



Diabetes Mellitus to Accelerated Atherosclerosis: Shared Cellular and Molecular Mechanisms in Glucose and Lipid Metabolism

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Abstract

Diabetes is one of the critical independent risk factors for the progression of cardiovascular disease, and the underlying mechanism regarding this association remains poorly understood. Hence, it is urgent to decipher the fundamental pathophysiology and consequently provide new insights into the identification of innovative therapeutic targets for diabetic atherosclerosis. It is now appreciated that different cell types are heavily involved in the progress of diabetic atherosclerosis, including endothelial cells, macrophages, vascular smooth muscle cells, dependence on altered metabolic pathways, intracellular lipids, and high glucose. Additionally, extensive studies have elucidated that diabetes accelerates the odds of atherosclerosis with the explanation that these two chronic disorders share some common mechanisms, such as endothelial dysfunction and inflammation. In this review, we initially summarize the current research and proposed mechanisms and then highlight the role of these three cell types in diabetes-accelerated atherosclerosis and finally establish the mechanism pinpointing the relationship between diabetes and atherosclerosis.

Keywords Diabetes · Atherosclerosis · Endothelial cells · Macrophages · Vascular smooth muscle cells

Abbreviations

ABCA1	ATP binding cassette subfamily A member 1
ABCG1	ATP binding cassette subfamily G member 1
ADA	American Diabetes Association
AGEs	Advanced glycation end products

AMPK	AMP-activated protein kinase
ASCVD	Atherosclerotic cardiovascular disease
ATP	Adenosine triphosphate
α-SMA/ACTA2	Alpha-smooth muscle actin
BAX	Bcl-2-associated X protein
Bhlhe40	Basic helix-loop-helix family member e40
circRNAs	Circular RNAs
COX	Cyclooxygenase
CTRP9	C1q/tumor necrosis factor-related protein 9
CVD	Cardiovascular disease
DCs	Dendritic cells
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
Drp1	Dynammin-related protein 1
ECM	Extracellular matrix
EGR-1	Early growth response protein 1
EndMT	Endothelial-to-mesenchymal transition
eNOS	Endothelial NO synthase
EPCs	Endothelial progenitor cells
ER	Endoplasmic reticulum
ERK1/2	Extracellular signal-regulated kinase 1/2
ETC	Electron transport chain

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ET-1	Endothelin-1	RUNX2	Runt-related transcription factor 2
FGF21	Fibroblast growth factor 21	SGLT2i	Sodium-glucose cotransporter 2 inhibitors
FFA	Free fatty acids	SM22 α /TAGLN	Smooth muscle 22 α
FPG	Fasting plasma glucose	SNO-GNAI2	S-nitrosylation of G-protein α -2
GLP-1	Glucagon-like peptide-1	SOD	Superoxide dismutase
GLP-1R	Glucagon-like peptide 1 receptor	STZ	Streptozotocin
GLUT1	Glucose transporter 1	TERT	Telomerase reverse transcriptase
GPRC5B	G-protein coupled receptor 5B of family C	TNF- α	Tumor necrosis factor- α
GSDMD	Gasdermin D	TRAF6	Tumor necrosis factor-associated factor 6
GSK3 β	Glycogen synthase kinase 3 β	T2DM	Type 2 diabetes mellitus
HAECs	Human aortic endothelial cells	UPR	Unfolded protein response
HbA1c	Glycated hemoglobin	VCAM-1	Vascular cell adhesion molecule-1
HCAECs	Human coronary artery endothelial cells	VSMCs	Vascular smooth muscle cells
HDAC6	Histone deacetylase 6		
HIF-1 α	Hypoxia inducible factor 1 α		
HG	High glucose		
HUVECs	Human umbilical vein endothelial cells		
H ₂ O ₂	Hydrogen peroxide		
H ₂ S	Hydrogen sulfide		
ICAM-1	Intercellular adhesion molecule-1		
IFN- γ	Interferon- γ		
IL	Interleukin		
KLF4	Krüppel-like factor 4		
LDL	Low-density lipoprotein		
LGALS3	Galectin-3		
lncRNAs	Long non-coding RNAs		
LPS	Lipopolysaccharide		
MCP-1	Monocyte chemotactic protein-1		
MMP	Matrix metalloproteinase		
mtDNA	Mitochondrial DNA		
mtDNA-CN	Mitochondrial DNA copy number		
MYH11	Myosin heavy chain 11		
NADPH	Nicotinamide-adenine dinucleotide phosphate		
NICD	Notch intracellular domain		
NOX	NADPH oxidases		
NLRP3	NLR family pyrin domain containing 3		
ox-LDL	Oxidized low-density lipoprotein		
OXPHOS	Oxidative phosphorylation		
PA	Palmitic acid		
PKC	Protein kinase C		
PKC β II	Protein kinase C β II		
PPAR δ	Peroxisome proliferator-activated receptor δ		
PPB	Pyrogallol-phloroglucinol-6,6-bieckol		
P38 MAPK	P38 mitogen-activated protein kinase		
RAGE	Receptor for advanced glycation end products		
RCN2	Reticulocalbin 2		
ROCK1	Rho-associated kinase 1		
ROS	Reactive oxygen species		

Introduction

The last several decades have observed an unanticipated global increase in the prevalence of diabetes mellitus (DM). Diabetes, a chronic endocrine disease stemming from insulin insufficiency with the symptom of hyperglycemia, is a dominant independent risk factor for a global epidemic of cardiovascular disease (CVD). Additionally, it remains the principal cause of premature deaths. The American Diabetes Association (ADA) recommends cutoffs for prediabetes and diabetes, the glycemic parameters that diagnose diabetes are glycated hemoglobin (HbA1c) $\geq 6.5\%$, fasting plasma glucose (FPG) ≥ 126 mg/dl, and 2-h postprandial glucose (2-h PG) ≥ 200 mg/dl [1]. According to the latest diabetes atlas demonstrated by the International Diabetes Federation, up to 537 million patients suffered from diabetes worldwide in 2021, which accounts for one-tenth of adults. Diabetics hold a growing risk for vascular diseases, containing the microvascular and macrovascular complications. Macrovascular complications include atherosclerosis that can ultimately manifest as stroke, myocardial infarction, and peripheral artery disease [2]. So, it is important to explore the underlying mechanisms linked between diabetes and atherosclerosis in order to attenuate the diabetic atherosclerosis.

It has been reported that there existed the solid relationship between diabetes mellitus and atherosclerosis in the literatures. In 2007, a study confirmed some genetic links between atherosclerosis and diabetes; for example, the genetic variation at the CALPN10, FABP4, PPARA, and PPARG loci may induce higher cardiovascular disease risk in patients with type 2 diabetes mellitus (T2DM) [3]. Another multi-ethnic genome-wide association study identified several new loci, such as TCF7L2, HNF1A, CTRB1, MRAS, and CCDC92 that are linked with both diabetes and atherothrombotic CVD [4]. These findings suggested that between atherosclerosis and diabetes, genetic variations may

increase individuals' susceptibility of patients with one disease to the other, making them more prone to developing both diabetes and atherosclerosis at the same time. Besides, previous work also established that diabetes mellitus and atherosclerosis shared some common pathological pathways, such as chronic inflammation and endothelial activation caused by disrupted blood flow, subsequent mitochondrial oxidative stress, extracellular matrix component changes, and cellular defense systems disruption [5]. Insulin resistance with hyperinsulinemia, hyperglycemia, and impairment of insulin signaling result in endothelial dysfunction and inflammation, vascular smooth muscle cells (VSMCs) phenotypic switch (proliferation, migration, and dedifferentiation), and monocyte/macrophage-derived foam cell formation due to the advanced glycation end product (AGE) production, elevated free fatty acids (FFA), protein kinase C (PKC) activation, oxidative stress, mitochondrial dysfunction, and epigenetic modifications, which demonstrates that all three cell types collectively facilitate the development of atherosclerosis [6].

