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REVIEW

Effect of diabetes on efferocytosis process

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Abstract

Diabetes is a complex of genetic, metabolic, and autoimmune disorders that are characterized by hyperglycemia. Elevated apoptotic cell count following defective clearance of dead cells that can cause chronic inflammation is a hallmark of the diabetic wound. Effective dead cell clearance is a prerequisite for rapid inflammation resolution and successful recovery. Efferocytosis is a multistep process in which phagocytes engulf the dead cells. Cell body elimination is of great significance in disease and homeostasis. Recent research has clarified that diabetic wounds have an enhanced load of the apoptotic cell, which is partly attributed to the dysfunction of macrophages in apoptotic clearance at the site of the diabetic wounds. In the current work, we highlight the pathways implicated in efferocytosis, from the diagnosis of apoptotic cells to the phagocytic swallowing and the homeostatic resolution, and explain the possible pathophysiological episodes occurring when the proceeding is abrogated. Also, we describe the last development in the management of inflammation in diabetes wound and future directions of surveillance.

Keywords Apoptotic cell · Diabetes · Efferocytosis

Introduction

Diabetes, a multifactorial disorder in metabolism, occurs when the insulin production by the pancreas is insufficient, or the body cannot effectively use the insulin [1]. The common characteristic of this condition is hyperglycemia chronically because of fault in carbohydrates, fat, and protein metabolism. Persistent hyperglycemia causes multiple organ dysfunction, including bone, nerves, blood vessels, eyes, kidneys, and heart [2, 3]. Diabetes has three main classes, including Type 1 diabetes mellitus (T1DM), Type 2diabete Mellitus (T2M), and Gestational diabetes mellitus (GDM). Those types are created from various causes. T1DM is usually observed in people lower than 30 years old. However, it may affect older people [4]. T1DM does not fully understand but is known for failing in insulin secretion via various causes such as an autoimmune or idiopathic attack, which destroys beta cells of Langerhans islets located in the pancreas [5]. Hence, curing it is principally accomplished by insulin replacement. Another diabetes type

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(T2M) is characterized by relative insulin deficiency caused by the defect in the beta-cell of the pancreas and insulin resistance [6]. Cardiovascular disease (CVD) is the main etiology of T2M-related diseases and deaths and requires severe management of blood pressure, glucose, and fat to minimize the risk of disease progression [7, 8]. Gestational diabetes is becoming more prevalent, together with type 2 diabetes and fatness [9]. Hyperglycemia, which develops during pregnancy, has been known for more than 50 years, but there is no universal consensus on high blood sugar levels that can be used to diagnose and treat "gestational diabetes" (GDM). Nowadays, GDM has been found to be the most prevalent medical complication during pregnancy, and the hyperglycemia outbreak has not been distinguished, and reports show that the number of young women with overt diabetes is increasing [10].

Apoptosis is a highly regulated cell death process. Both necrosis and apoptosis are the main cell death types. While necrosis is a traumatic version and accidental of cell death, apoptosis is a predefined cell suicide to particular victim cells for the greater profit of the organism. It is an ordinary physiologic process carried out in multicellular organisms [11]. Today, it has been well established that apoptosis brings benefits to the survival of multicellular organisms, whereby organisms maintain homeostasis and regulate the life cycle. Nevertheless, the remains many mysteries remain in the relevant research areas [12].

Macrophages engulf apoptotic cells in a process called efferocytosis[13]. Elimination of cellular corpses is critical in the treatment of disease and homeostasis. Through engulfment of dead cells, phagocytes, known as efferocytosis, help recycle cellular components in multicellular organisms. Autoimmune and other conditions can develop when the disposal of cell corpses is faulty. This attempt briefly reviews the relationship and mechanism of efferocytosis associated with diabetes disease. We first discuss the mechanism of efferocytosis and then explain related to diabetes in various aspects.

Mechanism of efferocytosis

Billions of cells die in the body of human beings to regulate immune responses, cell homeostasis and wound healing. Dying cells must be effectively removed to perform all these processes [14]. The clearance of dead cells, which usually occurs during human life, is termed efferocytosis [15]. Altogether, the processes of efferocytosis possess four phases: (1) The dead cells issue a "find me" signal, (2) the phagocytes are identified, and their contribution is determined in the liberation of the "eat me" signal on the cell body, (3) The dead cells are swallowed, and (4) the swallowed cells are destroyed [16].

Find-me signals

Apoptosis is physiological programmed cell death. Encapsulation of apoptotic cells in apoptotic bodies aid in the prohibition of diffusion of pro-inflammatory and inflammatory cell contents, subsequently recycling and excreting them via neighboring scavenger cells [17]. During programmed cell death, the signals are liberated by the cell into the environment to absorb the macrophages and agitate their scavenging potential of them. In this process, signaling molecules from apoptotic cells are released into the environment [18]. Apoptotic cells emit two categories of signals: extracellular vesicles and soluble molecules. 'find-me' Signals emitted from apoptotic cells include nucleotides, modified membrane lipids, and chemokines. The most well-known find-me are nucleotides such as uridine triphosphate and adenosine triphosphate.Apoptotic cells release these nucleotides into the environment via the pannexin-1 channel [19]. Sphingosine-1-phosphate (S1P), ATP / UTP, Lysophosphatidylcholine (LPC), and chemokines (Fractalkine) are other signals emitted by apoptotic cells [18, 20]. It should be noted that the signals of find-me fall into four basic categories: lysophosphatidylcholine (LPC), sphingosine-1-phosphate (S1P), CX3CL1, and nucleotides [21] (Fig. 1-A).

The efficiency and role of any find-me signal depend on the type of dead cell and phagocyte [22], as well as the diversity of find-me signals, suggests inherent redundancy, thereby ensuring the macrophages to recognize dead cell bodies.

Eat me signals

Cells that are dying display the signals of eat-me on their surface, considered as the signals of 'eat-me' include a. lack of phospholipid asymmetry in the cell membrane [23], b. displayed LPC to the surface of dying cells attaches to Fc receptors on scavenger cells like macrophages[24], c. Display of proteins in the endoplasmic reticulum (ER) lumen on the dying cell surface and the absence of " don't-eat-me " signals act as the signal of 'eat-me' [25]. Phagocytes discriminate dying cells from healthy neighbors through the signals of 'eat-me', which neighbors cells have the signals of 'don't-eat-me'. In other words, apoptotic cells issue the signals of find-me and eat-me to detect these signals via phagocytes can accelerate their ingestion; Reciprocally, the signals of don't-eat-me emitted by apoptotic cells can block their swallowing. Many investigations scrutinized the

stages of phagocytosis, and each stage is specifically identified [26, 27].

Engulfment of dead cells

When a phagocyte detects a dying cell, the dead cell engulfment needs quick plasma membrane detection, and the dead cell must be encapsulated quickly in phagocytes [28]. A dynamic network of actin under the cell membrane motivates phagocytes to environmental sampling. The phagocyte begins to rearrange the actin by detecting an apoptotic cell, allowing the plasma membrane to penetrate and localize, eventually forming the phagosome. Coordinated activation of kinases, like Srk, Syk, and protein kinase C (PKC) families, and phosphatase inactivation, like SHP-1, are signaling mechanisms that differentiate the receptor by activating actin regeneration and relevant pathways based on the involved receptor [29]. The two main mechanisms involved actin reorganization within spherocytosis, converging in the major regulator, Rac1, a member of the Rho family of GTPases. Rac1 activation is mediated in the first system through LDL receptor-related protein 1 (LRP1) and adapter protein GULP [30]. Overall, several important signals contribute to the Eat-me process: phosphatidylserine (PtdSer), which interacts with BAI1 and av-beta3. Another one is calreticulin (Calr) which interacts with lipoprotein receptor-related protein 1 (LRP1) (Fig. 2-B) [31]. However, healthy cells for shielding from phagocytosis express several signals called “Don’t eat me” including CD24, CD47, and CD31. These signals could bind to several receptors on phagocytes (Siglec-10, CD31, SIRP) and prevent the efferocytosis process (Fig. 2-C) [31].

Degradation of the engulfed cells

After recognizing and trapping the dying cell, the cell body and phagosome are well organized for a ruinous ending. Following the uptake of dying cells by the scavenger cells, the phagosome incorporates with the lysosomes. Because liposomes involve many types of lipases, proteases, and nucleases, this fusion causes the digestion of phagosome cargo [32].

When phagosomes ingest dead cells, they are targeted with lysosomes via a multi-stage maturation process. Immediately after phagosome formation, a dynamin-dependent membrane fracture begins, accompanied by numerous biochemical changes in the phagosome membrane [33].

After engulfment, several signals related to efferocytosis and wound-healing are promoted and cause a change in the metabolism of the immune system, immunosuppression, wound healing, and M2-like macrophage polarization, which significantly affects the local tissue microenvironment. Several nuclear receptors (NR), particularly liver X receptor (LXR) and peroxisome proliferator-activated receptor (PPAR), are stimulated in reaction to efferocytosis. In this process, apoptotic cells are immersed in LC3-associated phagocytosis (LAP) [34]. Subsequently, it fused with lysosomes and degraded efficiently. Then fatty acids productions such as 25-hydroxysterol active PPAR and LXR. This nuclear receptor induces the transcription of immunosuppressive cytokines, including TGF-beta1, IL-13, and IL-10. They also indicated that transcribed pro-efferocytosis machinery comprises Gas6, MertK, and Rac1 (Fig. 2) [34].

