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REVIEW

# Recent advances in the pathogenesis of microvascular complications in diabetes

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**Abstract** Millions of people worldwide have diabetes, which is diagnosed by fasting blood glucose levels exceeding 126 mg/dL. Regardless of the type of diabetes, prolonged hyperglycemia is damaging to several organs including eyes, kidneys, nerve, and/or heart. The damages are associated with a high risk of morbidity and mortality. Diabetes has been implicated in ischemia in the microvasculature of the target tissues, which occurs due to the insufficient perfusion of tissues. The resulting occlusion and pain affect the quality of life. Multiple therapeutic approaches have been proposed for a long time to overcome these vascular complications. Apart from systemically controlling high glucose levels, other therapeutic strategies are not well understood. In this review, we summarize the recent literature for biochemical/cellular targets that are being utilized for the treatment of diabetic microvascular diseases. These targets, which are closely associated with mitochondrial dysfunction, include the polyol and diacylglycerol-protein kinase C pathways, oxidative stress, non-enzymatic glycation and the formation of advanced glycation end products, and immune dysregulation/inflammation.

**Keywords** Diabetes · Complication · Inflammation · Protein kinase C · Oxidative stress · Advanced glycation end products

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## Introduction

The pathophysiology of vascular complications due to diabetes is mainly associated with hyperglycemia, dyslipidemia, epigenetic regulation, and genetics. These complications can be divided into macrovascular complications, which include coronary artery disease and cerebrovascular diseases, and microvascular complications. The three classic microvascular complications include retinopathy, nephropathy, and neuropathy, which are affected by blood sugar levels (Paneni et al. 2013; Barrett et al. 2017). Controlling blood glucose levels by specific anti-hyperglycemic drugs including metformin, sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors might prevent the onset and progression of diabetic microvascular complications (Mannucci et al. 2013). Interestingly, Barrett et al. (2017) emphasized that hyperglycemia is necessary, but not sufficient, to trigger diabetic microvascular diseases, and endogenous tissue damage in long-term diabetic patients. Many reports have demonstrated that multiple factors, such as cellular signaling, epigenetic regulation, and environmental phenotypes result in complex abnormalities in human subjects, which are associated with various diabetic microvascular complications.

Hyperglycemia is associated with the activation of protein kinase C (PKC), a family of serine/threonine-related protein kinases, which in turn is mediated by the

hyperglycemia-induced increase in the levels of calcium, diacylglycerol (DAG), phosphatidylserine, hydrogen peroxide, and superoxide. This results in abnormal vasculature characterized by endothelial dysfunction, smooth muscle cell proliferation, vascular permeability, and angiogenesis (Orr and Newton 1992; Koya and King 1998). In addition, oxidative stress due to increased production of reactive oxygen species (ROS), such as superoxide, in endothelial cells has been significantly associated with the pathogenesis of vascular diseases in the diabetic state (Sasaki and Inoguchi 2012). In the cardiovascular system, NADPH oxidases (NOX) play an important role in the production of superoxide in the vasculature (Lassegue et al. 2012). Additionally, an overflow of electrons through the electron transport complex of mitochondria is a major source of ROS as it increases the proton gradient under hyperglycemic conditions (Starkov 2008). Advanced glycation end products (AGEs) formed as a result of the non-enzymatic reaction between glucose and proteins or lipids play an important role in pathogenesis of cardiovascular diseases, diabetic retinopathy, nephropathy, and neuropathy, along with the aging process (Goldin et al. 2006). Receptors for AGE (RAGE) are expressed in a wide range of cells including endothelial cells, smooth muscle cells, pericytes, mesangial cells, podocytes, and neurons. Increased ROS production in these cells activates nitric oxide synthase (NOS) and the nuclear factor-kappa B (NF-kB) signaling pathway (Fakhruddin et al. 2017). Recent investigations have suggested that the metabolic effects of current anti-hyperglycemic drugs are mediated by their anti-inflammatory effects in type 2 diabetes, which in turn are associated with mitochondrial dynamics (Pollack et al. 2016; Wang et al. 2017). Furthermore, immunological polarization requires metabolic reprogramming that includes enhanced glycolysis and repurposing of the mitochondrial respiration chain, leading to insulin resistance (Van den Bossche et al. 2016; Jung et al. 2018). In this review, we revisit the immunological aspects of the medications used for the treatment of diabetic vascular complications (Fig. 1).

