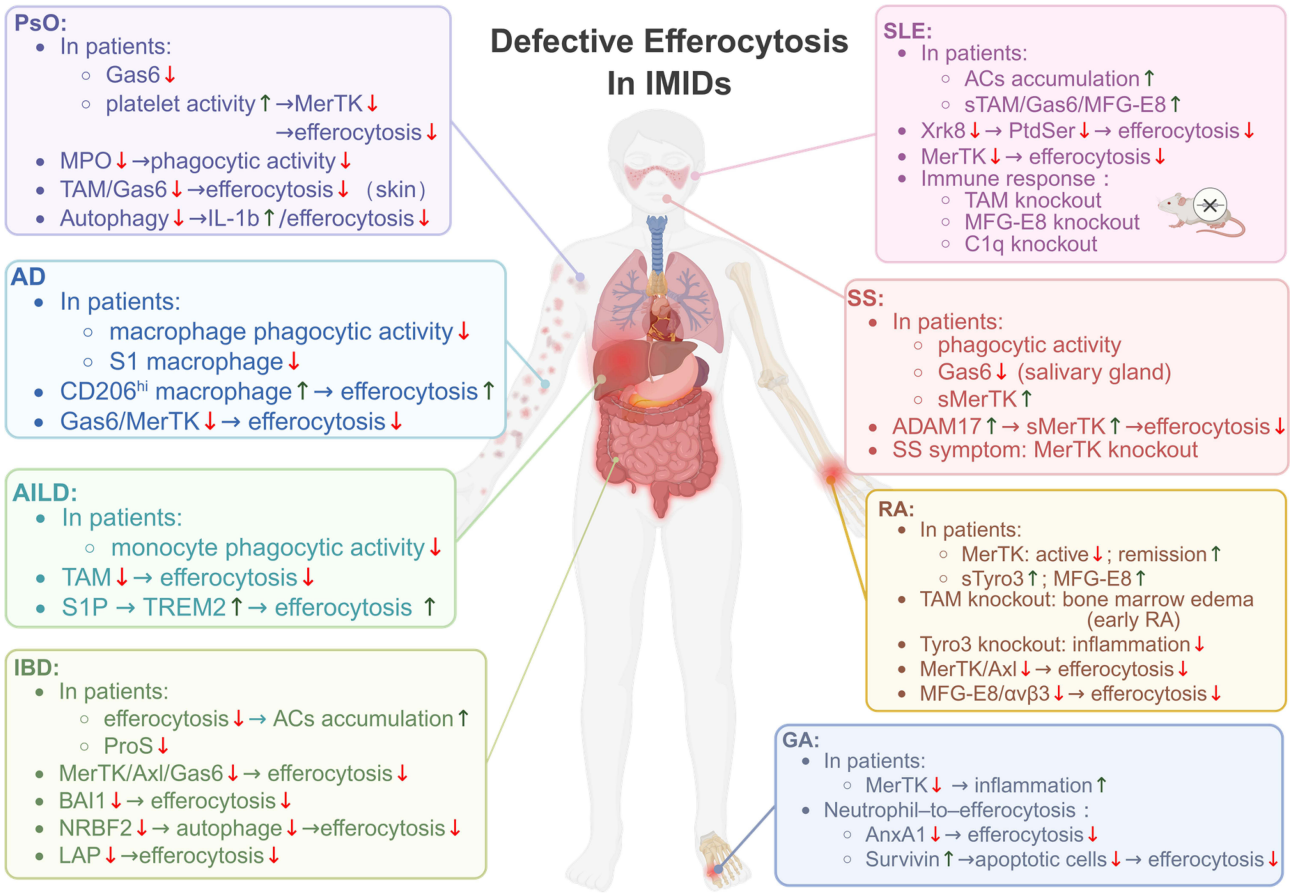

Figure 2 Defective efferocytosis across immune-mediated inflammatory diseases. Efferocytosis impairment is increasingly recognized as a pathogenic hallmark of IMIDs. Across systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, atopic dermatitis, psoriasis, autoimmune liver disease, inflammatory bowel disease, and gouty arthritis, impaired macrophage clearance of apoptotic cells drives chronic inflammation, autoantibody production, and tissue damage. Mechanistic studies highlight disease-specific disruptions in TAM receptor signaling (Tyro3, Axl, MerTK), bridging molecules (Gas6, ProS, MFG-E8, C1q), and cellular processes including autophagy and LAP, providing potential biomarkers and therapeutic targets. In the figure, downward arrows (↓) indicate reduced expression or activity compared to healthy controls, upward arrows (↑) indicate increased expression or activity, and dashed arrows (→) indicate pathogenic consequences or disease progression.
Abbreviations: AD, atopic dermatitis; ADAM17, a disintegrin and metalloproteinase 17; AILD, autoimmune liver disease; AnxA1, Annexin A1; GA, gouty arthritis; IBD, inflammatory bowel disease; NRBF-2, nuclear receptor-binding factor 2; PsO, psoriasis; RA, rheumatoid arthritis; S1P, sphingosine-1-phosphate; SLE, systemic lupus erythematosus; SS, sjögren's syndrome; TREM2, triggering receptor expressed on myeloid cells 2.

Apoptotic cells expose PtdSer on the outer leaflet of the plasma membrane. The phospholipid scramblase Xkr8 mediates this process, and its deficiency impairs PtdSer exposure, resulting in defective clearance. In Xkr8-deficient mice, apoptotic cells accumulate in the thymus, with concomitant reductions in PtdSer exposure and elevated serum titers of antinuclear antibodies (ANA) and anti–double-stranded DNA (anti-dsDNA) antibodies.[46] These findings provide direct experimental evidence for the central role of defective efferocytosis in SLE pathogenesis.

