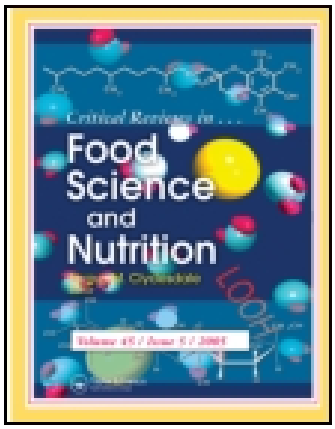

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Meta-Review of Protein Network Regulating Obesity Between Validated Obesity Candidate Genes in the White Adipose Tissue of High-Fat Diet-Induced Obese C57BL/6J Mice

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Mini Review Paper

Meta-Review of Protein Network Regulating Obesity Between Validated Obesity Candidate Genes in the White Adipose Tissue of High-Fat Diet-Induced Obese C57BL/6J Mice

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Worldwide obesity and related comorbidities are increasing, but identifying new therapeutic targets remains a challenge. A plethora of microarray studies in diet-induced obesity models has provided large datasets of obesity associated genes. In this review, we describe an approach to examine the underlying molecular network regulating obesity, and we discuss interactions between obesity candidate genes. We conducted network analysis on functional protein–protein interactions associated with 25 obesity candidate genes identified in a literature-driven approach based on published microarray studies of diet-induced obesity. The obesity candidate genes were closely associated with lipid metabolism and inflammation. Peroxisome proliferator activated receptor gamma (Pparg) appeared to be a core obesity gene, and obesity candidate genes were highly interconnected, suggesting a coordinately regulated molecular network in adipose tissue. In conclusion, the current network analysis approach may help elucidate the underlying molecular network regulating obesity and identify anti-obesity targets for therapeutic intervention.

Keywords Obesity, nutrigenomics, high-fat, C57BL/6J mouse, adipose tissue

INTRODUCTION

Obesity is a global health problem characterized by excess body fat, and is associated with many chronic diseases including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and certain types of cancer (Friedman, 2003; Adan et al., 2008; Bessesen, 2008; Hill et al., 2008). Despite recent advances in obesity research, the mechanisms underlying the pathogenesis of obesity are not fully understood. Obesity can develop due to a chronic imbalance between energy intake and energy expenditure, leading to greater energy storage and increased adipose tissue mass (Spiegelman and Flier, 2001).

Adipose tissue was for many decades regarded as a passive lipid and energy storage depot releasing fatty acids (FAs) and glycerol to be used as an energy source in other oxidative tissues in times of fasting or starvation (Flier, 2004). In the fed state adipose tissue primarily absorbs circulating FAs and triglycerides (TGs) (Frayn, 2002; Sharma and Staels, 2007), hence protecting other tissues from excessive FA flux (Frayn et al., 2005). More recently, it has been established that adipose tissue is a much

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more dynamic endocrine organ, capable of producing a wide range of hormones and cytokines, called adipokines (Kershaw and Flier, 2004; Hauner, 2005). So far, more than 100 adipokines have been identified and these molecules can affect inflammatory processes, endocrine and metabolic processes, and cardiovascular disease development. Hence, adipose tissue appears to play an integral part in both energy homeostasis and inflammation (Rajala and Scherer, 2003; Guerre-Millo, 2004; Trayhurn and Wood, 2004).

Recent development of microarray technology has now made it possible to analyze integrated system changes in the transcriptome underlying the development of obesity (Kim and Park, 2008; Lopez et al., 2003). However, despite the enormous amount of gene expression data available from obese animal models and obese humans, the disparity between microarray studies has impeded the coordinated interpretation of the changes in the transcriptome underlying obesity.

We, therefore, extensively mined published microarray datasets of gene expression changes in white adipose tissue (WAT) of high-fat diet (HFD) induced obese C57BL/6J mice. We selected 25 obesity candidate genes from these microarray studies, which have been independently validated. In the following, we provide a systemic overview of functional protein–protein interactions of these obesity candidate genes to better understand the pathophysiological changes contributing to the development of the obese phenotype.

Identification of Obesity Candidate Genes in White Adipose Tissue

Firstly, we identified adipose tissue microarray studies of high-fat diet fed C57BL/6J mice in the PubMed database. From these microarray studies, we extracted genes which were reported as differentially expressed following HFD feeding. From this gene list, we then searched for independent evidence that these genes are differentially expressed in obesity based on other analytical methods such as reverse transcription-polymerase chain reaction or northern blot analysis.

Twenty-five genes were selected and their specific cellular functions are summarized in Table 1. Of 25 genes, 6 genes were associated with lipid metabolism, 3 genes were associated with inflammation, and 7 genes were associated with signal transduction and transport. Overall, the expression of genes involved in FA synthesis [*acetyl CoA carboxylase* (*Acaca*), *fatty acid synthase* (*Fasn*), *stearoyl coenzyme A desaturase 1* (*Scd1*), and *stearoyl coenzyme A desaturase 2* (*Scd2*)] and lipid uptake [*lipoprotein lipase* (*Lpl*)] were significantly increased in the adipose tissue of HFD fed mice. The expression of *3-hydroxy-3-methylglutaryl CoA synthase 1* (*Hmgcs1*) involved in steroid synthesis was downregulated probably because high sterol intake inhibits *Hmgcs1* expression by negative feedback inhibition.