In addition to genetic and pathologic mechanisms, the clinical relationship between atherosclerosis and diabetes also has been well established. New oral drugs including the sodium-glucose cotransporter 2 inhibitors (SGLT2i) are utilized for the treatment of T2DM. SGLT2i, such as dapagliflozin, empagliflozin, and canagliflozin, demonstrates pleiotropic effects in protecting from cardiovascular diseases beyond their impact on hyperglycemia by landmark cardiovascular outcome trials recently. Of clinical relevance, it has been recently reported that major adverse cardiovascular events and cardiovascular death in T2DM patients with cardiovascular diseases were reduced by SGLT2i [7]. In addition, dulaglutide, a glucagon-like peptide 1 receptor (GLP-1R) agonist, has been investigated to prevent against atherosclerosis, indicating that these effects on cardiovascular disease are the result of lowering glucose [8]. The commonly used antidiabetic drugs in the clinic include SGLT2i, GLP-1R agonist, dipeptidyl peptidase-4 (DPP-4) inhibitors, and metformin. They are applied for anti-diabetic reduce glucose by decreasing glucose absorption from intestines or reabsorption from renal tubules and stimulating insulin secretions. At the same time, these agents also inhibit vascular inflammation [9, 10] endothelial dysfunction [11], modulate lipid profile (such as LDL-C reduction and HDL-C improvement) [12], and increase plaque stabilization [13], to alleviate atherogenesis.

In this review, we mainly summarize the existing pathological changes found in three key cell types that contribute to atherosclerosis in diabetes mellitus: endothelial cells, VSMCs, and macrophages. We finally aim to mechanistically integrate diabetes mellitus and atherosclerosis and list some attractive possibilities for modifying diabetic atherosclerosis which contains targeting glucotoxicity and

lipotoxicity, inhibiting cellular dysfunction, and promoting pro-resolution mechanisms.

Endothelial Cells in Diabetic Atherosclerosis

The endothelium is a monolayer of endothelial cells residing in the inner surface of arteries, veins, and capillaries. Endothelial cells serve a pivotal role in maintaining vascular homeostasis via regulating vascular tone, permeability, angiogenesis, and the target of anti-inflammatory and antithrombotic factors [14, 15].

Diabetes is a chronic endocrine disease, manifested by abnormally high blood glucose levels [16]. A progressive link between enhanced blood glucose levels and CVD existed, with higher HbA1c related to an increase in subclinical atherosclerosis risk with a particular elevated risk of mortality in elderly individuals [17, 18]. Under hyperglycemia conditions, dysfunction of the endothelium is presented with impairment of endothelium-dependent vasodilation, increased inflammatory adhesion molecules, hyperpermeability, and low-density lipoprotein (LDL) oxidation [19] (Fig. 1). Diabetes mellitus mainly affects endothelial homeostasis through glucotoxicity, although the definite mechanisms of high blood glucose-induced endothelial damage are complex and not fully elucidated. Notably, high blood glucose promotes the production of reactive oxygen species (ROS), which consequently interferes with a series of downstream pathways including AGE formation, PKC activation, and polyol pathway flux [20].

Intracellular high glucose induces the formation of AGEs, activates the PKC pathway, and facilitates mitochondrial dysfunction to produce excessive ROS, and the subsequent oxidative stress induces inflammation, which further promotes the production of ROS. The permeability of endothelial cell increases, which increases glucose uptake, LDL transcytosis, and monocyte/macrophage infiltration. Eventually, endothelial cells become dysfunctional and die.

Advanced Glycation End Products (AGEs)

Glycation reaction is a spontaneous non-enzymatic reaction of free-reducing sugars with amino groups of proteins, lipids, and nucleic acids, ultimately facilitating the formation of AGEs. Previous work has denoted that AGEs can be identified by tracing receptors on the cytomembrane, which contains receptor for advanced glycation end products (RAGE) and scavenger receptors (SR-A and SR-B) that influence the pathogenesis of diabetic complications [21, 22]. High levels of plasma AGEs in diabetic patients damage endothelial cells, and then the detrimental effect lasts after normal blood glucose levels are reached [23]. Of note, under hyperglycemic conditions, aging and erythrocyte glycation contributes

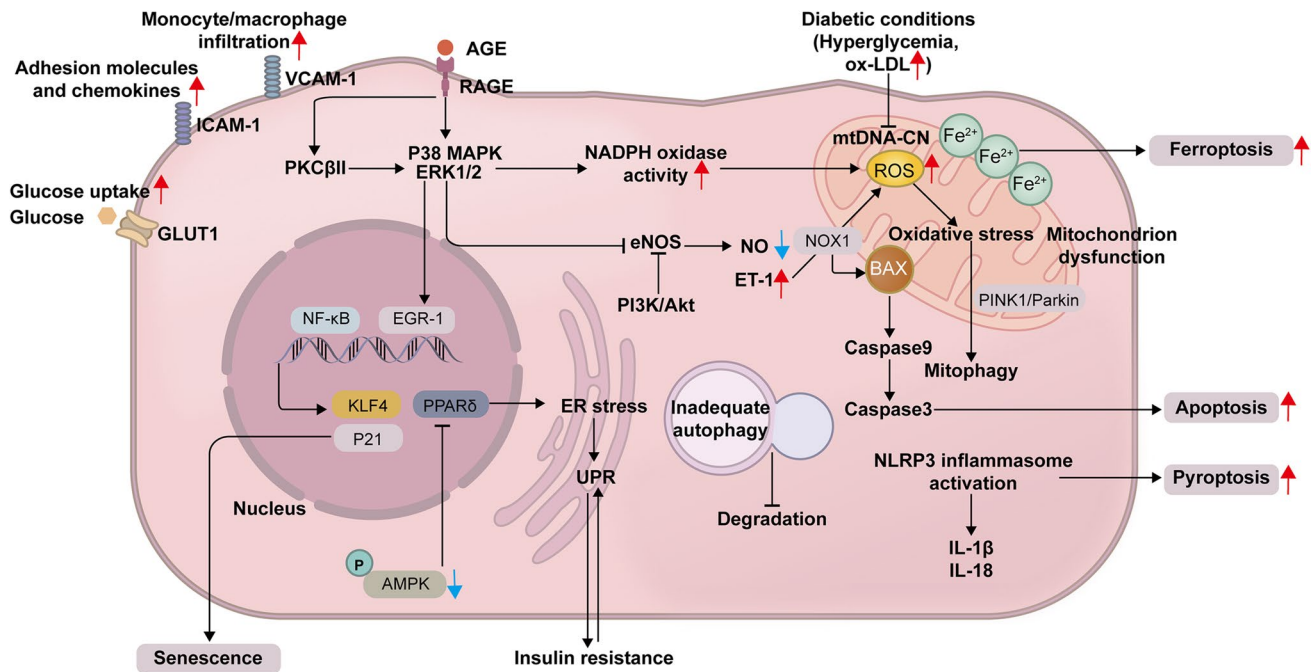


Fig. 1 Endothelial cell in diabetic atherosclerosis. Diabetic atherosclerosis initiates by endothelial cell dysfunction, increases endothelial cell permeability, promotes the expression of pro-inflammatory cytokines and adhesion factors, increases glucose uptake, LDL transcytosis, and monocyte/macrophage infiltration. eNOS uncoupling impairs the ability of endothelial cell-mediated vasorelaxation function and oxidative stress induced by excessive ROS production. Eventually, endothelial cells become dysfunctional and die. AGE, advanced glycation end product; AMPK, AMP-activated protein kinase; BAX, Bcl-2-associated X protein; EGR-1, early growth response protein 1; eNOS, endothelial NO synthase; ER, endoplasmic

reticulum; ERK1/2, extracellular signal-regulated kinase 1/2; ET-1, endothelin-1; GLUT1, glucose transporter 1; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1β; IL-18, interleukin-18; KLF4, Krüppel-like factor 4; mtDNA-CN, mitochondrial DNA copy number; NADPH, nicotinamide-adenine dinucleotide phosphate; NOX1, NADPH oxidase 1; P38 MAPK, p38 mitogen-activated protein kinase; PKCβII, protein kinase C βII; PPARδ, peroxisome proliferator-activated receptor δ; RAGE, receptor for advanced glycation end product; ROS, reactive oxygen species; UPR, unfolded protein response; VCAM-1, vascular cell adhesion molecule-1

to their engulfment by endothelial cells and leads to endothelial dysfunction [24]. An AGP-PPARγ axis was found to mediate the production of NO and ROS, which promoted the generation of AGEs in diabetic endothelial cell [25]. Exposure of human umbilical vein endothelial cells (HUVECs) to AGEs in vitro induced the diminishment of eNOS and NO production [26]. Similar results were observed in human coronary artery endothelial cells (HCAECs), where AGEs caused endothelial dysfunction by decreasing eNOS and increasing oxidative stress after the activation of p38 and ERK1/2 [27]. Mechanistically, hyperglycemia may also induce inflammation through an AGEs/PKCβII/ERK1/2 / EGR-1 pathway in HUVECs isolated from gestational diabetes mellitus patient umbilical cords [28].

