

Efferocytosis: An Emerging Therapeutic Strategy for Type 2 Diabetes Mellitus and Diabetes Complications

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Abstract: Increasing evidence indicates that chronic, low-grade inflammation is a significant contributor to the fundamental pathogenesis of type 2 diabetes mellitus (T2DM). Efferocytosis, an effective way to eliminate apoptotic cells (ACs), plays a critical role in inflammation resolution. Massive accumulation of ACs and the proliferation of persistent inflammation caused by defective efferocytosis have been proven to be closely associated with pancreatic islet β cell destruction, adipose tissue inflammation, skeletal muscle dysfunction, and liver metabolism abnormalities, which together are considered the most fundamental pathological mechanism underlying T2DM. Therefore, here we outline the association between the molecular mechanisms of efferocytosis in glucose homeostasis, T2DM, and its complications, and we analyzed the present constraints and potential future prospects for therapeutic targets in T2DM and its complications.

Keywords: type 2 diabetes mellitus, diabetes complications, efferocytosis, inflammation, apoptosis

Introduction

Physiologically, the recognition and elimination of apoptotic cells (ACs) comprise a host mechanism for maintaining homeostasis. Indeed, it is estimated that 100,000 cells in our bodies undergo apoptosis every second, before being engulfed by efferocytes.¹ Efferocytes are cells that can specifically and efficiently eliminate ACs, including professional types (macrophages, dendritic cells) and non-professional types (monocytes, fibroblastic cells, adjacent epithelial cells).² This clearance process is an evolutionally conserved process for removing ACs, known as efferocytosis, which inhibits secondary necrotic lysis of ACs and is crucial for restoring homeostasis after the occurrence of chronic inflammatory diseases.³ Currently, the resolution of inflammation in efferocytosis is believed to be attributed to four pathways:⁴ (1) inhibition of pro-inflammatory signals; (2) promotion of anti-inflammatory signals; (3) regulation of macrophage phenotype; and (4) improvement of Treg cell function. Although effective efferocytosis provokes efferocytes to exert anti-inflammatory benefits, invalid efferocytosis is responsible for secondary necrosis, causing further loss of contiguous cells.

Increasing evidence has shown that efferocytosis is essential to the development and progression of type 2 diabetes mellitus (T2DM) and its resulting complications.⁵ T2DM is a common chronic inflammatory illness with long-term consequences that widely affects all tissues and organs in the body.⁶ T2DM and its complications lead to increased morbidity, mortality, and healthcare costs.⁷ Although the occurrence of T2DM is closely related to genetic and environmental factors (eg, limited physical activity, bad eating habits, obesity, and aging), in general, its ultimate results from the imbalance of glucose metabolism in the body. Notably, compromised efferocytosis has been proposed to be closely related to pancreatic islet β cell destruction,⁸ adipose tissue inflammation,⁹ skeletal muscle dysfunction,¹⁰ and liver metabolism abnormalities,¹¹ all of which largely contribute to the imbalance of glucose homeostasis. Accordingly, efferocytosis failure seems to be an initial node leading to T2DM and its complications.

Efferocytosis involves several steps, including recruitment, recognition, engulfment, and degradation, and multiple signaling molecules in each step play crucial roles in effective efferocytosis. Therefore, here we summarize the general

mechanisms of efferocytosis and the role of efferocytosis failure in T2DM and its complications to provide a novel treatment approach for such diseases.

General Mechanisms of Efferocytosis

Recruitment

The effective elimination of ACs depends on the release of various “find me” signals, which are generally released at the early stage of apoptosis and lead to the migration and aggregation of efferocytes toward ACs (Figure 1A).

These “find me” signals allow efferocytes to accurately and effectively locate ACs that need to be cleared. The following “find me” signals have been identified: lipids (lysophosphatidylcholine [LPC]¹² and sphingosine 1-phosphate [S1P]¹³), proteins (chemokine C-X3-C motif ligand 1 [CX3CL1]),¹⁴ and extracellular nucleotides (adenosine triphosphate, [ATP] and uridine triphosphate, [UTP]).¹⁵ Specifically, LPC was the first “find me” signal to be discovered, and it is mainly formed through the hydrolysis of membrane phosphatidylcholine in ACs mediated by phospholipase A2 (PLA2), which relies on caspase-3 induction.¹² Additionally, suppression of ATPase class I type 8b member 1 (Atp8b1) and ATP-binding cassette transporter A1 (ABCA1) can abolish the release of LPC, which hinders the migration of