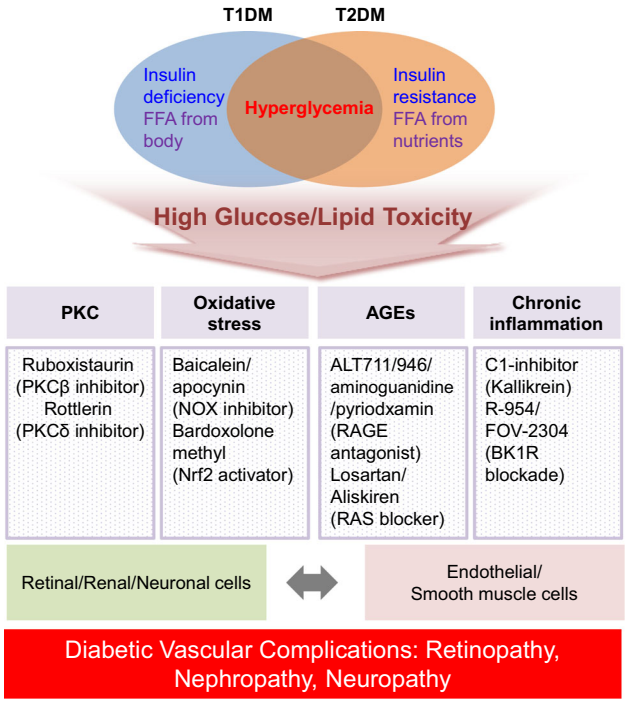


**Fig. 1** Available therapeutic drugs for diabetic vascular complications. High glucose and lipid toxicity leads to PKC activation, oxidative stress, AGEs, and chronic inflammation, which have been established targets in type 1 and type 2 diabetes. *AGEs* Advanced glycation products, *BK 1R* Bradkinin receptor 1, *FFA* Free fatty acids, *Nrf2* Nuclear factor (erythroid-derived 2) like 2, *PKC* Protein kinase C, *RAGE* Receptor of AGEs, and *RAS* Renin-angiotensin-system

## Diacylglycerol (DAG)-protein kinase C (PKC) pathway

PKC comprises a family of serine/threonine kinases that are activated in response to various signals. These include increased concentrations of DAG or calcium ions ($Ca^{2+}$). The PKC family is further sub-divided into three structurally and functionally distinct sub-families comprising the conventional (classical) isoforms (PKCα, βI, βII, and γ) activated by DAG and $Ca^{2+}$), novel isoforms (PKCδ, ε, η, and θ) activated by DAG, and atypical isoforms (PKCζ and λ/ι,) that do not require DAG or $Ca^{2+}$ for their activation (Isakov 2018). The increase in the concentration of the glycolytic intermediate, dihydroxyacetone-phosphate, mediated by elevated glucose increases the concentration of DAG, which leads to PKC activation in diabetic vascular complications like retinopathy, nephropathy, and neuropathy (Noh and King 2007). PKC activation increases the production of the extracellular matrix, and expression of transforming growth factor beta 1 (TGF-β1), which plays an important role in the progression of renal insufficiency. The therapeutic potential of several selective inhibitors of the PKC isoforms has been evaluated in large-scale and long-term clinical studies in diabetic patients to inhibit the progression of diabetic microvascular complications in different tissues.

Ruboxistaurin (LY333531) is an orally active PKC-β inhibitor. It has been studied in several animal models and human clinical trials for its ability to improve microvascular complications associated with diabetes. Interestingly, the combined analysis of data from two randomized, double-blind, placebo-controlled phase 3 trials suggested that ruboxistaurin at a dose of 32 mg/day can reduce the relative risk of sustained moderate visual loss by 50% in patients with diabetic macular edema (DME) (Sheetz et al.

2013; Bansal et al. 2013). Similarly, treatment with ruboxistaurin at 32 mg/day was reported to decrease the urinary albumin/creatinine ratio, while having no significant effect on the estimated glomerular filtration rate (eGFR) in patients with diabetic nephropathy, suggesting that ruboxistaurin may have a potential therapeutic effect against diabetic kidney disease (Tuttle et al. 2015). In another study, ruboxistaurin (10 mg/kg, p.o for 6 weeks) had a nephroprotective effect in rat models of diabetes induced by streptozotocin (STZ) by reducing the expression of TGF-β1/smad/Grb-2-related adaptor protein pathway, which is responsible for the progressive accumulation of extracellular matrix components that result in kidney fibrosis (Al-Onazi et al. 2016).

Enzastaurin (LY317615) is another PKC-β inhibitor that is orally administered. It was originally used to treat cancer by inhibiting the binding of ATP to PKC, resulting in the subsequent activation of PKC-β. However, its therapeutic potential could not be proven in clinical trials due to its limited efficacy (Bourhill et al. 2017). A preclinical report demonstrated that enzastaurin (25 mg/kg, p.o) reduced oxidative stress by reducing the expression of p66shc, a 66 kDa proto-oncogene Src homologous-collagen homologue, and NADPH oxidase in an STZ-induced early-diabetic nephropathy model (Cheng et al. 2018). Oral administration of PKC412 (midostaurin), an inhibitor of multiple PKC isoforms (α, β, and γ) and vascular endothelial growth factor (VEGF), at doses of 100 mg/day and 150 mg/day for 3 months reduced macular edema in diabetic subjects by significantly decreasing retinal thickening compared to the placebo group, despite concerns related to liver toxicity associated with its systemic administration (Campochiaro and Group 2004). Therefore, PKCβ might be the main target for treating microvascular diseases associated with diabetes. However, inhibiting PKC-β alone is not sufficient to delay the progression of diabetic complications.

