Published in final edited form as:

Trends Cell Biol. 2016 May ; 26(5): 341–351. doi:10.1016/j.tcb.2016.01.002.

Nuclear Mechanisms of Insulin Resistance

Sona Kang^{1,2}, Linus T-Y Tsai¹, and Evan D. Rosen¹

¹Division of Endocrinology, Beth Israel Deaconess Medical Center and Harvard Medical School

Abstract

Insulin resistance is a *sine qua non* of Type 2 diabetes, and is associated with many other clinical conditions. Decades of research into mechanisms underlying insulin resistance have mostly focused on problems in insulin signal transduction and other mitochondrial and cytosolic pathways. In contrast, relatively little attention has been paid to transcriptional and epigenetic contributors to insulin resistance, despite strong evidence that such nuclear mechanisms play a major role in the etiopathogenesis of this condition. In this review we summarize the evidence for nuclear mechanisms of insulin resistance, focusing on three transcription factors with a major impact on insulin action in liver, muscle, and fat.

What is insulin resistance and why is it important?

Insulin resistance is the condition in which a cell, tissue, or organism fails to respond appropriately to a given dose of insulin. Insulin performs a wide variety of functions, and not all of these activities need to be dampened in order to make a diagnosis of insulin resistance; typically insulin resistance refers to the metabolic actions of insulin, and specifically to the ability of insulin to promote glucose uptake into tissues like muscle and adipose and to repress glucose production in the liver. Insulin resistance is classically associated with Type 2 diabetes (T2D), where it is a driver of hyperglycemia. Currently, Type 2 diabetes affects 12–14% of US adults, and over half of all adults have pre-diabetes, a condition accompanied by significant insulin resistance (Menke et al., 2015).

Insulin resistance accompanies a wide range of pathological conditions, including obesity, lipodystrophy, sepsis, steroid use, growth hormone excess, polycystic ovarian disease, cancer, neurodegenerative disease, and even some physiological conditions, such as pregnancy. This can be modeled experimentally: investigators have developed numerous models of insulin resistance using a variety of chemical, drug, inflammatory, and nutritional challenges (Boucher et al., 2014). Thus arises a fundamental question: are there many independent paths to insulin resistance? Or do different perturbagens and clinical conditions converge on one or a few key pathways that are integral to any form of insulin resistance?

Correspondence to: Evan D. Rosen.

²Current address: Dept. of Nutritional Sciences and Toxicology, University of California, Berkeley

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

What are the current theories about the etiopathogenesis of IR?

Despite years of study, there is still great uncertainty concerning how cells and organisms become insulin resistant. Enormous effort has been expended delineating the signal transduction pathways activated by insulin, resulting in a fairly detailed map of the intermediates involved (Boucher et al., 2014). As predicted, mice lacking many of these signaling intermediates are profoundly insulin resistant, as are humans with similar loss-of-function mutations (Biddinger and Kahn, 2006, Huang-Doran and Savage, 2011). However, most insulin resistant people do not harbor such mutations, so attention has focused on other causes of insulin resistance, including endoplasmic reticulum stress, inflammation, accumulation of toxic lipid intermediates (such as diacylglycerol and acylcarnitines), and reactive oxygen species (Hotamisligil, 2010, Houstis et al., 2006, James et al., 2012, Olefsky and Glass, 2010). Data supporting the contribution of these non-mutually exclusive pathways to insulin resistance are strong, but mechanisms by which they ultimately affect insulin action are still unclear. Many investigators ultimately conclude that altered insulin signaling must underlie the final manifestation of the disease.

There are, however, suggestions that dysregulated insulin signaling *per se* does not lie at the heart of insulin resistance. First, experimental inducers of insulin resistance tend to provoke their effects over a time course inconsistent with alterations in signaling. For example, TNF reduces insulin sensitivity in cultured adipocytes only after several days (Kang et al., 2015). The received wisdom on TNF action, however, is that it induces inhibitory phosphorylation events on key components of the insulin signaling cascade, effects that can be demonstrated in minutes to hours. Second, insulin resistance can develop in cells or animals without discernable or reproducible changes in insulin signaling, and conversely, animals with an engineered insulin signaling deficiency do not uniformly develop insulin resistance under normal conditions (Cleasby et al., 2007, Hoehn et al., 2008, Kang et al., 2015, Kim et al., 1999, Nadler et al., 2001).

Could nuclear mechanisms play a role in insulin resistance?

There are compelling reasons to suspect that nuclear events, defined here as processes such as transcriptional and epigenetic regulation taking place in the nucleus, play a role in the development of insulin resistance. First, insulin sensitivity can be enhanced with drugs that primarily act through transcription factor targets, such as thiazolidinediones (TZDs), an activator of PPAR γ (Ahmadian et al., 2013, Soccio et al., 2014) and glucocorticoids, which activate the glucocorticoid receptor. Second, drugs that affect chromatin remodeling, such as certain HDAC inhibitors, are known to affect insulin sensitivity in cells, animal models, and human subjects (Masuccio et al., 2010). Third, mice with genetic alterations in chromatin modifying enzymes, such as Jhdm2a and Ehmt1, develop obesity and insulin resistance (Inagaki et al., 2009, Ohno et al., 2013, Tateishi et al., 2009). Finally, and perhaps most compelling, there is a very large body of literature that indicates that the risk of developing insulin resistance in later life is strongly affected by nutritional conditions experienced *in utero*. For example, pregnant rodents that undergo caloric restriction give birth to offspring that have a significantly greater chance of developing insulin resistance as adults (Rando and Simmons, 2015). The same phenomenon has been reported in human populations, as with

offspring of Dutch women who were pregnant during the ‘hunger winter’ of 1944–45 (Kyle and Pichard, 2006). Such examples of ‘metabolic memory’ are predicted to have an epigenetic basis, and there are data that support this mechanism directly, such as altered histone modification at the *Slc2a4* (Glut4) locus in the offspring of calorically-restricted rats (Raychaudhuri et al., 2008).

Systemic insulin sensitivity is determined by the interactions of several different tissues and cell types (Odegaard and Chawla, 2013, Tomas et al., 2004). Classically, most people think of insulin action at the liver, muscle and adipose tissue, as the organs most responsible for insulin-dependent glucose production and disposal. Recent data, however, suggest a significant role for other tissues as well, notably the brain, which does not take up glucose in response to insulin but which can regulate the actions of insulin in classical target tissues indirectly (Parlevliet et al., 2014). Cells of the immune system are another example; although not insulin sensitive themselves, their number and activation state has a major effect on insulin action locally (in adipose tissue, for example) and systemically (Mathis, 2013, Odegaard and Chawla, 2013). Thus, a transcription factor can cause insulin resistance indirectly via effects on macrophage polarization, for example (Eguchi et al., 2013).

Finally, we should keep in mind that several (non-mutually exclusive) nuclear events may be involved, including changes in transcription factor expression, binding, post-translational modifications, and protein-protein interactions with co-factors/chromatin modifiers. In all of these scenarios, the relevant output is altered target gene expression. These target genes could be obvious, such as those encoding classic insulin signaling proteins, but may also be obscure. For example, several genes were recently identified in adipocytes that are dysregulated in insulin resistant states and which cause insulin resistance when overexpressed; none of these genes participates in a pathway known to be involved in insulin action (Kang et al., 2015). In the next section, we highlight three separate transcription factors and co-factors with significant actions on insulin sensitivity, and we discuss possible mechanisms by which they exert these effects. Although we focus on a few notable examples, many others exist, including transcription factors, nuclear co-factors, and chromatin modifying enzymes; some of these are indicated in Table 1.