Disruption of receptor-mediated recognition further contributes to SLE. Triple knockout mice lacking the TAM receptors exhibit heightened autoimmunity and elevated autoantibody levels.[47] MerTK deficiency alone impairs efferocytosis and induces lupus-like features in mice.[48] Clinical investigations have also reported increased plasma levels of soluble TAM receptors and GAS6 in SLE patients.[49,50]

Bridging molecules are also implicated. MFG-E8 deficiency leads to splenomegaly and autoantibody-driven pathology in mice.[51] Elevated serum MFG-E8 levels in subsets of SLE patients further implicate this molecule as a potential biomarker of disease activity.[52] Similarly, C1q-deficient mice recapitulate autoimmune phenotypes characteristic of SLE, with defective apoptotic cell clearance observed in both C1q-deficient mice and humans, correlating with increased autoimmunity susceptibility.[53–56] ProS deficiencies have been associated with SLE and other autoimmune disorders, further highlighting the indispensable role of efferocytosis in maintaining self-tolerance.[57,58]

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Rheumatoid Arthritis

RA is a systemic autoimmune disease characterized by progressive joint destruction and systemic immunological abnormalities. Impaired efferocytosis has been implicated in RA pathogenesis by perpetuating chronic inflammation and accelerating joint damage. Similar observations have been reported in osteoarthritis (OA).[59]

TAM receptors are essential for the recognition and engulfment of apoptotic cells. Triple-knockout mice lacking Tyro3, Axl, and MerTK develop early hallmarks of RA, including bone marrow edema.[60,61] In murine models, MerTK or Axl deficiency leads to increased apoptotic cell accumulation within arthritic joints, exacerbating inflammation. In human synovial tissue, MerTK inhibition enhances inflammatory cytokine production.[62] The Axl–MerTK axis is a dynamic regulatory pathway influenced by synovial cell phenotypes, disease stage, and therapeutic interventions.[63] In synovial macrophages from healthy individuals, 90% co-express MERTK and CD206 ($MERTK^{+}CD206^{+}$), whereas this proportion drops to only 17.3% in patients with active RA. Notably, during remission, the proportion rises to 76.5%, approaching healthy levels.[64,65] In contrast, Ruiz et al found that *Tyro3*$^{-/-}$ mice exhibited reduced joint inflammation and bone erosion, suggesting that Tyro3 may contribute to synovial hyperplasia and osteoclast activation in arthritis.[66]

Ligands of the TAM receptor family, including Gas6 and ProS, also participate in efferocytosis by limiting apoptotic cell accumulation in arthritic joints.[62,67] In addition, integrin αvβ3 and MFG-E8 are key mediators in macrophage-mediated efferocytosis. αvβ3 exerts protective effects, alleviating symptoms of adjuvant-induced arthritis in rats.[68] MFG-E8 deficiency induces lupus-like disease in mice, accompanied by enhanced osteoclast activity, reduced osteoblast numbers, and dysregulated bone remodeling. These findings suggest that MFG-E8 not only contributes to defective efferocytosis in SLE but also plays an important role in bone metabolism.[69] Clinical data further reveal that serum MFG-E8 levels are reduced in RA patients compared with healthy controls, highlighting its potential role as both a biomarker and regulator of efferocytosis.[52] Recent high-resolution single-cell RNA sequencing (scRNA-seq) studies in RA and SLE have uncovered diverse macrophage and monocyte subsets with distinct efferocytosis-related transcriptional programs. These findings provide mechanistic insights into disease-specific clearance defects and may inform precision targeting of efferocytosis pathways for therapeutic intervention.[70–73]

Sjögren's Syndrome

SS is a systemic autoimmune disease characterized by lymphocytic infiltration and progressive destruction of exocrine glands, leading to xerostomia and keratoconjunctivitis sicca. Emerging evidence indicates that defective efferocytosis plays a critical role in sustaining glandular inflammation, autoantigen persistence, and systemic immune activation in SS. Patients with SS exhibit reduced phagocytic activity in circulating monocytes, and increased apoptosis of glandular epithelial cells has been observed in experimental models, suggesting an imbalance between apoptotic cell generation and clearance.[74,75] A study in SS model mice revealed increased apoptosis in glandular epithelial cells.[76]

Recent clinical and experimental studies highlight MerTK as a key regulator of efferocytosis in SS. MerTK expression in minor salivary gland biopsies correlates with histological focus scores, disease activity indices, and systemic organ involvement, whereas Tyro3 and Axl show weaker or no such associations, indicating receptor-specific functional specialization.[77] Moreover, elevated plasma levels of soluble MerTK (sMerTK) have been reported in SS patients and positively correlate with systemic inflammation, suggesting enhanced receptor shedding and impaired membrane-bound MerTK signaling.[78,79] MerTK-deficient mice develop SS-like phenotypes, including submandibular gland lesions, reduced salivary secretion, and autoantibody production.[79,80]

In addition, SS model mice show impaired efferocytosis in bone marrow–derived macrophages (BMDMs), defective MerTK signaling, and elevated serum soluble MerTK levels.[79] Mechanistically, chronic apoptotic burden may induce compensatory upregulation of MerTK in macrophages, dendritic cells, and salivary gland epithelial cells; however, excessive inflammatory signaling and receptor shedding can uncouple receptor expression from functional efferocytosis. SS model mice also show increased serum activity of a disintegrin and metalloproteinase 17 (ADAM17), which is known to mediate proteolytic cleavage of the MerTK extracellular domain. ADAM17-driven cleavage of MerTK generates soluble MerTK, thereby inhibiting efferocytosis, which may represent one of the mechanisms underlying efferocytosis dysfunction in SS.[81–83] In addition, clinical studies have reported decreased plasma Gas6 concentrations and reduced Gas6 expression in labial glands of SS patients, indicating impaired TAM ligand–receptor engagement in the glandular

microenvironment. As Gas6 functions as a critical opsonin linking phosphatidylserine-exposed apoptotic cells to TAM receptors, its deficiency is likely to exacerbate defective efferocytosis, thereby sustaining autoantigen exposure, aberrant antigen presentation, and chronic immune activation.[84]