On the other hand, genes involved in immune and inflammation [*interleukin 6* (*Il6*), *chemokine (C-C motif) ligand 2* (*Ccl2*, *MCP-1*), and *tumor necrosis factor alpha* (*Tnfa*)] were all upregulated. In addition, the expression of signal transduction and transporter-associated genes [*fatty acid binding protein 4* (*Fabp4*), *complement factor D* (*Cfd*), *leptin* (*Lep*), *and perxisome proliferator activated receptor* γ (*Pparg*)] were upregulated; however, *adiponectin* (*Adipoq*) expression was downregulated.

HFD feeding also affects the expression of glucose metabolism-associated genes. For example, increased expression of *glucose-6-phosphate dehydrogenase 2* (*G6pd2*) in adipose tissue appears to be related with insulin resistance, while decreased expression of *glucose transporter 4* (*Slc2a4*) and *sterol regulatory element binding transcription factor 1* (*Srebf1*) suggests some impairment of the insulin signaling pathway in HFD fed mice. Downregulated *glycerol-3-phosphate dehydrogenase 1* (*Gpd1*) suggests energy production by glycolysis and gluconeogenesis is decreased by HFD feeding.

Furthermore, the expression of genes associated with xenobiotic metabolism, involved in the detoxification of oxidative stress [*catalase (Cat)*] was inhibited by HFD. Other obesity candidate genes identified in adipose tissue of HFD fed mice included *cathepsin D* (*Ctsd*), *CCAAT/enhancer binding protein* α (*Cebpa*), *plasminogen activator inhibitor 1* (*Serpine 1*, *PAI-1*), *uncoupling protein 1* (*Ucp1*), and *uncoupling protein 2* (*Ucp2*) which were all upregulated, whereas *superoxide dismutase 1* (*Sod1*) was downregulated.

Analysis of Functional Protein Interactions Between Obesity Candidate Genes

Next, we used a network approach based on protein–protein interactions to determine functional connections between obesity candidate genes. Protein–protein interactions were extracted from the STRING database and a network was built using the active prediction method (confidence score above 0.8, network depth 2). We found 8 of 25 obesity genes were closely connected to each other in one-depth condition in which a protein is directly connected with another protein (pink block; Fig. 1). Furthermore, all nonconnected genes in the one-depth condition (17 genes) were found to be related when the analysis was extended to the two-depth condition. The network analysis suggested a high number of interactions are predicted to occur between the identified obesity candidate genes.

Pparg is a Core Gene in the Functional Protein Interactions of Obesity Candidate Genes

Pparg emerged as a central node among the selected obesity candidate genes in adipose tissue. *Pparg* belongs to the ligand-activated nuclear hormone receptor family and acts as a transcription factor in heterodimer formation with retinoid X receptor to modulate gene expression involved in adipocyte differentiation, FA uptake and storage (Ferre, 2004; Anghel and

Table 1 Lipid metabolism-associated genes differentially expressed in adipose tissue of HF-induced obese C57BL/6J mice

