

The Role of JNk Signaling Pathway in Obesity-Driven Insulin Resistance

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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Abstract: Obesity is not only closely related to insulin resistance but is one of the main factors leading to the formation of Type 2 Diabetes (T2D) too. The c-Jun N-terminal kinase (JNK) family is a member of the mitogen-activated protein kinase (MAPK) superfamily. JNK is also one of the most investigated signal transducers in obesity and insulin resistance. JNK-centric JNK signaling pathway can be activated by growth factors, cytokines, stress responses, and other factors. Many researches have identified that the activated phosphorylation JNK negatively regulates insulin signaling pathway in insulin resistance which can be simultaneously regulated by multiple signaling pathways related to the JNK signaling pathway. In this review, we provide an overview of the composition of the JNK signaling pathway, its regulation of insulin signaling pathway, and the relationship between the JNK signaling pathway and other pathways in insulin resistance.

Keywords: JNK signaling pathway, obesity, insulin resistance, type 2 diabetes

Introduction

In the past three decades, global overweight and obesity have risen rapidly because of the changes in human diets, travel and other lifestyles. Based on the current trend, the prevalence of overweight (BMI 25–29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²) (World Health Organization standards) in adults worldwide is predicted to rise from 33% in 2005 to 57.8% in 2030.¹ Therefore, lots of researches focus on metabolic diseases induced by obesity. In recent years, several studies have shown that chronic low-grade inflammation (e.g. IL-1 α , IL-1 β , IL-6, RANTES, MCP-1, TNF α) caused by obesity may be an important cause of insulin resistance and T2D.² Generally, insulin resistance precedes the initiate of T2D, refers to a pathological state that the body, especially peripheral tissues, does not respond properly to circulating insulin. It is an important mechanism for the development of T2D and the basis of obesity and metabolic diseases including hyperlipidemia, hypertension, cardiovascular disease.³ Recently, the current evidence indicates that factors affecting the development of insulin resistance in obese subjects are extremely complex and regulated by a variety of signaling pathways. JNK affecting insulin resistance is a member of the MAPKs superfamily and plays the essential role at the core of inflammatory response and oxidative stress. In the different tissues of obese subjects, inflammatory factors can be observed to cause continuous activation of JNK. The activated JNK acts on nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1) to produce more inflammatory factors, further reducing the sensitivity of insulin target cells towards insulin, finally to form a vicious circle

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and aggravate insulin resistance. Besides, a network framed by PPAR γ , NF- κ B and PTP1B signaling pathways crossing with JNK signaling pathway plays an important role in regulating insulin resistance. However, to our best knowledge, a comprehensive review discussing possible effects of JNK signaling pathway crossed with PPAR γ , NF- κ B and PTP1B signaling pathways in obesity-driven insulin resistance is missing. Simultaneously, a better understanding of JNK signaling pathway and the relationship between PPAR γ , NF- κ B, PTP1B signaling pathways and the JNK signaling pathway is necessary to appreciate important drug targets for the treatment and improvement of obesity-driven insulin resistance.⁴

Overview of the JNK Signaling Pathway

Since the 21st century, protein kinases have been an important research objective, and their roles are phosphorylation by other kinases, transferring amino acid residues to the ATP-terminal phosphate group for phosphorylation, or autophosphorylation. Based on the type of amino acid residue type of phosphorylated substrate protein, the protein kinases were classified into five categories: serine/threonine (Ser/Thr) protein kinase; histidine (His) protein kinase; tyrosine (Tyr) protein kinase; tryptophan (Trp) protein kinase; aspartyl/glutamyl protein kinase. MAPK, a class of Ser/Thr protein kinases, are widely found in mammalian cells. Currently, there are four members of the MAPK family, such as JNK/stress-activated protein kinase (SAPK), extracellular signal-regulated kinase (ERK1/2), p38, and ERK5. There are three JNK isoforms encoded by three different genes, JNK1 (Mapk8) and JNK2 (Mapk9) express ubiquitously, and JNK3 (Mapk10) expression is restricted to the brain, testis, heart, and pancreatic β -cells.⁵ Obesity, alcohol and radiation may activate the JNK signaling pathway to regulate the expression of inflammation, oxidative stress and proliferation-related genes and proteins.⁴ The JNK protein can be activated by two MAP2K (MKK4 and MKK7) which are located upstream of JNK. Both MKK4 and MKK7 can simultaneously phosphorylate JNK at threonine-183 and tyrosine-185 sites, but the difference is that MKK4 prefers to phosphorylate tyrosine, while MKK7 prefers to phosphorylate threonine. Besides, MKK4 and MKK7 are activated in turn by a series of upstream MAP3K which are regulated by plenty of different upstream factors, including TNF α and FFA.⁶⁻⁸ JNK was named c-Jun N-terminal kinase because it was