Atopic Dermatitis

AD is a chronic inflammatory skin disease frequently associated with elevated serum IgE levels and comorbid allergic disorders.[85] Recent studies have shown that macrophages accumulate within inflamed AD lesions.[86] Clinical investigations provide further evidence of impaired macrophage function. A clinical study of five AD patients reported reduced phagocytic capacity of monocyte-derived macrophages.[87]

Emerging evidence indicates that chronic inflammation in AD is linked to macrophage dysfunction. A recent study identified a profound depletion of the S1 macrophage subset ($FR\beta^{+}/CD163^{+}$) in AD skin. This subset normally displays high efferocytosis capacity, characterized by elevated expression of efferocytosis receptors and bridging molecules. Loss of S1 macrophages results in impaired efferocytosis, accumulation of apoptotic debris, secondary necrosis, and amplification of inflammation, thereby establishing a self-perpetuating cycle.[88]

Psychological stress has also been implicated in AD pathogenesis. Stress was shown to suppress the phagocytic function of anti-inflammatory $PD\text{-}L2^{+}$ macrophages by downregulating efferocytosis-associated genes such as Gas6 and MerTK. Accumulated apoptotic cells release damage-associated molecular patterns (DAMPs) ultimately exacerbate IgE-mediated allergic skin inflammation.[89] Experimental models of AD revealed that basophil-derived IL-4 and M-CSF can activate $CD206^{hi}$ macrophages, thereby enhancing efferocytosis.[90]

Psoriasis

PsO is a chronic immune-mediated skin disease with systemic inflammation that may give rise to multiple comorbidities.[91] A vicious feedback loop has been identified between activated platelets and efferocytosis-deficient macrophages. Activated platelets downregulate the phagocytic receptor MerTK, skewing macrophages toward the proinflammatory M1 phenotype with reduced efferocytosis capacity. In turn, efferocytosis-deficient macrophages activate platelets, enhancing the release of proinflammatory mediators and exacerbating the inflammatory microenvironment. This reciprocal amplification loop provides a mechanistic explanation for the chronicity of psoriasis.[92]

Within the psoriatic inflammatory milieu—particularly in subtypes with prominent neutrophil infiltration, such as generalized pustular psoriasis (GPP)—persistent neutrophil presence is a hallmark feature. This abnormal retention is driven not only by excessive activation and recruitment of neutrophils but also by a diminished capacity of macrophages to clear apoptotic neutrophils. Recent studies revealed that neutrophils deficient in myeloperoxidase (MPO) display elevated CD47 expression, enabling them to evade macrophage-mediated clearance. Single-cell RNA-Seq further demonstrated that, in MPO-deficient individuals, monocytes display an overall downregulation of phagocytosis-related signaling pathways along with markedly reduced expression of related genes. These findings suggest that MPO deficiency compromises both the clearance targets and the phagocytes themselves. Such defects lead to sustained apoptotic cell accumulation, amplifying tissue damage in a self-perpetuating cycle.[93]

Additional mechanistic insights come from mouse models of psoriasis, which demonstrate marked downregulation of TAM receptors and their ligand Gas6 in lesional skin.[94] In psoriasis patients with coexisting cardiometabolic risk factors, plasma Gas6 levels are further decreased.[95] In psoriatic mouse models, impaired macrophage autophagy in psoriatic models has been shown to increase IL-1β release, aggravating inflammation and impairing phagosome–lysosome fusion, ultimately diminishing efferocytosis capacity.[96]

Autoimmune Liver Disease

Autoimmune liver diseases (AILDs), encompassing autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, are characterized by chronic immune-mediated hepatobiliary injury, circulating autoantibodies, and prominent hepatic macrophage infiltration.[97] Hepatic macrophages, including Kupffer cells and infiltrating monocyte-derived macrophages, play a pivotal role in maintaining liver immune tolerance by clearing apoptotic hepatocytes and cholangiocytes. Clinical studies have demonstrated that patients with AILD exhibit significantly reduced phagocytic

activity in circulating monocytes compared with individuals with non-alcoholic fatty liver disease, and this impairment correlates with disease severity and inflammatory burden.[98] Mechanistically, dysregulation of TAM receptor signaling has been implicated in hepatic immune homeostasis. Downregulation of the TAM receptors impairs macrophage efferocytosis, reduce the efficiency of apoptotic cell clearance, and ultimately trigger a vicious cycle of self-antigen exposure and pro-inflammatory mediator release. These aberrantly released inflammatory mediators drive hepatic fibrosis, eventually leading to the progression of AILD to end-stage liver disease.[99,100]

Recent studies have also identified additional regulatory pathways controlling macrophage efferocytosis in liver inflammation.[101] Triggering receptor expressed on myeloid cells 2 (TREM2) has been described as a critical gatekeeper of hepatic immune homeostasis. S1P–induced upregulation of TREM2 promotes macrophage-dependent clearance of lipid-laden apoptotic hepatocytes, maintaining immune tolerance during simple steatosis. However, chronic inflammatory cues, such as TNF and IL-1β, induce ADAM17-mediated TREM2 shedding, leading to defective efferocytosis and accumulation of dying hepatocytes.