Impact of abnormal efferocytosis on diabetes

One of the major sources of autoantigens in diabetes is apoptotic β-cells. Autoimmune is facilitated by a high incidence of β-cell apoptosis or deficiencies in the clearance of apoptotic cells in pre-diabetes [35]. These cells transform into late apoptotic bodies and secondary necrotic cells, increasing insulitis, inflammation, and autoimmunity. If apoptotic β-cells are not removed quickly enough, they clump together, causing autoantigens to be released and inflammatory signals to be activated. On the other hand, loss of pancreatic β-cells due to abnormal efferocytosis might cause hyperglycemia and insulin insufficiency, which has been linked to the etiology of diabetes (Fig. 3) [36]. Several animal researches indicated that abnormal efferocytosis had been associated with diabetes [37, 38]. In table 1, we summarise the researches accomplished on efferocytosis and diabetes.

Factors contributing to the efferocytosis process in diabetes

Until now, numerous factors have been proposed as possible causes of diabetes. The following are some of the factors that contribute to this process:

Phagocytic oxidative stress can result in defective efferocytosis, impairing phagocytes’ ability to engulf apoptotic cells [39]. The phagocytic dysfunction in macrophages has been found as a known property of diabetes [40, 41]. Macrophages are involved in tissue regeneration and repair, which is impaired in diabetes, resulting in poor regeneration and delayed repair. This process is also affected by the microenvironment [42]. Efferocytosis is a critical cellular procedure for immune response and maintaining tissue homeostasis [43]. When tissue is injured, phagocytes swallow and

clear dead cells, resulting in an efficient resolution of the inflammation [44]. Numerous studies have shown that macrophage function is impaired in diabetes and is related to prolonged inflammatory response and harmful alteration in heart regeneration, thus increasing the risk of heart defeat and altering the outcome of the disease [45]. Efferocytosis decreased in diabetic wound macrophages, resulting in the apoptotic cell accumulation in inducing inflammation response.

Efferocytosis enhancers administering specialized pro-resolving mediators, such as maresin 1, LXA4, resolvin D1, or resolvin D2, which act as efferocytosis enhancers, improves efferocytosis while decreasing the incidence of phagocytic inflammation [46–48].

High glucose high glucose is one of the key characteristics of diabetes that can lead to efferocytosis dysfunction [49].

Mannan-binding lectin (MBL) as a serum protein can trigger the complement system and reinforce the phagocytic removal of different inflammatory parameters [51]. The oligomeric C-type lectin of MBL detects specific sugar patterns on the surface of apoptotic cells [52]. In a cross-sectional study to reveal a relationship between MBL with nephropathy among T1D subjects, the concentrations of MBL were greater in the study cases suffering from macrovascular disease.As well as, the MBL has been reported to increase apoptotic cell clearance in diabetic patients [53].

Adiponectin is a hormone derived from adipocytes that exerts anti-inflammatory and anti-diabetic performances. It employs the macrophages to facilitate the early apoptotic cell uptake that is substantial for the activity of immunity [54]. Mice deficient in adiponectin (APN-KO) showed impairment in their capacity for apoptotic thymocyte clearance. This hormone opsonizes the apoptotic cells, and the adiponectin-mediated phagocytosis causes the attachment of cell corpses to calreticulin located on the surface of macrophages. In this way, adiponectin enhances its anti-diabetic properties [55].

Apolipoprotein (apo) E4 One of the pivotal risk factors is apolipoprotein (apo) E4 for diverse inflammations and metabolic problems, like Alzheimer's disease (AD), atherosclerosis, and diabetes. The secretion of apoE4 promotes macrophage dysfunction and apoptosis by decreasing ER stress. The inflammatory responses and relevant metabolic disorders associated with polymorphism in apoE4 may be decreased by reducing ER stress in macrophages [56].

ER stress has the potential to impede the efferocytosis process [57]. In addition, it was shown that stress could develop diabetes and insulin resistance. The efferocytosis can be reinforced by the developmental endothelial locus-1 (DEL-1) via macrophage, suppressing the inflammation [58].

MERTK it was shown that Mer tyrosine kinase (MERTK) mediates efferocytosis in atherosclerotic lesions. This gene encoded Proto-oncogene tyrosine-protein kinase MER that engulfs apoptotic cells by interacting with the phosphatidylserine-binding proteins Gas6 or Protein S, which are bridging molecules [59].

MFG-E8 A study showed that a lake MFG-E8 gene in mice causes impairment in efferocytosis. Mice deficient in MFG-E8 receiving wild-type bone marrow revealed it resolved inflammation, supported angiogenesis, and improved wound closure [50].

Erythropoietin (EPO) signaling defective is a significant cause of abnormal efferocytosis leading to type 2 diabetes. S1P generated by apoptotic cells binds to the cognate receptor on macrophages, facilitating efferocytosis via the EPO-EPO receptor-peroxisome proliferator-activated receptor-γ signaling pathway [60].

Role of interventional treatment on efferocytosis

A diabetes case report showed that administration of Rituximab could induce efferocytosis in diabetic patients. It was reported that clearance is effective in tissue B-cell [61]. Rituximab, as an anti-CD20 antibody, might accomplish its effect by inducing the effect of Fc receptor-dependent phagocytosis [62]. The multifunctional molecule of the cluster of differentiation 36 (CD36) possesses separate binding sites for various ligands like modified phospholipids, free fatty acids, and thrombospondins. The CD36 serves as a scavenger receptor on phagocytes, thereby recognizing and internalizing apoptotic cells and erythrocytes infected with falciparum malaria [63, 64]. In diabetic patients, a high concentration of LDL causes a block in the cd36 receptor, which inhibits efferocytosis [65].

The phagocytosis of apoptotic cells can be suppressed by anti-tTG (tissue transglutaminase antibody) through peritoneal macrophages extracted from the pregnant non-obese diabetic (NOD) mouse model of type I mice expressing the surface enzyme. The anti-tTG antibodies can act via a decrease in the transamidation performance and declined apoptotic cell removal via the macrophages from the pregnant diabetic mice [66].

Defective efferocytosis is associated with T1D and other autoimmune conditions [67]. The main objective of T1D

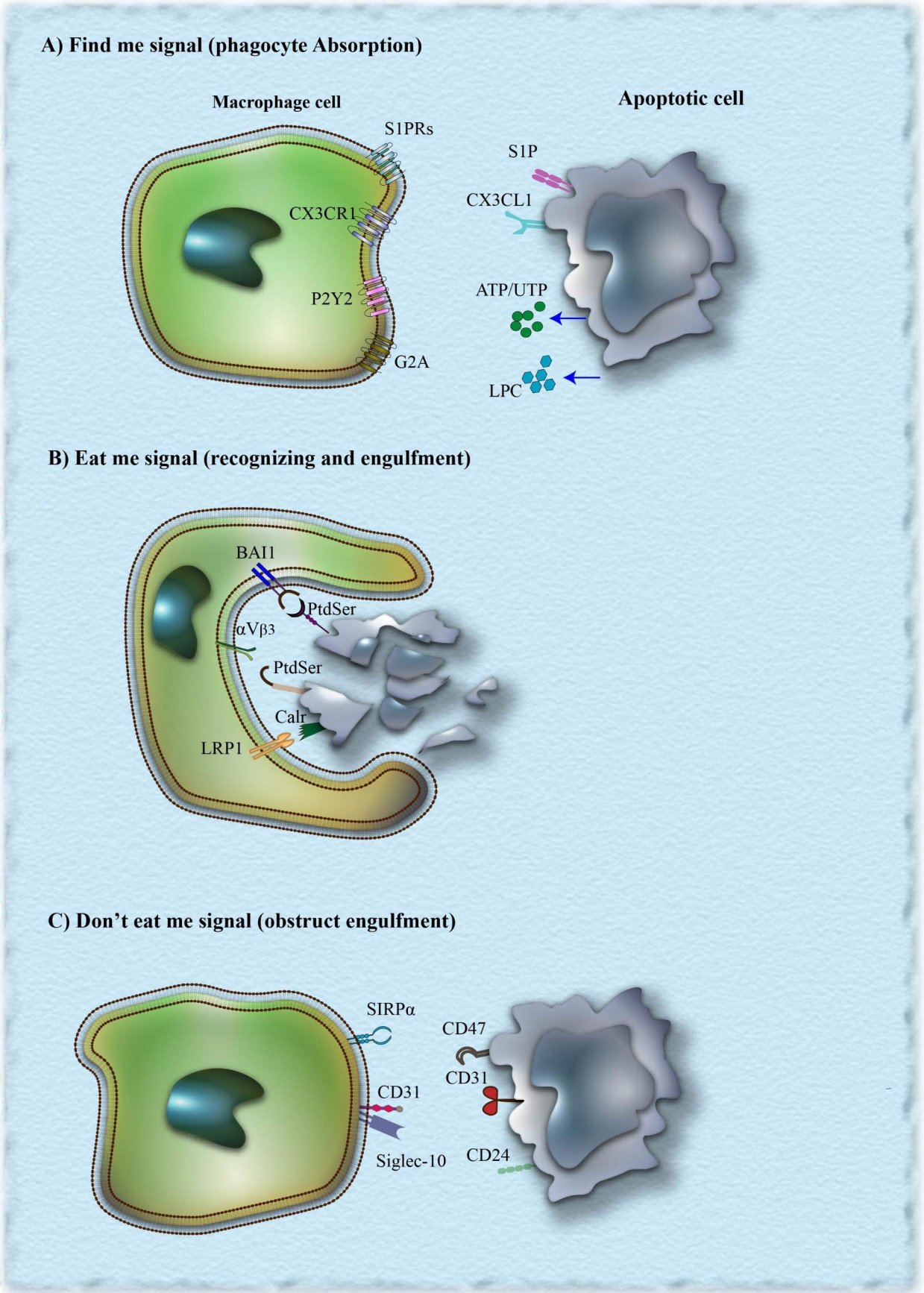

Fig. 1 Mechanisms of signaling in efferocytosis via different signals of (A) Find me (B) Eat me and engulfment (C) Don't eat me

