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REVIEW

Mechanisms of obesity-associated insulin resistance: many choices on the menu

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Obesity-associated insulin resistance is a major risk factor for type 2 diabetes and cardiovascular disease. In the past decade, a large number of endocrine, inflammatory, neural, and cell-intrinsic pathways have been shown to be dysregulated in obesity. Although it is possible that one of these factors plays a dominant role, many of these factors are interdependent, and it is likely that their dynamic interplay underlies the pathophysiology of insulin resistance. Understanding the biology of these systems will inform the search for interventions that specifically prevent or treat insulin resistance and its associated pathologies.

The number of obese individuals worldwide has reached 2.1 billion, leading to an explosion of obesity-related health problems associated with increased morbidity and mortality (Li et al. 2005; Olshansky 2005). Obese individuals develop resistance to the cellular actions of insulin, characterized by an impaired ability of insulin to inhibit glucose output from the liver and to promote glucose uptake in fat and muscle (Saltiel and Kahn 2001; Hribal et al. 2002). Insulin resistance is a key etiological factor for type 2 diabetes mellitus (T2DM), which has reached epidemic proportions: In the United States, ~6% of the current adult population is diagnosed with this disease. An additional 41 million people are prediabetic, with a constellation of insulin resistance, hypertension, and dyslipidemia that puts them at increased risk for cardiovascular morbidity and mortality (Zimmet et al. 2001; American Diabetes Association diabetes statistics at http://www.diabetes.org/diabetes-statistics/prevalence.jsp). Lifestyle changes, while desirable, have proven difficult to achieve. Thus, a better understanding of the molecular mechanisms underlying insulin resistance will be required to combat the epidemics of T2DM and cardiovascular disease that are fueled by obesity-associated insulin resistance. The association between obesity and insulin resistance is likely a cause-and-effect relationship since hu-

man and animal studies indicate that weight loss/gain correlates closely with increasing/decreasing insulin sensitivity, respectively (Sims et al. 1973; Freidenberg et al. 1988; Bak et al. 1992). In this review, we explore current ideas of how increased adipose mass predisposes to systemic insulin resistance, focusing on dysregulation of interconnected endocrine, inflammatory, neural, and cell-autonomous pathways.

Endocrine mechanisms

Fatty acids (FAs)

It has long been recognized that plasma FA concentrations are commonly elevated in obese individuals, mainly due to increased FA release associated with the expansion in fat mass (Gordon 1964; Bjorntorp et al. 1969; Jensen et al. 1989). Classically, FAs secreted from adipocytes have been considered to serve entirely as energy sources for other tissues of the body. The notion that these FAs function as endocrine factors that regulate metabolic function in target tissues was first suggested >40 years ago, when Randle et al. (1963) hypothesized that obesity-associated insulin resistance could be explained by competition between these increased circulating FAs and glucose for oxidative metabolism in insulin-responsive cells. More recently, glucose uptake rather than intracellular glucose metabolism has been implicated as the rate-limiting step for FA-induced insulin resistance (Shulman 2000). In this model, FAs and potentially several metabolites including acyl-CoAs, ceramides, and diacyglycerol serve as signaling molecules that activate protein kinases such as Protein Kinase C (PKC), Jun kinase (JNK), and the inhibitor of nuclear factor-κB (NF-κB) kinase-β (IKKβ). These kinases can then impair insulin signaling by increasing the inhibitory serine phosphorylation of insulin receptor substrates (IRS), the key mediators of insulin receptor signaling (Fig. 1A; for review, see Petersen and Shulman 2006).