Inflammatory Bowel Disease

IBD, comprising ulcerative colitis (UC) and Crohn's disease (CD), is characterized by immune dysregulation, persistent intestinal inflammation, and mucosal damage.[102–105] Increasing evidence suggests that defects in macrophage efferocytosis are closely associated with IBD development.[106,107] Studies have shown that patients with IBD have an increased number of apoptotic colonic epithelial cells.[108] The accumulation of apoptotic cells within the colon, together with impaired efferocytosis by macrophages, may contribute to disease exacerbation.[106] In a dextran sulfate sodium (DSS)-induced colitis mouse model, intestinal lamina propria macrophages showed increased expression of MerTK and Axl compared with controls. Moreover, *Axl*$^{-/-}$*MerTK*$^{-/-}$ mice were more susceptible to DSS injury, exhibiting more severe colitis symptoms, including altered stool consistency, blurred vascular patterns, and mucosal ulcerations upon colonoscopy.[109,110]

TAM ligands can also influence IBD progression by modulating efferocytosis. Patients with IBD exhibit reduced levels and impaired activity of ProS.[111–113] Similarly, *Gas6*$^{-/-}$ mice displayed greater sensitivity to DSS, with more severe colitis compared with WT mice.[109] MFG-E8 expression is dynamically regulated during DSS-induced colitis, being reduced in early stages but upregulated later. Additionally, *BAI1*$^{-/-}$ mice exhibited more severe colitis, with numerous uncleared apoptotic bodies observed in colonic epithelium.[106]

Efferocytosis is also closely linked to autophagy. Deficiency of the autophagy-associated gene nuclear receptor-binding factor 2 (NRBF2) reduced apoptotic cell clearance both in vivo and in vitro, and this impairment was associated with worsened IBD pathology. *NRBF2*$^{-/-}$ mice were more susceptible to DSS-induced colitis, showing more severe intestinal inflammation and greater apoptotic cell accumulation.[114] Enhancing LAP to boost efferocytosis was found to alleviate DSS-induced colitis, highlighting this pathway's therapeutic potential.[115]

Gouty Arthritis

GA features driven immune inflammation by MSU crystals. The resolution of this inflammation demands timely apoptosis and efferocytosis of recruited neutrophils. In GA, synovial fluid–infiltrating monocytes/macrophages exhibit low expression of MerTK, leading to impaired efferocytosis and a lack of effective anti-inflammatory and clearance mechanisms during the early phase of inflammation.[116] Annexin A1 (AnxA1), a glucocorticoid-regulated protein with anti-inflammatory properties. Notably, AnxA1 functions as a "find-me" signal on apoptotic neutrophils, enhancing macrophage efferocytosis.[117–119] In GA, AnxA1 has been shown to facilitate the resolution phase by inducing neutrophil apoptosis and ensuring their effective clearance, whereas AnxA1 deficiency impairs macrophage-mediated efferocytosis of apoptotic neutrophils.[120] Survivin, an anti-apoptotic protein upregulated in neutrophils during MSU-induced GA, can be targeted by YM155 to induce apoptosis and thereby accelerate efferocytosis and inflammation resolution.[121] Similarly, inhibition of Rho-associated kinase (ROCK) promotes neutrophil apoptosis and augments efferocytosis, facilitating the termination of acute inflammation.[122] Notably, most studies to date have focused on enhancing neutrophil apoptosis, whereas strategies aimed at directly boosting macrophage efferocytosis remain underexplored, representing a promising direction for future research.

To provide a comprehensive and comparative overview of the distinct mechanisms driving efferocytosis dysfunction across the spectrum of IMIDs, the key defects, molecular pathways, pathological consequences, and representative evidence for each disease are summarized in Table 1.

Therapeutic Strategies Targeting Efferocytosis in IMID

The pathological hallmark of IMID is chronic inflammation driven by aberrant immune activation. Restoring macrophage efferocytosis is therefore emerging as a promising immunomodulatory strategy. Enhancing efferocytosis holds the potential to simultaneously promote inflammation resolution, facilitate tissue repair, and re-establish immune tolerance (Figure 3).

Table 1 Disease-Specific Mechanisms and Consequences of Defective Efferocytosis Across Immune-Mediated Inflammatory Diseases (IMIDs)