Nuclear receptors as a paradigm for affecting insulin action in adipose tissue

Among transcription factors, the nuclear receptor (NR) superfamily plays a special role in regulating insulin sensitivity, given that they are activated by small ligands that are often fatty acid derivatives or other nutritional by-products. NRs thus provide a direct link between environmental conditions and the genome. Accordingly, several NRs have been implicated in the regulation of insulin action, most notably PPAR γ and the glucocorticoid receptor (GR). Other examples of NRs that have been implicated in insulin resistance include VDR, LXR, FXR, and LRH-1.

Peroxisome proliferator-activated receptor γ (PPAR γ)

The nuclear receptor best associated with insulin action is PPAR γ , most notably via its position as the target of TZDs, which are used clinically as insulin sensitizers. Although originally identified as a dominant regulator of adipogenesis, PPAR γ is now known to be expressed in many different tissues and cell types (albeit to a lower degree than adipose tissue) and to be involved in processes as distinct as lipid accumulation, glucose homeostasis, skeletal homeostasis, and inflammation (Ahmadian et al., 2013, Soccio et al., 2014). This broad tissue distribution has provoked numerous studies attempting to determine which site of action is most relevant for the insulin-sensitizing properties of PPAR γ (Fig. 1). Somewhat amazingly, specific deletion of PPAR γ in many different cell types, including adipose tissue, muscle, macrophages, and brain alters glucose homeostasis, and reduces the full activity of TZDs. The preponderance of evidence, however, suggests that adipose tissue is the major site of action for the insulin-sensitizing actions of PPAR γ (Chao et al., 2000, He et al., 2003, Sugii et al., 2009). Mice lacking PPAR γ in liver respond to TZDs normally unless adipose tissue is also defective (Chao et al., 2000), and liver- and muscle-specific PPAR γ knockout mice were shown to display insulin resistance, though to a much lesser degree than adipose-specific knockout animals, and show variable response to TZDs (Hevener et al., 2003, Norris et al., 2003). A role for PPAR γ has been speculated to be important in pancreatic β -cells, but while TZDs enhance insulin secretion from isolated islets in a PPAR γ -dependent manner, mice lacking islet PPAR γ have intact glucose homeostasis and respond normally to TZDs (Rosen et al., 2003).

Immune cells are another likely site of PPAR γ action. PPAR γ is highly expressed in macrophages, where it promotes alternative M2 polarization of macrophages (Bouhrel et al., 2007, Odegaard et al., 2007). Macrophage-specific depletion of PPAR γ conferred protection from diet-induced insulin resistance, though this is still improved by rosiglitazone (Hevener et al., 2007, Pascual et al., 2007). A more recent study has provided evidence that PPAR γ in a subset of regulatory T (Treg) cells plays a critical insulin-sensitizing role, as animals with PPAR γ deletion in this cell type show no response to pioglitazone (Cipolletta et al., 2012) in glucose metabolism and insulin sensitivity. Lastly, there are indications that the weight gain associated with PPAR γ activation is mediated partially through actions in the brain (Lu et al., 2011, Ryan et al., 2011). However, rosiglitazone still improved whole-body (but not hepatic) insulin sensitivity in mice lacking PPAR γ in the brain (Lu et al., 2011), indicating that CNS effects may account for some but not all the metabolic effects of TZDs.

What is the mechanism through which PPAR γ improves insulin sensitivity?

Several mechanisms have been proposed to explain the basis of the PPAR γ -dependent insulin-sensitizing effect. In adipose tissue, the lipogenic and anti-lipolytic actions of PPAR γ exert a so-called 'lipid steal' effect, in which fatty acids and other lipids are sequestered safely in adipose tissue. This counters the damaging actions of potentially toxic lipids in other tissues, which has been postulated to account for insulin resistance (Ye et al., 2004). TZDs also exert a direct glucose-lowering effect associated with improved insulin signal transduction in muscle and adipose (Iwata et al., 2001, Jiang et al., 2002). Yet another mechanism, at least in rodents, involves the ability of TZDs to promote 'browning' of white fat (Ohno et al., 2012, Qiang et al., 2012, Vernochet et al., 2009), which leads to increased

energy expenditure and improved whole body metabolism. PPAR γ also promotes both the expression and secretion of adiponectin, a potent insulin-sensitizing hormone (Riera-Guardia and Rothenbacher, 2008). Finally, the adipogenic actions of PPAR γ may also mediate some of the insulin-sensitizing effect; the reason for this may involve a variation of the ‘lipid steal’ hypothesis (with new adipocytes contributing to the safe storage of toxic lipid species) and may also reflect a healthier adipokine and anti-inflammatory profile in newly formed, smaller adipocytes than in large, hypoxic adipocytes.

PPAR γ is a transcription factor, of course, so its proximal actions are believed to involve alterations in gene expression, both positive and negative (Fig. 2). Positive targets include adiponectin, as well as a variety of lipogenic enzymes, transporters, and signal transduction intermediates. Negatively regulated genes in adipose tissue with relevance to insulin sensitivity include RBP4, resistin, and a variety of cytokines (Ahmadian et al., 2013). To date, several studies have been performed to comprehensively identify PPAR γ -dependent gene expression and binding events with and without TZD treatment (reviewed in (Lefterova et al., 2014). However, our knowledge of the core transcriptional and epigenetic events through which PPAR γ regulates insulin sensitivity remains incomplete.

Is targeting PPAR γ still a viable therapeutic strategy?

Despite the well-known anti-diabetic effects of TZDs, their clinical use has been restricted due to serious adverse effects such as weight gain, plasma volume expansion, bladder cancer, and increased risk of cardiac heart failure, although some of these fears may have been overblown (Soccio et al., 2014). Nonetheless, the negative reports of TZD adverse effects led to a pronounced chilling of the PPAR γ targeting programs of most major pharmaceutical companies. It remains to be seen whether the more reassuring data that has emerged recently will reinvigorate these activities. One promising area for future drug discovery relates to altering post-translational modifications of PPAR γ to help treat metabolic disease. For example, preventing PPAR γ phosphorylation at S112 preserved insulin sensitivity in response to a high fat diet, associated with reduced adipose hypertrophy, increased adiponectin, and reduced free fatty acid levels (Rangwala et al., 2003). Recent studies have also demonstrated that Erk/CDK5-dependent PPAR γ phosphorylation at S273 regulates a selective set of PPAR γ targets that are highly relevant to metabolic regulation (Choi et al., 2010, Choi et al., 2011). Furthermore, PPAR γ agonists and MEK inhibitors that block this phosphorylation event exert anti-diabetic effects without causing weight gain or hemodilution (Banks et al., 2015). Other potentially interesting PTMs of PPAR γ that may be amenable to therapeutic targeting include SUMOylation at Lys365 and Lys107, which mediates transrepression of inflammatory response genes, especially in macrophages (Pascual et al., 2007). SUMOylation at Lys107 can also lead to degradation of PPAR γ , and this can be blocked by FGF21; this may mediate the insulin-sensitizing actions of that hormone (Dutchak et al., 2012). Sirt1-mediated deacetylation of PPAR γ (Qiang et al., 2012) also leads to beneficial metabolic effects in metabolic syndrome.