originally discovered to be a kinase that specifically phosphorylates the nuclear transcription factor c-Jun, but the later studies indicated that many substrates are located downstream of the JNK signaling pathway, including the jun family, AP-1, P53, Bcl-2, c-myc, Mcl-1, Sab, ATF-2, insulin receptor substrate-1 (IRS-1), JNK interacting protein 1 (JIP1). Upon activation of the JNK signaling pathway, JNK is translocated from the cytoplasm into the nucleus and activates the c-Jun transcription factor by transphosphorylation of Ser63 and Ser73 in the amino-terminal active domain of the c-Jun transcription factor. The c-Jun transcription factor is activated and binds to the binding site of transcription factor activator protein-1 (AP-1) locating at the gene promoter, promoting the expression of proinflammatory genes and protein synthesis (e.g. TNF α , IL-1 β , IL-6 and IL-8),^{9,10} which plays an important role in impairing glucose tolerance by obesity-induced and insulin resistance. In JNK signaling pathway, JNK activity mainly regulates metabolism by phosphorylating its substrate and plays a crucial role in the occurrence and development of human diseases. Altogether, these pieces of evidence indicate that JNK has a significant effect on metabolism, especially in inflammation and obesity complications.

Obesity-Driven Insulin Resistance

The current view is that obesity is closely related to insulin resistance which usually occurs in the liver, muscle, and adipose tissue. Importantly, it shows that during obesity, activated JNK is elevated in mouse muscle, fat, and liver. JNK is one of the most investigated molecules in obesity models of insulin resistance, and studies have led to a new paradigm of how excess adiposity may cause insulin resistance.¹¹ Obesity induces chronic low-level inflammation, produces inflammatory factors and FFA to activate JNK signaling pathway in insulin target cells.² The inflammatory factor TNF α binds to its receptor to activate the JNK signaling pathway, which in turn regulates the expression of the TNF gene to form a vicious circle.^{6,12,13} Biopsy of subcutaneous adipose tissue in obese individuals showed an increased activation of phosphorylated JNK that further amplified the inflammatory response and impaired the insulin signaling pathway.^{14,15} Yang et al found that Liver-specific knockdown of JNK1 resulted in significant reductions in circulating insulin and glucose levels, by 57% and 16%, respectively. At the molecular level, JNK1 knockdown mice had a sustained and significant increase of hepatic Akt phosphorylation. Furthermore, knockdown of JNK1 enhanced insulin signaling in vitro.¹⁶ Prada et al found that TNF α and IL-6 levels were consistent with JNK activity, in skeletal muscle.¹⁷

The cause of insulin resistance in target organs is that inflammatory factors interfere with the IRS-1/PI3K/Akt/GLUT1-4 insulin signaling pathway, then attenuate glucose uptake and subsequent disposal mediated by insulin, and increase production and output of glycogen. Finally, insulin resistance occurs in insulin receptor cells.¹⁸ The energy supply for inflammatory cells comes from glucose. In an inflammatory state, with the increase of macrophages in adipose tissue, the demand of immune system for glucose increases. The body needs to provide a substrate for gluconeogenesis and increase the supply of glucose by increasing the breakdown of fat, which promotes lipolysis, and glucose and lipid metabolic disorder. On the other hand, inflammation in obese patients can damage the endothelial function and cause endothelial insulin resistance. At the same time, increased expression of inflammatory factors can increase the production of ROS (Reactive Oxygen Species, ROS), decrease the transcription of uncoupled protein (UCP) S, resulting in insufficient ability to scavenge oxygen-free radicals, which is the main cause of oxidative stress. Increased ROS content in obese people causes oxidative stress, in turn activates JNK and NF- κ B signaling pathways. With the JNK signaling pathway activated, JNK proteins regulate a variety of nuclear substrates and extranuclear substrates, for example, JNK regulates AP-1 and NF- κ B, controls the expression of many genes including pro-inflammatory cytokines to interfere with Insulin signaling pathway and GLU-T4 translocation, which results in insulin resistance.¹⁹

