JAK-STAT signaling and myocardial glucose metabolism

Miguel A Frias¹ and Christophe Montessuit²*

¹Division of Endocrinology, Diabetology and Nutrition; University of Geneva School of Medicine; Geneva, Switzerland;
²Division of Cardiology; Department of Medical Specialties; University of Geneva School of Medicine; Geneva, Switzerland

Keywords: cardiac myocytes, glucose metabolism, insulin, insulin resistance, Janus kinase, JAK, myocardium, signal transducer and activator of transcription, STAT, suppressor of cytokine signaling, SOCS

Abbreviations: Acetyl-CoA, acetyl-coenzyme A; ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; AMPK, AMP-activated protein kinase; Ang II, angiotensin II; AGTR1, angiotensin receptor type 1; CT-1, cardiotoxin-1; F1,6BP, fructose-1,6-bisphosphate; F2,6BP, fructose-2,6-bisphosphate; F6P, fructose-6-phosphate; GLUT1 or 4, facilitative glucose transporters; gp130, glycoprotein 130; Ins, insulin; IRα/β, insulin receptor, subunit α/β; IRS, insulin receptor substrate; LIF, leukemia inhibitory factor; LIFR, LIF receptor; mTORS, mammalian target of rapamycin complex 2; PDC, pyruvate dehydrogenase complex; PDH-E1, pyruvate dehydrogenase enzyme; PDK1-4, pyruvate dehydrogenase kinase 1 to 4; PDPK1, Phosphoinositde-dependent protein kinase 1; PDPK1-2, pyruvate dehydrogenase phosphatase 1 or 2; PFK-1, 6-phosphofructo-1-kinase; PFK-2, 6-phosphofructo-2-kinase; P3K, phosphoinositides 3-kinase; PIP3, phosphatidylinositol-3,4,5-trisphosphate; SGLT1, sodium-glucose cotransporter 1; SOCS3, suppressor of cytokine signaling 3; WISK, wortmannin-sensitive and insulin-stimulated protein kinase

JAK-STAT signaling occurs in virtually every tissue of the body, and so does glucose metabolism. In this review, we summarize the regulation of glucose metabolism in the myocardium and ponder whether JAK-STAT signaling participates in this regulation. Despite a paucity of data directly pertaining to cardiac myocytes, we conclude that JAK-STAT signaling may contribute to the development of insulin resistance in the myocardium in response to various hormones and cytokines.

Myocardial Glucose Metabolism

Overview

Life critically depends on the beating of the heart, an energy-consuming process fueled by hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP). In fact, the heart is the organ with the highest specific oxygen consumption, reflecting its intense, mostly aerobic, metabolic activity. The most important substrates for energy production in the normal myocardium are fatty acids, glucose and lactate, in decreasing order of importance. Together, anaerobic and aerobic metabolism of these substrates account for almost all of energy production in the normal adult heart, the respective contribution of each depending on the metabolic and hormonal status. Catabolic breakdown of glucose occurs in two stages: glycolysis, an anaerobic, cytoplasmic stage with low ATP yield (2 ATP/glucose), followed by aerobic oxidation of glycolysis-derived pyruvate in the mitochondria. Pyruvate is first converted to acetyl-CoA by the action of pyruvate dehydrogenase complex (PDC), the rate-limiting enzyme for glucose oxidation. Acetyl-CoA then enters the Krebs cycle, wherein it is oxidized to CO₂ with production of reducing equivalents, thereafter used in the electron transport chain to produce ATP with a much higher yield (34 ATP/glucose).

Importance of glucose metabolism for the myocardium

Among the myocardial substrates, glucose accounts for less than 25% of the energy production under normal conditions. It should not be surmised from this rather low figure that glucose is entirely dispensable for the heart. Indeed, although isolated perfused hearts can aerobically run for hours on fatty acids only, glucose becomes extremely important during episodes of ischemia and reperfusion. There are mostly two reasons for this requirement for glucose during metabolic stress: (1) energy can be obtained from glucose through glycolysis even in situations of hypoxia or ischemia and (2) ATP obtained from glycolysis, although scarce, is important for the maintenance of ionic homeostasis. Indeed ATP production and use is highly compartmentalized in the myocardium, and glycolytic ATP is preferentially used to fuel the sarcosomal and sarcoplasmic reticum pump.

