Role of 2-series prostaglandins in the pathogenesis of type 2 diabetes mellitus and non-alcoholic fatty liver disease (Review)

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Abstract. Nowadays, metabolic syndromes are emerging as global epidemics, whose incidence are increasing annually. However, the efficacy of therapy does not increase proportionately with the increased morbidity. Type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) are two common metabolic syndromes that are closely associated. The pathogenic mechanisms of T2DM and NAFLD have been studied, and it was revealed that insulin resistance, hyperglycemia, hepatic lipid accumulation and inflammation markedly contribute to the development of these two diseases. The 2-series prostaglandins (PGs), a subgroup of eicosanoids, including PGD_2, PGE_2, $PGF_{2\alpha}$ and PGI_2, are converted from arachidonic acid catalyzed by the rate-limiting enzymes cyclooxygenases (COXs). Considering their wide distribution in almost every tissue, 2-series PG pathways exert complex and interlinked effects in mediating pancreatic β-cell function and proliferation, insulin sensitivity, fat accumulation and lipolysis, as well as inflammatory processes. Previous studies have revealed that metabolic disturbances, such as hyperglycemia and hyperlipidemia, can be improved by treatment with COX inhibitors. At present, an accumulating number of studies have focused on the roles of 2-series PGs and their metabolites in the pathogenesis of metabolic syndromes, particularly T2DM and NAFLD. In the present review, the role of 2-series PGs in the highly intertwined pathogenic mechanisms of T2DM and NAFLD was discussed, and important therapeutic strategies based on targeting 2-series PG pathways in T2DM and NAFLD treatment were provided.

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Abbreviations: AA, arachidonic acid; Akt, serine/threonine kinase; apoB, apolipoprotein B; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; GSIS, glucose-stimulated insulin secretion; HFD, high-fat diet; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NEFAs, non-esterified fatty acids; NF-κB, nuclear factor-κB; NSAIDs, nonsteroidal anti-inflammatory drugs; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PKA, protein kinase A; PG, prostaglandin; PPAR, peroxisome proliferator-activated receptor; PUFAs, polyunsaturated fatty acids; TNF-α, tumor necrosis factor α; T2DM, type 2 diabetes mellitus; TG, triglyceride; VLDL, very low-density lipoprotein; WAT, white adipose tissue

Key words: prostaglandin, type 2 diabetes mellitus, non-alcoholic fatty liver disease, insulin resistance, hyperglycemia, hepatic lipid accumulation, inflammation

Contents

1. Introduction

Type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD), two common metabolic syndromes, are emerging as global epidemics, whose incidence are rising annually (1,2). T2DM is predominantly characterized by an assembly of hyperglycemia, hyperinsulinemia, insulin resistance and insulin deficiency (3). According to the Diabetes Atlas 9th edition published by the International Diabetes Federation (IDF), 463 million adults aged 20-79 years are suffering from diabetes mellitus worldwide, with the prevalence of diabetes mellitus in that age group being ~9.3%, and the total number of diabetic patients predicted to rise to 700 million (10.9%) by 2045 (1). In total, >90% of

the diabetic patients belong to T2DM, as estimated by IDF. NAFLD, currently the most common chronic liver disease, covers a wide disease spectrum, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), hepatic fibrosis, cirrhosis and hepatocellular carcinoma (HCC), which finally causes liver-associated mortality (4). A meta-analysis on NAFLD epidemiology reported a global prevalence of 25.24% in 2016 (2). In China, the prevalence has risen from 25.4% in 2008-2010 to 32.3% in 2015-2018 (5).

T2DM and NAFLD are closely associated. According to clinical data, the overall incidence of NAFLD is 55.5% among patients with T2DM (6), and NAFLD is an independent risk factor for T2DM, indicating a strong bi-directional relationship between T2DM and NAFLD (7,8). T2DM is a risk factor for progression from simple steatosis to NASH and advanced fibrosis. T2DM is associated with a high morbidity of NASH (9,10). Patients with simple steatosis often have a benign prognosis, whereas NASH can progress to cirrhosis, with patients eventually developing HCC (11,12). The prevalence of HCC is ~5-fold higher when the disease progresses from simple steatosis to NASH, leading to a markedly higher mortality rate (13,14). In addition, the presence of NAFLD in patients with T2DM is highly associated with the incidence of macro- and micro-vascular diabetic complications (15). It is harder to control blood glucose levels in patients with T2DM with NAFLD, compared with patients with only T2DM (16). Both T2DM and NAFLD can be caused by metabolic disorders, and share familiar or even the same risk factors and pathological mechanisms. Although studies have shown that the existing pathogenic mechanisms of T2DM and NAFLD include insulin resistance, hyperglycemia, hepatic lipid accumulation and inflammation (17-19), due to the multifaceted and intricate correlations between these two diseases, the underlying molecular mechanisms require further exploration.

Both T2DM and NAFLD can be largely influenced by dietary structure. The intake of Western diet contributes to the onset and development of T2DM and NAFLD (20-22). A Western diet is mainly characterized by high amounts of saturated fatty acids (such as palmitic acid), simple carbohydrates (corn syrup and fructose), low levels of polyunsaturated fatty acids (PUFAs; n-6 and n-3 PUFAs), and insufficient intake of protein and dietary fibers (22,23). In addition, there is a high intake of n-6 PUFAs (particularly linoleic acid) and a low intake of n-3 PUFAs [such as α-linolenic acid (ALA)] in this dietary pattern among patients with T2DM and NAFLD, which cause a high ratio of n-6/n-3 PUFAs (24). The intake of Western diets results in an increased level of n-6-PUFA-derived arachidonic acid (AA) and subsequent eicosanoid production [particularly 2-series prostaglandins (PGs)], and there is a decreased level of those derivatives from n-3 PUFAs in patients with T2DM and NAFLD (25-27). Decreased n-3 PUFAs, which are partly caused by an impaired ALA desaturation in the liver, can repress fatty acid oxidation and contribute to pro-lipogenic outcome by downregulating peroxisome proliferator-activated receptor-α (PPAR-α); they can also promote lipogenic and glycogenic capacity by upregulating sterol regulatory element-binding protein 1c (SREBP-1c) (24). Furthermore, the downregulation of PPAR-α by n-3 PUFAs depletion activates the nuclear factor-κB (NF-κB) and activating protein 1 in the liver, leading to a pro-inflammatory effect in patients with NAFLD (24). On the other hand, the increased n-6 PUFAs and its derivatives can influence the inflammatory state and disturb glucose and lipid metabolism (28-32). Linoleic acid can alter fatty acid transportation, mitochondrial function, inflammatory responses and oxidative stress by increasing PG release and activating PPAR-γ, interleukin-8 (IL-8) and the NF-κB signaling pathway (30,32). The J2-series PGs can promote adipocyte differentiation by directly activating PPAR-γ (31). Therefore, n-6 PUFAs and n-3 PUFAs exert various vital metabolic effects, and the levels of n-6 and n-3 PUFAs, which can be mediated by similar dietary patterns of T2DM and NAFLD (particularly a Western diet) are important for the pathological development of these two diseases.