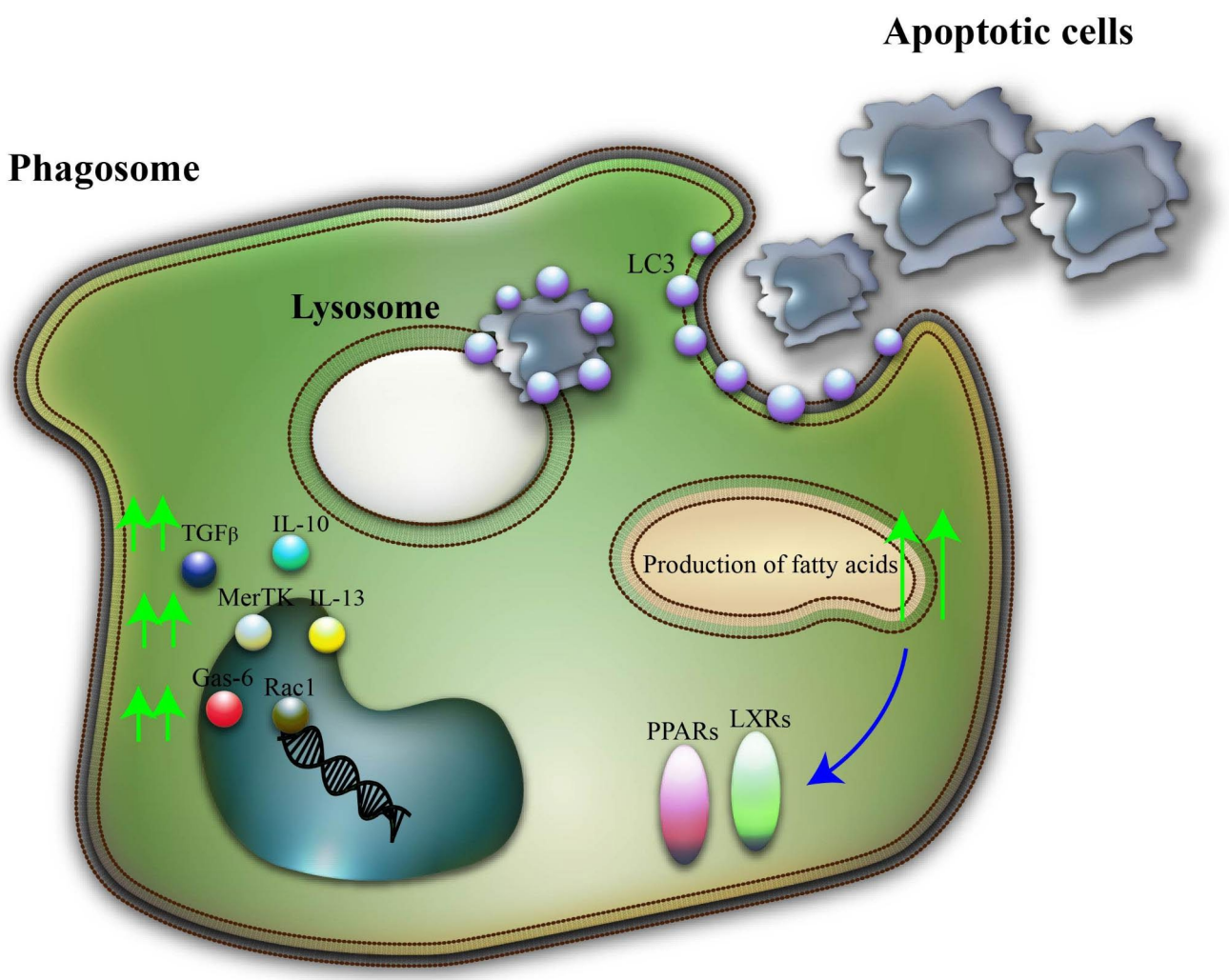

Fig. 2 Mechanism of signaling in post-engulfing which increases several functions such as efferocytosis, immunosuppression, wound healing, and M2-like Mφ, inducing cytokines

prevention is to stop the autoimmune response to β-cells. Surface alterations can occur following the apoptotic β-cells in T1D, in particular exposure to the phosphatidylserine (PS) of the inner leaflet of the plasma membrane, which differentiates them from living cells and allows them to be detected by efferocytotic receptors [26, 68]. Accordingly, a synthetic protocol to stop autoimmunity against β cells has been designed, including liposomal microparticles for mimicking apoptotic cells by detecting PS and full of insulin peptides. These liposomes inhibit T1D by re-establishing specific tolerance [69].

Liposomes that mimic apoptotic β-cells inhibited βcell-related autoimmunity and impeded the experimental T1D by producing tolerogenic DC. Such liposomes are composed of the PS- a key signal of the apoptotic cell membrane, and the β-cell autoantigens. To conclude, efferocytosis can be mimicked by PS-liposomes phagocytosis, resulting in functional and phenotypic alterations in human DCs responsible for the induction of tolerance [70].

Activating resting T lymphocytes initiate apoptotic death of activated T lymphocytes. In the onset of T1D, apoptosis resistance is of great importance in the activated autoreactive T lymphocytes, which move to the pancreas from the circulation and actively destroy the insular pancreatic structures. The apoptotic reaction to Phytohemagglutinin (PHA) was the strongest for T1DM decompensation [71]. Given that T cells are mainly exposed to apoptosis in reaction to the stimulation of PHA, we can speak of the great sensitivity of active T lymphocytes to induce apoptosis in T1DM subjects. The development of autoimmune conditions has links with increased target cell apoptosis, and a defect in phagocytic removal of apoptotic cells because of a dysfunction in efferocytosis, meaning phagocytosis of apoptotic cells [72].

In the apoptosis process, a large number of apoptotic vesicles were produced [73]. In a recent study in 2021,

Mesenchymal stem cells (MSCs)-derived apoptotic vesicles were employed to treat type 2 diabetes mice. They discovered that apoptotic vesicles were efferocytosed by macrophages and effectively controlled hepatic macrophage homeostasis to prevent type 2 diabetes [74]. In type 2 diabetes liver, apoptotic vesicles can promote macrophage reprogramming at the transcriptional level efferocytosis-dependent, resulting in macrophage accumulation suppression and macrophage transformation to an anti-inflammation phenotype. These authors also observed that calreticulin was exposed on the surface of apoptotic vesicles and acted as a crucial 'eat-me' signal driving apoptotic vesicles efferocytosis and macrophage regulatory effects at the molecular level. Notably, CRT-mediated efferocytosis of MSC-derived apoptotic vesicles aids type 2 diabetes therapy by reducing type 2 diabetes characteristics such as insulin resistance and glucose intolerance. Their data show that apoV functional efferocytosis improves type 2 diabetes by restoring hepatic macrophage homeostasis [74].

Inhibition of efferocytosis diabetic osteoporosis

DM is a persistent and chronic epidemic with associated complications increasing unabated, especially osteoporosis, which is broadly considered a new health concern worldwide [75]. A defect in bone regeneration that reduces bone mass increases bone fragility, decreases bone strength and microstructural changes in bone tissue, and leads to a high

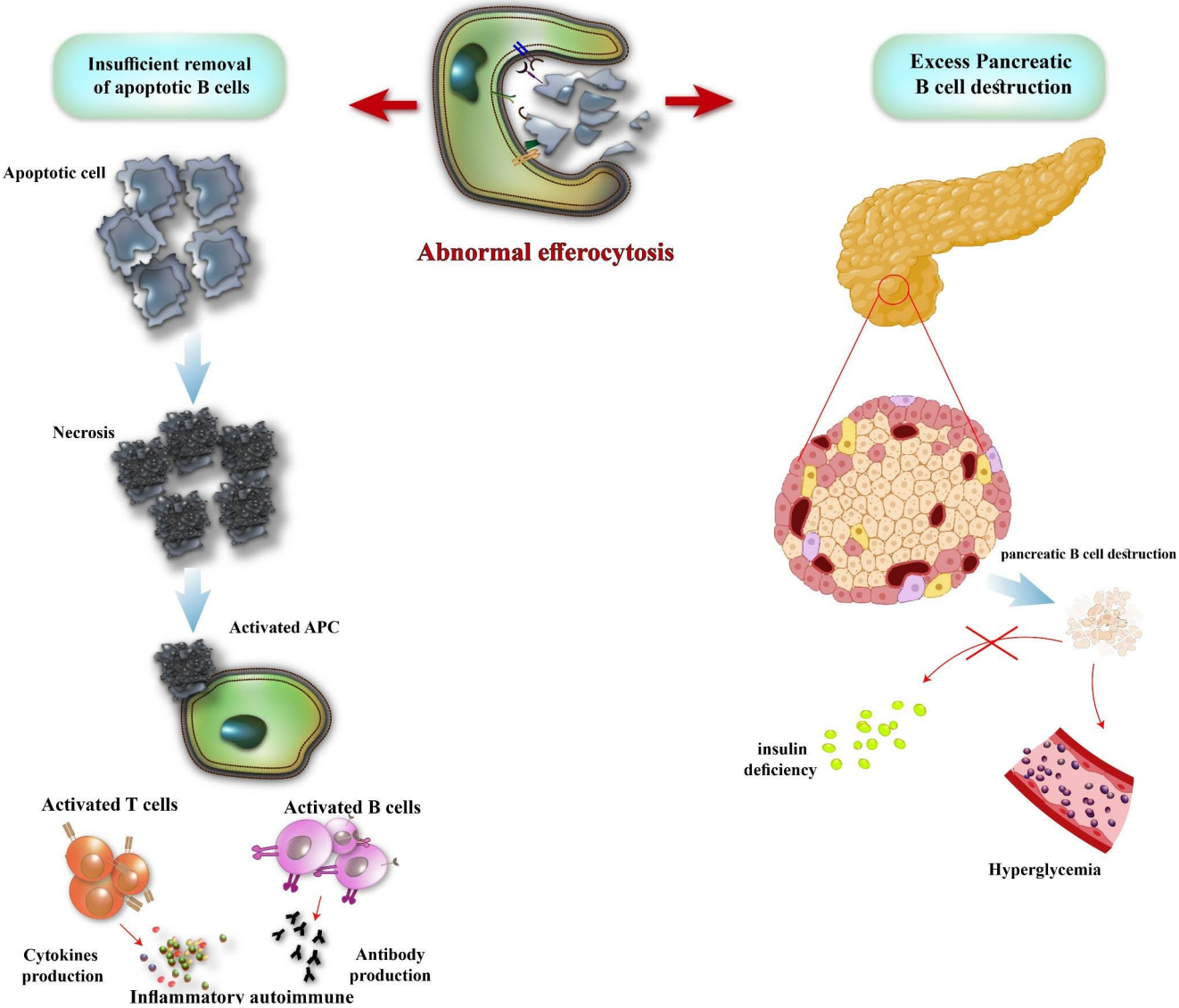

Fig. 3 The activation of antigen-presenting cells (APCs) is caused by an increase in the rate of β-cell apoptosis and/or deficiencies in efferocytosis, which contributes to inflammation. In contrast, pancreatic B cell death leads to hyperglycemia and insulin insufficiency