Gene name	Expression	Gene ontology (process)	References
Acetyl CoA carboxylase (Acaca)	↑	Acetyl-CoA metabolic process Fatty acid biosynthetic process Lipid homeostasis Lipid metabolic process Response to organic cyclic substance tissue homeostasis	(Al-Hasani and Joost, 2005; Srivastava et al., 2006; Kim and Kim, 2009)
Fatty acid synthase (Fasn)	↑	Fatty acid biosynthetic process Metabolic process Oxidation reduction	(Soukas et al., 2000; Harada et al., 2003; Al-Hasani and Joost, 2005; Srivastava et al., 2006; Mong et al., 2011)
3-hydroxy-3-methylglutaryl CoA synthase 1 (Hmgcs1)	↓	Cholesterol biosynthetic process Isoprenoid biosynthetic process Lipid biosynthetic process Metabolic process Response to organic nitrogen Steroid biosynthetic process Sterol biosynthetic process	(Soukas et al., 2000; Harada et al., 2003; Mong et al., 2011)
Lipoprotein lipase (Lpl)	↑	Lipid metabolic process Positive regulation of macrophage derived foam cell differentiation Triglyceride biosynthetic process Triglyceride catabolic process	(Harada et al., 2003; Al-Hasani and Joost, 2005; Srivastava et al., 2006)
Stearoyl coenzyme A desaturase 1 (Scd1)	↑	Brown fat cell differentiation Cholesterol esterification Fatty acid biosynthetic process Lipid metabolic process Oxidation reduction White fat cell differentiation	(Soukas et al., 2000; Soukas et al., 2001; Al-Hasani and Joost, 2005; Flachs et al., 2005; Nikonova et al., 2008)
Stearoyl coenzyme A desaturase 2 (Scd2)	↑	Fatty acid biosynthetic process Lipid metabolic process Oxidation reduction	(Soukas et al., 2000; Soukas et al., 2001)
Interleukin 6 (Il6)	↑	Glucagon secretion Immune response Interleukin-6-mediated signaling pathway Regulation of apoptosis Regulation of cell proliferation Regulation of cell shape	(Weisberg et al., 2003; Chen et al., 2005; Cole et al., 2010; Li et al., 2010; Kang et al., 2010; Orellana-Gavalda et al., 2011)
chemokine (C-C motif) ligand 2 (Ccl2, MCP-1)	↑	Chemokine-mediated signaling pathway Chemotaxis Cytokine-mediated signaling pathway Immune response Inflammatory response	(Chen et al., 2005; Kanda et al., 2006; Fukushima et al., 2009; Cole et al., 2010; Kang et al., 2010; Orellana-Gavalda et al., 2011)
Tumor necrosis factor alpha (Tnfa)	↑	Apoptosis Defense response Humoral immune response Immune response Inflammatory response	(Weisberg et al., 2003; Harada et al., 2003; Chen et al., 2005; Kim et al., 2008; Hagiwara et al., 2009; Cole et al., 2010; Li et al., 2010; Kang et al., 2010; Orellana-Gavalda et al., 2011)
Fatty acid binding protein 4 (Fabp4)	↑	Brown fat cell differentiation Cholesterol homeostasis Cytokine production Fatty acid metabolic process Transport White fat cell differentiation	(Harada et al., 2003; Al-Hasani and Joost, 2005; Soukas et al., 2000; Kim et al., 2008; Kim and Park, 2010)
Adiponectin (Adipoq)	↓	Adiponectin-mediated signaling pathway Brown fat cell differentiation Fatty acid beta-oxidation Fatty acid oxidation Glucose homeostasis	(Barnea et al., 2006; Hosogai et al., 2007; Hagiwara et al., 2009; Soukas et al., 2000; Soukas et al., 2001; Cole et al., 2010; Kang et al., 2010)
Complement factor D (Cfd)	↑	Notch signaling pathway Complement activation, alternative pathway Innate immune response Proteolysis	(Soukas et al., 2000; Soukas et al., 2001; Harada et al., 2003; Al-Hasani and Joost, 2005; Flachs et al., 2005; Chen et al., 2005)

(Continued on next page)

Table 1 Lipid metabolism-associated genes differentially expressed in adipose tissue of HF-induced obese C57BL/6J mice *(Continued)*

Gene name	Expression	Gene ontology (process)	References
Glucose transporter 4 (Slc2a4)	↓	Brown fat cell differentiation Carbohydrate transport Glucose homeostasis Glucose transport Hexose transmembrane transport Ion transmembrane transport Proton transport Transmembrane transport	(Moraes et al., 2003; Al-Hasani and Joost, 2005; Kang et al., 2010)
Leptin (Lep)	↑	Bile acid metabolic process Central nervous system neuron development Cholesterol metabolic process Eating behavior Glucose metabolic process Hormone metabolic process Insulin secretion Lipid metabolic process	(Harada et al., 2003; Van Schothorst et al., 2005; Marrades et al., 2006; Hosogai et al., 2007; Fukushima et al., 2009; Hagiwara et al., 2009; An et al., 2010)
Peroxisome proliferator-activated receptor γ (Pparg)	↑	Cell fate commitment Fat cell differentiation Fatty acid oxidation Inflammatory response Long-chain fatty acid transport Response to lipid Signal transduction Transcription White fat cell differentiation	(Soukas et al., 2000; Morton et al., 2004; Hosogai et al., 2007; Kim et al., 2008; Kim and Kim, 2009; Kim and Park, 2010)
Sterol regulatory element-binding transcription factor 1 (Srebf1)	↓	Cellular response to starvation Cholesterol metabolic process Insulin receptor signaling pathway Lipid metabolic process Regulation of fatty acid metabolic process Regulation of heart rate by chemical signal Regulation of insulin secretion Regulation of transcription Response to glucose stimulus Steroid metabolic process Transcription	(Nadler et al., 2000; Soukas et al., 2000; Al-Hasani and Joost, 2005; Srivastava et al., 2006; Kim et al., 2008)
Glucose-6-phosphate dehydrogenase 2 (G6pd2)	↑	Carbohydrate metabolic process Glucose metabolic process Metabolic process Oxidation reduction	(Soukas et al., 2000; Soukas et al., 2001; Orellana-Gavalda et al., 2011)
Glycerol-3-phosphate dehydrogenase 1 (Gpd1)	↓	NADH metabolic process NADH oxidation Carbohydrate metabolic process Gluconeogenesis Glycerol-3-phosphate catabolic process Glycerolipid metabolic process	(Harada et al., 2003; Kim and Kim, 2009; Balwierz et al., 2009; Kalupahana et al., 2010)
Catalase (Cat)	↓	Aerobic respiration Cholesterol metabolic process Hydrogen peroxide catabolic process Response to oxidative stress Response to reactive oxygen species Triglyceride metabolic process	(Rong et al., 2007; Hagiwara et al., 2009; Coate and Huggins, 2010)
Cathepsin D (Ctsd)	↑	Autophagic vacuole assembly Proteolysis	(Nadler et al., 2000; Tanaka et al., 2003; Meugnier et al., 2007; Li et al., 2010)
CCAAT/enhancer binding protein α (Cebpa)	↑	Brown fat cell differentiation Cell maturation Cytokine-mediated signaling pathway Fat cell differentiation Regulation of cell proliferation Regulation of transcription Regulation of transcription, DNA-dependent	(Soukas et al., 2000; Harada et al., 2003; Kim et al., 2008)

