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None of the authors haveany potential conflicts of interest to disclose

Abstract

Background:

The low available of Glut-4 transporters in sarcolemma of the cardiac cells is what characterizes the myocardial insulin resistance (MIR), which is triggered separately of generalized insulin resistance. Insulin receptors are quite evident in the heart muscle and vessels, and mitochondrial activity performs a significant function in MIR preserving cellular homeostasis by cell reproduction, cells livelihoods, and energy generation.

Objective:

To evaluate the MIR mechanism and through the signaling pathway design.

Methods:

PubMed database was employed to search for reviews publications with MIR. The referenced data of the signaling pathway was chosen aggregating references of the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. A signaling pathway was designed based on MIR research manuscripts, where we show several mechanisms included in the MIR. The KEGG server was employed to exploit the interrelationship protein-protein, and elaborate signaling pathway diagram. The signaling pathway mapping was carried out with PathVisio software.

Results:

We selected 42 articles from a total of 450 articles in the PubMed database that presented a significant association between the terms "insulin resistance myocardial" AND "signaling pathway". Founded on database-validated research papers, we choose well-founded pathways and we succeeded representative description of these pathways. The reproduction contigs taken from the KEGG database designed the signaling pathway of the bio-molecules that lead to MIR. Thus, the acting among multiple mechanisms releases factors that participate of the development of MIR.

Conclusion:

The interaction among various mechanisms and molecular interactions are important factors in development of MIR.

Keywords: Myocardial; Insulin resistance; Signaling pathway.

Introduction

Insulin resistance is a clinical/pathological status recognized through of hyperinsulinemia and altered glucose homeostasis, transforming various functions of the cell and contributing to the onset of several diseases. It has been observed that insulin resistance is present not only in type 2 diabetes but also in various organs and tissues, including the skeletal muscle, adipose tissue, and hepatic parenchyma, as well as the vascular tissue and cardiac muscle, which in majority cases are just evaluated in circumstances of the progression of chronic diseases[1]. It has been proposed that the heart is an organ that is not only a brand of systemic insulin resistance, 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[2]. MIR usually occurs at the same time as systemic insulin resistance or as a consequence of systemic insulin resistance[3,4].

The heart is an insulin-sensitive organ, and studies have demonstrated the occurrence of myocardial insulin resistance 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[5].

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 insulin resistance[6]. 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 insulin-resistance states will determine the MIR[2].

The purpose of this study was to evaluate the MIR mechanism and through the signaling pathway design based in research articles.

Methods

Modeling of Signaling Pathway of Myocardial Insulin Resistance

The planning of molecular pathway maps involved a meticulous extraction of molecular properties from in the medical literature, followed by the establishment of the several components in a series of interconnected occurrences.

Supported in research paper, we choose well-reasoned pathways and we collect characteristics expression outline from those pathways. PubMed database was employed to evaluate reviews publications who have researched the MIR. The referenced data of the signaling pathway was chosen aggregating references of the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

The KEGG is a database with signaling pathway maps, and references about biological process networks, genome sequencing, protein domains, aiming at understanding and using this data scientifically[7].

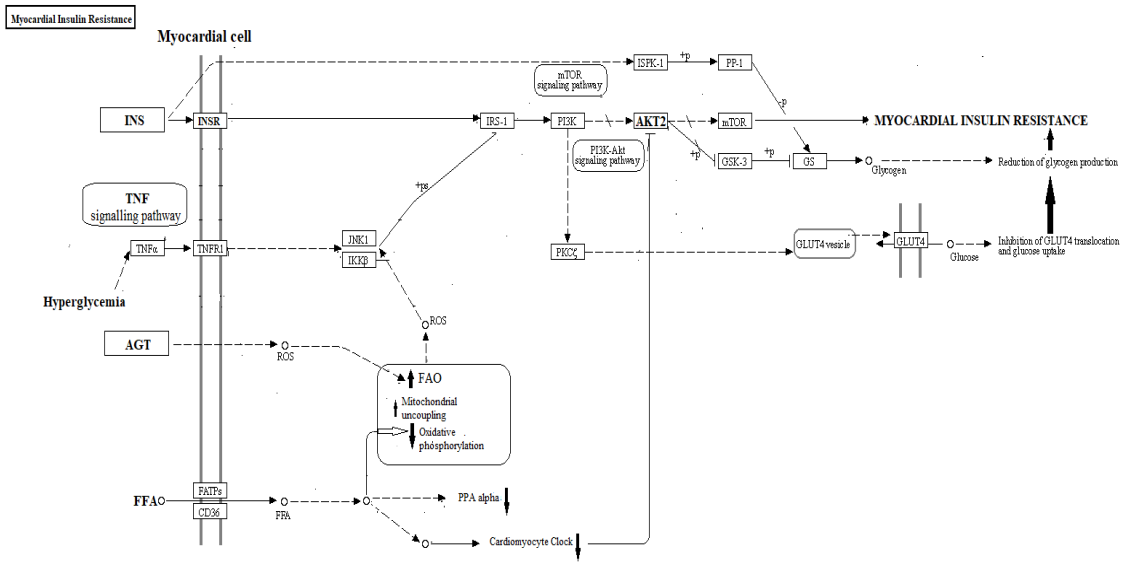
We evaluate a total of 15 signaling pathways in KEGG database, and for each signaling pathways we distinguish the proteins associated to the MIR. We evaluate a total of fifteen signaling pathways in KEGG database, and for each signaling pathways we distinguish the proteins associated to the MIR. We then confronted the proteins and the fifteen interrelations. The KEGG database contains information about proteins, including pathway data proven in diagrams that make it feasible to build the interactivity of proteins into complex organic methods.