As important derivatives of n-6 PUFAs, 2-series PGs are widely distributed in almost every tissue. In the PG synthesis pathway, four principal bioactive 2-series PGs are generated, including PGD_2, PGE_2, $PGF_{2\alpha}$ and PGI_2 (33). Clinical and experimental evidence has indicated that 2-series PGs are involved in the initiation and progression of numerous diseases, including diabetes mellitus (34), hypertension (35), obesity (36), fatty liver disease (37), vascular diseases (38), carcinoma (39), inflammatory bowel disease (40), rheumatoid arthritis (41), asthma and allergic diseases (42) and Alzheimer's disease (43). Studies have revealed that 2-series PGs play complex and interlinked roles in mediating metabolic homeostasis and systemic chronic inflammation (34,44-48). Moreover, 2-series PGs have bidirectional effects on insulin secretion and pancreatic β-cell proliferation during hyperglycemia (34). As PPAR-γ modulators, 2-series PGs regulate adipogenesis and lipolysis in lipid metabolism, leading to excessive fat deposit (44-46). In addition, 2-series PGs are involved in immune response by affecting various cytokines and immune cells, such as macrophages and monocytes, under insulin resistance, hyperlipidemic and diabetic status (44,47,48). Of note, the nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2-selective inhibitors (COXIBs) can interfere with 2-series PG synthesis by inhibiting cyclooxygenases (COXs), and have been widely used in anti-inflammation, analgesia, antiplatelet aggregation and anti-tumorigenesis treatment (49-51). However, the potential application of NSAIDs and COXIBs in the treatment of T2DM and NAFLD requires further investigation.

To the best of our knowledge, 2-series PGs play an important role in the development of T2DM and NAFLD. However, few studies have focused on the therapeutic effect of targeting the 2-series PG pathway in these two metabolic syndromes. Herein, the way in which 2-series PGs exert multifunctional effects on the highly intertwined pathogenesis of T2DM and NAFLD, including insulin resistance, hyperglycemia, hepatic lipid accumulation and inflammation, were systematically reviewed, and it was revealed that targeting the 2-series PG pathway may be an important therapeutic strategy in T2DM and NAFLD treatment.

2. PG biosynthesis

PGs belong to eicosanoids and have 1-, 2- and 3-series homologues. Each series of PGs is biosynthesized from different PUFAs, including dihomo-γ-linolenic acid (DGLA), AA and eicosapentaenoic acid (EPA) (52). DGLA is catalyzed by COXs

to produce 1-series PGs (such as PGE_1, PGG_1 and PGD_1), and can also be converted to AA by the enzyme Δ^5 desaturase (53). AA is the precursor of multiple important bioactive lipid mediators, including the 2-series PGs (such as PGE_2, PGD_2, $PGF_{2\alpha}$ and PGI_2) lipoxins, leukotrienes, resolvins, protectins and maresins (54).

To the best of our knowledge, the 1-series metabolites may be less closely associated with the correlation between T2DM and NAFLD, since a limited number of studies have been conducted. Furthermore, the 3-series PGs (such as $PGF_{3\alpha}$ and PGE_3) produced by EPA generally have a lower biological activity than their 1- and 2-series homologues (55). Therefore, the present review focused on the 2-series PGs that are the principal PGs derived from AA with a biological significance in T2DM and NAFLD.

The synthesis of 2-series PGs is precisely regulated (Fig. 1). Apart from being produced from DGLA, AA is mainly derived from cellular membrane phospholipids. Membrane phospholipids are esterified by PLA_2s to generate free AA. AA is subsequently converted to PGG_2, followed by a peroxidase reaction that immediately reduces PGG_2 to PGH_2 by the rate-limiting enzymes COXs (56). COXs mainly have two isoforms, COX-1 and COX-2. COX-1 is a constitutive isoform expressed in most tissues and involved in most physiological events, while COX-2 is highly expressed in response to physical, chemical and inflammatory stimuli (57). However, COX-2 is constitutively expressed in several tissues that are not associated with inflammation, such as the brain, kidney, thymus and gut (58,59). Then, PGH_2 is metabolized to PGE_2, PGD_2, $PGF_{2\alpha}$ and PGI_2 through different PG synthases (56,60). Next, a wide variety of PGs exert their biological functions by binding to their respective G protein-coupled receptors. PGE_2 is converted from PGH_2 by PGE synthase (PGES) and performs pleiotropic effects by binding to four distinct membrane PGE receptors (EP1-4). PGD synthases, including lipocalin-type PGDS (L-PGDS) and hematopoietic PGDS (H-PGDS), catalyze the isomerization of PGH_2 to PGD_2, which binds to PGD receptors (DP1 and DP2). PGI_2, an agonist of PGI receptor (IP), is generated by PGI synthase. $PGF_{2\alpha}$ is converted by PGF synthase and binds to PGF receptor (FP) (33).

The synthesized 2-series PGs affect various physiological and pathological processes, particularly the important pathogenesis of T2DM and NAFLD, which includes insulin resistance, hyperglycemia, hepatic lipid accumulation and inflammation (Fig. 2) (17-19). In the next section, the role of PGs in these pathogenic mechanisms will be further reviewed (Fig. 3).

3. PGs and insulin resistance

Insulin resistance is regarded as a key pathogenic mechanism that accounts for the interplay between T2DM and NAFLD. Insulin resistance is characterized by an impaired insulin sensitivity of liver and peripheral tissues, including skeletal muscle and adipose tissue. It is a crucial contributor to the other related pathogeneses, which includes hyperinsulinemia, hyperglycemia, dyslipidemia, ectopic lipid accumulation (such as in the liver) and inflammation (Fig. 2) (61). More specifically, first, insulin resistance contributes to hyperglycemia. Hepatic insulin resistance markedly increases hepatic glucose production, while peripheral insulin resistance enhances circulating non-esterified fatty acids (NEFAs) and decreases glucose uptake, together leading to elevated glycemia (62-65). Secondly, hepatic *de novo* lipogenesis, a primary initiation mechanism of liver fat formation, is facilitated by compensatory hyperinsulinemia and increased substrates (such as glucose and NEFAs) under insulin-resistant status in liver (64). Thirdly, insulin resistance is of great significance in the steatosis-to-NASH progression, as it is closely linked to aggravated inflammation, apoptosis and fibrogenesis in the liver (66). As for peripheral insulin resistance, adipose insulin resistance also triggers chronic low-grade inflammation by the release of adipokines and cytokines, which in turn maintains or even exacerbates the development of T2DM and NAFLD (67,68).

Accumulating evidence has revealed the important role of 2-series PGs in the development of insulin resistance (Fig. 3A) (37). Herein, the role of 2-series PGs in both hepatic and peripheral insulin resistance was discussed.

Hepatic insulin resistance. Hepatic insulin resistance is the key pathophysiological event during the development of T2DM and NAFLD, which is characterized by suppressed glycogenesis, increased gluconeogenesis and glycogenolysis, and augmented *de novo* lipogenesis (62-64). Insulin signaling has a different effect on hepatic glucose and lipid metabolism. Under insulin resistance, glucose metabolism becomes resistant to insulin action, while lipid metabolism remains sensitive to insulin or even enhanced by hyperinsulinemia (69). In combination, these metabolic alterations enhance hepatic glucose production, finally leading to hyperglycemia and liver lipid accumulation.

