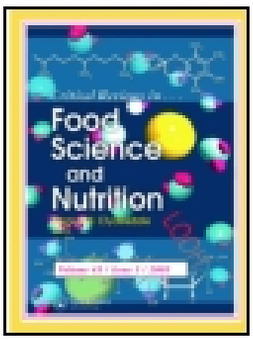

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REVIEW

Regulation of glucose metabolism by bioactive phytochemicals for the management of type 2 diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is the most prevalent disease and becoming a serious public health threat worldwide. It is a severe endocrine metabolic disorder that has the ability to induce serious complications in all kinds of organs. Although mechanisms of anti-diabetics have been described before, we focus here on the cellular and physiological mechanisms involved in the modulation of insulin and glucose blood levels. As obesity and inflammation are intimately associated with the development of T2DM, their possible relationships are also described. The effects of gut microbiota on insulin resistance have been recently investigated in clinical trials, and we discuss the potential mechanisms by which gut microbiota may improve glucose handling, especially via the metabolism of ingested phytochemicals. Among the historically supported effects of phytochemicals, their therapeutic potential for T2DM leads to consider these natural products as an important pool for the identification of novel anti-diabetic drug leads. This current research extends the descriptions of anti-diabetic effects of plants that are used in traditional medicines or as nutraceuticals. The objective of the present review is to make a systematic report on glucose metabolism in T2DM as well as to explore the relationships between natural phytochemicals and glucose handling.

KEYWORDS

Type 2 diabetes; metabolic pathways; gut microbiota; phytochemicals; new therapies

Introduction

Diabetes mellitus is a well-known public health issue, affecting 415 million people, causing around 5 million deaths and accounting for 14.5% of all-cause mortality worldwide in 2015 (International Diabetes Federation 2015). The World Health Organization reports that the worldwide prevalence of diabetes is expected to increase up to 642 million by the year 2040, with many new cases of diabetes occurring in developing countries, especially in Asia. This increase in diabetes prevalence will inevitably lead to the intensification of diabetes-related complications such as retinopathy, neuropathy, and cardiovascular diseases. Bommer et al. (2017) reported that the cost of diabetes worldwide was 1.31 trillion US dollars, or 1.8% of the global gross domestic product in 2015. The global estimation of diabetes expenditures is predicted to increase by 490 billions in the next 20 years (Zhang et al. 2010a). Type 2 diabetes mellitus (T2DM), also known as "non-insulin-dependent diabetes," accounts for 90% of all cases of diabetes. It is the most prevalent disease in many modern societies and is becoming a serious public health threat worldwide. It is a complex metabolic disorder characterized by insulin resistance (IR) and impaired islet β-cell function, which together result in an inability to supply sufficient insulin to meet the body's demands and eventual β cell loss. Individuals with T2DM experience difficulty in controlling their blood sugar level, which leads to high blood glucose level, glucose in the urine, and high blood insulin level.

The prevalence of T2DM has dramatically increased in Europe with 60 million people living with diabetes and 32 million more at risk (Schwarz et al. 2008). The Centers for Disease Control and Prevention reported diabetes mellitus

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affected 29.1 million Americans, or 9.3% of the population (Crawford 2017). Even more, the prevalence of T2DM in western countries reached an epidemic level, but which is worse in Asia (Kong et al. 2013). In Asia, rapid economic development in many countries has driven a great increase in diabetes prevalence in the recent decade. The prevalence of T2DM is rising, with many Asian countries featured in the top 10 countries with the highest numbers of persons with diabetes. Urbanization is linked to reduced physical activity, increased obesity rates, and a dietary shift toward more refined carbohydrates and increased fat intake (Ning et al. 2009; Ramachandran et al. 2008). Worldwide, China, and India are the top two countries with the most number of individuals suffering from diabetes, with Indonesia and Japan in seventh and ninth place, respectively (International Diabetes Federation 2015). The prevalence of diabetes in South East Asia is also expected to increase by 70% in the next 20 years. Risk scores derived in Caucasian populations might not perform well in Asian populations as there are different biological factors involved in the development of diabetes. Compared to Caucasians, the onset of diabetes in Asians occurs at lower body mass index (BMI) levels and at younger ages (Hu 2011). South Asians also experience early declines in β-cell function, as well as with more insulin resistant and a younger age of diabetes onset compared to other ethnic groups (DECODE Study Group 2003; Gujral et al. 2013). Studies have shown that Asian ethnicities have a 2- to 4-fold risk of developing T2DM compared to Caucasian ethnicity (Sacks et al. 2012; Urquia et al. 2011). In addition, Asians with T2DM are especially vulnerable to renal injury when compared to Caucasians (Kong et al. 2013). The waist-to-stature ratio is more strongly associated with T2DM than BMI in most Asian populations (He et al. 2009).

The mechanisms for this increased risk are likely a combination of both genetic and environmental factors (Tutino et al. 2014), including the fact that obesity may have a greater effect on IR in these populations compared to Caucasians (Retnakaran et al. 2006). More important, genetic factors play a crucial role in the pathogenesis of T2DM in the Asian population. A study reported that Asian Indians are excessively IR compared with Caucasians (Abate and Chandalia 2001). Recently, an excessive maternal transmission of T2DM was identified among Asian Indians (Chaithri et al. 2012). On the other hand, many environmental factors such as diet, lifestyle, are associated with the risk of T2DM in Indians (Ramachandran et al. 2001), as well as in other Asian populations such as Chinese. The high consumption of white rice, especially in East Asian, is significantly associated with a higher risk of T2DM (Hu et al. 2012).

The gut microbiota is essential for the development and regulation of host metabolism. The intestinal mucosal surface protects the host from pathogenic invasion; while it is tightly regulated with regard to its permeability and can influence the systemic energy balance. Consumption of diets high in sugar influences the microbiota composition and leads to an imbalanced microbial population in the gut. It has been hypothesized that the gut microbiota could be part of a mechanistic link between the consumption of unbalanced diets and T2DM (Qin et al. 2012).

While the causes of T2DM are still not completely understood, it is generally believed that T2DM results from both genetic and environmental factors. In recent years, great attention has being paid by the scientific community to the beneficial effects of phytochemicals on this disease (Cao et al. 2018; Carpéné et al. 2015; Loizzo et al. 2016; Vinayagam, Xiao, and Xu 2017; Xiao et al. 2015; Xiao and Högger 2015; Xiao 2017). The current review is to summarize the advance on the glucose metabolism by natural phytochemicals in T2DM, as well as to explore the relationship among metabolic pathways, gut microbiota, obesity, and inflammation. How microbial metabolites of the dietary phytochemicals modulate host glucose metabolism is also discussed.

What should reproduce the anti-diabetics: insulin mechanisms of action?

There are two main pathways for body to adjust the blood glucose: one by increasing the circulating levels of insulin and another by boosting the non-insulin-dependent glucose metabolism. Insulin secretion by β-cells of pancreatic islets plays one of the most important roles in our body for adjusting blood glucose and is essential for insulin-regulated glucose metabolism. One of the most rapid actions of insulin is to increase glucose uptake via the recruitment of the insulin-regulated glucose transporters (GLUT) in cells having functional insulin receptors, insulin signaling cascade and GLUT type 4 (GLUT4) carriers. By the way, insulin reduces blood glucose levels by removing it from the circulation. Insulin also triggers glycogen synthesis, glycolysis, and inhibition of hepatic glucose production, and at last regulates cell proliferation, apoptosis, and autophagy (Aikawa et al. 2000; Kane et al. 2002; Xing et al. 2015; Yamaguchi and Otsu 2012).

Insulin is not the sole glucoregulatory hormone, since also contributing to the glucose homeostasis are glucagon and amylin produced by the endocrine pancreas, and the incretins produced in the intestine: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide. Other hormones also participate, such as growth hormone, epinephrine, cortisol, and the atrial natriuretic peptides, which have recently shown to increase glucose uptake in GLUT4-containing tissues (Coué et al. 2018). However, this review will examine only the major metabolic pathways that have been researched and reported for explaining the mechanisms of anti-diabetics by insulin-like actions (Fig. 1).