(Continued on next page)

Table 1 Lipid metabolism-associated genes differentially expressed in adipose tissue of HF-induced obese C57BL/6J mice *(Continued)*

Gene name	Expression	Gene ontology (process)	References
		Transcription White fat cell differentiation	
Superoxide dismutase 1, soluble (Sod1)	↓	Activation of MAPK activity Anti-apoptosis Glutathione metabolic process Hydrogen peroxide biosynthetic process Response to oxidative stress Response to superoxide Superoxide anion generation Superoxide metabolic process	(Rong et al., 2007; Hagiwara et al., 2009; Hwang et al., 2009)
Plasminogen activator inhibitor 1 (Serpine 1, PAI-1)	↑	Negative regulation of Endopeptidase activity Positive regulation of coagulation Positive regulation of receptor-mediated endocytosis Regulation of angiogenesis Regulation of cell proliferation wound healing	(Moraes et al., 2003; Al-Hasani and Joost, 2005; Chen et al., 2005; Hosogai et al., 2007; Hagiwara et al., 2009)
Uncoupling protein 1 (mitochondrial, proton carrier) (Ucp1)	↑	Brown fat cell differentiation Mitochondrial transport Proton transport Transmembrane transport Transport	(Rong et al., 2007; Nikonova et al., 2008; Fukushima et al., 2009; Kim and Park, 2010)
Uncoupling protein 2 (mitochondrial, proton carrier) (Ucp2)	↑	mitochondrial transport response to superoxide transmembrane transport transport	(Harada et al., 2003; Morton et al., 2004; Fukushima et al., 2009; Orellana-Gavalda et al., 2011)

Wahli, 2007). There are two isoforms of *Pparg* which exist dependent on alternative promoter usage and splicing; *Pparg1* and *Pparg2*. *Pparg1* is ubiquitously found in WAT, brown adipose tissue (BAT), macrophages, liver, skeletal muscle, and other tissues (Chawla et al., 1994; Escher et al., 2001), whereas, *Pparg*2 is mainly expressed in WAT (Rahimian et al., 2001; Tontonoz et al., 1994). There have been many studies on the role of *Pparg* in adipose tissue. For example, treatment of Zucker rats with thiazolidinedione (TZD), which is a specific and synthetic ligand of *Pparg* is reported to lead to reduced visceral adipocyte size (Ferre, 2004). In addition, the use of TZD in T2DM patients is reported to lower plasma glucose concentrations via activation of *Pparg* (Boden et al., 2003; Gastaldelli et al., 2007). Specific deletion of the *Pparg* gene in adipocytes causes markedly reduced adipocytes number, elevated plasma TG, and FFA, while plasma leptin and adiponectin are decreased (He et al., 2003). However, complete depletion of adipose tissue, as in the case of fatless mice, causes a phenotype characterized by higher insulin resistance, glucose intolerance, hyperphagia, hyperlipidemia, and fatty liver (Gavrilova et al., 2003). Furthermore, *Pparg* knock-out mice display similar phenotypes to fatless mice (Jones et al., 2005). These findings suggest that *Pparg* plays an important role in adipocyte differentiation and adipogenesis, as well as maintaining metabolic homeostasis.

Cebpa, is a transcription factor which appears to act coordinately with *Pparg* during adipogenesis (Clarke et al., 1997; Freytag et al., 1994; Farmer, 2005). The differentiation of preadipocytes into mature adipocytes is highly dependent on the expression of *Pparg* and *Cebpa* (Rosen et al., 2000). When 3T3-L1 preadipocytes are treated with differentiation inducing agents a rapid induction of C/EBPβ and C/EBPδ occurs followed by increased expression of *Pparg* and *Cebpa* (Morrison and Farmer, 2000). Both *Pparg* and *Cebpa* are necessary for the differentiation of fibroblasts into adipocytes (Park et al., 2004). Past studies have established *Pparg* and *Cebpa* are responsible for coordinately directing the adipogenesis program governing adipose specific gene expression as well as the activation of other transcription factors (Wu et al., 1999).

Tcfap2a, also referred to as C/EBP undifferentiated protein has been identified as a *Cebpa* repressor (Jiang et al., 1998; Holt and Lane, 2001). In preadipocytes, *Cebpa* gene expression is repressed by *Tcfap2a* and repression is relieved during adipocyte differentiation by downregulation of *Tcfap2a* (Jiang et al., 1998). Furthermore, during differentiation of 3T3-L1 preadipocytes into mature adipocytes, the expression of *Cebpa* is increased and the kinetics of this process parallels the decline of *Tcfap2a* protein (Holt and Lane, 2001), indicating *Tcfap2a* is a suppressor of adipogenesis and fat cell development.

