Insulin Resistance a Dysfunction far Beyond the Beta Cell

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Short Report

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Abstract

Insulin resistance (IR) is recognized as a biological reaction to insulin stimulation in target tissues. IR alters glucose metabolism, resulting in an elevation in insulin production by beta-cells. The main condition that accompanies IR in our environment is obesity due to environmental factors, especially diet, which over the years has gradually taken hold in our civilization.

Objective: To describe the IR in different organs and present the signaling pathway project.

Methods: PubMed database was employed to search IR review publications. The referenced data of the signaling pathway was chosen by aggregating references from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. A signaling pathway was designed based on the IR research manuscripts, where we show various mechanisms involved. The KEGG server was employed to explore the protein-protein interrelationship, and devise the signaling pathway diagram. The mapping of the signaling path was performed with the PathVisio software, adapting to the model of KEGG PATHWAY Database: https://www.genome.jp/pathway/map04930.

Results: We selected articles from the PubMed database that featured the terms "insulin resistance" and "signaling pathway." Based on research articles validated by the database, we chose well-founded pathways and achieved a representative description of these pathways. Reproduction contigs taken from the KEGG database projected the signaling pathway of biomolecules leading to IR. Thus, the action between multiple mechanisms releases factors that participate in the development of IR.

Conclusion: Interaction between multiple mechanisms and molecular interactions are important factors in development of IR in various organs and systems.

Introduction

Human insulin is a peptide hormone produced by the beta-cells (β-cell) of the pancreas, and its release is dependent on glucose levels in the circulation, in addition amino acids, incretins and cholecystokinin also promote its release.[1] The main function of insulin is to maintain glucose homeostasis, enabling glucose absorption and inhibiting hepatic gluconeogenesis, besides acting as an anabolic hormone that favors not only the absorption of amino acids and fatty acids, but also promotes cell growth and energy storage. Insulin also acts by inhibiting catabolism including the gluconeogenesis aforementioned, proteolysis, and lipolysis.[2] Deficiency of insulin production or activity results in diabetes mellitus (DM), which can be either type 1 (T1DM) when there is a destruction of the β-cell by an autoimmune process, or type 2 (T2DM) in which there is a failure of the β-cell to produce insulin.[3]

Insulin resistance (IR) is clinically characterized as the inability of insulin to enhance glucose uptake and metabolism. IR is calculated with the use of homeostasis model assessment insulin resistance index (HOMA-IR) using the formula: fasting plasma glucose (mmol/L) × fasting serum insulin (mU/mL)/22.5.[4]

Several mechanisms have been suggested to justify the development of IR, among which are genetic alterations in proteins of the insulin action cascade, visceral fat thickening and fetal malnutrition. The consequences of IR have systemic repercussions. Thus, IR should be considered as a systemic disease with the need for early diagnosis and treatment in order to improve insulin action and consequently avoid complications.[5]

The intracellular signaling pathway of IR is complex, involving several factors and molecules, and activation of specific points has been demonstrated in individuals with insulin resistance. Alterations in normal insulin signaling pathways contribute as increased risk factors for the development of dysfunctions on the various organs. Therefore, if we take into consideration the repercussions of IR on the different organs, it is interesting to differentiate between the outcomes secondary to over activation of signaling pathways that remain sensitive to insulin versus changes that are a consequence of an impaired ability of insulin to regulate glucose metabolism.[6]

The purpose of this study was to evaluate the IR mechanism on the various organs and the signaling pathway design of the IR based in research articles.

Methods

The organization of molecular pathway maps included a detailed assessment of molecular properties from in the medical literature, accompanied by the implantation of the several elements in a sequence of interlinked occurrences.