Disease	Major Defect in Efferocytosis	Key Molecular Pathways/ Regulators	Pathological Consequences	Representative Evidence
SLE	Excess apoptotic burden and impaired apoptotic cell recognition	Xkr8-mediated PtdSer exposure; TAM receptors (MerTK, Axl, Tyro3); bridging molecules (C1q, MFG-E8, Gas6, ProS)	Accumulation of nuclear debris, immune complex formation, systemic autoimmunity	Xkr8$^{-/-}$ mice develop ANA/anti-dsDNA (mouse); TAM triple KO lupus-like phenotype (mouse); C1q deficiency strongly linked to human SLE (human)
RA	Reduced efferocytosis capacity of synovial macrophages and altered macrophage phenotypes	Decreased MerTK^{+}CD206^{+} macrophages; TAM receptor axis; αvβ3 integrin; MFG-E8	Persistent synovial inflammation, osteoclast activation, joint destruction	MerTK/Axl deficiency exacerbates arthritis; reduced serum MFG-E8; dynamic TAM expression across disease stages in human synovial macrophages
SS	MerTK shedding and ligand deficiency impair macrophage efferocytosis	MerTK–Gas6 axis; ADAM17-mediated MerTK cleavage; reduced Gas6 levels	Accumulation of apoptotic glandular epithelial cells, autoantigen persistence, systemic immune activation	Elevated sMerTK in SS; MerTK$^{-/-}$ mice develop SS-like phenotypes; reduced Gas6 in labial glands
AD	Loss of pro-efferocytosis macrophage subsets and cytokine-driven suppression of efferocytosis pathways	FRβ^{+}/CD163^{+} SI macrophages; MerTK and Gas6 downregulation; IL-4/ M-CSF signaling	Apoptotic debris accumulation, secondary necrosis, IgE-driven allergic inflammation	Depletion of SI macrophages in AD skin; stress suppresses Gas6/MerTK; IL-4/M-CSF enhances efferocytosis in models
PsO	Inflammatory platelet–neutrophil–macrophage feedback loop inhibiting efferocytosis	Platelet–macrophage crosstalk downregulates MerTK; reduced Gas6; neutrophil CD47 upregulation; impaired autophagy	Persistent neutrophil accumulation, chronic skin inflammation, systemic comorbidities	Platelet-induced MerTK suppression; MPO deficiency → CD47 upregulation; TAM/Gas6 downregulated in lesional psoriatic skin
AILD	TAM receptor and TREM2 dysfunction with receptor shedding	TAM receptors; TREM2; S1P signaling; ADAM17-mediated TREM2 shedding	Defective hepatocyte/ cholangiocyte clearance, fibrosis progression, and breakdown of hepatic immune tolerance	Reduced phagocytic capacity of circulating monocytes in AILD patients; TREM2 cleavage in chronic inflammation; macrophage-dependent tolerance loss
IBD	Impaired macrophage efferocytosis and autophagy-associated clearance pathways	TAM receptors; Gas6/ProS; MFG-E8; BAI1; NRBF2; LC3-associated phagocytosis (LAP)	Accumulation of apoptotic epithelial cells, mucosal inflammation, barrier disruption, and loss of intestinal tolerance	Axl$^{-/-}$MerTK$^{-/-}$ mice confers increased susceptibility to DSS-induced colitis; Gas6$^{-/-}$ worsens colitis; NRBF2 deficiency aggravates IBD
GA	Low MerTK expression and insufficient macrophage clearance of apoptotic neutrophils	MerTK; Annexin A1; Survivin; ROCK signaling	Delayed resolution of acute inflammation, prolonged neutrophil-driven inflammation, and transition to chronic gout	Reduced MerTK expression on synovial macrophages; AnxA1 promotes efferocytosis; ROCK inhibition accelerates resolution

Note: All abbreviations are defined in the main text.

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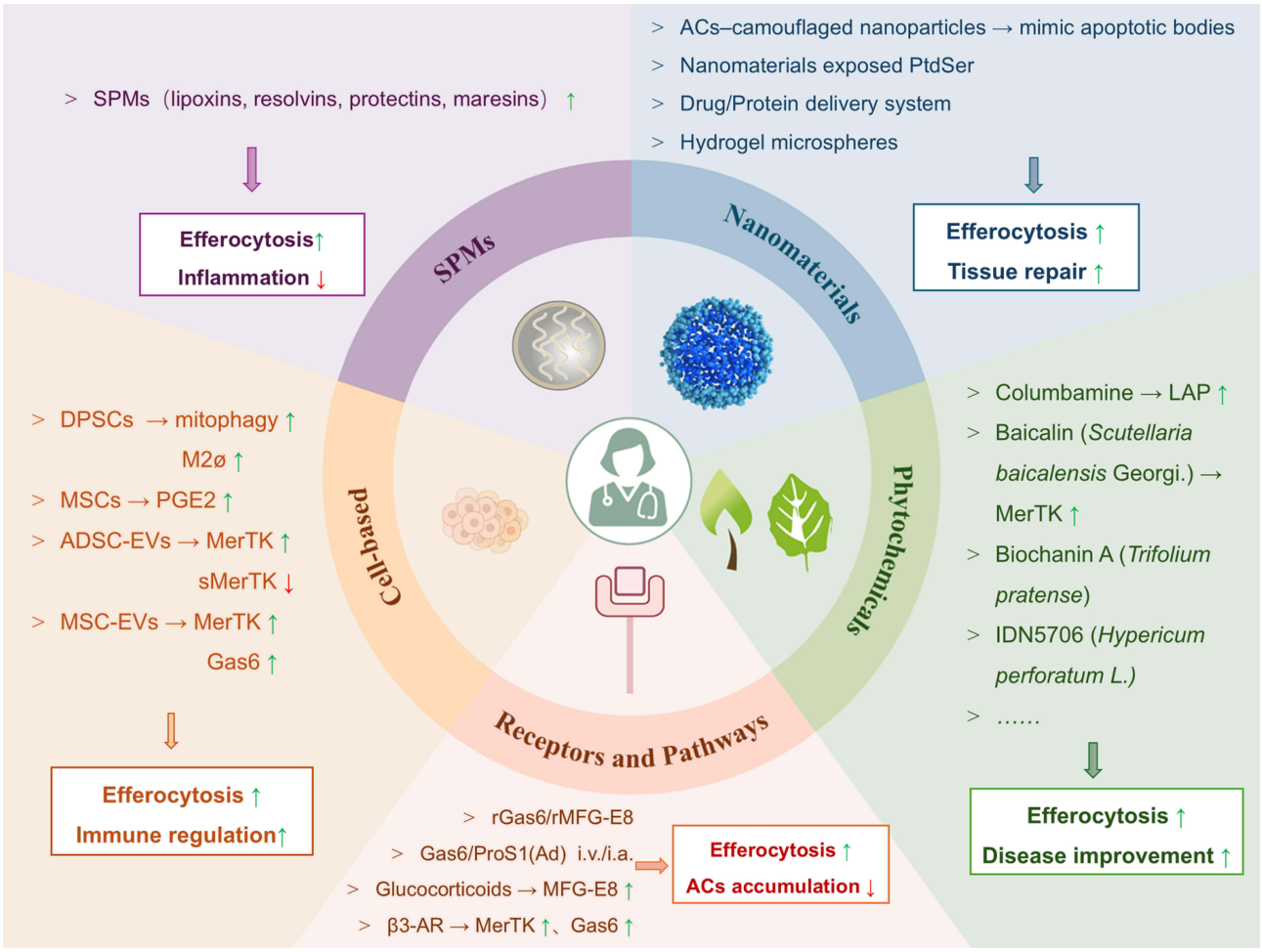