In addition to the adipocyte differentiation, *Pparg* plays a role in directing lipid storage in mature adipocytes (Rosen and Spiegelman, 2001; Way et al., 2001). *Pparg* promotes free fatty acid (FFAs) release from circulating lipoproteins and enhances FFA binding and uptake by regulating *Lpl* and *Fabp4* expression (Schoonjans et al., 1996; Ferre, 2004; Schachtrup et al., 2004). *Pparg* also promotes esterification of FFA to TG by regulating the expression of enzymes such as phosphoenol pyruvate carboxykinase (Olswang et al., 2002; Tontonoz et al., 1995), *Gpd1*, and diacylglycerol O acyltransferase (Anghel and Wahli, 2007).

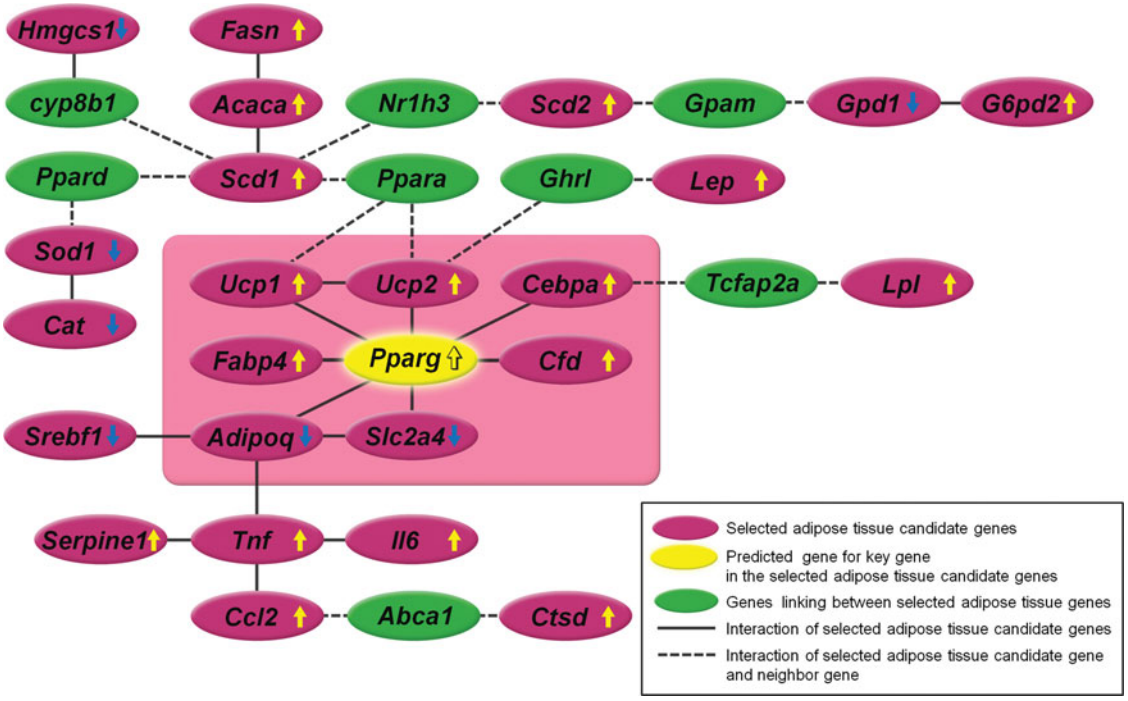

Figure 1 Functional protein–protein interaction between obesity candidate genes in the adipose tissue of high-fat diet induced obese C57BL/6J mice. Each circle represents one gene in the data set. There are 25 genes in this subcomponent of the protein interaction. Circles with solid lines denote proteins in the one-depth condition (pink box), where circles with dotted lines denote proteins in the two-depth condition. The circles colored pink, yellow, and green denote obesity candidate genes, core obesity candidate gene, and the genes linking between nondirected obesity candidate genes in the one-depth condition, respectively. Arrows indicate up- or downregulation of gene expression upon HFD consumption. Acaca, acetyl-coenzyme A carboxylase; Adipoq, adiponectin; Cat, catalase; Ctsd, cathepsin D; Cebpα, CCAAT/enhancer-binding protein alpha; Ccl2, chemokine (C-C motif) ligand 2; Cfd, complement factor D; Fabp4, fatty acid binding protein 4; Fasn, fatty acid synthase; G6pd2, glucose-6-phosphate dehydrogenase 2; Slc2a4, glucose transporter 4; Gpd1, glycerol-3-phosphate dehydrogenase 1; Hmgcs1, 3-hydroxy-3-methylglutaryl-coenzyme A synthase 1; Il6, interleukin 6; Lep, leptin; Lpl, lipoprotein lipase; Pparg, peroxisome proliferator-activated receptor gamma; PAI-1, plasminogen activator inhibitor type 1; Scd1, stearoyl coenzyme A desaturase 1; Srebf1, sterol regulatory element-binding transcription factor 1; Sod1, superoxide dismutase 1; Tnfa, tumor necrosis factor alpha; Ucp1, uncoupling protein 1; Ucp2, uncoupling protein 2. (Color figure available online.)