Based on research manuscripts, we choose well-reasoned pathways and we collect characteristics expression outline from those pathways. PubMed database was used to review the papers who have researched the IR. The parameterized data of the signaling pathway was selected integrating references of the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

KEGG is a database containing signal pathway diagrams and networks of biological processes, protein domain references and genome sequencing, with the goal of using this data scientifically.[7] The KEGG database has data on proteins, encompassing pathway information confirmed in diagrams that provide the assembly of the interrelationship of proteins in complex organic parameters. We evaluated all available KEGG IR signaling pathways, and for each signaling pathway we distinguished the associated proteins.

The design of the signaling pathway was performed using PathVisio software (version 3.3.0), being employed to graphically display the signaling pathway, as this tool allows visualization and editing of the biological signaling pathway. PathVisio is a freely available pathway editor on the internet, aggregated with the WikiPathways database that is also available for free download for biological pathway analysis.

Results And Discussion

When we put the term "insulin resistance" into PubMed, we identified 139,879 results, when we put the association of the terms "insulin resistance" and "signaling pathway" we found 2,244 results, when we put the association of the terms "insulin resistance" and "organs" we found 1,236 results, and when we put the association of the terms "insulin resistance" and "systems" we found 2,725 results. We selected only articles that presented a significant association between the terms used. In addition, we also evaluated manuscripts with IR in the various organs and systems: brain, hypothalamus, pituitary gland, thyroid gland, lung, heart, liver, pancreas, kidney, small intestine, large intestine, spleen, muscles, adipose tissue, vessels, and ovary.

The basic mechanisms of IR as well as their interaction with different proteins in triggering IR are presented in Figure 1, adapted from the KEGG PATHWAY
Database: https://www.genome.jp/pathway/map04930.

Insulin Resistance a Disease with Visibilization in Multiple Organs and Systems

In our work, we coupled a review study with computational modeling to relate the signaling pathway that triggers IR in different organs.

Insulin directs glucose uptake by adipocytes and skeletal muscle through the connection between insulin and the cellular insulin receptor. IR is explained as reduced cellular ability to respond to insulin activity in various metabolic pathways, including glucose transport to organs and tissues, and is linked to several clinical conditions, especially T2DM, as well as metabolic syndrome.[8]

We describe below the progression of IR in the various organs and systems: brain, hypothalamus, pituitary gland, thyroid gland, lung, heart, liver, pancreas, kidney, small intestine, large intestine, spleen, muscles, adipose tissue, vessels, and ovary.

Insulin Resistance and Brain

The brain is an important location for IR. Brain IR is described as the reduced response of brain neurons to insulin in order to carry out their metabolism and cognitive functions. These alterations would be the result of decreased expression of brain insulin receptors, error between insulin binding to its receptor, or inappropriate activation of the insulin signaling pathway. Thus, there will be altered insulin-related brain physiology with consequent neurotransmitters failure and damage to neuroplasticity.[9]

Several factors interfere with the transport of insulin to the brain, among them the sensitivity of the blood brain barrier transporter, as well as genetic background, obesity, age, triglyceride levels, and blood glucose levels.[10]

It has been considered that insulin does not interfere with glucose uptake in the brain, given that the vast majority of glucose transporters (GLUTs) are independent of insulin transporters. Research has suggested that the brain is capable of producing its own insulin, while most studies show that the β-cell is the source of brain insulin.[11,12]

The decreased insulin transport to the brain results from long-lasting peripheral hyperinsulinemia, leading to reduced insulin receptors at the blood-brain barrier, with consequent impairment of insulin action in the brain.[13] Another important factor in the development of brain IR would be the age-related reduction of insulin receptors in the brain, suggesting that brain IR is a T2DM-independent condition, leading to changes in synaptic plasticity and beta-amyloid load with cognitive dysfunction.[14]

Research shows strong evidence that brain IR shares pathological properties inherent to metabolic and cognitive alterations that are frequently found in T2DM, obesity and dementia. Thus, the action of insulin in the brain influences homeostatic functions, mediating cognitive function and reflecting on behavior and metabolic effects.[15]