Since AGEs matter in vascular complications in diabetes, the risk of subclinical atherosclerosis is assessed by detecting the scale of collected AGEs in the skin, skin autofluorescence was related to flow-mediated vasodilation independently, which acts as a sign of endothelial disorders [29].

Several treatment strategies with the involvement of AGEs and RAGE have been investigated. Specifically,

isosamidin is a preventive agent for methylglyoxal-mediated endothelial dysfunction, owing to the breakdown of the crosslinks of methylglyoxal-derived AGEs [30]. An anti-RAGE leads to the reduced vascular RAGE expression and increased collaterals for the clinical treatment of diabetic peripheral artery disease [31]. microRNA (miR)-21-3p was found to elevate the levels of soluble RAGE and compete with RAGE for binding AGE, which results in decreases in the production of ROS and inflammatory cytokines in HUVECs induced by high glucose concentrations [32]. As RAGE is a vital mediator of endothelial dysfunction, targeting of RAGE and intervention with the AGEs/RAGE signaling pathway are a promising therapeutic tool to alleviate the progression of diabetes-associated comorbidities.

Inflammation

Chronic inflammation is a common feature of diabetes and is known to increase the incidence of atherothrombotic events [33]. Excess saturated fatty acids, ceramides, and glucose in the blood of diabetics trigger the link between

the thioredoxin-interacting protein and the NLR family pyrin domain containing 3 (NLRP3) inflammasome [34]. The NLRP3 inflammasome is the major mediator of IL (interleukin)-1 β and IL-18 cytokine secretion activating pro-inflammatory pathways [35]. High blood glucose promotes the production of IL-1 β by pancreatic islets β cells, which leads to glucotoxicity and the functional damage of β cells [36]. Despite advances in glucose and lipid-lowering therapies, a significant proportion of diabetics suffers from several complications and eventually results in end-organ damage [37]. Indeed, plasma LDL-lowering treatments are highly effective in preventing atherosclerosis; however, they incur a significant burden of atherosclerotic cardiovascular disease (ASCVD), and extensive studies suggested that it is probably the outcome of residual inflammatory risk [35, 38]. One study revealed that NLRP3 knockdown inhibited NLRP3 inflammasome activation, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) expression in intima in diabetes-accelerated atherosclerosis mouse models [39]. Endothelial cells were exposed to high glucose inducing an increase of G-protein coupled receptor 5B of family C (GPRC5B), leading to a pro-atherogenic GPRC5B-dependent positive feedback loop through tyrosine kinase Fyn and NF- κ B activation [40]. Mechanistically, elevated levels of S-nitrosylation of G-protein alpha-2 (SNO-GNAI2) act with CXCR5 to induce Hippo/YAP-dependent endothelial inflammation. The treatment with melatonin reduces SNO-GNAI2, which was revealed as an efficient strategy for mitigating diabetic atherosclerosis [41]. Moreover, treatment with trelagliptin, a DPP-4 inhibitor, suppressed the level of pro-inflammatory chemokines and adhesion of monocytes via inhibiting NF- κ B signaling in human aortic endothelial cells (HAECs) [42]. Canagliflozin, an SGLT2 inhibitor, also ameliorates acetylcholine-induced vasodilation and reduces the expressions of VCAM-1 and ICAM-1 via an anti-inflammatory mechanism in experimental diabetic mice [43]. Together, these studies show that inflammation in endothelial cells facilitates the atherogenic process, indicating that targeting vascular inflammation can be an effective approach to mitigate diabetic atherosclerosis.

Oxidative Stress

Diabetes promotes atherosclerosis via increased oxidative stress which is attributed to an imbalance between the excessive ROS production and antioxidative factors, in favor of ROS [44]. ROS encompasses an array of derivatives derived from molecular oxygen produced by various ROS-generating enzymes, such as nicotinamide-adenine dinucleotide phosphate (NADPH) oxidases (NOX), the mitochondrial electron transport chain (ETC), uncoupled endothelial NO synthase (eNOS), and cyclooxygenase (COX). ROS

consists of non-radical species and free radical species, such as hydrogen peroxide (H₂O₂) and superoxide anion radical (O₂⁻) [45]. Endothelial cells are exposed to several factors that induce oxidative stress, including oxidized low-density lipoprotein (ox-LDL) [46], high blood glucose [47], and free fatty acids [48]. Notably, pancreatic islets β cells are extremely sensitive to ROS damage induced by high glucose and FFA owing to the subnormal expression of superoxide dismutase (SOD) and catalase, resulting in β cells dysfunction [49]. High blood glucose and insulin concentrations also stimulate aberrant NOX activation and lead to endothelial malfunction and overstimulation of NOX in diabetes, creating a cytotoxic microenvironment, where eNOS uncoupling impairs the ability of the endothelium to perform vasorelaxation and glucose transport [50]. Similar results were obtained with endothelium-restricted human endothelin (ET)-1 overexpression that caused perivascular oxidative stress, enhanced monocyte/macrophage infiltration, and aggravated atherosclerosis in T1DM through NOX1 [51]. Fibroblast growth factor 21 (FGF21) has an anti-oxidative capacity relevant to metabolic disorders and prevents high glucose (HG)-induced endothelial dysfunction and enhanced eNOS activity that leads to dilation of the aorta through activation of the CaMKK2-AMPK α signaling pathway in both type 1 and type 2 diabetes [52]. A study showed that endogenous gasotransmitter hydrogen sulfide (H₂S) against HG-induced damage of endothelial cells and reversed endothelial cell viability via activation of PI3K/Akt/eNOS signaling [53]. Therefore, HG-induced oxidative stress contributes to endothelial dysfunction, promoting the initiation and development of diabetes-associated atherosclerosis by damaging endothelia-dependent vascular relaxation and increasing permeability.

Endoplasmic Reticulum Stress

Endoplasmic reticulum (ER), a cellular organelle with multifunctional roles in transmembrane protein synthesis, folding, and translocation, participates in the production of cellular lipids and regulation of cellular Ca²⁺ uptake. Several pathophysiology conditions disrupt ER homeostasis, followed by the alternation of protein-folding which results in irreversible unfolded protein response (UPR) activation and is referred to as ER stress [54]. Moreover, ER plays a vital role in the regulation of endothelial function. Lipoprotein-cholesterol, inflammation, and oxidative stress incur endothelial dysfunction and ER stress [55, 56]. ER stress is also activated by insulin resistance and vascular endothelial dysfunction in diabetics [57]. Several studies indicated that the downregulation of AMPK/PPAR δ signaling in vascular endothelial cells was considerable in relation to the activation of hyperglycemia-induced ER stress [58–60], which is inhibited by the improvement of endothelial cell function.

The finding that anti-hyperglycemic drugs (metformin, SGLT2 inhibitors, and GLP-1 receptor agonists) attenuate tunicamycin or HG (27.5 mM dextrose)-induced dysfunction in HCAECs in vitro indicates a major role of cardiovascular protective effects [61]. Recent research revealed that treatment with stanniocalcin 1 secreted from mesenchymal stem cells (MSCs), which restored cell viability, decreased the inflammatory response and lipid deposition and ameliorated palmitic acid (PA)-triggered impairment in HUVECs through inhibiting ER stress and endothelial-to-mesenchymal transition (EndMT) [62].