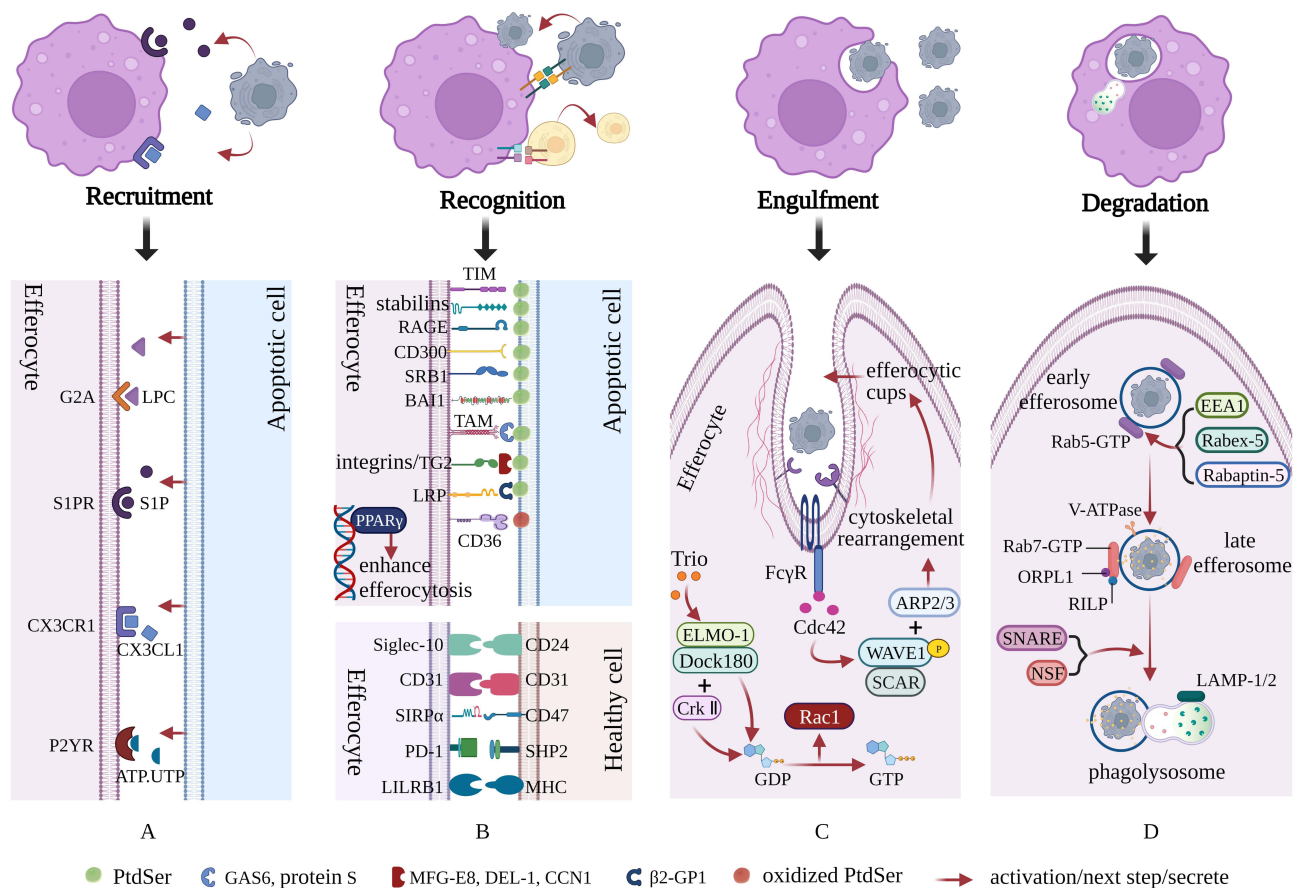


Figure 1 Molecular mechanisms of efferocytosis. Apoptotic cells (ACs) recruit efferocytes by releasing a series of molecules. Subsequently, efferocytes recognize ACs through unique “eat me” and “do not eat me” signals. Then, efferocytes engulf ACs through cytoskeletal recombination and the formation of efferocytic cups. Finally, ACs gradually degrade in mature phagolysosomes. **(A)** The effective elimination of ACs depends on the release of various “find me” signals, such as LPC, S1P, CX3CL1 and ATP/UTP, which result in the migration and aggregation of efferocytes toward ACs. **(B)** Once efferocytes are close enough to perform efferocytosis, “eat me” and “do not eat me” signals are used to distinguish between apoptotic cells and viable cells, while further cell-surface “eat me” and “do not eat me” signals assist with the subsequent stage of cell engulfment. **(C)** After recognition, efferocytes immediately initiate cytoskeletal rearrangements and the formation of efferocytic cups to rapidly complete the engulfment of ACs. This process largely relies on the Rho family of small GTPases, especially Rac-1, Rho G and Cdc42. **(D)** The degradation of ACs is finally completed after the newly generated efferosomes proceed through stages of early, late, and lysosomal interaction. During this process, Rab5-GTP and Rab7-GTP mediate the formation of early and late efferosomes, respectively. Additionally, these processes are accompanied by gradual acidification of the intracellular environment, which is beneficial to the degradation of ACs. Created with BioRender.com.

macrophages¹⁶ and monocytes¹⁷ to ACs, respectively. LPC binds and stimulates G2 accumulation (G2A),^{18,19} a G-protein-coupled receptor (GPCR) that is widely expressed on the surface of immune cells such as macrophages and dendritic cells. Although research on G2A is limited, its binding to LPC is a key initiator of efferocytosis and various pathophysiological reactions. S1P, derived from membrane sphingosine, is degraded by related enzymes and exerts a high affinity for S1P receptors 1–5 (S1PR1–5),²⁰ which can orchestrate numerous physiological processes, including invasion, adhesion, and migration of macrophages. CX3CL1, a cytokine with chemotactic functions, is currently the only known member of the CX3CL subfamily.²¹ As a specific chemokine receptor, CX3CR1 can only bind and stimulate CX3CL1. Subsequently, CX3CL1 interacts with CX3CR1 to form the CX3CL1/CX3CR1 signal axis, which mediates the chemotaxis and migration of macrophages.^{14,22} ATP and UTP are also critical AC “find me” signals that can be sensed by purinergic P2 receptors of monocytes and macrophages, especially P2Y receptors (P2YRs).²³ The deletion of ATP and UTP or artificial knockout of P2YRs significantly impairs the clearance of ACs.¹⁵ Notably, the release of ATP and UTP by ACs is controlled by pannexin-1 (PANX1) channels. The overexpression of PANX1 leads to extracellular ATP accumulation, eventually mediating the impairment of efferocytosis, increased inflammation of skeletal muscle, and insulin resistance (IR).²⁴ Furthermore, some other soluble ligands, including thrombospondin 1, chemokine-presenting apoptotic blebs, endothelial monocyte activating polypeptide II, tyrosyl tRNA synthetase, ribosomal protein S19 dimer, and annexin A1 (ANXA1), can also recruit efferocytes to areas where ACs accumulate, as previously reviewed.²⁵

Recognition

Once efferocytes are close enough to perform efferocytosis, a group of cell-surface chemicals known as “eat me” and “do not eat me” signals are used to distinguish between apoptotic and viable cells, which help with the subsequent stage of cell engulfment (Figure 1B).