The graphic design of the signaling pathway was prepared using PathVisio software (version 3.3.0), and was applied to the graphic display of the signaling pathway, as it is a tool that enables the visibility and editing of biological signaling pathways. PathVisio is a free download path editor, bundled with the WikiPathways community pathway database and freely available for biological pathway evaluation.

Results

When searching the PubMed database using the term "insulin resistance myocardial", we identified 4,373 results, and when using the association of the terms "insulin resistance myocardial" AND "signaling pathway" we found 450 results. We selected only 42 articles that presented a significant association between the terms used.

The basic mechanisms of insulin resistance as well as their interaction with different proteins in triggering of MIR are presented in Figure 1.



AGT: angiotensinogen; **AKT**: protein kinase B; **CD36**: cluster of differentiation 36; **FAO**: fatty acids oxidation; **FATPs**: Fatty acid transport proteins; **FFA**: free fatty acids; **GLUT4**: Glucose transporter type 4; **GS**: glycogen synthase; **IKK β**: nuclear factor-kB kinase β; **INS**: insulin; **INSR**: insulin receptor; **IRS1**: Insulin receptor substrate-1; **ISPK1**: insulin-stimulated protein kinase 1; **JNK1**: cJun NH2-terminal kinase 1; **mTOR**: Mammalian target of rapamycin; **OS**: oxidative stress; **GKS3**: glycogen synthase kinase 3; **PI3K**: phosphoinositide 3-kinase; **PKCC**: classical protein kinase C; **PP-1**; type-1 protein phosphatase; **PPAα**: peroxisome proliferators-activated receptor α; **ROS**: Reactive oxygen species; **TNFR**: tumor necrosis factor receptor; **TNF-α**: tumor necrosis factor alpha;

Figure 1. Insulin resistance Myocardial - Signaling pathway diagram design

Discussion

In our work, we interlink a revision study with computer molding to comprehend the signaling pathway leading to the MIR.

Insulin leads to glucose uptake by cardiac muscle, adipocytes, and skeletal muscle through the connection of insulin to the cellular insulin receptor. Insulin resistance is defined as the reduced cellular ability to respond to the insulin action of several metabolic pathways, involving the transport of glucose to the various tissues, and is associated with several clinical situations, especially with type 2 diabetes mellitus, as well as with atherosclerosis, hypertension, and the metabolic syndrome[8].

MIR is a metabolic disorder of the cardiomyocyte, arising from a reduction in the effectiveness of the myocardial cell to absorb glucose as well as reduced

mitochondrial function and endothelial nitric oxide synthase. Thus, MIR is an independent risk factor of systemic insulin resistance for heart disease[9].

We demonstrate the progression of MIR through a signaling pathway based on several studies. In the initial cascade for the development of MIR, the hyperglycemia, tumor necrosis factor (TNF-α), angiotensinogen (AGT), free fatty acids (FFA), and of course insulin are involved. Usually, the normal cardiomyocytes gets most of its energy force through of glucose oxidation and FFA when in the fed state and the fasting state, respectively[10].

Hyperglycemia has been linked to MIR, since hyperglycemia acts on the antilipolysis effect of insulin leading to elevation of FFA that regulates glucose utilization by the myocardial cell[11].