Figure 3 Therapeutic strategies targeting macrophage efferocytosis in immune-mediated inflammatory diseases. Defective efferocytosis drives persistent inflammation in IMIDs. Therapeutic interventions—including receptor agonists, nanomaterials, apoptotic cell infusion, stem cell–based therapies and phytochemicals—have been shown to enhance macrophage efferocytosis, thereby promoting inflammation resolution, tissue repair and immune tolerance.
Abbreviations: ACs, apoptotic cells; ADSC-EVs, Adipose-derived stem cell EVs; β3-AR, β3-adrenergic receptor; CIA, collagen-induced arthritis; DPSCs, dental pulp stem cells; EVs, extracellular vesicles; MSCs, Mesenchymal stem cells; MSC-EVs, MSC-derived EVs; SPMs, specialized pro-resolving mediators.

Targeting Receptors and Signaling Pathways

Therapeutic strategies directed at receptors involved in the efferocytosis process offer promising avenues for modulating disease progression and outcomes in IMIDs. In collagen-induced arthritis (CIA) mouse models, exogenous administration of Gas6 and ProS has been reported to promote efferocytosis and facilitate resolution of RA-associated inflammation.[67] Intra-articular delivery of Gas6 has been shown to restore macrophage engulfment of apoptotic cells, thereby reducing their pathological accumulation.[123] In SLE, glucocorticoids have been demonstrated to transcriptionally upregulate MFG-E8, selectively enhancing efferocytosis and ameliorating disease severity.[124] Similarly, in IBD, administration of recombinant MFG-E8 attenuates DSS-induced colitis by modulating efferocytosis.[125,126] Pharmacological activation of the β3-adrenergic receptor (β3-AR) has been shown to upregulate MerTK and Gas6 expression in macrophages, leading to enhanced efferocytosis capacity.[127]

Among efferocytosis-related receptors, MerTK represents a central therapeutic target for restoring defective apoptotic cell clearance in IMIDs. Pharmacological activation of MerTK signaling promotes macrophage-mediated efferocytosis and accelerates resolution of inflammation in multiple preclinical disease models. Agonistic activation of the TAM receptor axis, for example through Gas6 overexpression or MerTK agonists, reduces disease severity in experimental models of rheumatoid arthritis and multiple sclerosis, underscoring the potential of MerTK-centered therapies to reprogram macrophages toward pro-resolving phenotypes.[67,128–130]

Although MerTK activation generally exerts anti-inflammatory effects, therapeutic strategies must consider the mode of receptor engagement. For example, while ProS-mediated MerTK activation ameliorates experimental arthritis, treatment with agonistic MerTK antibodies paradoxically exacerbates disease by impairing efferocytosis and promoting secondary necrosis of neutrophils.[62] These findings highlight that ligand-based versus antibody-mediated MerTK activation may trigger distinct downstream signaling outcomes and underscore the importance of context-specific therapeutic design.

However, many efferocytosis-related molecules exert pleiotropic functions in immune regulation, tissue homeostasis, and cancer biology, raising concerns regarding potential off-target effects and long-term safety. Therapeutic targeting of efferocytosis therefore presents important challenges and safety considerations. For example, triple knockout of TAM receptors induces severe systemic autoimmunity in mice, highlighting their critical role in maintaining immune tolerance and underscoring the risk of unintended immune dysregulation when this pathway is manipulated.[47] These considerations emphasize the need for precise, context-dependent modulation strategies to ensure both efficacy and safety in efferocytosis-targeted therapies.

Nanomaterials

Nanomaterials have emerged as versatile platforms for developing multifunctional delivery systems that modulate efferocytosis in IMIDs.[131,132] Diverse biomimetic strategies, which simulate "eat-me" signals or target efferocytosis receptors, are being developed to reshape the inflammatory microenvironment. One representative strategy employs apoptotic chondrocyte membrane–camouflaged nanoparticles that display canonical "eat-me" signals, closely mimicking native apoptotic bodies in articular cartilage.[133] Similarly, a class of nanomaterials engineered to expose PtdSer signals selectively target inflammatory synovial macrophages, driving their anti-inflammatory polarization in RA.[134] Efferocytosis-mimicking nanovesicles have also been shown to sustain the balance between pro- and anti-inflammatory macrophage subsets within the joint, thereby preventing RA-associated bone erosion.[135] In another approach, a macrophage-based bioactive targeted drug delivery system demonstrated substantial therapeutic potential in RA.[136] In SLE, PtdSer-conjugated liposome-coated gold nanocages mimic apoptotic cells and deliver liver X receptor (LXR) agonists to macrophages, restoring defective clearance of apoptotic cells, reducing anti-dsDNA autoantibodies, attenuating inflammation, and alleviating kidney damage.[137]

In degenerative joint disease, cartilage lesion–targeted hydrogel microspheres were designed to restore efferocytosis, reverse chondrocyte senescence and accelerate cartilage repair in OA.[138] In PsO, a MerTK-targeted nanoplatform disrupted the macrophage–platelet feedback loop, thereby enhancing efferocytosis and ameliorating disease severity.[92] Targeted delivery of MerTK protein via cell membrane-engineered nanoparticles has been shown to enhance efferocytosis in diabetic mice and alleviate their atherosclerotic symptoms.[139]