Among all known “eat me” signals, phosphatidylserine (PtdSer) has been reported to be one of the most fundamental and pleiotropic mediators for achieving signal transduction between efferocytes and ACs.²⁶ As a phospholipid, PtdSer is mainly located within the cell membrane under physiological conditions. However, when a cell undergoes stress or apoptosis, PtdSer turns outward to the outer surface of the cell membrane, where it serves as an “eat me” signal, which is then recognized by ligands on adjacent macrophages.²⁷ Numerous receptors exposed on the surface of efferocytes have been associated with the PtdSer binding process on ACs. PtdSer is capable of binding efferocytes (macrophages, dendritic cells, fibroblastic cells, or endothelial cells) and strongly supporting the efferocytosis of ACs in a direct manner through receptors such as T cell immunoglobulin mucin receptors (TIMs: including TIM1,²⁸ TIM3,²⁹ and TIM4),³⁰ stabilins (stabilin1 and stabilin2),³¹ the receptor for advanced glycation end products (RAGE),³² the CD300 family (CD300a, CD300b and CD300c),^{33,34} scavenger receptor class B member 1 (SRB1),³⁵ and adhesion G protein-coupled receptor B1 (BAI1).³⁶ However, PtdSer is also linked to efferocytes through its interactions with certain bridge molecules, such as growth arrest-specific protein 6 (GAS6), protein S, milk fat globule factor-e8 (MFG-E8), developmental endothelial locus-1 (DEL-1), and beta-2-glycoprotein 1 (β 2-GP1). In brief, both GAS6 and protein S bridge PtdSer on ACs to the tumor-associated macrophage (TAM) tyrosine kinase receptors;³⁷ MFG-E8, DEL-1 and cellular communication network factor 1 (CCN1) bridge PtdSer on ACs to the α β 3/ α β 5 integrins;^{38–40} and β 2-GP1 bridges PtdSer on ACs to the low-density lipoprotein receptor-related protein (LRP).⁴¹ Notably, TAM receptors are composed of Tyro3, Axl, and Mer, each with differential affinity to their ligands.⁴² Moreover, oxidized PtdSer rather than nonoxidized PtdSer⁴³ is necessary for macrophage identification of ACs via the class B scavenger receptor CD36. Peroxisome-proliferator activated receptor gamma (PPAR γ), a major member of the transcription factor PPAR family, is postulated as the principal driver of inflammation reduction and efferocytosis enhancement due to upregulation of molecular elements such as CD36, transglutaminase 2 (TG2), Axl, and prototypic long pentraxin 3 (PTX3).⁴⁴ Notably, the recognition of ACs can be aided by additional signals. For instance, Fc receptors are capable of recognizing LPC on ACs via distinctive bridging ligand immunoglobulin M (IgM),⁴⁵ while complement component C1q and mannose-binding lectin (MBL) are responsible for the interaction of calreticulin and LRP1,^{46,47} which are located on the membrane surfaces of ACs and macrophages, respectively.

Although recognition of the “eat me” signal is a prerequisite for efferocytosis, cells emerging from the “eat me” signal are not necessarily bound to be engulfed. The appearance of “do not eat me” signals enable viable cells to

precisely avoid efferocytosis, facilitating cell survival. Moreover, CD24, CD31, CD47, Src homology region 2 domain-containing phosphatase-2 (SHP2), and major histocompatibility complex (MHC) distributed on healthy cells can interact with the inhibitory receptor sialic acid-binding Ig-like lectin-10 (Siglec-10),⁴⁸ CD31,⁴⁹ signal-regulatory-protein- α (SIRP α),⁵⁰ programmed cell death protein 1 (PD-1),⁵¹ and leukocyte immunoglobulin-like receptor B1 (LILRB1),⁵² respectively, strongly suppressing the efferocytosis of viable cells.

Engulfment

Once a relatively long period of recognition between efferocytes and ACs has passed, efferocytes will immediately initiate cytoskeletal rearrangement and synthesis to rapidly complete the engulfment of ACs⁵³ (Figure 1C).

During this process, activation of the Rho family of small GTPases (especially Rac-1, Rho G, Cdc42, and Rho A) through multiple signal pathways is a key step to synergistically facilitate cytoskeletal reorganization and the formation of efferocytic cups, completing the engulfment of ACs. The trimeric complex, composed of the phagocytic regulatory protein engulfment and cell motility protein 1 (ELMO-1), 180-kDa protein downstream of the dedicator of cytokinesis (Dock180), and Crk II appear to be favored by guanine nucleotide exchange factors (GEFs), the key regulators of Rac-1 activation via accelerating the exchange of GDP for GTP.⁵⁴ Indeed, Dock180 is a linker connecting the two domains, meaning that the SH3 domain of Dock180 can bind to ELMO-1, while the SH3 domain of Crk II can interact with Dock180.⁵⁵ Beyond that, Trio, the exchange agent functioning through the small GTPase Rho G, interacts with the complex of ELMO-1 and Dock180 to induce the active GTP-bound state of Rac-1.⁵⁶ The activation of Rac-1 subsequently activates SCAR, an actin nucleation promoting agent that has been considered to be the upstream molecule of verprolin homology domain-containing protein (WAVE).⁵⁷ Ultimately, the SCAR/WAVE1 complex nucleates the components of fresh actin filaments and forms efferocytic cups via recruiting the actin-related protein 2/3 (ARP2/3) complex.⁵⁷ Notably, Rac-1 activation occurs later than that of Cdc42.⁵⁸ In contrast to Rac-1, the activity of Cdc42-GEF is almost not delayed. After combining with Fc gamma receptor (Fc γ R), Cdc42 exhibits a strong ability to attract GEFs and promotes GDP/GTP exchange.⁵⁹ Moreover, when Cdc42 is entirely active through the action of GEFs, it then concentrates on regulating actin polymerization, elongating pseudopods, and shaping efferocytic cups through stimulating the Wiskott-Aldrich syndrome protein (WASP) family, the other actin nucleation-promoting factors.^{59,60} Additionally, RhoA can be activated by binding to mammalian diaphanous-related formin 1 (mDia1) and Rho-associated protein kinases (ROCK), and the degree of its activation is inversely proportional to the clearance intensity of phagocytic efferocytosis.⁶¹