Adipokines

Adipocytes also secrete metabolically active proteins (Fig. 1B; for review, see Rajala and Scherer 2003; Kershaw
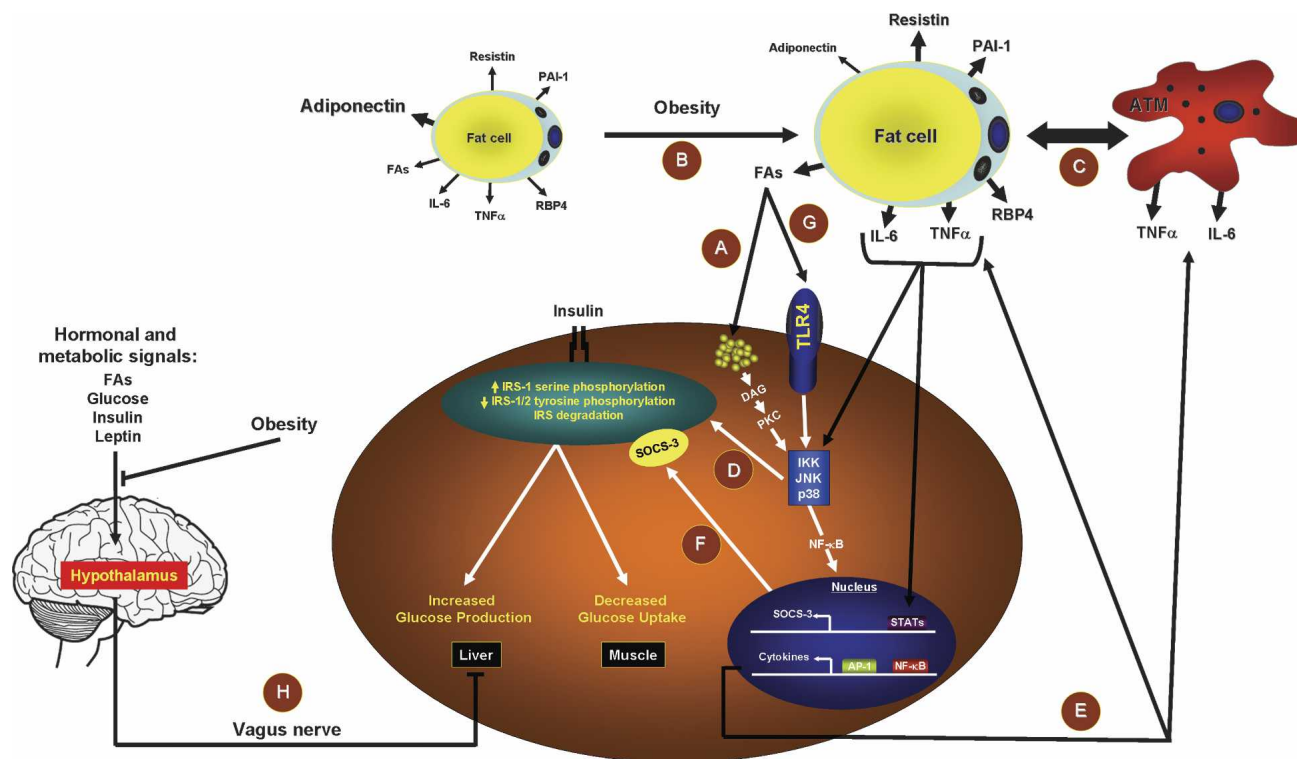
Figure 1. Endocrine, inflammatory, and neuronal pathways link obesity to insulin resistance. (*A*) The obesity-associated increase in FAs can trigger insulin resistance through intracellular metabolites that activate PKC, leading to the activation of serine/threonine kinases that inhibit insulin signaling. (*B*) Obesity-associated changes in secretion of adipokines that modulate insulin signaling. (*C*) Obesity-associated inflammatory factors. Obesity is characterized by an increase in the accumulation of ATMs, which increase the adipose tissue production of inflammatory cytokines that inhibit insulin signaling. (*D*) Endocrine and inflammatory mediators converging on serine/threonine kinases that inhibit insulin signaling. (*E*) Obesity-associated activation of NF-κB heightens inflammatory responses that exacerbate insulin resistance. (*F*) SOCS family proteins, induced by adipokines, induce insulin resistance either by interfering with IRS-1 and IRS-2 tyrosine phosphorylation or by targeting IRS-1 and IRS-2 for proteosomal degradation. (*G*) FAs also trigger insulin resistance by direct activation of TLR4 and the innate immune response. (*H*) Obesity-related alteration in the central response to hormonal and nutrient signals alters peripheral insulin sensitivity.

and Flier 2004). Leptin is an adipocyte-secreted hormone whose absence leads to dramatic metabolic derangements (Ingalls et al. 1950). The discovery of leptin by Friedman and colleagues in 1994 (Zhang et al. 1994) ushered in an era of receptivity to the notion that adipose tissue is an endocrine organ, and that increased adipose mass in obesity could lead to pathological changes in adipocyte hormones (adipokines) that regulate insulin sensitivity.

Adiponectin was independently characterized in 1995 and 1996 by four groups using different methods (Scherer et al. 1995; Choi-Miura et al. 1996; Hu et al. 1996; Maeda et al. 1996). Adiponectin is structurally related to complement 1q, is specifically expressed in differentiated adipocytes, and circulates at high levels in the bloodstream (Chandran et al. 2003). Adiponectin levels are low in obesity, and administration of adiponectin improves insulin resistance in animal models (Berg et al. 2001; Kubota et al. 2002; Diez and Iglesias 2003). *Adiponectin*-deficient mice develop premature diet-induced glucose intolerance and insulin resistance, and increased serum FAs (Kubota et al. 2002; Maeda et al. 2002). In contrast, transgenic overexpression of *adiponectin* in

mice leads to improved insulin sensitivity, glucose tolerance, and lower serum FAs (Maeda et al. 2002; Combs et al. 2004). Several mechanisms for adiponectin's metabolic effects have been described (Berg et al. 2001; Yamauchi et al. 2002). In the liver, adiponectin enhances insulin sensitivity, decreases influx of FAs, increases FA oxidation, and reduces hepatic glucose output (Combs et al. 2004). In muscle, adiponectin stimulates glucose use and FA oxidation probably via activation of the cellular fuel sensor, AMP-activated protein kinase (AMPK) (Fruebis et al. 2001; Tomas et al. 2002; Yamauchi et al. 2002).