## Oxidative stress

Traditional inducers of diabetic complications described above, which include activation of PKC, increased polyol pathway or hexosamine activity, and increased AGE formation, stem from the common pathway of increased mitochondrial ROS production (Brownlee 2001; Giacco and Brownlee 2010). Increased influx of glucose in cells as a result of increased blood glucose levels leads to excess production of pyruvate by glycolysis, and subsequently produces reducing equivalents, such as NADH/$FADH_2$ (Forbes et al. 2008). This, in turn, increases proton gradient and membrane potential ($\Delta\Psi m$), triggering the reverse flow of electrons to complex I of the electron transport chain (Liu et al. 2002). These well-orchestrated signaling cascades result in ROS production. Although somewhat controversial, the majority of superoxide production within mitochondria is thought to be driven by the action of complex I and III (Raha and Robinson 2000). Moreover, diabetes is features increased fatty acid oxidation, which is another trigger for increased mitochondrial ROS production (Schrauwen and Hesselink 2004). The applies to the classical sites of diabetic complications, including retinal endothelial cells, renal mesangial cells, neurons, and vascular endothelial cells (Du et al. 2000, 2003; Kiritoshi et al. 2003; Sifuentes-Franco et al. 2017).

Among several sources of ROS production in the kidney, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4 (NOX4) is considered the main enzyme that induces ROS formation in the diabetic milieu. This leads to endothelial dysfunction, inflammation, and apoptosis (Gorin and Wauquier 2015). Furthermore, *de novo* synthesis of DAG under hyperglycemic conditions activates PKC in the glomerulus. This creates a vicious circle dubbed the PKC-ROS loop, which causes mesangial expansion, thickening of the glomerular basement membrane, and endothelial dysfunction (Mahmoodnia et al. 2017). Numerous efforts have been made to decrease ROS production by the modulation of Nox4. Since AMP-activated protein kinase (AMPK) is a negative regulator of Nox4, activation of AMPK by treatment with 5-aminoimidazole-4-carboxamide-1-riboside (AICAR) can inhibit high glucose-induced expression of NOX4, and apoptosis in podocytes (Eid et al. 2010). Additionally, several studies have demonstrated that pharmacological inhibition of either Nox4 by GKT137831 or podocyte-specific deletion of NOX4 can be sufficient to prevent diabetic nephropathy in mouse models (Jha et al. 2014, 2016).

SS301 is a mitochondrion-targeted antioxidant peptide that was reported to protect mitochondria against ROS production, prevent apoptosis of human proximal tubule epithelial cells exposed to high glucose conditions, and alleviate proteinuria, glomerular hypertrophy, and tubular injury in *db/db* diabetic mice (Hou et al. 2018). Additionally, a recent clinical trial demonstrated that tocotrienol-rich vitamin E from palm oil (Tocovid), which has antioxidant and anti-inflammatory properties, significantly reduced the AGE metabolite, Nε-carboxymethyllysine, and reduced serum creatinine levels in diabetic patients with or without nephropathy (Tan et al. 2018). Baicalein is a flavonoid that has strong free radical scavenging activity. It also exhibited a nephroprotective effect against high fat diet/STZ-induced type 2 diabetic Wistar rats (Ahad et al. 2014). Furthermore, since Angiotensin II (Ang II) increases vasoconstriction of glomerular capillary followed by intraglomerular pressure and also acts as a regulator of Nox4, it is considered that the nephroprotective effect of

chymase, which is mediated by inhibitor of angiotensin receptor or aliskiren, a direct renin inhibitor, is partially attributed to their antioxidant potential (Park et al. 2013; Fakhruddin et al. 2017).

Additionally, either activation of nuclear factor-erythroid 2 (NF-E2) p45-related factor-2 (Nrf2) or inhibition of Keap1, a negative regulator of Nrf2, is another possible target to reduce oxidative stress-mediated diabetic complications. Nrf2 translocates into nuclei and activates the transcription of a series of antioxidant genes, such as heme oxygenase-1, glutathione peroxidase-2, and NAD(P)H-quinone oxidoreductase 1. A phase II clinical trial of bardoxolone methyl, a potent activator of Nrf2, demonstrated improved renal function in type 2 diabetic patients with chronic kidney disease (Pergola et al. 2011). Although a phase III clinical trial of bardoxolone methyl was terminated early due to a higher rate of cardiovascular events in patients randomized to the bardoxolone methyl group compared to the placebo group (de Zeeuw et al. 2013), a recent post-hoc analysis reported that bardoxolone methyl increased eGFR, thereby restoring kidney function in patients with type 2 diabetes and stage 4 chronic kidney disease (Chin et al. 2018).

In this context, numerous antioxidants have been used as therapeutic agents to ameliorate diabetic retinopathy. Diabetic retinopathy has also been significantly associated with the oxidation of fatty acids, resulting in the increased production of ROS by the Nox system (Calderon et al. 2017). Pharmacological agents, such as alpha-lipoic acid, astaxanthin, resveratrol, hesperetin, and telmisartan, have shown promising effects against diabetic retinopathy by the activation of antioxidant mechanisms, either in vitro or in vivo (Soufi et al. 2012; Kumar et al. 2013; Nebbioso et al. 2013; Ola et al. 2013; Wiley et al. 2014).