Although actin polymerization contributes to the formation of efferocytic cups and the accurate engulfment of ACs, the significant role of actin depolymerization in the dynamic equilibrium of efferocytosis cannot be overlooked. For instance, the presence of dynamin-2 at the plasma membrane is capable of blocking the phagosome formation.⁶²

Degradation

Following the engulfment of ACs, efferocytes completely transform into the endocytotic vesicle (early efferosome), which is then triggered by multiple signaling events to generate a late efferosome. Subsequently, the late efferosome fuses with the lysosome to generate a mature conformation, which initiates measures to interfere with ACs, completing the entire digestion and degradation process. During this complex and precisely regulated process, it is crucial to protect normal tissues and cells from damage in an immune tolerance manner, while it is also necessary to cope with the excessive amount of proteins, nucleotides, and lipids resulting from the apoptotic process (Figure 1D).

The Rab GTPase family of proteins, especially Rab5 and Rab7, are key mediators in the canonical degradation cyclical process through the effectors responsible for the exchange of GTP-bound conformation and GDP-bound conformation.⁶³ Control of early efferosome formation is governed by Rab5-GTP, which possesses fusion activity due to the activation and stabilization of several effectors, such as early endosomal antigen 1 (EEA1)⁶⁴ and complex of Rabex-5 and Rabaptin-5.⁶⁵ The process at this stage is relatively slow, with a half-life of approximately 15 min. Subsequently, the efferosome matures continuously from early to late stages, which is accompanied by the loss of Rab5-GTP and the acquisition of Rab7-GTP, mediated by the class C homotypic fusion and vacuole protein sorting (HOPS) complex.⁶³ Following the establishment of late efferosomes, strong acidic efferosome lumens abundant in antimicrobial

peptides and hydrolase are generated via vacuolar ATPase (V-ATPase), which results in the opening of the H⁺ channel and the influx of H⁺ into the lumen.⁶⁶ Central displacement of late efferosomes and partial formation of the efferosome/lysosome (phagolysosome) are controlled by the interaction of dynactin, dynein, and Rab7-GTP, the latter of which is activated by effectors, including Rab7-interacting lysosomal protein (RILP)⁶⁷ and oxysterol-binding protein-related protein 1 (ORPL1).⁶⁸ Additionally, without lysosome-associated membrane protein 1 (LAMP-1) and LAMP-2, the migration of the phagolysosomes toward the microtubule-organizing centrum is hampered.⁶⁹ Indeed, the formation and migration of phagolysosomes require tremendous attention to membrane fusion, which is a cumbersome and highly collaborative process. Soluble N-ethylmaleimide-sensitive fusion factor attachment protein receptor (SNARE) complex and N-ethylmaleimide-sensitive factor (NSF) are crucial components of membrane receptors, which serve as catalysts to facilitate membrane fusion.⁷⁰ Admittedly, the fusion of the membrane primarily depends on the assembly and disassembly of the SNARE complex, which incorporates (1) turning conformation of the syntaxin and manufacturing a precomplex of Q-SNARE proteins; (2) overcoming the repulsion and initiating SNARE complex formation; (3) unfolding the conformation of the clamping complex and accomplishing *cis*-SNARE complex establishment; (4) linking with SNAPs and NSF and recouping of the *cis*-SNARE complex; and (5) enzymatic hydrolysis and SNARE complex disassembly.⁷⁰ Following fusion, the acidic strength further strengthens in the phagolysosome lumen via proton pump transporters, allowing for the degradation of phagocytic cargoes and the elimination of apoptotic bodies. Additionally, noncanonical degradations are mediated by LC3 and liver X receptors (LXRs), which have been reported in previous reviews.⁷¹

During degradation, efferocytes also generate cytokines such as transforming growth factor- β (TGF- β), interleukin-10 (IL-10), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) to minimize inflammation, facilitate the regression of inflammation and the growth of adjacent cells, and maintain vascular integrity.⁷² Certainly, an explicit and accurate process of phagolysosome fusion and decomposition, as well as how the phagocytic cargoes are perfectly degraded in the phagolysosome, still merits further exploration.

Efferocytosis and Glucose Homeostasis

The normal blood glucose level is relatively stable, maintained at 3.89–6.11 mmol/L, which is the result of the dynamic balance between the production and consumption of glucose in the body. Usually, the production of glucose is highly controlled by three primary pathways: the digestion and absorption of sugary foods, hepatic glycogenolysis and gluconeogenesis of non-sugar substances. However, the consumption of glucose is governed by four main routes: aerobic oxidation; hepatic and muscle glycogen synthesis; mutation of other sugars; and transformation of adipose or amino acids. The above dynamic balance is regulated by various hormones, especially insulin and glucagon, which not only coordinate and restrict the metabolism of glucose, adipose, and amino acids, but also coordinate the metabolism of various organs and tissues, including adipose tissue, skeletal muscle and liver, to adapt to the changes in energy demand in the body through modulating the activity of critical enzymes. Once the defect appears in the insulin receptors of adipose tissue, skeletal muscle, the liver, or pancreatic islet β cells, glucose metabolism is dysregulated, resulting in the elevation of blood glucose and the occurrence of T2DM and associated complications. Accordingly, glucose homeostasis is a sophisticated and accurately mediated process, and any risk factors that affect the aforementioned metabolic pathways can contribute to the imbalance of homeostasis, among which, the failure of efferocytosis is one such risk factor that cannot be ignored.⁵ Below, we outline the impact of efferocytosis failure on glucose homeostasis, T2DM, and associated complications through pathological changes in different tissues (Figure 2).