Mitochondrial Dysfunction

Since the mitochondrial is the principal organelle for adenosine triphosphate (ATP) generation, it is considered to be the cell “power plant,” where more than 90% of total cellular production of ATP is carried out by oxidative phosphorylation (OXPHOS) in the mitochondrial ETC [63]. Mitochondrial is not only an important organelle in cellular energy metabolism, but also the primary source of ROS which damages ETC proteins and mitochondrial DNA (mtDNA) [64]. T2DM and atherosclerosis are characterized by mitochondrial dysfunction and oxidative stress [65]. A follow-up study found that mitochondrial DNA copy number (mtDNA-CN), a substitute biomarker of mitochondrial dysfunction, is lower and related to cardiovascular complications in T2DM [66]. Moreover, an in vitro hyperglycemia model in HUVECs induced mitochondrial ROS and increased SIRT1-mediated PINK1/Parkin-dependent mitophagy; these effects can be attenuated by the treatment with liraglutide (a GLP-1 receptor agonists) [67]. Consistent with this finding, treatment with metformin significantly suppressed the progression of diabetic atherosclerosis via inhibition of mitochondrial fission in endothelial cells in streptozotocin (STZ)-induced diabetic mice, which was associated with activated AMPK-mediated blockage of dynamin-related protein 1 (Drp1) expression and translocation to the mitochondrial [68]. All findings above indicate that lowering mitochondrial dysfunction is a potential therapeutic target to limit atherosclerosis in diabetes.

Senescence

Senescence, a vital risk factor for endothelial dysfunction, is an elementary step in a series of events associated with the initiation and progression of ASCVD and other endothelial dysfunction-related diseases. Endothelial cell senescence can impair the vascular endothelium which is induced by HG and ox-LDL [14]. HUVEC overexpression of C1q/tumor necrosis factor-related protein 9 (CTRP9) significantly decreased the expression of Krüppel-like factor 4 (KLF4) and cyclin-dependent kinase inhibitor p21 and increased

the expression of telomerase reverse transcriptase (TERT) which prevented HG-induced endothelial senescence [69]. A study found that MSC-derived extracellular vesicles attenuated endothelial cell senescence through miR-126a/Src in natural aging and T2DM mouse models [70]. Moreover, in vitro studies showed that the DPP-4 inhibitor anagliptin protected against oxidative and glucolipotoxicity stresses induced cellular senescence in HUVECs [71].

Autophagy

Autophagy is an endogenous protective system for maintaining cellular homeostasis. Emerging studies unraveled an important autophagy function of endothelial cells, including modulating the response of endothelial cell to metabolic stresses and endothelial plasticity [72]. Autophagy is emerging as a crucial modulator of diabetes. For example, LDL has activity similar to insulin and inhibits endothelial cell autophagy via activation of the PI3K/Akt/mTOR signaling and enhancing glucose uptake by translocating the glucose transporter 1 (GLUT1) that increases the incidence of diabetes [73]. Moreover, endothelial-specific mTORC1 deletion alleviates hindlimb ischemia in diabetic mice partly via activation of autophagy [74]. Forearm vein endothelial cells isolated from diabetic patients have been shown to have impaired NO signaling and inadequate autophagy [75]. Furthermore, high glucose inhibits CAV1-CAVIN1-LC3B signaling-mediated autophagic degradation, promotes the LDL transcytosis across endothelial cells, and the development of atherosclerosis [76]. Consistent with these findings, endothelial-specific *Sirt6* overexpression in diabetic *ApoE*^{-/-} mice ameliorates atherosclerotic plaque formation, through not only SIRT6-mediated acetylation of caveolin-1 that triggers its autophagic degradation but also suppression of high glucose-induced LDL transcytosis [77]. Recently, GLP-1 therapy was found to attenuate H₂O₂-stimulated endothelial dysfunction and overly stimulate autophagy and restore histone deacetylase 6 (HDAC6) in a GLP-1R-ERK1/2-dependent manner [78]. Suppression of the glycogen synthase kinase 3 β (GSK3 β) might be important for restoring endothelial cell homeostasis and reducing atherogenesis through increasing basal autophagy and recovering impaired lysosome acidification in HAECs [79]. In addition, regular exercise protects the arteries from vascular disease by stimulating endothelial cell autophagy through decreased interleukin-1 receptor antagonist [80].

Apoptosis, Necroptosis, Pyroptosis, Ferroptosis

Cell death maintaining homeostasis and preventing the development of diseases contains two forms, programmed and non-programmed. Programmed cell death mostly refers to apoptosis, necroptosis, and pyroptosis, while

non-programmed cell death refers to necrosis. Ferroptosis was revealed as a new type of cell death [81]. First and foremost, endothelial apoptosis is significantly enhanced in diabetic endothelial cells and high glucose cultured HUVECs, which contributes to vascular remodeling during development [82, 83]. Recent research revealed that high glucose might induce HUVECs apoptosis via reduced H₂S levels and impaired the downstream PI3K/Akt/eNOS signaling, which links to hyperglycemia-caused vascular injuries [53]. Moreover, inflammatory factor tumor necrosis factor-associated factor 6 (TRAF6) also has a major contribution to hyperglycemia-induced endothelial cell dysfunction, such as apoptosis and endothelial-monocyte adhesion [84]. A recent study revealed that supra-nutritional selenium intake was related to augmented diabetes risk through induced endothelial cell apoptosis, ER stress, and increased ROS production [85]. Treatment with vitexin, a polyphenolic flavonoid, decreased apoptosis in HG-induced HUVECs via disrupted Wnt/ β -catenin and Nrf2 signaling [86]. Furthermore, notoginsenoside Fc (Fc) protects against HG-induced rat aortic endothelial cell dysfunction by inhibiting apoptosis and reducing the production of pro-inflammatory cytokines through a PPAR γ -mediated pathway [87].

Furthermore, there is an evidence for a negative interaction between apoptosis and necroptosis, while exogenous H₂S alleviates high glucose-induced HUVEC injury through inhibiting necroptosis [88]. Other evidence consolidates the vital contribution of pyroptosis in endothelial dysfunction; for example, under hyperglycemic conditions, pyroptosis in endothelial cells causes the initial atherosclerosis through the TLR4/NF- κ B pathway [89]. In addition, renal glomerular endothelial cells exposed to HG undergo pyroptosis through the caspase-1-gasdermin D (GSDMD) canonical pathway [90]. Moreover, long noncoding RNA KCNQ10T1/miR-214/caspase-1 signaling mediated pyroptosis induced by HG in diabetic human and rat corneal endothelium [91]. These findings reveal a potential therapeutic benefit in targeting endothelial cell death and delaying the progression of atherosclerosis during diabetes.

Consequently, the chain of events that results in diabetic atherosclerosis is attributed to vascular local endothelial dysfunction, which is caused by disturbed flow in areas of arterial curvature or branching. This flow pattern acts on endothelial cells to stimulate multiple inflammatory pathways, derange vascular permeability, and increase expression of proinflammatory cytokines and adhesion molecules, such as monocyte chemoattractant protein-1 (MCP-1), VCAM-1, ICAM-1, and E-selectin, which recruit circulating monocytes and T cells [92]. Of note, hyperglycemia and lipoprotein abnormalities further trigger monocyte adhesion to endothelial cells [93]. Meanwhile, high glucose and CD36 deficiency facilitate the LDL transcytosis across the arterial wall, where they are easily modified by oxidation, and

macrophages internalize ox-LDL that lead to the development of lipid-engorged macrophage, called foam cells, which make a contribution to early fatty streak formation in the artery wall [76, 94].

Overall, a lot of current studies demonstrate that diabetic atherosclerosis is triggered by endothelial dysfunction, which increase inflammation and ROS production. Ameliorating endothelial cell dysfunction may inhibit the onset of diabetic atherosclerosis.

Macrophages in Diabetic Atherosclerosis

Under normal homeostasis, macrophages reside in the adventitia where they interact with VSMCs to regulate blood vessel diameter and contribute to steady-state functions. In atherosclerotic lesions, macrophages are the most abundant immune cell subset localizing under the endothelium and contribute to lipid retention (Fig. 2). In response to endothelial activation, classical monocytes are recruited to the intima and differentiated into macrophages [95]. Then, the NLRP3 inflammasome in macrophage is activated in the context of diabetes and induces pro-inflammatory (M1) macrophage formation with mitochondrial dysfunction, which impairs lysosome function. The phagocytic efficiency of macrophage increases and leads to the foam cell formation. At the same time, NLRP3 inflammasome is activated, and cholesterol outflow decreases. Finally, increasing pyroptosis and necrosis and decreasing apoptosis of macrophages inhibit macrophage removal from plaque and form to necrotic core.