## Advanced glycation end products (AGEs)

In general, AGEs are the final products derived from the Maillard reaction, which is a non-enzymatic glycation reaction between free amino groups and sugars or aldehydes, as a result of exposure to high glucose and glycemic memory (Brahma et al. 2017). AGEs mediate their effect by binding to RAGEs on different cell types, and are associated with several microvascular and macrovascular complications in diabetic patients (Goldin et al. 2006). Long-lived structural proteins like collagen, and lens crystalline, which are modified by sequential formation of AGEs, have been characterized by the conversion of reversible Schiff-base adducts to covalently bound Amadori products. These rearrangements terminate in the formation of irreversibly bound compounds, known as AGEs, have been implicated in the formation of plaque, basement membrane thickness, and reduced vascular elasticity, which result in tissue dysfunction (Ulrich and Cerami 2001). Furthermore, the interactions of AGEs with RAGE directly activate multiple intracellular signaling pathways, gene expression, and secretion of pro-inflammatory molecules accompanied by increased production of free radicals that contributes to the development of pathological complications associated with diabetes (Meenatchi et al. 2017; Rhee and Kim 2018).

Pharmacological inhibitors of AGEs have been developed and assessed in a number of preclinical and clinical studies. Pharmacological inhibitors, such as aminoguanidine, pyridoxamine, benfotiamine, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker (ARB), thiazolidinediones, statins, and ALT-711 (alagebrium) have been evaluated for their anti-glycating effects in humans. Aminoguanidine, a well-known anti-glycating agent, inhibits the formation of AGEs. Unfortunately, aminoguanidine has adverse effects on diabetic patients, which include myocardial infarction, congestive heart failure, arterial fibrillation, anemia, and gastrointestinal disturbance (Barrett et al. 2017). Additionally, in spite of several clinical studies, the use of alagebrium (formerly known as ALT-711) developed by Alteon, Inc. to break AGE crosslinks as a treatment for diabetic vascular complication remains questionable.

Pyridoxamine, a form of vitamin B6, prevents the transformation of protein-Amadori intermediates to protein-AGEs by trapping carbonyl intermediates. A phase 3 clinical trial of pyridoxamine (NCT02156843) was completed in December 2017. Treatment with pyridoxamine reduced serum creatinine levels in type 1 and type 2 diabetic patients with nephropathy. On the other hand, the ARB candesartan was reported to suppress levels of oxidative markers by inhibiting the production of AGEs and RAGE expression, thereby improving the cardiovascular system of type 2 diabetic patients with essential hypertension (Ono et al. 2013). Although many clinical trials have been conducted to show the importance of AGEs in diabetic complications and the benefits of anti-AGE treatment, no compound with anti-AGEs activity is commercially available yet. Appropriate human data analysis should be made available for compounds with anti-AGEs activity, which include ALT-946, OPB-9195, tenilsetam, and LR-90 (Nenna et al. 2015). There are the multiple adverse biological mechanisms in diabetic conditions leading to vascular complications including retinopathy, neuropathy, and neuropathy (Fig. 2).

