Efferocytosis in multisystem diseases (Review)

YIFAN ZHANG[1,2], YIRU WANG[1,2], JIE DING[1,2] and PING LIU[1]

[1]Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200032;
[2]Shanghai University of Traditional Chinese Medicine, Shanghai 201203, P.R. China

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Abstract. Efferocytosis, the phagocytosis of apoptotic cells performed by both specialized phagocytes (such as macrophages) and non-specialized phagocytes (such as epithelial cells), is involved in tissue repair and homeostasis. Effective efferocytosis prevents secondary necrosis, terminates inflammatory responses, promotes self-tolerance and activates pro-resolving pathways to maintain homeostasis. When efferocytosis is impaired, apoptotic cells that could not be cleared in time aggregate, resulting in the necrosis of apoptotic cells and release of pro-inflammatory factors. In addition, defective efferocytosis inhibits the intracellular cholesterol reverse transportation pathways, which may lead to atherosclerosis, lung damage, non-alcoholic fatty liver disease and neurodegenerative diseases. The uncleared apoptotic cells can also release autoantigens, which can cause autoimmune diseases. Cancer cells escape from phagocytosis via efferocytosis. Therefore, new treatment strategies for diseases related to defective efferocytosis are proposed. This review illustrated the mechanisms of efferocytosis in multisystem diseases and organismal homeostasis and the pathophysiological consequences of defective efferocytosis. Several drugs and treatments available to enhance efferocytosis are also mentioned in the review, serving as new evidence for clinical application.

Correspondence to: Professor Ping Liu, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, 725 South Wan-Ping Road, Shanghai 200032, P.R. China
E-mail: liuping0207@126.com

Abbreviations: ACs, apoptotic cells; AD, Alzheimer's disease; AKT, protein kinase B; ALI, acute lung injury; AMPK, AMP-activated protein kinase; ARDS, acute respiratory distress syndrome; ATP, adenosine triphosphate; Aβ, amyloid β protein; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CX3CL1, CX3C chemokine ligand 1; CX3CR1, CX3C chemokine receptor 1; dsDNA, anti-double-stranded DNA; ERK5, extracellular signal-regulated kinase 5; GAS6, growth arrest specific protein 6; GXK, Guan Xinkang; HMGB1, high mobility group box-1; IBD, inflammatory bowel disease; LPC, lyso-phosphatidylcholine; LRP1, low-density lipoprotein receptor related proteins 1; LXR, liver X receptor; Mertk, Mer tyrosine protein kinase receptor; MFGE8, milk fat globule-epidermal growth factor 8; MI, myocardial infarction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NLRP3, NLR family, pyrin domain containing 3; PD, Parkinson's disease; PPAR, peroxisome proliferator receptor; ProS, Protein S; PtdSer, phosphatidylserine; RA, rheumatoid arthritis; ROS, reactive oxygen species; SCARF1, scavenger receptor class F member 1; SLE, systemic lupus erythematosus; SRB1, scavenger receptor 1; SS, Sjogren's syndrome; T1D, type 1 diabetes; TAM, TYRO3/Axl/MER tyrosine kinase receptor; TIM, T-cell immunoglobulin and mucin domain-containing molecule

Key words: efferocytosis, cardiovascular diseases, respiratory diseases, liver and intestine diseases, autoimmune diseases, neurodegenerative diseases

Contents

1. Introduction

Efferocytosis refers to the physiological process in which phagocytic cells clear apoptotic cells (ACs) (1). Phagocytosis involves both specialized phagocytes (such as macrophages) and non-specialized phagocytes (such as epithelial cells) (2).

Efferocytosis can be divided into four stages (2) (Fig. 1): i) 'Find me' stage. Chemotactic factors induce macrophages to recognize and surround ACs. The 'find me' signal molecules released by ACs are recognized by homologous receptors on the surface of phagocytes, to induce the migration and recruitment of phagocytes to ACs (3). ii) 'Eat me' stage. Phagocytic receptors of macrophages recognize and bind to the 'eat me' signal molecules of ACs through bridging molecules. Following the programmed cell apoptosis, the 'eat me' signal molecule ligands on the AC surface are exposed, which can directly bind to the 'eat me' signal molecule receptors on the surface of phagocytes (4). Then, one end of the bridging molecules, as signal molecules related to efferocytosis, binds to the ligand of 'eat me' signal molecule of ACS and the other end binds to the receptor of the 'eat me' signal molecule on the

surface of the phagocyte. Therefore, the phagocytes recognize and capture ACs in the direct 'ligand-receptor' binding form and the indirect 'ligand-bridging molecule-receptor' binding form (5). iii) Endocytosis stage. The 'eat me' signal molecules binding to phagocytic receptors activate the programmed cell removal system to form 'a phagocytic cup' and complete the endocytosis of ACs (6). iv) 'Post-phagocytosis' stage. Macrophages further digest and degrade apoptotic cell debris, activating multiple metabolic signaling pathways (7). After phagocytic cells engulf ACs, phagosomes are formed and then fuse with primary lysosomes to form phagolysosomes (8). When the phagolysosome matures, it begins to degrade ACs and release anti-inflammatory cytokines such as IL-10 and TGF-β (5).

In efferocytosis, a number of molecules function to clear ACs promptly so that normal tissues cannot be damaged. First, the 'find me' signal molecules, consisting of direct ligand molecules and indirect signal molecules, are released after cell apoptosis. The direct ligand molecules include triphosphate nucleotides ATP, uridine-5'-triphosphate (9), lyso-phosphatidylcholine (10) and sphingosine-1-phosphate (11). The indirect signal molecules include CX3C chemokine ligand 1 (CX3CL1) protein (12). Second, the 'find me' signal is received by phagocytic cell receptors. Then the phagocytic receptors, including receptor G2 accumulation (13), CX3C chemokine receptor 1 (CX3CR1) (12), low-density lipoprotein receptor related proteins 1 (LRP1) (14) and scavenger receptor class B type 1 (SRB1), directly interact with 'eat-me' signal molecules on the surface of ACs, such as phosphatidylserine (PtdSer) (15), oxidized phospholipids and endoplasmic reticulum-resident protein calreticulin (16). The phagocytic receptors, such as Mer tyrosine protein kinase receptor (Mertk) (17), also interact with 'eat-me' signal molecules indirectly through bridging molecules (5). Extracellular bridging molecules link phagocytes with ACs, activate the phagocytic function of phagocytes and remove the ACs, such as milk fat globule-epidermal growth factor (MFGE8), serum complement C1q, transglutaminase 2, human growth arrest specific protein 6 (GAS6) and protein S (ProS) (17). These signaling molecules and extracellular bridging molecules are key to efferocytosis. In addition, the 'not eat me' signal in non-apoptotic cells prevents viable cells from being cleared by phagocytes. Among them, the best-known signal molecule is CD47 (18; Table I).

