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Dissecting the Role of Insulin Resistance in the Metabolic Syndrome

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Abstract

Purpose of Review—Over twenty years ago, insulin resistance was postulated to play a central role in the pathogenesis of the metabolic syndrome. However, this has been difficult to prove, leading to a great deal of controversy within the field. Recent studies in mice and humans with genetic defects in insulin signaling have allowed us, for the first time, to dissect which features of the metabolic syndrome can be caused by insulin resistance.

Recent Findings—Mice with liver specific knockout of the insulin receptor (LIRKO) show that hepatic insulin resistance can produce (1) hyperglycemia; (2) increased Apob secretion and atherosclerosis; and (3) increased biliary cholesterol secretion and cholesterol gallstones. Many of these changes may be due to dis-inhibition of the transcription factor, FoxO1. Yet, neither LIRKO mice nor humans with insulin receptor mutations develop the hypertriglyceridemia or hepatic steatosis associated with the metabolic syndrome.

Conclusion—These data point to a central role for insulin resistance in the pathogenesis of the metabolic syndrome, as hyperglycemia, atherosclerosis, and cholesterol gallstones can all be caused by insulin resistance. However, hypertriglyceridemia and hepatic steatosis are not due directly to insulin resistance, and should be considered pathogenically distinct features of the metabolic syndrome.

Keywords

Hepatic fatty acid metabolism; sterol regulatory element binding protein-1c; forkhead box O1; cholesterol gallstones; dyslipidemia

Introduction

The prevalence of the metabolic syndrome has reached epidemic proportions in our society, with more than one in four adults in the United States affected [1]. This disorder is characterized by a constellation of symptoms which includes obesity, dyslipidemia with hypertriglyceridemia and low HDL-cholesterol, glucose intolerance, gallstones, hypertension and non-alcoholic fatty liver disease (NAFLD)[2]. Insulin resistance was suggested to play a central role in the development of the metabolic syndrome over twenty years ago [3]. Since then, we have accrued a large body of literature documenting a correlation between insulin resistance, dyslipidemia, atherosclerosis, gallstones and NAFLD. However, proving a causal role for insulin resistance has remained difficult [4].

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Insulin Action and Insulin Resistance

Insulin resistance is defined clinically in terms of the failure of insulin to maintain glucose homeostasis. Hence, various measurements of glucose and insulin are used to assess insulin resistance, with the hyperinsulinemic euglycemic clamp being the gold standard. While this definition is very useful clinically, it fails to address the fact that insulin regulates many processes within the cell in addition to glucose metabolism. Furthermore, it implies that all of the processes regulated by insulin become resistant to insulin in parallel with glucose metabolism, and this is likely false.

Here, we will use the phrase insulin resistance to mean a defect in insulin signaling. Since a comprehensive description of insulin signaling is beyond the scope of this review, we will highlight several of the major nodes in the insulin signaling pathway, and two transcription factors, Foxo1 and Sterol Regulatory Element Binding Protein (Srebp)-1c, that are regulated by insulin. This will serve to illustrate how defects in insulin signaling could contribute to the metabolic syndrome, but it should be recognized that many other signaling events and targets are involved.

Insulin binds to and activates the insulin receptor, a tyrosine kinase residing in the plasma membrane, which in turn phosphorylates targets such as the insulin receptor substrate (IRS) proteins, Irs1 and Irs2 (reviewed in [5]). This initiates a complex cascade of events. One major branch of insulin signaling is mitogen activated protein (MAP) kinase, which is primarily associated with the proliferative effects of insulin. The other major branch of insulin signaling is the class Ia forms of phosphatidylinositol 3-kinase (PI 3-kinase), which mediates most of the metabolic effects of insulin. PI 3-kinase, in turn, activates the atypical PKCs, PKC-λ (lambda) and PKC-ζ (zeta), and Akt.

Akt inactivates Foxo1 by phosphorylating it on residues Thr-24, Ser-256, and Ser-319 [6]. Phosphorylated Foxo1 is excluded from the nucleus, and targeted for degradation. Insulin may also regulate Foxo1 by acetylation [7] and modulation of its transcriptional co-activator, peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PGC)-1α [8;9]. In the absence of insulin, Foxo1 activates transcription both directly, by binding to insulin response elements (IREs) in the promoters of its target genes [10], and indirectly by co-activating other transcription factors [11].