PGs have a dual effect on mediating hepatic insulin signaling; however, their impact remains inconclusive. These metabolites can be generated in hepatocytes, such as parenchymal hepatocytes (70) and Kupffer cells (71), acting as negative mediators for insulin signaling. Previous experimental research has shown that the use of COX-2 inhibitors in an obese rat model resulted in decreased PGE metabolites and improved systemic insulin sensitivity by increasing glucose uptake, repressing hepatic glucose production and decreasing hepatic triglyceride (TG) contents (37). Furthermore, PGE_2 can disrupt hepatic insulin signaling, which most likely resembles the IL-6-induced interference on insulin signaling (72). Via EP3 receptor, PGE_2 activates extracellular signal-regulated kinase 1/2 (ERK1/2) and subsequently promotes serine phosphorylation of insulin receptor substrate (IRS) 1. This finally prevents glycogen synthesis in cultured hepatocytes by interfering with insulin-dependent serine/threonine kinase (Akt) activation (72). Another study revealed that PGE_2-induced oncostatin M (OSM) production in liver Kupffer cells attenuated insulin-dependent IRS/PI3K/Akt signaling, leading to a repressed glucokinase expression and increased TG accumulation in hepatocytes (71). The intrinsic mechanism is that increased OSM promotes phosphorylation of signal transducer and activator of transcription 3 (STAT3) to induce transcription of cytokine signaling 3 (SOCS3) (71). Consistent with *in vitro* results, this mechanism is also responsible for the development of hepatic insulin resistance, steatosis and elevated plasma glucose level in murine NAFLD models. It is recommended

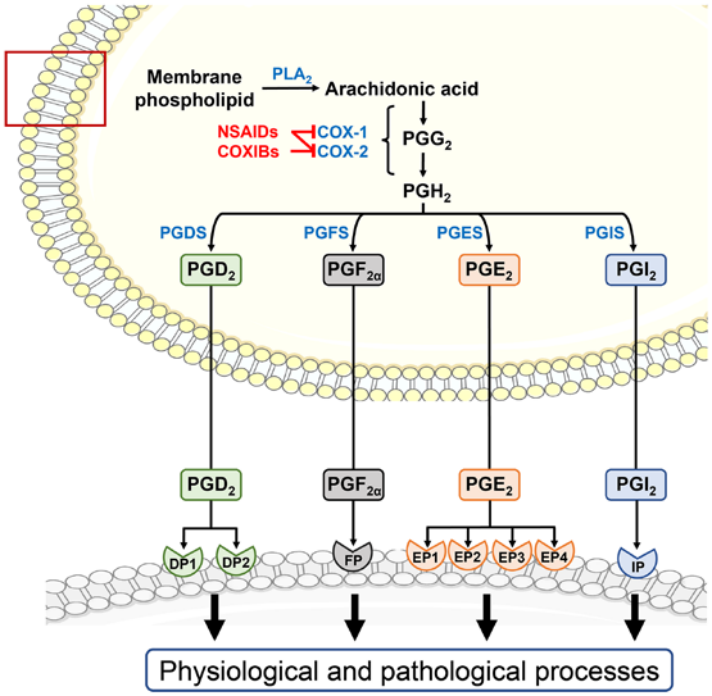

Figure 1. Overview of 2-series PG biosynthesis pathways. AA is generated by PLA_2 from membrane phospholipids. Both COX-1 and COX-2 convert AA to PGG_2 and subsequently PGH_2. PGH_2 is metabolized by different PG synthases (PGDS, PGFS, PGES and PGIS) to produce PGD_2, $PGF_{2\alpha}$, PGE_2 and PGI_2, respectively. PGs act by binding to their specific receptors, including PGD receptors (DP1-2), PGF receptor (FP), PGE receptors (EP1-4) and PGI receptor (IP), and are involved in various physiological and pathological processes. AA, arachidonic acid; PLA_2, phospholipase A_2; COX, cyclooxygenase; PG, prostaglandin; PGG_2, prostaglandin G_2; PGH_2, prostaglandin H_2; PGD_2, prostaglandin D_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PGE_2, prostaglandin E_2; PGI_2, prostacyclin; DP1-2, PGD receptor 1-2; FP, PGF receptor; EP1-4, PGE receptor1-4; IP, PGI receptor; PGDS, PGD synthase; PGFS, PGF synthase; PGES, PGE synthase; PGIS, PGI synthase.

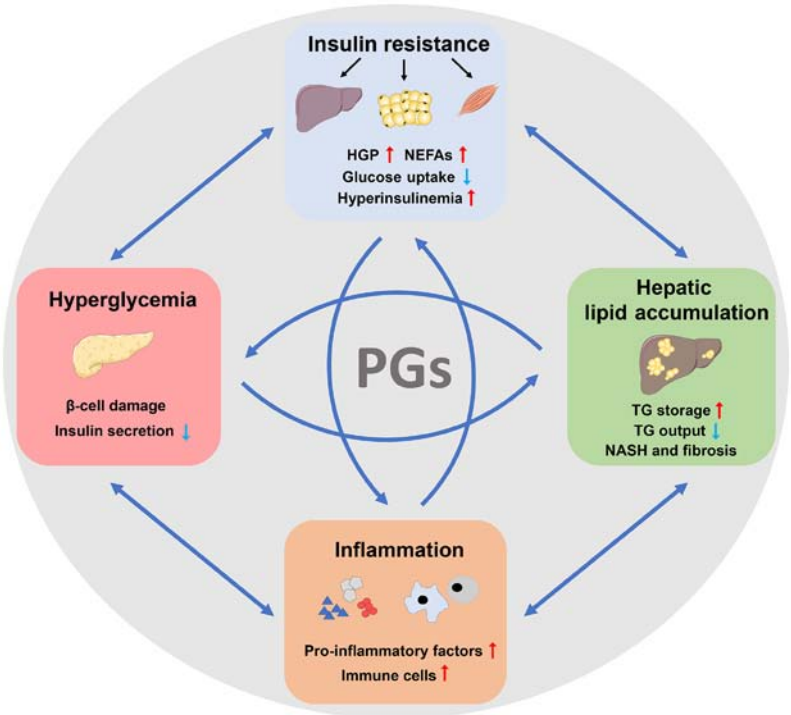

Figure 2. Schematic diagram of the 2-series PGs influence on the pathogenesis of T2DM and NAFLD. 2-Series PGs can affect four critical and highly intertwined important pathogenic mechanisms of T2DM and NAFLD, including IR, hyperglycemia, hepatic lipid accumulation and inflammation. The whole-body IR initiates or exacerbates the other three pathogenic mechanisms by increasing HGP, NEFAs, hyperinsulinemia, inflammatory mediator release (such as adipokines and cytokines) and decreasing glucose uptake. Hyperglycemia directly results from β-cell damage and decreased insulin secretion, which leads to glucotoxicity and induces both inflammation and hepatic lipid storage. Hepatic lipid accumulation is mainly caused by increased TG storage and diminished TG output. The induced lipotoxicity in the liver can accelerate hepatic or systemic inflammation. Inflammation is triggered under these metabolic stresses and responds with increased levels of inflammatory factors and immune cell recruitment in IR, β-cell damage and progression from hepatic steatosis to NASH and advanced fibrosis. T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; IR, insulin resistance; HGP, hepatic glucose production; NEFAs, non-esterified fatty acids; TG, triglyceride; NASH, non-alcoholic steatohepatitis.

