Yu *et al. Cell Communication and Signaling* (2025) 23:114
https://doi.org/10.1186/s12964-025-02113-2

Cell Communication and Signaling

REVIEW Open Access

Metabolic reprogramming of peritoneal mesothelial cells in peritoneal dialysis–associated fibrosis: therapeutic targets and strategies

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Abstract

Peritoneal dialysis (PD) is considered a life-saving treatment for end-stage renal disease. However, prolonged PD use can lead to the development of peritoneal fibrosis (PF), diminishing its efficacy. Peritoneal mesothelial cells (PMCs) are key initiators of PF when they become damaged. Exposure to high glucose-based peritoneal dialysis fluids (PDFs) contributes to PF development by directly affecting highly metabolically active PMCs. Recent research indicates that PMCs undergo metabolic reprogramming when exposed to high-glucose PDFs, including enhanced glycolysis, impaired oxidative phosphorylation, abnormal lipid metabolism, and mitochondrial dysfunction. Although this metabolic transition temporarily compensates for the cellular damage and maintains energy levels, its long-term impact on peritoneal tissue is concerning. Multiple studies have identified a close association between this shift in energy metabolism and PF, and may promote the progression of PF through various molecular mechanisms. This review explores recent findings regarding the role and mechanism of PMC metabolic reprogramming in PF progression. Moreover, it provides a summary of potential therapeutic strategies aimed at various metabolic processes, including glucose metabolism, lipid metabolism, and mitochondrial function. The review establishes that targeting metabolic reprogramming in PMCs may be a novel strategy for preventing and treating PD-associated fibrosis.

Introduction

Currently, there are 697.5 million patients with chronic kidney disease worldwide [1], with over 2.5 million receiving renal replacement therapy [2]. Globally, peritoneal dialysis (PD) is the primary treatment for end-stage renal disease (ESRD), constituting approximately 11% of all dialysis and 9% of kidney replacement therapies [3, 4]. Nonetheless, peritoneal fibrosis (PF) poses a formidable challenge for the widespread clinical application of PD. PF is one of the pathological changes occurring gradually in the peritoneum due to chronic inflammation and infection, and it is also one of the primary causes of PD technique failure, being responsible for 30% of such failures [5–7]. The 3-year PD technique survival rates range from 29 to 91% worldwide [4, 8, 9]. During long-term PD treatment, the progression of peritoneal fibrosis is closely linked to PD technique failure, reduced patient survival, and the development of other complications [10, 11]. Effective interventions to prevent PF progression

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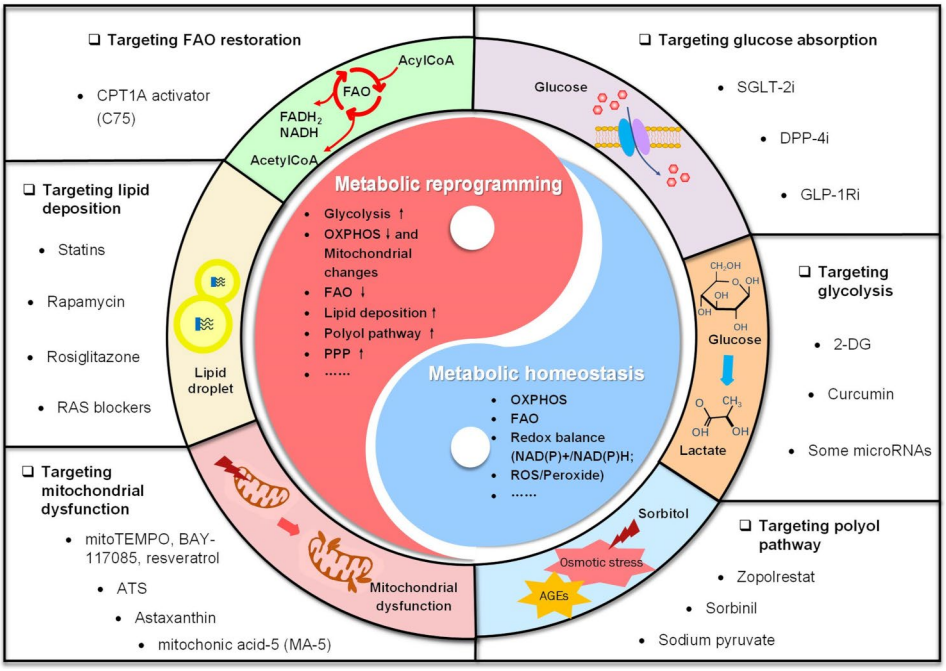
Graphical Abstract



Keywords Metabolic reprogramming, Peritoneal mesothelial cells, Peritoneal dialysis, Peritoneal fibrosis, Therapeutic target

are lacking, highlighting the necessity to investigate the mechanisms underlying PF.

Glucose containing peritoneal dialysis fluid (PDF)-mediated PF is a key factor limiting PD efficacy [12–14]. High-glucose PDFs create an osmotic gradient that facilitates water and solute removal from the peritoneal cavity. The biological incompatibility of high-glucose PDFs involves factors, such as elevated osmolarity (10–50 times greater than serum) [7], glucose degradation product formation during heat sterilization [15], and advanced glycation end product (AGE) production in the peritoneal cavity [7, 16]. High-glucose-induced PF is commonly associated with metabolic abnormalities, inducing a diabetes-like condition within the peritoneal cavity [17]. However, the metabolic mechanisms underlying PF remain unclear.

Peritoneal mesothelial cells (PMCs), the first line of defense on the peritoneum surface, are crucial for peritoneum defense and function during PD, thereby maintaining homeostasis, managing fluid transport, being involved in tissue repair, and responding to immune challenges [6, 18–20]. Highly metabolically active PMCs undergo considerable metabolic alterations during prolonged PD to maintain peritoneal homeostasis [21]. Prolonged PD exposure to high-glucose solutions alters PMC metabolism, characterized by hyperglycolysis, ultimately resulting in PF [22]. This exposure also causes PMC injury and mesothelial-mesenchymal transition (MMT) by triggering mitochondrial dysfunction and oxidative stress [23, 24]. Such changes compromise peritoneal integrity and function, making PMC metabolic reprogramming a central factor in PD-related fibrosis.

Metabolic alterations in PMCs are pivotal for determining the prognosis of patients undergoing PD. The structural and functional modifications induced by long-term PD are intricately associated with the metabolic activities of PMCs [25]. High - glucose PDFs can cause mesothelial cell dysfunction and induce MMT, initiate and accelerate PF, and affect the patient's technical survival rate and long - term prognosis [26]. Moreover, the metabolic activities of PMCs are linked to the peritoneal inflammatory response [27, 28]. This inflammatory response not only compromises peritoneal integrity but also affects systemic inflammation and patient prognosis [29]. Additionally, high-glucose PDFs can lead to abnormal lipid metabolism, further impacting PMC function and the patient's overall metabolic state [30]. In conclusion, a comprehensive understanding of the mechanisms underlying metabolic changes in PMCs is crucial for the development of new treatment strategies.

Recent studies have focused on the pathological and physiological mechanisms of metabolic reprogramming

in PMCs and their role in promoting PD-related fibrosis. This review highlights the potential of targeting metabolic reprogramming as a novel approach to delay PF progression, offering new therapeutic strategies for preventing and treating PD-related fibrosis (Table 1).

Metabolic reprogramming and PF progression

Metabolic reprogramming, a mechanism wherein cells alter their metabolic patterns to support proliferation, growth, and energy demands, is a hallmark of cancer [31, 32]. While most cells generate energy primarily through oxidative phosphorylation (OXPHOS), tumor cells preferentially utilize glycolysis to produce adenosine triphosphate (ATP) even in oxygen-rich environments, a phenomenon known as the Warburg effect [33]. However, metabolic reprogramming occurs in non-tumor cells following genetic and environmental changes [34, 35]. Substantial alterations in the intracellular metabolic pool often accompany metabolic reprogramming [36]. This cellular adaptation helps cells resist external stress and acquire new functions. Moreover, it is intricately linked to the onset and progression of diseases.