Foxo1 activates expression of a diverse set of targets, including the gluconeogenic enzymes, glucose-6-phosphatase (*G6pc*) and phosphoenolpyruvate carboxykinase (*Pck1*). Therefore, activation of Foxo1 increases fasting glucose and impairs glucose tolerance [12] whereas knockdown of Foxo1 decreases gluconeogenic gene expression and decreases serum glucose levels [13;14]. Microsomal triglyceride transfer protein (*Mttp*), which promotes the lipidation of apolipoprotein B (Apob), a rate-determining step in VLDL secretion [15], is also a target of Foxo1[16]. Thus, Apob secretion is increased by expression of constitutively active Foxo1, and decreased by knockdown of Foxo1 [16]. Finally, Foxo1 promotes the expression of the cholesterol efflux transporters, *Abcg5* and *Abcg8* [17]. These transporters form heterodimers which reside on the canalicular membrane of the hepatocyte and regulate the efflux of cholesterol into the bile [18;19].

The signal transduction pathways regulating Srebp-1c are not as clear. It has been suggested that Irs1 is more important than Irs2 [20;21] in the activation of Srebp-1c, but this has not been observed in all studies [22]. Mice lacking PI 3-kinase activity in the liver show decreased expression of Srebp-1c and its target gene, fatty acid synthase, as well as reduced serum and hepatic triglycerides, implicating a role for PI 3-kinase in the regulation of Srebp-1c [23]. Consistent with this, reconstitution of PKC-λ in the livers of these mice increased Srebp-1c but reconstitution of Akt, the other major target of PI 3-kinase, did not [23]. Moreover,

knockout of PKC-λ reduces Srebp-1c, its lipogenic targets, and triglyceride accumulation, in the liver [24]. Taken together, these data indicate that insulin activates Srebp-1c through a pathway involving Irs1, PI 3-kinase, and PKC-λ, though other pathways have also been implicated [25;26].

Insulin stimulates Srebp-1c transcription [27] and maturation [28], and could further regulate Srebp-1c by phosphorylation [29;30] and ubiquitination [31]. Srebp-1c promotes expression of all of the genes required for the synthesis of monounsaturated fatty acids [32;33]. Consequently, mice that lack Srebp-1c show a diminished lipogenic response to insulin [34] and mice overexpressing Srebp-1c show increased lipogenic gene expression and increased hepatic triglyceride content [32]. Moreover, in leptin deficient *ob/ob* mice, which show massive hepatic steatosis, knockout of Srebp-1c dramatically reduces lipogenic gene expression and the accumulation of hepatic triglycerides [35]. This indicates that Srebp-1c is necessary for the development of hepatic steatosis.

Insulin Resistance In Vivo

Liver Insulin Receptor Knockout (LIRKO) mice were created using the cre/LoxP system to specifically ablate the insulin receptor in hepatocytes, resulting in >95% deletion of the insulin receptor in the liver [36;37]. Therefore, these mice manifest complete hepatic insulin resistance, and show increased expression of the gluconeogenic genes, increased hepatic glucose output, marked glucose intolerance and hyperglycemia [36;37].

LIRKO mice show normal levels of serum cholesterol, but the distribution of this cholesterol is pro-atherogenic, with increased VLDL cholesterol and decreased HDL cholesterol, recapitulating some features of the dyslipidemia associated with the metabolic syndrome in humans [38]. The mechanism underlying the decrease in HDL cholesterol remains under investigation, but the increase in VLDL cholesterol is due, in part, to increased secretion of Apob, the principle protein component of the VLDL particle [38]. This is consistent with the facts that insulin inhibits Apob secretion both by promoting its degradation [39;40], and preventing Foxo1 mediated transcription of *Mttp* [16]. In addition, on an atherogenic diet, LIRKO mice have decreased expression of the LDL receptor, a key determinant of serum cholesterol levels [38]. This results in decreased LDL clearance, and diet-dependent hypercholesterolemia [38]. Consequently, LIRKO mice are exquisitely sensitive to atherosclerosis, with 100% of LIRKO mice, but no controls, developing atherosclerosis after three to four months on an atherogenic diet [38].

LIRKO mice also show marked derangements in the expression of bile acid synthetic enzymes. Bile acids play an important role in the absorption of dietary cholesterol, but also appear to function as hormones in the regulation of energy metabolism [41]. A decrease in *Cyp7b1* is one of the most prominent changes in gene expression observed in the LIRKO liver by microarray analysis [17]. Cyp7b1 is the first enzyme of the acidic pathway of bile acid synthesis specific to that pathway. The acidic pathway produces largely chenodeoxycholate (CDCA).

Consequently, LIRKO bile shows a relative decrease in the muricholates, the metabolites of chenodeoxycholate, making it more lithogenic [17]. Whether these changes in the bile salt profile also alter energy expenditure has yet to be determined, but could be relevant to the metabolic syndrome phenotype. Interestingly, *Cyp7b1* mRNA levels are also decreased in the livers of mice made insulin deficient by streptozotocin treatment, and mice that are insulin resistant secondary to leptin deficiency or high fat feeding, indicating the importance of insulin in the regulation of this enzyme [17].