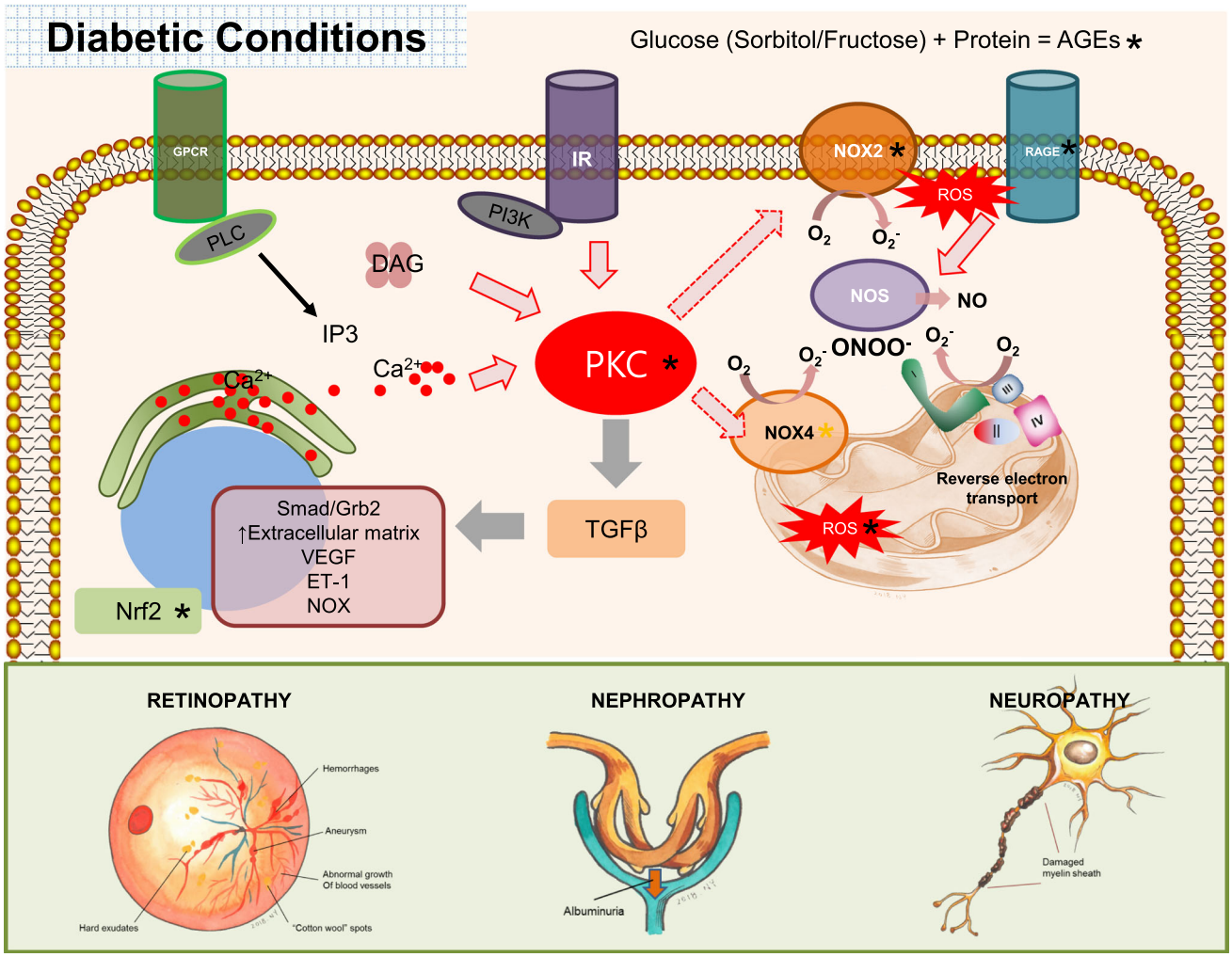


**Fig. 2** Schematic diagram of adverse mechanisms in development of diabetic vascular complications. Excess glucose simultaneously intensifies the DAG-PKC pathway, increases ROS produced by either NOX2 or NOX4, and circulating AGEs levels, creating a vicious cycle. Various clinical trials have clarified that a drug for one molecular target might not be sufficient to delay the progression of diabetic complications. *AGEs* Advanced glycation products, *DAG* Diacylglycerol, *GPCR* G-coupled protein receptor, *IR* Insulin receptor, *NOX* NADPH oxidase, *NOS* nitric oxide synthase, *Nrf2* Nuclear factor (erythroid-derived 2) like 2, *PI3K* Phosphoinositide 3 kinase, *PLC* Phospholipase C, *PKC* Protein kinase C, *ROS* Reactive oxygen species, and *RAGE* Receptor of AGEs. The clinical trials for diabetic vascular complications with the compounds are marked with the asterisks

## Chronic low-grade inflammation

Chronic low-grade inflammation in multiple organs increases the risk of developing obesity, diabetes, cardiovascular diseases, and cancer. This highlights the major role of the immune system in the etiology of metabolic disorders (Hotamisligil 2017). Recent reports suggested that cellular metabolism is coordinated by the immune system for numerous immune-metabolic diseases governed by metabolic reprogramming (Mills et al. 2016). Recently, anti-inflammatory drugs have been used for the treatment of diabetes and associated vascular complications. For example, empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, reduced low-grade inflammation and improved endothelial function in Zucker diabetic fatty rats (Steven et al. 2017). Thus, the well-established anti-diabetic drugs, which can suppress high glucose levels by suppressing the DAG-PKC signaling pathway and oxidative stress, might also regulate the immunological responses.

The kinin-kallikrein system is associated with inflammation, vascular function, blood pressure regulation, and nociceptive responses in addition to retinal thickening and retinal vascular permeability, which are blocked by bradykinin (BK) receptor antagonists (Kita et al. 2015). Kallikrein is a serine protease that regulates activation of innate inflammation and intrinsic coagulation cascade, resulting in the cleavage of factor XII and high-molecular-weight kininogen XII to XIIa in an intrinsic coagulation cascade. To minimize the inflammatory responses

mediated by increased activity of kallikrein, C1-inhibitor (C1-INH) and 1-benzyl-1H-pyrazole-4-carboxylic acid 4-carbamimidoyl-benzylamide have been developed as a neutralizing antibody against plasma kallikrein and a small bio-molecule inhibitor, respectively (Clermont et al. 2011). On the other hand, blockade of BK1R, either by selective peptide antagonists, such as R-954 and FOV-2304, or a non-peptide antagonist, such as LF22-0542, reduced the expression of induced NOS and cyclooxygenase-2, which are potential mediators of inflammation and which in turn are associated with retinal vascular abnormalities (Barrett et al. 2017).