Natural ligands of *Pparg* include FAs such as oleic acid, linoleic acid, eicosapentaenoic acid, and arachidonic acid. Therefore, *Pparg* can act as a lipid sensor and modulate gene expression in response to changing FFA availability (Dreyer et al., 1992; Issemann and Green, 1990). Furthermore, *Pparg* also stimulates de novo FFA synthesis by regulating directly or indirectly the expression of *Fasn*, *Acaca*, and *Scd1* (Fig. 1). *Scd1* is expressed mainly in liver and adipose tissue, while adipose *Scd2* expression is strongly induced in HFD fed mice (Kaestner et al., 1989). Interestingly, loss of *Scd2* in mature adipocytes is reported to be associated with decreased *Pparg* protein level. In addition, *Scd2* depletion has been shown to decrease the metabolic labeling of *Pparg* protein but not the protein degradation rate, indicating that *Pparg* protein translation may be inhibited by *Scd2* (Christianson et al., 2008). It is clear from the obesity candidate gene network (Fig. 1) that *Pparg* regulates a sophisticated network of other transcription factors and their corepressors and coactivators such as *Tcfap2a*, *Ppara*, *Ppard*, and nuclear receptor subfamily 1 (*Nr1h3*). Therefore, *Pparg* is likely to have widespread effects on many more genes in adipose tissue, but these remain to be characterized.

Functional Protein Interactions of Adipokines in Obesity

Adipose tissue integrates hormonal signals from different body parts and responds to extracellular stimuli by secreting its own signaling molecules called adipokines, which effect the systemic regulation of energy homeostasis including lipid and glucose metabolism (Wajchenberg, 2000). Since adipose tissue is a mixture of adipocytes, macrophages, and stromal cells, a large proportion of adipokines are also released from cells other than adipocytes with the exception of adiponectin and leptin (Fain et al., 2004). Deregulation of adipokine secretion can lead to the development of metabolic syndrome, characterized by obesity and altered metabolism (Bergman et al., 2001; Grundy, 2004).

So far the most studied adipokine is a small 16 kDa polypeptide *Lep* (from the Greek *leptos*, meaning thin). It is produced mainly by adipocytes, and shows a strong positive correlation with the mass of adipose tissue. *Lep* directly binds to its receptors and inhibits appetite but the absence of *Lep* or its receptor leads into uncontrolled food intake and obesity (Halaas et al., 1995). However, this does not apply to all the cases. In several

obesity models, despite high levels of endogenous *Lep* or treatment with exogenous *Lep*, there was no improvement of obesity (Frederich et al., 1995). In fact, it has often been found that the level of circulating *Lep* is even higher in obese people compared to that of nonobese people (Considine et al., 1996). One explanation for these observations is that high sustained *Lep* concentrations result in *Lep* resistance similar to insulin resistance in T2DM. In contrast to *Lep*, *Ghrl* is a hormone mainly produced in the stomach that increases food intake by directly stimulating neuropeptide Y/agouti-related protein (NPY/AgRP) neurons in the arcuate nucleus of the hypothalamus (ARH) (Grove and Cowley, 2005). Since the levels of *Ghrl* increase greatly before meals and the levels decrease after meals, it has been suggested to be the gut signal that initiates a meal. It, therefore, is considered the counterpart of *Lep* which directly inhibits ARH NPY/AgRP through the *Lep* receptor and induces satiation (Cowley and Grove, 2004).

Adiponectin encoded by the *Adipoq* gene is one of the major adipokines secreted by adipocytes (Chandran et al., 2003). Plasma *Adipoq* is inversely correlated with the mass of adipose tissue, and *Adipoq* gene expression is reportedly down-regulated in obesity (Ukkola and Santaniemi, 2002). In addition, weight reduction significantly increases circulating *Adipoq* levels in humans (Coppola et al., 2009). In obese mice *Adipoq* reportedly stimulates the AMP activated protein kinase signaling pathway in skeletal muscle and the liver, thereby regulating insulin sensitivity, FA oxidation, and glucose metabolism (Yamauchi et al., 2002). Several studies suggest *Adipoq* plays a role in regulating insulin sensitivity. For example, plasma *Adipoq* is reported to be associated with visceral fat accumulation and insulin resistance in Japanese men with T2DM (Yatagai et al., 2003). Also it has been reported that plasma *Adipoq* decreases in parallel with reduced insulin sensitivity before T2DM development in Rhesus monkeys (Hotta et al., 2001). As shown in Fig. 1, decreased expression of *Adipoq* was also associated with decreased *Slc2a4* expression. In fact, *Adipoq* has been reported to increase insulin stimulated glucose uptake, via increased *Slc2a4* expression and recruitment of *Slc2a4* to the plasma membrane (Al-Hasani and Joost, 2005). Hypoadiponectinemia is reportedly more closely related to insulin resistance than the degree of obesity, and furthermore *Adipoq* appears to be an independent risk factor for metabolic syndrome (Renaldi et al., 2009; Weyer et al., 2001). *Adipoq* is also an important mediator of *Pparg* agonist-mediated insulin sensitivity improvement as well because administration of TZD increases *Adipoq* (Kamei et al., 2006).