Beyond joint and vascular disorders, efferocytosis-targeting nanomaterials have shown promise in chronic tissue repair. Apoptotic neutrophil membrane–modified liposomes enhanced efferocytosis and accelerated wound healing in chronic diabetic wounds.[140] A nanosized magnesium particle uses PtdSer-mimetic "eat-me" signals to trigger macrophage efferocytosis, reinforcing gut-liver barrier integrity and reducing inflammation, and exemplifies biomimetic PtdSer-targeting nanomaterials for immunomodulation and tissue repair.[141] Oxidation-responsive nanoparticles carrying the proresolving annexin A1–mimetic peptide Ac2-26 selectively release Ac2-26 at ROS-rich inflamed sites in IBD, promoting efferocytosis of apoptotic neutrophils, macrophage phenotypic switching, and mucosal healing.[142] These examples highlight the translational potential of biomimetic nanomaterials that integrate "eat-me" signals and molecular targeting to restore efferocytosis and resolve inflammation across diverse tissues.

Cell-Based Therapies

Targeting apoptotic cells and cell-based interventions represent innovative therapeutic strategies for modulating efferocytosis in immune-mediated inflammatory diseases.[143,144] In CIA mice, apoptotic cell infusion markedly reduced joint inflammation and attenuated bone erosion.[145] Similar benefits were observed in DSS-induced colitis, administration of apoptotic cells alleviated intestinal inflammation severity.[146]

Recent studies have further highlighted the therapeutic potential of stem cells in enhancing efferocytosis. A study on osteoarthritis of the temporomandibular joint found that dental pulp stem cells (DPSCs) enhance the efferocytosis capacity of macrophages both in vivo and in vitro.[147] Mesenchymal stem cells (MSCs) have also demonstrated efficacy in IBD by modulating efferocytosis to sustain immune regulation and tissue repair.[148] Beyond whole-cell therapies, extracellular vehicles (EVs) derived from stem cells have emerged as potent modulators of efferocytosis. Adipose-derived stem cell EVs (ADSC-EVs) enhanced efferocytosis through ADAM17/MerTK regulation, thereby improving sepsis-associated acute kidney injury.[149] Similarly, MSC-derived EVs (MSC-EVs) promoted macrophage efferocytosis, potentially through the MerTK–ERK–COX2 axis, and hold considerable promise in treating ischemia–reperfusion injuries across multiple organs.[150] In SLE, MSC-EVs not only enhanced macrophage efferocytosis but also recruited Treg cells, offering a novel immunomodulatory strategy.[151,152]

Clinical evidence further supports the application of stem cell–based approaches in IMID. Multiple trials are underway worldwide.[153,154] Notably, a Phase III clinical trial involving 212 patients demonstrated that allogeneic expanded ADSCs (Cx601) were both effective and safe in treating complex perianal fistulas in IBD (NCT01541579). These findings suggest that stem cell–based therapies, particularly those harnessing efferocytosis modulation, may hold transformative potential in the future management of IMID.

Phytochemicals

Phytochemicals, a diverse class of naturally occurring compounds in plants, have shown considerable potential as modulators of efferocytosis for therapeutic purposes. Columbamine, a small molecule alkaloid isolated from traditional herbal medicine, was reported to trigger LAP and enhance efferocytosis, thereby attenuating inflammation in DSS-induced colitis models.[115,155] Baicalin is the main active ingredient primary isolated from the Chinese herb, *Scutellaria baicalensis* Georgi. It has been shown to upregulate the MerTK receptor, thereby promoting macrophage efferocytosis to mitigate disease progression.[156] Hyperforin is one of the key constituents of *Hypericum perforatum L*. Its tetrahydro-derivatives IDN5706 have demonstrated the ability to enhance macrophage efferocytosis, alleviating synovial inflammation in OA models.[157] Biochanin A (BCA), a natural isoflavone abundant in red clover (*Trifolium pratense*), has been found to reduce arthritis severity in antigen-induced arthritis mice, in part by enhancing efferocytosis.[158] Compared with conventional pharmacological agents, phytochemicals may offer advantages such as lower toxicity and fewer side effects, highlighting their promise as a source of safe and effective natural products for future therapeutic development.

Specialized Pro-Resolving Mediators

A class of endogenous lipid mediators known as specialized pro-resolving mediators (SPMs) has emerged as potent regulators of inflammation resolution and efferocytosis.[159,160] SPMs, including lipoxins, resolvins, protectins, and maresins, are enzymatically derived from omega-3 and omega-6 polyunsaturated fatty acids and actively orchestrate the termination of inflammation without compromising host defense.[161] These mediators represent a paradigm shift from immunosuppression toward resolution pharmacology.