Researchers found that fatty acids were converted into acyl-CoA when free fatty acids increased in the blood, then increased DAG, activated PKC θ , changed the phosphorylation site of IRS-1, interfered the activation of PI3K, and affected GLUT4 translocation to cell surface; therefore, glucose utilization of insulin-mediated was reduced. Another research indicates that free fatty acids inhibit uptake glucose in various tissues after insulin stimulation, which reduces glucose oxidation and glycolysis, decreases insulin sensitivity of tissues.²⁰

Regulation of Insulin Signaling Pathway by the JNK Signaling Pathway

Insulin is an important hormone, regulating the metabolism of carbohydrate and fat and the physiological functions of cells through PI3K-AKT signaling pathway. After insulin activates Akt via PI3K, Akt was proposed to participate in the metabolic regulation of insulin by four mechanisms: promoting glycogen synthesis through glycogen synthase

kinase 3 (GSK3);³ regulating vesicles translocation in intracellular glucose carriers (mainly GLUT4); inhibiting fatty acid oxidation and hepatocyte gluconeogenesis through Akt/PKB phosphorylates transcription factor PGC-1 α ; insulin decreases cAMP levels and inhibits PKA to activate hormone-sensitive lipase via PI3K and Akt-dependent signaling pathways, finally, lipolysis is inhibited.

Chronic low-grade inflammation and FFA induced by obesity can activate JNK to phosphorylate insulin receptor substrates (IRS) 1 and 2 at Ser/Thr residues¹⁸ and dephosphorylate IRS-1 Tyr residues,²¹ which not only prevents IRS from activating downstream PI3K also the interaction of IRS with its upstream insulin receptor (IR). After the conduction of the PI3K-AKT insulin signaling pathway is blocked, the sensitivity of target cells to insulin decreases, which stimulates the body to continuously produce insulin to eliminate excess glucose in the blood. However, in islet β cells, compensatory insulin synthesis format hyperinsulinemia and add the burden of islet β -cell secretion,²² eventually, leading to hyperproliferation and the trend of apoptosis to form insulin resistance even T2D.²³ This is one of the mechanisms that JNK activity links to insulin resistance during obesity. This view is supported by a series of studies. Yang et al used gene knockout technology to selectively silence the JNK1 gene in mouse adipose tissue.¹⁶ They found that the lack of JNK1 in adipose tissue inhibited insulin resistance induced by a high-fat diet in the liver. More importantly, inactivation of the JNK2 gene also enhanced the sensitivity of the cell to insulin.⁴ To test the role of JNK, Han et al established a macrophage-selective JNK deficiency mouse model feeding with a high-fat diet and found that only JNK-deficient mouse macrophages were still sensitive to insulin.²⁴ JNK gene silencing decreases IRS-1 Ser 307 phosphorylation, increases Tyr phosphorylation, enhances insulin signaling, and increase cell sensitivity to insulin. Meanwhile, JNK gene silencing inhibits the expression of inflammatory genes, alleviates insulin resistance. For instance, δ -tocotrienol can inhibit the activity of JNK to reduce the transcriptional activities of inflammation-related factors AP-1 and NF- κ B, which alleviates insulin resistance. In conclusion, these studies indicate that JNK activity may cause insulin resistance; therefore, JNK is a potential target for insulin resistance therapy.²⁵

The Relationship Between JNK and Other Signaling Pathways in Insulin Resistance

In cell, multiple signal pathways crossing and interacting with each other form an extremely complex network,

which is called Signaling Crosstalk. Signaling Crosstalk occurs when the transducer is stimulated by one or more extracellular factors, possibly in the cytosol or nucleus. In addition, it reflects at all levels of the signal path, ultimately, to enhance or suppress signaling pathways. With advanced technology and thorough researches of signal pathways, reports on Signaling Crosstalk of the JNK signal path have sharply increased in recent years. The JNK signaling pathway in obesity-driven insulin resistance may be activated by inflammatory factors and FFA, which results in more inflammatory factors to form a vicious cycle and aggravate insulin resistance. In this progression, PPAR γ , NF- κ B, and PTP1B signaling pathways crossing with the JNK signaling pathway contribute to regulate the conduction of the insulin signaling pathway in target cells and the level of inflammatory factors in various tissues. Importantly, clarifying the relationship between the JNK signaling pathway and other signaling pathways is of great significance for finding targets for drug therapy and treating diabetes.