Studies show that the use of intranasal insulin increases brain insulin signaling, improving brain IR and reducing neuropathological changes and consequently cognitive dysfunctions. Thus, the relevance of the insulin signaling pathway in the central nervous system is clear, and is a favorable target for interventions towards the prevention of brain IR and consequent prevention and treatment of cognitive disorders.[16]

Insulin resistance and Hypothalamus

In the hypothalamus, insulin performs two important controls, the control of food intake and glucose metabolism, which if controlled has their effects on obesity and T2DM. Thus, the lack of control of these functions occurs due to hypothalamic IR, which has obesity as its main etiology, followed by the abusive consumption of saturated fat. The inflammatory process triggered by the inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) and c-Jun N-terminal kinases is activated by saturated fatty acids that will induce the hypothalamic IR. Enzymes such as tyrosine phosphatases dephosphorylate the insulin receptor which also leads to hypothalamic IR. In addition, hypothalamic IR is also triggered by chronic hyperinsulinemia activates the mammalian target of rapamycin pathway which increases phosphorylation of insulin receptor substrate 1. Other factors associated with hypothalamic IR include altered insulin transport to the central nervous system and hypothalamic gliosis.[17]

The action of insulin in the hypothalamus causes an inhibitory effect on insulin circulation and consequently on glucose production. The reduction in glucose production is necessary for metabolic control, and hypothalamic IR plays an important role in the pathophysiology of T2DM. Thus the hypothalamic IR reduces the suppressive effects of insulin in the hypothalamus on glucose production, and also reduces tyrosine phosphorylation and protein kinase B in the hypothalamus.[18]

Study has shown that insulin secretion by β-cell is inversely associated with hypothalamic insulin sensitivity in humans, and hypothalamic IR is related to increased insulin secretion, suggesting that hypothalamic insulin signaling is related to functional modulation of pancreatic β-cell.[19]

Hypothalamic IR also determines hepatic IR in addition to increased visceral fat and lipid accumulation.[20]

Studies have shown that blocking the κB/NF-κB pathway, more precisely the use of IKKβ inhibitors can reverse hypothalamic IR. It has also been reported that the use of metformin alone or associated with acetyl salicylic acid reduces interleukin-6 levels reducing hypothalamic inflammation and consequent weight reduction.[21]

Insulin resistance and Pituitary

It has been shown that pituitary responses are associated with IR. The pituitary gland has insulin receptors associated with β-endorphin regulating food intake.

In the pituitary gland, insulin stimulates the production of growth hormone by promoting the production of IGF-1 by the liver.[22] Increased serum levels of growth hormone lead to decreased insulin action in peripheral tissues, as well as reduced GLUT-1 expression in adipocytes and thus the development of IR.[23]

Studies have shown that antidiuretic hormone (AVP) is implicated in the control of glucose homeostasis encompassing the metabolic syndrome and IR. AVP is involved in plasma osmolality and hydration status impacts AVP levels. Studies show that hydric restriction increases AVP secretion with the development of hyperglycemia and higher IR.[24] Thus, there is a causal relationship between ADH, water intake and IR.

The effects of prolactin on glucose metabolism can vary, depending on various conditions. Studies show that prolactin acts on the growth of β-cells indicating an effect against T2DM, while other experimental studies have shown that prolactin inhibits adiponectin and interleukin production in the adipocyte leading to IR. A recent study evaluated the association of prolactin levels in the normal range with the HOMA-R index and the results showed that higher prolactin levels, but within physiological levels, were associated with IR.[25]

The first work demonstrating that adrenocorticotropic hormone administration induces IR was done by Johns and Houssay, and clinical findings have been demonstrated in Cushing's disease.[26,27]

The association between gonadotropins and IR is debatable, since in vitro insulin stimulates the elevation of FSH and LH, which has not been demonstrated in vivo. However, in obese individuals it has been shown that chronic IR can alter the FSH/LH.[28]