Efferocytosis is essential for human health, because it can prevent the deleterious effects of cell necrosis, thus maintaining the tissue and organ homeostasis (19) and the normal immune response (20). Apart from preventing secondary necrosis, efferocytosis has three functions: Terminating inflammatory responses, promoting self-tolerance and activating pro-resolving pathways (21). Efferocytosis triggers the production of anti-inflammatory and tissue-reparative cytokines, while defective efferocytosis may lead to hyperinflammation and diseases (5).

The present study summarized the current knowledge of efferocytosis and the links between efferocytosis and body homeostasis. Further, it reviewed the consequences of impaired efferocytosis in multisystem diseases (Fig. 2; Table II). Several drugs and treatments available to enhance efferocytosis are also mentioned to provide new evidence for clinical application.

2. Cardiovascular diseases

Studies on genome-wide association have discovered that common genetic variants in the chromosome 9p21 confer the risk of coronary artery disease, myocardial infarction (MI) (22) and ischemic stroke (23). The expression of calreticulin protein is reduced in the plaques of these allele carriers (24), while the area of the necrotic core and the number of ACs increase in the plaques of atherosclerosis (25). Calreticulin, located in the endoplasmic reticulum, serves a crucial role in cardiac embryogenesis. It affects cardiac development and myofibrillogenesis and is involved in the pathophysiology of several cardiac pathologies (26). Calreticulin binds to the 'eat me' ligand on the surface of ACs, activating LDLR4 on the surface of phagocytic cells and inducing phagocytosis (14). Therefore, the reduction of calreticulin protein of these allele carriers suppresses the 'eat me' signal and weakens the phagocytosis of ACs. This explains why efferocytosis is independent of traditional risk factors (such as hypertension, dyslipidemia, diabetes and smoking) of cardiovascular diseases (27).

Atherosclerosis, a major pathological basis for cardiovascular and cerebrovascular diseases, is also the key process in other diseases, such as chronic cerebral insufficiency and cerebral infarction. Atherosclerosis is considered to be a cholesterol storage disease and a lipid-driven inflammatory disease (28). Cholesterol loading is hypothesized to cause pro-inflammatory cytokine secretion and form intracellular cholesterol microcrystals that activate the inflammasome (29). In addition, cholesterol-laden macrophages are 'foam cells' that die easily and release their contents in advanced lesions and thereby can worsen the inflammatory status (30). As atherosclerosis is an inflammatory disease, various factors involved in the inflammatory response may be related to the formation of atherosclerotic plaques (31). TNF-α is elevated in the pro-inflammatory early-stage of atherosclerosis. TNF-α inhibits MFGE8, Mertk and LRP1 by activating the Toll-like receptor (TLR) (32) and upregulates CD47 expression to activate the 'not eat me' signal (33). TNF-α weakens the efferocytosis and prevents timely clearance of ACs, thereby aggravating the inflammatory response and further worsening atherosclerosis (34). The above reactions form a vicious circle. Therefore, the effect of efferocytosis is gradually impaired as the atherosclerotic plaque progresses.

In atherosclerosis, the clearance of ACs is essential to resolve inflammation. Efferocytosis promotes the resolution of inflammation in a stepwise manner. One step is to recognize and engulf ACs, which prevents AC accumulation and inflammatory agent secretion (35). The engulfment of ACs results in the acquisition of excess cellular materials such as lipids, carbohydrates, proteins and nucleic acids (36). Macrophages need to activate degradation and efflux pathways for increased metabolic load, which is crucial for inflammatory resolution and tissue repair (19). For instance, lipid metabolism activates the nuclear receptors peroxisome proliferator-activated receptor (PPAR) and liver X receptor (LXR)-α, helping release anti-inflammatory cytokines, such as IL-10 and TGF-β (37,38). Efferocytosis within the plaque is impaired when atherosclerotic plaque develops in the late stage (39). A study has confirmed that the ratio of apoptotic cell clearance is nineteen times higher in human tonsils as compared with