Activation of PKC-β in diabetic atherosclerosis increases the secretion of IL-18 by macrophages while reducing the expression of IL18-binding protein. These events result in increased endothelial dysfunction, monocyte adhesion, and accelerated atherosclerosis. This effect is reportedly restored by the administration of the PKC inhibitor ruboxistaurin (Durpes et al. 2015). Obesity induces a phenotypic switch from M2 to M1 macrophages, leading to an imbalance in the ratio of M1/M2, which in turn aggravates inflammation of adipose tissues and induces insulin resistance associated with pro-inflammatory cytokines (Lumeng et al. 2007). Paradoxically, TGF-β triggers fibrotic responses in the diabetic kidney, such as expansion of mesangial matrix and the increased expressions of collagen IV and fibronectin. Recent studies have reported that TGF-β has a potent anti-inflammatory effect on immune cells, thereby conferring a protective effect against diseases with chronic inflammation, such as diabetes. Furthermore, insulin activates endothelial NOS by increasing its phosphorylation status and expression of VEGF and heme oxygenase-1 and suppressing the expression of vascular cell adhesion molecule 1. All these insulin-induced events are associated with anti-inflammatory and antioxidant effects on the endothelial cells. Taken together, these findings suggest that insulin resistance leads to inflammation and vice versa, which further leads to tissue dysfunction.

Lipotoxicity and glucolipotoxicity resulting from excessive accumulation of harmful lipid species and glucose, respectively, at ectopic sites that include liver, muscle, and heart causes meta-inflammation, which is mediated by mitochondrial and endoplasmic reticulum (ER) stress, which in turn results in the recruitment of immune cells including macrophages (Ito et al. 2016; Ryan and O'neill 2017). This leads to the activation of the inflammasome and recruitment of inflammatory macrophages, such as T cells, and other immune effectors (Ertunc and Hotamisligil 2016). Recruitment of M1 macrophages, interferon-gamma (IFN-γ)-secreting Th1 cells, CD8+ T cells, and B cells by adipose tissues results in local inflammation, which further promotes systemic inflammation, and results in obesity-induced insulin resistance by impairing the action of insulin (McLaughlin et al. 2017). Hypoxia inducing factor-1-alpha-pyruvate dehydrogenase kinase 1—(PDK1)-mediated glycolytic reprogramming leads to elevation in the level of lactate and is an essential process for the activation of macrophage migration. A stable isotope-assisted metabolomics analysis revealed that citrate synthesized from pyruvate is converted to itaconate, an antimicrobial metabolite, and is utilized for lipogenesis, rather than citrate oxidation, while increased glutamine uptake was shown to replenish the tricarboxylic acid cycle in lipopolysaccharide (LPS)-activated macrophages (Semba et al. 2016). The increased rate of aerobic glycolysis in M1 macrophages in response to LPS treatment is primarily mediated by expression of PDK1 (Tan et al. 2015). Similarly, recent metabolomic and transcriptomic analyses have suggested that T cell (CD8+) activation requires aerobic glycolysis along with the attenuation of mitochondrial respiration, suggesting that metabolic reprogramming by the pyruvate dehydrogenase (PDH) complex (PDC) could be a potential therapeutic target in immune cells, similar to the Warburg effect (Peng et al. 2016; Phan et al. 2016).

Recently, we also demonstrated that mitochondrial PDC, a central metabolic node that catalyzes the conversion of pyruvate to acetyl-CoA at the expense of lactate formation, is associated with metabolic disorders including obesity and insulin resistance and is primarily regulated by pyruvate dehydrogenase kinase (PDK) activity in several tissues (Park et al. 2018). A significant decrease in PDC activity in the peripheral blood mononuclear cells of patients with sepsis suggested that dichloroacetate, a drug that inhibits conversion of active PDH into inactive PDH, can be used as a therapeutic drug for the treatment of sepsis (Nuzzo et al. 2015). It has been reported that microphthalmia transcription factor mediated increase in the activity of mitochondrial PDC in mast cells plays an important role in evoking the allergic responses (Sharkia et al. 2017). For a long time, it has been accepted that the prolonged ER stress plays a primary role in the development of many diseases including obesity and chronic inflammatory diseases, which affects the synthesis and folding of proteins, lipid trafficking, and metabolism via $Ca^{2+}$ homeostasis, which in turn is regulated by intracellular c-Jun N-terminal kinase/p38 mitogen-activated protein kinase (JNK/p38 MAPK) pathways (Hotamisligil and Davis 2016).