Regulation of glucose metabolism

Glucose metabolism in the myocardium is tightly regulated; there are three major steps regulating the rates at which the two stages of glucose breakdown proceed (Fig. 1): (1) Glucose transport from the extracellular space; (2) the phosphofructokinase reaction, which is the first committing step of glycolysis; and (3) the intramitochondrial conversion of pyruvate to acetyl-CoA, which is the first step of pyruvate oxidation.

1) Glucose transport occurs mostly by facilitated diffusion through selective transport proteins of the GLUT family.
In cardiac myocytes, mostly two isoforms of glucose transporter, GLUT1 and GLUT4, are involved. GLUT1, which predominates during fetal and early postnatal period, is located mainly in the sarcolemma under basal conditions. GLUT4 on the other hand is the main isoform present in fully differentiated cardiac myocyte. GLUT4 is mainly located in intracellular membrane compartments and is translocated to the cell surface in response to various stimuli. As a result, the major determinant of glucose uptake into cardiac myocytes at physiological glucose concentrations is the number of GLUT4 transporters present at the cell surface. However, in addition to facilitated diffusion, cotransport of sodium and glucose by the cotransporter SGLT1 has been recently reported in mouse heart and found to be stimulated in response to insulin and leptin.

The most important stimuli triggering translocation of GLUT4 in cardiac myocytes are insulin, ischemia and workload. Signaling in response to insulin and leading to stimulation of glucose transport in short involves recruitment and activating tyrosine phosphorylation of insulin receptor substrates proteins (IRS-1, -2, and -3), activation of phosphoinositide-3-kinases (PI3K), and activating phosphorylation of Akt. Ischemia on the other hand increases the AMP to ATP ratio within the cardiac myocytes, leading to activation of the AMP-activated kinase (AMPK) by both allosteric phosphorylation on threonine 172 of the catalytic AMPKα subunit. Both activated Akt and AMPK phosphorylate and inactivate the Rab-GTPase AS160; this relieves an inhibition of GLUT4 translocation. For a more detailed discussion of the mechanisms controlling GLUT4 translocation in the myocardium, the interested reader is referred to a recent review.

2) The phosphofructokinase reaction converts fructose-6-phosphate to fructose-1,6-bisphosphate. This is the first committed step in glycolysis, and as such, it determines the rate at which glycolysis proceeds downstream. The activity of 6-phosphofructo-1-kinase (PFK-1) is allosterically regulated in negative feedback loops by ATP and citrate. Importantly, in cardiac myocytes it is strongly activated by a glucose metabolite that is not part of the glycolysis pathway sensu stricto, fructose-2,6-bisphosphate. This metabolite is produced from fructose-6-phosphate by the enzyme 6-phosphofructo-2-kinase 2 (PFK-2; the heart isoenzyme is different in both gene

---

**Figure 1.** Principal points of regulation of glucose metabolism in cardiac myocytes. Glucose enters cardiac myocytes by facilitated diffusion through GLUT (mostly GLUT4) transporters and to a minor extent by cotransport with sodium through SGLT1. Glycolysis yields pyruvate, which is converted to acetyl-CoA to undergo mitochondrial oxidation in the Krebs cycle. Principal points of regulation are transmembrane transport, regulated by translocation of GLUT4, the PFK-1 reaction, which is stimulated by F2,6BP, and activity of the pyruvate dehydrogenase complex, regulated by phosphorylation by PDH kinases or dephosphorylation by PDH phosphatases. See text for details. Abbreviations: AMPK, AMP-activated protein kinase; F1,6BP, fructose-1,6-bisphosphate; F2,6BP, fructose-2,6-bisphosphate; F6P, fructose-6-phosphate; GLUT1 or 4, facilitative glucose transporters; Ins, insulin; IRα/β, insulin receptor, subunit α, respectively β; PDC, pyruvate dehydrogenase complex; PDPC1-2, pyruvate dehydrogenase kinase 1 to 4; PDPC1-2, pyruvate dehydrogenase phosphatase 1 or 2; PFK-1, 6-phosphofructo-1-kinase; PFK-2, 6-phosphofructo-2-kinase; SGLT1, sodium-glucose cotransporter 1; WISK, wortmannin-sensitive and insulin-stimulated protein kinase.
and function from the liver and muscle isoenzymes). Similar to glucose transport, activity of the heart PFK-2 is stimulated in response to insulin, ischemia and workload. Insulin signaling activates a wortmannin-sensitive protein kinase (WISK), whose molecular identity remains unsure, but which is distinct from Akt; ischemia, as described above, activates AMPK and workload activates Akt. All three kinases phosphorylate and activate PFK-2, thereby accelerating glycolysis.