Macrophage Polarization

Most studies in the field of macrophage phenotypes in atherosclerosis focus on proinflammatory (M1) and anti-inflammatory (M2) [96]. M1 macrophages response to interferon- γ (IFN- γ) and the Toll-like receptor ligand lipopolysaccharide (LPS), while M2 macrophages response to IL-4 [97]. Hyperglycemia potentiates atherosclerosis progression and retards plaque regression by increasing the expression of proinflammatory genes, such as those encoding IL-1 β , IL-6, and tumor necrosis factor- α (TNF- α), while causing a resistance to M2-associated gene expression [98, 99]. In addition, macrophages uptake ox-LDL to form foam cells leading to atherosclerosis. Indeed, AGEs are localized in foam cells within the atherosclerotic lesions, contributing to endothelial dysfunction and arterial stiffness [100, 101]. Macrophages have heterogeneity at the single-cell level, and different macrophage subsets can coexist within a tissue. Although single-cell data from atherosclerotic plaques have become available [102], a detailed analysis of the macrophage alignment

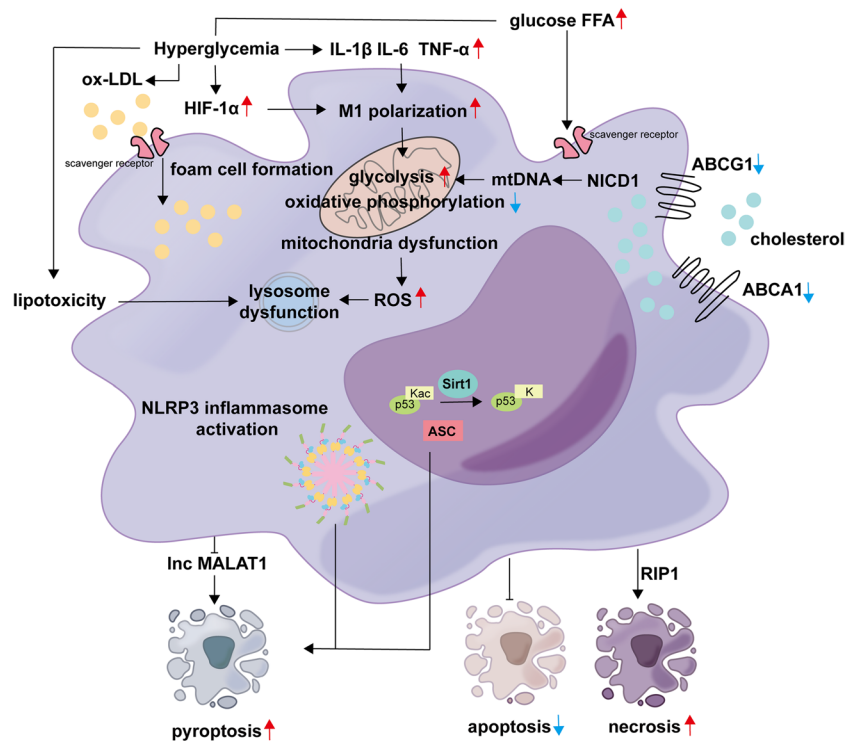


Fig. 2 Macrophage in diabetic atherosclerosis. Under the condition of hyperglycemia, the M1 polarization of macrophages increases and more ox-LDL is phagocytic to form foam cells. In addition, macrophage mitochondrial and lysosome dysfunction increases. At the same time, NLRP3 inflammasome is activated, and cholesterol outflow decreases. Eventually, the increase of pyroptosis and necrosis of macrophages and the decrease of apoptosis promote atherosclerosis progression.

ABCA1, ATP binding cassette subfamily A member 1; ABCG1, ATP binding cassette subfamily G member 1; ASC, apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain; FFA, free fatty acid; HIF-1 α , hypoxia-inducible factor 1 α ; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; NICD, Notch intracellular domain; ox-LDL, oxidized low-density lipoprotein; TNF- α , tumor necrosis factor- α

and compartment with data from diabetic atherosclerosis is lacking.

Mitochondria Dysfunction

Mitochondria that play central roles in ATP production are exquisitely sensitive to their environs and can be easily damaged. Macrophages with functioning mitochondria maintain an appropriate balance between energy storage and consumption, while abnormal lipid and glucose metabolism caused by insulin resistance impairs mitochondrial function [103]. Generally, the metabolism of M1 macrophage depends on glycolysis, while M2 macrophage relies on the oxidative phosphorylation pathway [104, 105]. It was recently reported that hypoxia-inducible factor-1 activation shifted cellular energy metabolism from oxidative phosphorylation to glycolysis and promoted polarization of M1 macrophage in a state of insulin resistance induced by obesity [106, 107]. Besides, the activated NOTCH1 pathway also leads to mitochondrial metabolism reprogramming for M1 macrophage polarization. In M1 macrophages, activated NOTCH1 liberates its intracellular domain which increases mitochondrial

glucose oxidation [108] and promotes mtDNA transcription. mtDNA expression enhances mtROS levels that in turn augment M1 gene expression. These lines of evidence show that insulin resistance reprograms macrophage polarization into M1 macrophages, and mitochondrial dysfunction shifts the energy supply from oxidative phosphorylation to glycolysis.

Lysosomal Defects

Under hyperglycemic conditions, mitochondrial dysfunction also impairs lysosome function, which leads to an increase in ROS production and blocks autophagic flux in macrophages [109]. This agrees with a recent study that phagocytosis of apoptotic pancreatic β cells caused lysosomal permeabilization and subsequently generated ROS that activated M1 macrophage inflammasome [110]. Lipid toxicity caused by insulin resistance can also lead to lysosomal dysfunction in macrophage [111]. Obesity causes immune cell infiltration, including macrophage, into adipose tissue that increases insulin resistance. Lysosomal stress/dysfunction occurs in adipose tissue macrophages in obesity-associated insulin resistance [112]. In conclusion, mitochondrial dysfunction

of macrophage in the context of diabetes also leads to lysosomal stress/injury.

Increased Phagocytic Activity

The accumulation of glycation and AGEs occurs during normal aging or in the development of several diseases, such as diabetes and atherosclerosis [113]. Glycation modulates cytokine expression and alters the phagocytic efficiency of macrophage [113]. Scavenger receptors can recognize modified low-density lipoproteins, such as ox-LDL and acetylated LDL [114]. In atherosclerotic plaque, ox-LDL is mainly known as the important source of intracellular lipid accumulation. Moreover, modified LDL including ox-LDL, has a lower affinity to LDL receptor. It is internalized mainly through unspecific phagocytosis, which results in cholesterol accumulation. These processes lead to the foam cell formation and accelerate the process of atherosclerosis [115]. In addition to ox-LDL, in the case of T2DM, raising glucose and FFA levels, insulin resistance, and lowering HDL cholesterol all result in increasing expression of scavenger receptor on macrophages, thereby contributing to T2DM and related atherosclerosis [116].

Inhibited Reverse Cholesterol Transport

Hyperglycemia can lead to lipoprotein clearance and cholesterol excretion disorders. Glycemic control by SGLT2i treatment can improve plasma lipoprotein profiles by heparin sulfate proteoglycan-dependent clearance mechanisms. Further research suggests that the bile acid transporters ABCG5 and ABCG8 in the conversion of cholesterol to bile acids reduce the risk of atherosclerosis [117]. These are consistent with the role of reverse cholesterol transport transporters, such as ABCA1 and ABCG1. A recent study found that the application of reconstituted HDL-polarized macrophages to the M2-type, increased ABCA1 and ABCG1 expression, and improved the characteristics of diabetes-related atherosclerosis [118]. Another study found that a miR-325 inhibitor decreased the lipid content and facilitated the cholesterol efflux in RAW264.7 cells by the PPAR γ -LXR-ABCA1 pathway [119]. In conclusion, dysregulation of lipid metabolism in diabetic atherosclerosis leads to high plasma TG levels, impairs cholesterol efflux, and M2-type polarization of macrophages, resulting in foam cell formation and proatherogenic lipid profile, which is closely related to the onset and progression of atherosclerosis.