A recent randomized controlled trial found that patients with ESRD undergoing PD exhibited substantial metabolic disturbances, which were associated with adverse clinical outcomes [37]. PD techniques have faced considerable limitations owing to the development of high-glucose PDFs-mediated PF and ultrafiltration failure. Exposure to high-glucose PDFs is closely linked to metabolic disorders [38, 39], inflammatory responses [6], activation of the renin-angiotensin system (RAS) [40], and angiogenesis in the peritoneum [41, 42]. These factors contribute to PMC damage, death, apoptosis, and MMT, resulting in the promotion of PF and even adverse outcomes [13, 17]. Thus, glucose-containing PDFs-induced metabolic reprogramming may substantially affect peritoneal pathophysiology.

Two key mechanisms underlie high-glucose PDFs-induced fibrosis: the production of AGE, accompanied by a decrease in the ultrafiltration osmotic pressure gradient due to heightened expression of glucose transporter type 1 (GLUT-1), and an increase in the nicotinamide adenine dinucleotide (NADH)/nicotinamide adenine dinucleotide (NAD+) ratio (NADH/NAD+), causing a pseudohypoxia state in peritoneal tissues and cells [22, 43]. These conditions can lead to peritoneal damage and subsequent fibrosis. High-glucose PDF-induced PF is closely associated with metabolic disorders, including abnormal glycolysis, mitochondrial dysfunction, impaired OXPHOS, and disrupted lipid homeostasis [22, 39, 44, 45]. In summary, prolonged exposure to high-glucose PDFs induces metabolic reprogramming and promotes PF progression, highlighting the important role of metabolism in PD-related fibrosis (Fig. 1).

Metabolism reprogramming in PMCs during PD

Glucose metabolism

During long-term PD treatment, PMCs undergo substantial alterations [46], such as metabolic reprogramming in response to stimulation by glucose-based PDFs, characterized by increased activation of glycolytic and polyol pathways, alongside OXPHOS inhibition [21, 24, 47, 48]. Prolonged maintenance of PMCs in this abnormal metabolic state increases energy demand and drives abnormal biological responses, including changes in cell phenotype, proliferation, apoptosis, and senescence [21, 48]. Thus, the metabolic reprogramming of PMCs is an important cellular process that mediates PD-related fibrosis.

Glycolysis

Glycolysis, a relatively inefficient anaerobic pathway used for the production of ATP, converts glucose into various products such as pyruvate and lactate. During long-term PD treatment, PMCs undergo a marked shift in glucose metabolism toward glycolysis [21, 48, 49]. Increased glycolysis in PMCs, stimulated by high glucose levels, elevates the NADH/NAD + ratio and lactate levels, resulting in the formation of a hypoxic intracellular environment [13, 47]. This pseudohypoxic environment induces pathological changes in PMCs including cell damage, apoptosis, and senescence [7, 22, 50]. The pseudohypoxia hypothesis is based on two primary factors. First, the excessive intracellular lactate concentrations impair lactate dehydrogenase function, disrupting normal intracellular and NADH/NAD + compensatory mechanisms for hypoxia in the tricarboxylic acid (TCA) cycle [51]. Second, activation of the intracellular expression of hypoxia-inducible factor-1 (HIF-1) induces chronic injury in PMCs [43], leading to the secretion of various pro-fibrotic and angiogenic factors that impair organ function [43, 52, 53].

PMCs undergo glucose metabolic reprogramming to reduce oxidative metabolism, promote ATP production, and enhance cell survival [48]. This reprogramming involves inhibiting OXPHOS via the GLUT-1 pathway and enhancing glycolysis by upregulating essential glycolysis genes, corresponding enzymes, and glucose transporter proteins [13, 48]. Excessive glycolysis caused by high glucose levels can damage PMCs through several alternative pathways. For example, hyperglycolysis in PMCs activates the NLRP3 inflammasome, leading to PF development [54]. Moreover, inhibiting glycolysis in the context of high-glucose PDFs reduces transforming growth factor beta 1 (TGF-β1)-induced cellular MMT and PF in mice [48]. While brief periods of mild hypoxia may enhance cell survival and recovery, prolonged exposure to hypoxia can result in cell damage and death [44]. Thus, the compensatory reprogramming of glucose metabolism in PMCs due to long-term exposure to

Table 1 Overview of therapeutic targets and associated mechanisms in metabolic reprogramming for prevention of PF progression

Targeting strategies	Drugs/ compounds	Targeting protein	Animal/cell models	Mechanism/Intervention effects	References
Glucose absorption	Empagliflozin	SGLT-2	An acute PD model of rats and an in vitro model of primary HPMCs	Suppressing SGLT-2 activity and inhibiting glucose uptake	[99]
	Empagliflozin	SGLT-2	A rat PF model and a cell model (HMrSV5 cell line) induced by high-glucose PDFs	Suppressing SGLT-2 activity, inhibiting TGF-β/Smad signaling, and ameliorating peritoneal fibrosis	[101]
	Canagliflozin	SGLT-2	A rat PF model induced by HG-PDFs and an in vitro model (HMrSV5 cell line) induced by high glucose	Ameliorating glucose-mediated peritoneal hypoxia, peritoneal fibrosis, and peritoneal thickening	[52]
	Phloretin	SGLT-1 and SGLT-2	A PD model of rats	Inhibiting glucose uptake and improving ultrafiltration	[156]
	Sitagliptin	DPP4	A chlorhexidine gluconate (CG)-induced PF model of rats	Reversing the MMT process, angiogenesis, oxidative stress, and inflammation	[112]
	Exendin-4	GLP-1R	A CG-induced PF model of rats	Suppressing DPP-4 activity, the TGF/Smad3 pathway, the NF-κB pathway, and MMT	[112]
Glycolysis	2-deoxyglucose (2-DG)	Glycolytic enzymes	A mouse PF model induced by high-glucose PDFs and an in vitro model (primary HPMC and MeT-5 A cell line) induced by TGF-β1	Blocking hyperglycolysis, MMT, and the development of peritoneal fibrosis	[48]
	microRNA (miR-26a, miR-21a, miR-200a)	Glycolytic enzymes	A mouse PF model induced by high-glucose PDFs and a cell model (primary HPMC and MeT-5 A cell line) induced by TGF-β1	Suppressing hyperglycolysis, MMT, and fibrogenesis	[48]
The polyol pathway	Zopolrestat	Aldose reductase (AR)	A chronic PD model of rats	Decreasing fibrosis and angiogenesis during chronic peritoneal exposure	[61]
	Sorbinil and sodium pyruvate	TGF-β1 and MCP-1	A primary HPMC model induced by HG	Reducing sorbitol accumulation and hyperosmolality, and preventing peritoneal membrane damage	[62]
Lipid deposition	Simvastatin	RhoA and Rac1	A high glucose-based PDFs induced PD model of rats and an in vitro model of primary HPMCs	Inhibited MMT changes	[124]
	Fluvastatin	SGK1	An in vitro model of cultured HPMC induced by high-glucose PDFs	Decreasing the expression of SGK1 and fibronectin, and meliorating the progression of PF	[157]
	Rapamycin	LDLr	A mouse PD model and a cultured HPMC model induced by high-glucose PDFs	Improving the disruption of intracellular lipid homeostasis	[66]
	Rosiglitazone	PPAR-γ	A mouse PF model induced by high-glucose PDFs and a primary HPMC model induced by TGF-β1	Reducing the accumulation of AGEs and inflammation, and preserving the mesothelial cells monolayer	[158]
	Valsartan	LDLr	A PF model of mice and a HPMC line induced by high glucose	Decreasing intracellular RAS activity, improving lipid homeostasis, and reducing ECM accumulation	[40]
	AT2 siRNA	AT1/LOX-1	A cell (HMrSV5 cell line) model induced by high glucose	Blocking LOX-1, reversing ox-LDL deposition, and ameliorating ECM accumulation	[76]
	GSK343	EZH2/ Klotho	A cell (HMrSV2 cell line) model induced by high glucose	Reducing lipid deposition, peritoneal fibrosis, and EMT	[39]
FAO	C75	CPT1A	Mouse PD models induced by high-glucose PDFs and cell models (primary HPMC and Met5A cell line) induced by TGF-β1	Restoring FAO, reversing the profibrotic phenotype in PMCs, and reducing PF	[45]
Mitochondrial dysfunction	Metformin	AMPK/PGC-1α	A mouse PF model induced by high-glucose PDFs	Improving mitochondrial morphological manifestations, inhibiting apoptosis of PMCs, and alleviating PF	[151]