Insulin resistance and Thyroid

Thyroid hormones play an important role in glucose metabolism by stimulating glycogenesis and gluconeogenesis in the liver. In addition, thyroid hormones regulate the expression of GLUT-4 and phosphoglycerate kinase which facilitates peripheral glucose metabolism. Studies show that thyroid disorders in diabetics are more frequent than in the non-diabetic population.[29]

Studies have shown that there is a significant correlation between IR and thyroid function in obese subjects. Another significant correlation has been found between IR and nodular thyroid disease.[30]

Insulin resistance and Lung

It has been shown that the presence of insulin receptors in the lung can influence both the function and structure of the lung, predisposing to diseases of the respiratory system. IR is an independent risk factor for respiratory dysfunction development.[31]

IR leads to lung dysfunction through several pathways. IGF-1 alters the contractility of airway smooth muscle, stimulating its proliferation. Studies have shown that relationship between severe asthma and leptin resistance. Adiponectin and cytokines, which is related to IR, acts as pro-inflammatory at the lung level by inducing fibroblast production. There is also an association between IR and bronchial hyperresponsiveness. In animal models it has been shown that airway inflammation reduces enzymes that reduce phosphorylation of insulin receptors, leading to changes that induce pro-inflammatory response and IR.[32]

The association between RF and obstructive sleep apnea has been demonstrated in non-obese individuals, as well as in individuals with mild sleep apnea. Similarly, studies have shown a higher prevalence of RF in individuals with pulmonary hypertension unrelated to obesity.[33]

Insulin resistance and Heart

It has been proposed that the heart is an organ that is not only a brand of systemic IR, as well as of myocardial insulin resistance (MIR), with MIR being an independent risk factor for heart disease.

The MIR is defined by the impairment of glucose uptake and utilization as an energy source by cardiac muscle.[34] MIR usually occurs at the same time as systemic insulin resistance or as a consequence of systemic IR.[35,36]

The heart is an insulin-sensitive organ, and studies have demonstrated the occurrence of MIR especially in subjects with heart failure, where a significant association between MIR and the development of heart failure has been found even in metabolically compensated diabetic subjects.[37]

The intracellular signaling pathway of MIR is complex, involving several factors and molecules, and activation of specific points in the myocardium has been demonstrated in individuals with IR.[38] Alterations in normal insulin signaling pathways such as those occurring in MIR contribute as increased risk factors for the development of cardiac dysfunctions. Therefore, if we take into consideration the repercussions of insulin resistance on the heart, it is interesting to differentiate between the outcomes secondary to over activation of signaling pathways that remain sensitive to insulin versus changes that are a consequence of an impaired ability of insulin to regulate glucose metabolism.

The complex outcomes of insulin signaling pathways in cardiac muscle associated with the systemic metabolic changes that define IR states will determine the MIR.[34]

Insulin resistance and Liver

The first organ that insulin reaches after its release by the beta cells is the liver. Thus the liver controls glucose metabolism according to body demand in response to insulin. Several mechanisms regulating insulin signaling in the liver are emerging as important targets involving various intracellular signals.

Individuals with T2DM have hepatic selective IR, characterized by the failure of insulin to inhibit gluconeogenesis without modification in the activation of lipogenesis leading to elevated triglycerides and severe hyperglycemia. "Pathway selective hepatic IR" has explained the mechanism of lipid synthesis and glucose production by the hepatic metabolic state. According to "pathway selective hepatic IR" Akt would not be able to efficiently activate mammalian target of rapamycin complex-1 as well as sterol regulatory element-binding protein-1c leading to lipid synthesis. Hepatic IR is complex and involves metabolic changes between peripheral tissues and the liver. It has been stated that the effect of the absence of hepatic autonomic insulin and abnormal glucose release by the liver as a function of the attrition of specific insulin receptors in the liver, are compensated by Forkhead box O-1 attrition. This may involve some extrahepatic mechanisms in regulating hepatic glucose production. The reduction in hepatic glucose production mediated by insulin is also associated with the reduction of hepatic acetyl CoA through the white adipocyte.[39]