Pancreatic Islet β Cell Destruction

Insulin is generated by the islet β cells and is the only hormone in the body that lowers blood glucose. Undoubtedly, apoptosis of islet β cells is a key feature of the pathogenesis of T2DM. Indeed, numerous studies on T2DM have shown that the destruction of islet β cells is accompanied by an increased proliferation of macrophages residing within the pancreas,^{73–75} which is conducive to the secretion of insulin after the death of islet β cells induced by intraperitoneal injection of streptozotocin (STZ).⁷⁵ Furthermore, islet macrophages, which are mainly responsible for the production of IGF-1 outside the liver, also optimally exert efferocytosis to attenuate islet inflammation and reduce IR.⁷⁵ Consequently,

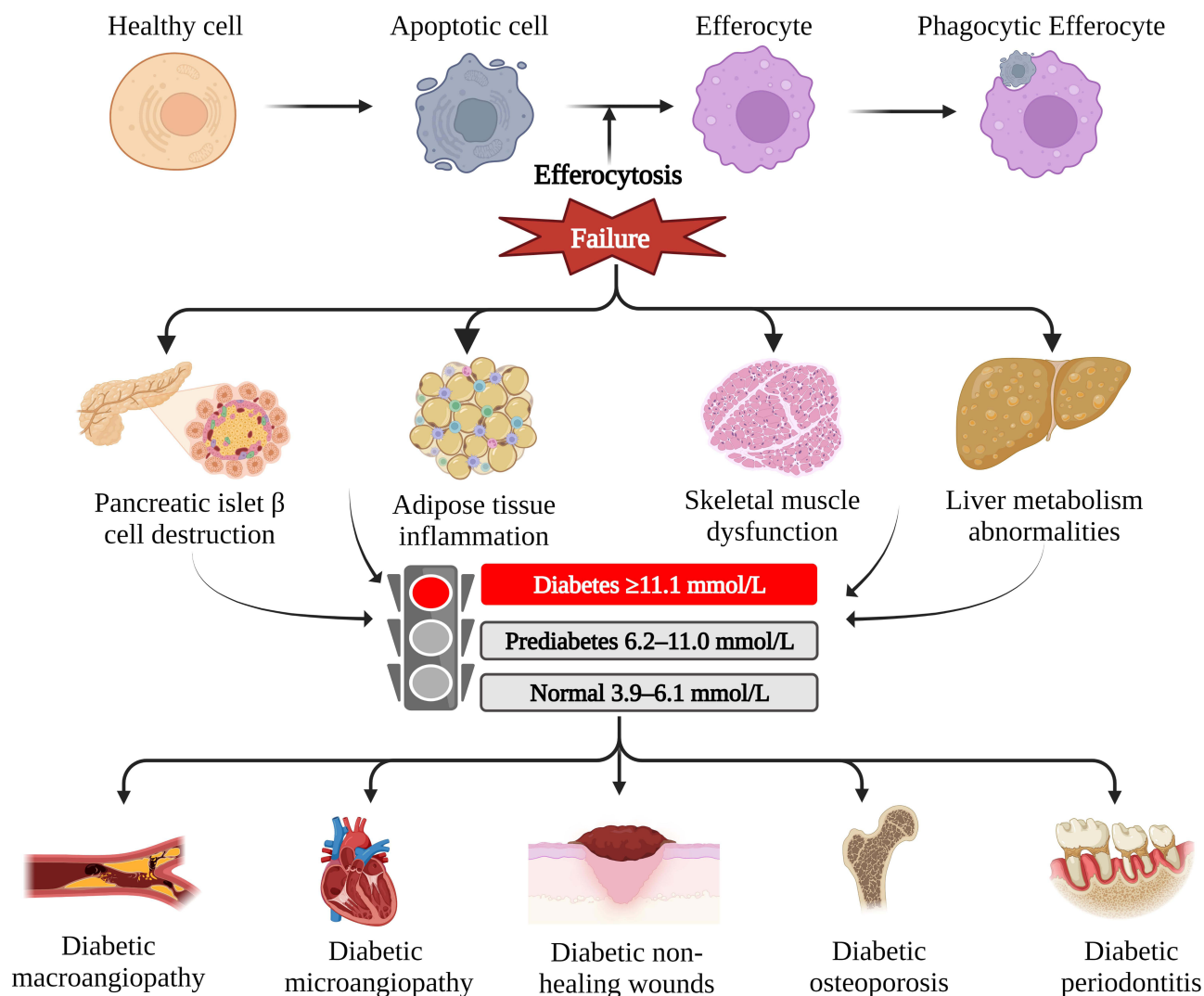


Figure 2 Efferocytosis failure leads to T2DM and its complications. Efferocytes have the function of clearing ACs in a non-inflammatory manner through what is called efferocytosis. Effective efferocytosis depends on the complex regulation of several processes, including recruitment, recognition, engulfment, and degradation. Defective efferocytosis triggers pancreatic islet β cell destruction, adipose tissue inflammation, skeletal muscle dysfunction, and liver metabolism abnormalities, all of which contribute to the occurrence of T2DM and complications, including diabetic macroangiopathy, diabetic microangiopathy, diabetic non-healing wounds, diabetic osteoporosis and diabetic periodontitis. Created with BioRender.com.

failed efferocytosis of islet macrophages can cause pancreatic islet β cell destruction, further disrupting glucose homeostasis. Moreover, the prolonged stimulation of high glucose (HG) in blood is capable of generating advanced glycation end products (AGEs), which not only cross-link with a variety of proteins, contributing to kidney, retina, and cardiovascular system damage,⁷⁶ but can also be recognized by RAGE to activate multiple signal pathways to contribute to the occurrence of T2DM and its complications via enhancing oxidative stress and tissue inflammation.⁷⁷ Beyond this, the concentration of AGEs is significantly increased in diabetic wounds, and exogenous addition of AGEs drives macrophage death and inflammation.⁷⁸ Further evidence has provided support for the role of AGEs in suppressing the macrophage-mediated efferocytosis of islet β cells through restraining Rac1 activity and cytoskeletal rearrangement; ultimately, this facilitates the expansion of islet inflammation and further destruction of islet β cells and dramatically reduces insulin secretion,⁸ indicating that impaired efferocytosis is a key pathogenic element for complications of diabetes. However, Ward et al reported that during T2DM, the function of macrophages changes as a consequence of apoptotic islet β cell uptake, in that they exert beneficial anti-inflammatory effects in the early stage and play a destructive pro-inflammatory role in the late stage.⁷⁹ The underlying mechanism may be related to the significant

accumulation of ACs that need to be eliminated at the late stage⁷⁹ or the different microenvironments in which islet macrophages reside.⁸⁰ Thus, the exact mechanisms underlying efferocytosis in pancreatic islet β cell destruction have not yet been completely clarified and merit further exploration.