TNFα is an important endocrine and paracrine regulator produced by activating macrophages and monocytes with immune and inflammatory activity and cellular pleiotropic actions. TNF-α is associated with the onset of insulin resistance, as its elevation leads to metabolic dysregulation in various tissues including the myocardium. TNF-α is an important pro-inflammatory mediator, and high levels of TNF-α induce insulin resistance at the myocardial cell level through activation of various transcriptional pathways, thereby altering insulin signaling through serine phosphorylation[12]. Tumor necrosis factor receptor 1 (TNFR1), is the main membrane receptor that binds TNF- α, which can activate other transcription factors mediating cell survival and regulating inflammation, and is linked to mitochondrial abnormalities in cardiac muscle, as well as myocardial insulin resistance[13].

AGT is α-globulin that is part of the renin-angiotensin system a regulator of blood pressure and fluid-electrolyte balance. AGT is synthesized in the liver and in adipose tissue and is a relevant regulator of blood pressure, being involved in insulin resistance through muscle vasoconstriction. Furthermore, hyperglycemia elevates the transcription of AGT secretion from the local angiotensin-converting enzyme[14]. Overexpression of angiotensinogen in myocardium decreased the level of cardiac fatty acid oxidation simultaneously with the reduction of medium chain acyl CoA dehydrogenase, of carnitine palmitoyl transporterase 1 and of (Peroxisome proliferator-activated receptor-α (PPARα)[15].

FFA is lipid species resulting from triacylglycerol by ester bond cleavage secondary to the action of lipase. As mentioned earlier, the myocardial cell receives most of its energy force through FFA when in the fasting state[10]. Thus, elevations in

circulating FFA levels involve molecular mechanisms that lead to modifications in insulin signaling in cardiomyocytes that will determine MIR[16]. FFA penetrates the cardiomyocytes carried by transport proteins or through passive diffusion. FFA uptake by the myocardial cell also occurs via cluster of differentiation 36 through insulin stimulation[17].

INSR is a heterotetrameric receptor belonging to the family of tyrosine kinase receptors being formed by two α subunits spanning the extracellular segment, and two β subunits includes transmembrane and intracellular control[18]. It has been reported the different actions of insulin and the importance of its altered signaling in individuals presenting with MIR, which are characterized by reduced INSR activity[19].

Insulin acting directly on the myocardial cell will stimulate, through the mammalian target of rapamycin (mTOR) signaling pathway, insulin-stimulated protein kinase-1 and protein phosphatase 1, which due to its main role in muscle glycogen production is a determinant in the pathogenesis of MIR due to the reduction of glycogen in cardiomyocytes[20].

In the central part of the MIR progression signaling pathway cascade the following components are involved: cJun NH2-terminal kinase 1 (JNK1), nuclear factor-kB kinase β (IKK β), reactive oxygen species (ROS), peroxisome proliferators-activated receptor α (PPAα), fatty acids oxidation (FAO), Insulin receptor substrate-1 (IRS1), phosphoinositide 3-kinase (PI3K), and protein kinase, classic (PKCC).

JNK1 is a stress-stimulated protein kinase, and is involved in the development of MIR[21]. The mechanism involving JNK1 in MIR is explained by inhibition of insulin signaling mediated by serine-307 phosphorylation of IRS-1[22]. Another key point in triggering MIR by increased JNK1 arising from increased macrophage concentration in myocardial tissue.

IKKβ is one of two serine-threonine kinases that inhibit insulin action by decreasing phospho-tyrosine residues of IRS1 inducing insulin resistance[23]. IKKβ is able to interfere with metabolic branch of insulin signaling directly by phosphorylating IRS1 or by phosphorylating inhibitor of nuclear factor-κB having insulin resistance as a consequence. Furthermore, IKKβ plays an important role in the regulation of pro-apoptotic activity as a feedback to oxidative stress[24]. Similarly, IKK stimulated by TNF-α resulting in an upregulation of inflammatory mediators also plays a key role in the induction of MIR[25].

Studies have demonstrated the behavior of ROS in myocardial dysfunction associated with insulin resistance. There is evidence that ROS mediate cardiac injury from MIR by modifying protein signaling, altering cardiomyocyte metabolism, and promoting cardiac dysfunction. Hyperglycemia and insulin resistance induces an increase in ROS, initiating intracellular molecular signaling. Thus, cardiomyocyte-ROS act as an important messenger in the MIR signaling pathway[26].