3) Activity of the pyruvate dehydrogenase complex (PDC) commits glycolysis-derived pyruvate to intramitochondrial oxidation in the Krebs cycle. The PDC is a multienzyme complex carrying out three successive reactions leading to the biosynthesis of acetyl-CoA. The first and rate-limiting reaction is decarboxylation of pyruvate by the pyruvate dehydrogenase enzyme (PDH-E1). The PDH-E1 can be inhibited by phosphorylation on three specific serine residues on its α subunit by PDH kinase, of which there exists four isoforms (PDK1–4). Conversely, two PDH phosphatases (PDPC1 and PDPC2) dephosphorylate and activate PDH-E1; this phosphatase activity is stimulated by insulin.

**JAK-STAT Signaling in the Myocardium**

**Overview**

Many signaling pathways have been found in myocardium, including the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. The JAK-STAT signaling pathway transduces signals from extracellular ligands such as cytokines, growth factors and hormones to the nucleus to orchestrate the appropriate cellular response.

Four members of the JAK family, (JAK1, JAK2, JAK3, and TYK2) and seven STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6) have been identified in mammals. Although STAT proteins are structurally related, their activations and effects present a high degree of specificity for the different STAT isoforms. The JAK/STAT pathway can be activated by many cytokines, including all interferons and high density lipoproteins. The beneficial effect of STAT3 in the heart is confirmed in experiments using mice overexpressing STAT3 in the myocardium. These mice are less sensitive to ischemia-reperfusion injury and to doxorubicin (a cardiotoxic drug) exposure than wild-type mice.

In non-stimulated cells, JAK proteins are associated with the membrane receptors and are inactive. Inactive STAT proteins are located in the cytosol in a monomeric form. Activation occurs when the cytokine binds to its membrane receptor, the bound-receptor dimerizes and JAK proteins are activated by transphosphorylation. Activated JAK proteins can phosphorylate the tyrosine residues located in the intracellular section of the receptor, which become the docking sites for the Src 2 domains (SH2) of the STAT proteins that are recruited. Recruited STAT proteins are thus activated via JAK proteins by phosphorylation on the tyrosine residue situated near the SH2 domain. Once phosphorylated on the tyrosine residue, STAT monomers form hetero- or homo-dimers, which translocate to the nucleus where they can bind to the DNA and induce the transcription of target genes.

Although this is the classical activation process, other tyrosine kinases are able to activate STAT proteins; for example, growth factor receptors containing an intrinsic tyrosine kinase activity (EGF and PDGF receptors) as well as non-receptor tyrosine kinases (Src, Abl) can directly activate the members of the STAT family.

Activation of the JAK-STAT signaling pathway is a complex process, which can be stopped or negatively regulated by several processes including dephosphorylation, nuclear export and negative regulators such as SOCS (suppressors of cytokine signaling) and PIAS (protein inhibitor of activated STAT). For a more detailed discussion of the mechanisms of STAT regulation, the interested reader is referred to a recent review.

**Role of JAK-STAT in the heart**

JAK1, JAK2, and TYK2 and all the members of STAT family are expressed in the heart. Among these proteins STAT3 and STAT1 are the most studied.