Adipose Tissue Inflammation

Adipose tissue is the pivotal energy storage depot and is also perceived as the largest endocrine organ of the body, which can induce the overproduction of multiple cytokines, free fatty acids (FFAs), and pro-inflammatory factors. A certain amount of adipose tissue not only guarantees the supply of energy and enhances the body's ability to adapt to food deficiency environments but also participates in the synthesis and decomposition of glucose and regulates insulin signal transduction. High accumulation of adipose tissue, such as in overweight and obese people, gives rise to adipocyte inflammation, adipocyte dysfunction, and even adipocyte apoptosis through phenotypic transformation in adipose tissue and overproduction of pro-inflammatory mediators, such as FFAs.⁸¹ Additionally, massive aggregation of macrophages is the central event in adipocyte apoptosis, which also results in a long-term concentration of low-grade inflammation in the area around the adipose tissue to eventually allow for increased adipocyte death.⁸² In this state, adipose tissue inflammation is responsible for the persistent decrease in insulin sensitivity, which hastens the occurrence of continuous hyperglycemia and T2DM.⁸³ Indeed, a previous study showed that in an in vitro co-culture of apoptotic adipocytes and macrophages, apoptotic adipocytes promoted the expression of genes related to efferocytosis and were cleared by the enhanced macrophage efferocytosis.⁸⁴ However, this effect was eliminated by knocking down the arachidonate 15-lipoxygenase (*ALOX15*) gene or suppressing the expression of ALOX15 protein by drugs.⁸⁴ Furthermore, apolipoprotein E 4 (*APOE4*) gene replacement mice fed a high-fat diet have been shown to develop a pathological decline in insulin sensitivity, at least partly due to macrophages carrying *APOE4*.⁸⁵ Deeper research confirmed that the dramatic defects in efferocytosis were predominantly due to the expression of APOE4 protein in macrophages destroying adipocytes and worsening adipose tissue inflammation through strengthening endoplasmic reticulum stress (ERS).⁸⁶ TG2, serving as a binding partner for integrin β 3, is directly linked to MFG-E8 and jointly facilitates efferocytosis of macrophages to achieve engulfment of apoptotic adipocytes.⁸⁷ The loss of TG2 severely influences insulin sensitivity of mice fed high-fat diets via defective efferocytosis; however, this deficiency can be reversed by LXR agonists, thereby partially alleviating IR.⁸⁸ Admittedly, efferocytosis is capable of limiting inflammation and is conducive to the restoration of impaired tissues by efficiently and precisely eliminating apoptotic adipocytes.⁹ Exosomes from adipose-derived stem cells stimulate macrophages to switch from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype,⁸⁹ which is accompanied by the supplement of anti-inflammatory factor IL-10 and the loss of pro-inflammatory factors such as tumor necrosis factor alpha (TNF- α) and nitric oxide (NO),⁹⁰ which in turn reduce inflammation in adipose tissues and improve insulin sensitivity.⁹¹ In addition, M2 macrophages also support the generation of brown adipose tissues through the non-inflammatory clearance of adipocyte remnants and the coordinated production of PPAR ligands.⁹²

Skeletal Muscle Dysfunction

Skeletal muscles are the main organs responsible for movement in the human body, and as a consequence, they demand the utmost nutrients to supplement energy. According to statistics, 80–90% of glucose is absorbed and utilized by the skeletal muscle after glucose ingestion.⁹³ As the dominant regulator of glucose absorption and utilization, skeletal muscle dysfunction is a pivotal point in driving disorders of glucose metabolism and systemic IR. Although exhausted islet β cells cannot be repaired, merely rescuing the function of the skeletal muscle is sufficient to improve IR and increase insulin sensitivity.^{94,95} Fully functional skeletal muscles are required for healthy glucose homeostasis, and several studies have demonstrated that optimum efferocytosis is necessary to maintain normal skeletal muscle function. Specifically, DEL-1, an integrin ligand, is perceived as an endogenous anti-inflammatory element that positively regulates neutrophil chemotactic recruitment and enhances macrophage efferocytosis.⁹⁶ Later studies confirmed that increasing the expression of DEL-1 is a powerful solution to skeletal muscle dysfunction, as it suppresses skeletal muscle inflammation and upturns IR through inhibiting silent mating type information regulation 2 homolog-1 (SIRT1)/sarcoplasmic reticulum Ca²⁺ ATPase 2 (SERCA2)-mediated signaling⁹⁷ and activating the AMP-activated protein kinase (AMPK)/haemoxygenase (HO)-1 signal pathway.⁹⁸ ANXA1, one of the “find me” signals of efferocytosis, is considered to be a critical regulator of