NLRP3

Chronic sterile inflammation significantly drives diabetes-associated atherosclerosis [6, 120]. Sterile inflammation and downstream activation of the inflammasome have been

involved in complications associated with diabetes [121]. In diabetes and atherosclerosis, the NLRP3 inflammasome is the prominent inflammasome family member [35, 122]. A recent study confirmed that neutrophil extracellular traps (NETs) persisted in diabetes and impaired atherosclerosis resolution by increasing inflammasome in macrophage [123]. In addition, treatment of bone marrow-derived macrophages with MCC950, a NLRP3 selective inhibitor, significantly dampened pro-inflammatory cytokine secretion in response to diabetogenic mediators. MCC950 treatment reduced mononuclear macrophage contents, inflammatory gene expression, cell adhesion, and fibrous cap thickness in experimental atherosclerosis [124]. Metformin, one of the most widely used first-line medications for type 2 diabetes therapy, inhibited NLRP3 inflammasome activation in macrophage [125]. These results are consistent with a protective role for SGLT2i-modulated NLRP3 inflammasome activity in human macrophage [126, 127]. Other studies have found that in type 1 diabetes, the macrophage inflammatory state was triggered by the NLRP3/iNOS pathway [128]. The NLRP3 inflammasome in macrophage is activated in the context of diabetes, induces pro-inflammatory macrophage formation, and promotes the progression of diabetic atherosclerosis. Thus, inhibition of inflammation is a promising therapeutic target for diabetic atherosclerosis.

Epigenetic Mechanisms of Macrophage Activation

Recently, the field of epigenetics affords new insights into the pathogenesis of T2DM, while also providing potential new opportunities for therapy. Epigenetic mechanisms are known as crucial controllers of macrophage phenotype. Epigenetic enzymes can regulate macrophages and alter gene expression by adding or removing acetyl or methyl groups [129]. A review summarized the epigenetics-mediated macrophage activation mechanisms in T2DM into the following aspects: (1) hyperlipidemia increased DNA methylation and inhibition of anti-inflammatory gene expression, (2) hyperglycemia-promoted macrophage activation depends on NF- κ B pathway by increasing activating methylation marks, (3) hypoxia-activated macrophage via histone acetylation, (4) inflammatory macrophage activation impaired wound healing [130]. A recent study revealed that epigenetic regulation of S100A9 and S100A12 affected the monocyte-macrophage system under hyperglycemic conditions [131]. Circular RNAs (circRNAs) are involved in various disease processes as a novel class of endogenous RNAs. A study showed that circPPM1F modulated M1 macrophage activation in type 1 diabetes mellitus through the circPPM1F/HuR/PPM1F/NF- κ B axis [132]. In addition, *hsa_circ_0060450*, the sponge of miR-199a-5p, can suppress the JAK-STAT signaling pathway to inhibit macrophage-mediated inflammation in type 1 diabetes mellitus [133]. It was found that

another type of non-coding RNA, long non-coding RNA (lncRNAs), was increasingly implicated in the pathological process of diabetes complications. Under normal conditions, lncRNA DRAIR decreased the enrichment of repressive histone modifications by inhibiting the recruitment of histone methyltransferase G9a, which allowed anti-inflammatory gene expression. However, under diabetic conditions, down-regulation of DRAIR and subsequently upregulation of G9a reversed these events, resulting in anti-inflammatory gene repression, monocyte activation, and chronic inflammation [134].

Hyperglycemia Induces Trained Immunity in Macrophages

Hyperglycemia is a major feature of T1DM and T2DM, and treatment mainly focuses on lowering blood glucose. Although hypoglycemic therapy, while effective in reducing vascular risk in type 1 diabetes patients, was not associated with glycemic control [135, 136]. However, in T2DM, lowering glucose had no or moderate effect on atherosclerosis-related vascular outcomes [137, 138]. Persistent risk of cardiovascular complications after glycemic control is associated with metabolic memory [137]. Hyperglycemia can induce trained innate immunity of bone marrow-derived macrophages, thereby increasing aortic root atherosclerosis [139]. In addition, hyperglycemia-induced trained phenotype also occurs in human monocytes [140].

Macrophage Apoptosis

Dyslipidemia accompanying type 2 diabetes is a major risk factor for atherosclerosis. The cholesterol accumulation and oxidized products in the arterial wall recruit monocyte into the subendothelial layer. Monocyte can differentiate into macrophage and subsequently become foam cells to participate in plaque formation. Studies also demonstrated that apoptosis was the mainly method for macrophage removal from plaque, which significantly reduced foam cell formation [141]. Potentiation of atherosclerosis by hyperglycemia is mainly through increasing macrophage proliferation and decreasing apoptosis as revealed by feeding mice with atherogenesis high-fat diet [142]. A review systematically summarized the pathways by which insulin resistance promoted ER stress-induced macrophage apoptosis and plaque progression. First, ER stress activated the MEK-ERK-SERCA pathway to lower cytoplasmic calcium, leading to enhanced activation of calcium-mediated apoptotic pathways. Then, pattern recognition receptors, such as scavenger receptors, which are synergistic with ER stress-inducing apoptosis, increased in insulin-resistant macrophage. Finally, increased nuclear FoxO induced I κ B ϵ , suppressing a

compensatory NF- κ B cell-survival pathway in insulin-resistant macrophage [143].

Pyroptosis, Ferroptosis, Necroptosis

Previous studies demonstrated that macrophages underwent an apoptotic phenotype transformation in diabetes. Recent studies found other types of macrophage death in addition to apoptosis, such as pyroptosis, ferroptosis, and necroptosis. Pyroptosis has been associated with inflammatory diseases as a type of programmed cell death, including diabetic atherosclerosis. One study found that sinapic acid abated the pyroptosis of macrophage by downregulation of lncRNA-MALAT1 by using a rat model of diabetic atherosclerosis [144]. A recent study reached the same conclusion that hyperglycemia could induce macrophage pyroptosis, thereby contributing to periodontal pathogenesis in diabetes [145]. Interestingly, macrophage pyroptosis and subsequently triggered macrophage function impairments could be reversed by metformin [146]. Another study revealed a novel lipid-regulated pathway associated with SIRT1-p53-ASC signaling and pyroptosis in macrophage [147]. The NLRP3 inflammasome relates to various human diseases by regulating pyroptosis [148]. Thus, compounds inhibiting NLRP3 inflammasome activation can be potential treatments for these diseases. Another study discovered a novel potent pyroptosis inhibitor against NLRP3-dependent pyroptosis in macrophage [149]. Necroptosis is a programmed cell death pathway dependent on RIP1 and distinct from apoptosis [150, 151]. Previous work established that RIP1-dependent necroptosis in Jurkat and U937 cells is enhanced under conditions of hyperglycemia [152]. One question that needs to be asked, however, is whether macrophage necrosis has a role in diabetes. Most studies in macrophage ferroptosis have only been carried out in a small number of areas, including atherosclerosis associated with hyperuricemia [153]. Thus, detailed studies are required to determine the role of macrophage-programmed cell death in diabetes.

Macrophages are widely regarded as therapeutic targets because they are involved in all stages of atherosclerosis. The chain of pathological events that results in atherosclerosis development is known to be triggered by endothelial dysfunction. In response to endothelial activation, classical monocytes adhere to the arterial wall, migrate to the intima, and then differentiate into macrophage that actively uptake lipids through phagocytosis and become lipid-laden macrophage foam cells [95]. One possibility is that hyperglycemia plays an important role in atherosclerosis through extracellular mechanisms. AGEs accumulate in diabetic patients and affect endothelium activation and adhesion molecule expression on the surface which promotes monocytes/macrophage adhesion and entrance into the subendothelial space

during the initial stages of atherosclerosis. Moreover, these molecules increase cytokine release by macrophage, maintaining a pro-inflammatory environment within the developing plaque [115]. Macrophage apoptosis in atherosclerotic lesions has been studied in the last few years. Reduced apoptosis in macrophage accelerates atherosclerosis likely through lipid core formation and plaque rupture [154].