Mitochondrial repurposing is required for metabolic reprogramming. This repurposing is characterized by increased aerobic glycolysis and decreased oxidative phosphorylation for ATP production, which in turn are associated with a shift in the balance in mitochondrial dynamics between mitochondrial fission and fusion (Van den Bossche et al. 2016; Buck et al. 2016). Furthermore,

ER stress-mediated increase in the mitochondria-associated ER membrane has been associated with the upregulation of inflammatory genes and VEGF in vasculature, leading to enhanced permeability of the outer mitochondrial membrane (Thoudam et al. 2016). Several clinical studies are currently assessing the effects of metformin in this context and evaluating whether metformin mediates its effects via modulation of the inflammatory state. A recent study suggested that metformin can attenuate dynamin-related protein (Drp1)-induced mitochondrial fragmentation during the progression of diabetes-accelerated atherosclerosis in an AMPK-dependent manner (Wang et al. 2017). We demonstrated that induced ER stress by high glucose and/or insulin resistance plays a primary role in mitochondrial dynamics governed by $Ca^{2+}$ level consistent with the increased ER-mitochondria contact sites (Fig. 3a). Likewise, repurposing mitochondria by fission generates ROS rather than ATP compared to elongated mitochondria (Fig. 3b)

According to preclinical studies that assessed the anti-inflammatory effects of previously known anti-diabetic drugs, the doses used for treatment were much higher than those used in clinical practice (Pollack et al. 2016). Therefore, we should keep in mind the doses, methods, and duration of drug administration for determining the appropriate clinical studies and should also consider the appropriate end-points for patient criteria.

## Clinical perspective of recently developed anti-diabetic drugs concerning diabetic microvascular complications

Beyond the glucose lowering effect, recently developed anti-diabetic drugs have been highlighted for their effects on microvascular complications. Dipeptidyl peptidase-4 (DPP4) inhibitors reduce blood glucose by potentiating the actions of the incretin hormone glucagon-like peptide 1 (GLP-1), which can be degraded by DPP4. In experimental models of diabetic nephropathy, a series of DPP4 inhibitors such as sitagliptin, linagliptin, vildagliptin, and gemigliptin exhibited both a glucose lowering effect and renoprotective effects including the prevention of tubulointerstitial fibrosis and glomerulosclerosis and reduced albuminuria, consistent with a decrease in oxidative stress markers (Alter et al. 2012; Kanasaki et al. 2014; Jung et al. 2016; Kanasaki 2018). More specifically, linagliptin was reported to ameliorate kidney fibrosis in type 1 diabetic mice by inhibiting the endothelial-to-mesenchymal transition (Kanasaki et al. 2014).

Likewise, DPP4 inhibitors have a protective effect against other microvascular complications, such as retinopathy and neuropathy (Avogaro and Fadini 2014). The beneficial effects might be derived from the inhibition of inflammatory features of immune cells by decreasing monocyte adhesion or decreasing inflammatory cytokines such as tumor necrosis factor-alpha, interleukin (IL)-6, and IL-1β (Avogaro and Fadini 2014). Intriguingly, DPP-4 has protease activities on substrates other than GLP-1. These include stromal cell-derived factor 1-alpha, brain natriuretic peptide, and neuropeptide Y-1. The results are interference with vascular tone regulation, inflammation, or cell migration (Kawanami et al. 2016), demonstrating that the protective effect of DPP4 inhibitors on microvascular complications could be in part achieved by these off-target effects.

The GLP-1 receptor agonist also protects from diabetic microvascular complications. In one study, long-term liraglutide administration reduced diabetic nephropathy by 22%, defined as new-onset albuminuria, doubled the serum creatinine level, and lead to an estimated glomerular filtration rate below 45 mL/min/1.73 $m^2$. It also led to the need for continuous renal-replacement therapy or death from renal disease (Marso et al. 2016b). This renoprotective effect was also confirmed in a clinical trial with semaglutide (Marso et al. 2016a).

Lastly, SGLT2 inhibitors improve hyperglycemia by increasing the excretion of urinary glucose that accompanies natriuresis. This restores tubuloglomerular feedback, which is impaired in diabetic nephropathy. Subsequently, glomerular hyperfiltration is reduced, beneficially affecting glomerular albumin filtration. SGLT2 inhibitors can also reduce renal hypertrophy, albuminuria, and inflammation by reducing glycemia (Wanner 2017). Indeed, treatment with the SGLT2 inhibitor empagliflozin in a type 1 diabetic animal model attenuated renal growth and albuminuria, as well as decreased inflammatory markers in the kidney (Vallon et al. 2014). Since the glucose lowering effect is tightly coupled with microvascular complications, it is not easy to dissect the glucose lowering effect from the preventive effect of microvascular complications in human clinical trials. Nevertheless, the benefits were convincingly proven in the recent EMPA-REG OUTCOME mega clinical trial involving empagliflozin (Wanner et al. 2018). In addition, another clinical trial with dapagliflozin demonstrated a decreased renal composite outcome comprising a greater than 40% decrease in eGFR to $< 60$ mL/min/1.73 $m^2$, ESRD, or death from renal or cardiovascular cause (Wiviott et al. 2019). Taken together, the pleiotropic effects of new and recently developed classes of anti-diabetic agents provide additional benefits in microvascular complications, especially in diabetic nephropathy. The emerging evidences have been solidly accumulated by succeeding large clinical trials.