the elimination of inflammation in bone marrow.⁹⁹ Importantly, only macrophages carrying the *ANXA1* gene can clear senescent neutrophils from the bone marrow⁹⁹ and promote the repair and regeneration of damaged skeletal muscles via regulating the receptor for lipoxin A4 (FPR2/ALX) and the downstream AMPK intracellular signaling pathway.¹⁰⁰ Moreover, nuclear factor IX (NFIX), a benign macrophage profibrotic agent, is linked with the resolution of inflammation after skeletal muscle injury.¹⁰¹ Further probing has revealed that NFIX is required for phenotypic transformation and function of phagocytes and that inhibition of negative pathways of efferocytosis such as RhoA-ROCK1 can boost NFIX expression and restore damaged skeletal muscles to allow healing.¹⁰² As a cell-surface transmembrane receptor that binds to PtdSer, SRB1 is widely distributed on macrophages.¹⁰³ The lack of SRB1 is not conducive to the recovery of impaired skeletal muscle function as it is not only a new functional molecule that converts macrophages from pro- to anti-inflammatory phenotypes but is also an upstream factor in the MAP kinase (MAPK) inflammatory signaling pathway of macrophages.¹⁰⁴ The absence of MFG-E8, a potent PtdSer receptor-driver, is another reason why it is difficult to recover from damaged skeletal muscle as it inhibits the anti-inflammatory effect of efferocytosis¹⁰⁵ and counteracts the proliferation of myoblasts mediated by extracellular regulated protein kinase (ERK) and protein kinase B (Akt) activation.¹⁰⁶ Furthermore, PPAR γ ,¹⁰⁷ TG2,¹⁰⁸ or TAM¹⁰⁹ knockdown mice all exhibit disordered macrophage phenotypic transformation, which is insufficient to eliminate damaged skeletal muscle cells, promote skeletal muscle regeneration, and restore innate skeletal muscle function. Intriguingly, neuron-derived clone 77 (Nur77), a negative inflammatory regulator, and PPAR γ play opposite roles in different macrophage subpopulations, in that Nur77 is capable of antagonizing the effects of PPAR γ , expanding the scope of inflammation and prolonging skeletal muscle tissue repair.¹¹⁰ However, the specific mechanism underlying the antagonistic effect between Nur77 and PPAR γ is currently unknown.

Liver Metabolism Abnormalities

The associations between efferocytosis, glucose homeostasis, and liver metabolism are particularly sophisticated.¹¹¹ As another key organ for maintaining normal glucose homeostasis, in addition to being the primary site for gluconeogenesis and glycogen synthesis, the liver also plays a crucial role in indirectly regulating blood glucose levels through governing the lipid metabolism. Furthermore, the liver is the earliest organ to receive and manage insulin,¹¹² and it is also unique in that it has two opportunities to degrade insulin: the first through the liver's portal vein, and the second through the systemic circulation. Approximately 75% of insulin is degraded in these ways.¹¹³ Abnormalities in liver metabolism inevitably lead to insulin metabolism disorder. Generally, glycogenolysis and adipose synthesis in the liver depend on the interaction between insulin and liver insulin receptors. However, this interaction is weakened in patients with T2DM, which leads to a high-risk combination of hyperglycemia and hyperlipidemia.¹¹⁴ Liver metabolism abnormalities form the other core pathological mechanism of glucose homeostasis. Importantly, defective efferocytosis has emerged as a critical risk factor for aberrant liver metabolism, even mediating chronic hepatocyte death.¹¹⁵ Studies have demonstrated that dead fat-laden hepatocytes are engulfed by liver macrophages carrying *ANXA1*, suggesting that the efferocytosis of liver macrophages contributes to regulating lipid metabolism, and preventing inflammatory expansion, thereby restoring liver metabolic function.¹¹⁶ Apoptotic vesicles derived from mesenchymal stem cells (MSCs) induce the efferocytosis of liver macrophages in mice with T2DM, which allows for the improvement of hepatic steatosis and the advancement of insulin sensitivity through the calreticulin "eat me" signal.¹¹¹ Subsequent studies have corroborated that powerful efferocytosis confers liver macrophages with the ability to block mitochondria-derived damage-associated molecular patterns (mito-DAMPs), thereby hindering the formation of liver fibrosis and aiding in abnormal liver metabolism repair.¹¹⁷ Besides, as a bridge molecule between PtdSer and $\alpha\text{v}\beta3/\alpha\text{v}\beta5$, CCN1 is beneficial to wound healing in diabetic *Lepr* (db/db) mice,⁴⁰ suggesting that efferocytosis is helpful for various complications caused by glucose metabolism disorder and decreased IR in patients with T2DM. CCN1 also triggers the degradation of apoptotic neutrophils and the appropriate generation of TGF- β to restore damaged liver tissue and cellular function.¹¹⁸

Efferocytosis in Pathologies and Therapeutic Opportunities of T2DM Development

Efferocytosis depends on the formation of efferocytic cups and phagolysosomes, which is a distinctive degradation process to clear ACs in a non-inflammatory manner. Efferocytosis is extraordinarily well coupled to the principal pathologies of T2DM, an illness with chronic low-grade inflammation that requires indispensable anti-inflammatory treatment.¹¹⁹ In vivo experiments have revealed an increase in the number of dead cells with IR due to defects in efferocytosis.⁸⁶ Animal experiments have found that adiponectin, a susceptibility gene and therapeutic target for T2DM, is responsible for defect-free efferocytosis by linking with calreticulin on macrophages.¹²⁰ Moreover, obesity is known to be a critical determinant of T2DM. Indeed, previous studies have shown that macrophage-mediated AC clearance was significantly disrupted in obese mice, which was reversed by exogenous addition of erythropoietin (EPO).¹²¹ Despite the incomplete mechanistic understanding of how glucose affects efferocytosis, the findings mentioned above may indicate ways to target the efferocytosis in obesity and even T2DM. Intriguingly, a previous animal study found that failed or defective efferocytosis in obesity and T2DM is induced by elevated levels of saturated fatty acids (FAs), whereas feeding a fish oil diet abundant in omega-3 FAs is sufficient to reverse the aforementioned dilemma.¹²² Additionally, physical activity, an extraordinarily useful physical therapy for T2DM, enhances the activity of macrophage efferocytosis to mitigate inflammation and enhance insulin sensitivity via the augmentation of *DEL-1* expression levels.⁹⁸ Despite few studies on clinical drugs targeting efferocytosis to intervene in T2DM, non-pharmacological methods, such as changing dietary habits and strengthening exercise, have verified that potent efferocytosis represents a promising therapeutic target for T2DM.