Table 1 Different studies related to efferocytosis in diabetes

Diabetes 1/2	Animal/cell line/ human	gene	function	Efferocytosis	Professional/ nonprofessional phagocyte	ref
Diabetes Type 2	diabetic (db/db) mice	ADAM9	miR-126 direct target ADAM9	Increased	Macrophage	[95]
Diabetes Type 2	C57BL/6 mice diabetic (db/db) mice	MFG-E8	bridging molecule between apoptotic cells and macrophage	Increased	Macrophage	[50]
Diabetes Type 1	diabetes-prone (NOD) mice normal (Balb/c) mice		mechanism of disposal of self-antigen	Decreased	Macrophage	[41]
type 2 diabetes	Human/ diabetic (db/db) mice	FasL	elevated apoptotic cell burden at the wound site	Decreased	Macrophage	[102]
Diabetes Type 1		MBL	trigger the complement system and enhance phagocytic removal	Increased		[53]
Diabetes Type 2	adiponectin-deficient (APN-KO) mice	adiponectin	binding to calreticulin on the macrophage cell surface	Increased		[55]
Diabetes Type 1	Human	Rituximab		Increased		[61]
Diabetes Type 2	Human	LDL	a block in the cd36 receptor	Decreased		[65]
Diabetes type 2	C57BL/6 mice	apoE4	cholesterol transport	Decreased	Macrophage	[56]
	Lepr$^{db/db}$ diabetic mice	CCN1	a bridging molecule attaching with apoptotic cells, and macrophages to trigger efferocytosis .	Increased	Macrophage	[119]
diabete type 1	NOD mice	Insulin peptides(A,B)	are epitopes targeted in autoimmune diabetes and specific β-cell.	Increased	T cell	[69]
diabetes type 1	diabetic *db/db* mice	MFG-E8	bridging molecule between the macrophage and apoptotic cells	Increased	peritoneal macrophages	[101]
diabetes type 1	Human	Phosphatidylserine	the key signal of apoptotic cell membrane—and β-cell autoantigens	decreased	tolerogenic dendritic cell (DC)	[70]
Diabetes Type 2	J774a.1 macrophage-like cells MIN6	NLRP3 IL-1β	Inflammation mediator pro-inflammatory cytokines	decreased	Macrophage	[140]
	C57BL/KsJ-db/db mice	Annexin A1-Derived Peptide Ac2-26	high activity in declining inflammation and improving	Increased	Macrophage(M2)	[122]
	C57BL/6J (B6) mice	DEL-1/SIRT1	suppressive performances in inflammation, ER stress and oxidative stress.	Increased	Macrophage	[58]

risk of fracture, known as diabetic osteoporosis [76]. Tissue-specific polykaryon macrophage that attaches to or near a bone surface is constructed via differentiating macrophage progenitor cell or a monocyte called an osteoclast (OC). As a heterogeneous cluster of immune cells, Tissue-resident macrophages have performances such as iron processing, clearance of cellular debris, and critical roles in tissue immune supervision, inflammation resolution, and infection response. Also, they play an acritical role in recruiting granulocytes into the tissue from the circulation [77, 78]. Depending on the damage grade, neutrophils cumulate in the tissue and quickly undergo apoptosis [79].

In vivo failure to remove dead cells aggravates inflammation, suggesting a prominent role of efferocytosis in moderating the inflammation in phagocytes to enhance inflammation resolution [80, 81].

Role of efferocytosis in wound healing in diabetic

The intractability of diabetic wounds can be attributed to complex parameters like prevention of angiogenesis, abnormal inflammatory responses, and dysfunction of phagocytosis by macrophages [101]. Efferocytosis is an intrinsic activity of wound macrophages [102]. Faulty efferocytosis during a diabetic situation enhances inflammatory responses and necrotic core formation, finally leading to atherosclerosis, autoimmune problems, and delayed wound healing

[102]. Previously data indicated that defective efferocytosis in a mouse model of diabetes resulted in the apoptotic cell accumulation in the wounds in a maintained pro-inflammatory microenvironment [102]. In addition, it was showed hatThe efferocytosis can be successful in the progression of pro-inflammatory M1 to reparative M2 macrophage [87, 88].

As stated earlier, macrophage alteration has a pivotal performance in the induction of efferocytosis. Diabetic wounds develop a variety of inflammatory cytokines and chemokines like AGE, MCP-1, DAMPs, and IL-1β in the wound microenvironment that mutually induce NLRP3 and IL-1R1 signal pathways. These events prevent the polarization of macrophages and directly affect the efferocytosis process [103, 104] (Fig. 4). Impaired phagocytic function of macrophages (apoptotic removal performance) at the diabetic wound site; is associated with an increased count of apoptotic cells[102]. Other effective factors that increase the apoptotic cell load in the diabetic wound are the elevated level of oxidative stress, the induction of protein kinase C (PKC), and the acceleration of apoptosis affected via advanced glycation end-products (AGEs) [105, 106]. The incremental count of apoptotic cells enhanced the inflammatory response in wounds in diabetic wounds. Accurate apoptotic cell removal through the macrophages at the wound site causes the decreased secretion of diabetic wound macrophages and inflammatory cytokines [107]. Fundamental changes in bone marrow precursors, as well as pro-inflammatory wounds, cause a steady increase in the count of wound monocytes (Mo) / macrophages (Mφ) and dysregulate their phenotype, thereby resulting in faulty wound healing during diabetic situations [108, 109]. Factors involved in the normalization of macrophages' non-healing wounds include: targeting the RAGE pathways and NLRP3 inflammasome/IL- 1β [110], and changing epigenetic modifications in the genes related to dysregulated macrophage phenotype [111]. Numerous studies showed that targeting monopoiesis can help to improve diabetic wound healing and normalize wound Mφ accumulation because increased steady-state diabetes-related monopoiesis help increase the

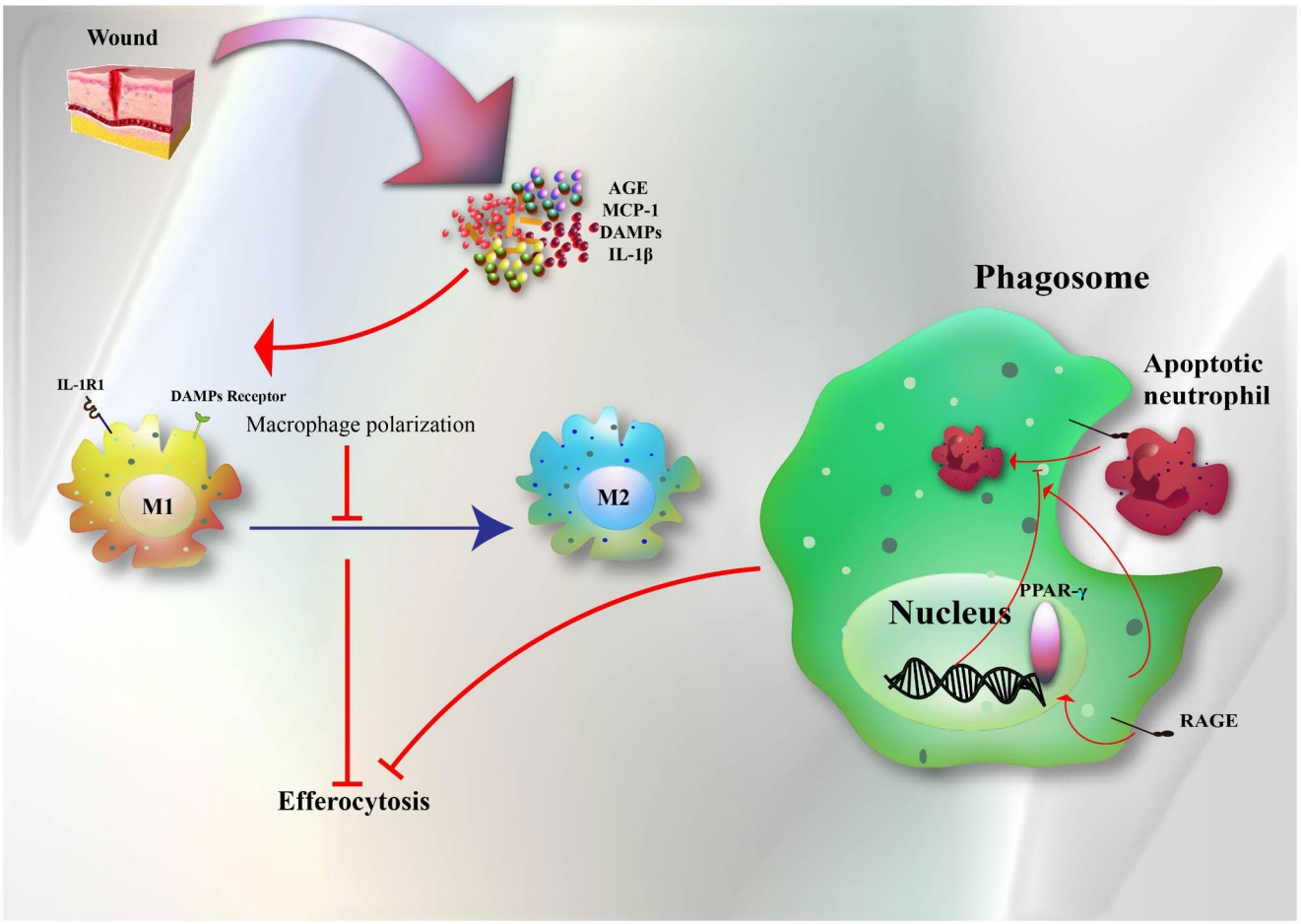

Fig. 4 Efferocytosis impairment in the diabetic wound. Reduction of PPAR-γ and elevation of RAGE signaling could decrease the performance of phagocytosis in wound diabetes. Therefore, the accumulation of necrotic and neutrophils increased. On the other hand, elevated inflammatory chemokines and cytokines in wound diabetes promote IL-1R1 and NLPR3 signaling to dysregulate macrophage polarization