Table 1 (continued)

Targeting strategies	Drugs/compounds	Targeting protein	Animal/cell models	Mechanism/Intervention effects	References
	mitoTEMPO, BAY-117,085, and resveratrol	mtROS, NF-κB, and IL-1β	In vitro models of primary HPMCs and mesothelial cell line (Met5A cell line)	Allowing the maintenance of a healthy mitochondrial population and protecting PMCs from inflammatory injury	[23]
	Astragalus Total Saponins (ATS)	PGC-1α/NRF1/TFAM	A rat PD model and an incubated HPMC model induced by high-glucose PDFs	Promoting mitochondrial synthesis and inhibiting apoptosis	[152]
	Astaxanthin (AST)	NF-κB	An in vitro model of temperature-sensitive mesothelial cells (TSMCs cell line) induced by HG	Attenuating glucose-induced ROS from mitochondria, inflammatory cytokine production, NF-κB activation, and EMT	[153]
	Mitochonic acid-5 (MA-5)	TGF-β/MCP1	A CG-induced PF model of mice	Restoring mitochondrial function, and ameliorating chlorhexidine gluconate-induced PF	[154]

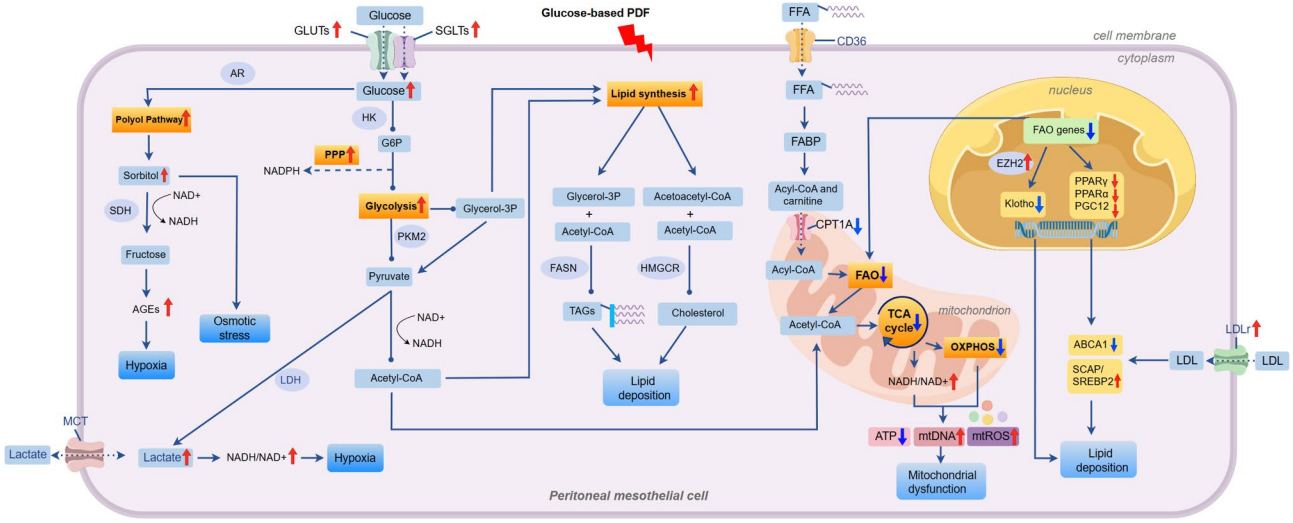


Fig. 1 Metabolic reprogramming in PMCs during PD. Long-term PD induces metabolic reprogramming as an adaptive response to high-glucose PDFs. This involves alterations in glucose metabolism, characterized by enhanced activity of glycolytic, polyol, pentose phosphate pathways, alongside OXPHOS inhibition. Subsequently, upregulation of intracellular damage factors and a considerable increase in the NADH/NAD + ratio exacerbate cellular pseudohypoxia, injury, and death. Concurrently, lipid metabolism reprogramming occurs due to impaired efflux, leading to lipid deposition and lipotoxicity injury. Impaired FAO affects mitochondrial function and cellular energy metabolism balance. FAO, fatty acid oxidation; OXPHOS, oxidative phosphorylation; PD, peritoneal dialysis, PDF, peritoneal dialysis fluid

high-glucose PDFs exacerbates cellular hypoxia and damage, ultimately resulting in PF and ultrafiltration failure.

OXPHOS

Under physiological conditions, glucose undergoes aerobic degradation processes, including the TCA and OXPHOS, ultimately converting it into H_2O and CO_2. Mitochondrial OXPHOS drives ATP production through the respiratory electron transport chain [55]. However, high-glucose environments inhibit mitochondrial OXPHOS, increase glucose consumption, enhance glycolysis, and disrupt lipid metabolism, resulting in a substantial increase in the cellular NADH/NAD + ratio [47]. Similarly, cellular pseudohypoxia induced by high-glucose PDFs leads to the shutdown of mitochondrial OXPHOS. Thus, high-glucose PDFs impair normal mitochondrial OXPHOS and induce the metabolic reprogramming of PMCs.

Impaired mitochondrial OXPHOS primarily arises from high-glucose PDF-induced mitochondrial dysfunction, leading to PMC injury and PF [24, 56, 57]. High-glucose PDFs causes pathological damage to mitochondria of PMC via various mechanisms, including TCA cycle enzyme deficiency, mitochondrial DNA damage, mitochondrial reactive oxygen species (mtROS) accumulation, and mitochondrial membrane damage, thereby inhibiting mitochondrial respiration and OXPHOS [23, 24, 48]. Clinical peritoneal samples from patients on continuous ambulatory peritoneal dialysis further support this, demonstrating that high-glucose PDFs may promote toxic free radical production during mitochondrial metabolism in PMCs, resulting in cumulative mitochondrial

DNA damage [58, 59]. Moreover, mitochondrial dysfunction plays a considerable role in PF progression through tumor necrosis factor-α-induced cyclooxygenase-2 expression, prostaglandin E2 production, and activation of NLRP3 inflammasomes in PD-related PF [23, 60]. Mitochondrial dysfunction and impaired OXPHOS represent the vital causes of high-glucose PDF-induced PMC injury, highlighting their critical role as potential targets for PF treatment.

Polyol pathway

The polyol glucose metabolic pathway also exerts potentially deleterious effects on the peritoneum during long-term PD [61, 62]. The polyol pathway, a high-glucose-driven pathway, involves the reduction of NADPH-dependent glucose to sorbitol by aldose reductase (AR), followed by NAD+-dependent oxidation to fructose by sorbitol dehydrogenase [63, 64]. Under physiological conditions, most glucose is phosphorylated to glucose-6-phosphate (G6P) by hexokinase (HK), with a minor portion of non-phosphorylated glucose entering the polyol pathway, which has been attributed to the lower affinity of AR for glucose compared to that of HK [65]. However, a substantial increase in glucose concentration enhances polyol pathway activation to increase intracellular glucose metabolism [22]. The polyol pathway increases the intracellular NADH/NAD + ratio, exacerbating cellular hypoxia and enhancing the accumulation of intracellular ROS, ultimately leading to high-glucose-induced oxidative stress [22, 64]. Additionally, the polyol pathway induces the intracellular accumulation of poorly permeable sorbitol, increasing cell osmolarity and hypertonicity and resulting in cellular edema [65].

Moreover, the enhanced polyol pathway exacerbates PMC injury and enhances PF development through various downstream molecular mechanisms. In vitro studies have demonstrated that exposure to high-glucose PDFs leads to the activation of the polyol pathway in PMCs, thereby impairing cell function and causing injury via the upregulation of TGF-β1 and MCP-1 synthesis [62]. Conversely, studies conducted in rats have revealed that inhibition of the polyol pathway using AR activity inhibitors attenuates PF and angiogenesis [61]. Overall, abnormal activation of the polyol pathway represents a potential risk factor for PF in patients undergoing PD.