IRS/PI3K/AKT-GLUT4 pathway activators

Insulin receptor substrate 1 (IRS-1) and IRS-2, the two major substrate proteins generated by phosphorylation of Ser/Tyr in insulin receptor, bind to and activate the phosphatidylinositol 3-kinase (PI3K). The activation of PI3K is a key step of insulin-induced glucose transport (Tanti et al. 1994). In some extent, the protein p85 sub-unit of PI3K can

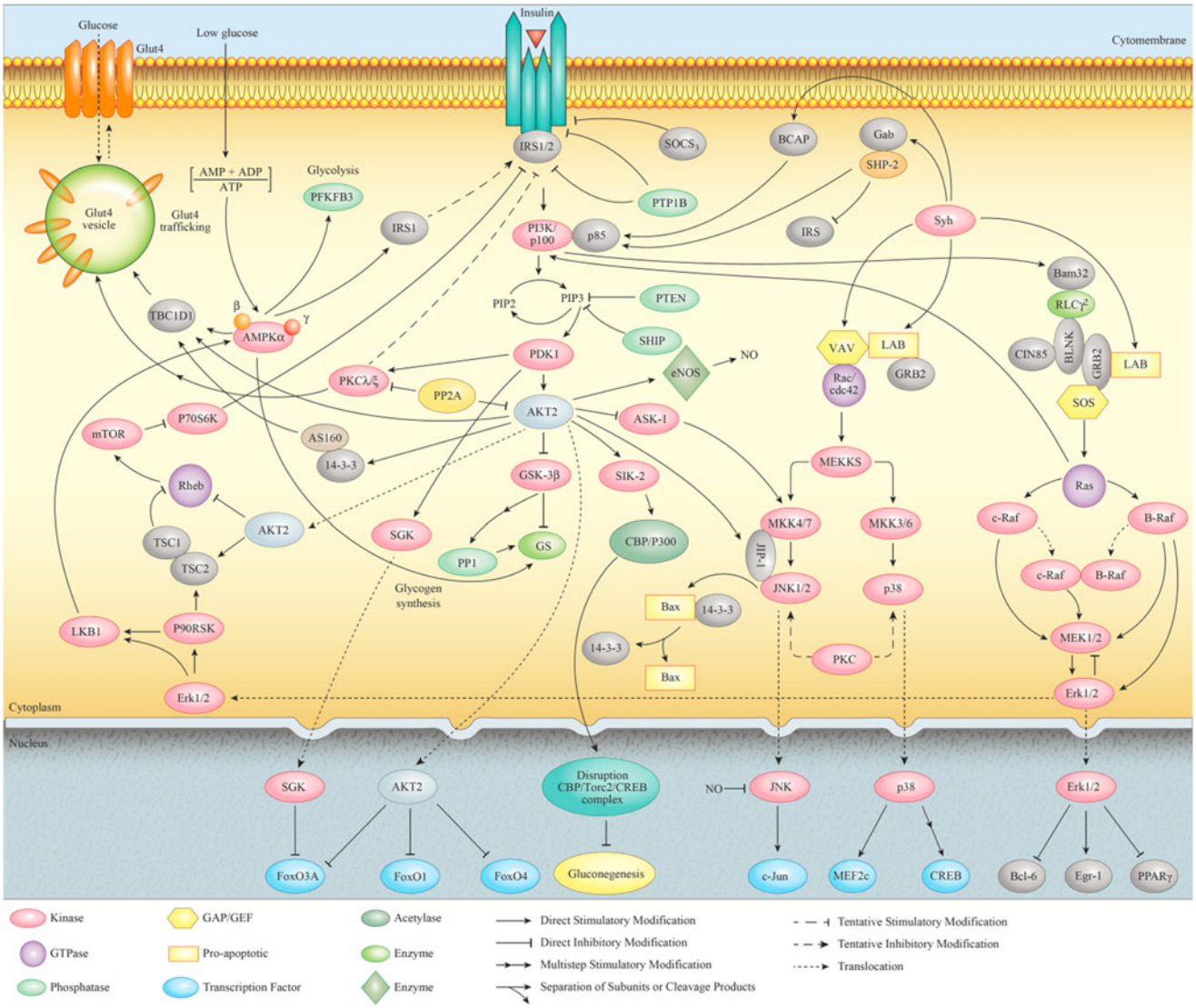

Figure 1. Main signaling pathways recruited to adjust the blood glucose.

improve the IR. The generation of phosphatidylinositol 3,4,5-trisphosphate, which can lead to activation of the three known AKT (protein kinase B) isoforms by pyruvate dehydrogenase kinase, isozyme 1 (PDK1), is accompanied by the activation of PI3K. AKT is by phosphorylation of Thr308 by PDK1 and is a key pleiotropic kinase that affects insulin function on glucose metabolism. It can deactivate glycogen synthase kinase (GSK) and inhibit some pro-apoptotic factors, such as FoxO3A, FoxO1, and FoxO4 in cell nucleus (Paradis and Ruvkun 1998), and cytoplasmic GSK-3β with the development of cell (Mora et al. 2005). Meanwhile, it can also activate the translocation of GLUT4 by phosphofructokinase (Kadowaki et al. 2012; Kahn and Saltiel 2011; Manning and Cantley 2007). At the cell surface, GLUT4 permits the facilitated diffusion of circulating glucose down its concentration gradient into muscle and fat cells. Within cells, glucose is rapidly phosphorylated by glucokinase in the liver and hexokinase in other tissues to form glucose-6-phosphate, which then enters glycolysis or is polymerized into glycogen. Glucose-6-phosphate cannot diffuse back out of cells, which also serves to maintain the concentration gradient for glucose to passively enter cells (Watson et al. 2004). Moreover, GLUT4 finalizes the IRS1/2/PI3K/AKT signaling pathway, as it is the insulin-regulated glucose transporter.

JNK/MAPK/ERK pathway

The mitogen-activated protein kinase (MAPK) signaling pathways, including c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinases (ERK) pathway, are among the more altered pathways in models of diabetes and obesity (Chen et al. 2018). The JNK signaling has been shown to contribute to a variety of pathological processes associated with diabetes, obesity, heart disease, and cancer (Kane et al. 2002). The molecules JNKs, key members of MAPK family, are named after their capacities to phosphorylate and activate the Jun family of AP-1 transcription factors (Chang and Karin 2001; Hibi et al. 1993). Compared with classical MAPK/ERK signaling, JNK pathway is more closely related to glycometabolism than lipid metabolism. The JNK/MAPK pathway comprises a sequential three-tiered

kinase cascade. An upstream MAP3K (MEKKs/ASK1) phosphorylates and activates the MAP2K (MKK4, MKK7, MKK3, or MKK6), which then regulates the downstream MAPKs (such as JNKs/p38 MAP kinase) (Chang and Karin 2001; Meloche and Pouysségur 2007). The ASK1 could lead to negative regulation of IRS1 and be deactivated by AKT2. MEKKs are activated by Vav proteins, being members of the guanine nucleotide-exchange factors which are GDP/GTP exchange factors for Rho/Rac GTPases. Vav is activated by tyrosine phosphorylation of Syh and SHP-2, which can directly inhibit phosphorylation of IRS. Small G-protein can be distributed into Rho, Rac, and Cdc42 for its function. In other words, the activation of MEKKs is accompanied with activation of regulators of cell cycle or cell reorganization such as Rac and Cdc42.

Advances in genomics and molecular genetics have revealed that the extracellular signal-regulated kinase (ERK) signaling pathway is known as MAPK pathway and a key signaling cascade for modulating multiple cellular functions by phosphorylating and inducing its downstream targets (Chen et al. 2001). ERK/MAPK pathway plays an important role on diabetes and malignancies by the regulation of cell differentiation, proliferation, growth, apoptosis, gene expression, and others (Degen et al. 2012; Mandal, Becker, and Strebhardt 2016; Mebratu and Tesfaigzi 2009; Reddy et al. 2003; Zhang and Liu 2002). The SHP-2 and Syh of Erk/MAPK pathway as initial signaling is the same with JNK/MAPK pathway, which initiates the formation of a "signalosome" composed of the tyrosine kinases, GRB2/BLNK-related adaptor proteins, signaling enzymes such as PLCγ2, PI3K, and Vav, and small GTPases such as SOS and Ras (Goodnow et al. 2010; Harwood and Batista 2010). SOS is involved in Ras signaling activation and also acts as a guanine nucleotide exchange factor for Rac to transduce signals from Ras to Rac. In addition, the Ras GTPase subfamily plays a key role in this pathway and activates the MEKK1/2 by phosphorylation of B-Raf or c-Raf. Furthermore, MEK1/2 can activate ERK kinases (ERK1/2), which inhibits Bcl-6 and PPARγ or induces Egr-1 DNA-binding activity in the nucleus.