A function of nearly all SPMs is to enhance macrophage-mediated efferocytosis.[161,162] Mechanistically, SPMs bind to specific G-protein coupled receptors on macrophages, promoting Rac1-mediated cytoskeletal reorganization, increasing the expression of efferocytosis receptors such as MerTK, and shifting macrophages toward a pro-resolving phenotype. The relationship between efferocytosis and SPMs is bidirectional. During the digestion stage of efferocytosis, macrophages upregulate 12/15-lipoxygenase expression, leading to increased endogenous generation of SPMs, which in turn facilitate subsequent rounds of efferocytosis and sustained resolution.[163–165]

Accumulating evidence supports the therapeutic potential of SPMs in immune-mediated inflammatory diseases. In IBD, SPMs reduce intestinal inflammation and promote mucosal healing, with emerging evidence indicating a role in modulating tumor-promoting inflammation in colitis-associated cancer Current studies have demonstrated the therapeutic potential of SPMs.[163] In RA, SPMs attenuate synovial inflammation and bone erosion by enhancing the efferocytosis of apoptotic neutrophils within the joint microenvironment.[160,163,166] In a rabbit model of GA, early COX-2–dependent PGE_2 production has been shown to drive lipid mediator class switching toward SPM biosynthesis, accompanied by Formyl Peptide Receptor2 (FPR2) upregulation and enhanced macrophage efferocytosis and pro-resolving

polarization.[167] Collectively, these findings highlight SPMs as promising efferocytosis-targeting pro-resolving therapeutics, although challenges related to stability, receptor redundancy, and translational delivery remain to be addressed.

Conclusion and Future Directions

Efferocytosis has emerged as a central mechanism for maintaining tissue homeostasis and immune tolerance. Its dysregulation is increasingly recognized as a common pathogenic feature across IMIDs, including SLE, RA, and IBD. These defects arise from a complex network of regulatory disturbances, such as downregulation of efferocytosis receptors, perturbations imposed by the chronic inflammatory microenvironment, and metabolic imbalances.

From a therapeutic perspective, efferocytosis represents not merely an immunological phenomenon but a tractable target for intervention. These advances highlight the potential of efferocytosis-centered interventions to address pathogenic immune dysregulation more precisely than conventional anti-inflammatory treatments. Strategies such as modulating TAM receptor signaling pathways, employing nanomaterials to enhance apoptotic cell clearance, and engineering biomaterials to restore efferocytosis are rapidly evolving into next-generation immune-modulatory approaches. Such advances underscore the potential of efferocytosis-centered interventions to correct pathogenic immune dysregulation more precisely than conventional anti-inflammatory therapies.

Nevertheless, therapeutic manipulation of efferocytosis is complicated by its context-dependent and pleiotropic functions, raising concerns about unintended immune dysregulation or tissue-specific off-target effects. Moreover, the spatiotemporal heterogeneity of efferocytosis across tissues and disease stages remains poorly characterized, posing challenges for precision intervention.

The intricate interplay between macrophage efferocytosis and IMID presents both challenges and opportunities. Despite promising preclinical findings, key questions remain unresolved—such as identifying robust biomarkers for efferocytosis, defining optimal timing and delivery of interventions, and understanding long-term impacts on immune homeostasis. Bridging the gap between mechanistic insights and clinical translation will be essential. By deepening our understanding of efferocytosis and developing targeted strategies, there is a realistic prospect of shifting IMID therapy from mere inflammation control toward the re-establishment of durable immune equilibrium.

Highlights

- Define efferocytosis as a central mechanism preserving immune tolerance and tissue homeostasis.
- Reveal defective efferocytosis as a shared driver of chronic inflammation across IMIDs.
- Emphasize macrophage TAM signaling and bridging molecules as key clearance checkpoints.
- Propose efferocytosis restoration as a cross-disease strategy to resolve inflammation.

Abbreviations

β2M, β2-microglobulin; ACs, apoptotic cells; AD, atopic dermatitis; ADAM17, a disintegrin and metalloproteinase 17; ADSC, adipose-derived stem cell; AILD, autoimmune liver disease; BAI1, brain-specific angiogenesis inhibitor 1; CD, Crohn's disease; CIA, collagen-induced arthritis; cox-2, cyclooxygenase-2; CRT, calreticulin; CX3CL1, CX3C ligand 1; DCs, dendritic cells; DAMPs, damage-associated molecular patterns; DEL-1, developmental endothelial locus-1; DOCK180, dedicator of cytokinesis 180; DPSCs, dental pulp stem cells; DSS, dextran sulfate sodium; ELMO, engulfment and cell motility protein 1; EVs, extracellular vesicles; FPR2, formyl peptide receptor 2; GA, gouty arthritis; G2A (GPR132), G protein-coupled receptor 132; GAS6, growth arrest-specific protein 6; GPP, generalized pustular psoriasis; IBD, inflammatory bowel disease; IMIDs, immune-mediated inflammatory diseases; LAP, LC3-associated phagocytosis; LPC, lysophosphatidylcholine; LXR, Liver X Receptor; MerTK, MER tyrosine kinase; MFG-E8, milk fat globule-epidermal growth factor 8; MPO, myeloperoxidase; MSCs, mesenchymal stem cells; MSU, monosodium urate; NRBF2, nuclear receptor-binding factor 2; OA, osteoarthritis; PD-L1, programmed death-ligand 1; PtdSer, phosphatidylserine; ProS, protein S; PsO, psoriasis; RA, rheumatoid arthritis; SCARF1, scavenger receptor class F member 1; SIRPα, signal regulatory protein alpha; SLE, systemic lupus erythematosus; S1P, sphingosine-1-phosphate; SPMs, specialized pro-resolving mediators; SS, Sjögren's syndrome; TAM (Tyro3, Axl, MerTK), the TAM family of receptor tyrosine kinases;

TIMs (TIM-1 and TIM-4), T cell immunoglobulin and mucin domain-containing proteins; TLR, Toll-like receptor; UC, ulcerative colitis.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Author Contributions

Zelin He: Conceptualization, Investigation, Visualization, Writing – original draft. Nuoshi Chen: Conceptualization, Investigation, Writing – review & editing. Yan Zhang: Conceptualization, Validation, Writing – review & editing. Hongyan Du: Conceptualization, Supervision, Funding acquisition, Resources, Writing – review & editing. Ligang Jie: Conceptualization, Supervision, Funding acquisition, Resources, Writing – review & editing. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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