Lipid metabolism

Recent reports have implicated lipid metabolism in PF [39, 66]. Long-term exposure to high-glucose PDFs disrupts normal lipid metabolism in PMCs, with impaired fatty acid oxidation (FAO) and abnormal lipid deposition leading to imbalances in cellular energy metabolism [39, 66]. Triglycerides mainly consist of free fatty acids (FAs). Notably, FA homeostasis is maintained through their synthesis, transport, and metabolism. FA influx is mediated by increased expression of CD36, known as the scavenger receptor B2 [67]. Enhanced *de novo* FA synthesis is mediated by SREBP-1 C, FASN, and SCD-1 [68]; and β-oxidation of FAs is mediated by the rate-limiting enzyme carnitine palmitoyltransferase 1 A (CPT1A) [69]. Alternatively, cholesterol synthesis is regulated by HMGCR, while its efflux is mediated by ABCA1 and ABCG1 [70]. Abnormalities in these processes can result in the accumulation of intracellular lipids, leading to lipotoxic injury [13, 71]. Thus, disruption of lipid homeostasis represents an important mechanism involved in the development of high-glucose PDF–induced fibrosis.

High-glucose PDFs may promote PF by dysregulating lipid metabolism through various molecular pathways [13, 38, 39]. FAO, a major source of ATP and NADPH predominantly observed in mitochondria, is impaired in PMCs, promoting the progression of PF [45, 72]. Nonetheless, restoration of mesothelial FAO in PD animal models increases ATP and NADPH production, reverses mitochondrial superoxide production, maintains mitochondrial homeostasis, and preserves peritoneal structure during PD [45, 73]. In a peritonitis mouse model, the upregulation of FAO during inflammation promoted the resolution of inflammation by providing sufficient energy [74]. Thus, FAO plays an important functional role in PD-associated PF and may be a promising therapeutic target. High glucose levels induce the abnormal expression of angiotensin II type 2 receptor (AT2R), mTOR complex 1 (mTORC1), and Klotho, interfering with lipid metabolism. This leads to apoptosis, inflammation, and oxidative stress, which, in turn, activate the downstream TGF-β1 signaling pathway and MMT, ultimately leading to fibrosis [13, 75]. Moreover, high-glucose stimulation disrupts lipid metabolism through the activation of the sterol-regulatory element-binding protein-2/cleavage-activating protein pathway (SCAP/SREBP-2) and increased expression of HIF-1α, thereby promoting angiogenesis and PF [13, 66]. Therefore, restoring normal lipid metabolism in PMCs may serve as a novel therapeutic strategy for improving peritoneal injury.

Abnormal lipid deposition can cause lipotoxic damage and, thus, serves as an important contributor to PD-related fibrosis. High-glucose-induced lipotoxicity can directly exacerbate the expression of extracellular matrix (ECM) components, leading to the loss of epithelial characteristics in human peritoneal mesothelial cells (HPMCs), ultimately resulting in fibrotic changes [76]. In vitro and in vivo studies have revealed that Klotho, a key gene involved in lipid metabolism, promotes MMT and PF induced by high glucose PD [39]. Moreover, the histone lysine methyltransferase, enhancer of zeste homolog 2 (EZH2) can directly regulate Klotho expression through epigenetic modifications; thus, inhibiting EZH2

expression attenuates Klotho-mediated lipid deposition and PF [39]. Additionally, in vitro studies revealed that inhibition of AT2R promotes lipid disorder-mediated ECM deposition by upregulating lectin-like oxidized lipoprotein receptor-1 (LOX-1), resulting in intracellular deposition of lipid droplets in HPMCs [76]. Furthermore, in vitro and in vivo studies have demonstrated that high-glucose PDFs reduces ABCA1 expression through inhibition of peroxisome proliferator-activated receptor γ (PPARγ) activity, impairing lipid efflux and promoting lipid deposition [39]. Alternatively, CD36 acts as a metabolic regulator by mediating lipid sensing and transport. Notably, high glucose-induced upregulation of CD36 may lead to metabolic disorders by downregulating the PPARγ pathway; however, there are limited studies investigating these interactions in PD models.

The intricate and close relationship between lipid metabolism and mitochondria adversely affects mitochondrial function when lipid disorders occur [77, 78]. Notably, a high-glucose environment induces dysregulation of mitochondrial oxidative metabolism and increases mtROS generation, impairing mitochondrial lipid utilization and promoting lipid accumulation [79]. Lipotoxicity induces mitochondrial metabolic stress and dysfunction in diabetic mouse models, triggering the release of mtDNA and activation of the cGAS-STING pathway, ultimately promoting inflammation and apoptosis [80]. Disturbances in lipid metabolism may also potentially impede mitochondrial dynamics, leading to reduced mitochondrial function in PMCs.

Overall, lipid metabolism disorders induced by high-glucose PDFs contribute to PF progression, involving impaired lipid metabolism processes such as FAO, lipid efflux, and lipid deposition in PMCs.

Other metabolic alterations

In addition to glucose and lipid metabolism, other metabolic pathways such as amino acid metabolism, ketone body (KB) metabolism, and pentose phosphate pathway (PPP) play important roles in metabolic reprogramming [81–83] However, there has been limited research in the field of PD. A thorough investigation into the role of these metabolic processes can provide a better understanding of the pathophysiological process of PF and offer more effective solutions for clinical treatment.

The PPP, branching off from glycolysis, is considered the first step in glucose metabolism, serves as a major source of NADPH, and is a vital component in cell biosynthesis, metabolism, and cellular redox homeostasis [84]. Notably, high glucose levels can directly stimulate increased cellular glucose uptake, leading to an increase in the metabolic substrate G6P, thereby increasing its flow into the PPP [85]. Previous studies have confirmed that PPP plays a crucial role in combating oxidative stress and maintaining metabolic and redox homeostasis by reducing NADP to NADPH [86]. Therefore, PPP activity may rise in response to prolonged exposure to high-glucose PDFs as a means to regulate oxidative stress. However, comprehensive studies investigating PPP in the context of PD are limited; therefore, further studies are needed to confirm its involvement in PF.

Research into the mechanisms underlying amino acid metabolism in PMCs is lacking. A widespread loss of peritoneal proteins and amino acids has been observed in patients undergoing PD, potentially due to the use of high-glucose-based PD strategies [87]. Amino acid-based PD techniques appear to better preserve the ultrastructure, viability, and protein biosynthesis of HPMCs than conventional glucose-based PD [88, 89]. Notably, glutamine metabolism plays a potential protective role against PF [90, 91]. Glutamine, the most abundant free amino acid in the human body, contributes to DNA, RNA, and protein synthesis. Moreover, it promotes ATP production through OXPHOS [92]. A human clinical trial has revealed that glutamine deficiency during PD is associated with peritoneal pathological mechanisms, including impaired stress response and impaired host defense [91]. However, the precise mechanism underlying the protective effects of amino acid metabolism remains unclear and requires further investigation.

Recent advancements in our understanding of KB metabolism have revealed that KBs serve as alternative sources of ATP and regulate protein post-translational modifications, modulation of inflammation, and regulation of oxidative stress [93, 94]. Furthermore, KBs serve as important regulators of mitochondrial and nuclear metabolism and engage in complex competitive interactions with other OXPHOS substrates including glucose and FAs [95]. Given the pleiotropic effects of KBs, we postulate that KB metabolism may play an important role in the metabolic reprogramming of PMCs. However, evidence to support this hypothesis is currently lacking.

Therapeutic targets

The role of high-glucose PDFs in PF development is evident; however, effective interventions are still lacking. Nonetheless, glucose-based PDFs remains the most widely used type of PD, primarily due to cost limitations, challenges in promoting the use of biocompatible PDFs, and issues with the clinical translation of existing drugs. Metabolic abnormalities in PMCs can induce pathological changes, such as inflammation, oxidative stress, lipid deposition, and fibrosis. Thus, early interventions targeting glucose metabolism, mitochondrial function, and lipid metabolism may prove more efficacious than addressing individual downstream events. Various drugs and compounds aimed at modulating glycolysis, lipid metabolism, and other metabolic processes have shown

promise in ameliorating PMC damage and inhibiting PF progression (Table 1).