Resistin was identified in 2001 as an adipocyte-specific secreted protein whose expression is down-regulated by anti-diabetic drugs targeting the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) (Holcomb et al. 2000; Kim et al. 2001; Steppan et al. 2001). Serum resistin is elevated in rodent obesity, and infusion or sustained expression of resistin produces insulin resistance (Rajala et al. 2003; Rangwala et al. 2004; Satoh et al. 2004; Qi et al. 2006). Conversely, mice lacking *resistin* have improved glucose homeostasis (Banerjee et al. 2004). This effect is mediated at least in part via increased activity of AMPK and decreased expression of

gluconeogenic enzymes in the liver. Moreover, resistin has been shown to induce the expression of Suppressor of Cytokine Signaling-3 (SOCS-3), a well-known negative regulator of insulin signaling (Emanuelli et al. 2001), both in vitro and in vivo (Steppan et al. 2005). The role of resistin in humans is less certain. While mouse resistin is exclusively expressed in white adipose tissue, human resistin is mainly expressed in circulating mononuclear cells (Savage et al. 2001; Steppan et al. 2001; Patel et al. 2003). Some studies show increased resistin expression and serum levels in association with obesity and insulin resistance (Vidal-Puig and O'Rahilly 2001; C.L. McTernan et al. 2002; P.G. McTernan et al. 2002; Wang et al. 2002; Smith et al. 2003; Osawa et al. 2004, 2005). However, other studies failed to show such an association (Janke et al. 2002; Kielstein et al. 2003; Patel et al. 2003). Intriguingly, recent studies in humans show a consistent association between resistin and inflammation (Lehrke et al. 2004; Reilly et al. 2005; Pang and Le 2006; Senolt et al. 2006).

Several other adipokines are also associated with inflammation. Plasminogen activator inhibitor-1 (PAI-1) is a member of the serine protease inhibitor family and is the primary inhibitor of fibrinolysis by inactivating tissue-type plasminogen activator. PAI-1 is expressed by adipocytes as well as stromal vascular cells in adipose depots (Fain et al. 2004). Plasma PAI-1 levels are elevated in obesity and insulin resistance and predict future risk for T2DM (Mertens and Van Gaal 2002; Juhan-Vague et al. 2003). Mice with targeted deletion in *PAI-1* have decreased weight gain on a high-fat diet, increased energy expenditure, improved glucose tolerance, and enhanced insulin sensitivity (Ma et al. 2004).

Interleukin-6 (IL-6) is a cytokine that is closely associated with obesity and insulin resistance (Fernandez-Real and Ricart 2003). Adipose tissue IL-6 expression accounts for ~30% of systemic IL-6, and circulating IL-6 concentrations are positively correlated with obesity, impaired glucose tolerance, and insulin resistance (Bastard et al. 2002). Plasma IL-6 concentrations predict the development of T2DM (Vozarova et al. 2001), and peripheral administration of IL-6 induces hyperlipidemia, hyperglycemia, and insulin resistance in rodents and humans (Stith and Luo 1994; Tsigos et al. 1997; Petersen et al. 2005). IL-6 impairs insulin signaling in part by downregulation of IRS and up-regulation of SOCS-3 (Rieusset et al. 2004). Assessing a role for IL-6 in murine models has been problematic because *IL-6* knockout mice are paradoxically insulin resistant (Wallenius et al. 2002).

Tumor necrosis factor α (TNFα) is a cytokine initially described as an endotoxin-induced factor (Carswell et al. 1975). TNFα was the first cytokine to be implicated in the pathogenesis of obesity and insulin resistance (Hotamisligil et al. 1993). Adipose tissue expression of TNFα is increased in obese rodents and humans and positively correlated with adiposity and insulin resistance (Hotamisligil et al. 1993; Fernandez-Real and Ricart 2003; Hotamisligil 2003; Ruan and Lodish 2003). Recent studies suggest that macrophages are the major source of TNFα in adipose tissue (Weisberg et al. 2003). Chronic

exposure to TNFα induces insulin resistance both in vitro and in vivo (Ryden et al. 2002; Ruan and Lodish 2003). Treatment with neutralizing soluble TNFα receptors improves insulin sensitivity in rodent obesity (Hotamisligil et al. 1993; Cheung et al. 1998). Targeted gene deletion of *TNFα* or its receptors significantly improves insulin sensitivity and circulating FAs in rodent obesity (Uysal et al. 1997). Several potential mechanisms for TNFα's metabolic effects have been described, including the activation of serine kinases such as JNK and p38 mitogen-activated protein kinase (MAPK) that increase serine phosphorylation of IRS-1 and IRS-2, making them poor substrates for insulin receptor-activating kinases and increasing their degradation (Hotamisligil et al. 1996; Stephens et al. 1997). In humans, circulating TNFα levels are increased in obese nondiabetic and T2DM individuals, but the correlation between insulin resistance and plasma TNFα levels is relatively weak (Hotamisligil et al. 1995; Nilsson et al. 1998; Zinman et al. 1999; Miyazaki et al. 2003).