Multiple studies have demonstrated a beneficial and protective role of STAT3 in the heart. This role has mainly been pointed out by data from animal experiments. As STAT3 knockout mice result in early embryonic lethality, specific cardiac myocyte STAT3 knockout (STAT3-KO) mice have been a useful tool to investigate STAT3 in the heart. The use of these mice and of the pharmacological inhibitor of JAK2 (AG490) demonstrates a protective and anti-apoptotic role of STAT3. This role has mainly been demonstrated in the model of ischemia reperfusion injury. Thus STAT3-KO mice submitted to 1 h ischemia followed by 24 h of reperfusion show a significantly increased infarct size. STAT3 is also involved in pro-survival processes such as ischemic pre- and post-conditioning. Ischemic pre- and post-conditioning protocols result in a significant reduction in infarct size and an improvement of cardiac function when compared with non-conditioned hearts. In STAT3-KO mice and in experiments using pharmacological JAK inhibitors, these protective effects are reduced. It is also possible to mimic ischemic conditioning with pharmacological compounds. In this context STAT3 has been shown to play a role in cardioprotection afforded by tumor necrosis factor α, insulin, melatonin, sphingosine-1-phosphate, and high density lipoproteins. The beneficial effect of STAT3 in the heart is confirmed in experiments using mice overexpressing STAT3 in the myocardium. These mice are less sensitive to ischemia-reperfusion injury and to doxorubicin (a cardiotoxic drug) exposure than wild-type mice.

In addition of these pro-survival actions, STAT3 is involved in adaptive hypertrophy. Hypertrophy is initially beneficial and contributes to reduce wall stress and oxygen consumption in the overloaded heart; this serves to maintain normal cardiac output. Transgenic mice with myocardium STAT3 overexpression show signs of hypertrophy by 12 weeks of age. The hearts display enlarged left ventricles and enhanced expression of hypertrophic genes (β-myosin heavy chain, atrial natriuretic peptide). Members of the IL-6 family (LIF, CT-1 and IL-6) activate the JAK-STAT3 signaling pathway via the activation of the gp130 receptor and have been shown to be potent mediators of cardiac hypertrophy. gp130 receptor engagement can prevent heart failure through inhibition of apoptosis and induction of compensatory hypertrophy, via STAT3 activation.
In contrast to the protective role of STAT3, STAT1 has been attributed deleterious actions. Indeed, in cultured cardiomyocytes STAT1 is activated by hypoxia–reoxygenation and enhances apoptosis by activating the pro-apoptotic targets caspase1, Fas, and FasL.\(^{40}\) Inhibition of STAT1 confers protection against hypoxia–reoxygenation. In vivo, STAT1 is activated during ischemia-reperfusion and hearts from STAT1-KO mice submitted to ischemia-reperfusion have a smaller infarct than wild type mice.\(^{41}\) Recently, STAT1 has been shown to reduce autophagy, which participates in post-infarction cardioprotection.\(^{31}\) Interestingly, experiments in cultured fibroblasts and cardiac cells using STAT overexpression showed that the pro-apoptotic action of STAT1 can be counteracted by the relative expression of STAT3.\(^ {40,42}\) The balance between STAT1 and STAT3 activation might thus play a role in the determination of cell fate.

**Interaction between JAK-STAT Signaling and Myocardial Glucose Metabolism**

**Participation of JAK-STAT in insulin and AMPK signaling**

Given the ubiquitous nature of both JAK-STAT signaling and glucose metabolism, one may wonder about the involvement of the former in the regulation of the latter in the heart. The first question to ponder is whether JAK-STAT signaling is activated in response to insulin or metabolic stress, the two most important stimuli of glucose metabolism in the myocardium. Indeed it has been shown very early that insulin activates JAK2 in all insulin-responsive tissues, including the heart, in vivo in rats;\(^ {13}\) this observation was further extended to JAK1 in cultured cells.\(^ {44}\) Independently STAT5 was found to be tyrosine-phosphorylated in response to insulin;\(^ {45}\) it was later confirmed that STAT5 phosphorylation could occur both independently of and through JAK activation.\(^ {46,47}\) STAT3 was also found to be activated in response to insulin in the heart, thus mediating the cardioprotective effects of the hormone.\(^ {31,48}\) In an intriguing crosstalk between canonical pathways, JAK2 activated by other hormones such as growth hormone (GH) or leptin can phosphorylate IRS-1 and IRS-2 on tyrosine residues and thereby recruit and activate PI3K.\(^ {49,50}\) This however is not sufficient to stimulate glucose metabolism.