Targeting glucose metabolism

Glucose metabolism plays a crucial role in the pathogenesis of PF. Recent studies have explored strategies to impede PF progression by reducing glucose absorption, inhibiting glycolysis, and decreasing the NADH/NAD + ratio. Numerous studies have highlighted the potential of targeting glucose metabolism to inhibit PF progression, with various metabolism-targeting drugs and compounds showing promise in the mitigation of peritoneal injury and fibrosis. Nonetheless, further investigation is needed before using these drugs as novel therapeutic strategies for PF (Fig. 2).

Targeting glucose absorption

Several anti-diabetic agents that reduce peritoneal glucose absorption exert protective effects against PF. The expression of glucose transporters in PMCs is influenced by glucose concentration, affecting the peritoneal response to inflammation, ECM production, and PF progression [96, 97]. Inhibitors of GLUT-1 and sodium glucose cotransporter-2 (SGLT-2) are effective inhibitors of glucose absorptions. In preclinical studies, GLUT-1 inhibitors have demonstrated efficacy in targeting glycolysis and inhibiting glucose uptake [98]. However, their clinical application requires further development of these drugs and compounds.

Conversely, SGLT-2 inhibitors, such as empagliflozin, dapagliflozin, and canagliflozin, have been widely used in clinical practice. SGLT-2 inhibitors hold the potential to reduce glucose absorption during PD, thereby attenuating MMT, fibrosis, and ultrafiltration failure through various mechanisms, including inhibiting SGLT-2 activity [99], alongside Nrf2/HO-1 [100], HIF [52], and TGF-β/Smad signaling [101]. However, the peritoneal protective effect of SGLT-2 inhibitors remains debatable. A study conducted on a rat model of acute PD determined that SGLT-2 inhibitors failed to reduce glucose uptake or increase ultrafiltration [102]; conversely, other studies using animal models of chronic PD have demonstrated

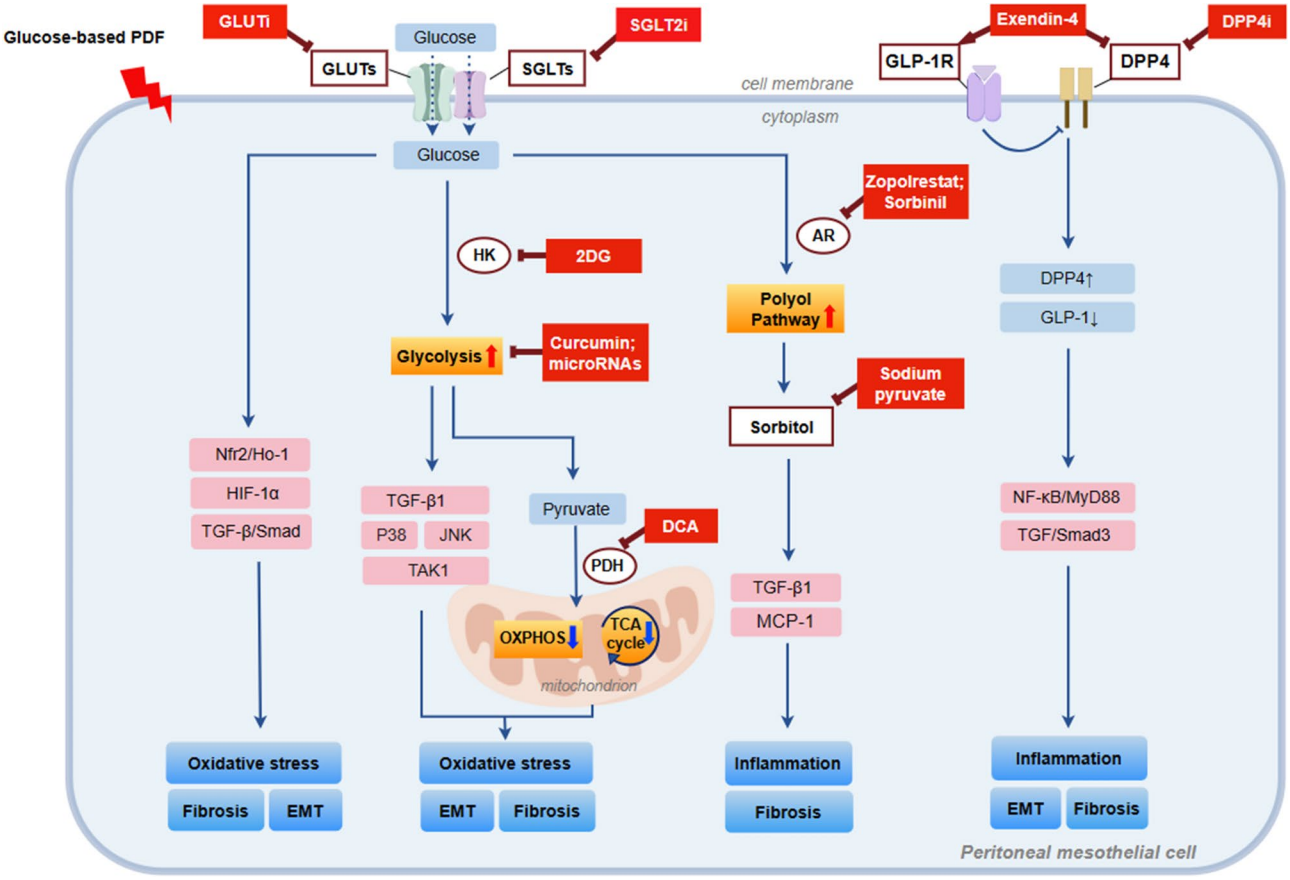


Fig. 2 Targeting glucose metabolism in PMCs. Potential therapeutic strategies include targeting inhibiting glucose uptake using SGLT-2, GLUT-1, DPP-4, or GLP-1R inhibitors, hyperglycolysis inhibition using 2-DG, curcumin, or specific microRNAs (microRNA-26a and microRNA-200a), polyol pathway inhibition, and sorbitol clearance using zopolrestat (an AR inhibitor), sorbinil, or sodium pyruvate. 2-DG, 2-deoxyglucose; AR, aldose reductase; PMC, peritoneal mesothelial cell; SGLT-2, sodium glucose cotransporter-2; GLUT-1, glucose transporter type 1; DPP-4, Dipeptidyl peptidase-4; GLP-1R, Glucagon-like peptide 1 receptor

that SGLT-2 inhibitors improve PF and function [17, 99, 101]. Therefore, further research is needed to clarify the peritoneal protective mechanisms of SGLT-2 inhibitors and determine whether these discrepancies in acute or chronic peritoneal injury responses are accurate. Recent studies have shown that SGLT − 2 inhibitors not only affect glucose metabolism but also have a significant impact on lipid and other related metabolic pathways. They positively influence lipid metabolism through multiple mechanisms, including lowering blood lipids, improving the ratio of low-density lipoprotein (LDL) particles, regulating lipid synthesis and transport, promoting fatty acid oxidation, and ketone body production [103–105]. They also enhance mitochondrial function, reduce oxidative stress, and increase mitochondrial synthesis [106, 107]. Moreover, recent research has reported that they can improve glycine metabolism [108]. The findings indicate that the effects of SGLT-2 inhibitors on peritoneal metabolism may extend beyond the scope of glucose metabolism. However, research on their impact in patients undergoing PD is still preliminary, necessitating further investigation.