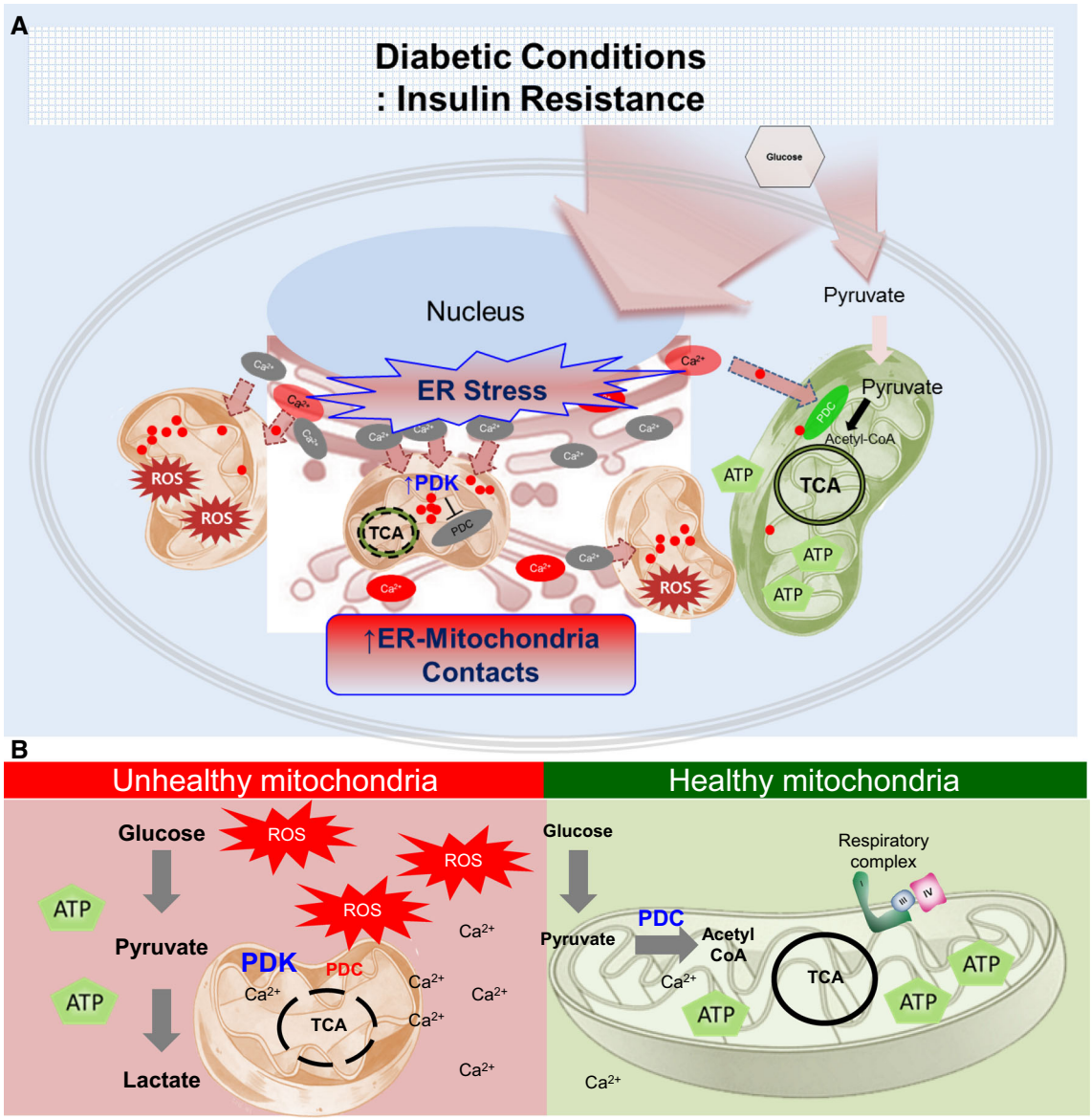


**Fig. 3** Proposed mechanism for induced ER stress on mitochondrial dynamics mediated by increased PDK activity leading to mitochondrial fission in diabetic conditions. Excessive $Ca^{2+}$ transport from ER to mitochondria causes mitochondrial fission associated with increased ROS and reduced ATP production compared to the elongated mitochondria in immunological activation during the development of diabetic complications. *ER* Endothelium reticulum, *ROS* Reactive oxygen species, *PDC* Pyruvate dehydrogenase complex, *PDK* Pyruvate dehydrogenase kinase, and *TCA* Tricarboxylic acid cycle

## Conclusions

The currently available drugs for the treatment of type 2 diabetes lower blood glucose levels via diverse mechanisms. Additionally, their anti-inflammatory effects might be mediated via their metabolic effects on hyperglycemia and hyperlipidemia or direct modulation of the immune system. Metabolic reprogramming is indispensable for distinct immune cell polarization and plasticity, which has been implicated in mitochondrial function. Oxidative stress mediated by mitochondrial repurposing plays a pivotal role in the development of diabetic complications by activating PKC and increasing the formation of AGEs, which in turn leads to metabolic abnormalities. Therapeutic strategies to prevent diabetic complications like retinopathy, nephropathy, and neuropathy are multi-factorial. Therefore, it is crucial to understand the fundamental mechanisms by which regulation of mitochondrial function allows the validation of new targets to prevent vascular complications in addition to the intensive glycemic control by well-known anti-diabetic drugs.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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