Similarly, several studies have reported activation of STAT3, and perhaps STAT1, 5, and 6, in the ischemic myocardium or in cardiac myocytes submitted to simulated ischemia,\(^ {49,40,51-53}\) situations that entail AMPK activation. The participation of AMPK in STAT activation, or AMPK activation downstream to STAT activation, have to the best of our knowledge not been reported. We have observed activation of STAT5 in cardiac myocytes in response to the ATP-synthase inhibitor oligomycin concomitantly with strong AMPK activation, but again without proof of causality.\(^ {54}\)

**Participation of JAK-STAT in the regulation of glucose metabolism**

Having established that JAK-STAT signaling could be activated in response to stimuli that increase glucose metabolism, we now have to consider whether JAK-STAT signaling actually contributes to the stimulation of glucose metabolism. Regarding this issue the literature is remarkably scarce, and almost nonexistent as to the myocardium. In skeletal myotubes, which are similar to cardiac myocytes in the regulation of glucose metabolism, insulin-stimulated GLUT4 translocation and glucose uptake is not affected by JAK2 silencing, whereas the proliferative effects of insulin are blunted.\(^ {55}\) Similarly, pharmacological inhibition of JAK2 with AG490 fails to prevent the stimulatory effect of leptin on glucose transport in myotubes.\(^ {56}\) On the other hand leptin increases Na-glucose cotransport in the myocardium by increasing expression of SGLT1,\(^ {7}\) which was shown to be driven by JAK2 activity.\(^ {37}\)

Let us now turn our attention to the converse possibility, which is that JAK-STAT signaling impedes myocardial glucose metabolism instead of stimulating it. Indeed several factors known to activate JAK-STAT signaling in the myocardium have also inhibitory effects on glucose metabolism (Fig. 2). These include angiotensin II (Ang II),\(^ {58,60}\) low concentrations of cardiotrophin-1 (CT-1),\(^ {54,61}\) GH,\(^ {50,62}\) and leukemia inhibitory factor (LIF).\(^ {63,64}\) A common effect of these factors is the upregulation of suppressor of cytokine signaling 3 (SOCS3) expression,\(^ {54,60,64}\) although to date this has only been shown in non-myocardial tissues for GH.\(^ {65}\) SOCS3, in addition to exerting a negative feedback on JAK-STAT signaling in the myocardium,\(^ {66-68}\) is able to reduce insulin signaling by preventing autophosphorylation of the insulin receptor,\(^ {69}\) reducing interaction of IRS with the IR and with PI3K\(^ {70}\) and by promoting proteasomal degradation of IRS.\(^ {71}\) In cardiac myocytes overexpression on STAT3 has indeed been associated with insulin resistance induced by PPARx and PPARy agonists\(^ {72}\) and by low concentrations of cardiotrophin-1.\(^ {54}\) The requirement of JAK-STAT signaling for the upregulation of SOCS3 expression has not to date been firmly established in cardiac myocytes; SOCS3 overexpression has only been tightly associated with STAT3 activation.\(^ {66,68}\) In other tissues and cell types SOCS3 transcription is driven by activated STAT3\(^ {53}\) and STAT5,\(^ {74,75}\) and it seems reasonable to assume that it could be similar in the myocardium. Indeed, in cardiac myocytes exposed to low concentrations of CT-1, pharmacological inhibition of STAT5 activity suppressed SOCS3 overexpression and restored insulin signaling and insulin-stimulated glucose transport.\(^ {54}\) Upstream of STATs SOCS3 expression seems to be at least in part dependent on JAK2 activity, as it can be reduced by the JAK2 inhibitor AG490.\(^ {76}\)

Obviously a reduction in glucose metabolism could also result from diminished expression of the main glucose transporter GLUT4. Both LIF and low concentrations of CT-1 reduce GLUT4 expression in cardiac myocytes.\(^ {54,64}\) Whereas there is no evidence for the JAK-STAT axis involvement in this effect of LIF, only “guilt by association”, pharmacological inhibition of STAT5 activity indeed restored GLUT4 expression reduced by a low dose of CT-1. Other mechanisms, independent of gene expression, may operate to reduce insulin signaling when the JAK-STAT axis is activated. Thus in cardiac myocytes stimulated concomitantly with both Ang II and insulin, the branch of insulin signaling downstream of IRS phosphorylation leading to stimulation of glucose metabolism, i.e. PI3K activation and subsequent Akt recruitment and activation, is reduced.\(^ {77}\) This occurs while IRS association
with JAK2 is increased, suggesting that JAK2 activation reduces insulin signaling to glucose transport by sequestering IRS. In contrast ERK1/2 activation in response to insulin is potentiated by Ang II; ERK1/2 activation is known to be detrimental to the stimulation of glucose transport in cardiac myocytes.