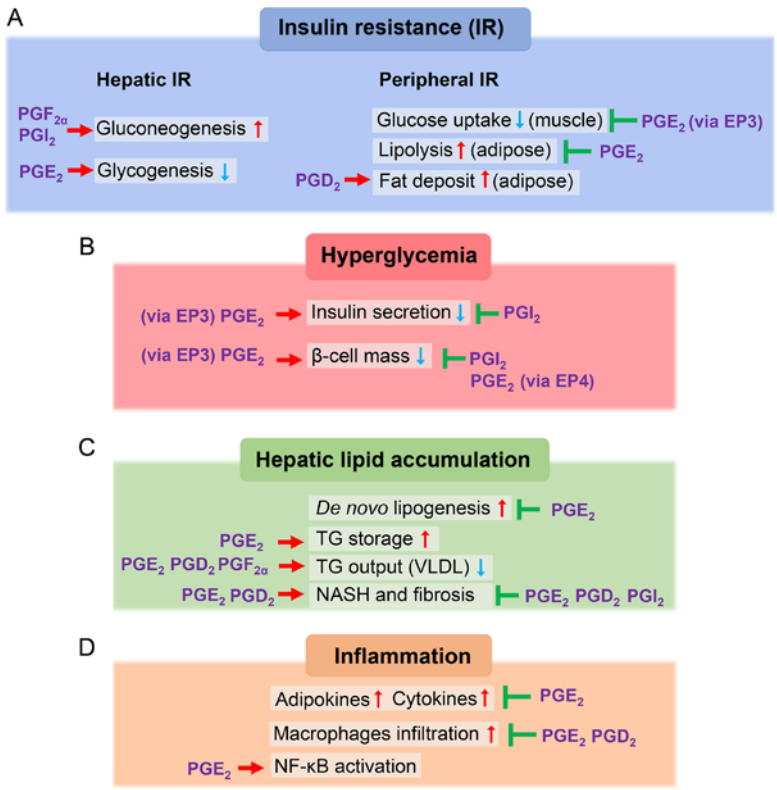

Figure 3. Role of 2-series PGs in the four pathogenesis of T2DM and NAFLD. (A) Insulin resistance. (B) Hyperglycemia. (C) Hepatic lipid accumulation. (D) Inflammation. T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease.

that the PGE_2-dependent feed-forward loop for NAFLD development is most likely due to the suppression of fatty acid and TG consuming pathways (fatty acid oxidation and TG export), independently of the inhibition of insulin-induced fatty acid synthesis (71).

The negative effects of PGs on insulin signaling are closely associated with hepatic glucose homeostasis (particularly gluconeogenesis). Gluconeogenic action is considerably increased under insulin resistance (73). A previous study revealed that the suppression of the hepatic $PGF_{2\alpha}$-FP axis improved insulin resistance and glucose homeostasis in *ob/ob* mice partially via decreased hepatic gluconeogenesis (74). Under fasting conditions, $PGF_{2\alpha}$ activates FP receptors in hepatocytes to upregulate gene expression levels of gluconeogenic rate-limiting enzymes, phosphoenolpyruvate carboxykinase (PCK1), and glucose-6-phosphatase (G6Pase) (74). The precise underlying mechanism is that FP receptor coupling with G protein Gq facilitates Ca^{2+} release and subsequently activates Ca^{2+}/calmodulin-dependent protein kinase II γ, which accelerates p38-dependent forkhead box protein O1 (FOXO1) nuclear translocation (74). Another study revealed that treatment with high doses of acetylsalicylic acid suppressed hepatic gluconeogenesis through the inhibition of the COX-2/PGI_2/IP axis for further improvement of diabetes (75). Hepatic gluconeogenesis was revealed to be inhibited by the downregulation of PGI_2 or disruption of IP receptor in a mouse model of T2DM through the activation of the $G_{\alpha s}$/protein kinase A (PKA)/cAMP-response element binding protein pathway and inhibition of $G_{\beta\gamma}$/PI3K-$_\gamma$/protein kinase C (PKC)-$_\zeta$/tribbles homolog 3/Akt/FOXO1 pathway, which is involved in insulin signaling, both of which subsequently repressed the expression of G6Pase and PCK1 in hepatocytes (75). These results demonstrated that PGs can promote gluconeogenesis under insulin resistance.

Of note, PGs can also exert a protective effect on hepatic insulin signaling through the regulation of COX-2 under the stress of lipid overload, although COX-2 is widely recognized as a pro-inflammatory mediator. Hepatic COX-2 overexpression in mice fed with high-fat diet (HFD) caused a threefold increase of PGE_2 and elicited preservation against hepatic insulin resistance. COX-2-dependent PG synthesis has been revealed to mediate insulin signaling by increasing the Akt and AMP-activated protein kinase phosphorylation level and decreasing the protein tyrosine phosphatase-1β expression level in fatty livers or hepatocytes exposed to fatty acids (76).

Peripheral insulin resistance. Insulin action in adipocytes and muscles is closely correlated with glucose and lipid metabolism in T2DM and NAFLD. The adipocyte insulin resistance can decrease intracellular TG storage and induce lipolysis, which decreases fat content and increases the release of NEFAs. Elevated circulating NEFAs can further lead to a redistribution of fat depot from adipose tissue into the liver and muscles, namely ectopic fat accumulation (65). Furthermore, adipose insulin resistance facilitates the release of adipokines (such as adiponectin, leptin and resistin) and cytokines [such as tumor necrosis factor α (TNF-α), IL-6 and IL-1β], leading to chronic low-grade inflammation in T2DM and NAFLD (67,68). On the other hand, insulin resistance primarily impairs glucose uptake in muscle tissue, which results in hyperglycemia and subsequently increases glucose delivery to the liver for further hepatic lipogenesis (77).

PGs mostly exert preventive effects against adipose insulin resistance and mediate adipogenesis in adipocytes. PGs may improve insulin sensitivity by altering inflammatory status, alleviating hepatic steatosis and overweight under obese status (78). In both subcutaneous and epididymal adipose tissues, the increased COX-2 activity enhances various PGs levels, including PGE_2, which further improves the inflammatory profile including increased levels of TNF-α, IL-33 and IL-4. This subsequently contributes to increased insulin sensitivity in adipocytes and downregulates mRNA levels of PPAR-γ and CCAAT/enhancer-binding protein α (37,78). In addition, particularly under HFD treatment, mice with selective COX-2 overexpression in adipocytes resulted in a mass reduction of inguinal white adipose tissue (WAT) and decreased hepatic steatosis when compared with the littermate control (78). This finding suggested that COX-2-derived PGs may be benign mediators of type 2 immunity cues in subcutaneous WAT under deranged metabolism.

Consistent findings are shown in studies examining PGE_2-EP3 signaling, which has a benefit for preventing insulin resistance and reducing fat deposit in adipose tissue. *EP3* gene knockout in mice has been revealed to result in diabetes and obesity (79). The $EP3^{-/-}$ mice gained more weight than the $EP3^{+/+}$ mice when fed with an HFD, and were endowed with more severe insulin resistance and adipose accumulation in the epididymis and liver. The increased fat mass and enlarged adipocyte size in epididymal WAT are associated with evoked inflammatory status, characterized by increased macrophage infiltration, upregulated TNF-α, monocyte chemoattractant protein-1 (MCP-1) and IL-6 expression levels and necrosis. The underlying mechanism involves the EP3 receptor knockout-induced interruption of PGE_2 signaling attenuating the PGE_2-evoked inhibition of isoproterenol-stimulated lipolysis (79,80). In addition, abnormal lipid distribution occurred alongside insulin resistance following the disruption of the PGE_2-EP3 pathway when exposed to an HFD challenge. Among the group of $EP3^{-/-}$ mice fed with HFD, the increase of adipocyte mass and size in WAT was lower in those heavier mice, leading to a relatively increased redistribution of fat depot in liver and skeletal muscle. However, this was not observed in the group of $EP3^{+/+}$ mice (79). This also suggested that in obese cases, PGE_2-EP3 signaling may prevent excessive ectopic lipid deposition, which can subsequently cause lipid-induced hepatic and muscle insulin resistance.