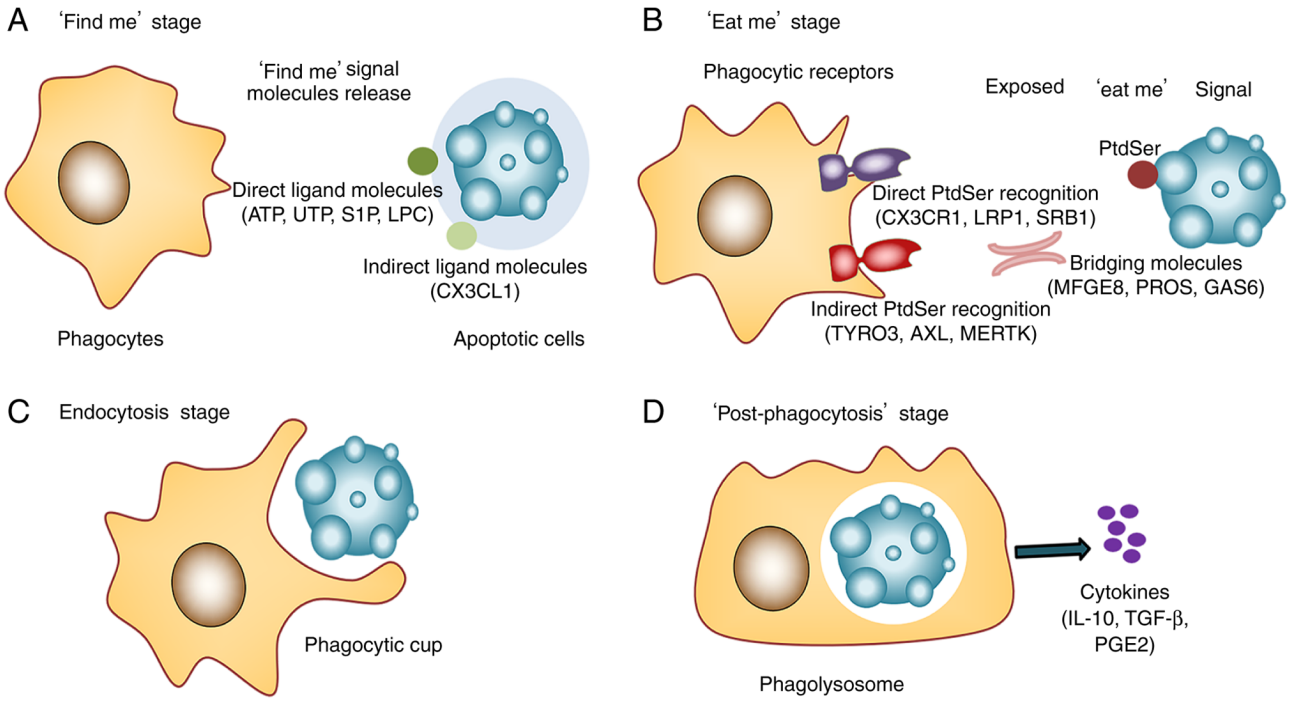

Figure 1. Four stages of efferocytosis. (A) 'Find me' stage. Chemotactic factors induce macrophages to recognize and surround ACs. The 'find me' signal molecules released by ACs are recognized by phagocytes, inducing the migration and recruitment of phagocytes to ACs. (B) 'Eat me' stage. Phagocytic receptors of macrophages recognize and bind to the 'eat me' signal molecules of ACs. (C) Endocytosis stage. Forming 'a phagocytic cup' completes the endocytosis of ACs. (D) 'Post-phagocytosis' stage. Macrophages further digest and degrade apoptotic cell debris, activating multiple metabolic signaling pathways. ATP, triphosphate nucleotides adenosine triphosphate; UTP, uridine-5'-triphosphate; S1P, sphingosine-1-phosphate; LPC, lyso-phosphatidylcholine; CX3CL1, CX3C chemokine ligand 1; CX3CR1, CX3C chemokine receptor 1; LRP1, low-density lipoprotein receptor related proteins 1; SRB1, scavenger receptor 1; MFGE8, milk fat globule-epidermal growth factor; ProS, protein S; PtdSer, phosphatidylserine; GAS6, growth arrest specific protein 6; TYRO3/AXL/MERTK, TAM receptors.

human atherosclerotic plaques (40). Schrijvers *et al* (40) found more apoptotic cells outside lesional phagocytes in advanced human coronary artery lesions. Defective efferocytosis leads to post-apoptotic cellular necrosis and the release of proinflammatory factors (41). Failed AC clearance, increased inflammation (42) and worsened atherosclerosis (43,44) were found in mice lacking TIM-4, Mertk, MFGE8, or Pro S. As macrophage apoptosis accelerates under defective efferocytosis, the lipid-laden necrotic core enlarges with the progression of atherosclerotic plaques (45). Thinning fibrous cap, high-level inflammatory cytokines, apoptosis of intimal cells and expansion of the lipid-laden necrotic core all contribute to vulnerable plaques and acute coronary artery syndrome (46). The absence of efferocytosis signals also inhibits the subsequent intracellular cholesterol reverse transportation pathways (24), then promotes foam cell formation and initiates the development of atherosclerosis. C1q protects early atherosclerosis by promoting macrophage survival and improving the function of macrophage foam cells (47).

Effective efferocytosis can inhibit secondary cell necrosis and prevent dead cells from releasing inflammatory factors and toxic molecules, thereby slowing down atherosclerosis progression and reducing plaque vulnerability (32). Enhanced efferocytosis can reverse hypoxia in murine atherosclerosis to prevent necrotic core expansion (48). Natalicone ZB, the specific agonist of LXR, can facilitate efferocytosis, inhibit plaque formation and reduce the area of necrotic core (49). Conventional anti-atherosclerotic drugs, such as statins and non-steroidal PPAR γ agonists, can enhance efferocytosis in plaques (50,51). In atherosclerosis treatment, statin can reduce cholesterol and inflammation, repress the highly expressed Ras homologous gene family member A, a negative regulator of phagocytosis in atherosclerotic lesions (50).

Experimental results have confirmed the regulatory role of extracellular signal-regulated kinase 5 (ERK5) in macrophage phagocytosis. ERK5, one of the mitogen-activated protein kinases, can maintain macrophage phagocytosis and prevent atherosclerosis progression (32). In $LDLR^{-/-}$ mice, ERK5 gene knockout can aggravate atherosclerosis and inhibit the expression of efferocytosis-related proteins (52). ERK5 inhibitor can downregulate the phagocytosis of RAW264.7 cells *in vitro* (53). Thus, it can be concluded that regulating efferocytosis of macrophages through ERK5 can exert an anti-atherosclerosis effect.

Efferocytosis also serves a role in other cardiovascular diseases. In Wan *et al* (54), Mertk could clear apoptotic cardiomyocytes following MI, thus mitigating the progression to heart failure, while suppressed efferocytosis could increase infarct size, promote adverse ventricular remodeling and left ventricle functional deterioration after MI and ease the occurrence of cardiomyopathy.

These studies implicate that impaired efferocytosis can result in secondary necrosis, inflammation, cholesterol reverse disorder and thus lead to cardiovascular diseases, such as atherosclerosis and acute coronary artery syndrome. As a crucial modulator in cardiovascular diseases, efferocytosis is worthy of further investigation.

