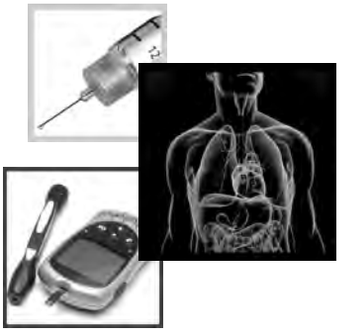
EDITORIAL

Diabetes Management



Fatty acid receptor GPR120: its potential role in islet function and Type 2 diabetes mellitus

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"GPR120 has critical roles in lipid metabolism and energy balance, providing crucial regulation of insulin metabolism and of normoglycemia."

Diabetes mellitus is a chronic disease that represents a major socioeconomic burden worldwide; approximately 90–95% of patients are diagnosed as Type 2 diabetes mellitus (T2DM) among the new cases of diabetes. Pancreatic islet β-cell failure is one of the key features of T2DM, which is resultant from chronic hyperglycemia and hyperlipidemia, thus eventually leading to β-cell insulin secretion deficiency and β-cell apoptosis. Specifically, compensatory β-cell insulin secretion becomes inadequate and T2DM risks increase when islet-cell failure develops as a result of various factors such as glucotoxicity and lipotoxicity [1]. Meanwhile, insulin resistance leads to hyperglycemia and lipid accumulation as islet β-cell compensatory responses to increased insulin resistance fall, concomitant with progressive reduction in islet β-cell function, leading to eventual islet failure and with decreased β-cell mass and insulin deficiency as seen in the later stages of T2DM [1]. Notwithstanding the existence of this evidence, the detailed mechanism(s) by which hyperglycemia and hyperlipidemia induce islet failure thus T2DM have yet to be elucidated.

In this context, chronic hyperglycemia dramatically upregulates pancreatic islet lipid metabolism through substrate availability, leading to changes in glucose and lipid metabolic enzymes and alteration of critical transcription factors [2]. Increased lipid accumulation and prolonged hyperglycemia are the most likely main causes of islet apoptosis and islet failure. Hyperlipidemia and lipotoxicity in islets, which are concomitant with decreased glucose-stimulated insulin secretion, contribute to islet dysfunction and increased induction of islet β-cell apoptosis [3]. In view of this fact, identification of agents that can target intra-islet lipid accumulation and glucose stress is required. In addition, islet lipotoxicity and glucotoxicity also trigger islet endoplasmic reticulum (ER) stress, activating apoptotic pathways and increasing misfolded protein formation, thus contributing further to increased

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apoptosis, common mechanisms known to increase both insulin resistance and islet dysfunction [4]. Therefore, ER stress regulation and reduction in islet inflammation, as well as reduction in the associated apoptosis, are potential targets for the maintenance of islet function.

Potential role of fatty acid receptors in pancreatic islets

It is well known that free fatty acids (FFAs) can act as metabolic substrates in pancreatic islet cells, contributing to reductions in insulin secretory responsiveness. This sort of effect is directly mediated by important signaling pathways for extracellular environmental factors through several cell surface G-protein-coupled receptors (GPCR), the so-called orphan receptors, on islet cells; they include GPR40, -41, -43, -84, -119 and -120 [5]. Among these, GPR40 and GPR120 are sensors for medium- to long-chain fatty acids, which can regulate islet insulin secretion [6]. GPR40 is one of the well-studied surface GPCRs for FFA in islet β-cells, and its signaling pathway contributes directly to the promotion of insulin secretion through increases in Ca^{2+} influx [7] and indirectly through stimulation of the release of incretin hormones [8]. Ablation of GPR40 reduces the compensatory response of islet insulin secretion to high-fat diet-induced insulin resistance [9]. Although GPR40 contributes to almost the half of FFA-induced acute insulin secretion, it may not be involved in the chronic effects of FFAs on insulin secretion [10]. Interestingly, the regulatory effect of GPR40 on insulin secretion is not altered by glucose challenge [9] and thus other signaling pathways are believed to be involved in the modulation of islet glucolipotoxicity in T2DM.