In conclusion, M1 macrophages increase and M2 macrophages decrease in diabetic atherosclerosis, but the heterogeneity of macrophages needs further study at the single-cell level. Repairing mitochondrial dysfunction and lysosomal dysfunction may be a therapeutic strategy. Effective ways for increasing apoptosis of macrophages may reduce the necrotic core, thereby stabilizing atherosclerotic plaques and reducing acute coronary syndrome.

Smooth Muscle Cells in Diabetic Atherosclerosis

VSMC participants in both early and late-stage atherosclerosis. In the early atherosclerosis lesion, migration of VSMCs from the media into the intima promotes plaque formation, while VSMCs in advanced plaque form a protective fibrous

cap to cover the necrotic core [155]. Worse blood glucose control in diabetics significantly alters VSMC phenotypes, such as α -SMA + VSMCs, macrophage-like VSMCs, smooth muscle foam cells, VSMC-derived osteochondrogenic cells, senescent VSMCs, and synthetic vascular smooth muscle cells, owing to loss of mitochondrial homeostasis. At the same time, intracellular mitochondrial dysfunction and autophagic flux blockade, ROS production and pro-inflammatory (IL-1 β , IL-6, and TNF- α) expression increase, leading to an increased pro-inflammatory cell response. The apoptosis of VSMCs decreases, and the proliferation and migration increase, which promotes the migration of VSMCs into the subendothelial layer (Fig. 3), which relates to the development of macrovascular and microvascular diseases [156].

α -SMA⁺VSMCs

Under stress stimuli, VSMCs switch from a pro-contractile to a pro-synthetic state, which is called a phenotypic switch or cell dedifferentiation [157]. Phenotypic switching is defined by the loss of classical contractile markers (such as alpha-smooth muscle actin (α -SMA/ACTA2), smooth muscle 22 alpha (SM22 α /TAGLN), and

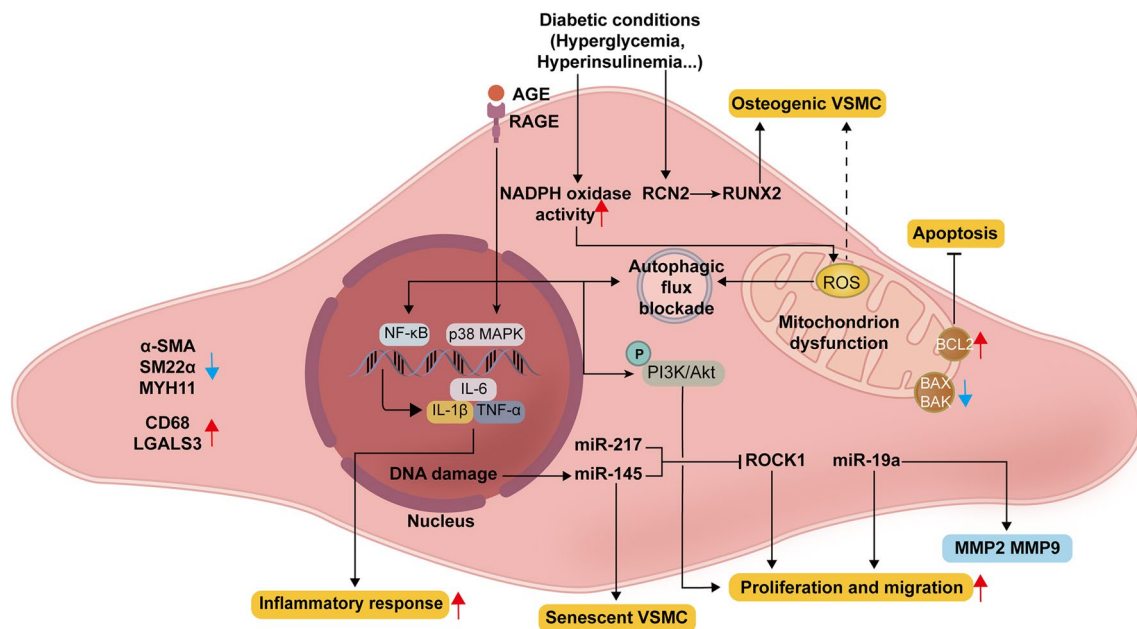


Fig. 3 VSMC in diabetic atherosclerosis. Under diabetic conditions, VSMCs undergo a phenotypic switch with decreasing expression of the contraction phenotypic markers, such as α -SMA, SM22 α , and MYH11. VSMCs are transformed into macrophage-like, osteogenic-like, and senescent VSMCs. At the same time, intracellular mitochondrial dysfunction and autophagic flux blockade, ROS production, and pro-inflammatory (IL-1 β , IL-6, and TNF- α) expression increase, leading to an increased pro-inflammatory cell response. At the same time, the apoptosis of VSMCs decreases, and the proliferation and

migration increase, which promotes the migration of VSMCs into the subendothelial layer. The solid line is the proven signal pathway, and the dashed line is the signal pathway yet to be proved. α -SMA, alpha-smooth muscle actin; LGALS3, galectin-3; MMP, matrix metalloproteinase; MYH11, myosin heavy chain 11; RCN2, reticulocalbin 2; ROCK1, Rho-associated kinases 1; RUNX2, Runt-related transcription factor 2; SM22 α , smooth muscle 22 alpha; TNF- α , tumor necrosis factor- α

smooth muscle cell myosin heavy chain 11 (MYH11) and acquire of synthetic organelles, proliferation and migration properties, secretion of various cytokines and extracellular matrix (ECM) proteins, which plays a pivotal role in intimal hyperplasia and atherogenesis [155, 158]. For instance, excessive AGEs facilitate a switch of VSMCs from a contractile to a synthetic phenotype and increase production and secretion of collagen I through activation of the NF- κ B pathway [159].

Macrophage-Like VSMCs

VSMC-derived macrophage-like cells exist in both human [160] and mouse [161] atherosclerotic plaques. Macrophage-like VSMCs upregulate typical macrophage markers, such as CD68, galectin-3 (LGALS3), and MCP-1, and improve efferocytosis function which stimulates lipid accumulation and foam cell expansion [162].

Smooth Muscle Foam Cells

Lipid-overladen foam cells are traditionally viewed as monocyte-differentiated macrophage, while recent studies have revealed that VSMCs also transform into foam cells and make up at least half of the foam cell population [102]. Lipid transport occurs through scavenger receptors (such as CD36, SRA, LOX-1) and cholesterol efflux transporter (such as ABCA1 and ABCG1). Excessive lipid uptake and decreased efflux in cells can cause foam cell formation [163]. Recently, the major AGEs, Ne-(carboxymethyl) lysine, was found to promote VSMC-derived foam cell formation and induce VSMCs transdifferentiate to a macrophage-like phenotype in the arterial plaque of diabetic patients through activation of RAGE [162].

VSMC-Derived Osteochondrogenic Cells

Vascular calcification is not only a consequence of a high calcium and phosphorous milieu, but also a result of an imbalance between osteochondrogenic signaling and anti-calcific events. The transform of VSMCs to an osteochondrogenic state is a central step during vascular calcification [164]. Indeed, vascular calcification depends on AGEs/RAGE in diabetic VSMCs [165]. Moreover, considerable evidence revealed that excessive ROS accelerated the osteochondrogenic transdifferentiation of VSMCs [166] and salusin- β regulated VSMC calcification via activation of NADPH/ROS-mediated Klotho downregulation [167]. Reticulocalbin 2 (RCN2) and Runt-related transcription factor 2 (RUNX2) were also positively correlated with the

calcification process of VSMCs under diabetic conditions [168].

Senescent VSMCs

In atherosclerotic plaques, senescent VSMCs are attributed to the replicative senescence (with telomere shorting) and stress-induced premature senescence in reply to DNA damage and oxidative stress-induced stimuli, which can promote atherosclerosis progression [169]. In VSMCs cultured from T2DM patients, markers of DNA damage and subsequent cellular senescence were significantly elevated and associated with increased miR-145 [170]. Additionally, lncRNA-ES3 was also related to the high glucose-treated calcification/senescence of HASMCs by directly binding to the basic helix-loop-helix family member e40 (Bhlhe40) [171].