PPAα is a nuclear receptor that commands a number of genes in different pathways of lipid metabolism and also plays an important role in MIR. PPAα in the cardiomyocyte plays an important role in the mechanism of FAO via FA transport, beta-oxidation, and esterification, and regardless of the elevation of FA mobilization, its activators reduce plasma FFAs[27]. It has been suggested that the negative regulation of MIR by PPAα would be associated with PPAα-inhibition mediated through the PIK3/AKT/ mTOR signaling pathways[28].

Myocardial FAO is a complex system, and studies have shown that FAO has with consequences damage to the cardiomyocyte due to alterations in mitochondrial metabolism with blockage of glucose oxidation, increased production of lactic acid and hydrogen ions leading to MIR with heart failure[29,30]. Thus, studies suggest that reducing the efficacy of FAO would result in the accumulation of long-chain FA with consequent production of harmful lipid metabolites hastening the development of MIR[31].

IRS-1 is the key molecule in insulin signaling and its phosphorylation is one of the links in triggering the insulin resistance signaling pathway. IRS-1 is essential for the activity and homeostasis of the heart, and hyperinsulinemia inducing metabolic stress leads to its suppression in cardiomyocytes being one of the trigger points of MIR[32]. IRS-1 then attracts and activates PI3K, initiating a series of signaling events leading to the triggering of AKT and its various targets. Thus, MIR is related to the activation of this pathway due to IRS-1 deficiency[33].

PI3K are heterodimeric groups consisting of mediating and catalytic subunits that are involved in glucose metabolism and also participate in various cellular activities ranging from cell growth to apoptosis. Investigation of PI3K activity in insulin signaling has been evaluated, and studies show that its activity is decreased in insulin resistance[34]. In MIR, altered PI3K-related insulin signaling is associated with reduced cardiomyocyte FAO rates occurs as a function of mitochondrial dysfunction and reduced PPARα expression[35].

PKCc is a family of serine/threonine kinases that are important factors in cellular physiology, playing a central role in signaling for various cellular responses, and may influence insulin signaling through serine phosphorylation of IRS-1[36]. Hyperglycemia activates PKCc, and insulin resistance in muscle demonstrated that PKCc are chronically controlled and phosphorylated in insulin resistance. In addition, PKCc-mediated phosphorylation regulates glycogen synthase with its own changes in its signaling in myocytes related to insulin resistance[37]. Thus, the manifestation of PKCc in muscle is enough to control the insulin signaling cascade with changes in cardiomyocyte glucose metabolism[38].

In the final outcome of the MIR signaling cascade are implicated: insulin-stimulated protein kinase 1 (ISPK1); type-1 protein phosphatase (PP-1); AKT2; mTOR; gliycogen synthase kinase 3 (GKS3); and glucose transporter type 4 (GLUT4).

ISPK-1 is part of the family of serine/threonine protein kinases called ribosomal S6 kinases. ISPK-1 is mainly expressed in muscle and contributes to the pathogenesis of the intensified insulin deficiency of glycogen synthesis[39]. ISPK-1 may interfere with insulin's performance on metabolism by phosphorylating regulatory proteins. ISPK-1 may interfere with insulin's performance on metabolism by phosphorylating regulatory proteins. ISPK-1 directly activates the activation of PP-1 by phosphorylation of the serine in the G subunit of this protein[40]. Oxidative stress on PP-1 causes a reduction in glycogen production that will trigger MIR.

AKT2 is one of the three isoforms of the AKT family and performs an important function in the insulin signaling pathway. Studies show that AKT1 and AKT2 are the most prevalent isoforms in the myocardium, and the AKT2 isorform is critical for glucose uptake by the myocardial cell, an effect that is not dependent on AKT1, thus playing an important role in the development of MIR[41]. In addition, AKT2 participates in the phosphorylation of mTOR, activating the AKT/mTOR signaling cascade that culminates in the triggering of MIR[2].

GSK3 acts in protein biosynthesis, in addition to regulating cellular metabolism, and reducing glycogen. GSK3 has been linked to glucose homeostasis and the triggering of insulin resistance because of its role in controlling glycogen synthesis. Blocking the action of GSK3 leads to improved insulin action. GSK3 in cardiomyocyte and MIR has been shown to be associated with oxidative stress and reduced glycogen production[42].

Conclusion:

MIR demands a number of factors in its signaling pathway, and the interaction among various mechanisms and molecular interactions are important factors in development of MIR.

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