Glucocorticoid receptor (GR)

Another nuclear receptor transcription factor with pronounced effects on insulin action is the glucocorticoid receptor (GR, encoded by *NR3C1*), which mediates the metabolic effects of

endogenous and synthetic glucocorticoids (Oakley and Cidlowski, 2011, Patel et al., 2014). Activation of hypothalamic-pituitary-adrenal (HPA) axis by stress, including fasting, induces glucocorticoid synthesis and secretion from the adrenal cortex (Patel et al., 2014). Glucocorticoids exert a wide range of actions on metabolic tissues, the net effect of which is to raise blood sugar as required by the brain. Prolonged GR activation is associated with metabolic dysregulation, including insulin resistance, as occurs in Cushing's syndrome (Plotz et al., 1952) or after long-term exposure to pharmacological doses of glucocorticoids (Rizza et al., 1982).

How does GR promote insulin resistance at the molecular level?

Glucocorticoids bind to the ligand binding domain of the GR in the cytoplasm, where it is sequestered by binding to Hsp90, Hsp70, and other chaperone proteins, and cause it to translocate to the nucleus (Fig. 2). Once in the nucleus, GR can alter gene expression in one of two ways. First, it can bind directly to glucocorticoid response elements (GREs) in the enhancers and promoters of various genes as a homodimer. Alternatively, GR can bind to other transcription factors as part of a 'tethered' complex that does not contact DNA directly. Both mechanisms can be used to promote gene activation or repression (Patel et al., 2014). There has been a longstanding belief that the beneficial actions of glucocorticoids, such as suppression of inflammation, primarily utilize the tethering model, and that adverse consequences of steroid action, including insulin resistance, require homodimerization and direct DNA binding. Recent studies call this into question, as mice that contain a mutation in the homodimerization domain of GR that does not affect tethering, display reduced insulin sensitivity at baseline, and still develop full insulin resistance upon treatment with dexamethasone (Roohk et al., 2013). It is true, however, that GR does directly bind and regulate a number of genes involved in gluconeogenesis, lipogenesis, and insulin signal transduction (Patel et al., 2014, Wang et al., 2004). In addition to these genomic actions of GR, nongenomic effects have also been proposed to contribute to glucocorticoid-induced insulin resistance; dexamethasone can inhibit insulin signaling very rapidly in cultured adipocytes in a manner that is not reversed by inhibiting transcription, for example (Lowenberg et al., 2006).

What tissues are critical for GR to regulate insulin sensitivity?

Most cells express the GR, including adipose tissue, muscle, and liver. In liver, GR activation promotes hepatic glucose output, an effect considered to be due to direct regulation of key gluconeogenic genes like *Pck1* and *G6pc*. Thus, mice with liver-specific GR knockout or knock-down have reduced hepatic glucose output (Opher et al., 2004) (Fig. 1). It is worth noting, however, that GR may also control gluconeogenesis via extra-hepatic sites like the hypothalamus, as direct injection of dexamethasone into the arcuate nucleus causes hepatic insulin resistance (Yi et al., 2012). These actions are independent of, but enhanced by, the increased food intake and weight gain associated with chronic glucocorticoid administration (Castonguay, 1991).

In skeletal muscle, chronic GR activation contributes to insulin resistance by inhibiting protein synthesis and promoting proteolysis, thus releasing amino acids which are used as substrate for glucose production. Glucocorticoids also inhibit insulin-stimulated glucose

uptake. The underlying mechanism for this is not well understood but a recent ChIP-Seq study has shown that GR directly targets genes involved in insulin signaling (Kuo et al., 2012). GR mRNA levels in the skeletal muscle of diabetic patients correlates with the degree of insulin resistance, and expression normalizes following the administration of insulin sensitizers (Bodine et al., 2001).

Although the precise role of adipose tissue GR in the glucose metabolism and insulin resistance remains to be addressed *in vivo*, many studies have shown that activation of GR suppresses insulin-stimulated glucose uptake assay in cultured adipocytes (Houstis et al., 2006, Kang et al., 2015). GR causes this, in part, by directly regulating the expression of several downstream effector genes (e.g. *Vdr*, *Tmem176a*, *Serpina3n*, *Lcn2*), which reduce insulin-stimulated glucose uptake in as yet unclear ways. Interestingly, adipocyte GR can be activated by TNF- α in a partially ligand-independent way, representing an extraordinary example of an anti-inflammatory transcription factor mediating the metabolic effect of a pro-inflammatory cytokine (Kang et al., 2015).

Control of insulin sensitivity by PGC1 α and FOXO1

FOXO transcription factors are key regulators of metabolism and are canonical mediators of insulin-dependent changes in gene expression (reviewed in (Kitamura, 2013)). There are four mammalian FoxO genes (*FoxO1*, *FoxO3a*, *FoxO4*, and *FoxO6*) which have overlapping functions (Arden, *Oncogene* 2009). Although no common polymorphisms in the *FOXO1* locus have been directly linked to insulin resistance or diabetes by large scale genome-wide association studies, a functional network analysis of the genes nearest GWAS signals for glycemic traits implicate FOXO1 as a shared interactor with multiple GWAS candidate proteins (Morris et al., 2012).

In the liver, insulin promotes the accumulation of lipid and represses gluconeogenesis; the latter is the major determinant of systemic glucose homeostasis in the fasted state. Among the many factors that regulate gluconeogenesis, the transcription factor FOXO1 and the co-factor PGC-1 α have been identified as having a major role (Fig. 1). Liver-specific triple knockout of FOXO1, FOXO3a, and FOXO4 show increased fasting hypoglycemia, increased glucose tolerance, and enhanced insulin sensitivity with decreased plasma insulin levels; comparisons with single knockouts suggest all three work synergistically to regulate hepatic insulin sensitivity (Haeusler et al., 2010). Whole body FOXO6 knockouts also show decreased hepatic glucose production and enhanced insulin sensitivity (Calabuig-Navarro et al., 2015).

FOXO1 is thought to primarily effect insulin sensitivity in adipose tissue via inhibition of adipocyte differentiation, though transgenic expression of a dominant-negative FOXO1 in mature adipocytes improves glucose and insulin tolerance and increases energy expenditure in mice on high-fat diet (Nakae et al., 2008). In the pancreas, FOXO1 is involved in β -cell dysfunction via multiple mechanisms including suppression of β -cell proliferation, mediating oxidative, ER, and hypoxic stress, and increasing apoptosis (reviewed in (Kitamura, 2013)). FOXO1 has also been shown to mediate insulin-regulated activity of hypothalamic neurons, with constitutively active FOXO1 causing hyperphagia, increased body weight, and inhibition of leptin action. Mice with Agrp neuron-specific deletion of

FOXO1 are lean with reduced food intake and suppressed hepatic glucose production (Ren et al., 2012).

FOXO factors generally, and FOXO1 in particular, are regulated by a variety of post-translational modifications, including phosphorylation and acetylation (reviewed in (Calnan and Brunet, 2008)). In its nonphosphorylated state, FOXO1 localizes to the nucleus, where it binds its cognate motif and drives expression of key insulin-regulated genes, such as *G6pc* (encoding glucose 6-phosphatase) (Fig 3). Insulin causes Akt-mediated phosphorylation of FOXO1 at residues T24, S256, and S319, resulting in its exclusion from the nucleus, where it is subsequently ubiquitinated and degraded. FOXO proteins are also a key element of the oxidative stress response pathway, which causes insulin resistance in multiple tissues.