The most recent adipokine to emerge as a contributor to obesity-induced insulin resistance is retinol-binding protein 4 (RBP4). RBP4 was identified as an adipokine whose expression is increased in the adipose tissue of mice rendered insulin resistant by adipose-specific inactivation of the glucose transporter GLUT4 (Yang et al. 2005). RBP4 is highly expressed in liver as well as adipose tissue, and its circulating levels have been shown to correlate with obesity and insulin resistance in rodents (Yang et al. 2005). In humans, RBP4 levels have been shown to be elevated in several groups of insulin-resistant subjects (Graham et al. 2006; Gavi et al. 2007), but not all studies have shown such differences (Janke et al. 2006; Takashima et al. 2006). It has been suggested that increased serum RBP4 levels might contribute to insulin resistance by impairing insulin-stimulated glucose uptake in muscles and elevating hepatic glucose production, although the mechanism is not fully clear (Yang et al. 2005).

Other adipocyte factors

Cortisol is another endocrine factor produced by adipose tissue. Elevated glucocorticoid levels cause insulin resistance and T2DM (Seckl et al. 2004), primarily by opposing the anti-gluconeogenic effects of insulin in the liver. Circulating glucocorticoid levels are near normal in obesity (Hautanen et al. 1997). However, adipose tissue contains 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which converts the inactive metabolite, cortisone, to cortisol. Transgenic overexpression of *11β-HSD1* selectively in mouse adipose tissue produces a syndrome of visceral obesity, insulin resistance, and diabetes (Masuzaki et al. 2001), suggesting that increases in endogenous 11β-HSD1 that have been observed in adipose tissue of obese humans and rodents (Livingstone et al. 2000; Rask et al. 2001; Paulmyer-Lacroix et al. 2002) contribute to obesity-associated insulin resistance, in part due to increased delivery of glucocorticoids to the liver via the portal vein. Indeed, liver-specific antago-

nism of glucocorticoid action reduces hepatic glucose output and improves glucose control in animal models of obesity-associated insulin resistance (Jacobson et al. 2005).

In addition to states of glucocorticoid excess, visceral adiposity is characteristic of people with an "apple-shaped" fat distribution, who appear to have a greater risk of developing insulin resistance than individuals with more peripheral "pear-shaped" fat distribution (Kabir et al. 2005). The "portal theory" suggests that insulin resistance in the liver arises from visceral fat drainage directly into the liver via the portal vein (Bergman et al. 2007). The increased delivery of FA and cortisol, as well as adipokines (Bujalska et al. 1997; Fontana et al. 2007), could promote hepatic insulin resistance by the mechanisms discussed earlier. Other molecular differences between visceral and peripheral fat may also contribute to insulin resistance associated with visceral adiposity (Gesta et al. 2006; Fontana et al. 2007).

Inflammatory mechanisms

Systemic chronic inflammation has been proposed to have an important role in the pathogenesis of obesity-related insulin resistance (Hotamisligil et al. 1995; Weisberg et al. 2003; Xu et al. 2003; Wellen and Hotamisligil 2005). Unequivocal experimental, epidemiological, and clinical evidence produced during the past decade causally links inflammation to the development of insulin resistance and T2DM (Dandona et al. 2004; Shoelson et al. 2006). It has been shown that biomarkers of inflammation, such as TNFα, IL-6, and C-reactive protein (CRP), are present at increased concentrations in individuals who are insulin resistant and obese, and these biomarkers predict the development of T2DM. Activation of inflammatory pathways in hepatocytes is sufficient to cause both local (Arkan et al. 2005) as well as systemic insulin resistance (Cai et al. 2005). Furthermore, obesity is characterized by macrophage accumulation in white adipose tissue, which has added another dimension to our understanding of the development of adipose tissue inflammation in obesity (Weisberg et al. 2003; Xu et al. 2003). Adipose tissue macrophages (ATMs) are likely to contribute to the production of several of the adipokines discussed earlier. A causative role of ATMs in obesity-associated insulin resistance has been recently supported by studies showing that inhibition of macrophage recruitment in obesity ameliorates the insulin resistance seen in animal models (Fig. 1C; Kanda et al. 2006; Weisberg et al. 2006; Lumeng et al. 2007).