Proliferation and Migration

VSMC proliferation and migration play an important role in the pathologic process of vascular disease, including atherosclerosis and restenosis. A study indicated that suppressing the proliferation and migration of VSMCs through restraint of the Pin1/BRD4 pathway could possibly mitigate diabetic atherosclerosis [172]. Other studies showed that hyperlipidemia elevated VSMC proliferation and intima-media thickness of the aortas via a CCL5/CCR5-mediated phenotypic switching, which can be reversed by pyrogallol-phloroglucinol-6,6-bieckol (PPB) [173]. Not surprisingly, AGEs, as an important inducing factor in diabetic atherosclerosis, may activate PI3K/Akt signaling through RAGE and thus accelerate the proliferation and migration of HASMCs [174]. Mechanistically, poly (ADP-ribose) polymerase 1 induced diabetic neointimal hyperplasia by promoting VSMC proliferation and migration, through downregulating tissue factor pathway inhibitor (TFPI2) [175]. Epigenetics and transcription are involved in the regulation of VSMC phenotypic switch in arterial remodeling [176]. For example, differing from VSMC senescence, miR-145 occurs a protective role in HG-induced excessive proliferation and migration of VSMCs by suppressing Rho-associated kinase 1 (ROCK1) [177]. Treatment with miR-127 drastically induced VSMC cycle arrest, reduction of proliferation and migration, and increasing of apoptosis by targeting ROCK1 [178]. Moreover, miR-19a promotes VSMC proliferation and invasion via increasing level of matrix metalloproteinase (MMP)-2, MMP9, α -SMA, and SM22 α by inhibiting the RAS homolog family member B [179]. Under diabetic conditions, acarbose, an α -glucosidase inhibitor, increased the expression of miR-143 and decreased the phosphorylation of PI3K/Akt and focal adhesion kinase, resulting in reduced VSMC migration and proliferation [180]. Of note, these data provide a potential therapeutic benefit

in targeting epigenetic factor miRNAs in regulating VSMC function and atherogenesis.

Mitochondria Dysfunction, Defective Autophagy, and Lysosomal Impairment (Apoptosis, Pyroptosis, and Ferroptosis)

Retaining mitochondrial homeostasis is essential for maintaining the contractile phenotype of VSMCs to protect against calcification [181]. Mitochondrial superoxide dismutase 2 acts as a crucial gateway within VSMCs through counteracting ROS to block the progression of subsequent vascular calcification [182]. In another study, hyperinsulinemia induced the migration and proliferation of VSMCs accompanied by oxidative stress and alterations in mitochondrial physiology, therefore, providing a crosstalk between mitochondrial dysfunction and oxidative stress [183]. Counteracting mitochondrial dysfunction in VSMCs is an innovative therapeutic strategy for diabetic-associated atherosclerosis. Autophagy is an adaptive stress response and degrades cells by lysosomal phagocytosis that is closely linked to the pathogenesis of diabetic vascular calcification. Mechanistically, upregulation of extracellular matrix protein periostin impairs the fusion of autophagosomes and lysosome that results in the blockade of autophagic flux in AGE-treated VSMCs [184]. Moreover, treatment with alpha-lipoic acid has a protective function on VSMCs in T2DM, significantly elevated H₂S levels, and downregulated autophagy through activation of the AMPK/mTOR pathway [185]. Furthermore, H₂S also inhibits the proliferation and promotes apoptosis of VSMCs. Current evidence suggests that hyperglycemia-caused VSMC apoptosis is linked to decreased expression of dopamine D1 receptor and cystathionine- γ -lyase, a major enzyme for endogenous H₂S formation in diabetic mice [186].

Inhibition of VSMC apoptosis through administration of sitagliptin, a DPP-4 inhibitor, reduced atherosclerotic lesions in diabetic *ApoE*^{-/-} mice through the reduction of oxidative stress, increased expression of β -catenin and suppressed production of proinflammatory cytokines [187]. Both pyroptosis and iron overload of VSMCs decreased the thickness of the fibrous cap by triggering the loss of collagen and matrix, which promote plaque instability and rupture [188, 189]. A recent study showed that *Ecklonia cava* extract and PPB decreased pyroptosis in palmitate-treated endothelial cells and VSMCs, which alleviated cellular dysfunction, including downregulating the expression of caspase-1, IL-1 β , and IL-18 via inhibiting the TLR4/NF- κ B pathway [89]. Moreover, studies revealed that treatment with metformin attenuated PA-stimulated ferroptosis and enhanced the antioxidative capacity of VSMCs via NRF2 signaling activation [190]. These findings indicate a crucial role of VSMCs in the pathogenesis of diabetic atherosclerosis.

As described above, by adapting different phenotypes, VSMCs might have beneficial or maladaptive effects on atherogenesis and plaque stability. Hyperglycemia and hyperlipidemia stimulate abnormal proliferation, migration, and invasion of VSMCs from the middle layer to the lining layer of the artery and is a crucial process of accelerating cardiovascular complication in diabetes, which is characterized by pathological intimal thickening and formation of extracellular lipid pools [172]. Additionally, in diabetic patients, increased NLRP3 inflammasome activity combined with elevated levels of pro-inflammatory cytokines (such as IL-1 β , IL-18, and IL-1 β) act on VSMCs, which increases monocyte-VSMC interactions and promotes cell proliferation [124]. Of note, pathological intimal thickening can progress to fibroatheromas, form fibrous cap, and enlarge the necrotic core, which led to foam cell accumulation and insufficient efferocytosis of senescence and apoptotic VSMCs [191].

To sum up, the role of VSMCs in diabetic atherosclerosis remains to be studied. Which phenotype VSMCs transform into and how to affect the thickness of the fiber cap to influence plaque stability remain to be further investigated.

Conclusion and Perspectives

The above studies indicate that diabetes and atherosclerosis are closely correlated, including pathophysiological mechanism and clinical relevance. In detail, insulin resistance, dyslipidemia, and hyperglycemia in diabetes lead to endothelial dysfunction, promote proinflammatory M1 macrophage polarization, and induce VSMC proliferation, migration, and foam cell formation, which accelerate the progression of atherosclerosis and plaque rupture. However, the cellular heterogeneity in diabetic atherosclerotic plaques remains to be further explored. The different diabetes-associated atherogenic factors are relevant to the different phases (initiation, development, and thrombogenesis of atherosclerosis lesions). Therefore, the way to control the insulin resistance, dyslipidemia, and hyperglycemia is conducive to improving the subsequent cell pathological changes and further to inhibit atherosclerosis progression.

In the clinic, in addition to plaque formation, hyperglycemia also has an impact on plaque stability, leading to acute coronary syndrome with high mortality of patients. Extensive studies have indicated that hypoglycemic drugs play an anti-atherosclerotic role in improving lipid profiles, endothelial disorders, and vascular inflammation. Randomized clinical trials and many clinical studies have demonstrated the cardiovascular benefits of SGLT2i, GLP-1R agonist, DPP-4 inhibitor, pioglitazone, acarbose, and metformin applied in diabetes mellitus patients. Besides, studies have confirmed that hypoglycemia drugs can stabilize atherosclerotic

plaques. Hence, it is suggested that appropriate glycemic control and reduction of risk factors are the most useful strategies to protect against clinically diabetic atherosclerosis. However, some hypoglycemic agents have no significant cardiovascular protective effect, such as sulphonylureas and insulin. Thus, it should be stressed how to select drugs for diabetics' patients with or without cardiovascular diseases. In addition, since the concept of hyperglycemia was profoundly changed, the glycemic control should focus not only on reaching and maintaining optimal blood glucose as early as possible, but also on reducing transient intermittent hyperglycemia and glucose variability to extend time in the normal glucose range [192].

Besides existing researches, the mechanisms of anti-atherosclerosis effects of hypoglycemic agents still need further elucidation. Furthermore, it is essential to reveal the signaling pathways, identify specific potential drug targets, and ultimately decipher novel therapeutic approaches.

Author Contribution All authors contributed to the study's conception and design. NZ, XY, and AQ had the idea for the article. XZ, YS, and FG performed the literature search. NZ, XY, BY, and AQ drafted and critically revised the work. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

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