Diabetic Macroangiopathy

Theoretically, the impairment of efferocytosis may contribute to specific compromises of diabetic macroangiopathy owing to the fact that the accumulation of ACs and persistent inflammation are unfavorable for endothelial function, clearance of apoptotic foam cells, and smooth muscle cell survival, all of which eventually lead to the development of atherosclerosis.¹²³ Defective efferocytosis is postulated as a predominantly hazardous player in atherosclerosis,¹²⁴ and reinforcement of efferocytosis aids in the reduction of atherosclerosis.^{125,126} Alternatively, the favorable remediation effect of cardiac function after myocardial infarction (MI) is attributed to cardiac macrophage efferocytosis, which generates VEGF in a CD36-dependent manner to reduce inflammation and promote lymphangiogenesis.¹²⁷ The deletion of legumain, a gene encoding endolysosomal cysteine protease that is highly expressed in macrophages, has a prejudicial impact on cardiac function recovery after MI as it causes efferocytosis failure, widespread inflammation, and accumulation of apoptotic cardiomyocytes.¹²⁸ Although how efferocytosis affects specific diabetic macroangiopathy remains an unanswered research question, evidence shows that efferocytosis plays a positive role in both T2DM and macroangiopathy individually, implying that it also contributes to the pathogenesis of diabetic macroangiopathy, highlighting the direction for future research.

Diabetic Microangiopathy

Partial mechanisms underlying diabetic cardiomyopathy (DCM) are closely associated with the loss of efferocytosis. Experimental studies have shown that salvage of defective efferocytosis in diabetes can promote the degradation of apoptotic cardiomyocytes and repair the damage of adjacent cardiomyocytes through overexpression of microRNAs-126.¹²⁹ Furthermore, mice with DCM appear to show a reduction in LC3-mediated canonical autophagy and a high accumulation of apoptotic cardiomyocytes.¹³⁰ LC3 is the critical driver of phagolysosome formation as LC3 depletion prevents efferosome-lysosome fusion,^{131,132} suggesting that the accumulation of apoptotic cardiomyocytes may be partially attributed to the defect in efferocytosis induced by the suppression of LC3-associated phagocytosis.

Diabetic Non-Healing Wounds

Non-healing wounds are the most common and distressing chronic complications of T2DM, and efficient efferocytosis is one of the decisive methods that positively regulates the wound-healing process.^{133,134} Both in vivo and in vitro

experiments have confirmed that enhancing the efferocytosis of dendritic cells is beneficial for wound healing through inhibition of solute carrier family 7 member 11 (SLC7A11) function to increase aerobic glycolysis.¹³⁵ Additionally, increasing the expression of MFG-E8¹³⁶ achieves the same therapeutic effect. Single-cell RNA sequencing has revealed that the upregulation of Axl contributes to wound closure independent of efferocytosis,¹³⁷ suggesting the involvement of other mechanisms. Interestingly, a new hybrid biomaterial composed of formyl-met-leu-phe (fMLP), FasL-conjugated silica nanoparticles (SiO₂-FasL),¹³⁸ and ANXA1 N-terminal peptide Ac2-26¹³⁹ were found to successfully reduce inflammation and promote wound healing by accelerating efferocytosis to generate anti-inflammatory factors and eliminate excess neutrophils. Additionally, low-dose aspirin,¹⁴⁰ insulin,¹⁴¹ modified collagen gel¹⁴² for external use, and Naoxintong (NXT)¹⁴³ for oral administration, a Chinese patent medicine, are known to facilitate wound repair owing to effective efferocytosis via promoting macrophages to switch from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype.

Diabetic Osteoporosis

Osteoporosis is a common disease in elderly people, with osteoporosis caused by T2DM considered the most detrimental.¹⁴⁴ Experiments in mice models have revealed that the PPAR β/δ agonist¹⁴⁵ and exendin-4 synergized with vitamin D¹⁴⁶ aid in the improvement of diabetic osteoporosis due to the correction of macrophage dysfunction via facilitating M1/M2 macrophage polarization. Co-culture of osteoclasts (OCs) and neutrophils in the HG environment revealed an increase in apoptotic neutrophils and a loss of efferocytosis of OCs, which could be reversed by an efferocytosis activator such as lipoxin A4 and insulin.¹⁴⁷ Alternatively, lipoxin A4 and insulin significantly increased the number and efferocytosis of OCs and increased the bone absorption markers and bone mineral content in rats with STZ-induced diabetic osteoporosis.¹⁴⁷

Diabetic Periodontitis

Diabetic periodontitis is a serious oral disease, which results from accumulation of apoptotic neutrophils and is characterized by chronic inflammation and, in severe cases, may result in periodontal abscess, tooth loss and even other more pernicious diabetes complications.¹⁴⁸ Some studies have identified persistent cellular inflammation and severe periodontal damage due to the decreased efferocytosis of macrophages lacking *SIRT6* after HG stimulation via the indirect inhibition of the DEL-1/CD36 “eat me” signaling axis,¹⁴⁹ suggesting that reinforcement of efferocytosis may aid in the recovery of diabetic periodontitis.

Conclusion

The prompt clearance of ACs is indispensable for the preservation of homeostasis and recovery from inflammatory injury.³ Here, we provide an overview of the available research showing that massive accumulation of ACs and the proliferation of persistent inflammation due to defective efferocytosis are closely associated with pancreatic islet β cell destruction, adipose tissue inflammation, skeletal muscle dysfunction, and liver metabolism abnormalities, all of which are fundamental pathological mechanisms of T2DM. However, the research on efferocytosis in T2DM and its associated complications is still emerging. Indeed, the exploration of efferocytosis in diabetic wound healing is fairly widespread, but research on diabetic angiopathy, such as diabetic cardiocerebrovascular disease, diabetic nephropathy, and diabetic retinopathy, remains rare. Additionally, some animal experiments have confirmed that reasonable diet, physical exercise, and insulin-targeted enhancement of efferocytosis are beneficial to T2DM and its complications; however, the treatment measures applied to clinical research and research on other glucose-lowering medications such as metformin remain unclear. The research trajectory aimed at investigating efferocytosis in individuals with T2DM and its complications remains extensive. However, it is undeniable that efferocytosis has become a promising research direction for T2DM and its complications.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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