Insulin resistance and Pancreas (β cell)

Pancreatic β-cells have receptors for insulin and IGF-1. Insulin plays a key role in controlling glucose-stimulated insulin secretion. In pancreatic IR there is hyperinsulinemia, which by itself is capable of

inducing IR by insulin toxicity.[40]

Pancreatic β-cells dysfunction and IR are complex and interrelated in triggering diabetes. Both β-cells dysfunction and IR induce hyperglycemia with increased insulin demand. The hyperglycemia resulting from β-cells dysfunction the insulin signaling within glucose receptors are altered chronifying the hyperglycemia. Thus, b-cell dysfunction is replaced by IR in the induction of T2DM.[41]

The aggression to the β-cells that leads to IR include the inflammatory process induced by cytokines, obesity, excess intake of free fatty acids and saturated fat. A reduction in the quantity and function of β-cells are the triggering factors of diabetes.[42]

The β-cells initially compensate for IR by elevating insulin secretion, which maintains normal blood glucose levels. This glucose homeostasis is maintained by adapting the amount and function of these β-cells that oppose IR up to presumably the maximum of their stimulation.[43]

The ability of β-cells to proliferate in response to IR is extremely important for glycemic control and prevention of progression to T2DM. It is the proliferation of mature β-cells that are responsible for preserving the amount of β-cells in adulthood. Other islet endothelial factors can also elevate β-cells proliferation, and islet-1 factor is critical for maintaining proliferation and preventing β-cells apoptosis.[44]

Thus, b-cell dysfunction indicates an advanced stage for the onset of diabetes, since insulin is being secreted insufficiently to meet the demand.

Insulin resistance and Kidney

The kidney is able to produce glucose through renal neoglycogenesis, and much of this glucose is used by the kidney itself, but hyperglycemia may occur due to this renal production of glucose.[45]

The kidney contributes to hypertension in IR by retaining sodium due to the action of insulin, and the action of leptin in the hypothalamus activates the sympathetic nervous system in the renal vessels inducing hypertension.[46]

Studies suggest that selective impairment of the insulin signaling pathway in IR is observed in the kidney. Inhibition occurs via IRS1 inhibition, while preservation occurs via IRS2 in the renal proximal tubule. The IRS2 pathway causes sodium retention triggering hypertension and edema. In addition, change IRS1 signaling leads to inhibition of gluconeogenesis, which can trigger hyperglycemia by maintaining glucose production. In the glomerulus there is also deterioration of the structure and function of podocytes and endothelial cells leading to diabetic nephropathy.[47]

Insulin resistance and Small intestine

The small intestine plays a relevant role in IR. The small intestine produces incretin hormones (GLP1 and GIP) after food ingestion that is able to stimulate and potentiate insulin secretion.[48]

GLP1 and GIP, besides the actions on the islets and gastrointestinal tract, also act on the central nervous system, reducing hunger, increasing the uptake of glucose by the muscle, and reducing the hepatic production of glucose. These actions of GLP1 and GIP are called insulin-mimetic actions.[49]

Experiments with obese animals treated with exanetide, increased Akt production in the liver and adipose tissue, returning to normal insulin signaling as a function of reduced endoplasmic reticulum stress. The use of exanetide in the obese is able to reduce the activation of protein kinase R-like ER kinase, demonstrating that this drug besides improving insulin secretion also improves insulin sensitivity by reducing endoplasmic reticulum stress.[50]

Insulin resistance and Large intestine

Studies of the intestinal flora have shown that in obese people the intestinal flora is different from lean individuals. In obese people there is an elevation of circulating levels of intestinal-generated lipopolysaccharide.[51]