Similar improvement on insulin resistance has also been observed with PGD_2 action. A previous study has reported that PGD_2 overproduction improved insulin sensitivity in transgenic mice overexpressing human H-PGDS (81). Furthermore, PGD_2 in WAT was majorly generated by H-PGDS in macrophages (82). PGD_2 polarized macrophages from an inflammatory M1 state towards its anti-inflammatory M2 state. This polarization of macrophages was positively correlated with adipose insulin sensitivity (82). These results suggested that PGD_2 may improve adipose insulin resistance by regulating macrophage polarization.

However, PGD_2-mediated adipose insulin sensitivity is associated with increased body weight, adipocyte size and lipid deposition (81,83-86). Augmented H-PGDS-mediated PGD_2 increase is observed in adipose tissue in obese cases and remains high even after weight loss, which indicates that PGD_2 may act as a biological driver to regain weight (83). Furthermore, L-PGDS-induced PGD_2 in WAT was found to deteriorate adipose insulin resistance, increase adipose size, enhance serum cholesterol and TG levels in a study using fatty acid-binding protein 4 (aP2)-Cre/L-$PGDS^{flox/flox}$ mice (84). The underlying mechanism of the PGD_2-induced weight gain has been studied, and has revealed pronounced adipogenesis in WAT through the activation of the transcription and expression levels of adipogenic genes, such as PPAR-γ, aP2 and lipoprotein lipase (81,84). Similarly, an *in vitro* study revealed that Δ^{12}-PGJ_2, a metabolite of PGD_2, could accelerate adipogenesis in a PPAR-γ-dependent and -independent manner in differentiated 3T3-L1 cells (85). In addition, the PGD_2-mediated lipogenic process can also be due to its function in adipose lipolysis. PGD_2 increases intracellular TG levels by suppressing lipolysis through repressing cyclic adenosine monophosphate (cAMP)-PKA-hormone-sensitive lipase (HSL) axis via Gi-coupled DP2 receptor, which is dominantly expressed in adipocytes (86). This process prevents intracellular TGs in lipid droplets from hydrolytic action of HSL that may result in elevated circulating TGs. Briefly, PGD_2-mediation on lipolysis is likely to improve individual metabolic disturbances including insulin resistance, dyslipidemia and hyperglycemia, despite the presence of worsening fat accumulation in peripheral tissue and weight gain (86). In combination, these results suggested that PGD_2 can induce weight gain and adipose accumulation by facilitating adipogenesis and inhibiting lipolysis, which is associated with the improvement in insulin sensitivity. However, the altered fat topography and disturbed adipocyte metabolism caused by PGs may gradually predispose to the glucose intolerance in T2DM and NAFLD (87-89). The underlying mechanism is that the excessive lipid storage in adipose tissue can induce adipocyte insulin resistance and further evokes lipolysis, leading to elevated circulating NEFAs and exacerbated whole-body insulin sensitivities (87-89).

In addition to their impacts on adipose insulin resistance, PGs are also correlated with muscle insulin resistance. During the development of T2DM and NAFLD, increased delivery of NEFAs can accelerate intramyocellular lipid accumulation, which causes muscle insulin resistance. In addition, insulin-stimulated glucose transport is impaired in insulin-resistant muscles, which can happen prior to the occurrence of overt T2DM (90-92). PGs have been implicated in the translation of insulin-dependent glucose uptake into skeletal muscle (93) and, meanwhile, PGE_2 enhances insulin sensitivity to increase muscle glycolysis (94). In addition, COX-2-induced PGE_2 production alleviates the fatty acid-induced inflammatory process in skeletal muscle cells (95). Furthermore, intramuscular fat accumulation was observed in global deletion of EP3 receptors in diabetic mice with diet-induced obesity (79). These results suggested that the PGE_2 signaling pathway may improve muscle insulin resistance. However, the intrinsic mechanism remains poorly understood.

In the aforementioned pathogenic mechanisms, 2-series PGs are most likely to aggravate hepatic insulin resistance but prevent peripheral insulin resistance. The aggravated hepatic insulin resistance eventually initiates or exacerbates hyperglycemia, hepatic lipid accumulation and inflammation, which in turn can be affected by these metabolic stresses during the

progressive disease course. Moreover, the improved peripheral insulin resistance ameliorates blood biochemical indexes and inflammatory status, but leads to excess fat storage in muscle or adipose tissue. To date, the understanding of how 2-series PGs affect the insulin signaling pathway and the underlying molecular mechanism is lacking. Further investigations of key molecular targets will shed light onto the translational application in the treatment of T2DM and NAFLD.

4. PGs and hyperglycemia

Hyperglycemia is a hallmark of dysregulated glucose metabolism that contributes to the initiation and progression of T2DM and NAFLD (Fig. 2). When insulin resistance occurs, chronic hyperglycemia can induce insulin release by pancreatic β-cells, thus contributing to hyperinsulinemia (96). Under insulin resistance and hyperinsulinemia, elevated glycemia and circulating NEFAs can cause the deleterious impairment of various organs and tissues, processes that are referred to as glucotoxicity and lipotoxicity, respectively (97,98). In the pancreas, glucotoxicity and lipotoxicity can account for β-cell failure and subsequent insulin secretion deficiency (97-99). In addition, hepatic gluconeogenesis can be facilitated by insulin resistance, most likely contributing to hyperglycemia by increasing the hepatic glucose output. These mechanisms collectively contribute to hyperglycemia during the development of T2DM and NAFLD.

A previous study has demonstrated the close correlation between 2-series PG action and the development of hyperglycemia (Fig. 3B). First, COX-1 and COX-2 participate in the control of glycemia (100). In a 2-week clinical trial of high-dose aspirin treatment among nine patients with T2DM, aspirin treatment was revealed to reduce fasting plasma glucose and improves insulin sensitivity in cases with diabetes (101). In addition, the increased formation of PGs and PG metabolites has been observed in T2DM, including PGE_2, PGI_2 in islet or blood, and 15-keto-dihydro-$PGF_{2\alpha}$, 8-iso-$PGF_{2\alpha}$ in urine (102-106). However, interference with the PGE_2/EP3 signaling pathway through the blockade of the EP3 receptor in mice has been reported to predispose to systemic insulin resistance; in addition, insulin secretion also increases, finally contributing to hyperglycemia (79,107). These observations imply the multifunctional involvement of 2-series PGs in the development of hyperglycemia.

β-cell failure includes β-cell dysfunction and β-cell mass deficiency, which remain the two major causes of hyperglycemic pathogenesis. β-cell dysfunction and apoptosis reduce insulin secretion and deplete β-cell mass, respectively (108). Due to their involvement in inflammation and oxidative stress signaling pathways, PGs mainly act as an initial and deteriorative pathological element for β-cell failure, leading to hyperglycemia.