accumulation of Mφ in diabetic wounds [112, 113]. Additionally, it revealed that PPAR-γ in wound healing via the clearance of apoptotic wound neutrophils has a significant role[114, 115]. Another research RAGE receptor regulates the count of neutrophils in diabetic wounds, reduces macrophage phagocytes' ability, and is strictly related to defect diabetic wound healing [116] (Fig. 4).

The wound healing can be accelerated by mesenchymal stem cells (MSCs) in diabetic mice[101, 117]. Large quantities of MFG-E8 are produced by MSCs [118]. It should be noted that the secretion of MFG-E8 in granulation tissue was significantly decreased in diabetic mice when compared with healthy mice. The MFG-E8 derived from MSCs may speed the healing of diabetic wounds through the promotion of angiogenesis, the apoptotic cell removal, and the M2 macrophage infiltration, thereby blocking inflammatory cytokines at the wound site [101].

The infiltration of neutrophils is the first phase in healing the wounds, although the timely removal via macrophage engulfment, or efferocytosis, is important for effective tissue regeneration. The certain pathway for removing neutrophils in wound healing is not clear. CCN1 plays an important role in the efferocytosis of neutrophils as a bridging molecule that links phosphatidylserine, the signal of 'eat-me' on apoptotic cells, and $\alpha_v\beta_3/\alpha_v\beta_5$ integrins in macrophages to induce efferocytosis [119].

Failed wound healing is a common side effect of diabetes. The macrophages of diabetic wounds show abnormal phenotypes and dysfunctional efferocytosis that can lead to excessive accumulation of neutrophils and long-term inflammation, thus impairing wound healing [120]. Great potential can be seen for the ANXA1 N-terminal derived peptide Ac2-26 in reducing the inflammatory response and facilitating repair. Following the Ac2-26 treatment, the closure of diabetic wounds can be accelerated, the neutrophil count can be down-regulated, the angiogenesis can be improved, and the deposition of collagen can be seen [121]. Moreover, the use of Ac2-26 accelerated the recruitment of macrophages and up-regulated the number of macrophages secreting CD206 as a marker for M2 macrophages. In addition, the Ac2-26 impeded the TNF-α and IL-6 expression levels and up-regulated the TGF-β, IL-10, and VEGFA expression levels in diabetic wound healing. Accordingly, the use of Ac2-26 in diabetic wounds displays the pro-repair and anti-inflammatory impacts through a decrease in the accumulation of neutrophils and an increase in the development of M2 macrophage [122].

Insulin act as a modulator of inflammatory reactions. The insulin-degrading enzyme overexpression results in inadequate insulin levels in diabetic skin within wound healing, thereby decreasing the recovery rate of diabetic wounds [123].

Studies stated that insulin increased neutrophil apoptosis and subsequently induced macrophage polarization. Insulin re-established phagocytosis performance and enhanced the phagocytosis-induced apoptosis process in neutrophils [120]. Moreover, it is shown that insulin therapy increased efferocytosis of apoptosis neutrophils by macrophages and therefore triggered macrophages to change their polarization state to M2 from M1 [124]. To conclude, investigations confirmed that the exogenous insulin accelerated diabetic wound healing through restoration of inflammatory response.

Resolution of inflammation in efferocytosis in diabetes

T1D or insulin-dependent diabetes is an autoimmune condition in which the pancreas yields low or no insulin. Because the immune system targets the pancreatic islets and eliminates insulin-producing cells, the pancreas produces little or cannot produce insulin [125]. It has been proven that an abnormal immune response to healthy cells, tissues, and organs leads to autoimmune disease. Some of the factors that cause the breaking of tolerance in pancreatic beta-cells include Neoantigens (defective ribosomal products (DRiP), hybrid insulin peptides (HIP), posttranslational modifications(PTM), Splicing), endoplasmic reticulum (ER) stress, type 1 interferon(IFN) signature, CXCLl0, HLA upregulation, metabolites (adenosine, nutrients), hypoxia, innervations, ECM small pancreas, gluten, inflammation, Age, genetics [126, 127]. Central and peripheral tolerance are two main categories of Immune tolerance, with numerous layers of active regulation. Immature T-cells in central tolerance with very low affinity for human leukocyte antigen A (HLA) and very high reactivity to self-proteins in the thymus are removed [128]. Immune cells in peripheral tolerance may ignore and not respond to the particular antigen. The existence of molecules like PD-L1, PD-1, and CTLA-4 on self-tissue or immune cells can regulate the immune response and reduce the activation of immune cells. Other mechanisms that lead to immune tolerance include regulatory T cells (Tregs), tolerogenic dendritic cells (tolDC), and suppressing the effector immune cells [126, 129]. Tissue is damaged following the presence of autoantibodies and autoreactive B cells and T cells implicated in the pathological inflammatory response [127]. Autoimmune conditions like T1DM are developed by activating inflammatory mediators [130]. Resolvins can favorably impact this process via the stimulation of several signaling pathways. As well as resolvins can prevent the uptake of leukocytes to the inflammation site by triggering non-inflammatory monocyte employment and inducing macrophages to elevate the

efferocytosis capacity towards apoptotic neutrophils [131, 132]. Following the prevention of leukocyte recruitment, inflammation resolution, pain relief, and regeneration and repair of damaged tissue can occur [133–135]. The risk of autoimmune diseases increases with defects in the inflammation resolution and inflammatory signals [67, 136].

Pancreatic β cells have specialized functions in the secretion and release of insulin in response to glucose. The inner environment of insulin granules causes an acidic environment that is maintained by ATPases and allows insulin to crystallize around zinc molecules [137]. Insulin crystals in lysosomes break down slowly. Following the engulfment, pathogenic crystals (calcium pyrophosphate dihydrate, monosodium urate, cysteine, and cholesterol crystals) penetrate the lysosomal membrane and induce NLRP3 inflammasome [138, 139]. Insulin crystals from β-cell efferocytosis activate the inflammasome and liberate IL-1β from the macrophages. Based on this content, preservation of macrophage lysosomal performance has been highlighted as a therapeutic intervention for the progression of diabetes [140].

Rol of microRNAs in controlling efferocytosis in diabetes

The microRNAs (miRNAs), or short non-coding RNA, can regulate the gene expression and exhibit the function in the development of various types of diabetes mellitus. It is reported that miRNAs regulate several critical genes in beta-cells and insulin. Furthermore, their level changes were introduced as a novel biomarker for diagnosing long-term diabetes complications [82, 83]. Recently, miRNAs possess pivotal performances in developing immune conditions by regulating macrophage performances. The miRNAs are complexly implicated in fine-tuning basic macrophage activities like efferocytosis, phagocytosis, inflammation, tumor progression, and tissue repair [84–86, 141, 142].

miR-21 is one of the miRNAs mentioned to impact efferocytosis effectively. Elevation in the level of miR-21 can convert macrophages to fibroblast-like cells. In the crosstalk of keratinocytes with myeloid cells, the extracellular vesicle (EV)-packaged miR-21 is substantial for cell conversion (Fig. 5). Fluid-derived EV in patients with the healing