Table I. Summary of efferocytosis related molecules.

Author(s), year	Role in efferocytosis	Cell source	Molecules	(Refs.)
Elliott *et al*, 2009	'Find me' signal	Apoptotic cells	ATP, UTP	(9)
Lauber *et al*, 2003			LPC	(10)
Gude *et al*, 2008			S1P	(11)
Truman *et al*, 2008			CX3CL1	(12)
Peter *et al*, 2008		Phagocytic cells	G2A	(13)
Truman *et al*, 2008			CX3CR1	(12)
Gardai *et al*, 2005			LRP1,	(14)
Gardai *et al*, 2005			SRB1	(14)
Elliott *et al*, 2009			P2Y2	(9)
Appelt *et al*, 2005	'Eat me' signal	Apoptotic cells	PtdSer	(15)
Nagata *et al*, 2010			oxidized phospholipids, endoplasmic reticulum-resident protein calreticulin	(16)
Geng *et al*, 2017		Phagocytic cells	TAM, TIM, TG2	(17)
Geng *et al*, 2017	Bridging molecules	Apoptotic/ phagocytic cell	MFGE8, GAS6, Pro S, serum complement C1q, Thbs1, Anx I	(17)
Ravichandran, 2010	'Not eat me' signal	Apoptotic cells	CD47, CD31	(18)
Gheibi Hayat *et al*, 2019		Phagocytic cells	SIRPα	(201)

Anx I, Annexin I; ATP, triphosphate nucleotides adenosine triphosphate; CX3CL1, CX3C chemokine ligand 1; CX3CR1, CX3C chemokine receptor 1; GAS6, human growth arrest specific protein 6; G2A, receptor G2 accumulation; LPC, lyso-phosphatidylcholine; LRP1, low-density lipoprotein receptor related proteins 1; MFGE8, milk fat globule-epidermal growth factor; PtdSer, phosphatidylserine; ProS, protein S; P2Y2, purnoreceptor-2; SIRPα, signal regulatory protein alpha; SRB1, scavenger receptor 1; S1P, sphingosine-1-phosphate; TAM, TYRO3/Axl/MER tyrosine kinase receptor; TG2, transglutaminase 2; TIM, T cell immunoglobulin mucin; Thbs1, thrombospondin 1; UTP, uridine-5'-triphosphate.

3. Respiratory diseases

Lung diseases are closely related to efferocytosis due to the complex inflammatory and immune responses. When lung inflammation occurs, neutrophils are quickly recruited to the airways. Following phagocytosis of pathogens, neutrophils undergo apoptosis. This process is regulated by multiple genes and multiple factors, such as LPS, TNF-α, Fas/Fas-L pathway, apoptotic genes, interleukins, interferons and Caspase protein (55). Phagocytosis clears apoptotic neutrophils to prevent the release of toxic substances and the subsequent damage to the surrounding tissues, thereby alleviating inflammation (55). Effective efferocytosis protects normal airways, alveolar structures and even the lung tissues (56). For example, Lee *et al* (57) found Mertk overexpression could attenuate bleomycin-induced lung injury in mice.

By contrast, due to impaired efferocytosis, the number of uncleared ACs increases, which prolongs inflammatory response in the mouse and human models of chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) (58). COPD is characterized by chronic inflammation, extracellular matrix destruction and increased apoptosis of airway epithelial cells and neutrophils (59). The macrophage-mediated efferocytosis in the lungs of COPD patients weakens significantly, while efferocytosis strengthens in COPD patients who use statins (60).

Similarly, patients with CF or allergic asthma display protracted inflammation caused by defective efferocytosis (61,62). CF is a heritable disease with infection, airway inflammation and bronchiectasis (63). Sputa examination has shown more ACs in CF patients compared with those with chronic bronchitis (64). Asthma is a complex syndrome with airflow obstruction, bronchial hyper-responsiveness and airway inflammation (65). The resolution of ovalbumin-induced allergic airway inflammation is delayed in Mer-deficient mice (66). Targeting T-cell immunoglobulin and mucin domain-containing molecule (TIM) 1, a member of TIM receptor family, can modulate airway inflammation in mouse models of airway hyper-responsiveness (67). Grabiec *et al* (68) indicate that the deficiency of Axl receptor tyrosine kinase accelerates asthma progression by exaggerating airway inflammation. The prognosis of acute lung injury (ALI) in mouse models is also influenced by defective efferocytosis. MFGE8 deficient mice with lipopolysaccharide (LPS)-induced acute ALI showed increased inflammatory cytokines and decreased survival (69). Mertk can attenuate LPS-induced lung injury (70).

Common respiratory drugs, such as statins, macrolides and corticosteroids, can alleviate respiratory symptoms by enhancing efferocytosis. Macrolide antibiotics are reported to promote efferocytosis by upregulating the expression of bridging molecules such as collectins (71). These drugs have already been used to treat COPD, cystic fibrosis, or asthma (72). Mannose receptor may be a target of azithromycin to improve phagocytic ability (71). Azithromycin restores the phagocytic function of the airway macrophages by binding to PtdSer in COPD (73). Corticosteroids enhance efferocytosis by downregulating CD47-signal

Table II. Summary of efferocytosis related molecules and multisystem diseases.