Potential role of GPR120 in islet function & the involvement of β-arrestin signaling

As another medium–long-chain fatty acid-sensitive orphan receptor, GPR120 has been identified as an omega-3 target, which is able to signal both anti-inflammatory and insulin-sensitizing effects [11]. Activation of GPR120 recruits β-arrestin 2 (βArrt2) to form a GPR120–bArrt2 complex that interacts with TAB1 so as to inhibit its interaction with TAK1, thereby suppressing proinflammatory signaling pathways, as well as increasing expression and translocation of glucose transporters in adipocytes [11]. In GPR120-ablated animals, insulin resistance was increased and the rescue effect of omega-3 supplementation on high-fat diet induced insulin resistance was abolished [11]. Furthermore and more interestingly, lack of a functional GPR120 decreases adipocyte differentiation and lipogenesis, as well as promotes hepatic lipogenesis and reduces insulin signaling, together contributing to the development of obesity, fatty liver and glucose intolerance. In adipocytes from obese humans, GPR120 expression is much higher than in adipocytes from lean controls, probably due to the mutated exon sequencing of GPR120 in obese subjects [12]. Overall, GPR120 has critical roles in lipid metabolism and energy balance, providing crucial regulation of insulin metabolism and of normoglycemia. Although GPR120 is indirectly involved in functional regulation of pancreatic islets which is one of the key organs in the control of blood glucose, its direct roles in the islet itself has yet to be fully elucidated. In our preliminary studies, GPR120 expression in islets was decreased by glucose but not by palmitic acid, in contrast to the effects of glucose on GPR40 but consistent with the earlier observation that high-fat diet-fed mice showed unaltered islet GPR120 mRNA levels [9]. These data indicate a potential glucose-dependent role of GPR120 in modulating islet lipid metabolism and islet β-cell function, with a potential involvement of bArrt2-TAB1/TAK1 signaling.

Potential SREBP–GPR120 signaling in islet function & the development of diabetes

Fish oil, which is rich in DHA, is reported to be a suppressor of sterol regulatory element-binding 1 in the mouse liver [13]. The sterol regulatory element-binding proteins (SREBPs) are transcription factors that are known for their roles in the regulation of lipid and cholesterol metabolism, while they have other nonclassical roles such as induction of cell apoptosis [4]. SREBPs exhibit relationships of their activity with glucose concentrations, suggestive of a regulatory role in the modulation of insulin signaling pathways, thus maintaining glycemic control [14,15]. In light of these findings, it is plausible to propose a role for SREBPs in pancreatic islet function. Indeed, several studies have shown that T2DM islets specifically overexpress SREBP-1, which contributes to β-cell glucolipotoxicity [16]. Increases in SREBP-1c, together with decreased IRS2, lead to insulin resistance in obese mice [17]. Furthermore, SREBPs trigger various factors known to impair insulin secretion, particularly under lipotoxic conditions [18]. Therefore, islet SREBP signaling might be a critical transcription factor for β-cell lipid metabolism and survival, contributing to

the pathogenesis of T2DM. Glucose can rapidly stimulate SREBP-1c maturation via the Jak/STAT pathway and increase lipogenic gene expression, thereby increasing lipogenic flux and lipid accumulation in skeletal muscle cells, and thereby increasing muscle insulin resistance [19]. In this regards, omega-3 is a good suppressor of SREBP-1c, associated with improvement of hepatic triglyceride metabolism and reduced lipid accumulation, partially through activation of PPARγ [20]. We therefore hypothesize that the diminished GPR120 signaling seen with high-glucose concentrations may increase islet SREBP production, in turn increasing lipid accumulation in pancreatic islet cells and thus increasing islet inflammation, apoptosis and dysfunction.

In light of this information and of the gaps in knowledge identified, demonstration of beneficial effects of increased availability of GPR120 signaling on the adverse effects of glucotoxicity, lipotoxicity and inflammation through local β-arrestin and/or SREBP regulation will establish a critical role for GPR120 in islet function; it will provide support for clinical observations that omega-3 supplementation has beneficial effects on the risk of T2DM; it will also provide a novel and safe therapeutic strategy for maintaining islet function and glycemia.

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