JNK Signaling Pathway and PPAR γ Signaling Pathway

Peroxisome proliferator-activated receptors (PPARs) are a kind of ligand-activated nuclear transcription factors composed of α , β (also known as δ) and γ subtypes, belonging to II type nuclear receptor superfamily. Currently, PPAR members that have been recognized are PPAR α , PPAR β/δ , PPAR γ . There are so many researches indicating that PPAR γ plays a central role in adipocyte differentiation, sugar and lipid metabolism, inflammatory response, atherosclerosis, and the improvement of insulin resistance.^{26,27} PPAR γ ligands inhibit the expression of various inflammation-related genes, including inducible nitric oxide synthase, matrix metalloproteinases, and interleukins. These behaviors may also be associated with obesity-related insulin resistance, because macrophage accumulation and gene expression in adipose tissue have been proven to play an important role in the pathogenesis of obesity-driven insulin resistance.^{28,29} Therefore, it is meaningful to illuminate that the PPAR γ signaling pathway regulates obesity-driven insulin resistance in improving insulin resistance and treating T2D.

TNF- α inhibits the transcriptional activity of PPAR γ by activating ERK and JNK in chronic low-grade inflammation caused by obesity.^{30,31} ERK and JNK inhibit PPAR γ

function through directly phosphorylating PPAR γ at Ser112 residue, and this phosphorylation leads to inhibition of PPAR γ transactivation.³² Similarly, histone deacetylase 3 is a co-repressor of PPAR γ in the presence of inflammatory factors, such as TNF- α .³³ Histone deacetylase 3 binds to heterodimers of PPAR γ and retinoid X receptors, which reduces PPAR γ transcriptional activity.³⁴ Inflammation-induced downregulation of PPAR γ has an important consequence that adiponectin (a hormone produced exclusively by adipocytes) expression is decreased. Whether in vitro and in vivo, PPAR γ agonists can increase the expression and secretion of adiponectin.³⁵ This adipocyte-specific cytokine adiponectin is involved in the regulation of insulin sensitivity in target cells. The lack of PPAR γ in fat cells, adiponectin expression, the ability of storing fat, and insulin sensitivity will decrease.³⁶ Gavrilova et al found that the selective loss of PPAR γ in mouse skeletal muscle and liver resulted in severe systemic insulin resistance, which also confirmed the above results (Figure 1).³⁷

Activated PPAR forms a heterodimer with the retinoic acid x receptor, binding to specific regions of the DNA sequence to regulate transcriptional activation of downstream target genes. PPAR γ improve insulin resistance by two ways: The promotion of glucose and fatty acid metabolism will accelerate fatty acid consumption, lower the TG content in the liver and muscle, improve the high-fat diet-induced obesity and insulin resistance,³⁸ Adipose cells reduce the secretion of TNF- α and other signaling molecules to alleviate the body's inflammatory state and activation of the JNK signaling pathway. The expression level of PPAR γ in the diabetic group was significantly lower than the normal group, but the expression of AP-1 and NF- κ B increase. Activated AP-1 and NF- κ B have functions to regulate the gene expression of various inflammatory factors, which plays an important role in pathophysiological processes, including cell proliferation, differentiation, apoptosis, and inflammatory response (Figure 1). Moreover, AP-1 and NF- κ B can activate JNK transcriptional activity and induce insulin resistance in obese patients. However, elevated PPAR γ activity will be accompanied by a decrease in AP-1 and NF- κ B expression, reduced in inflammation of the body, and blocking JNK signaling pathway.^{39,40} PPAR γ is an essential molecule in obesity-induced inflammation, intersects with the JNK signaling pathway and regulates the expression of adiponectin, which may indirectly reduce the expression of inflammatory factors to improve insulin resistance.