Author(s), year	Diseases	Molecules	(Refs.)
Fricker *et al*, 2012	Alzheimer's disease	MFGE8 ↓	(146)
Zheng *et al*, 2012		Tyro3 ↓	(145)
Kojima *et al*, 2016	Atherosclerosis	CD47 ↑	(33)
Holden *et al*, 2019		GAS6 ↓	(202)
Brophy *et al*, 2019		LRP1 ↓	(203)
Ait-Oufella *et al*, 2008; Zhang *et al*, 2019; Thorp *et al*, 2008		Mertk ↓	(204-206)
Ait-Oufella *et al*, 2007		MFGE8 ↓	(44)
Boisvert *et al*, 2006		TG2 ↓	(207)
Waterborg *et al*, 2018	Arthritis	TAM receptors ↓	(122)
Grabiec *et al*, 2017	Asthma	Axl ↓	(68)
Qi *et al*, 2013	Autoimmune hepatitis	TAM receptors ↓	(111)
Wan *et al,* 2013	Cardiomyopathy	Mertk ↓	(54)
Bosurgi *et al*, 2013	Colon cancers	Axl ↓	(101)
Akitake-Kawano *et al*, 2013		GAS6 ↓	(103)
Bosurgi *et al*, 2013		Mertk ↓	(101)
Llacuna *et al*, 2010	Liver ischemia/reperfusion injury	GAS6 ↓	(95)
Aziz *et al*, 2012	Lung damage	MFGE8 ↓	(69)
Gong *et al*, 2019	Lupus nephritis	AXL ↑	(208)
Gong *et al*, 2019		GAS6 ↑	(208)
Gong *et al*, 2019		Mertk ↑	(208)
Tworkoski *et al*, 2013	Melanoma	Mertk ↑	(209)
Demarest *et al*, 2013		Tyro3 ↑	(210)
Tutusaus *et al*, 2020	Non-alcoholic steatohepatitis	Mertk ↓	(85)
Xie *et al*, 2015	Non-small cell lung cancer	Mertk ↑	(211)
Lew *et al*, 2020	Retinal degeneration	Mertk ↓	(177)
Walport *et al*, 1998	Systemic lupus erythematosus	C1q ↓	(212)
Huang *et al*, 2017		MFGE8 ↑	(213)
Zhu *et al*, 2014		Mertk ↑	(214)
Bertolaccini *et al*, 2003		Pro S ↓	(215)
Ramirez-Ortiz *et al*, 2013		SCARF1 ↓	(120)
Xiao *et al*, 2012		TIM 1 ↓	(119)
Chen *et al*, 2015	Sjogren's syndrome	GAS6 ↓	(131)
Qin *et al*, 2015		Axl ↓	(132)
Qin *et al*, 2015		Tyro3 ↓	(132)
Peng and Elkon, 2011	Type 1 diabetes mellitus	MFGE8 ↓	(216)
Avilla *et al*, 2011	Thyroid cancer	Axl ↑	(217)
Avilla *et al*, 2011		Tyro3 ↑	(217)
Bossi *et al*, 2014	Wound healing	C1q ↓	(180)

GAS6, growth arrest specific protein 6; LRP1, low-density lipoprotein receptor related proteins 1; MFGE8, milk fat globule-epidermal growth factor; SCARF1, scavenger receptor class F, member 1; TAM receptors, Tyro3/Axl/Mertk; TG2, transglutaminase 2; TIM1, T-cell immunoglobulin and mucin domain-containing molecule 1.

regulatory protein (SIRP) and upregulating Mertk (74). Glucocorticoids, the most commonly used drugs for asthma and COPD, enhance macrophage phagocytosis *in vitro* and restore the efferocytosis of macrophages in the airway of patients with asthma by regulating Mertk and Pro S (75,76). Grégoire *et al* (77) also found that blocking high mobility group box-1 (HMGB1) and activating AMP-activated protein kinase (AMPK) by metformin could enhance AC clearance and decrease lung inflammation in patients with acute respiratory distress syndrome (ARDS).

Several chronic lung diseases are characterized by an increased lung burden of uningested apoptotic cells and sustained lung inflammation (58). The efferocytic process favors tissue repair and inflammation suppression (78). Existing

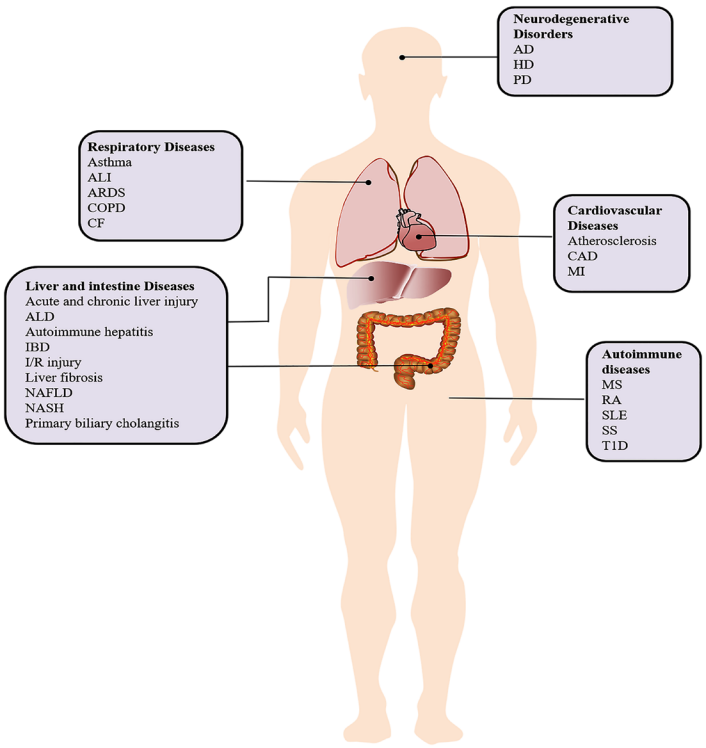

Figure 2. Efferocytosis in multisystem diseases. AD, Alzheimer's disease; ALD, alcoholic liver disease; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CAD, Coronary artery disease; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; HD, Huntington's disease; IBD, inflammatory bowel disease; I/R injury, ischemia-reperfusion injury; MI, Myocardial infarction; MS, multiple sclerosis; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PD, Parkinson's disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; T1D, type 1 diabetes.

therapies such as corticosteroids, statins and macrolides may function in part by augmenting apoptotic cell clearance.

4. Liver and intestine diseases

Kupffer cells and other myeloid phagocytic cells, the most important hepatic efferocytes, are attracted into the liver to remove ACs after injury (79). Bukong *et al* (80) found that acute alcohol use could significantly impair the clearance of neutrophil extracellular traps by macrophages, which could contribute to prolonged liver inflammation and injury. Mediators released by neutrophils during NETosis can directly corrupt the recognition of apoptotic cells by phagocytes: HMGB1, for example, initiates pro-inflammatory signal whilst simultaneously preventing efferocytosis by obscuring PS recognition (81). In patients with alcoholic liver disease, alcohol and alcohol metabolites increase liver inflammation and steatosis (82). Wang *et al* (83) found alcohol inhibits MFGE8 gene expression and impairs efferocytosis and thus leading to hepatocyte necrosis, which explains why alcohol can cause liver damage from another perspective.