Several signaling pathways link the endocrine and inflammatory mechanisms of insulin resistance (Fig. 1D). An important kinase likely to mediate the cross-talk between inflammatory and metabolic signaling is JUN N-terminal kinase1 (JNK1), a serine/threonine protein kinase that is activated by many inflammatory stimuli including TNFα (Hirosumi et al. 2002). In both genetic and dietary animal models of obesity, JNK1 activity is increased in the liver, muscle, and adipose tissue, and loss of *JNK1* prevents insulin resistance (Hirosumi et al. 2002). Modulation of hepatic JNK1 in adult animals also

produces systemic effects on glucose metabolism, which underscores the importance of this pathway in the liver (Nakatani et al. 2004). Activation of JNK1 leads to serine phosphorylation of IRS-1 that impairs insulin action (Aguirre et al. 2000; Gao et al. 2004). In addition, IKKβ is a mediator of TNF-induced insulin resistance (Yuan et al. 2001). Activation of NF-κB caused by continuous low-level expression of *IKKβ* in hepatocytes from a transgenic mouse model leads to moderate systemic insulin resistance (Cai et al. 2005). Moreover, inhibition of IKKβ in human diabetics by high-dose aspirin treatment also improves insulin signaling (Yin et al. 1998; Hundal et al. 2002). IKKβ can impact insulin signaling both by directly phosphorylating IRS-1 on the inhibitory serine residues (Yin et al. 1998; Gao et al. 2002) and by phosphorylating inhibitor of NF-κB (IκB), thus activating NF-κB, a transcription factor that, among other targets, stimulates production of multiple inflammatory mediators including TNFα and IL-6 (Shoelson et al. 2003). This might trigger a vicious loop of heightened inflammatory responses that feed into the negative regulation of insulin signaling discussed earlier (Fig. 1E).

Another class of inflammatory mediators contributing to obesity-induced insulin resistance are SOCS proteins, which constitute a negative feedback pathway in cytokine signaling (Fig. 1F). At least three members of the SOCS family (SOCS-1, SOCS-3, and SOCS-6) have been implicated in cytokine-mediated inhibition of insulin signaling (Emanuelli et al. 2001; Mooney et al. 2001; Rui et al. 2002), either by interfering with IRS-1 and IRS-2 tyrosine phosphorylation or by targeting IRS-1 and IRS-2 for proteosomal degradation (Rui et al. 2002; Ueki et al. 2004a). Interestingly, recent studies reported increases in SOCS-3 in obese rodents, and reduction in *SOCS-3* expression results in resistance to high-fat-diet-induced obesity and insulin resistance (Howard et al. 2004; Shi et al. 2004; Ueki et al. 2004a). In contrast, overexpression of *SOCS-1* and *SOCS-3* in the liver causes systemic insulin resistance (Ueki et al. 2004b).

Finally, recent studies have provided more clues to the interrelationship between obesity, inflammation, stress, and insulin resistance (Matsuzawa et al. 2005; Shi et al. 2006; Suganami et al. 2007). Shi et al. (2006) showed that Toll-Like Receptor 4 (TLR4), which plays a critical role in innate immunity, is activated by FAs and that mice lacking *TLR4* are substantially protected from the ability of systemic lipid infusion to induce insulin resistance (Fig. 1G). Moreover, Matsuzawa et al. (2005) showed that ASK1, a member of the MAPK kinase–kinase (MAP3K) family, specifically mediates a branch of TLR4 signaling through a reactive oxygen species (ROS)-dependent pathway. Given the ability of ASK1 to activate the JNK pathway (Tobiume et al. 2001), this finding may provide an additional link between innate immunity, cellular stress, and insulin resistance.

Neural mechanisms

A key role for the brain in glucose homeostasis was suggested more than a century ago (Bernard 1854). Recent

evidence now indicates that the brain processes information from adiposity signals such as insulin and leptin, which circulate in proportion to body fat mass, and integrates this input with signals from nutrients such as FAs (Burcelin et al. 1999; Niswender et al. 2001; Obici et al. 2003; Seeley and Woods 2003; Pocai et al. 2006). In response, the brain sends signals to control feeding behavior and substrate metabolism in ways that promote homeostasis of both energy stores and fuel metabolism (Fig. 1H).

Both leptin and insulin play a role in the central control of peripheral glucose metabolism. The insulin resistance of lipodystrophic and leptin-deficient mice is ameliorated by central leptin administration at doses that are much lower than the systemic doses needed to achieve the same phenotype (Ebihara et al. 2001; Asilmaz et al. 2004; Pocai et al. 2005a). Moreover, inhibition of hypothalamic insulin receptor function results in hepatic insulin resistance and impaired inhibition of hepatic glucose output (Obici et al. 2002a,c). Peripheral and brain insulin receptors are both required for normal insulin action (Okamoto et al. 2004), although central administration of insulin alters glucose homeostasis in mice with reduced hepatic insulin receptors (Buettner et al. 2005). Intriguingly, leptin and insulin both induce the expression of SOCS-3, and sensitivity to both insulin and leptin is augmented in mice with reduced neuronal expression of *SOCS-3* (Mori et al. 2004).