Reactive oxygen species (ROS) induce JNK-mediated phosphorylation of FOXO1, driving increased transcriptional activation of target genes, which include antioxidant scavengers (Kawamori et al., 2006). Transcriptional profiling of cells expressing a non-phosphorylatable mutant FOXO1 display up-regulated ROS response genes (Greer et al., 2007), while the vast majority of other FOXO1 targets are unchanged. FOXO1 is also activated by AMP-activated Protein Kinase (AMPK) phosphorylation, and its activation inhibits gluconeogenesis in the liver and glucose oxidation in muscle. In response to oxidative stress, β -catenins also directly interact with FOXO1 to increase its transcriptional activity (Almeida et al., 2007, Essers et al., 2005). Such β -catenin/FOXO1 interactions in liver have been shown to contribute to regulation of gluconeogenic gene expression and glucose homeostasis (Ip et al., 2015).

FOXO1 activity is also modulated by acetylation, serving as a direct target of the histone acetyltransferases CBP and p300, and the histone deacetylases SIRT1 and SIRT2. The effect of acetylation on FOXO1 activity appears to be context-dependent, with data showing positive, negative, and dual effects on transactivation (reviewed in (Daitoku et al., 2011)). FOXO1 acetylation status is determined by the relative balance of protein acetylases (CBP, p300, and PCAF) and deacetylases (Sir2/Sirt family). FOXO1 acetylation promotes phosphorylation by Akt and inhibits DNA binding (Matsuzaki et al., 2005). Meanwhile, SIRT1-mediated deacetylation of FOXO family proteins, as occurs in response to ROS, promotes nuclear translocation and gluconeogenic gene expression, even in the face of Akt activation (Frescas et al., 2005). FOXO factors can also be activated by O-GlcNAcylation following increased oxidative stress; this modification is increased in diabetic livers and is associated with increased FOXO-driven expression of gluconeogenic and ROS detoxifying genes (Housley et al., 2008).

In the liver, the co-activator PGC-1 α is a key insulin-responsive transcriptional regulator of gluconeogenesis. PGC-1 α is induced in liver on fasting, is elevated in models of insulin resistance, and can activate the entire transcriptional profile of gluconeogenesis (Herzig et al., 2001, Yoon et al., 2001). The induction of gluconeogenesis by PGC-1 α is mediated via direct interaction with FOXO1; Akt-mediated phosphorylation and expulsion of FOXO1 from the nucleus disrupts the FOXO1–PGC-1 α interaction, thereby suppressing gluconeogenesis (Puigserver et al., 2003).

Concluding remarks

Insulin sensitivity is a carefully regulated process that goes awry in many different pathophysiological states. Its role as a major driver of Type 2 diabetes means that we must understand its antecedents and its consequences, in order to develop better and more rational targets for therapeutic intervention (see Outstanding Questions). Numerous theories have emerged to explain how insulin resistance develops and progresses, most of which involve changes in insulin signal transduction, or other processes that center on the cytosol, or organelles like mitochondria and the endoplasmic reticulum. Here we have endeavored to draw attention to transcriptional and epigenetic events that play an equally important role. These pathways involve a wide variety of organs and cell types and numerous molecular actors, including transcription factors, co-factors, and chromatin-modifying enzymes. They utilize a widely varying repertoire of mechanisms that include direct effects on the expression of insulin signaling components, repression or enhancement of inflammation, effects on cellular differentiation, and actions on targets with as yet unspecified roles in insulin sensitivity. Some of these pathways, such as those involving nuclear hormone receptors or chromatin-modifying enzymes, are inherently ‘druggable’, while other factors may prove to be more resistant to pharmacological intervention. Regardless, full explication of nuclear mechanisms and their downstream effectors will broaden our understanding of insulin resistance and should enable the identification of novel drug targets.

Outstanding Questions

- What are the key gene targets that mediate the effects of relevant transcription factors and cofactors on insulin action? Does each transcription factor work on its own set of targets, or are there a common set of critical genes that are co-regulated by multiple factors?
- How are transcriptional effects in different tissues, such as liver, adipose, muscle, brain, and immune cells, coordinated so that they produce a unified effect on metabolism?
- What are the molecular mechanisms through which transcription factors regulate genes involved in insulin resistance? Are core subsets of co-factors and chromatin marks utilized?
- Other than PPAR α agonism, can transcriptional and epigenomic pathways be manipulated to improve insulin sensitivity in patients? How many of these pathways are ‘druggable’, and how can we achieve tissue-selective effects?

References

1. Ahmadian M, Suh JM, Hah N, Liddle C, Atkins AR, Downes M, Evans RM. PPARgamma signaling and metabolism: the good, the bad and the future. *Nature medicine*. 2013; 19:557–566.
2. Almeida M, Han L, Martin-Millan M, O’Brien CA, Manolagas SC. Oxidative stress antagonizes Wnt signaling in osteoblast precursors by diverting beta-catenin from T cell factor-to forkhead box O-mediated transcription. *The Journal of biological chemistry*. 2007; 282:27298–27305. [PubMed: 17623658]