In addition to these changes in bile acid metabolism, the cholesterol transporters *Abcg5* and *Abcg8* are increased three-fold at the mRNA levels in LIRKO livers, consistent with increased

Foxo1 activity. This results in a three-fold increase in biliary cholesterol secretion and an increase in the cholesterol saturation index [17]. This finding is important because increased biliary secretion contributes to cholesterol gallstone formation in obese humans [42;43]. Not surprisingly, when fed a lithogenic diet, 36% of LIRKO mice, but none of the controls, develop cholesterol gallstones after one week[17].

Some of these metabolic parameters have been studied in another model of hepatic insulin resistance, in which the major targets of the insulin receptor, Irs1 and Irs2, are both ablated in the liver (LIrs1,2DKO mice). LIrs1,2DKO mice show increased expression of *G6pc* and *Pck1*,hyperglycemia and hyperinsulinemia [44]. Genetic ablation of Foxo1 in the livers of LIrs1,2DKO mice decreases gluconeogenic gene expression, fasting glucose, and insulin levels, underscoring the importance of Foxo1 in this phenotype [22;44].

The metabolic syndrome is also associated with increased expression of Srebp-1c, lipogenesis, triglyceride secretion, and hepatic triglycerides [45]. These features of the metabolic syndrome are conspicuously absent in mice and humans with defects in the insulin receptor. The secretion of VLDL triglycerides is decreased by 50% in LIRKO mice, even as secretion of Apob is increased. The uncoupling of triglyceride and Apob secretion results in VLDL particles that are relatively enriched in cholesterol, and potentially more atherogenic. Similarly, LIrs1,2DKO mice also show a 50% decrease in VLDL triglyceride secretion, and both models show a 50% reduction in serum triglycerides [22;38]. Concomitant with these changes, both LIRKO and LIrs1,2DKO mice have more than two-fold reductions in Srebp-1c, decreased expression of the lipogenic enzymes, and normal hepatic triglyceride content [22;38;44]. Similarly, humans with mutations in the insulin receptor show decreased levels of serum triglycerides and VLDL that is relatively enriched in cholesterol; moreover, they do not show increased levels of lipogenesis or hepatic triglycerides[46].

There are at least two possible explanations why hypertriglyceridemia and hepatic steatosis develop in the metabolic syndrome, but not in mice or humans with insulin receptor mutations. First, insulin resistance in the metabolic syndrome may be due to defects in the downstream components of the insulin signaling pathway, rather than the insulin receptor itself [5,21]. This would produce a fundamentally different type of insulin resistance. Defects in the insulin receptor produce “complete insulin resistance,” in which all pathways fail to respond to insulin, as observed in LIRKO livers. In contrast, lesions in the distal portion of the insulin signaling cascade produce “pathway specific insulin resistance” as they affect only a subset of the processes regulated by insulin. It has been postulated that insulin resistance in the metabolic syndrome is pathway specific: although the Akt/FoxO1 pathway becomes resistant, the PKC-λ / Srebp-1c pathway does not. Hence, insulin loses its ability to suppress FoxO1, gluconeogenic enzymes, *Mttp*, *Abcg5* and *Abcg8*, but retains its ability to stimulate Srebp-1c and the lipogenic enzymes. According to this model, hyperinsulinemia, which evolves with the metabolic syndrome, maximally stimulates Srebp-1c and lipogenesis, and this is the major driver of hypertriglyceridemia and hepatic steatosis in the metabolic syndrome [2;3;5;47]. Consistent with this, humans with defects in Akt develop hypertriglyceridemia and hepatic steatosis, though humans with defects in the insulin receptor do not [46].

Second, the metabolic syndrome is triggered by environmental and genetic factors, which could exert effects that are independent of insulin resistance. Srebp-1c is regulated not only by insulin, but by different dietary components, such as carbohydrates and polyunsaturated fatty acids [48;49], and hormones, including endocannabinoids and leptin. [50;51]. Thus, changes in the hormonal and metabolic milieu that are unrelated to insulin could induce Srebp-1c, hypertriglyceridemia and hepatic steatosis independently of insulin resistance in the metabolic syndrome.

Summary

The metabolic syndrome in humans is an exceedingly complex disorder, characterized by numerous derangements in the hormonal and metabolic milieu. Insulin resistance, i.e. a defect in insulin signaling, is only one of these derangements. LIRKO mice, LIrs1,2DKO mice and humans with insulin receptor mutations have enabled us to dissect those components of the metabolic syndrome which are due to insulin resistance, from those which are not. LIRKO mice show that hepatic insulin resistance produces hyperglycemia, increased apoB secretion, and increased biliary cholesterol secretion. Many of these changes may be due to dis-inhibition of Foxo1, which appears to regulate all of these processes. In contrast, activation of Srebp-1c, hypertriglyceridemia and hepatic steatosis can not be attributed to hepatic insulin resistance—i.e., an inability of insulin to activate its targets in the liver. They are instead driven by either hyperinsulinemia with continued responsiveness of Srebp-1c to insulin, other factors present in the metabolic syndrome, or both.