IRS1/AKT/mTOR-AMPK signaling pathway

IRS1/AKT/mTOR signaling pathway represents a key pathway for genetic variation, diabetes, and obesity by cell growth control and autophagy inhibition in cytoplasm (Ganley et al. 2009; Magnuson et al. 2012). PI3K first converts phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3), which activates AKT2 via PDK1 kinase. After that, the activated AKT2 inactivates the conserved serine/threonine protein kinases mTOR (mammalian target of rapamycin) by Rheb-GTPase, which is controlled directly or indirectly by AKT2, or indirectly through the control of tuberous sclerosis complexes (TSC1/TSC2). Finally, mTOR inhibits ribosomal protein S6 kinase (p70S6k), which intensely inhibits phosphorylation of IRS1 by the insulin receptor (Yin et al. 2017). However, AMP-dependent protein kinase (AMPK) signaling is opposite to IRS1/AKT/mTOR pathway and gets in touch with each other by Erk1/2 in cytoplasm. AMPK has been identified as a critical positive regulator of autophagy, especially as an emerging drug target for T2DM and the metabolic syndrome (Hardie 2011; Zhang et al. 2009). AMPK not only directly activates IRS1 and participates in blood glucose metabolism, but also induces autophagy by inhibition of AKT/mTOR pathway. Since under low-glucose conditions, the increase in AMP/ATP ratio activates AMPK, this tends to stimulate hexose uptake.

The major tissues involved in the regulation of glucose homeostasis

T2DM is characterized by the increase in blood glucose levels, and such excess of glucose alter in a non-enzymatic manner the circulating proteins by glycation. Moreover, T2DM is a non-contagious and severe endocrine metabolic disorder that induces serious complications in various organs (Su et al. 2017), either as a consequence of excessive glucose or in response to be altered levels of hormones and signaling molecules that impact all these organs toward an integrated function. Indeed insulin is increased in T2DM, leading to a state called hyperinsulinism. This aims to stimulate glucose uptake by the so-called insulin-responsive tissues (mainly skeletal and cardiac muscles as well as adipose tissues). Unfortunately, hyperinsulinism is often accompanied by IR, a state of weak responsiveness of the target tissues, thereby the increased hormone levels do not achieve to elevate sufficiently the glucose uptake by peripheral tissues and cannot efficiently elevate the rate of glucose removal from the circulation. Instead, chronically elevated insulin results in increased hepatic glucose output and *de novo* lipogenesis.

In insulin-sensitive organs, such as skeletal muscle and adipose tissue, epigenetic modifications might be important in the pathogenesis of T2DM, as the changes alter the function profile of genes influencing the control of glucose metabolism (Fig. 2). T2DM also develops an inability of the cells to utilize the secreted insulin for helping in glucose management: then corresponds to glucose intolerance and IR (Catalogna et al. 2016; Gugliucci 2016; Sharabi et al. 2015). It can cause severe secondary complications such as liver dysfunction, kidney failure, heart attack, and nerve damage (Hoshino, Hoshino, and Nishino 2016; Jin et al. 2015; Lastra et al. 2010; Manna et al. 2010). The life-threatening T2DM associated complications include long-term damage, dysfunction, and failure of the vital organs such as eyes (retinopathy), kidneys (nephropathy), peripheral nerves (neuropathy), and heart vessels (cardiovascular diseases).

Insulin normally inhibits gluconeogenesis and initiates glucose uptake in the muscle and adipose tissues for the maintenance of normal blood glucose levels. Adipose tissue acts as a critical metabolic organ and produces a number of hormones and cytokines such as adiponectin, leptin, tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and MCP1, that in turn modify the functions of other cells in the organism (Kristensen et al. 2015; Zhang et al. 2016). Adiponectin

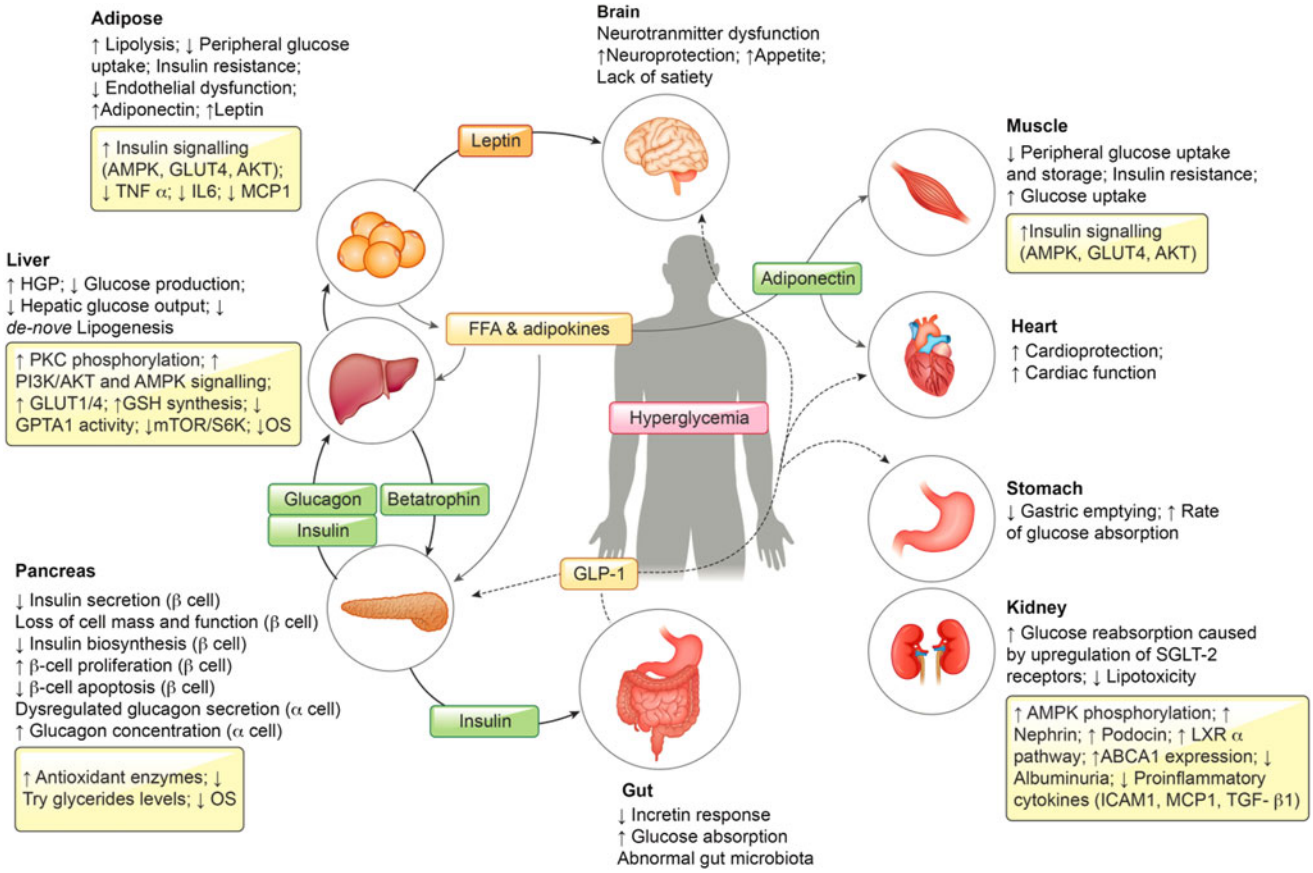

Figure 2. Tissues involved in the regulation of glucose homeostasis.

secreted from adipose tissue exerts insulin-sensitizing and anti-atherogenic activities. However, in adipose tissue, hyperglycemia enhances lipolysis and endothelial dysfunction. Lastly, in the digestive tract, high blood glucose levels inhibit incretin response and lead to glucose absorption and abnormal gut microbiota (Zappas et al. 2017).