Functional Protein Interactions of Inflammation-Associated Genes in Obesity

Some of the obesity candidate genes were associated with inflammation, which is in agreement with past studies suggesting a close interrelationship between obesity and inflammation (Wellen and Hotamisligil, 2003; Wellen and Hotamisligil, 2005), although the precise mechanisms have not been fully elucidated. *Cfd* also known as adipsin is a serine protease secreted by adipocytes. Since it is involved in the alternative complement pathway of the complement system, a high level of expression in adipocytes suggests a role for adipose tissue in immune system as well. It has been shown that *Cfd* also stimulates glucose transport for TG storage and inhibits lipolysis in adipocytes (Ronti et al., 2006). Macrophages are part of the innate immune defense system and significantly increased macrophage infiltration to adipose tissue is reported (Weisberg et al., 2003; Xu et al., 2003). Many macrophage and inflammation-related genes were also reported to be dramatically increased in WAT in an animal model of obesity (Xu et al., 2003). Colocalization of metabolically active adipocytes and macrophages in adipose tissue appears to amplify cytokine production, while infiltration of inflammatory cells leads to adipocyte dysfunction (Wellen and Hotamisligil, 2003). One study suggests that *Adipoq* may have anti-inflammatory effects by inhibiting the production of inflammation-associated cytokines such as *Tnfa* and *Il6* (Zhao et al., 2005).

Tnfa is a 26 kDa transmembrane protein that is cleaved to a smaller active 17 kDa protein (Anghel and Wahli, 2007). It is known to be involved in systemic inflammation; however, adipocyte *Tnfa* production exerts only a local effect since it can not be secreted. Hence, systemic *Tnfa* primarily originates from macrophages (Weisberg et al., 2006). Although there is no clear relationship between the levels of plasma *Tnfa* and obesity, the expression of *Tnfa* in WAT correlates well with obesity and insulin resistance (Bullo et al., 2002; Winkler et al., 2003). Chronic exposure of mice to *Tnfa* induces insulin resistance and decreases adipose tissue mass, whereas, *Tnfa* gene knockout improves insulin sensitivity in obese mice (Prins et al., 1997). *Tnfa* regulates expression of other adipokines in WAT as well. For example, the expression of *adipoq* is downregulated by *Tnfa*, whereas *Il6* is upregulated by *Tnfa* (Zhang et al., 1990). *Adipoq* inhibits *Tnfa* production, therefore increased *Tnfa* may actually result in an amplification of the inflammatory environment leading to adipocyte dysfunction. *Il6* is a multifunctional cytokine involved in cell-to-cell signal transduction in the immune system. It is abundantly expressed in many different cell types including immune cells, fibroblasts, and many endocrine cells (Tracey and Cerami, 1993; Van Snick, 1990). Majority of plasma *Il6*, however, is produced by adipocytes, especially visceral adipocytes (Anghel and Wahli, 2007). Levels of plasma *Il6* are reported positively correlated with obesity and insulin resistance, while decreased *Il6* improves insulin sensitivity similar to *Tnfa* (Bastard et al., 2002).

Tnfa also influences the level of *PAI-1* and *Ccl2*. *PAI-1* is a serine protease inhibitor protein (*serpin*) that is a major inhibitor of tissue plasminogen activator and urokinase which activates plasminogen activator. Thus, increased expression of PAI-1 causes inhibition of fibrinolysis and the physiological breakdown of blood clots. PAI-1 is mainly produced by the endothelium, but is also expressed and secreted by WAT in rodents and humans (Alessi et al., 2000; Pandey et al., 2005).

Circulating levels of PAI-1 are correlated with obesity and insulin resistance (Juhan-Vague et al., 2003; Alessi and Juhan-Vague, 2006); however, the underlying mechanisms are not well understood. It has been suggested that the inhibition of fibrinolysis by PAI-1 may be responsible for the high incidence of cardiovascular diseases associated with obesity (Skurk and Hauner, 2004). *Ccl2*, also known as monocyte chemotactic protein-1 (MCP-1), is a small cytokine belonging to the C-C chemokine family. It recruits various inflammatory cells to the sites of inflammation (Carr et al., 1994; Xu et al., 1996) and the level of *Ccl2* is known to be increased in obesity (Weisberg et al., 2006). Increased expression of *Ccl2* in adipocytes is thought to be associated with the inflammatory response of adipose tissue in obesity. Chemokine (C-C motif) receptor 2 (CCR2) knock-out mice are characterized by reduced food intake, adipose tissue mass and macrophage numbers, combined with lower adipose tissue inflammation (Weisberg et al., 2006). In addition, CCR2 knock-out mice show elevated adiponectin, reduced steatosis, and improved insulin sensitivity (Weisberg et al., 2006). On the contrary, overexpression of *Ccl2* in adipose tissue results in increased macrophage infiltration (Kamei et al., 2006). TZD treatment in adipose tissue culture decreases *Ccl2* levels and similar effects are observed in T2DM patients as well (Bruun et al., 2005; Pfutzner et al., 2005). These findings suggest that activation of *Pparg* by *Pparg* agonists exerts beneficial effects on the production of a whole range of adipokines including *adipoq*, *Tnfa*, *Il6*, *PAI-1*, and *Ccl2*.