Conclusions

The role of insulin resistance in the metabolic syndrome has been a topic of intense debate [4]. Recent data suggest that insulin resistance is sufficient to produce not only glucose intolerance, but also increased biliary cholesterol secretion, atherosclerosis, and cholesterol gallstones. This argues that the metabolic syndrome is not merely a collection of abnormalities that should be considered and treated independently, as some experts have advocated [4]. Rather, the metabolic syndrome is truly a syndrome, in which many, though not all, components arise from a common pathophysiological disturbance, namely insulin resistance. Further work will be necessary to define the precise molecular defects in insulin signaling that underlie the metabolic syndrome in humans.

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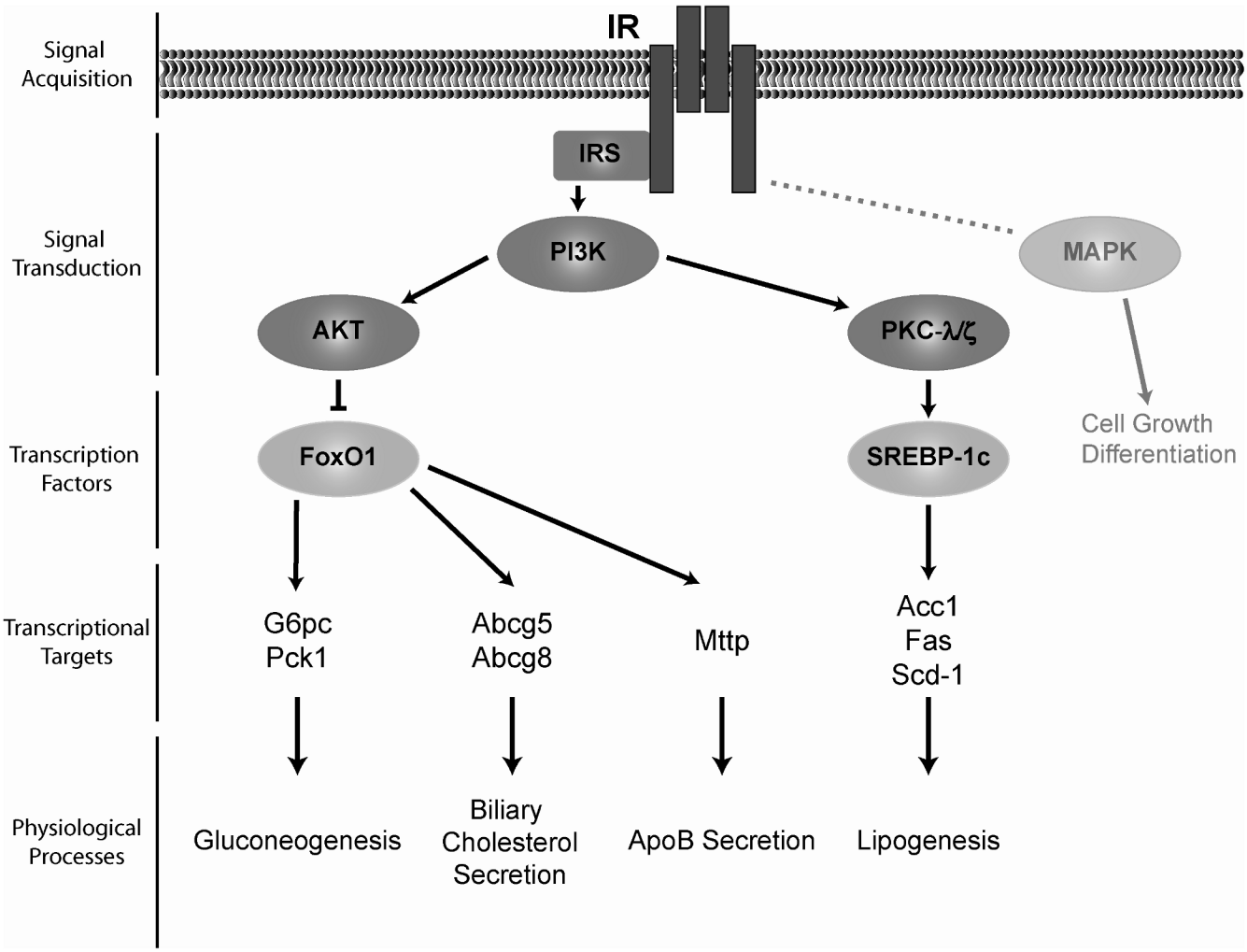

Figure 1.
The insulin signaling cascade. Insulin triggers a complex, branching network of signaling events. Shown here is a summary of the major nodes of this cascade, two important transcription factors, Foxo1 and Srebp-1c, and their targets.