Pancreas plays a critical role in glucose homeostasis since it is its endocrine part that secretes the glucose-lowering hormone insulin and its opponent glucagon (Grgurevic et al. 2016). Insulin decreases blood glucose levels. However, long-term high blood glucose levels impair insulin secretion by pancreatic β-cells and a loss of cell mass and insulin biosynthesis capacity can occur (Keane and Newsholme 2014; Mohan et al. 2015; Rutter et al. 2015). Similarly, sustained hyperglycemia can lead to dysregulated glucagon secretion by pancreatic α-cells and elevated glucagon concentration (Song et al. 2014).

Liver also plays an important role in ameliorating T2DM via participating in PKC phosphorylation, P13K/AKT and AMPK signaling regulation (Steinbrenner 2013), GLUT1/4 and glutathione (GSH) synthesis, as well as decreasing glutamic-pyruvic transaminase activity (GPTA), mTOR/S6K, and oxidative stress (Cordero-Herrera et al. 2015). While most tissues are unable to utilize the excess of secreted insulin to affect glucose metabolism, the resistance in liver produces increase in hepatic glucose production, high hepatic glucose output, and *de novo* lipogenesis (Catalogna et al. 2016; Gugliucci 2016; Sharabi et al. 2015).

In addition, hyperglycemia promotes lipid accumulation and glucose reabsorption caused by upregulation of sodium-dependent glucose transporters 2 (SGLT2) receptors in the diabetic kidney (Vallon and Thomson 2017; National Kidney Foundation 2012). Furthermore, it has been proven that proinflammatory cytokines such as MCP-1 and TGF-β1 play a key role in the development of diabetic nephropathy (Du et al. 2015). Persistent hyperglycemia not only promotes the rate of glucose absorption and slows gastric emptying in stomach, but also alters cardiac function (Chen et al. 2017; Maji and Samanta 2017). Similarly, IR induces neurotransmitter dysfunction (Hiriart et al. 2014), declines neuroprotection, increases appetite, and reduces satiety (João et al. 2016).

Type 2 diabetes, obesity, and inflammation

Obesity is strongly associated with an increased risk of T2DM and cardiovascular disease. All these conditions are also now recognized as having an inflammatory component (Fig. 3). A number of cytokines and inflammatory signaling pathways have been shown to be involved in the development of T2DM, thus, increased serum levels of several inflammatory biomarkers, including tumor necrosis factor-α (TNF-α), C reactive protein (CRP), high molecular weight adiponectin, and interleukin (IL)-6, produced at least in part by white adipose tissue in obese subjects, have been reported. The potential role of inflammation in obesity

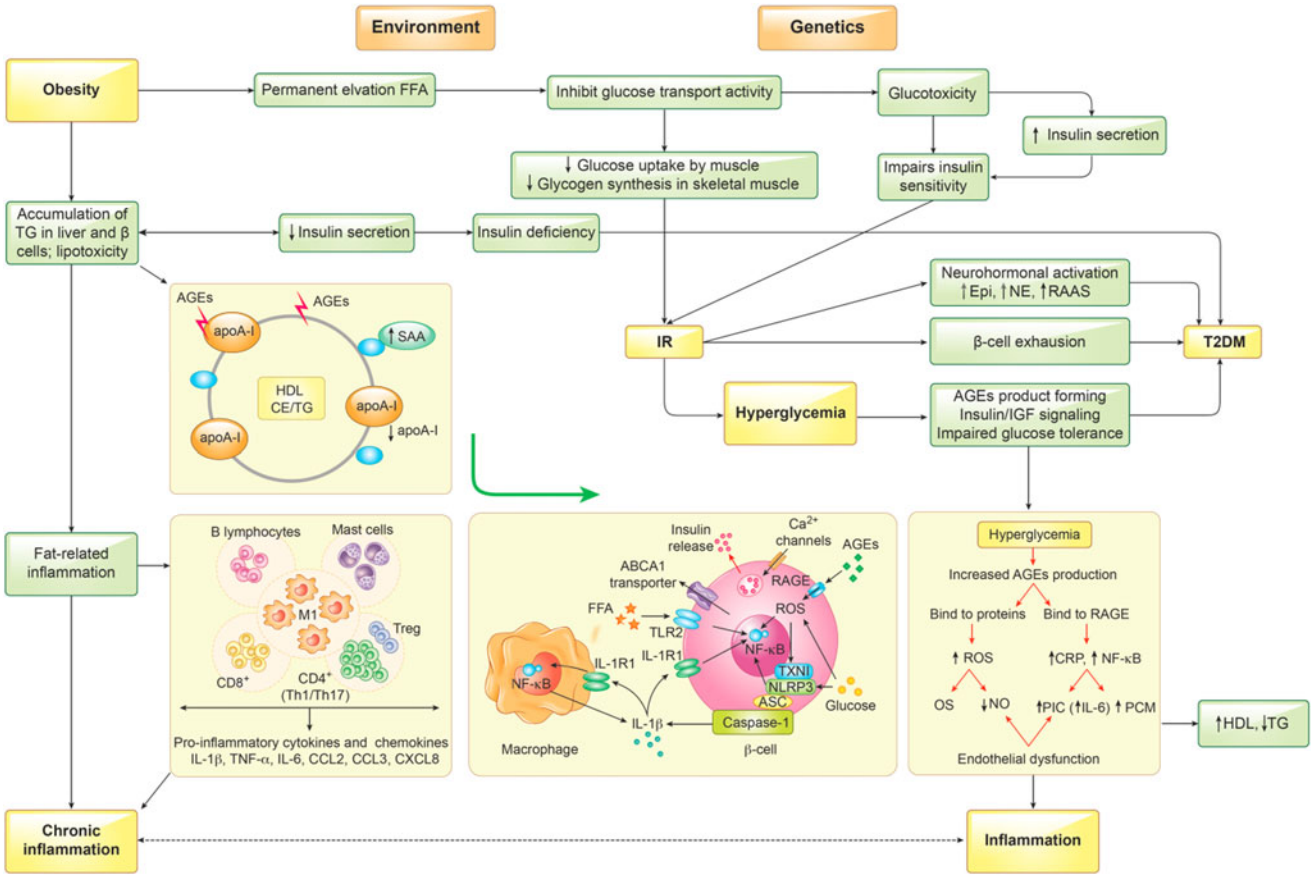

Figure 3. The relationships among type 2 diabetes, obesity, and inflammation.

complications is offering further insight into the relationship between T2DM and cardiovascular disease, and it has led to a greater interest on specific therapeutic targeting. Accordingly, poor glycemic control is positively correlated with levels of inflammatory cytokines such as IL-6 and IL-1β in the circulating blood stream (Calle and Fernandez 2012). However, only scarce studies have also shown that the benefit of anti-inflammatory medication for the treatment of T2DM (Weisberg et al. 2008). In this context, there is evidence that a hyperglycemic state increases blood–brain barrier permeability (Hawkins et al. 2007), allowing these inflammatory cytokines to reach neuronal environment (Perry et al. 2017).

Effects of gut microbiota and metabolic endotoxemia/bacteremia on diabetes

Altered gut microbiota composition in diabetes

The endogenous gut microbiota is considered to be a "forgotten organ" participating in the whole-body metabolism (O'Hara and Shanahan 2006). There are approximately 10^{14} bacteria belonging to more than 1,000 phylotypes in human gut (Whitman et al. 1998). Although the composition of human gut microbiota shows great variation among individuals, most bacteria belong to six well-known bacterial divisions/phyla: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* (Eckburg et al. 2005; Lozupone et al. 2012). The *Bacteroidetes* and *Firmicutes* account for 60–90% of the consortium (Neish 2009). Healthy human gut mainly harbors anaerobic bacteria, the number of which is far more than the aerobic and facultative anaerobic bacteria (Sommer and Bäckhed 2013). They comprised predominant obligatory anaerobes belonging to the genera *Bacteroides*, *Eubacterium*, *Clostridium*, *Ruminococcus*, *Peptococcus*, *Peptostreptococcus*, *Bifidobacterium*, and *Fusobacterium*. The following subdominant facultative anaerobes are *Escherichia*, *Enterobacter*, *Enterococcus*, *Klebsiella*, *Lactobacillus*, and *Proteus* (Guarner and Malagelada 2003). However, human gut harbors limited numbers of archaea (mainly *Methanobrevibacter smithii*), eukaryotes (mainly yeasts), and viruses (mainly phages) (Reyes et al. 2010). Several experimental reports have suggested that diet plays a dominant role in forming and changing the bacterial community composition of human gut (Hildebrandt et al. 2009). Moreover, the compositional changes in gut microbiota represent an etiological factor in the development of both IR and T2DM. Recent studies have shown that the gut microbial inhabitants have an influence on the onset of metabolic diseases such as obesity and diabetes. Turnbaugh et al. (2006) confirmed that obesity is associated with the shift in relative abundance of the two dominant bacterial phyla, the *Firmicutes* and the *Bacteroidetes*. Specifically, a larger proportion of *Firmicutes* and relatively lower abundance of the phylum *Bacteroidetes* were observed in obese individuals, suggesting that both of them were correlated with energy intake and adiposity (Murphy et al. 2010; Ravussin et al. 2012).