In addition to glucose transporter proteins, novel antidiabetic medications, such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, may improve the pathophysiology of PD-associated fibrosis. DPP-4, a type II integral membrane glycoprotein with serine peptidase activity, primarily targets the enteric insulin GLP-1 [109]. DPP4 inhibitors, such as sitagliptin and linagliptin, exhibit hypoglycemic effects and demonstrate cytoprotective pleiotropic effects, including anti-inflammatory and antifibrotic actions [110, 111]. Previous studies have identified DPP4 as a substantial factor associated with PF [112]. Notably, in vitro and in vivo experiments have revealed that DPP4 inhibitors and exendin-4 can mitigate PD dysfunction and exhaustion by suppressing DPP-4 activity, the TGF/Smad3 pathway, the NF-κB pathway, and MMT [112]. Therefore, approaches targeting DPP-4 are potential therapeutic strategies for PF.

Targeting the polyol pathway

The polyol pathway plays a deleterious role in the peritoneum during long-term PD. Studies have indicated that the use of polyol pathway inhibitors can help reduce glucose-mediated peritoneal damage and enhance the long-term survival of PMCs [61, 62]. For example, zopolrestat, an AR inhibitor, alters the NADH/NAD + ratio by inhibiting AR activity in the polyol pathway, thereby impeding the conversion of glucose to sorbitol. Zopolrestat reportedly reduces peritoneal angiogenesis and fibrosis in a rat model of PF induced by high-glucose dialysate [61]. However, zopolrestat is not currently available for human use owing to its side effects. Nonetheless, other drugs have also been found to target the polyol pathway to delay PF progression, including sorbinil and sodium pyruvate [62]. In vitro studies have demonstrated that sorbinil and sodium pyruvate can alleviate PMC damage by inhibiting high-glucose–induced intracellular TGF-β1 and MCP-1 synthesis, as well as by enhancing intracellular sorbitol clearance [62].

Pyruvate contributes to improved sorbitol clearance, therefore, some studies have investigated methods for delaying PF progression based on pyruvate metabolism. Pyruvate dehydrogenase (PDH), a key enzyme that couples glycolysis with the Krebs cycle, has emerged as an important target for this therapeutic approach, with its anti-fibrotic effects being closely linked to its activity [113, 114]. Dichloroacetic acid (DCA), a potent inhibitor of PDH kinase, modulates the transfer of pyruvate to the Krebs cycle, thereby maintaining PDH activity and increasing intracellular energy [114]. Notably, DCA has demonstrated high efficacy in inhibiting fibrosis [113, 115]. Additionally, L-carnitine exerts anti-fibrotic effects by maintaining PDH activity through the reduction of PDH kinase activity and mitochondrial acetyl-CoA production [7, 116]. However, the efficacy of these drugs requires further validation.

Targeting glycolysis

Targeting glycolysis has also emerged as a promising therapeutic strategy for the treatment of PF. Notably, 2-deoxyglucose (2-DG), a glucose derivative that inhibits glycolysis [117], directly blocks hyperglycolysis by inhibiting HK activity, thereby suppressing the TGF-β1–induced fibrotic cell phenotype and subsequent PF in mice [48]. Additionally, curcumin has also been identified as a drug that targets glycolysis [118, 119]. Curcumin, a diketone derived from plant rhizomes, possesses anti-inflammatory, antimicrobial, and anticancer properties [119, 120]. Curcumin reportedly downregulates the expression and activity of HK, phosphofructokinase-2, glucose transporter type 4 (Glut4), and monocarboxylate transporter 4 (MCT4) in hepatic stellate cells [121]. Moreover, prior studies have confirmed the substantial protective effects of curcumin against glucose PD effluent–induced MMT and PF [122, 123]. These findings suggest that curcumin inhibits several steps in the glycolytic pathway [121]. Furthermore, certain microRNAs found in the peritoneum, such as microRNA-26a and microRNA-200a, target hyperglycolysis and fibrotic signaling in PMCs [48]. However, the effectiveness and safety of these methods require further investigations.

Targeting lipid metabolism

Recent studies have established that lipotoxicity mediates the progression of PF [39, 124]. Consequently, targeting lipid metabolism has become a key focus of current

research. Medications aimed at improving lipid metabolism and identifying novel targets may represent new therapeutic strategies to slow the progression of PD-related fibrosis (Fig. 3).

Targeting lipid deposition

Statins are lipid-lowering drugs that inhibit cholesterol synthesis by competitively inhibiting 3-hydroxy-3-methyl-glutaryl CoA (HMG-CoA) reductase, thereby blocking the conversion of HMG-CoA to methylglutarate [125]. Several statins, including atorvastatin, pitavastatin, and simvastatin, exhibit anti-fibrotic effects [126–128]. In both in vivo and in vitro PD models, statins inhibit MMT via the mevalonate pathway, thereby preserving peritoneal integrity and inhibiting PF [124]. Additionally, statins may alleviate peritoneal inflammation, fibrosis, and angiogenesis by modulating glutathione reductase activity and the TGF-β pathway [129]. However, prolonged use of statins may increase insulin resistance, disrupt lipid metabolism, and exacerbate inflammation and fibrosis [130, 131]. Moreover, simvastatin did not attenuate PF in a rat model of PD [132]. Thus, the anti-fibrotic effects of statins remain controversial, and further studies are required to determine their potential as therapeutic strategies in PD.

Rapamycin, a commonly used immunosuppressant targeting mTOR, has demonstrated anti-fibrotic effects and improves peritoneal membrane transport function in PD models [133, 134]. Recent studies have revealed its ability to inhibit intracellular lipid accumulation by blocking mTORC1 activity, thereby regulating lipid homeostasis and reversing low-density lipoprotein receptor (LDLr) dysfunction. Consequently, rapamycin exhibits a clear protective effect against lipid disorder-mediated PF [13, 135]. Furthermore, rapamycin can enhance intracellular lipid homeostasis by inhibiting cellular lipid uptake and increasing cholesterol efflux, thereby exerting a substantial protective effect against high-glucose PDF-induced fibrosis [66]. However, the safety and efficacy of rapamycin remain unclear.

PPARγ, an important nuclear receptor that controls the transcription of specific genes, is crucial in the interaction between lipid and glucose metabolism [136, 137]. Inhibiting PPARγ activity disrupts intracellular lipid efflux, leading to lipid droplet deposition and subsequent lipid disorder–mediated peritoneal injury and fibrosis [66]. Several studies using animal models of PD have revealed that the PPAR-γ agonist, rosiglitazone, protects peritoneal integrity and reduces PF by mitigating the accumulation of AGEs and inflammation [138,