A so-called "proof of concept" experiment, where a cocktail of antibiotics, was administered to an obese animal, it was observed that after the use of these antibiotics there was a restoration of the insulin signaling pathway, with reduced activation of c-Jun N-terminal kinase, drastically reducing the levels of intestinal-generated lipopolysaccharide.[52]

Another important "proof of concept" was the transplantation of intestinal flora from obese mice to lean mice. The result showed that the lean mice increased more weight compared to the control group, in addition to developing IR.[53]

Thus, alterations in the intestinal flora are able to induce changes in metabolism that are consequences of elevated intestinal-generated lipopolysaccharide levels

Insulin resistance and Spleen

The monocyte that is produced in the bone marrow does not go directly to the adipose tissue, but is stored in the spleen. Thus, every time an inflammatory process occurs, the monocytes move from the spleen to the site of inflammation.

Studies show that the splenectomized obese individual does not present IR, because there will be a normal insulin signaling pathway, not presenting the inflammatory phenomenon. In the splenectomized individual there is a lack of enough monocytes to differentiate monocytes-1 and induce the inflammatory phenomenon in the adipose tissue.[54]

Thus, a hypercaloric diet activates the inflammatory pathways, activates endoplasmic reticulum stress, activates TOLL-4, inducing IR in the hypothalamus, liver and muscle; at the same time there is an expansion of the adipose tissue mass, which recruits monocytes that move into the adipose tissue and differentiate. So the induction of IR is a clear phenomenon, but the aggravation of IR in the obese becomes spleen-dependent, due to the monocytes differentiating into macrophages at the splenic level, inducing IR.[55]

Insulin resistance and Muscle

In muscle, the phosphorylation of IRS 1 and 2 receptors control the translocation of GLUT4 to the plasma membrane and Akt controls glycogen synthesis and lipogenesis (Pederson et al., 2001). In the obese individual, glucose uptake is reduced due to lower tyrosine phosphorylation of IRS1 and lower activation of Akt. One of the main mechanisms of the lower phosphorylation of IRS1 is a consequence of serine-kinase activation that leads to conformational alteration of insulin receptors. Thus, the failure of GLUT4 translocation in the obese individual in response to insulin triggers IR.[56]

The IR is expressed in muscle through reduced glucose uptake promoted by insulin being a result of altered insulin signaling. Studies have shown that muscle IR is related to mitochondrial oxidative stress.[57]

In the occurrence of endoplasmic reticulum stress, the activation of Ikappa kinase (IKK) and c-Jun N-terminal kinase (JNK), which leads to the intracellular phosphorylation of IRS1 in serine, is fundamental. Another mechanism would be the activation of TOLL-like receptors, mainly in macrophages, which show hypersignaling in obese people. Study in animals with mutation in TOLL4, hyperlipidic diet does not cause IR by not activating IKK and JNK by not activating insulin receptors.[58]

Recent studies evaluating post-bariatric surgery individuals noted the occurrence of the drastic reduction in serum levels of the amino acids valine, isoleucine, and leucine, which are branched-chain amino acids and activate the mammalian-target of rapamycin inducing IR through phosphorylation of IRS1 at serine.[59]

Insulin resistance and Adipose Tissue

Dysfunctional adipose tissue is crucial in promoting IR. In the obese, adipocytes increase in volume making them dysfunctional, with recruitment of macrophages that lead to pro-inflammatory states with release of pro-inflammatory cytokines. Fat infiltration also occurs in several organs causing lipotoxicity and dysregulation of mitochondria, lysosomes, and endoplasmic reticulum resulting in systemic inflammation and altered glucose homeostasis.[60]

Studies show that both visceral adipose tissue and subcutaneous adipose tissue are associated with IR. Therefore, the dysfunctional adipocyte releases e excess free fatty acids, reactive oxygen species, and pro-inflammatory cytokines inducing IR, through inflammation triggered lysosome dysfunction and endoplasmic reticulum stress.[61]

Brown adipose tissue and white adipose tissue participate in energy homeostasis. The white adipose tissue is deposited under the skin and around the organs, serving as a reservoir for storage of lipids and secreting adiponectin and leptin. The brown adipose tissue, on the other hand, functions in the modulation of the energy balance and in the energy expenditure from excess food intake or in the body's response to low temperatures.[62] Brown adipose tissue activates thermogenesis through endocrine factors, as well as due to the "browning" of white adipose tissue.