Glucose-stimulated insulin secretion (GSIS) commonly occurs when β-cells are constantly exposed to high glucose stimulation (109). To a certain extent, PGs act as a potential negative modulator of GSIS. A number of studies have demonstrated that PGE_2 attenuates GSIS. PGE_2 is the predominant E-series PG in islets formed by COX-2, the dominant form of COX in the pancreas (110-112). COX-2 expression is significantly upregulated in pancreatic islets under hyperglycemic conditions (113,114). COX-2-dependent PGE_2 generation is augmented by group X secretory phospholipase A_2 and eventually suppresses GSIS *in vitro* and *in vivo* (115). PGE_2 equally inhibits both two phases of GSIS in HIT cells, which is associated with reduced cAMP accumulation mediated by pertussis toxin-sensitive G protein (Gi) (116). Among PGE receptors, EP3 receptor is the most abundant PGE receptor type in islets (112), which is overexpressed in islets from patients with T2DM (117,118). Previous research has indicated that PGE_2 coupling with EP3 receptor is highly associated with a reduction of insulin secretion in terms of β-cell dysfunction. Meng *et al* (118) revealed that the PGE_2-stimulated gene expression of PG EP3 receptor subtype led to intracellular cAMP reduction, accompanied by a downregulated phosphorylation level of Akt and forkhead box 'Other' (Foxo) in HIT-T15 cells (118). Kimple *et al* (103) confirmed that this active PGE_2/EP3 receptor pathway in islets depended on coupling to G-proteins of the Gi subfamily *in vivo*. In addition, EP3 receptor agonists can antagonize glucagon-like peptide-1 (GLP-1) signaling, leading to reduced cAMP production and attenuated GSIS (103). Hence, since GLP-1 treatment is not effective in all patients with T2DM (119), as a non-competitive antagonist of GLP-1 receptor, EP3 receptor may be a potent target for improving the GLP-1 effect in anti-diabetic therapeutics (103,120). Another observation revealed that PGE_2 presents an impotent influence on GSIS suppression in rat islets exposed to epinephrine-induced glucose overload (121). Under hyperglycemic states, crosstalk between PGs and other inflammatory factors has a profound effect on glycemic control. Systemic inflammatory responses are upregulated in T2DM individuals (122), characterized by elevated levels of lipid molecules, including PGs and cytokines such as TNF-α (123), IL-1β (124), IL-6 (125) and IL-8 (126), in correspondence with the decline of their natural antibodies (127). In PG signaling, COX-2 is involved in IL-1β-induced auto-stimulation in islets (111). The COX-2 expression and activity are upregulated by IL-1β-induced NF-κB activation, resulting in a negative effect on GSIS caused by increased PGE_2 via EP3 receptor (112). Recently, the IL-1β/COX-2/PGE_2 pathway loop has been revealed as the underlying mechanism for the onset and progression of diabetes, which leads to β-cell inflammatory impairments by downregulating the expression of β-cell functional genes pancreatic and duodenal homeobox 1, NK6 homeobox 1 and MAF bZIP transcription factor A (124). As previously mentioned, PGE_2 can impact GSIS through different receptors and also by interacting with inflammatory reaction in hyperglycemia.

Considering other PGs, PGI_2 also plays a pivotal role in the protection of β-cell function and survival via IP receptor signaling. The IP receptor/cAMP/PKA/nephrin signaling pathway participates in the preservation of β-cell function and mass *in vitro* and *in vivo*. IP receptor agonism augments insulin release in pancreatic β-cells and promotes the viability of MIN6 β-cells as a consequence of intracellular cAMP increase, PKA activation and subsequent nephrin phosphorylation (104). Consistently, a study revealed that selexipag, a prodrug form of IP receptor agonist, exerted a similar improvement on GSIS and β-cell mass in diabetic mice (104).

Deficient β-cell mass is recognized as another essential event that results in elevated glycemia in T2DM

progression (128,129). Apart from delaying the GSIS process, COX-2/PGE_2 signaling also plays a role in the regulation of β-cell proliferation and apoptosis. In a model of transgenic mice overexpressing COX-2 and microsomal prostaglandin E synthase 1 (mPGES-1), increased PGE_2 appeared to be associated with a significant reduction in the number of β-cells and further caused severe hyperglycemia (130). A different study concluded that the blockade of EP3 receptor and activation of EP4 receptor enhanced human β-cell proliferation and survival *ex vivo*, suggesting a reciprocal effect of different EP receptors on the mediation of β-cell failure in T2DM (117). Furthermore, an EP3 receptor antagonist improved β-cell proliferation partly by enhancing phospholipase C-γ1 activity in young mouse islets rather than in old ones, while the EP4 receptor was activated to exert the same protective effect in human β-cells only with combination of EP3 inhibition. In terms of promotion of β-cell survival, forkhead box protein M1, a critical β-cell proliferation factor, is upregulated by EP3 antagonist and EP4 agonist in islets from obese T2DM individuals (117). However, EP4 has further been revealed to be involved in PKA signaling activation through a G_S-coupled mechanism in the survival of mouse β-cells, which is proposed to facilitate the phosphorylation of eukaryotic initiation factor 4E and PKC-ε in a putative downstream mechanism (117). In addition, α-subunit of the heterotrimeric G_z protein ($G\alpha_z$), a member of the $G\alpha_i$ family, may couple to EP3 in pancreatic β-cells (131). The global deletion of $G\alpha_z$ can block the PGE_2/EP3 pathway, which subsequently results in a robust increase in β-cell mass and augments GSIS by cAMP upregulation in mice with both insulin resistance and glucose intolerance (120). In addition, EP3 receptor knockout in HFD-fed mice was revealed to promote β-cell proliferation (79), which is consistent with the aforementioned $G\alpha_z$-null data. Notably, in human islets from patients with T2DM and MIN6 β-cells, palmitate can upregulate the expression levels of COX-2 and EP3 receptor, which initiates β-cell apoptosis through the COX-2/PGE_2/EP3 pathway (132). These results demonstrated that the PGE_2 pathway can inhibit proliferation and induce apoptosis in β-cells exposed to glucotoxicity and lipotoxicity.

Based on the available studies of 2-series PG-mediated glycemic control, the PGE_2 and PGI_2 signaling pathways are considered crucial pathogenic contributors in the regulation of β-cell function and proliferation, although PGE_2 exerts completely different effects on hyperglycemia through EP3 and EP4 receptors. Furthermore, PGs, mainly $PGF_{2\alpha}$ and PGI_2, can enhance circulating blood glucose by accelerating gluconeogenesis and glycogenolysis through insulin signaling (described in *Hepatic insulin resistance*). Enhanced glycemia can be predisposed to excessive glucose accumulation in the liver which can be converted to lipid formation. Therefore, targeting the 2-series PG pathway can be a promising therapeutic strategy for the protection and recovery of both β-cell and liver abnormalities.

5. PGs and hepatic lipid accumulation

Elevated circulating lipid contents (such as cholesterol, TG and NEFAs) are a characteristic of T2DM and NAFLD (Fig. 2) (133-135). Lipotoxicity alone or in combination with glucotoxicity is highly associated with the impairment of insulin sensitivity in various organs. Previous clinical studies have revealed that lipid infusion contributes to hepatic insulin resistance (136). In addition, the accumulation of hepatic lipid contents, particularly TGs, is an initiation of liver steatosis. Liver steatosis is the first hit in the progression of NAFLD, whose onset is due to insulin resistance (19,137). The direct contributors to excess lipid storage in the liver include increased circulating NEFAs, accelerated *de novo* lipogenesis, overloaded dietary fat and inadequate lipid oxidation (64,65,134,138). In turn, hepatic steatosis induces subacute intrahepatic inflammation through the NF-κB pathway as a pathogenic mechanism for exacerbated hepatic and systematic insulin resistance both in NAFLD and T2DM (19,139).