Defective efferocytosis also contributes to other liver diseases, such as fatty liver disease and primary biliary cholangitis (2). Following the phagocytosis of ACs, phagocytes increase cholesterol efflux activity to maintain lipid homeostasis. The engagement of PS receptors activates PPAR γ/δ and LXR, the regulators of cellular lipid homeostasis (37) and upregulates the phagocytic receptors, such as the TAM family, to accommodate to the increased cholesterol induced by phagocytosis (36,84). Excessive accumulation of fatty acids caused by defective efferocytosis triggers oxidative stress and lipid peroxidation, leading to liver cell death/apoptosis, inflammation, liver steatosis and even lipotoxic liver cell damage. GAS6 and Mertk can protect cultured primary mouse hepatocytes against lipid toxicity via protein kinase B (AKT)/signal transducers and activators of transcription 3 (STAT3) signaling (85). The enhanced oxidative stress response and the reactive oxygen species (ROS) expression in fatty liver tissues exacerbate non-alcoholic fatty liver disease (NAFLD) (86). Mertk can protect primary macrophages from oxidative stress-induced apoptosis (87). The significantly upregulated NLR family, pyrin domain containing 3 (NLRP3) inflammasome aggravates NAFLD greatly (88). However, a study showed that TIM4 reduced the inflammation in NAFLD by suppressing NLRP3 inflammasome (89). High-level hepatocyte apoptosis is found in non-alcoholic steatohepatitis (NASH) patients (90). The delayed removal of apoptotic liver cells can cause liver damage, inflammation and fibrosis (91). Liver fibrosis, the pathological result of various chronic liver diseases, is associated with the dysregulation and polarization of M1/M2 macrophages (92). Efferocytosis can alleviate liver fibrosis by stimulating M2 macrophage polarization (93). Rantakari *et al* (94) clearly showed that the absence of stabilin-1 aggravates fibrosis in chronic liver injury following CCl4 administration.

TIM4 and GAS6 are critical proteins in the resolution of hepatic ischemia-reperfusion injury (95). The administration of recombinant GAS6 can protect GAS6-knockout mice from fulminant hepatic failure (96). GAS6 also protects primary mouse hepatocytes from hypoxia-induced cell death through AKT phosphorylation and diminishes inflammatory cytokines *in vitro* (95). In acute and chronic liver injury, the

elevated Galectin-3 expression can facilitate phagocytosis via Mertk (97). Triantafyllou *et al* (98) demonstrate that Mertk^{+} macrophage, as a novel hepatoprotective target, can promote resolution responses and quell tissue-destructive responses following acute liver injury.

Phagocytic clearance of ACs also serves a role in intestinal inflammatory disorders. In the acute phase of murine experimental colitis, MFGE8 expression decreases in inflamed colons (99). However, recombinant MFGE8 ameliorates colitis by reducing inflammation and improving disease parameters, suggesting that it may be a useful therapeutic agent for colitis (99). A number of studies indicate that the receptor tyrosine kinases Axl and Mertk can promote the resolution of inflammation, serving as a potential therapeutic target for inflammatory bowel disease (IBD) (100-102). Compared with wild-type mice, Axl$^{-/-}$Mertk$^{-/-}$mice and GAS6$^{-/-}$ mice are more sensitive to dextran sulfate sodium, presenting with more severe colitis signs and more weight loss (101,103).

Effective efferocytosis prevents apoptotic or necrotic cells from forming cell debris that can induce liver and intestine damage (81,104). Efferocytosis serves a role in liver diseases by regulating lipid metabolism, inflammation and polarization (81). Also, since efferocytosis promotes the resolution of inflammation, it can be used to treat intestinal inflammatory disorders (104).

5. Autoimmune diseases

A large number of cells undergo apoptosis during the development and homeostasis of the body (105). There are two main pathways of apoptosis, extrinsic or death receptor pathway and intrinsic or mitochondrial pathway, which have been identified (106). Patients with autoimmune diseases show high levels of apoptotic cells, partly attributed to the massive apoptosis in phagocytes or in tissue cells, such as glomerular cell, epidermal keratinocytes and T cells (107). Efficient AC clearance maintains immune homeostasis by eliminating auto-antigens, as well as producing anti-inflammatory and immunosuppressive signals (3). By contrast, under defective efferocytosis, ACs cannot be removed in time (108). As a result, uncleared ACs may rupture and release harmful contents such as autoantigens, thus promoting immune response and resulting in autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 diabetes (T1D) and multiple sclerosis (MS) (109). Genetic evidence from mouse studies has demonstrated that failed or delayed efferocytosis might cause immune system disorders and the release of auto-antigens (110). TAM triple-knockout mice can develop autoimmune hepatitis at the age of six months, with rising transaminases and titers of autoantibodies to antinuclear antigen (111).

SLE damages multiple organs, such as the skin, joints, kidney, lungs, nervous system, heart and blood vessels (112). Autoantibodies against nuclear antigens, such as antinuclear antibodies and anti-double-stranded DNA (dsDNA), are found in SLE patients (113). Macrophages from SLE patients possess a weaker capability to engulf ACs (114). Defective clearance of ACs has been demonstrated to promote the autoantibody production *in vivo* (115). An analysis of 50 SLE patients indicates that GAS6/ProS-TAM system is associated with the disease activity of SLE in several ways (116). Several PS receptors and PS opsonins serve an essential role in efferocytosis, chronic inflammation and age-dependent autoimmunity. TAM triple (Mertk$^{-/-}$, Axl$^{-/-}$, Tyro3$^{-/-}$) knockout mice develop a poly-autoimmune syndrome resembling SLE, with elevated titers of autoantibodies, uncontrolled B and T cell proliferation and lymphocyte accumulation (117). Similarly, TIM4-deficient mice, with hyperactivated T and B cells, develop autoantibodies to dsDNA, a specific antibody to SLE (118). Furthermore, knockouts of TIM-1 (119), scavenger receptor class F member 1 (SCARF1) (120) and CD300f (121) all share a common phenotype with SLE-like autoimmunity. These observations are evidenced by the defective AC clearance as an etiological cause of SLE.