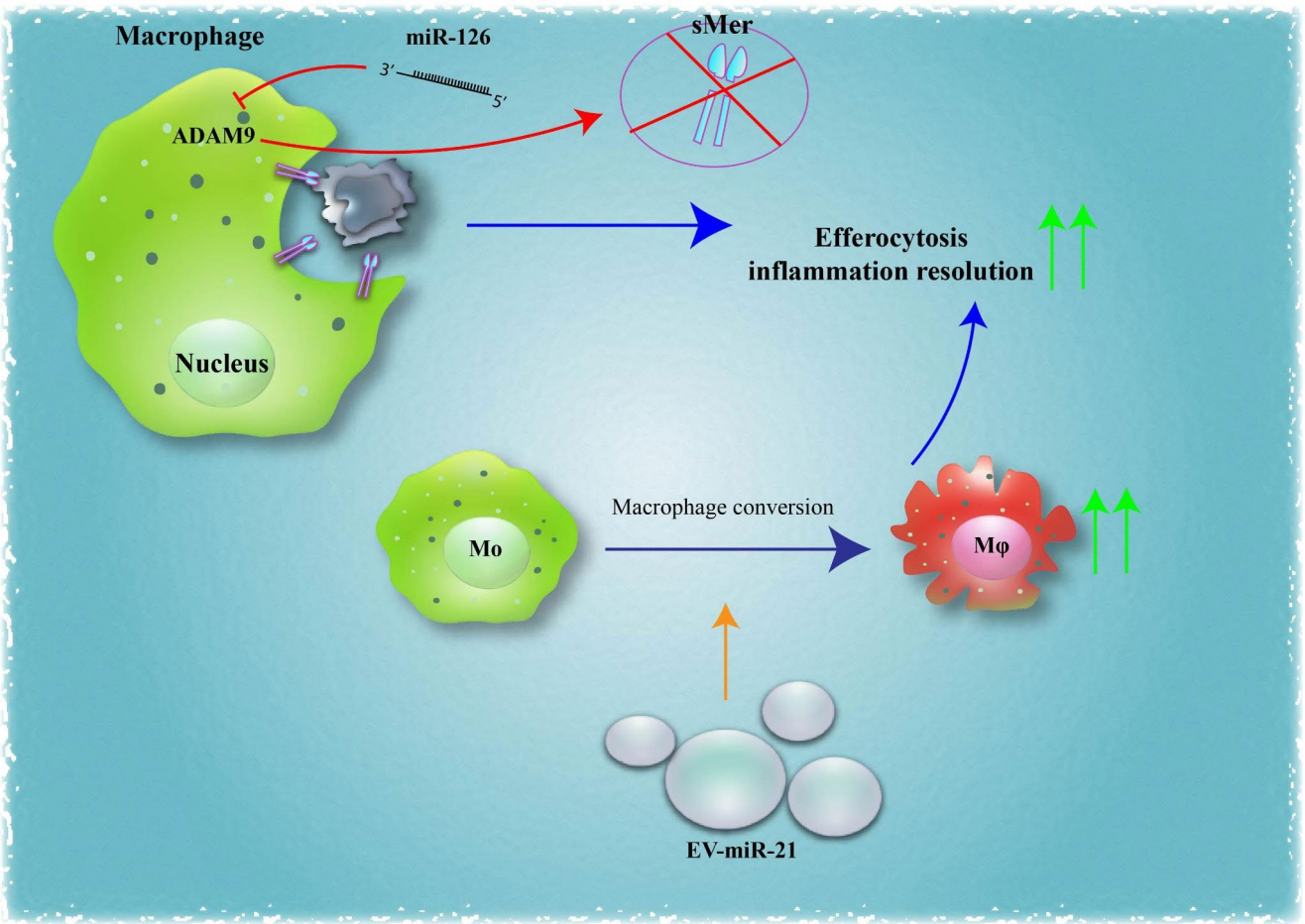

Fig. 5 miRNAs have a role in the efferocytosis process in diabetes. miR-21 with promoting macrophage conversion help to efferocytosis in diabetes mellitus. miR-126 is a direct inhibitor of ADAM9. ADAM9 with cleavage merTK to sMer and subsequently contributes to hindering efferocytosis

chronic wound is rich in miR-21 and results in more efficient cell conversion than in the fluid of non-healing subjects. It is reported that failed conversion in diabetic wound tissue is improved by nanoparticles-mediate delivery of targeted miR-21 to macrophages [89].

Another miRNA that has a significant role in diabetes is miR-126. miR-126 is considered a DM biomarker, and its loss carries a risk of abnormal angiogenesis, vascular leakage, and peripheral artery disease [90–93]. miR-126-5p can impede the progression of cervical cancer the human through the regulation of the cancer cell apoptosis directly by targeting Bcl-2 [94]. The secretion of miR-126 is declined in human diabetic failing heart tissues when compared with non-diabetic normal heart tissues, which led us to investigate the miR-126 performance in diabetic efferocytosis so that miR-126 overexpression in macrophages applying mimics decreased expression of ADAM9 [95]. Moreover, the luciferase assay's target validation highlighted the ADAM9 as a direct target of miR-126 in macrophages [95]. Otherwise, when ADAM9 is inhibited, MerTK protein remains uncut, and subsequently, efferocytosis increases (Fig. 5). The secretion of ADAM9 is elevated in exposure to a great glucose level, which is reversed via miR126 mimic transfection in macrophages under HG conditions. The HG treatment in macrophages can elevate the level of a soluble MerTK (sMer).

The MerTK protein can be interestingly cleaved by the ADAMs in exposure to a great glucose level; thus, it will be inactivated [95]. The ADAM family of metalloproteases are cellular mediators, with the first known role in gamete fusion, which suggests their adhesion properties in intercellular interactions and involvement in tumor biology. The ADAM proteins are vital factors in regulating neoplastic procedures because of their impact on cell migration, adhesion, cell signaling, and proteolysis [93]. The ADAM17 breaks transmembrane MerTK, and generates the sMer [39]. The soluble MerTK inactivates the protein and prevents macrophage removal of apoptotic cells, thrombosis, and platelet aggregation in mice [39, 96]. Based on documents, the MerTK causes pyrenocyte engulfment via fundamental macrophages in erythroblastic islands and enhances the acute lymphoblastic leukemia survival in central nervous system, as the signals of 'eat me or 'eat me not' [97, 98]. Macrophages are the main source of MerTK secretion and thus progress efferocytosis and impede inflammation [99, 100].

Conclusions

An integral part of cell circulation in various organs is apoptosis. If the dead cells are not cleaned enough, and their contents are not released, the tissue is damaged, and prolonged inflammation occurs. It is clear that defective phagocytosis of dead cells in the pancreas leads to the onset and progression of chronic diabetic inflammation. In recent years, information on the pathways implicated in efferocytosis and potent pharmacological targets has been significantly enhanced, increasing the clearance efficiency of apoptosis. Because reduced phagocytosis is associated with an increase in inflammation, targeting efferocytosis to increase dead cell clearance may contribute to diabetic wound healing.

Declarations

Conflict of interest There was no conflict of interest in the current study.

References

1. Rajkumar V, Levine SN (2022) *Latent Autoimmune Diabetes*, in *StatPearls*. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.: Treasure Island (FL)
2. Bardsley JK, Want LL (2004) Overview of diabetes. Crit Care Nurs Q 27(2):106–112
3. De Freitas GR et al (2021) Dry eyes in patients with diabetes mellitus. Prim Care Diabetes 15(1):184–186
4. von Scholten BJ et al (2021) Current and future therapies for type 1 diabetes. Diabetologia 64(5):1037–1048
5. Atkinson MA, Eisenbarth GS (2001) Type 1 diabetes: new perspectives on disease pathogenesis and treatment. The Lancet 358(9277):221–229
6. Zhou B et al (2016) Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4· 4 million participants. The Lancet 387(10027):1513–1530
7. Chatterjee S, Khunti K, Davies MJ (2017) Type 2 diabetes. The Lancet 389(10085):2239–2251
8. Marx N et al (2021) Guideline recommendations and the positioning of newer drugs in type 2 diabetes care. Lancet Diabetes Endocrinol 9(1):46–52
9. Coustan DR (2013) Gestational diabetes mellitus. Clin Chem 59(9):1310–1321
10. McIntyre HD et al (2019) Gestational diabetes mellitus. Nat reviews Disease primers 5(1):1–19
11. Kerr JF (2002) History of the events leading to the formulation of the apoptosis concept. Toxicology 181:471–474
12. King K, Cidlowski J (1998) Cell cycle regulation and apoptosis. Annu Rev Physiol 60(1):601–617
13. Cotter T, deCathelineau AM, Henson PM (2003) The final step in programmed cell death: phagocytes carry apoptotic cells to the grave. Essays Biochem 39:105–117
14. Peter C et al (2010) Dangerous attraction: phagocyte recruitment and danger signals of apoptotic and necrotic cells. Apoptosis 15(9):1007–1028
15. Arandjelovic S, Ravichandran KS (2015) Phagocytosis of apoptotic cells in homeostasis. Nat Immunol 16(9):907–917
16. Poon IK et al (2014) Apoptotic cell clearance: basic biology and therapeutic potential. Nat Rev Immunol 14(3):166–180
17. D'Arcy MS (2019) Cell death: a review of the major forms of apoptosis, necrosis and autophagy. Cell Biol Int 43(6):582–592