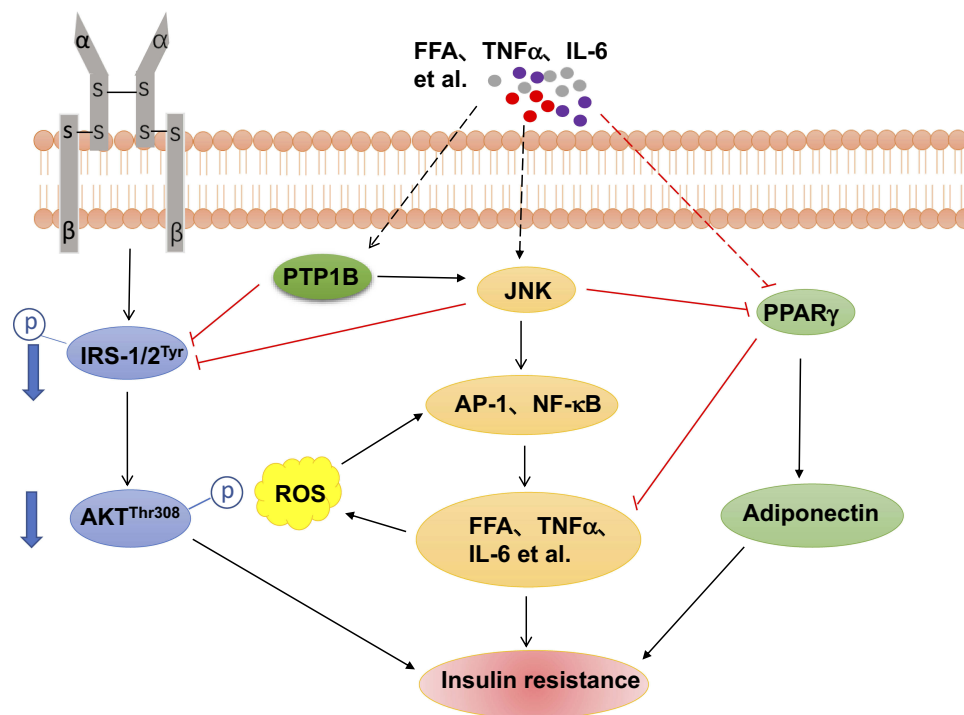


Figure 1 A general model for the relationship between JNK signaling pathway and the others, in the obesity-driven insulin resistance. JNK plays a critical role in obesity-induced pro-inflammatory state, leading to enhanced production of pro-inflammatory factors such as IL-1 β , TNF α and IL-6. These factors are likely to induce impaired glucose metabolism and insulin resistance in a number of ways (see text for details). For example, JNK inhibits insulin signaling pathway and increases the production of inflammatory cytokines. Pro-inflammatory factors regulate PPAR γ to control the expression of adiponectin and pro-inflammatory state. NF- κ B signaling pathway can be affected by JNK to regulate the expression of inflammation cytokines. PTP1B activated by inflammation cytokines may block the insulin signaling pathway and activate JNK signaling pathway to aggravate insulin resistance.

JNK Signaling Pathway and NF- κ B Signaling Pathway

Nearly all cells have IKK/NF- κ B signaling system, including NF- κ B family, inhibitor I κ B family, and IKK multi-component protein kinase complex. The I κ B protein family is an inhibitor of NF- κ B, and mainly includes I κ B α , I κ B β , and I κ B Σ . Under normal conditions, I κ B α can covalently bind to NF- κ B dimers P65 and P50 in the cytoplasm to mask the nuclear localization signal (NLS) of NF- κ B, preventing its nuclear translocation. Due to the presence of I κ B α , NF- κ B is quiescent in the cytoplasm, but a variety of extracellular stimuli can activate IKK β that can phosphorylate I κ B α to dissociate I κ B α from NF- κ B. Therefore, NF- κ B is transferred to the nucleus to regulate the expression of inflammation-related factors. However, its overexpression is an important factor leading to insulin resistance.