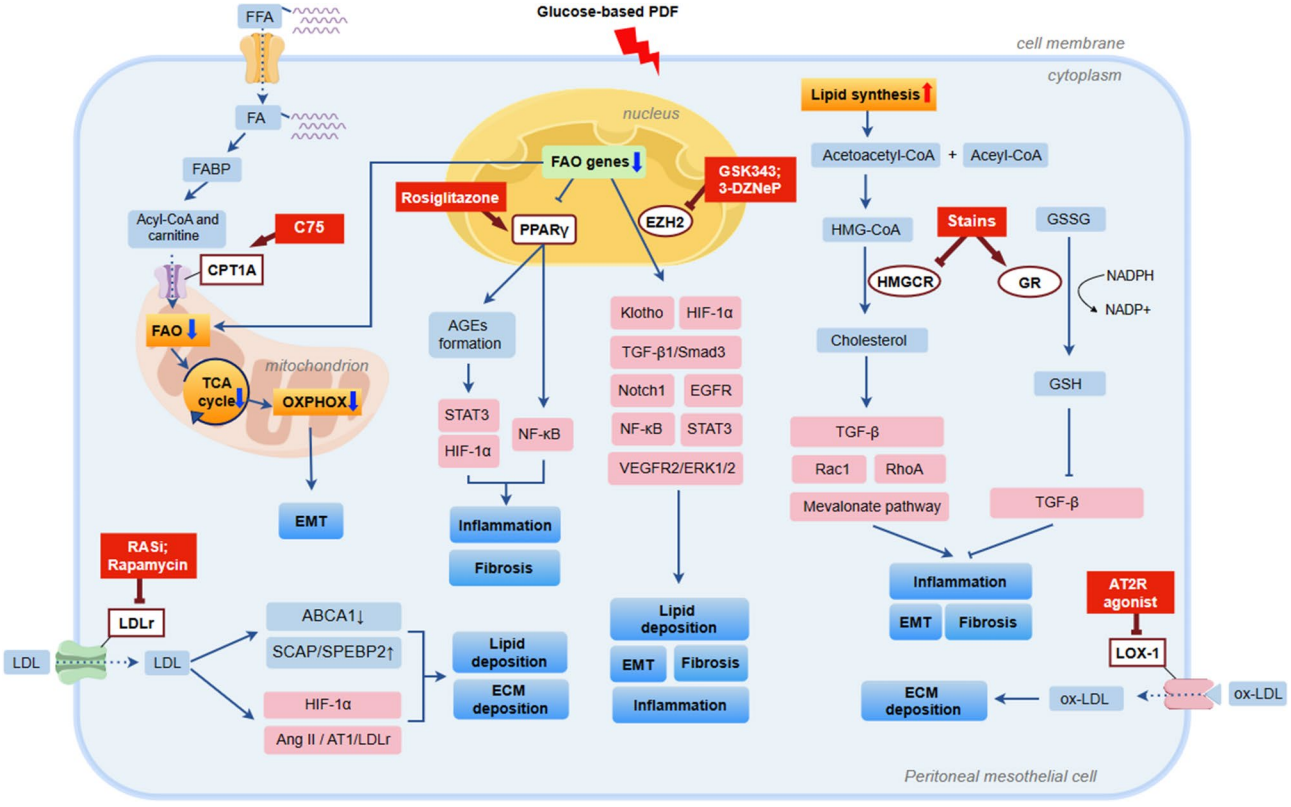


Fig. 3 Targeting lipid metabolism in PMCs. Potential therapeutic strategies include restoring and enhancing FAO using CPT1A agonists (C75), inhibiting lipid synthesis and uptake, and promoting cholesterol efflux using agents, such as rapamycin, rosiglitazone (a PPAR-γ agonist), and RAS blockers. FAO, fatty acid oxidation; PMC, peritoneal mesothelial cell; RAS, renin-angiotensin system

139]. Additionally, PPARγ can inhibit the expression of GLUT1, thereby maintaining metabolic homeostasis and alleviating high-glucose PDF-induced PF [140, 141]. Given its dual role in both glucose and lipid metabolism, PPARγ stands out as a potentially ideal target for treating high-glucose-induced PF, providing further elucidation of its mechanism of action.

Abnormal activation of RAS has been implicated in lipid disorder-mediated PF [40, 76]. Specifically, RAS activation is crucial in regulating the LDLr pathway [40]. In vitro studies have shown that increased intracellular RAS activity impairs lipid homeostasis by disrupting the LDLr pathway and promoting ECM accumulation in HPMCs [40]. Moreover, AT2Rs ameliorate lipid disturbances and attenuate ECM accumulation in HPMCs by suppressing lectin-like oxidized LOX-1 [76]. Therefore, RAS blockers may maintain lipid homeostasis and protect against peritoneal injury.

EZH2 and Klotho also represent potential targets for modulating lipid metabolism in the treatment of PF [39, 142–144]. Specifically, EZH2 promotes lipid deposition and fibrosis, whereas Klotho is involved in lipid metabolism and possesses anti-fibrotic properties [39, 143, 144]. EZH2 inhibitors, such as GSK343 and 3-deazaneplanocin A, attenuate high-glucose-induced lipid deposition, MMT, angiogenesis, and PF [142, 145]. Furthermore, EZH2 inhibition mitigates lipid deposition and PF by suppressing EZH2 expression and restoring Klotho expression [39]. Klotho protects the peritoneum from PF by down-regulating the Wnt/β-catenin signaling pathway in a PD mouse model [144].

Targeting FAO restoration

Dysfunctional FAO in mesothelial cells promotes PD-associated PF; thus, enhancing FAO may be a therapeutic approach for PF [45]. The rate-limiting step in FAO is the translocation of long-chain FAs into mitochondria via CPT1A [69]. Notably, reduced expression of CPT1A has been associated with fibrosis [146, 147]. A recent study demonstrated that treatment of PD mice with a CPT1A activator (C75) restored FAO, reversed the pro-fibrotic phenotype in mesothelial cells, and reduced PF by upregulating CPT1A expression [45]. Consequently, CPT1A has emerged as a promising target for PF treatment. Alternatively, adipsin, stilbenes, and resveratrol metabolites are compounds known to enhance mitochondrial energy metabolism and increase FAO, potentially serving as therapeutic agents for PF [148–150]. However, further research is needed to validate their efficacy as PF treatments.

Targeting mitochondrial dysfunction

Preserving mitochondrial integrity may be a novel therapeutic approach for protecting the peritoneum from PD-induced fibrosis [23, 24]. For example, mitoTEMPO (an mtROS scavenger), BAY-117,085 (an NF-κB inhibitor), and resveratrol (an anti-inflammatory antioxidant) alleviate mitochondria-induced inflammation in mesothelial cells by protecting mitochondrial function [23]. Moreover, Wu et al. [151] found that proliferator-activated receptor-γ coactivator (PGC)-1α overexpression or metformin treatment can attenuate PF by preserving mitochondrial morphology and preventing damage to mitochondrial structure through activation of the AMPK-PGC-1α pathway. Astragalus total saponins (ATS) alleviate PF by promoting mitochondrial synthesis and inhibiting PMC apoptosis [152]. Alternatively, astaxanthin can eliminate glucose-induced mtROS in PMCs and inhibit MMT during PD, thereby demonstrating antioxidant and anti-inflammatory activities [153]. Furthermore, mitochonic acid-5 (MA-5) restored mitochondrial function, by inhibiting macrophage infiltration and oxidative stress, thus relieving PF in mice [154]. Ultimately, these findings suggest that targeting the mitochondria is a promising therapeutic approach for PF (Fig. 4).

Discussion

The metabolic reprogramming of PMCs is a crucial event in the progression of PD-associated PF. Initially serving as an adaptive response to counteract damaging effects of high-glucose PDFs, metabolic pattern shifts caused by high glucose can lead to metabolic disorders, resulting in cellular damage, inflammation, and eventual cell death, forming the so-called "honey trap." Consequently, long-term exposure to hyperglycemic environments induces sustained metabolic reprogramming, trapping PMCs in the "honey trap," impairing the cells' ability to adapt to physiological conditions and ultimately resulting in chronic peritoneal inflammation and fibrosis.

Despite increasing understanding, substantial breakthroughs in the prevention and treatment of PF remain elusive. Recent studies have highlighted the correlation between PMC metabolic reprogramming and PD-related fibrosis, offering a novel direction for the treatment of PF. Nonetheless, several challenges remain in the development of effective therapeutic strategies for PF. A primary concern is the predominant focus on PMCs in current research, leaving uncertainties regarding potential metabolic alterations in other peritoneal cells types during PD, such as fibroblasts, macrophages, endothelial cells, T cells, and adipocytes. Therefore, exploring the role and mechanisms of metabolic dysfunction in the entire peritoneum in future clinical and translational research, including investigating the role of metabolic reprogramming in other peritoneal cells during PD treatment, is crucial.