The site of RA inflammation contains uncleared ACs, suggesting that RA is related to impaired efferocytosis. Waterborg *et al* (122) show that the deficiency of Axl and Mertk worsens arthritis in mice, whereas overexpressing their ligands ProS1 and GAS6 to activate these receptors can ameliorate arthritis. Other studies have demonstrated that activating LXR/PPAR γ exerts therapeutic effects on the mouse model with inflammatory arthritis (123-125).

T1D is a T cell-mediated autoimmune disorder with insulin deficiency and hyperglycemia (126). Inefficient clearance of apoptotic pancreatic cells may aggravate inflammation and necrosis, thus accelerating the release of autoantigens (127). Defective wound healing is a characteristic of patients with T1D. Due to incomplete phagocytosis, dead cells accumulate at the wound site, which leads to inflammation and retard wound healing (128). Das *et al* (129) demonstrate that MFGE8$^{-/-}$ mice develop systemic inflammation and MFGE8 exerts a potential therapeutic effect on diabetic wound.

Sjogren's syndrome (SS) is a chronic, progressive autoimmune disease, with dry mouth and eyes as the most frequent symptoms. The accumulation of ACs and a type I interferon signature have been observed in patients with SS and mouse models. The function of TAMs in efferocytosis and interferon response dampening is impaired in SS (130). Chen *et al* (131) found that decreased plasma GAS6 concentration is associated with SS and thus GAS6 may be a novel independent risk factor for SS. Similarly, another study shows that the level of Tyro3 and Axl was decreased in SS patients (132). These findings suggest that efferocytosis may be associated with disease activity or inflammation in SS.

Glucocorticoids, the most widely-used anti-inflammatory drugs, are used to treat SLE by promoting AC clearance and alleviating inflammation in an MFGE8-dependent way (133). Glucocorticoids can also upregulate Mer (134) and increase the expression of annexin A1 and lipoxin A receptors (135,136). Long-term effects of glucocorticoids are reported to be dependent on PPARγ (137).

When efferocytosis fails, ACs can rupture and release cellular materials. Then the released cellular materials stimulate inflammatory and immunogenic reactions, which are likely to trigger an autoimmune response (138). Glucocorticoids treat autoimmune diseases by promoting efferocytosis, which provides more ideas for future treatment (139).

6. Neurodegenerative disorders

Phagocytosis in the brain is accomplished by microglia, a resident macrophage in the brain and spinal cord. The central

nervous system also requires efficient efferocytosis to achieve homeostasis by clearing the dying cells and preventing the spillover of proinflammatory and neurotoxic molecules (140). Defective efferocytosis may lead to multiple neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease. Excessive ACs have been detected in patients with neurodegenerative diseases (141). MFGE8, an endogenous protective factor, regulates microglial phagocytosis of apoptotic neurons and inhibits inflammation (142). In the central nervous system of mice, microglial cells lacking Mertk fail to clear ineffective synaptic connections, thus impairing hippocampal development and propagating neuronal damage (143).

AD is characterized by the accumulation of hyperphosphorylated protein tau and amyloid β (Aβ) (144). Zheng *et al* (145) found that Aβ generation is significantly decreased by Tyro3 receptor overexpression in the cell model. A significant increase of amyloid plaques in the hippocampus and plaque-associated clusters of astroglia has been detected in a Tyro3$^{-/-}$ AD transgenic mouse model (145). Neuroinflammation serves a key role in AD development and progression. The expression of MFGE8, an anti-inflammatory agent, decreases in a mouse model of AD (146). Evidence suggests that MFGE8 can suppress A1 astrocytes and regulate microglia M1/M2 alteration to prevent the death of neurons and oligodendrocytes by regulating NF-κB and PI3K-AKT (147,148). Recombinant MFGE8 may have the potential to treat chronic inflammation in AD, through inhibiting MAPK and NF-κB signaling pathways (149).

PD is a progressive neurological disorder characterized by α-synuclein deposit (150). Dysregulated microglia phagocytosis has been recognized in PD and defective phagocytosis has also been observed in the monocytes of patients with PD (151). In PD models, CX3CR1$^{-/-}$ mice show microglial neurotoxicity (152). Studies also reveal that microglia phagocytosed and cleared cellular debris of degenerating neurons through C1q-mediated pathway and scavenger receptors (153,154). In the central nervous system, microglial phagocytic function is supported by bridging proteins (such as MFGE8 or Pro S) and TAM-receptor kinases (such as Axl and Mer) to clear PS-exposing neurons (155,156). The study of Nakashima *et al* (157) suggests that MFGE8 may prevent PD by reversing the reduced mesencephalic dopamine neurons. Chronic neuroinflammation is also crucial in PD. Ghahremani *et al* (158) conclude that efferocytosis can change the macrophage phenotype into anti-inflammatory phenotype.

In conclusion, neuronal apoptotic debris is cleared by phagocytic cells through efferocytosis. Then the release of proinflammatory and antigenic autoimmune constituents is inhibited, which enhances the neuronal survival and axonal regeneration. The tremendous therapeutic potential of efferocytosis for neurodegenerative diseases requires further preclinical development.