Interleukin-6 is secreted by both brown and white adipocytes, and is implicated in the triggering of IR in obese. However, transplantation of brown adipocytes into the abdominal cavity of obese mice with IR has been shown to completely reverse IR as these brown adipocytes have the uncoupling protein 1 which is an important target in fighting DM diabetes and reducing body fat mass.[63]

Insulin resistance and Vessels

IRSs are present in the endothelial cells of vessels, and vascular endothelial cell dysfunction triggers vascular diseases in particular atherosclerosis. Activation of nitric oxide synthase in endothelial cells producing nitric oxide through insulin signaling preserves the integrity of the vascular barrier, which is of fundamental importance to prevent retention of atherogenic lipoproteins in the subendothelial space. In addition, nitric oxide attenuates the induction and development of atherosclerosis by inhibiting the accumulation of monocyte-derived macrophages in the vessel intima. Thus, vascular IR plays an important role in the pathogenesis of vasculopathies.[64]

Insulin activation via the phosphatidylinositol-3-kinase (PI3K) pathway also promotes endothelial nitric oxide production that produces vasodilation, whereas insulin activation via mitogen-activated protein kinase (MAPK) produces vasoconstriction and changes in vascular cell growth. In IR, the PI3K activation is selectively impaired, whereas MAPK is naturally preserved and activated. Thus, selective impairment in insulin-mediated nitric oxide production may favor the triggering of IR, in addition to atherogenesis, endothelial dysfunction, and hypertension.[65]

Insulin resistance and Ovary

Polycystic ovary syndrome (POCS) is a common disorder of premenopausal women characterized by chronic anovulation, hyperandrogenism, and is associated with hyperinsulinemia.[66]

Several proteins participate in the pathophysiology of PCOS and IR, including adiponectin, apelin, vaspin, visfatin, copeptin, PAI-1, irisin, and zonulin. Other proteins have been proposed as markers of IR in PCOS among them resistin, ghrelin, leptin, but their participation is still controversial.[67]

IRSs are found on granulosa cells, theca cells, and in the ovarian stroma. Laboratory studies have shown that binding to insulin receptors leads to phosphorylation of these receptors, elevating the production of androgens, estrogen and progesterone. This demonstrates that insulin is integral to ovarian physiology especially in steroid production.[68] Hyperinsulinemia may amplify the effects of insulin-like growth factor (IGF)-1 by modulating IGF receptors in the ovaries and regulating the production of insulin-like growth factor-binding protein-1.[69] Another theory for PCOS is that hyperstimulation of the ovaries leading to increased androgens would be caused by IR from hyperinsulinemia.[70]

Conclusion

Interaction between multiple mechanisms and molecular interactions are important factors in development of IR in various organs and systems. Thus, several organs can induce IR, and 42 mechanisms are capable of being activated in the induction of IR.

The occurrence of IR induces a subclinical inflammatory process characterized by endoplasmic reticulum stress and hyperinsulinemia. Some consequences of IR are due to hyperinsulinemia, others are due to alterations in carbohydrate metabolism itself. The consequences of IR may lead to cognitive changes, non-alcoholic fatty liver disease, acanthosis nigricans, polycystic ovarian syndrome, myocardial changes, pulmonary hypertension, dyslipidemia, atherosclerosis, and cancer.

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Declarations

Competing interests: no potential conflict of interest relevant to this article was reported.