PGs markedly contribute to the dysregulation of the lipid metabolism in hepatic lipid accumulation (Fig. 3C). PGE_2 acts synergistically with insulin in the pathogenesis of hepatic steatosis, but their roles remain discordant and controversial. PGE_2 decreases the activity of lipogenic enzymes in primary hepatocytes *in vitro* through sustained ERK1/2 activation, thereby attenuating insulin-dependent phosphorylation of Akt kinase. This finally abrogates insulin signaling and further alleviates SREBP-1c pathway in hepatic *de novo* lipogenesis (140). Furthermore, short-term blockade of PGE_2 signaling by EP3 antagonist in mice with diet-induced obesity caused a significant reduction of TG content in skeletal muscle and slightly increased hepatic TGs (107). As a result, it can be hypothesized that PGE_2 elicits preservation against hepatic steatosis. However, other observations vary from this hypothesis. A previous study has indicated that extracellular PGD_2, PGE_2 and $PGF_{2\alpha}$ diminish the secretion of very low-density lipoprotein (VLDL)-apolipoprotein B (apoB) to promote steatosis in primary hepatocytes (141). The reduction of VLDL-apoB is correlated with decreased TG transportation and impaired cellular TG recycling, which finally results in a reduced TG output. In addition, only PGE_2 can completely antagonize the IL-6-induced secretion of VLDL-apoB in hepatocytes (141). Furthermore, PGE_2 acts synergistically with insulin and enhances the incorporation of glucose into TGs in hepatocytes. PGE_2 and insulin synergistically inhibit lipolysis, mitochondrial β-oxidation and VLDL synthesis, which are mediated by PGE_2-dependent suppression of adipose TG lipase, carnitine palmitoyltransferase-1 and apoB-mediated lipidation, respectively (140). Moreover, apoB and microsomal transfer protein are downregulated by PPAR-γ-coactivator-1α and PCK1 in insulin-dependent and PGE_2-dependent manners. In combination, these events contribute to a reduced TG breakdown and increased fat droplets in hepatocytes (140). In terms of NAFLD development *in vivo*, under HFD feeding, increased COX-2 activity and PGE_2 concentration also results in hepatic steatosis in mice mostly through NF-κB activation and lipid peroxidation enhancement. An aggravation of insulin resistance also appears with increased levels of serum alanine aminotransferase and total hepatic fatty acids (142). Another putative mechanism of hepatic steatosis formation involves CD36-mediated PG levels in the liver. Although the expression level of CD36 was 5-fold higher in hepatic steatosis liver than in normal liver, the global deletion of CD36 in *ob/ob* mice aggravated hepatic lipid accumulation by significantly suppressing the outputs of VLDL, apoB and TGs by increasing hepatic PGD_2, PGE_2 and $PGF_{2\alpha}$ (143). Based on

these experiments, PGs including PGD_2, PGE_2 and $PGF_{2\alpha}$ may accelerate the initiation and progression of hepatic steatosis.

Conversely, beraprost sodium, a PGI_2 analog, was revealed to be effective in ameliorating metabolic disturbances in obesity and obesity-associated T2DM. Various manifestations were revealed to be improved by PGI_2 analog treatment, including hepatic steatosis, adipose hypertrophy, glucose intolerance, hyperglycemia, hyperinsulinemia and other related complications, such as pancreatic fibrosis and nephropathy (144). This suggests that PGI_2 can be beneficial to the treatment of obesity-associated T2DM and NAFLD.

Since the mediation of PGs on hepatic lipid accumulation is ambiguous, the precise mechanism requires further study. Considering the findings of the aforementioned studies, it can be hypothesized that various PGs (PGD_2, PGE_2 and $PGF_{2\alpha}$) promote hepatic lipid accumulation, mostly through facilitating TG storage and inhibiting TG output by repressing lipolysis, fatty acid oxidation and VLDL synthesis. In addition, under insulin resistance, PGs can increase *de novo* lipogenesis and promote the development of hepatic steatosis. As hepatic lipid accumulation is the initial step of NAFLD as well as a risk factor for T2DM, the inhibition of the 2-series PG pathway may be a potential option for treating NAFLD.

6. PGs and inflammation

Systemic chronic inflammation is a health-damaging phenotype that plays a central role in multiple metabolic syndromes, including T2DM and NAFLD (Fig. 2) (145,146). 2-Series PGs have multifunctional effects on the promotion and resolution of inflammation following the occurrence of insulin resistance, β-cell failure and hepatic steatosis (Fig. 3D) (37,71,78,79,82,112,142). PGs, TNF-α, IL-1β and IL-6 have been recognized as the major inflammatory mediators in T2DM and NAFLD (102,145-148). There are multifaceted interactions between PGs and other inflammatory molecules or cells in the pathogenic mechanisms of T2DM and NAFLD. As aforementioned, COX-2-derived PGs disrupt insulin signaling by activating the STAT3/SOCS3 signaling pathway in the liver or interacting with TNF-α and ILs in WAT (37,71,78), whereas, in obesity, PGD_2 and PGE_2 mediate macrophage polarization and infiltration with downregulated TNF-α, MCP-1 and IL-6 in WAT, leading to an improvement in peripheral insulin resistance (79,82). In turn, when peripheral insulin resistance occurs, adipokines and cytokines are released from dysfunctional adipose tissues and subsequently induce inflammation, which is associated with β-cell failure and hepatic steatosis. COX-2-derived PGE_2 contributes to β-cell dysfunction in GSIS via IL-1β-induced NF-κB activation (112), and hepatic lipid accumulation via NF-κB activation (142). NF-κB-mediated inflammation is important in the pathogenesis of T2DM and NAFLD. PGs may be involved in inflammatory processes mostly through NF-κB pathway activation with or without coaction with other inflammatory factors. The inhibitor κB kinase β (IKK-β)/NF-κB pathway plays a critical role in chronic hepatic inflammation, leading to insulin resistance and steatohepatitis, in which TNF-α and IL-1β are also involved (19,139).

Hepatic inflammation is a landmark in the development of NASH, which is also triggered by progressed insulin resistance and other injurious stimuli, such as glucotoxicity and lipotoxicity (149-152). Progressively, NASH-related hepatic fibrosis and cirrhosis become long-term manifestations of NAFLD. Hepatic fibrosis is characterized by high-density extracellular matrix protein deposition (153). Both NASH and liver fibrosis can be exacerbated in NAFLD with comorbidity of T2DM (154,155). T2DM-promoted NASH is attributed to peripheral insulin resistance, intrahepatic lipotoxicity and M1 macrophage recruitment in adipose tissue (156-158). The activated M1 macrophages secrete pro-inflammatory cytokines, including MCP-1, TNF-α and IL-1β, which induce systemic inflammation. These cytokines are further delivered to the liver and cause steatohepatitis (159). Therefore, insulin resistance, hyperglycemia, hyperinsulinemia and hyperlipidemia are key factors for pro-inflammatory status in hepatic inflammation, in which PGs are involved as inflammatory mediators. In addition, the upregulation of transforming growth factor-β (TGF-β) and connective tissue growth factor in T2DM can lead to NAFLD-related fibrosis progression (160,161).

PGs are correlated with the progression from hepatic steatosis to NASH. The upregulated expression of COX-2 and mPGES-1, the key enzymes of PGE_2 synthesis, is closely associated with NASH activity score in human liver from patients with NASH (162). Lipidomics profiling was performed in a clinical cohort that attempted to describe the hepatic inflammatory characteristic of NASH. As a result, the plasma PGE_2 level was revealed to be elevated only in patients with NASH, while the level of 13,14-dihydro-15-keto-PGD_2, a metabolite degraded from PGD_2, was found to be remarkably higher in the NASH group, compared with the simple steatosis or control groups (163). As a consequence, it is reasonable to suggest that PGs, particularly PGE_2, may aggravate the course of NAFLD.