7. Tumors

Efferocytosis also serves an essential role in tumors. Apoptotic cell clearance can have deleterious consequences within the tumor microenvironment, potentially affecting the natural progression of the disease and cancer treatments. Efferocytosis can help generate a tumor-tolerant, immunosuppressive tumor micro-environment (159). In the tumor microenvironment, tumor-associated macrophages, which are largely polarized to the M2-like phenotype through PPAR-γ and LXR-α, exert pro-tumor effects by promoting angiogenesis, suppressing T cell infiltration and cytotoxic T cell function, remodeling extracellular matrix to promote invasion and metastasis of cancer cells and suppressing the immune system (160-162). Efferocytosis upregulates TAM receptor expression to promote macrophage polarization towards an immunosuppressive phenotype (163). Namely, the escape of malignant cells is supported by TAM-mediated efferocytosis, negative regulation of dendritic cell activity and dysregulated production of chemokines. MerTK overexpression has been found in a number of human cancers, including myeloid and lymphoblastic leukemia, melanoma and gliomas (164-166). Thus, TAM receptors on macrophages serve as exciting targets for cancer therapy by effecting macrophage phenotype and efferocytosis (167). A growing amount of evidence suggests that efferocytosis in the tumor microenvironment accelerates tumor progression, which provides new ideas for tumor treatment. For example, the blockade of PtdSer interacting with the efferocytosis of phagocytes sufficiently can inhibit tumor progression and metastasis (168). Studies demonstrate that Axl and Mer contribute to cell survival, migration, invasion, metastasis and chemosensitivity, which can be used as therapeutic targets (169-171).

Cancer cells have been found to escape from phagocytosis by upregulating 'don't eat me' molecules on their surface (172). Willingham *et al* (173) found that CD47 was highly expressed in ovarian, breast, colon, bladder, glioblastoma, hepatocellular carcinomas and prostate tumor cells; a high level of CD47 mRNA expression was associated with a decreased survival. Anti-CD47 antibodies can promote phagocytosis, inhibit tumor growth and prevent tumor metastasis. The anti-CD47 antibodies enhance cancer cell phagocytosis via inhibiting the SIRPα axis in anti-cancer therapy (174). These results suggest CD47 as a therapeutic target for solid tumors. Combing anti-CD47 antibodies and tumor-targeting therapies can achieve higher anti-cancer efficacies.

Other studies support that the enhanced efferocytosis can exert anti-tumor effects. A previous study has revealed that multiple myeloma is associated with reduced efferocytosis by monocytes (175). Some studies have demonstrated that the loss of Axl, Mertk and GAS6 can promote colon cancer (101,103). Axl, Mertk and GAS6 can limit inflammation and reduce the risk of inflammation-associated colorectal cancer (176). The above evidence suggest the double edge sword role of efferocytosis in tumor. Therefore, the specific mechanism of efferocytosis in tumor requires further clarification.

8. Discussion

Efferocytosis can maintain homeostasis in biological evolution. Efferocytosis not only serves a role in the above-mentioned diseases, but also affects other diseases, such as skin diseases, retinal degeneration and wound healing. Loss of the phagocytosis receptor Mertk causes overt retinal degeneration (177). The protein CCN1 is a critical opsonin in skin injury by acting as a bridging molecule in neutrophil efferocytosis (178).

Abnormal activation of complement-mediated phagocytosis also affects retinal diseases, such as glaucoma and age-related macular degeneration (179). C1q is found to stimulate endothelial cells proliferation and migration and to promote tube formation and sprouting of new vessels (180). C1q may represent a valuable therapeutic agent for wound healing. The critical role of efferocytosis in multisystem diseases provides new directions for the prevention and treatment of these diseases. More extensive and in-depth studies are needed to clarify the pathophysiological mechanism of efferocytosis in diseases.

Traditional Chinese medicine, which features multi-components, multi-targets, multi-pathways and multi-effects, shows clear advantages in the treatment of diseases (181). Therefore, research on the role of traditional Chinese medicine in regulating efferocytosis promises a new direction of therapy development. More and more studies are being carried out on natural products for efferocytosis regulation.

Our previous studies (182-184) demonstrate the key role of efferocytosis in the development of atherosclerosis and the regulatory effect of efferocytosis on atherosclerosis. Guan Xin Kang (GXK), a formula designed by our research group and composed of *Astragalus*, *Salvia*, *Leonurus*, *Trichosanthes kirilowii*, *Pinellia ternate* and Scallions white, can improve the pathological changes in thoracic aorta, increase the phagocytosis rate of splenic macrophages and upregulate the protein expression of thrombospondin 1 (182) and TAM receptors (Tyro3/Axl/Mertk) in $LDLR^{-/-}$ mouse (184). The expression of Mertk protein in RAW264.7 cells can be upregulated by sera medicated with GXK (183). The above results indicate that efferocytosis regulation may be effective in treating atherosclerosis. Treatment with catechins in rats can result in anti-atherogenic properties (185). Kaempferol, luteolin, ellagic acid and berberine can upregulate SR-BI expression and further inhibit ox-LDL uptake in macrophages (186-189). Caffeic acid and ferulic acid possess anti-atherogenic properties by enhancing HDL-mediated cholesterol efflux from the macrophages (190). These natural products, which have been proved to inhibit foam cell formation via efferocytosis (191), are potential drugs to improve cardiovascular diseases.

There are also several natural products that can regulate macrophage activation, recruitment and polarization to reduce inflammation, attenuate lipid accumulation and improve insulin sensitivity in NASH treatment, such as sparstolonin B (192), berberine (193) and celastrol (194). Baicalin promotes macrophage polarization to the M2-type in mice with IBD by enhancing the phagocytosis and efferocytosis of macrophages (195,196). Polysaccharides from *Ganoderma lucidum* modulate microglial phagocytosis to attenuate neuroinflammation (197). An increasing number of natural products, such as pycnogenol (198), polysaccharides from the roots of *Sanguisorba officinalis* (199) and tea polysaccharides (200), enhance the phagocytic function of macrophages and could be used to treat diseases.

Having fewer adverse effects and multi-target properties, natural products are prospective medicinal components for the treatment of multi-system diseases in the future. Therefore, more research is needed to explore the mechanism of Chinese medicine that can regulate efferocytosis and provide reliable basis for disease treatment.

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Authors' contributions

YZ conceptualized the review, performed the literature search and drafted the manuscript. YW and JD helped to draft and revise the manuscript. PL edited and revised the paper. All authors have read and approved the final version of the manuscript to be published.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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