In line with these observations, in myotubes rendered insulin resistant by incubation with ceramides JAK2 silencing restored Akt activation and insulin-stimulated glucose transport. Collectively these results suggest that JAK2 may depress the Akt to glucose uptake signaling axis selectively in insulin-resistant states.

A last mechanism by which JAK-STAT signaling activation could reduce glucose metabolism is by driving expression of a PDH kinase; in adipocytes the expression of PDK4 is mediated by STAT5 in response to prolactin. Indeed Ang II, which activates STAT5, induces PDK4 expression in cardiac myocytes, although JAK-STAT signaling was not investigated in the latter study. We observed however in cardiac myocytes exposed to CT-1 and displaying STAT5 phosphorylation a slight reduction of PDH-E1 phosphorylation.

In conclusion, despite a paucity of data directly pertaining to the myocardium, it appears that JAK-STAT signaling does not significantly participate in the stimulation of glucose metabolism by insulin or metabolic stress in the heart. On the contrary, JAK-STAT signaling most likely mediates the development of insulin resistance induced by various cytokines. Again, the literature is remarkably scarce of results obtained in heart-relevant experimental models; many of the above conclusions are extrapolated from data obtained in skeletal muscle or adipocytes, and therefore should be taken with caution. Whether this shortage of information results from an actual lack of experiments or from abstaining to report negative results remains unknown.

Disclosure of Potential Conflicts of Interest
There is no conflict of interest to disclose.

Acknowledgments
Research in the authors’ labs is supported by grants from the Swiss National Science Foundation (310030_146537 to C Montessuit), the Fondation Carlos et Elsie de Reuter (to C Montessuit), the Fondation Gustave et Simone Prévot (to C Montessuit and MA Frias) and the Wolfermann Naegli Stiftung and Jubiläumsstiftung (to MA Frias).
References

1. Opie LH. The Heart: Physiology, from Cell to Circulation. 3rd ed. Philadelphia, New York: Lippincott-Raven; 1994.

2. Stryer L. Biochemistry. 2nd ed. San Francisco: WH Freeman and Company; 1981.

3. Lopaschuk GD, Gamble J. The 1993 Merck Frosst Award. Acetyl-CoA carboxylase: an important regulator of fatty acid oxidation in the heart. Can J Physiol Pharmacol 1994; 72:1101-9; PMID:7882173; http://dx.doi.org/10.1139/y94-156.

4. Bowker-Kinley MM, Davis WI, Wu P, Harris RA, Podewski E, et al. Signal transducer and activator of transcription 3 is required for myocardial capillary formation. Proc Natl Acad Sci U S A 1997; 94:3801-5; PMID:9108058; http://dx.doi.org/10.1074/jbc.275.14.10002.

5. Banerjee SK, McCaffin KR, Pastor-Soler NM, Ahmad F. SGLT1 is a novel cardiac glucose transporter that is perturbed in disease states. Cardiovasc Res 2009; 84:111-8; PMID:19509029; http://dx.doi.org/10.1093/cvr/cvp190.

6. Wheeler TJ, Fell RD, Hauck MA. Translocation of two glucose transporters in heart: effects of rotenone, uncouplers, workload, palmitate, insulin and anoxia. Biochim Biophys Acta 1994; 1196:191-200; PMID:7841183; http://dx.doi.org/10.1006/bbap.2001.1128.

7. Sun D, Nguyen N, DeGrado TR, Schwaiger M, Bonvouisot FC 3rd. Ischemia induces translocation of the insulin-responsive glucose transporter GLUT4 to the plasma membrane of cardiac myocytes. Circulation 1994; 89:793-8; PMID:8313568; http://dx.doi.org/10.1161/01.CIR.89.2.793.