In contrast to obesity, T2DM-associated microbial dysbiosis is comparatively modest. The gut microbiome in T2DM is characterized by lower levels of short-chain fatty acids (SCFA)-producing bacteria (*Eubacterium rectal*, *Faecalbacterium prausnitzii*, *Roseburia intestinalis*, etc.) and higher levels of known or potential opportunistic pathogens (*Clostridium hathewayi*, *C. ramosum*, and *Eggerthella lenta*) (Qin et al. 2012). Pioneering studies have shown that functional changes in gut microbiota contribute to the increases in plasma glucose concentrations (Clemente et al. 2012). Influence of gut microbiota on the development of diabetes is summarized in the present review (Fig. 4).

Gut microbiota and host energy balance and storage

The gut microbiota has been reported to participate in the host metabolic functions and energy balance by fermenting undigested carbohydrates, which activate host satiety and decrease food intake (Chambers et al. 2015). Undigested dietary carbohydrates are important sources of energy for human colon microbiota, which can utilize nearly all of the major plant and complex glycans, such as two members of the *Bacteroides fragilis* group: *Bacteroides thetaiotaomicron* and *B. ovatus* (Martens et al. 2011). Interestingly, Bifidobacteria are dominant and prevalent members of the (early) microbiota having access to glycans in the gut through mutualistic cross-feeding or resource-sharing activities, indicative of a "social behavior". The SCFAs (principally acetate, propionate, and butyrate) modulate the intestinal barrier functions and can escape from the gut to influence systemic health as well. Being bacterial fermentation products, these SCFAs can act in colonic epithelium (butyrate) or be absorbed to act further in peripheral tissues (acetate and propionate) (Lin et al. 2012). SCFAs activate the gut hormones GLP-1 and peptide YY (PYY) through G-protein coupled receptor 43/41 (GPR 43/41), also known as free fatty acid receptor 2/3 (FFAR 2/3) (Kaji et al. 2014). Several seminal research studies showed that GLP-1 and PYY suppress appetite and energy intake (Lin et al. 2012; Nøhr et al. 2013; Tolhurst et al. 2012). GLP-1 is a gut hormone, secreted from the intestine in response to meal ingestion, which stimulates insulin secretion and inhibits glucagon release in a dose-dependent fashion (Mazidi et al. 2017). Kjems et al. (2003) reported that GLP-1 led to increased insulin secretion in T2DM patients. The activated GPR 43 inhibits fat accumulation in adipose tissue by suppressing insulin signaling in adipocytes (Kimura et al. 2013). The same GPR 43 receptor also participates in regulation of inflammatory responses in immune cells (Maslowski et al. 2009). The impacts of microbiota on IR and metabolic syndrome were reported in males who received an autologous fecal microbiota transplant, or an allogenic transplant from healthy donors. Subjects showed a significant improvement in peripheral sensitivity to insulin corresponding to an increase in microbial diversity in the bowel and butyrate-producing bacteria (Vrieze et al. 2012).

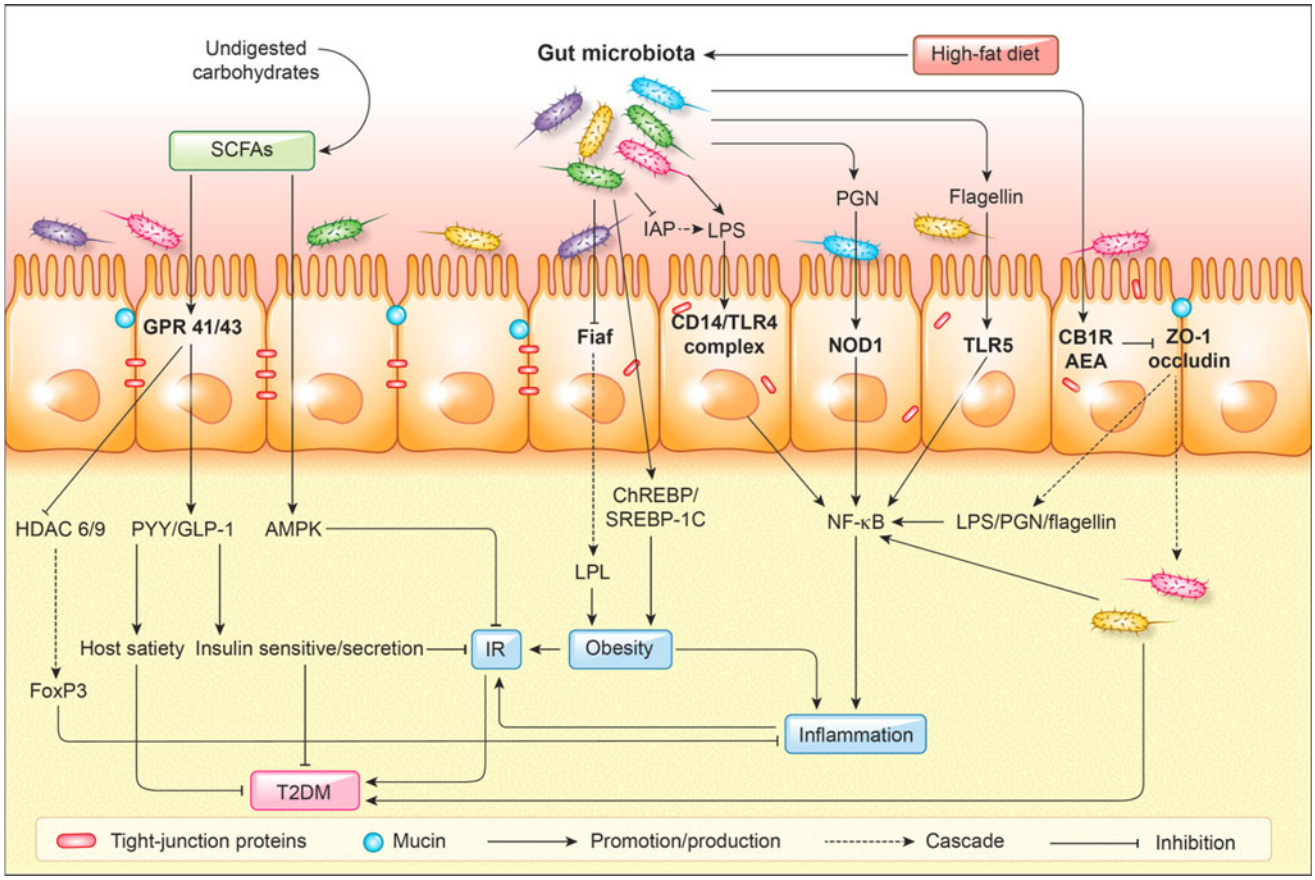

Figure 4. Effects of gut microbiota and metabolic endotoxemia/bacteremia on diabetes mellitus.