Inflammation induced by obesity activates JNK and NF- κ B signaling pathways in insulin target cells, which plays a key role in insulin resistance.^{41,42} At the cellular level, Inflammation induced by obesity may be involved in phosphorylation of the transcription factor NF- κ B leading to an

increase of the expression of TNF α and IL-6 genes associated with insulin resistance.⁴³ Inflammatory cytokines may inhibit IRS-1 Tyr phosphorylation in the insulin signaling pathway, also lead to increase in JNK phosphorylation, and decrease Akt phosphorylation. In addition, IRS-1, Akt and JNK are three upstream targets of NF- κ B. Activated JNK and inhibited Akt activity can increase NF- κ B activation, resulting in inflammatory factor synthesis and aggravating insulin resistance (Figure 1).⁴⁴⁻⁴⁶ Therefore, Inflammation induced by obesity can activate various inflammatory mechanisms through JNK and NF- κ B signaling pathways, which promote the expression of inflammatory factors, inhibiting insulin signal transduction to form insulin resistance.⁴⁷

JNK Signaling Pathway and PTP1B Signaling Pathway

Protein tyrosine phosphatase 1B (PTP1B) is the first isolated and purified PTP and its structure has been elucidated by X-ray crystallography. Studies have shown that the expression and activation of PTP1B are increased in obese subjects and PTP1B negatively regulates insulin signaling pathways.⁴⁸ PTP1B can

dephosphorylate Tyr residue of IR or IRS to attenuate insulin signaling pathway (Figure 1).^{49,50} In muscle, transgene over-expression of PTP1B results in impairing insulin signaling pathway, lowering glucose uptake in tissues, thus forming insulin resistance. In contrast, PTP1B deficient mice were resistant to gain weight, showed increased insulin sensitivity, and still maintained insulin sensitivity during a high-fat diet, suggesting that insulin signaling can be enhanced by PTP1B inhibition.⁵¹

Obese subjects have double muscle ceramide content of lean subjects.⁵² At the molecular level, ceramide is capable of inhibiting several different intermediates in the insulin signaling pathway. Treatment of cells with short-chain ceramide analogs or bacterial sphingomyelinase block insulin-stimulated Tyr phosphorylation of IRS-1 as well as subsequent recruitment and activation of PI3K.⁵³ Also, knockdown of PTP1B lentivirus in myocytes prevents ceramide from reducing IRS-1 and Akt phosphorylation, suggesting that PTP1B can be considered as one of the mediators of ceramide-induced insulin resistance in myocytes. Moreover, Taheripak et al found that PTP1B inhibition activates Akt by increased signaling through insulin receptor substrates/PI3K or decreased signaling through ROS/JNK pathways.⁵⁰ In skeletal muscle cells, hyperglycemia, FFA, and inflammation contribute to the over-expression of PTP1B and the activation of PTP1B is mediated by the ceramide-JNK-NF- κ B signaling pathway. Activated NF- κ B enters the nucleus and binds to DNA leading to the expression of the inflammatory factor-related gene. Excessive inflammatory factors induce PTP1B overexpression impairing the insulin signaling pathway, which causes disorder of glucose and lipid metabolism, finally, to form insulin resistance.⁴⁹ These findings offer a novel insight into the beneficial effects of the regulation of insulin-sensitivity by PTP1B, and promote the potential application of molecular targets toward the management of insulin resistance in obesity and diabetes.

Conclusion

It is intriguing that chronic inflammation caused by obesity activates JNK and its related pathways, leading to impair glucose and lipid metabolism, block insulin signaling, and lower insulin sensitivity of insulin target cells. It is one of the important causes of T2D. In recent years, people have made great progress in the research of the JNK signaling pathway. A large number of JNK substrates and regulatory molecules have been discovered, which provides new ideas for the further study, such as the role of JNK signaling pathways and others crossed with it in obesity-driven insulin resistance. At the same time, we should recognize that JNK can be regulated by many factors and it is a conserved and extremely complex signaling pathway.

Explaining these problems as soon as possible will help people understand JNK signaling pathway, provide important drug targets for the treatment and improvement of obesity-driven insulin resistance, and accelerate the basic research results of the JNK signaling pathway to clinical application.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (No 81373314, 81741130), the Guangdong Basic and Applied Basic Research Foundation (No 2019A1515011866), Guangzhou Municipal Science and Technology Program (No 201707010245, 201704020117), the Cooperation project of Guangzhou Jinan Meisu Biotechnology Co., Ltd and Jinan University (Grant Nos/GZJDA2019-02, GZJDA2020-01), and Key Scientific Research Projects of Regular Universities of Guangdong Province in 2019 (Grant No. 2019KZDXM011).

Disclosure

The authors report no conflicts of interest in this work.

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