8. Bertrand L, Hornan S, Beauloye C, Vanoverschelde J-L. Insulin signalling in the heart. Cardiovasc Res 2008; 79:238-48; PMID:18390897; http://dx.doi.org/10.1016/j.cvr.2008.03.030.

9. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol 2012; 13:501-12; PMID:22436748; http://dx.doi.org/10.1038/nrm3313.

10. Thong FSL, Bilan PJ, Klip A. The Rab GTPase-activating protein AS160 integrates Akt, protein kinases and protein kinase signals regulating GLUT4 traffic. Diabetes 2007; 56:414-23; PMID:17529386; http://dx.doi.org/10.2337/db06-0900.

11. Montessuit C, Lerch R. Regulation and dysregulation of glucose transport in cardiomyocytes. Biochim Biophys Acta 2013; 1833:84-86; http://dx.doi.org/10.1016/j.bbadis.2012.08.009; PMID:22967513.
Double mechanism of signal transducer and activator of transcription 5 activation by the insulin receptor. Mol Cell Endocrinol 2002; 16:276-79; PMID:12456798; http://dx.doi.org/10.1016/S0303-7162(02)00129-5

Coffier PJ, van Puijenbroek A, Burgerness BM, Klop-de Jonge M, Koenderman L, Bos JL, Kruier W. Insulin activates STAT3 independently of p21ras-ERK and PI3K-signal transduction. Oncogene 1997; 15:2529-38; PMID:9299641; http://dx.doi.org/10.1038/ sj.101204129

Kellerer M, Koch M, Metzinger E, Mucksh J, Capp C, Haring HU. Leptin activates PI3-kinase in C2C12 myotubes via janus kinase-2 (JAK-2) and insulin receptor substrates-2 (IRS-2) dependent pathways. Diabetologia 1997; 40:1358-62; PMID:9388430; http://dx.doi.org/10.1007/s001250050583

Thionne ACP, Carvalho CRO, Saad MJ. Growth hormone stimulates the tyrosine kinase activity of JAK2 and induces tyrosine phosphorylation of insulin receptor substrates and Shc in rat tissues. Endocrinology 1999; 140:55-62; PMID:9888607; http://dx.doi.org/10.1207/s10775229en.2003-0788

Goodman MD, Koch SE, Afzal MR, Butler KL. STAT subtype specificity and ischemic preconditioning in mice: is STAT3 enough? Am J Physiol Heart Circ Physiol 2011; 300:H522-6; PMID:21131482; http://dx.doi.org/10.1152/ajpheart.00231.2010

Negro S, Kunisada K, Tone E, Funamoto M, Oh H, Kishimoto T, Yamashita-Takahira K. Activation of JAK3 positively regulates cytokine responsive pathways in rat acute myocardial infarction. Cardiovasc Res 2000; 47:797-805; PMID:10974228; http://dx.doi.org/10.1016/S0008-6363(00)01138-3

Omura T, Yoshiyama M, Ishikura F, Kobayashi H, Takeuchi K, Beppu S, Yoshikawa J. Myocardial ischemia-reperfusion injury is mediated by STAT3 in rat acute myocardial infarction. Cardiiovasc Res 2000; 47:797-805; PMID:10974228; http://dx.doi.org/10.1016/S0008-6363(00)01138-3

Asrih M, Lerch R, Papageorgiou I, Pelleux C, Montessuit C. Differential regulation of stimulated cytokine signaling-3 Provides a novel interface in the cross-talk between angiotensin II and insulin signaling systems. Endocrinology 2005; 146:579-88; PMID:15514089; http://dx.doi.org/10.1210/en.2004-0466

Latchman DS. Cardiotrophin-1 (CT-1): a novel hypertrophic and cardioprotective agent. Int J Exp Pathol 1999; 80:189-96; PMID:9583628; http://dx.doi.org/10.1111/j.1365-2613.1999.00114.x

Lu C, Schwarzbauer G, Sperling MA, Devaskar SU, Girard J, Van Obberghen E. Stat 5B, activated by glucagon and activated by glucokinase gene transcription. Endocrinology 1999; 140:1977-84; PMID:10803028; http://dx.doi.org/10.1210/jbc.273.3.1285