18. Lauber K et al (2003) Apoptotic cells induce migration of phagocytes via caspase-3-mediated release of a lipid attraction signal. Cell 113(6):717–730
19. Elliott MR et al (2009) Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. Nature 461(7261):282–286
20. Truman LA et al (2008) CX3CL1/fractalkine is released from apoptotic lymphocytes to stimulate macrophage chemotaxis. Blood The Journal of the American Society of Hematology 112(13):5026–5036
21. Abdolmaleki F et al (2018) The role of efferocytosis in autoimmune diseases. Front Immunol 9:1645
22. Elliott MR, Koster KM, Murphy PS (2017) Efferocytosis signaling in the regulation of macrophage inflammatory responses. J Immunol 198(4):1387–1394
23. Segawa K, Nagata S (2015) An apoptotic 'eat me'signal: phosphatidylserine exposure. Trends Cell Biol 25(11):639–650
24. Kim SJ et al (2002) I-PLA2 activation during apoptosis promotes the exposure of membrane lysophosphatidylcholine leading to binding by natural immunoglobulin M antibodies and complement activation. J Exp Med 196(5):655–665
25. Gardai SJ et al (2005) Cell-surface calreticulin initiates clearance of viable or apoptotic cells through trans-activation of LRP on the phagocyte. Cell 123(2):321–334
26. Hochreiter-Hufford A, Ravichandran KS (2013) Clearing the dead: apoptotic cell sensing, recognition, engulfment, and digestion. Cold Spring Harb Perspect Biol 5(1):a008748
27. Wu Y, Tibrewal N, Birge RB (2006) Phosphatidylserine recognition by phagocytes: a view to a kill. Trends Cell Biol 16(4):189–197
28. Richards DM, Endres RG (2014) The mechanism of phagocytosis: two stages of engulfment. Biophys J 107(7):1542–1553
29. Rosales C, Uribe-Querol E (2017) *Phagocytosis: a fundamental process in immunity.* BioMed research international, **2017**
30. Ma Z et al (2002) Regulation of Rac1 activation by the low density lipoprotein receptor–related protein. J Cell Biol 159(6):1061–1070
31. Wang L et al (2020) Potential Mechanisms and Effects of Efferocytosis in Atherosclerosis. Front Endocrinol (Lausanne) 11:585285
32. Rink J et al (2005) Rab conversion as a mechanism of progression from early to late endosomes. Cell 122(5):735–749
33. Boada-Romero E et al (2020) The clearance of dead cells by efferocytosis. Nat Rev Mol Cell Biol 21(7):398–414
34. Werfel TA, Cook RS (2018) Efferocytosis in the tumor microenvironment. Semin Immunopathol 40(6):545–554
35. Mathis D, Vence L, Benoist C (2001) *β-Cell death during progression to diabetes.* Nature, **414**(6865): p. 792–798
36. Vives-Pi M, Rodríguez-Fernández S, Pujol-Autonell I (2015) How apoptotic β-cells direct immune response to tolerance or to autoimmune diabetes: a review. Apoptosis 20(3):263–272
37. Morioka S, Maueröder C, Ravichandran KS (2019) Living on the Edge: Efferocytosis at the Interface of Homeostasis and Pathology. Immunity 50(5):1149–1162
38. Doran AC, Yurdagul A Jr, Tabas I (2020) Efferocytosis in health and disease 20(4):254–267
39. Thorp E et al (2011) Shedding of the Mer tyrosine kinase receptor is mediated by ADAM17 protein through a pathway involving reactive oxygen species, protein kinase Cδ, and p38 mitogen-activated protein kinase (MAPK). J Biol Chem 286(38):33335–33344
40. O'Brien BA et al (2002) Clearance of apoptotic β-cells is reduced in neonatal autoimmune diabetes-prone rats. Cell Death & Differentiation 9(4):457–464
41. Marée AF et al (2005) Quantifying macrophage defects in type 1 diabetes. J Theor Biol 233(4):533–551
42. Goren I et al (2007) Systemic anti-TNFα treatment restores diabetes-impaired skin repair in ob/ob mice by inactivation of macrophages. J Invest Dermatology 127(9):2259–2267
43. Tabas I (2005) *Consequences and therapeutic implications of macrophage apoptosis in atherosclerosis: the importance of lesion stage and phagocytic efficiency.* Arteriosclerosis, thrombosis, and vascular biology. 25:2255–226411
44. Thorp E, Tabas I (2009) Mechanisms and consequences of efferocytosis in advanced atherosclerosis. J Leukoc Biol 86(5):1089–1095
45. Naghavi M et al (2003) From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 108(14):1664–1672
46. Fredman G et al (2015) Targeted nanoparticles containing the proresolving peptide Ac2-26 protect against advanced atherosclerosis in hypercholesterolemic mice. Sci Transl Med 7(275):275ra20
47. Martinez RM et al (2018) *Lipoxin A4 inhibits UV radiation-induced skin inflammation and oxidative stress in mice*.J Dermatol Sci,
48. Viola JR et al (2016) Resolving Lipid Mediators Maresin 1 and Resolvin D2 Prevent Atheroprogression in Mice. Circ Res 119(9):1030–1038
49. An Y et al (2019) *Activation of ROS/MAPKs/NF-κB/NLRP3 and inhibition of efferocytosis in osteoclast-mediated diabetic osteoporosis.* FASEB journal: official publication of the Federation of American Societies for Experimental Biology. 33:12515–1252711
50. Das A et al (2016) Correction of MFG-E8 resolves inflammation and promotes cutaneous wound healing in diabetes. J Immunol 196(12):5089–5100
51. Saevarsdottir S, Vikingsdottir T, Valdimarsson H (2004) The potential role of mannan-binding lectin in the clearance of self-components including immune complexes. Scand J Immunol 60(1–2):23–29
52. Nauta AJ et al (2003) Mannose-binding lectin engagement with late apoptotic and necrotic cells. Eur J Immunol 33(10):2853–2863
53. Saevarsdottir S et al (2005) Mannan binding lectin as an adjunct to risk assessment for myocardial infarction in individuals with enhanced risk. J Exp Med 201(1):117–125
54. Yamauchi T et al (2003) Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 423(6941):762–769
55. Takemura Y et al (2007) Adiponectin modulates inflammatory reactions via calreticulin receptor-dependent clearance of early apoptotic bodies. J Clin Invest 117(2):375–386
56. Cash JG et al (2012) Apolipoprotein E4 impairs macrophage efferocytosis and potentiates apoptosis by accelerating endoplasmic reticulum stress. J Biol Chem 287(33):27876–27884
57. An Y et al (2019) Activation of ROS/MAPKs/NF-κB/NLRP3 and inhibition of efferocytosis in osteoclast-mediated diabetic osteoporosis. Faseb j 33(11):12515–12527
58. Kwon CH et al (2020) Clinically confirmed DEL-1 as a myokine attenuates lipid-induced inflammation and insulin resistance in 3T3-L1 adipocytes via AMPK/HO-1- pathway. Adipocyte 9(1):576–586
59. Wu Y, Tibrewal N, Birge RB (2006) Phosphatidylserine recognition by phagocytes: a view to a kill. Trends Cell Biol 16(4):189–197
60. Ge Y, Huang M, Yao YM (2022) Efferocytosis and Its Role in Inflammatory Disorders. Front Cell Dev Biol 10:839248
61. Bitzan M et al (2008) Rituximab treatment of collapsing C1q glomerulopathy: Clinical and histopathological evolution. Pediatr Nephrol 23(8):1355–1361
62. Chao MP et al (2010) Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. Cell 142(5):699–713

63. Albert ML et al (1998) Immature dendritic cells phagocytose apoptotic cells via αvβ5 and CD36, and cross-present antigens to cytotoxic T lymphocytes. J Exp Med 188(7):1359–1368
64. Greenberg ME et al (2006) Oxidized phosphatidylserine–CD36 interactions play an essential role in macrophage-dependent phagocytosis of apoptotic cells. J Exp Med 203(12):2613–2625
65. Hijazi H, Waggiallah H, Alagib A (2013) Oxidative low density lipoprotien prohibited plasmodium falciparum clearance in type 2 diabetes mellitus via cluster differentiation 36. North Am J Med Sci 5(12):703–706
66. Sóñora C et al (2014) Anti-tissue transglutaminase antibody inhibits apoptotic cell clearance by macrophages in pregnant NOD mice. J Reprod Immunol 103(1):59–66
67. Eizirik DL, Colli ML, Ortis F (2009) The role of inflammation in insulitis and β-cell loss in type 1 diabetes. Nat Reviews Endocrinol 5(4):219–226
68. Villalba A et al (2020) Preclinical evaluation of antigen-specific nanotherapy based on phosphatidylserine-liposomes for type 1 diabetes. Artif Cells Nanomed Biotechnol 48(1):77–83
69. Pujol-Autonell I et al (2015) *Use of autoantigen-loaded phosphatidylserine-liposomes to arrest autoimmunity in type 1 diabetes*. PLoS ONE, **10**(6)
70. Rodriguez-Fernandez S et al (2018) *Phosphatidylserine-liposomes promote tolerogenic features on dendritic cells in human type 1 diabetes by apoptotic mimicry.* Frontiers in Immunology, **9**(FEB)
71. Lugovaya A et al (2019) Spontaneous and activation-induced apoptosis of peripheral blood mononuclear cells in the pathogenesis of type 1 diabetes mellitus. Med Immunol (Russia) 22(1):123–134
72. Lugovaya AV et al (2020) Spontaneous and activation-induced apoptosis of peripheral blood mononuclear cells in the pathogenesis of type 1 diabetes mellitus. Med Immunol (Russia) 22(1):123–134
73. Kakarla R et al (2020) Apoptotic cell-derived exosomes: messages from dying cells. Exp Mol Med 52(1):1–6
74. Zheng C et al (2021) Apoptotic vesicles restore liver macrophage homeostasis to counteract type 2 diabetes. J Extracell Vesicles 10(7):e12109
75. Hie M, Yamazaki M, Tsukamoto I (2009) Curcumin suppresses increased bone resorption by inhibiting osteoclastogenesis in rats with streptozotocin-induced diabetes. Eur J Pharmacol 621(1–3):1–9
76. Saito M, Marumo K (2010) Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. Osteoporos Int 21(2):195–214
77. Davies LC et al (2013) Tissue-resident macrophages. Nat Immunol 14(10):986–995
78. Soehnlein O, Lindbom L (2010) Phagocyte partnership during the onset and resolution of inflammation. Nat Rev Immunol 10(6):427–439
79. Bain S et al (1997) Tetracycline prevents cancellous bone loss and maintains near-normal rates of bone formation in streptozotocin diabetic rats. Bone 21(2):147–153
80. An Y et al (2019) Activation of ROS/MAPKs/NF-κB/NLRP3 and inhibition of efferocytosis in osteoclast-mediated diabetic osteoporosis. FASEB J 33(11):12515–12527
81. Green D, Oguin T, Martinez J (2016) The clearance of dying cells: table for two. Cell Death & Differentiation 23(6):915–926
82. Kantharidis P et al (2011) Diabetes complications: the microRNA perspective. Diabetes 60(7):1832–1837
83. Regazzi R (2018) MicroRNAs as therapeutic targets for the treatment of diabetes mellitus and its complications. Expert Opin Ther Targets 22(2):153–160
84. Roy S (2016) miRNA in Macrophage Development and Function. Antioxid Redox Signal 25(15):795–804
85. Singh RP et al (2013) The role of miRNA in inflammation and autoimmunity. Autoimmun Rev 12(12):1160–1165
86. Sen CK, Ghatak S (2015) miRNA control of tissue repair and regeneration. Am J Pathol 185(10):2629–2640
87. Kim SY, Nair MG (2019) Macrophages in wound healing: activation and plasticity. Immunol Cell Biol 97(3):258–267
88. Das A et al (2016) Correction of MFG-E8 Resolves Inflammation and Promotes Cutaneous Wound Healing. Diabetes 196(12):5089–5100
89. Sinha M et al (2018) *Direct conversion of injury-site myeloid cells to fibroblast-like cells of granulation tissue*.Nature Communications, **9**(1)
90. Dastah S et al (2020) *Aerobic exercise leads to upregulation of Mir-126 and angiogenic signaling in the heart tissue of diabetic rats*.Gene Reports, **21**
91. Banerjee J et al (2020) Senescence-associated miR-34a and miR-126 in middle-aged Indians with type 2 diabetes. Clin Experimental Med 20(1):149–158
92. Liu Y et al (2014) The role of circulating microRNA-126 (miR-126): a novel biomarker for screening prediabetes and newly diagnosed type 2 diabetes mellitus. Int J Mol Sci 15(6):10567–10577
93. Zampetaki A et al (2010) Plasma microRNA profiling reveals loss of endothelial miR-126 and other microRNAs in type 2 diabetes. Circ Res 107(6):810–817
94. Wang C et al (2017) miR-126-5p Restoration Promotes Cell Apoptosis in Cervical Cancer by Targeting Bcl2l2. Oncol Res 25(4):463–470
95. Suresh Babu S et al (2016) *MicroRNA-126 overexpression rescues diabetes-induced impairment in efferocytosis of apoptotic cardiomyocytes*.Scientific Reports, **6**
96. Sather S et al (2007) A soluble form of the Mer receptor tyrosine kinase inhibits macrophage clearance of apoptotic cells and platelet aggregation. Blood 109(3):1026–1033
97. Krause S et al (2015) Mer tyrosine kinase promotes the survival of t(1;19)-positive acute lymphoblastic leukemia (ALL) in the central nervous system (CNS). Blood 125(5):820–830
98. Toda S, Segawa K, Nagata S (2014) MerTK-mediated engulfment of pyrenocytes by central macrophages in erythroblastic islands. Blood 123(25):3963–3971
99. Cai B et al (2020) Macrophage MerTK Promotes Liver Fibrosis in Nonalcoholic Steatohepatitis. Cell Metabol 31(2):406–421e7
100. Choi JY et al (2013) Upregulation of Mer receptor tyrosine kinase signaling attenuated lipopolysaccharide-induced lung inflammation. J Pharmacol Exp Ther 344(2):447–458
101. Uchiyama A et al (2017) Mesenchymal stem cells-derived MFG-E8 accelerates diabetic cutaneous wound healing. J Dermatol Sci 86(3):187–197
102. Khanna S et al (2010) Macrophage dysfunction impairs resolution of inflammation in the wounds of diabetic mice. PLoS ONE 5(3):e9539
103. Barman PK, Koh TJ (2020) Macrophage Dysregulation and Impaired Skin Wound Healing in Diabetes. Front cell Dev biology 8:528–528
104. Li K et al (2021) *MRP8/14 mediates macrophage efferocytosis through RAGE and Gas6/MFG-E8, and induces polarization via TLR4-dependent pathway*. 236:1375–13902
105. Brownlee M (2001) Biochemistry and molecular cell biology of diabetic complications. Nature 414(6865):813–820
106. Kim SY et al (2022) Efferocytosis and enhanced FPR2 expression following apoptotic cell instillation attenuate radiation-induced lung inflammation and fibrosis. Biochem Biophys Res Commun 601:38–44