Obesity-associated nutrients such as FAs also have central effects on insulin action. Central infusion of oleic acid potently increases hepatic insulin sensitivity in rats (Obici et al. 2002b), and similar effects were noted after central infusion of an inhibitor of carnitine palmitoyltransferase-1 (CPT-1) (Obici et al. 2003), which increases hypothalamic fatty acyl-CoA by reducing FA oxidation. Central CPT-1 inhibition activates neurons in brain stem areas that control parasympathetic outflow and increased hepatic insulin sensitivity through a mechanism that involves activation of vagal efferent fibers that supply the liver (Pocai et al. 2005b).

The CNS is also critical to circadian rhythms, and mice lacking a key component of the molecular circadian clock in the hypothalamus (*Clock* mutants) develop a metabolic syndrome of hyperlipidemia, hepatic steatosis, and hyperglycemia (Turek et al. 2005). Misalignment of food intake with the expression levels of neuroactive peptides, such as leptin, could create metabolic imbalances that alter insulin sensitivity. This is supported by a recent human study that reported that workers with alternating shift work had a higher risk for developing diabetes compared with their day shift counterparts (Suwazono et al. 2006).

Cell-intrinsic mechanisms

Ectopic fat storage

Chronically, the increased circulating FAs and other lipids that occur in obesity lead to ectopic fat storage as triglycerides in muscle and liver (Fig. 2A). Ectopic lipid accumulation has been implicated in insulin resistance (Unger and Orci 2000; McGarry 2002), potentially due to triglyceride turnover and production of the FA-derived signaling molecules noted above, or to activation of deleterious intracellular pathways such as ROS, mitochondrial dysfunction, or endoplasmic reticulum (ER) stress as discussed below.

Oxidative stress

Systemic oxidative stress, defined as a persistent imbalance between the production of highly reactive molecular species (chiefly oxygen and nitrogen) and antioxidant defenses, correlates with fat accumulation in humans and mice (Fig. 2B; Halliwell 1995; Rosen et al. 2001; Evans et al. 2002). The hypothesis that oxidative stress is a causative factor in the development of insulin resistance has been supported by several studies that showed that reversal of the imbalance between ROS and antioxidants improves insulin resistance in mice and humans (Khamaisi et al. 1997; Jacob et al. 1999; Konrad et al. 1999; Maddux et al. 2001; Haber et al. 2003; Furukawa et al. 2004; Fridlyand and Philipson 2006; Houstis et al. 2006). Many of the human studies on the link between oxidative stress and insulin resistance focus on the generation of ROS by hyperglycemia in diabetic patients, implicating ROS as a consequence of diabetes-induced hyperglycemia and not a causative factor for insulin resistance (Evans et al. 2002, 2003). However, since insulin resistance is evident before the development of chronic (fasting) hyperglycemia, it is unlikely that insulin resistance at the prediabetic stage results from oxidative stress triggered by hyperglycemia per se (Reaven and Chen 1996; DeFronzo 2004). The increase in ROS in the prediabetic stage is more likely due to obesity-related elevations of FAs that cause oxidative stress due to increased mitochondrial uncoupling and β oxidation, leading to the increased production of ROS (Wojtczak and Schonfeld 1993; Carlsson et al. 1999; Rao and Reddy 2001; Yamagishi et al. 2001). In healthy subjects, infusion of FAs causes increased oxidative stress and insulin resistance that is reversed by infusion with antioxidants such as glutathione (Paolisso et al. 1992, 1996; Paolisso and Giugliano 1996).