3. Banks AS, McAllister FE, Camporez JP, Zushin PJ, Jurczak MJ, Laznik-Bogoslavski D, ... Spiegelman BM. An ERK/Cdk5 axis controls the diabetogenic actions of PPARgamma. *Nature*. 2015; 517:391–395. [PubMed: 25409143]
4. Baranowski M. Biological role of liver X receptors. *Journal of physiology and pharmacology : an official journal of the Polish Physiological Society*. 2008; 59(Suppl 7):31–55. [PubMed: 19258656]
5. Biddinger SB, Kahn CR. From mice to men: insights into the insulin resistance syndromes. *Annual review of physiology*. 2006; 68:123–158.
6. Bodine SC, Stitt TN, Gonzalez M, Kline WO, Stover GL, Bauerlein R, ... Yancopoulos GD. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. *Nature cell biology*. 2001; 3:1014–1019. [PubMed: 11715023]
7. Boucher J, Kleinriders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. *Cold Spring Harbor perspectives in biology*. 2014:6.
8. Bouhrel MA, Derudas B, Rigamonti E, Dievart R, Brozek J, Haulon S, ... Chinetti-Gbaguidi G. PPARgamma activation primes human monocytes into alternative M2 macrophages with anti-inflammatory properties. *Cell metabolism*. 2007; 6:137–143. [PubMed: 17681149]
9. Calabuig-Navarro V, Yamauchi J, Lee S, Zhang T, Liu YZ, Sadlek K, ... Dong HH. Forkhead Box O6 (FoxO6) Depletion Attenuates Hepatic Gluconeogenesis and Protects against Fat-induced Glucose Disorder in Mice. *The Journal of biological chemistry*. 2015; 290:15581–15594. [PubMed: 25944898]
10. Calnan DR, Brunet A. The FoxO code. *Oncogene*. 2008; 27:2276–2288. [PubMed: 18391970]
11. Castonguay TW. Glucocorticoids as modulators in the control of feeding. *Brain research bulletin*. 1991; 27:423–428. [PubMed: 1959040]
12. Chao L, Marcus-Samuels B, Mason MM, Moitra J, Vinson C, Arioglu E, ... Reitman ML. Adipose tissue is required for the antidiabetic, but not for the hypolipidemic, effect of thiazolidinediones. *The Journal of clinical investigation*. 2000; 106:1221–1228. [PubMed: 11086023]
13. Choi JH, Banks AS, Estall JL, Kajimura S, Bostrom P, Laznik D, ... Spiegelman BM. Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARgamma by Cdk5. *Nature*. 2010; 466:451–456. [PubMed: 20651683]
14. Choi JH, Banks AS, Kamenecka TM, Busby SA, Chalmers MJ, Kumar N, ... Griffin PR. Antidiabetic actions of a non-agonist PPARgamma ligand blocking Cdk5-mediated phosphorylation. *Nature*. 2011; 477:477–481. [PubMed: 21892191]
15. Cipolletta D, Feuerer M, Li A, Kamei N, Lee J, Shoelson SE, ... Mathis D. PPAR-gamma is a major driver of the accumulation and phenotype of adipose tissue Treg cells. *Nature*. 2012; 486:549–553. [PubMed: 22722857]
16. Cleasby ME, Reinten TA, Cooney GJ, James DE, Kraegen EW. Functional studies of Akt isoform specificity in skeletal muscle in vivo; maintained insulin sensitivity despite reduced insulin receptor substrate-1 expression. *Mol Endocrinol*. 2007; 21:215–228. [PubMed: 17021050]
17. Daitoku H, Sakamaki J, Fukamizu A. Regulation of FoxO transcription factors by acetylation and protein-protein interactions. *Biochimica et biophysica acta*. 2011; 1813:1954–1960. [PubMed: 21396404]
18. Dutchak PA, Katafuchi T, Bookout AL, Choi JH, Yu RT, Mangelsdorf DJ, Kliewer SA. Fibroblast growth factor-21 regulates PPARgamma activity and the antidiabetic actions of thiazolidinediones. *Cell*. 2012; 148:556–567. [PubMed: 22304921]
19. Eguchi J, Kong X, Tenta M, Wang X, Kang S, Rosen ED. Interferon regulatory factor 4 regulates obesity-induced inflammation through regulation of adipose tissue macrophage polarization. *Diabetes*. 2013
20. Essers MA, de Vries-Smits LM, Barker N, Polderman PE, Burgering BM, Korswagen HC. Functional interaction between beta-catenin and FOXO in oxidative stress signaling. *Science*. 2005; 308:1181–1184. [PubMed: 15905404]
21. Frescas D, Valenti L, Accili D. Nuclear trapping of the forkhead transcription factor FoxO1 via Sirt-dependent deacetylation promotes expression of glucogenetic genes. *The Journal of biological chemistry*. 2005; 280:20589–20595. [PubMed: 15788402]

22. Greer EL, Oskoui PR, Banko MR, Maniar JM, Gygi MP, Gygi SP, Brunet A. The energy sensor AMP-activated protein kinase directly regulates the mammalian FOXO3 transcription factor. *The Journal of biological chemistry*. 2007; 282:30107–30119. [PubMed: 17711846]
23. Haeusler RA, Kaestner KH, Accili D. FoxOs function synergistically to promote glucose production. *The Journal of biological chemistry*. 2010; 285:35245–35248. [PubMed: 20880840]
24. He W, Barak Y, Hevener A, Olson P, Liao D, Le J, ...Evans RM. Adipose-specific peroxisome proliferator-activated receptor gamma knockout causes insulin resistance in fat and liver but not in muscle. *Proceedings of the National Academy of Sciences of the United States of America*. 2003; 100:15712–15717. [PubMed: 14660788]
25. Herman MA, Peroni OD, Villoria J, Schon MR, Abumrad NA, Bluher M, ...Kahn BB. A novel ChREBP isoform in adipose tissue regulates systemic glucose metabolism. *Nature*. 2012; 484:333–338. [PubMed: 22466288]
26. Herzig S, Long F, Jhala US, Hedrick S, Quinn R, Bauer A, ...Montminy M. CREB regulates hepatic gluconeogenesis through the coactivator PGC-1. *Nature*. 2001; 413:179–183. [PubMed: 11557984]
27. Hevener AL, He W, Barak Y, Le J, Bandyopadhyay G, Olson P, ...Olefsky J. Muscle-specific Pparg deletion causes insulin resistance. *Nature medicine*. 2003; 9:1491–1497.
28. Hevener AL, Olefsky JM, Reichart D, Nguyen MT, Bandyopadhyay G, Leung HY, ...Ricote M. Macrophage PPAR gamma is required for normal skeletal muscle and hepatic insulin sensitivity and full antidiabetic effects of thiazolidinediones. *The Journal of clinical investigation*. 2007; 117:1658–1669. [PubMed: 17525798]
29. Hoehn KL, Hohnen-Behrens C, Cederberg A, Wu LE, Turner N, Yuasa T, ...James DE. IRS1-independent defects define major nodes of insulin resistance. *Cell metabolism*. 2008; 7:421–433. [PubMed: 18460333]
30. Hogan MF, Ravnskjaer K, Matsumura S, Huising MO, Hull RL, Kahn SE, Montminy M. Hepatic Insulin Resistance Following Chronic Activation of the CREB Coactivator CRTC2. *The Journal of biological chemistry*. 2015; 290:25997–26006. [PubMed: 26342077]
31. Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell*. 2010; 140:900–917. [PubMed: 20303879]
32. Housley MP, Rodgers JT, Udeshi ND, Kelly TJ, Shabanowitz J, Hunt DF, ...Hart GW. O-GlcNAc regulates FoxO activation in response to glucose. *The Journal of biological chemistry*. 2008; 283:16283–16292. [PubMed: 18420577]
33. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature*. 2006; 440:944–948. [PubMed: 16612386]
34. Huang-Doran I, Savage DB. Congenital syndromes of severe insulin resistance. *Pediatric endocrinology reviews : PER*. 2011; 8:190–199. [PubMed: 21525795]
35. Iizuka K, Bruick RK, Liang G, Horton JD, Uyeda K. Deficiency of carbohydrate response element-binding protein (ChREBP) reduces lipogenesis as well as glycolysis. *Proceedings of the National Academy of Sciences of the United States of America*. 2004; 101:7281–7286. [PubMed: 15118080]
36. Inagaki T, Tachibana M, Magoori K, Kudo H, Tanaka T, Okamura M, ...Sakai J. Obesity and metabolic syndrome in histone demethylase JHDM2a-deficient mice. *Genes to cells : devoted to molecular & cellular mechanisms*. 2009; 14:991–1001. [PubMed: 19624751]
37. Ip W, Shao W, Song Z, Chen Z, Wheeler MB, Jin T. Liver-specific expression of dominant-negative transcription factor 7-like 2 causes progressive impairment in glucose homeostasis. *Diabetes*. 2015; 64:1923–1932. [PubMed: 25576056]
38. Iwata M, Haruta T, Usui I, Takata Y, Takano A, Uno T, ...Kobayashi M. Pioglitazone ameliorates tumor necrosis factor-alpha-induced insulin resistance by a mechanism independent of adipogenic activity of peroxisome proliferator-activated receptor-gamma. *Diabetes*. 2001; 50:1083–1092. [PubMed: 11334412]
39. James AM, Collins Y, Logan A, Murphy MP. Mitochondrial oxidative stress and the metabolic syndrome. *Trends in endocrinology and metabolism: TEM*. 2012; 23:429–434. [PubMed: 22831852]