Butyrate and acetate were reported to elevate (AMPK) activity (Gao et al. 2009; Sakakibara et al. 2006), which then stimulates glucose uptake and fat oxidation as well as inhibits fatty acid and glycogen synthesis (Inoki et al. 2012). Moreover, acting as a histone deacetylase 6/9 (HDAC 6/9) inhibitor, butyrate was proved to promote FoxP3 expression and both number and function of FoxP3 (+) Treg cells (Beier et al. 2012; Tao et al. 2007). On the other hand, the gut microbiota promotes fat storage by suppressing the fasting-induced adipose factor (Fiaf), which is a circulating lipoprotein lipase inhibitor in the gut epithelium (Bäckhed et al. 2007). The resulting increased lipoprotein lipase activity was associated with the microbiota-induced enlargement of adipose tissue (Bäckhed et al. 2004). The gut microbiota also markedly enhances the hepatic triglyceride synthesis by activating the gene expression of the two key transcriptional factors: carbohydrate response element binding protein (ChREBP) and sterol response element binding protein 1c (SREBP-1c) (Shen et al. 2013). ChREBP and SREBP-1c are both critical for hepatocyte lipogenesis due to their independent effects in mediating glucose signaling and insulin action in liver, respectively, thus improving glucose absorption and insulin levels (Dentin et al. 2004). Hence, the influences of gut microbiota on host energy balance and storage represent a possible pathway linking gut microbiota and obesity and diabetes. The proper modification of diet resulting in functional rearrangement of microbiome could be considered to be treatment of first stages of T2DM (Zhao et al. 2018b).

Metabolic endotoxemia/bacteremia, gut barrier function and diabetes

Gut microbiota-derived metabolic endotoxemia is reported to participate in the onset and progression of inflammation and metabolic complications. Several studies have demonstrated that dietary fat facilitates the development of metabolic endotoxemia, such as increased plasma levels of bacterial lipopolysaccharide (LPS) that is a component released from the cell wall of Gram-negative bacteria (Amar et al. 2008). LPS is one of the pathogen-associated molecular patterns (PAMPs) that also include peptidoglycan (PGN), flagellin, lipoproteins, and even more factors. The PAMPs are recognized by the pattern-recognition receptors (PRRs), including the Toll-like receptors (TLRs) and the Nod-like receptors (NLRs). The interaction between the PRRs and the PAMPs induces cytokine and interferon production, which triggers the proinflammatory signaling cascades in body peripheral tissues of the body (Icaza-Chávez 2013).

LPS and PGN molecules bind to TLR4 and NOD1 receptors, respectively, thus participating in diet-induced inflammation and IR (Cani et al. 2007; Schertzer et al. 2011). TLR5 is expressed on the apical and basolateral surface of intestinal epithelium, which detects bacterial flagellin from both Gram-positive (e.g., *Listeria monocytogenes*) and Gram-negative bacteria (e.g., *Salmonella typhimurium*) (Hayashi et al. 2001). The activation of TLR5 strongly promotes nuclear factor NF-κB production and driven inflammatory responses (Letran et al. 2011). The gut mucosal surface is the key site of pathogenic bacteria and metabolic endotoxemia entry into the body and the initiation of metabolic endotoxemia. The endocannabinoid lipid anandamide (AEA) and its receptors cannabinoid receptors 1 (CBR1) in endocannabinoid (eCB) system are involved in the regulation of gut barrier function during obesity (Alhouayek and Muccioli 2012). Muccioli et al. (2010) found that gut microbiota regulates the CB1R expression and AEA content in the intestine. Furthermore, such endocannabinoid (eCB) system regulates epithelial permeability through the distribution and localization of tight-junction proteins (Muccioli et al. 2010). Additionally, mucus layer has long been recognized as an important ingredient providing protective gut barrier for the host. Muc2 is the major glycosylated mucin produced in the small and large intestine (Johansson et al. 2008). Normal gut microbiota can stimulate the secretion of Muc2 mucin in the goblet cells to ensure the integrity of the mucous layer structure and thus maintain gut barrier function (Johansson and Gordon 2011). Altogether, improvement of gut barrier integrity reduces metabolic endotoxemia and bacteremia, as well as lowers inflammation and glucose intolerance. Intestinal alkaline phosphatase (IAP) has been recognized to play a crucial role in LPS detoxification by dephosphorylating and detoxifying the phosphate residues of LPS (Bates et al. 2007). More interestingly, expression of IAP has been shown to be regulated by the gut microbiota and its activity could be increased by the diet (Lallès 2010). Enhanced IAP activity may, therefore, contribute to the reduction of metabolic endotoxaemia and gut permeability in T2DM and obesity.

Future physiological studies are needed to elucidate how the intestinal branched chain amino acids and other amino acids enter the bloodstream and from which intestinal location they are absorbed. Furthermore, investigations of how dietary changes alone or in combination with microbial or pharmacological interventions may impact the microbiome. Gut microbiota are also responsible for the extensive metabolism of phytochemicals such as polyphenols and hence contribute largely to the oral bioavailability of phytochemicals and thereby influences their potential antidiabetic activities (Eid et al. 2017).

Probiotics and/or prebiotics could be a promising approach to improve insulin sensitivity by favorably modifying the composition of the gut microbial community, reducing intestinal endotoxin concentrations, and decreasing energy harvest. The anti-diabetic effects of probiotics include reduction of proinflammatory cytokines via a NF-κB pathway, reduced intestinal permeability, and lowered oxidative stress. The ability to produce SCFAs is a feature shared by many different probiotic taxa. SCFAs play a key role in glucose homeostasis through multiple potential mechanisms of action in tissues: (1) insulinotropic and satiety effects mediated by gut hormones; (2) GLP-1 and peptide YY production; (3) β-cell-protective effect due to reduced oxidative stress; (4) decreased pro-inflammatory cytokines; (5) antilipolytic activity; and (6) enhanced insulin sensitivity via GLUT4 through the up-regulation of AMPK signaling

(Favaretto et al. 2014). Moreover, the antidiabetic effect has been shown after administration of probiotics containing certain strains of *Lactobacillus*, with a concomitant reduction in endotoxemia (Li et al. 2017).

The activation or suppression of the TLRs by microbial signals can dictate the tone of the immune response and thereby contribute to the regulation of the energy homeostasis (Spiljar et al. 2017). Since the microbiota-derived signals influence functions of distant organs and can change susceptibility to metabolic diseases, they can be considered as instrumental for the treatment of metabolic chronic diseases.

Bioactive natural products for diabetes mellitus

Several plant and mushroom species, including a number of those have been used in traditional Chinese medicine, have now been shown to exert anti-diabetic effects. The future potential of the bioactive natural products used in diabetes treatment will be based on the modification of structures of biologically active compounds (leads), in order to obtain safer, more selective, or more bioavailable molecules, which is a primary requirement for drug development. New approaches for the identification and characterization of natural products are being developed that may address some of challenges related to the development of plant-based therapeutics. Resupplying from the original plant species is very unfeasible to meet the huge market demands upon commercialization of a natural product, and alternative resupply approaches are being developed that rely on biotechnological production or chemical synthesis. Over 9,000 herbs have known medicinal applications among various cultures and countries. Many plants have been investigated for their beneficial use in different types of diabetes and reported in numerous scientific journals. However, understanding the scientific material basis of traditional Chinese medicine herbal formulas at the molecular level remains a considerable challenge. Examples of these medicinal plants are described below since they play a key role in managing diabetes.

Scientists have discovered that plants have great efficacy to produce numerous bioactive molecules dealing with the problem of diabetes mellitus in recent years (Supplementary Table 1). These natural products consist of large quantities of bioactive compounds including phenolic compounds, oligo-/polysaccharides, terpenoids, curcumin, xanthones, thiosugar derivatives, tannins, chalcones, phenolic acids, alkaloids, and amino acids (Goto et al. 2010). And it is crucial to understand the mechanism behind the biological effects of these compounds for the prevention and treatment of T2DM.

Flavonoids are a type of polyphenols that includes a great number of compounds showing important differences in their structure. They can limit the hyperglycemic response following food intake. For example, apigenin regulates hyperglycemia by increasing the serum insulin levels while rutin improves IR and increases glucose uptake (Kappel et al. 2013); and quercetin mitigates the diabetes by stimulating insulin secretion and inhibiting aldolase reductase in diabetic patients (Bahmani et al. 2014). In addition, resveratrol as a natural biologically active polyphenol compound present in different plant species has beneficial effects in relation to diabetes (Szkudelski and Szkudelska 2015). Thus, it appears that, alongside their widely recognized antioxidant capacity, other properties not totally characterized confer to flavonoids and anthocyanins their capacity to mitigate diabetes.