Moreover, metabolic reprogramming is a complex process that involves multiple metabolic pathways. While

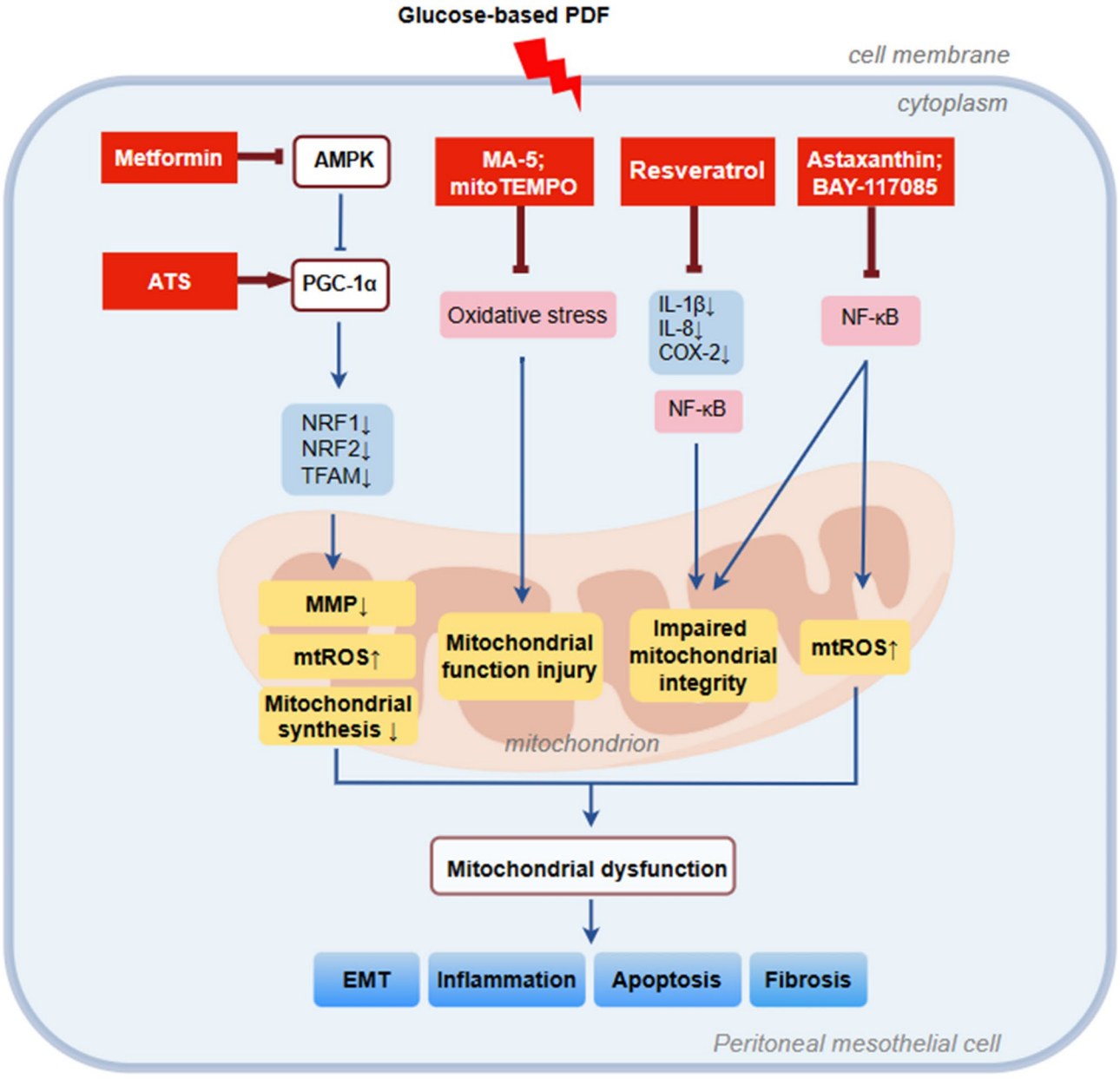


Fig. 4 Targeting mitochondrial function in PMCs. Strategies include using mitoTEMPO (a mitochondrial ROS scavenger), BAY-117,085 (an NF-κB inhibitor), and resveratrol (the natural anti-inflammatory antioxidant) to protect and reduce mitochondrial damage. Alternatively, ATS promotes mitochondrial synthesis, while AST and MA-5 inhibit mitochondrial oxidative stress, protecting mitochondrial function. AST, astaxanthin; ATS, astragalus total saponins

existing studies predominantly investigating PF have focused on glucose and lipid metabolism, the mechanisms and regulation of other metabolic processes, such as amino acid metabolism, ketone body metabolism, and the PPP, remain unclear. Clarifying the specific interactions between multiple these metabolic processes also require further elucidation. Finally, while interventions targeting metabolism have shown promise in animal and cellular experiments, clinical translation of these strategies remains limited. Furthermore, some of the existing clinical drugs possess potential adverse and off-target effects. Therefore, the clinical application of drugs and compounds that target metabolism requires further investigation and validation to ensure their safety and efficacy in PF management.

Conclusions and perspectives

The metabolic pathways discussed in this paper represent novel endogenous targets closely related to PMC homeostasis and PD-associated fibrosis. While previous research predominantly focused on cellular MMT, apoptosis, and death, recent studies have shifted toward

investigating the metabolic mechanisms of PMCs. Notably, the balance between glucose metabolism, lipid metabolism, and mitochondrial respiration is increasingly recognized as crucial for cellular energy production and homeostasis maintenance [53]. Notably, preclinical studies investigating several anti-fibrotic drugs targeting metabolic pathways are currently underway [155], sparking a growing interest in exploring the restoration of metabolic homeostasis in mesothelial cells as a potential therapeutic approach for PD-associated fibrosis. Although recent studies have identified a strong relationship between PMC metabolism and PF, research on metabolic reprogramming in PMCs is still in its early stages. In conclusion, ongoing research into metabolic reprogramming offers a promising avenue for enhancing our understanding of the mechanisms driving PD-related fibrosis and may ultimately lead to the development of novel therapeutic strategies aimed at treating PF.

Abbreviations

PD	Peritoneal dialysis
SRD	End-stage renal disease
PMCs	Peritoneal mesothelial cells
PDFs	Peritoneal dialysis fluids
AGE	Advanced glycation end products
MMT	Mesothelial–mesenchymal transition
OXPHOS	Oxidative phosphorylation
RAS	Renin-angiotensin system
GLUT-1	Glucose transporter type 1
NADH	Nicotinamide adenine dinucleotide
NAD+	Nicotinamide adenine dinucleotide
NADH/NAD+	Nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide ratio
HIF-1	Hypoxia-inducible factor-1
TCA	Tricarboxylic acid
mtROS	mitochondrial reactive oxygen species
AR	Aldose reductase
G6P	Glucose-6-phosphate
HK	Hexokinase
ROS	Reactive oxygen species
FFAs	Free fatty acids
FAs	Fatty acids
AT2R	Angiotensin II type 2 receptor
mTORC1	mTOR complex 1
SCAP/SREBP-2	Sterol-regulatory element-binding protein-2/cleavage-activating protein pathway
HPMCs	Human peritoneal mesothelial cells
EZH2	Enhancer of zeste homolog 2
LOX-1	Lectin-like oxidized lipoprotein receptor-1
PPARγ	Peroxisome proliferator-activated receptor γ
KB	Ketone body
PPP	Pentose phosphate pathway
SGLT-2	Sodium glucose cotransporter-2
DPP-4	Dipeptidyl peptidase-4
GLP-1	Glucagon-like peptide-1
PDH	Pyruvate dehydrogenase
DCA	Dichloroacetic acid
2-DG	2-Deoxyglucose
CG	Chlorhexidine gluconate
Glut4	Glucose transporter type 4
MCT4	Monocarboxylate transporter 4
HMG-CoA	3-hydroxy-3-methyl-glutaryl CoA
LDL	Low-density lipoprotein
LDLr	Low-density lipoprotein receptor
ATS	Astragalus total saponins
AST	Astaxanthin
MA-5	Mitochonic acid-5
TGF-β1	Transforming growth factor beta 1
PGC	Peroxisome proliferator-activated receptor-γ coactivator
ECM	Extracellular matrix
FAO	Fatty acid oxidation

Acknowledgements
We thank FigDraw (https://www.figdraw.com/) for providing the original material for the figures. We thank the Chongqing Key Laboratory of Precision Diagnosis and Treatment for Kidney Diseases platform for the technical and facility support.

Author contributions
Fang Yu: Formal analysis, Investigation, Visualization, Resources, and Writing-original draft. Jia Chen: Validation and Supervision. Xiaoyue Wang: Investigation, and Visualization. Shihui Hou: Formal analysis and Investigation. Hong Li: Validation and Investigation. Yaru Yao: Validation and Visualization. Yani He: Conceptualization, Supervision, Resources, and Writing-review&editing. Kehong Chen: Project administration, Supervision, Resources, and Writing-review&editing.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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Received: 12 November 2024 / Accepted: 17 February 2025
Published online: 27 February 2025

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