40. Jiang G, Dallas-Yang Q, Li Z, Szalkowski D, Liu F, Shen X, ...Zhang BB. Potentiation of insulin signaling in tissues of Zucker obese rats after acute and long-term treatment with PPARgamma agonists. *Diabetes*. 2002; 51:2412–2419. [PubMed: 12145152]
41. Kang S, Tsai LT, Zhou Y, Evertts A, Xu S, Griffin MJ, ...Rosen ED. Identification of nuclear hormone receptor pathways causing insulin resistance by transcriptional and epigenomic analysis. *Nature cell biology*. 2015; 17:44–56. [PubMed: 25503565]
42. Kawamori D, Kaneto H, Nakatani Y, Matsuoka TA, Matsuhisa M, Hori M, Yamasaki Y. The forkhead transcription factor Foxo1 bridges the JNK pathway and the transcription factor PDX-1 through its intracellular translocation. *The Journal of biological chemistry*. 2006; 281:1091–1098. [PubMed: 16282329]
43. Kim YB, Nikouline SE, Ciaraldi TP, Henry RR, Kahn BB. Normal insulin-dependent activation of Akt/protein kinase B, with diminished activation of phosphoinositide 3-kinase, in muscle in type 2 diabetes. *The Journal of clinical investigation*. 1999; 104:733–741. [PubMed: 10491408]
44. Kitamura T. The role of FOXO1 in beta-cell failure and type 2 diabetes mellitus. *Nature reviews. Endocrinology*. 2013; 9:615–623.
45. Kuo T, Lew MJ, Mayba O, Harris CA, Speed TP, Wang JC. Genome-wide analysis of glucocorticoid receptor-binding sites in myotubes identifies gene networks modulating insulin signaling. *Proceedings of the National Academy of Sciences of the United States of America*. 2012; 109:11160–11165. [PubMed: 22733784]
46. Kyle UG, Pichard C. The Dutch Famine of 1944–1945: a pathophysiological model of long-term consequences of wasting disease. *Current opinion in clinical nutrition and metabolic care*. 2006; 9:388–394. [PubMed: 16778567]
47. Lefterova MI, Haakonsson AK, Lazar MA, Mandrup S. PPARgamma and the global map of adipogenesis and beyond. *Trends in endocrinology and metabolism: TEM*. 2014; 25:293–302. [PubMed: 24793638]
48. Li P, Fan W, Xu J, Lu M, Yamamoto H, Auwerx J, ...Olefsky JM. Adipocyte NCoR knockout decreases PPARgamma phosphorylation and enhances PPARgamma activity and insulin sensitivity. *Cell*. 2011a; 147:815–826. [PubMed: 22078880]
49. Li Y, Xu S, Giles A, Nakamura K, Lee JW, Hou X, ...Zang M. Hepatic overexpression of SIRT1 in mice attenuates endoplasmic reticulum stress and insulin resistance in the liver. *The FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2011b; 25:1664–1679. [PubMed: 21321189]
50. Lowenberg M, Tuynman J, Scheffer M, Verhaar A, Vermeulen L, van Deventer S, ...Peppelenbosch M. Kinome analysis reveals nongenomic glucocorticoid receptor-dependent inhibition of insulin signaling. *Endocrinology*. 2006; 147:3555–3562. [PubMed: 16574792]
51. Lu M, Sarruf DA, Talukdar S, Sharma S, Li P, Bandyopadhyay G, ...Olefsky JM. Brain PPAR-gamma promotes obesity and is required for the insulin-sensitizing effect of thiazolidinediones. *Nature medicine*. 2011; 17:618–622.
52. Masuccio F, Verrotti A, Chiavaroli V, de Giorgis T, Giannini C, Chiarelli F, Mohn A. Weight gain and insulin resistance in children treated with valproate: the influence of time. *Journal of child neurology*. 2010; 25:941–947. [PubMed: 20207607]
53. Mathis D. Immunological goings-on in visceral adipose tissue. *Cell metabolism*. 2013; 17:851–859. [PubMed: 23747244]
54. Matsuzaki H, Daitoku H, Hatta M, Aoyama H, Yoshimochi K, Fukamizu A. Acetylation of Foxo1 alters its DNA-binding ability and sensitivity to phosphorylation. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102:11278–11283. [PubMed: 16076959]
55. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988–2012. *JAMA : the journal of the American Medical Association*. 2015; 314:1021–1029. [PubMed: 26348752]
56. Michael LF, Wu Z, Cheatham RB, Puigserver P, Adelmant G, Lehman JJ, ...Spiegelman BM. Restoration of insulin-sensitive glucose transporter (GLUT4) gene expression in muscle cells by the transcriptional coactivator PGC-1. *Proceedings of the National Academy of Sciences of the United States of America*. 2001; 98:3820–3825. [PubMed: 11274399]

57. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir V, ...Meta-analysis C. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nature genetics*. 2012; 44:981–990. [PubMed: 22885922]
58. Nadler ST, Stoehr JP, Rabaglia ME, Schueler KL, Birnbaum MJ, Attie AD. Normal Akt/PKB with reduced PI3K activation in insulin-resistant mice. *American journal of physiology. Endocrinology and metabolism*. 2001; 281:E1249–1254. [PubMed: 11701440]
59. Nakae J, Cao Y, Oki M, Orba Y, Sawa H, Kiyonari H, ...Hayashi Y. Forkhead transcription factor FoxO1 in adipose tissue regulates energy storage and expenditure. *Diabetes*. 2008; 57:563–576. [PubMed: 18162510]
60. Norris AW, Chen L, Fisher SJ, Szanto I, Ristow M, Jozsi AC, ...Kahn CR. Muscle-specific PPARgamma-deficient mice develop increased adiposity and insulin resistance but respond to thiazolidinediones. *The Journal of clinical investigation*. 2003; 112:608–618. [PubMed: 12925701]
61. Oakley RH, Cidlowski JA. Cellular processing of the glucocorticoid receptor gene and protein: new mechanisms for generating tissue-specific actions of glucocorticoids. *The Journal of biological chemistry*. 2011; 286:3177–3184. [PubMed: 21149445]
62. Odegaard JI, Chawla A. The immune system as a sensor of the metabolic state. *Immunity*. 2013; 38:644–654. [PubMed: 23601683]
63. Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, Morel CR, Subramanian V, Mukundan L, ... Chawla A. Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance. *Nature*. 2007; 447:1116–1120. [PubMed: 17515919]
64. Oh J, Riek AE, Darwech I, Funai K, Shao J, Chin K, ...Bernal-Mizrachi C. Deletion of macrophage Vitamin D receptor promotes insulin resistance and monocyte cholesterol transport to accelerate atherosclerosis in mice. *Cell reports*. 2015; 10:1872–1886. [PubMed: 25801026]
65. Ohno H, Shinoda K, Ohyama K, Sharp LZ, Kajimura S. EHMT1 controls brown adipose cell fate and thermogenesis through the PRDM16 complex. *Nature*. 2013; 504:163–167. [PubMed: 24196706]
66. Ohno H, Shinoda K, Spiegelman BM, Kajimura S. PPARgamma agonists induce a white-to-brown fat conversion through stabilization of PRDM16 protein. *Cell metabolism*. 2012; 15:395–404. [PubMed: 22405074]
67. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. *Annual review of physiology*. 2010; 72:219–246.
68. Oosterveer MH, Matak C, Yamamoto H, Harach T, Moullan N, van Dijk TH, ...Schoonjans K. LXR-1-dependent glucose sensing determines intermediary metabolism in liver. *The Journal of clinical investigation*. 2012; 122:2817–2826. [PubMed: 22772466]
69. Opherk C, Tronche F, Kellendonk C, Kohlmuller D, Schulze A, Schmid W, Schutz G. Inactivation of the glucocorticoid receptor in hepatocytes leads to fasting hypoglycemia and ameliorates hyperglycemia in streptozotocin-induced diabetes mellitus. *Mol Endocrinol*. 2004; 18:1346–1353. [PubMed: 15031319]
70. Parlevliet ET, Coomans CP, Rensen PC, Romijn JA. The brain modulates insulin sensitivity in multiple tissues. *Frontiers of hormone research*. 2014; 42:50–58. [PubMed: 24732924]
71. Pascual G, Ricote M, Hevener AL. Macrophage peroxisome proliferator activated receptor gamma as a therapeutic target to combat Type 2 diabetes. *Expert opinion on therapeutic targets*. 2007; 11:1503–1520. [PubMed: 18028013]
72. Patel R, Williams-Dautovich J, Cummins CL. Minireview: new molecular mediators of glucocorticoid receptor activity in metabolic tissues. *Mol Endocrinol*. 2014; 28:999–1011. [PubMed: 24766141]
73. Plotz CM, Knowlton AI, Ragan C. Natural course of Cushing's syndrome as compared with the course of rheumatoid arthritis treated by hormones. *Annals of the rheumatic diseases*. 1952; 11:308–309. [PubMed: 13017491]
74. Puigserver P. Tissue-specific regulation of metabolic pathways through the transcriptional coactivator PGC1-alpha. *Int J Obes (Lond)*. 2005; 29(Suppl 1):S5–9. [PubMed: 15711583]
75. Puigserver P, Rhee J, Donovan J, Walkey CJ, Yoon JC, Oriente F, ...Spiegelman BM. Insulin-regulated hepatic gluconeogenesis through FOXO1-PGC-1alpha interaction. *Nature*. 2003; 423:550–555. [PubMed: 12754525]

76. Puigserver P, Spiegelman BM. Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 alpha): transcriptional coactivator and metabolic regulator. *Endocrine reviews*. 2003; 24:78–90. [PubMed: 12588810]
77. Qiang L, Wang L, Kon N, Zhao W, Lee S, Zhang Y, ...Accili D. Brown remodeling of white adipose tissue by SirT1-dependent deacetylation of Ppargamma. *Cell*. 2012; 150:620–632. [PubMed: 22863012]
78. Rando OJ, Simmons RA. I'm eating for two: parental dietary effects on offspring metabolism. *Cell*. 2015; 161:93–105. [PubMed: 25815988]
79. Rangwala SM, Rhoades B, Shapiro JS, Rich AS, Kim JK, Shulman GI, ...Lazar MA. Genetic modulation of PPARgamma phosphorylation regulates insulin sensitivity. *Developmental cell*. 2003; 5:657–663. [PubMed: 14536066]
80. Raychaudhuri N, Raychaudhuri S, Thamotharan M, Devaskar SU. Histone code modifications repress glucose transporter 4 expression in the intrauterine growth-restricted offspring. *The Journal of biological chemistry*. 2008; 283:13611–13626. [PubMed: 18326493]
81. Ren H, Orozco IJ, Su Y, Suyama S, Gutierrez-Juarez R, Horvath TL, ...Accili D. FoxO1 target Gpr17 activates AgRP neurons to regulate food intake. *Cell*. 2012; 149:1314–1326. [PubMed: 22682251]
82. Riera-Guardia N, Rothenbacher D. The effect of thiazolidinediones on adiponectin serum level: a meta-analysis. *Diabetes, obesity & metabolism*. 2008; 10:367–375.
83. Rizza RA, Mandarino LJ, Gerich JE. Cortisol-induced insulin resistance in man: impaired suppression of glucose production and stimulation of glucose utilization due to a postreceptor defect of insulin action. *The Journal of clinical endocrinology and metabolism*. 1982; 54:131–138. [PubMed: 7033265]
84. Roohk DJ, Mascharak S, Khambatta C, Leung H, Hellerstein M, Harris C. Dexamethasone-mediated changes in adipose triacylglycerol metabolism are exaggerated, not diminished, in the absence of a functional GR dimerization domain. *Endocrinology*. 2013; 154:1528–1539. [PubMed: 23493372]
85. Rosen ED, Kulkarni RN, Sarraf P, Ozcan U, Okada T, Hsu CH, ...Spiegelman BM. Targeted elimination of peroxisome proliferator-activated receptor gamma in beta cells leads to abnormalities in islet mass without compromising glucose homeostasis. *Molecular and cellular biology*. 2003; 23:7222–7229. [PubMed: 14517292]
86. Ryan KK, Li B, Grayson BE, Matter EK, Woods SC, Seeley RJ. A role for central nervous system PPAR-gamma in the regulation of energy balance. *Nature medicine*. 2011; 17:623–626.
87. Schenk S, McCurdy CE, Philp A, Chen MZ, Holliday MJ, Bandyopadhyay GK, ...Olefsky JM. Sirt1 enhances skeletal muscle insulin sensitivity in mice during caloric restriction. *The Journal of clinical investigation*. 2011; 121:4281–4288. [PubMed: 21985785]
88. Soccio RE, Chen ER, Lazar MA. Thiazolidinediones and the promise of insulin sensitization in type 2 diabetes. *Cell metabolism*. 2014; 20:573–591. [PubMed: 25242225]
89. Sugii S, Olson P, Sears DD, Saberi M, Atkins AR, Barish GD, ...Evans RM. PPARgamma activation in adipocytes is sufficient for systemic insulin sensitization. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106:22504–22509. [PubMed: 20018750]
90. Tateishi K, Okada Y, Kallin EM, Zhang Y. Role of Jhdm2a in regulating metabolic gene expression and obesity resistance. *Nature*. 2009; 458:757–761. [PubMed: 19194461]
91. Tomas E, Kelly M, Xiang X, Tsao TS, Keller C, Keller P, ...Ruderman NB. Metabolic and hormonal interactions between muscle and adipose tissue. *The Proceedings of the Nutrition Society*. 2004; 63:381–385. [PubMed: 15294059]
92. Vernochet C, Peres SB, Davis KE, McDonald ME, Qiang L, Wang H, ...Farmer SR. C/EBPalpha and the corepressors CtBP1 and CtBP2 regulate repression of select visceral white adipose genes during induction of the brown phenotype in white adipocytes by peroxisome proliferator-activated receptor gamma agonists. *Molecular and cellular biology*. 2009; 29:4714–4728. [PubMed: 19564408]
93. Wang JC, Derynck MK, Nonaka DF, Khodabakhsh DB, Haqq C, Yamamoto KR. Chromatin immunoprecipitation (ChIP) scanning identifies primary glucocorticoid receptor target genes.