Polysaccharides are a class of important compounds preventing T2DM. *Ganoderma lucidum* polysaccharides (GLP) decreased plasma insulin concentration and reversed HFD-induced systemic IR (Xu et al. 2017). GLP ameliorated low-grade chronic inflammation, induced lipolysis in adipose tissues, and decreased plasma triglyceride. GLP also regulated composition of gut microbiota implicated in obesity and T2DM development (Chang et al. 2015; Xu et al. 2017). So far, there are six possible mechanisms by which polysaccharides mitigate T2DM: (1) reducing carbohydrates decomposition and absorption; (2) restricting α-glycosidase enzymes in bowel; (3) scavenging free radicals and lipid peroxidation reduction; (4) elevating plasma insulin and declining pancreatic glucagon; (5) increasing hepatic glycogen and regulating inflammatory cytokines and gut microbiota composition; and thereby (6) restoring an adequate insulin sensitivity (Wang et al. 2017).

Plant terpenoids mitigate diabetes with almost the same efficacy as polysaccharides. The mechanisms of actions of terpenoids include reducing blood glucose level, increasing glycogenesis and decreasing glycogenolysis, as well as inhibiting aldose reductase. By these mechanisms, they can also achieve the same efficacy as the previously described compounds. As an example, curcumin is representative of the curcuminoids that can be extracted from the root of Curcumalonga. Curcumin has anti-carcinogenic and antioxidant effects (Duvoix et al. 2005; Shishodia et al. 2005). Although curcumin has been reported to inhibit glucose transporter activity (Green et al. 2014; Nabavi et al. 2015), such an action expected to impair glucose handling by peripheral tissues can instead reduce absorption of dietary glucose by direct inhibition of GLUT proteins in intestinal epithelial cells and contribute to a hypoglycemic effect (Gunnink et al. 2016).

Xanthones possess antidiabetic activity. The most known xanthonoid is mangiferin, which is a glucoside of norathyriol. It acts at least via two mechanisms such as decreasing resistance and/or increasing insulin sensitivity, and its glycoside moiety can impair several carbohydrate-metabolizing enzymes (Raut et al. 2016).

Thiosugar derivatives also show strong inhibitory activity against α-glucosidases. Tannins can produce denaturation of proteins and therefore, can trigger nonspecific inhibition of α-glucosidase, too. Indeed, condensed tannins can inhibit α-amylase and a higher inhibition can be achieved as the degree of polymerization increases. The antidiabetic effect of chalcones might be related to the anti-atherosclerotic activity of 2-hydroxy-4′-methoxychalcone, which has been reported to stimulate PPAR-γ expression in human aortic smooth muscle cells. The group of chalcones could, therefore, be

considered as natural PPAR-γ activators enhancing the cell sensitivity to insulin, somewhat reproducing the stimulation by the thiazolidinediones, the pharmacological agonists of reference for this nuclear factor.

The antidiabetic mechanism of alkaloids can be summarized by two axes: (1) repairing or stimulating proliferation of pancreatic β-cells, stimulating the secretion of insulin, increasing the sensitivity to insulin, decreasing resistance, increasing glycogenesis and inhibiting gluconeogenesis; (2) decreasing the level of glucogenic enzymes. Besides, S-allyl cysteine is a sulfur-containing amino acid found in garlic that has been found to promote glucose uptake and metabolism. Furthermore, it can also facilitate insulin secretion, thereby decreasing blood glucose levels.

The potential antidiabetic application of phenolic acids has been proposed when observing that they elevate glucokinase activity and accumulate glycogen in the liver. In addition, the antidiabetic properties of gallic acid rely on its ability to induce glucose uptake by stimulating GLUT4 translocation. Recent literature supports that polyphenols can inhibit pancreatic α-amylase or α-glucosidases, and this adds an additional mechanism to their hypoglycemic effect. Like gallic acid, another natural phenolic acid, ellagic acid, has been shown to inhibit glycogen phosphorylase and therefore to prevent hepatic glucose output when the liver has its glycogen stores intact (Kyriakis et al. 2015). Hence, the beneficial effects of dietary polyphenols rely on their modification to host digestive enzymes. It the case of the above-mentioned phenolic acids, their antidiabetic properties can be either increased (if active metabolites are generated) or diminished (if metabolites are inactive) after the digestion process. In fact, it has been demonstrated that ellagic acid undergoes a series of bacteria-mediated transformations leading to the appearance of urolithins (Cerda et al. 2005; Espin et al. 2013). Such metabolism probably limits the available amount of phytochemical able to act in the organism, but more importantly, once ingested, ellagic acid and ellagitannins generate among members of urolithins, urolithin A, recently shown to increase muscle function in rodents and to potentially delay age-related dysfunctions (Ryu et al. 2016). Since, in the polyphenol-related studies, a large amount of interindividual variation can be observed in the microbial metabolism and absorption of certain polyphenols (Shortt et al. 2018), the task to characterize the major agents involved in the promising antidiabetic actions of phytochemicals will likely conduct to a personalized nutritional approach, consisting in giving a combination of agents working in synergism, as in the case of polyphenols (Carpéné et al. 2015), or aiming at providing both the phytochemical of interest together with prebiotic or probiotic supplements to facilitate the generation of the active metabolites.

In addition to the multiple actions of dietary polyphenols in the gut, phytochemicals such as fibers, and polysaccharides play a vital role in modulating gut microbiota (phylum *Bacteroidetes*, *Firmicutes* and *Firmicutes*/*Bacteroidetes* ratio, and genus *Akkermansia*, *Bifidobacteria*, *Lactobacillus*, *Bacteroides* and *Prevotella*) through SCFAs, bile acids (BAs), and LPS (Lyu et al. 2017). The administrations of natural phytochemicals lead to increase the abundance of phylum *Bacteroidetes*, and genus *Akkermansia*, *Bifidobacteria*, *Lactobacillus*, *Bacteroides*, and *Prevotella*, while reduced phylum *Firmicutes* and *Firmicutes*/*Bacteroidetes* ratio in gut. Additionally, the consumption of functional oligosaccharides can reduce the risk of chronic diseases, such as cardiovascular disease, obesity, and diabetes mellitus (Zhao et al. 2018a). Oligofructose was reported to promote the growth of beneficial bacteria such as *Bifidobacterium*, *Lactobacillus*, and *Bacteroides*, and to benefit diabetic individuals (Dehghan et al. 2014). Xylooligosaccharide highly promotes the population of *Bifidobacteria* population *in vitro* and decreases the abundances of the genera *Enterorhabdus*, *Howardella*, and *Slackia* in pre-diabetic subjects (Yang et al. 2015). There are also evidence that chitosan oligosaccharides (COS) improve the disturbance in glucose metabolism and reverse the dysbiosis of gut microbiota in diabetic mice. *In vitro* studies suggest that COS might reduce the glucose transport in Caco-2 cells and promote glucose uptake of adipocyte cells (Meng et al. 2016). COS could reduce fasting blood glucose and increase insulin secretion in *db/db* mice (Kim et al. 2014). COS treatment improves the disturbance in glucose metabolism and reverses the dysbiosis of gut microbiota in diabetic mice by promoting *Akkermansia* and suppressing *Helicobacter* (Zheng et al. 2018). This was confirmed by decreased blood glucose level, reversed IR, enhancement of intestinal integrity, suppression of inflammation and inhibition of lipogenesis in epididymal adipose tissue of diabetic mice after treatment of COS. Natural phytochemicals interact with gut microbiome and alter the microbial metabolites including SCFAs, BAs, and LPS, which are correlated with T2DM.

Challenges and perspectives

Why does T2DM get progressively worse over time? What is the most effective way to slow down or to prevent this progress? The growing prevalence of obesity and T2DM results in an overload of patients at very high short-term cardiovascular risk. There is an increasing need for new options to treat diabetes at its early stage, especially T2DM, due to an ineffective control of its long-term evolution in patients.

The modification of natural products for medical use

Although the natural products are normally valuable lead compounds, they rarely can be directly used in clinical applications. From the standpoint of drug innovation, it is necessary to modify natural product structures, because the aim in generation of secondary metabolites by organisms is to protect themselves from natural enemies as well as the environment. The final aim of modifying natural products is to develop active compounds into medicines. Structural modifications are necessary to achieve this goal. The strategy is therefore to increase potency and selectivity, to improve physicochemical, biochemical, and pharmacokinetic

properties, to eliminate or reduce adverse effects, to simplify the structural complexity, including removal of redundant atoms and chirality while retaining activities, and to generate patentable compounds. Lastly, another interest of biotechnology for synthesizing phytochemical-like derivatives is justified when the amount of active substance required per patient during prevention or chronic treatment, requires the equivalent of large quantities of plants, at the risk of putting the concerned species in danger of disappearing from the current biodiversity. As an example, the natural product O-glucoside phlorizin is a well-documented, potent glucosuric agent that was subsequently shown to be a nonselective SGLT inhibitor. Because of its inhibition of SGLT1 with poor metabolic stability due to its susceptibility to β-glucosidase-mediated cleavage, as a lead compound, O-glucoside phlorizin was modified. Canagliflozin, simplifying structures from phlorizin, entered into clinical trials and was approved by the FDA in 2013 for the treatment of T2DM (Nomura et al. 2010).