Yasukawa H, Hoshijima M, Gu Y, Nakamura T, Pradervand S, Hanada T, Hanakawa Y, Yoshimura LG, Furlanetto RW, Mooney RA. Suppressor of cytokine signaling-3 Provides a novel interface between the STAT5A-mediated induction of pyruvate dehydrogenase kinase-4 (PDK-4) and cardiac myocytes. Cardiovasc Res 2011; 89:262-32; PMID:19821810; http://dx.doi.org/10.1016/j.cird.1994.10.2626

Florholmen G, Thoresen GH, Rustan AC, Jensen C, Christensen G, Aas V. Leukaemia inhibitory factor inhibitory factor stimulates glucose transport in isolated cardiomyocytes and induces insulin resistance after chronic exposure. Diabetologia 2006; 49:724-31; PMID:16489474; http://dx.doi.org/10.1007/s00125-006-0550-6

Adams TE, Hansen JA, Stark R, Nicola NA, Hilton DJ. Bcl-2 upregulates Glucose hormone preferentially induces the rapid, transient expression of SOCS-3, a novel inhibitor of cytokine receptor signaling. J Biol Chem 1998; 273:1285-7; PMID:9436588; http://dx.doi.org/10.1074/jbc.273.3.1285

Yasukawa H, Hoshijima M, Gu Y, Nakamura T, Pradervand S, Hanada T, Hanakawa Y, Yoshimura LG, Furlanetto RW, Mooney RA. Suppressor of cytokine signaling-3 is a biomechanical stress-inducible gene that suppresses gp130-mediated cardiac myocyte hypertrophy and survival pathways. J Clin Invest 2001; 108:1459-67; PMID:11714737

Calegar V, Bezerra RMN, Tonsoni MA, Torsoni AS, Franchini KG, Saad MJ, Velloso LA. Suppressor of cytokine signaling 3 is induced by angiotensin II and stimulates glucose transport in isolated cardiomyocytes. J Endocrinol 2011; 210:129-38; PMID:21572573; http://dx.doi.org/10.1677/joe.0.1810129

Carvalheira JBC, Calegari VC, Zecchin HG, Nadruz W Jr., Guimaraes RB, Ribeiro EB, Franchini KG, Velloso LA, Saad MJ. The cross-talk between angiotensin and insulin differentially affects phosphatidylinositol 3-kinase- and mitogen-activated protein kinase-mediated signaling in rat heart: implications for insulin resistance. Endocrinology 2003; 144:5564-43; PMID:12600006; http://dx.doi.org/10.1210/en.2003-0788

Velloso LA, Foli J, Sun XJ, White MF, Saad MJ, Kahn CR. Cross-talk between the insulin and angiotensin signaling systems. Proc Natl Acad Sci U S A 1996; 93:13589-94; PMID:8938704; http://dx.doi.org/10.1073/pnas.93.22.12490

Asrih M, Pelleux C, Papageorgiou I, Lerch R, Montessuit C. Role of ERK1/2 activation in micro-tubule stabilization and glucose transport in cardiomyocytes. Am J Physiol Endocrinol Metab 2011; 301:E836-43; PMID:21777966; http://dx.doi.org/10.1152/ajpendo.00160.2011

White UA, Couleur AA, Miles TK, Stephens JM. The STAT3A-mediated induction of pyruvate dehydrogenase kinase 4 expression by prolactin or growth hormone in adipocytes. Diabetes 2007; 56:1623-9; PMID:17560981; http://dx.doi.org/10.2337/db06-1286

Mori J, Basu R, McLean BA, Das SK, Zhang L, Patel VB, Wagg CS, Kassis Z, Lopesachuck GD, Oudit GY. SOCS-3-induced hypertrophy and diastolic dysfunction are associated with selective reduction in glucose oxidation: a metabolic contribution to heart failure with normal ejection fraction. Circ Heart Fail 2012; 5:493-503; PMID:22207569; http://dx.doi.org/10.1161/CIRCHEARTFAILURE.112.960705

Hosseinzaedeh Z, Bhavork SK, Shojaeifard M, Saxena A, Merches K, Sopiani M, Alesarian I, Lang F. Stimulation of the glucose carrier SGTL1 by JAK2. Biochem Biophys Res Commun 2011; 408:208-13; PMID:21406183; http://dx.doi.org/10.1016/j..bbrc.2011.03.036