Figures

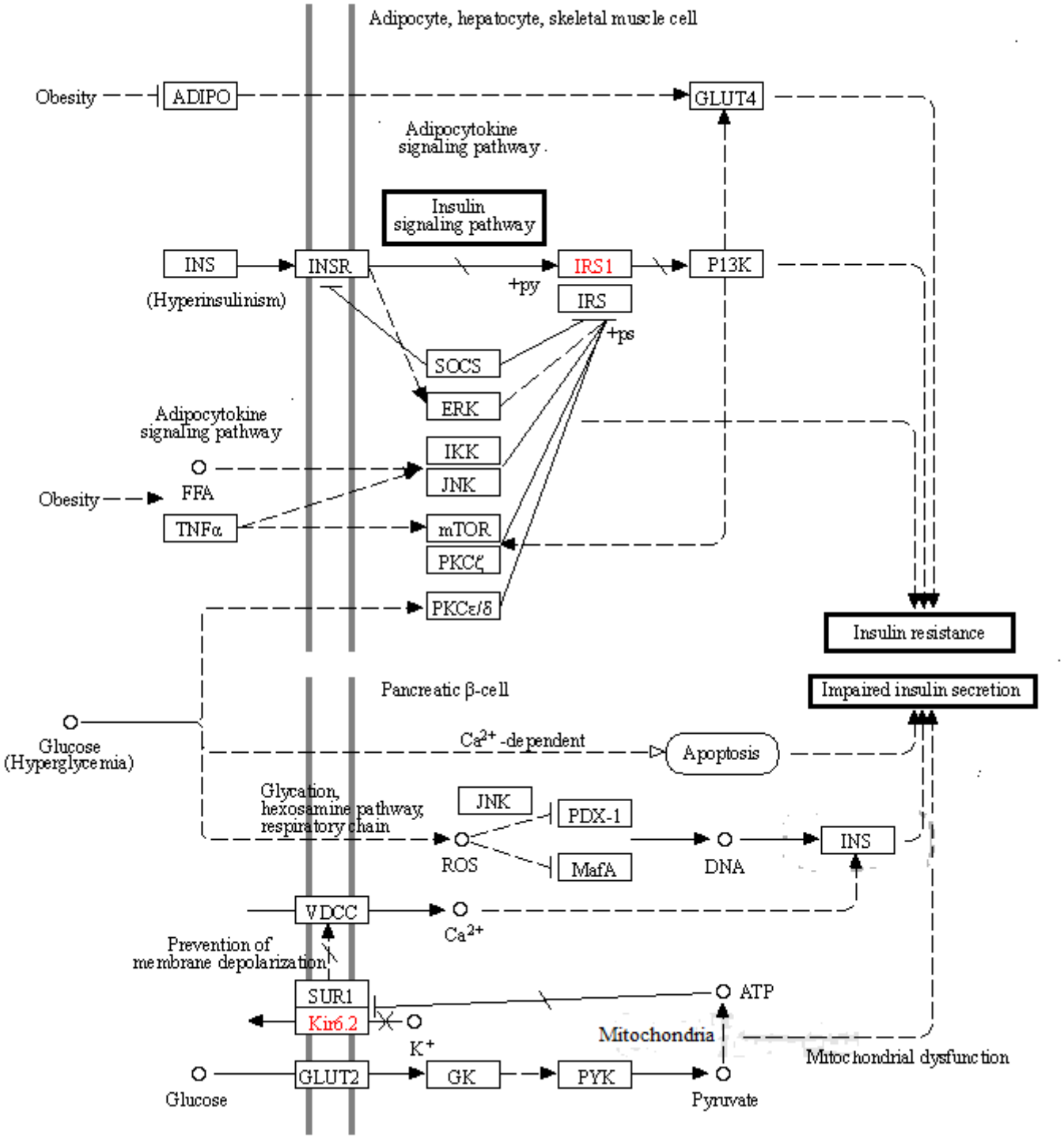

Figure 1

Insulin resistance - Signaling pathway diagram design

Source: Adapted from the KEGG PATHWAY Database.