Several recent studies have addressed the molecular mechanisms by which oxidative stress might lead to insulin resistance. In vitro, ROS and oxidative stress lead to the activation of multiple serine/threonine kinase signaling cascades (Kyriakis and Avruch 1996; Evans et al. 2003). These activated kinases can act on a number of potential targets in the insulin signaling pathway, including the insulin receptor and the family of IRS proteins. For IRS-1 and IRS-2, an increase in serine phosphorylation decreases the extent of the activating tyrosine phosphorylation (Birnbaum 2001; Evans et al. 2003). The kinases that have been shown to be activated by oxidative stress include JNK, p38 MAPK, and IKKβ (Blair et al. 1999; Aguirre et al. 2000; Maddux et al. 2001; Yuan et al. 2001; Hirosumi et al. 2002).
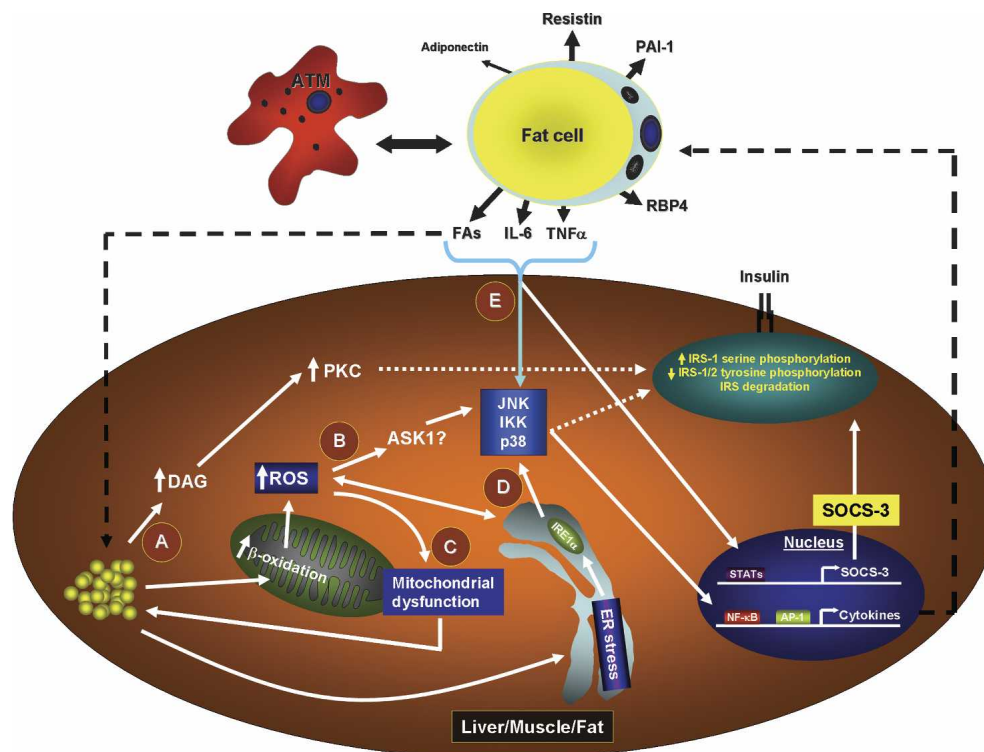
Figure 2. Obesity-associated intrinsic mediators of insulin resistance. Obesity leads to the dysregulation of several cell-intrinsic pathways that have a negative impact on insulin signaling. (*A*) Obesity leads to ectopic fat storage and an increase in FA metabolites that inhibit insulin signaling through activation of PKC in liver and muscle. (*B*) Excess accumulation of lipids can trigger an increase in ROS generated by mitochondrial β oxidation. Excess in ROS leads to activation of several serine/threoning kinases (JNK, IKK, and p38 MAPK) that inhibit insulin signaling either directly through IRS-1 or IRS-2 serine phosphorylation or indirectly through a series of transcriptional events mediated by NF-κB. (*C*) Obesity is linked to mitochondrial dysfunction, which further exacerbates insulin resistance by increasing intracellular lipid accumulation. (*D*) Obesity leads to the activation of cellular ER stress responses that suppress insulin signaling through the activation of JNK or through a potential increase in ROS production. (*E*) Cell-intrinsic mechanisms of obesity-associated insulin resistance can be intensified by cell-extrinsic modulators such as endocrine and inflammatory signals.

Mitochondrial dysfunction

Insulin resistance and T2DM are associated with a decrease in mitochondrial function that contributes to the ectopic fat accumulation in muscle and fat (Petersen and Shulman 2006). Petersen et al. (2003) found that severe insulin resistance is associated with significantly higher levels of triglycerides in both muscle and liver in the elderly. These changes were accompanied by decreases in both mitochondrial oxidative activity and mitochondrial ATP synthesis, both indicative of a decrease in mitochondrial function. Other studies have revealed similar decreases in mitochondrial activity and increases in intramyocellular fat content in young insulin-resistant offspring of parents with T2DM, a group that has a strong tendency to develop diabetes later in life (Petersen et al. 2004). It was suggested that the insulin-resistant subjects accumulate more intramyocellular fat due to a decrease in the number of muscle mitochondria caused by a decrease in the expression of nuclear-encoded genes that regulate mitochondrial biogenesis, such as PPARγ coactivator 1 α (*PGC-1α*) (Wu et al. 1999) and *PGC-1β* (St-Pierre et al. 2003). This idea is supported by microar-

ray studies that show that PGC-1-responsive genes are down-regulated in obese Caucasians with impaired glucose tolerance and T2DM (Mootha et al. 2003), and *PGC-1α* and *PGC-1β* are themselves down-regulated in obese diabetic and overweight nondiabetic Mexican-Americans (Patti et al. 2003). Finally, activation or induction of PGC-1α has recently been shown to be associated with improved mitochondrial function as well as increased insulin sensitivity in both animals and humans (Lagouge et al. 2006; Mensink et al. 2007). These data support the idea that insulin resistance in humans might arise from defects in mitochondrial function, which in turn lead to increases in intracellular FA metabolites (fatty acyl-CoA and diacylglyerol) that disrupt insulin signaling in the muscle as well as the liver as discussed in the previous section.