107. Krzyszczyk P et al (2018) The role of macrophages in acute and chronic wound healing and interventions to promote pro-wound healing phenotypes. Front Physiol 9:419
108. Yan J et al (2018) Diabetes impairs wound healing by Dnmt1-dependent dysregulation of hematopoietic stem cells differentiation towards macrophages. Nat Commun 9(1):1–13
109. Mirza RE et al (2013) Blocking interleukin-1β induces a healing-associated wound macrophage phenotype and improves healing in type 2 diabetes. Diabetes 62(7):2579–2587
110. Wang Q et al (2017) *Blocking AGE-RAGE signaling improved functional disorders of macrophages in diabetic wound.* Journal of diabetes research, **2017**
111. Gallagher KA et al (2015) Epigenetic changes in bone marrow progenitor cells influence the inflammatory phenotype and alter wound healing in type 2 diabetes. Diabetes 64(4):1420–1430
112. Yang F et al (2010) Essential role for Smad3 in angiotensin II-induced tubular epithelial–mesenchymal transition. J Pathol 221(4):390–401
113. Barman PK, Koh TJ (2020) Macrophage dysregulation and impaired skin wound healing in diabetes. Front Cell Dev Biology 8:528
114. Chen H et al (2015) Macrophage peroxisome proliferator-activated receptor γ deficiency delays skin wound healing through impairing apoptotic cell clearance in mice. Cell Death Dis 6(1):e1597
115. Mirza RE et al (2015) Macrophage PPARγ and impaired wound healing in type 2 diabetes. J Pathol 236(4):433–444
116. Wang Q et al (2017) *Blocking AGE-RAGE Signaling Improved Functional Disorders of Macrophages in Diabetic Wound*. 2017:1428537
117. Chatzigeorgiou A et al (2010) The pattern of inflammatory/anti-inflammatory cytokines and chemokines in type 1 diabetic patients over time. Ann Med 42(6):426–438
118. Uchiyama A et al (2015) Protective effect of MFG-E8 after cutaneous ischemia–reperfusion injury. J Invest dermatology 135(4):1157–1165
119. Jun JI, Kim KH, Lau LF (2015) *The matricellular protein CCN1 mediates neutrophil efferocytosis in cutaneous wound healing*. Nature Communications, **6**
120. Lima MH et al (2012) Topical insulin accelerates wound healing in diabetes by enhancing the AKT and ERK pathways: a double-blind placebo-controlled clinical trial. PLoS ONE 7(5):e36974
121. Huang JJ et al (2020) Annexin A1-derived peptide Ac2-26 facilitates wound healing in diabetic mice. Wound Repair and Regeneration 28(6):772–779
122. Huang JJ et al (2020) Annexin A1-derived peptide Ac2-26 facilitates wound healing in diabetic mice. Wound Repair and Regeneration 28(6):772–779
123. Chen X, Liu Y, Zhang X (2012) Topical insulin application improves healing by regulating the wound inflammatory response. Wound Repair and Regeneration 20(3):425–434
124. Yang P et al (2021) *Topical insulin application accelerates diabetic wound healing by promoting anti-inflammatory macrophage polarization*.Journal of Cell Science, **133**(19)
125. Gullo D et al (2021) Insulin autoimmune syndrome misdiagnosed as an insulinoma in a woman presenting with a pancreatic cystic lesion and taking alpha lipoic acid: a lesson to be learned. Hormones 20(3):593–595
126. Erdem N, Montero E, Roep BO (2021) Breaking and restoring immune tolerance to pancreatic beta-cells in type 1 diabetes. Curr Opin Endocrinol Diabetes Obes 28(4):397–403
127. Wang L, Wang FS, Gershwin ME (2015) Human autoimmune diseases: a comprehensive update. J Intern Med 278(4):369–395
128. Klein L, Robey EA, Hsieh C-S (2019) Central CD4 + T cell tolerance: deletion versus regulatory T cell differentiation. Nat Rev Immunol 19(1):7–18
129. Malhotra D et al (2016) Tolerance is established in polyclonal CD4 + T cells by distinct mechanisms, according to self-peptide expression patterns. Nat Immunol 17(2):187–195
130. Baccala R et al (2007) TLR-dependent and TLR-independent pathways of type I interferon induction in systemic autoimmunity. Nat Med 13(5):543–551
131. Mitchell S et al (2002) Lipoxins, aspirin-triggered epi-lipoxins, lipoxin stable analogues, and the resolution of inflammation: stimulation of macrophage phagocytosis of apoptotic neutrophils in vivo. J Am Soc Nephrol 13(10):2497–2507
132. Libreros S et al (2020) A New E-Series Resolvin: RvE4 Stereochemistry and Function in Efferocytosis of Inflammation-Resolution. Front Immunol 11:631319
133. Milligan G, Stoddart LA, Brown AJ (2006) G protein-coupled receptors for free fatty acids. Cell Signal 18(9):1360–1365
134. Peterson EA, Sun J (2022) *Leukocyte-Mediated Cardiac Repair after Myocardial Infarction in Non-Regenerative vs*.Regenerative Systems.**9**(2)
135. Vandendriessche S et al (2021) Complement Receptors and Their Role in Leukocyte Recruitment and Phagocytosis. Front Cell Dev Biol 9:624025
136. Abdolmaleki F et al (2020) Resolvins: emerging players in autoimmune and inflammatory diseases. Clin Rev Allergy Immunol 58(1):82–91
137. Halban PA (1991) Structural domains and molecular lifestyles of insulin and its precursors in the pancreatic beta cell. Diabetologia 34(11):767–778
138. Martinon F et al (2006) Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 440(7081):237–241
139. Prencipe G et al (2014) Inflammasome activation by cystine crystals: implications for the pathogenesis of cystinosis. J Am Soc Nephrol 25(6):1163–1169
140. Engelen-Lee JY et al (2018) Histopathology of Listeria meningitis. J Neuropathol Exp Neurol 77(10):950–957
141. Suresh Babu S et al (2016) MicroRNA-126 overexpression rescues diabetes-induced impairment in efferocytosis of apoptotic cardiomyocytes. Sci Rep 6(1):36207
142. Mahmoudi A et al (2022) MicroRNAs and Efferocytosis: Implications for Diagnosis and Therapy. Mini Rev Med Chem