- Proceedings of the National Academy of Sciences of the United States of America. 2004; 101:15603–15608. [PubMed: 15501915]
94. Wang Z, Shah OJ, Hunter T. The transcriptional coactivators p/CIP and SRC-1 control insulin resistance through IRS1 in obesity models. *PloS one*. 2012; 7:e36961. [PubMed: 22859932]
95. Ye JM, Dzamko N, Cleasby ME, Hegarty BD, Furler SM, Cooney GJ, Kraegen EW. Direct demonstration of lipid sequestration as a mechanism by which rosiglitazone prevents fatty-acid-induced insulin resistance in the rat: comparison with metformin. *Diabetologia*. 2004; 47:1306–1313. [PubMed: 15232684]
96. Yi CX, Foppen E, Abplanalp W, Gao Y, Alkemade A, la Fleur SE, ...Kalsbeek A. Glucocorticoid signaling in the arcuate nucleus modulates hepatic insulin sensitivity. *Diabetes*. 2012; 61:339–345. [PubMed: 22210324]
97. Yoon JC, Puigserver P, Chen G, Donovan J, Wu Z, Rhee J, ...Spiegelman BM. Control of hepatic gluconeogenesis through the transcriptional coactivator PGC-1. *Nature*. 2001; 413:131–138. [PubMed: 11557972]
98. Yoshizaki T, Milne JC, Imamura T, Schenk S, Sonoda N, Babendure JL, ...Olefsky JM. SIRT1 exerts anti-inflammatory effects and improves insulin sensitivity in adipocytes. *Molecular and cellular biology*. 2009; 29:1363–1374. [PubMed: 19103747]
99. Yoshizaki T, Schenk S, Imamura T, Babendure JL, Sonoda N, Bae EJ, ...Olefsky JM. SIRT1 inhibits inflammatory pathways in macrophages and modulates insulin sensitivity. *American journal of physiology. Endocrinology and metabolism*. 2010; 298:E419–428. [PubMed: 19996381]

Trends

- The pathogenesis of insulin resistance, a major component of Type 2 diabetes, has been the subject of extensive study, much of which has focused on signaling events or mitochondrial and endoplasmic reticulum dysfunction.
- A large body of data converges to suggest that insulin resistance also involves transcriptional and epigenomic (i.e. nuclear) events.
- Several nuclear receptors regulate insulin sensitivity in both positive and negative ways, including PPAR α and the glucocorticoid receptor (GR).
- Insulin sensitivity can be affected by many transcription factors, co-factors, and chromatin-modifying enzymes working coordinately in different tissues and cell types.

	WAT	Muscle	Liver	Brain	Immune cells
PPAR γ	↑ Browning ↑ Glucose uptake ↑ Insulin signaling ↑ Lipid storage ↓ ↑ Adipokine secretion	↑ Glucose uptake ↑ Insulin signaling ↓ Lipid storage	↑ Lipogenesis	↑ Food intake	↓ Inflammation
GR	↑ Lipolysis ↓ Glucose uptake ↓ Inflammation ↓ Insulin signaling	↑ Proteolysis ↓ Glucose uptake ↓ Glycogen synthesis ↓ Insulin signaling	↑ Gluconeogenesis ↑ TG synthesis ↓ TG lipolysis	↑ Food intake	↓ Inflammation
FOXO	↓ ↑ Adipokine secretion ↓ Glucose uptake ↓ Adipocyte differentiation	↑ Atrophy ↑ Autophagy ↓ Differentiation ↓ Type 1 (slow twitch) fibers	↑ <i>De novo</i> lipogenesis? ↑ Gluconeogenesis ↑ TG accumulation? ↓ Glycolysis	↑ Body weight ↑ Food intake ↑ Response to leptin ↑ Hepatic lipid oxidation ↑ Hepatic glucose production	↑ Apoptosis ↑ ROS resistance ↓ Proliferation

Figure 1.

Multi-organ effects of PPAR γ , GR, and FoxO1 and their impact on insulin sensitivity. Multiple sites of action for these transcription factors contribute to their effects on metabolism and glycemic control. See text for details.

Figure 2.

Different modes of transcriptional regulation by PPAR γ and GR in insulin sensitivity. In fat, muscle, and liver, ligand activation of PPAR γ induces heterodimerization with RXR, allowing DNA binding to specific response elements and subsequent transcriptional activation. Negative regulation by PPAR γ , as occurs with pro-inflammatory genes in immune cells, is incompletely understood but likely involves ‘tethering’ via direct interactions with other transcription factors. Ligand binding of GR induces homodimerization of GR, allowing DNA binding to activate and repress GR target genes in multiple tissues. Similar to PPAR γ , GR can exert trans-repression via tethering to other transcription factors to repress genes in inflammation.

Figure 3.

Transcriptional activity of FOXO1 and PGC-1α in hepatic glucose production. FOXO1 is a key driver of gluconeogenic gene expression (e.g. *Pck1* and *G6pc*) in the liver. Its activity is regulated by a variety of factors, including phosphorylation by Akt, which reduces FOXO1 levels in the nucleus, and by phosphorylation via AMPK, which promotes its activity. Other post-translational modifications, such as O-linked GlcNAcylation and acetylation, also affect the activity of FOXO1, as does interaction with the co-factor PGC-1α. See text for more details.

Table 1

Selected additional transcription factors, co-factors, and epigenomic modifiers that have an impact on insulin sensitivity.

Factor	Tissue	Effect on Insulin Action	Mechanism	Ref
Transcription Factor				
LXRα	WAT	Increased	Enhances Glut4 expression	(Baranowski, 2008)
	Liver	Increased	Suppresses gluconeogenesis	(Baranowski, 2008)
VDR	Macrophage	Increased	Promotes M2 macrophage polarization	(Oh et al., 2015)
	Adipocyte	Decreased	Inhibits glucose uptake	(Kang et al., 2015)
ChREBP	WAT	Increased	Promotes glucose transport	(Herman et al., 2012)
	Liver	Increased	Promotes lipogenesis and glycolysis	(Iizuka et al., 2004)
LRH-1	Liver	Increased	Promotes glucose uptake	(Oosterveer et al., 2012)
Transcriptional Co-factor				
SRC1, p/CIP	WAT, muscle	Decreased	Suppresses insulin signaling	(Wang et al., 2012)
NCoR	WAT	Decreased	Suppresses PPAR γ action	(Li et al., 2011a)
CRTC2	Liver	Decreased	Promotes gluconeogenesis	(Hogan et al., 2015)
PGC-1α	Liver	Decreased	Promotes gluconeogenesis	(Puigserver, 2005)
	Muscle	Increased	Enhances Glut4 expression	(Michael et al., 2001)
	WAT/BAT	Increased	Enhances browning/thermogenesis	(Puigserver and Spiegelman, 2003)
Epigenomic Modifier				
Jhdm2a	WAT	Increased	Promotes browning	(Tateishi et al., 2009)
Sirt1	WAT	Increased	Inhibits inflammation	(Yoshizaki et al., 2009)
	Muscle	Increased	Enhances glucose uptake	(Schenk et al., 2011)
	Liver	Increased	Inhibits ER stress	(Li et al., 2011b)
	Macrophage	Increased	Inhibits inflammation	(Yoshizaki et al., 2010)