The decrease in mitochondrial function associated with obesity and insulin resistance might seem paradoxical given that it is known that functional mitochondria are needed for an FA-induced increase in ROS (Evans et al. 2002). It is possible that an increase in ROS due to FA oxidation occurs early during the development of insulin resistance and prior to mitochondrial dysfunction.

At a later stage, ROS might lead to a decrease in mitochondrial function that then leads to the accumulation of fat in the muscle and liver, exacerbating the insulin resistance phenotype via the mechanisms mentioned above (Fig. 2C).

ER stress

Another intracellular pathway implicated in insulin resistance is the ER stress response (Fig. 2D; Ozcan et al. 2004, 2006; Nakatani et al. 2005; Ozawa et al. 2005). In a seminal study, Ozcan et al. (2004) showed that obesity imposes a strain on the ER machinery, thereby triggering an ER stress response that activates JNK and impairs the insulin signaling pathway. Supporting a causal link between peripheral ER stress and insulin resistance, more recent studies have demonstrated protection against obesity-induced T2DM in mice by overexpression of ER chaperones, while knockdown of chaperones was diabetogenic (Nakatani et al. 2005; Ozawa et al. 2005). Furthermore, animal treatment with chemical chaperones that alleviated obesity-induced ER stress led to improvement in insulin sensitivity (Ozcan et al. 2006). The mechanism by which obesity leads to ER stress is not clear. One possibility is that ectopic lipid storage might trigger ER stress by sheer mechanical stress or perturbations in intracellular nutrient and energy fluxes, and severe changes in tissue architecture (Ozcan et al. 2004). Also, chronic elevation of FAs has been shown to induce ER stress (Karaskov et al. 2006). Finally, it is also possible that ER stress might lead to an increase in oxidative stress that in turn might contribute to the insulin resistance seen in the above studies (Haynes et al. 2004).

Lessons learned from anti-diabetic drugs

Thiazolidinediones (TZDs) represent a novel class of anti-diabetic agents that enhance hepatic and muscle insulin sensitivity in both humans and animals with obesity-associated T2DM (Rangwala and Lazar 2004; Yki-Jarvinen 2004). TZD action is primarily attributable to binding and activating PPARγ, a nuclear receptor that is expressed at high levels in adipose tissue (Chawla et al. 1994; Tontonoz et al. 1994) and functions as the master regulator of adipocyte differentiation and metabolism (Lehmann et al. 1995; Spiegelman 1998; Lehrke and Lazar 2005). Many of the beneficial actions of TZDs can be explained by the repartitioning of FAs to adipose tissue and away from the muscles, liver, and circulation (Lehrke and Lazar 2005). TZDs also reduce the expression of adipokines that contribute to insulin resistance, while increasing the circulating levels of adiponectin (Sharma and Staels 2007). In addition, TZDs have anti-inflammatory effects including transrepression of TNFα production by macrophages and decreased macrophage infiltration of adipose tissue (Xu et al. 2003; Di Gregorio et al. 2005; Pascual et al. 2005). Thus, the anti-diabetic effects of TZDs are due to the simultaneous reversal of many of the abnormalities that contribute to obesity-associated insulin resistance.

Concluding remarks: too many choices on the menu or a poster child for systems biology?

Obesity-associated insulin resistance is a complex disorder. Molecular biology research has made tremendous strides in discovering and delineating many more contributors to insulin resistance than were anticipated even a decade ago. Indeed, given the explosion of candidate molecules, systems, and pathways that have been shown to have the potential to cause insulin resistance, the view that one factor is primarily responsible for the link between obesity and insulin resistance is clearly simplistic. Multiple endocrine, inflammatory, and neural pathways are simultaneously disturbed and can further modulate signaling pathways that are cell-intrinsic (Fig. 2E) and functional in various metabolic tissues including fat, liver, and muscle, in addition to the immune and nervous systems. When one pathway is disturbed, its interconnections with the others lead to changes in other systems that exacerbate the problem. Furthermore, many of these pathways and mediators are involved in other serious diseases including tumors and autoimmune disorders. The present and future challenge is to determine which element(s) that are disturbed in the insulin-resistant milieu could be corrected with favorable metabolic outcomes without causing or exacerbating other diseases. This will require a detailed understanding of each system and how they are interconnected in humans.

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