MicroRNAs as pharmacological targets in diabetes

Recently, small noncoding RNAs with approximately 22-nucleotides, of a novel class termed microRNAs (miRNAs), were found to play a key role as important transcriptional and post-transcriptional inhibitors of gene expression in fine-tuning the target messenger RNAs. It is predicted that over 30% of human genes are regulated by miRNAs. Several of them are implicated in the pathogenesis of T2DM and have become an intriguing target for therapeutic intervention. Recent data suggest that miRNAs play a direct role in insulin secretion, pancreatic islet development, β-cell differentiation, and indirectly control glucose and lipid metabolism, thereby being involved in diabetes-associated complications. The ubiquity of miRNAs in body fluids and their association with the disease pathogenesis have made them important players for prognosis, diagnosis and management of T2DM. MiRNAs are regarded to regulate insulin biosynthesis and secretion in pancreatic β-cells, insulin sensitivity in skeletal muscle and adipose tissue, as well as glucose and lipid metabolism in liver. The first evidence of miRNAs controlling the β cell activities was demonstrated by Poy and his colleagues (Poy et al. 2004). They demonstrated that miR-375 regulates secretory activities of β-cells. Its silencing increases glucose-stimulated insulin secretion in murine pancreatic β-cell lines and in isolated primary β-cells. MiR-375 knockout mice exhibited increased pancreatic α-cells, elevated plasma glucagon levels, gluconeogenesis and hepatic glucose output. Moreover, MiR-7a was recognized to be a negative regulator of adult β-cell proliferation by targeting various components in mTOR signaling pathway (Wang et al. 2013). In mouse models, the specific overexpression of miR-200 in β-cell induced their apoptosis and promoted severe T2DM under stress conditions by negatively regulating β-cell chaperone Dnajc3 or p58IPK and caspase inhibitor Xiap (Belgardt et al. 2015). Other findings have reported various miRNA signatures associated with T2DM, newly diagnosed cases and vascular complications. Currently, it is supposed that specific miRNAs play a critical role in the development of diabetic vascular complications. Although there are numerous studies implicating the role of specific miRNAs in β-cell biology, they were mainly performed *in vitro* on cell lines only. Thus, it is of great necessity and urgency to validate those studies by *in vivo* approaches. There is also a need to obtain more data on miRNA expression in human samples for highlighting their potential roles in T2DM progression. However, pharmacological over-inhibition or overexpression by administration of miRNA mimics or miRNA inhibitors may potentially have off-target effects. More substantial research and standardization of techniques are required to determine the efficacy and feasibility of miRNAs as diagnostic tools to be routinely used as prognostic markers of T2DM and complications.

Novel therapies for type 2 diabetes mellitus

Numerous recent studies on novel antidiabetic drugs aimed at improving insulinopenia with fewer side-effects than the current insulinotropes (glucokinase activators, G protein-coupled receptor ligands, ultra-long-acting insulins). Novel approaches for reducing hyperglycemia have focused interest on gluconeogenesis inhibitors and even on new drugs with unusual therapeutic pathways, such as the GLP-1 analogues or agents that prevent the catabolism of incretins, or even inhibitors of the urinary glucose reabsorption (sodium-glucose co-transporter inhibitors). The recent tests of the blockade of other metabolic pathways seem to indicate that it is possible to affect T2DM by influencing energy metabolism, as in the cases for diacylglycerol acyl-transferase inhibitors and 11β-HSD1 inhibitors. In addition, herbal drugs have previously been reported to be beneficial in hyperglycemia control worldwide, and about 800–1,200 herbs or their products have largely been used as anti-diabetic medicines to regulate the diabetes (Kavishankar et al. 2011; Zhao et al. 2018b). In contrast to conventional synthetic drugs, they are generally perceived as safe, harmless and without deleterious side effects such as gastrointestinal or cardiovascular complications. Therefore, herbal drugs can provide an alternative therapy for this medical challenge.

Conclusions

The growing prevalence of T2DM results in an overload of patients with very high short-term cardiovascular risk. Recent surveys have shown that most of the diabetic patients using chronic prescription medications are also associating herbal supplements or vegetal rich diets without understanding the risks of such combination. The co-administration of natural products along with conventional medicines is believed to induce a modified bioavailability of the prescribed drugs and, to a lesser extent, to change the fluxes of various metabolic pathways. Systematic studies are still necessary in order to unravel the roles of phytochemicals since even the physicians are not always aware of the risk of such interactions. Unless validated, natural phytochemicals

should be avoided as supplements for patients undergoing chemotherapy in order to avoid the risk of decreased availability. To pour more complexity, natural products may lead to an increase of the drug concentration when administered in short-term regimen, but may induce an increased metabolism and decreased effect after prolonged intake. Alongside the recommended prevention involving diet modifications, optimal treatment with the good combination of drugs and natural phytochemicals remains to be established. Since dysbiosis of the human gut microbiota impacts the serum metabolome and contributes to IR, and since there are the inter-individual variations of the microbiota, a personalized approach should be considered. Nevertheless, these emergent microbial targets have the potential to diminish IR and to reduce the incidence of common metabolic and cardiovascular disorders. They, therefore, deserve to be considered to contribute as an essential step in the modification of the ingested phytochemicals capable of either generating active metabolites or hampering the beneficial effect of the ingested active principles. The objective of the present study was to make a systematic review on glucose metabolism in T2DM as well as to explore, among metabolic pathways, the multiple relationships between gut microbiota, inflammation, diabetes and obesity.

Abbreviations

AEA	Endocannabinoid lipids anandamide
AMPK	AMP-dependent protein kinase
Bas	Bile acids
BMI	Body mass index
CBR1	Receptors cannabinoid receptors 1
ChREBP	Carbohydrate response element binding protein
COS	Chitosan oligosaccharides
CRP	C reactive protein
eCB	endocannabinoid
Erk	Extracellular signal-regulated kinases
FFAR 2/3	Free fatty acid receptor 2/3
GLP-1	Glucagon-like peptide-1
GLUT4	Glucose transporter type 4
GPR 43/41	G-protein coupled receptor 43/41
GPTA	Glutamic-pyruvic transaminase activity
GSH	Glutathione synthesis
GSK	Glycogen synthase kinase
HDAC 6/9	Histone deacetylase 6/9
IAP	Intestinal alkaline phosphatase
IL-6	Iinterleukin-6
IR	Insulin resistance
IRS-1	Insulin receptor substrate 1
IRS-2	Insulin receptor substrate 2
JNK	c-Jun N-terminal kinase
LPL	lipoprotein lipase
MAPK	Mitogen-activated protein kinase
MIN6	Murine pancreatic β-cell lines
NLRs	Nod-like receptors
P70S6k	protein S6 kinase
PAMPs	Pathogen-associated molecular patterns
PDK1	Pyruvate dehydrogenase kinase isozyme 1
PGN	Peptidoglycan
PIP2	Phosphatidylinositol-4,5-bisphosphate
PIP3	Phosphatidylinositol-3,4,5-trisphosphate
PI3K	Phosphatidylinositol 3-kinase
PRRs	The pattern-recognition receptors
PYY	Peptide YY; SAC: S-allylcysteine
SCFA	short-chain fatty acids
SGLT2	Sodium-dependent glucose transporters 2
SREBP-1c	Sterol response element binding protein 1c
T2DM	Type 2 diabetes mellitus
mTOR	mammalian target of rapamycin
TCM	Traditional Chinese medicine
TNF-α	Tumor necrosis factor-α
TLRs	The Toll-like receptors
TSC1/TSC2	Tuberous sclerosis complexes $^1/_2$
ZO-1	Zonula Occludens-1

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