However, there are some discrepancies in the impact of PGs and COX-2 activity on the development of NASH under dietary nutritious stress. An *in vivo* study revealed that hepatocyte-specific COX-2 transgenic mice (hCOX-2-Tg) with an increased level of PGE_2 improved intrahepatic steatosis, ballooning and inflammation (164). This was partially achieved by decreasing the plasma levels of pro-inflammatory cytokines (such as IL-1β, IL-6, TNF-α and MCP-1), and inhibiting macrophage recruitment and infiltration in steatohepatitis liver induced by a methionine- and choline-deficient diet (MCDD) (164). In addition, there are ameliorations of augmented oxidative stress and apoptosis in liver samples with NASH (164). Similarly, under a NASH diet, hepatic PGE_2 production derived from mPGES-1 is increased to potently inhibit monocyte-derived macrophage infiltration, which is associated with PGE_2-induced suppression of TNF-α-triggered responses in hepatocytes. These responses consist of pro-inflammatory cytokine IL-1β production and hepatocyte apoptosis (162). These results suggest a combined action of PGs and other inflammatory factors in NASH development. Furthermore, the blockade of L-PGDS in PGD_2 signaling rapidly accelerates non-alcoholic simple steatosis to severe steatohepatitis in nutrition overload or normal conditions (165). This progression to NASH is also accompanied by enhanced lipogenic gene expression (such as SREBP-1c and liver X receptor α) and deranged metabolic features, including progressed insulin resistance and increased fasting glucose, insulin and lipid levels in the blood (165). With

regards to the PGI_2/IP pathway, under MCDD conditions, IP-receptor-knockout (IP-KO) mice had accelerated progression to steatohepatitis, with greater iron deposition due to marked oxidative stress. PGI_2-IP signaling prevents the development of NASH in anti-inflammatory response, as evidenced by the suppressed expression of MCP-1 and TNF-α in lipopolysaccharide-stimulated Kupffer cells *in vitro*. Consistently, the Kupffer cell-induced expression levels of MCP-1 and TNF-α were progressively increased in IP-KO mice, and the oxidative stress-induced hepatic iron deposition was reduced in the MCDD-induced steatohepatitis liver, suggesting that PGI_2 signaling inhibits inflammation and influences the antioxidant reaction in NASH (166). Thus, PG appears to play a protective role against hepatic steatohepatitis, most likely under disturbed metabolism in NAFLD and T2DM progression.

The key mechanisms of hepatic fibrosis include a disbalance between fibrogenesis and fibrinolysis and the activation of hepatic stellate cells (HSCs) and Kupffer cells in response to various stimuli (167,168). Numerous studies have revealed that PGs facilitate the development of hepatic steatosis, steatohepatitis and fibrosis (169-171). In a prospective cohort research of 361 patients with NAFLD, daily aspirin use induced less severity of histologic characteristics of NAFLD and significantly decreased the risk of fibrosis initiation and progression in a duration-dependent manner, when compared with the non-regular use of aspirin (172). It was further suggested that the antifibrotic effect of long-term aspirin treatment is attributed to its involvement in inhibiting NF-κB and IKK-β signaling (173). Furthermore, plasma bioactive lipids, such as PGE_2 and PGI_2, have been regarded as useful markers for prognosis in liver cirrhosis (174). In accordance with clinical evidence, the upregulation of COX-2 was positively correlated with fibrosis formation in liver from a carbon tetrachloride (CCl_4)-induced fibrotic mouse model (175). Conversely, it was revealed that COX-2-derived PGE_2 could suppress fibrogenesis and NASH progression (176,177). In hCOX-2 Tg mice with diet-induced NASH, PGE_2 attenuated CCl_4-induced liver fibrosis by decreasing the activation and proliferation of HSCs and increasing apoptosis by suppressing microRNA (miR)-23a and miR-28a expression (164,178). In addition, COX-2-derived PGE_2 was revealed to suppress collagen synthesis through the downregulation of collagen type I α1, α smooth muscle actin and collagen binding protein-1 in HSCs under TGF-β1-induced conditions (178,179). These results demonstrated that the COX-2/PGE_2 pathway prevents the development of liver fibrosis through growth-suppressive and pro-apoptotic effects on HSCs.

To sum up, during the progression of T2DM and NAFLD, PGs may primarily act by interacting with other inflammatory factors, as well as mediating the NF-κB signaling pathway, which plays an important role in the chronic inflammation caused by glucotoxicity and lipotoxicity in a variety of organs. PGs can serve as pro-inflammatory mediators in the impairment of insulin sensitivity, glycemia and hepatic lipid metabolism. However, PGD_2, PGE_2 and PGI_2 also exert anti-inflammatory effects and improve peripheral insulin resistance, NASH and related fibrosis. Due to the complex action of PGs in the inflammatory process, the use of COX inhibitors in T2DM and NAFLD treatment should be given more consideration, and further explorations are highly warranted.

7. Conclusion and future perspectives

The comorbidity of T2DM and NAFLD is well recognized and has become an area of increased investigation over past decades. Nowadays, considerable evidence has highlighted the roles of 2-series PGs in the pathogenesis of T2DM and NAFLD. 2-Series PGs are important lipid molecules that are widely distributed in various organs. These exert multifunctional effects on the four highly intertwined pathogeneses of T2DM and NAFLD, including insulin resistance, hyperglycemia, hepatic lipid accumulation and chronic inflammation. PGs potently mediate insulin resistance, which subsequently induces pathological alterations including hyperinsulinemia, hyperglycemia, dyslipidemia and ectopic lipid accumulation. In addition, PGs can directly impact hyperglycemia by decreasing insulin secretion, pancreatic β-cell proliferation and increasing gluconeogenesis. In addition, PGs contribute to hepatic lipid accumulation by enhancing hepatic lipogenesis and decreasing TG output. Moreover, PGs distinctly establish a close interaction with inflammatory processes in the progression of T2DM and NAFLD.

Most 2-series PGs exert negative effects on the progression of T2DM and NAFLD. Therefore, the application of COX inhibitors such as aspirin and celecoxib beyond their conventional use on vascular diseases, rheumatoid arthritis and pain is emerging as a promising option for T2DM and NAFLD treatment. However, certain aspects of the application of PG pathways should be considered. First, some PGs are beneficial to the prevention of T2DM and NAFLD development to a certain extent, suggesting that the clinical use of COX inhibitors requires careful consideration and highlighting the potential therapeutic use of PGs and their derivates in the prevention and control of T2DM and NAFLD. Secondly, since the existing NSAIDs and COXIBs are associated with several side effects, it is meaningful to perform molecular modification of these drugs and develop new treatment strategies, to aim to accurately modulate the PG pathway in related organs such as the pancreas, liver and adipose tissues. Overall, due to the important role of 2-series PGs in T2DM and NAFLD, additional studies associated with the molecular mechanisms of PGs in the pathogenesis of T2DM and NAFLD are highly warranted. These studies will provide new and more precise therapeutic strategies based on targeting PG pathways in the treatment of these two diseases.

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Authors' contributions

JG, WW and XZ conceived the study. WW and XZ wrote and prepared the original manuscript. JG and WW contributed to the review of the manuscript. JG and WW were responsible for the funding acquisition. All authors read the final manuscript and agree to be accountable for the content of the work.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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