Functional Protein Interactions of Lipid Metabolism-Associated Genes in Obesity

Among the obesity candidate genes, some were associated with lipid and cholesterol metabolism. *Hmgcs1* is the first and rate-limiting enzyme of sterol biosynthesis which catalyzes acetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). In the adipocytes of HFD fed animals, the expression of *Hmgcs1* is downregulated, which has been suggested to be due to a feedback mechanism to maintain cholesterol homeostasis (Goldstein and Brown, 1990). ATP-binding cassette transporter 1 (*Abca1*), also known as the cholesterol efflux regulatory protein is a member of the ATP-binding cassette (ABC) transporters superfamily and is tightly regulated by transcriptional and posttranscriptional mechanisms (Luciani et al., 1994). *Abca1* is a major transporter responsible for phospholipid and cholesterol efflux (Schmitz and Langmann, 2001), which also regulates HDL formation (Oram and Vaughan, 2000). Mutations of *Abca1* therefore have been associated with familial HDL deficiency (Ordovas, 2000) and the pathogenesis of atherosclerosis (Guo et al., 2006). In obesity, the expression of *Abca1* is increased probably to maintain cholesterol homeostasis in adipocytes and to offer protective effects against atherosclerosis (Ferre, 2004).

Ctsd is a lysosomal aspartic protease and activated at pH 5 in the endosome of hepatocytes (Authier et al., 2002). Recently, it has been reported that *Ctsd* expression is upregulated during adipocyte differentiation, and in adipose tissue of obese C57BL/6J mice as well as obese humans (Masson et al., 2011). Moreover, suppression of *Ctsd* expression in preadipocytes leads to lipid-depletion and inhibits the expression of adipocyte differentiation markers including *Pparg*, hormone sensitive lipase, and *Fabp4* (Masson et al., 2011). Interestingly, inhibition of *Ctsd* activity or expression reduced *Abca1* expression, whereas, the expression of *Ctsd* increased both *Abca1* mRNA expression and protein abundance (Haidar et al., 2006), which suggests that *Ctsd* plays an important role in intracellular cholesterol trafficking and *Abca1*-mediated cholesterol efflux. *Srebf1,* also known as sterol regulatory element binding protein 1 (Srebp1) is a member of the basic helix-loop-helix-leucine zipper transcription factor family (Yokoyama et al., 1993). *Srebf1* binds to the sterol regulatory element-1 (SRE1) in the promoter region of various genes involved in sterol biosynthesis and activates gene transcription. *Srebf1* is synthesized as a precursor protein in the endoplasmic reticulum. Thereafter *Srebf1* is cleaved, activated, and translocates to the nucleus. Sterol reportedly inhibits the cleavage of the precursor *Srebf1* and thereby reduces gene transcription. *Adipoq* administration suppresses *Srebp1c* expression in hepatocytes (Awazawa et al., 2009), whereas 3T3-L1 fibroblasts overexpressing *adipoq* exhibit more prolonged and robust Srebp1c expression (Al-Hasani and Joost, 2005). Seo *et al*. also showed that adenoviral overexpression of *Srebp1c* elevated *adipoq* mRNA and protein abundance in 3T3-L1 adipocytes (Seo et al., 2004). Furthermore, *Srebp1c* may play an important role in the production of a potent *Pparg* ligand (Kim et al., 1998). *G6pd2* is the first and rate-limiting enzyme of the pentose phosphate pathway (Spolarics, 1999). It has been reported that *G6pd2* is highly expressed in the adipocytes of obese animals and ectopic overexpression of *G6pd2* resulted in dysregulated lipid metabolism and insulin resistance (Park et al., 2005).

Functional Protein Interactions of Energy Metabolism and Oxidative Stress-Associated Genes in Obesity

Another interesting obesity candidate gene involved in energy metabolism was *Ucps,* which encodes a mitochondrial transmembrane protein that uncouples oxidative phosphorylation from ATP generation and dissipates energy as heat. *Ucp1* expression is known to be restricted to BAT (Nicholls et al., 1978). However, recent evidence showed that chronic treatment of *Pparg* agonist strongly induces *Ucp1* gene expression in WAT as well (Kim et al., 1998; Petrovic et al., 2010). Nevertheless, *Ucp1* induction in WAT alone is not sufficient to increase energy expenditure (Sell et al., 2004) as these cells retain WAT characteristics (Petrovic et al., 2010). Activation of *Ppara* leads to an increase in *Ucp2* expression and enzymes involved in β-oxidation. Unlike *Ucp1*, *Ucp2* is ubiquitously expressed and *Ucp2* expression is also increased by TZDs in adipocytes (Camirand et al., 1998). *Ucp* is an interesting obesity candidate gene, because potentially therapeutic activation of *Ucp* could

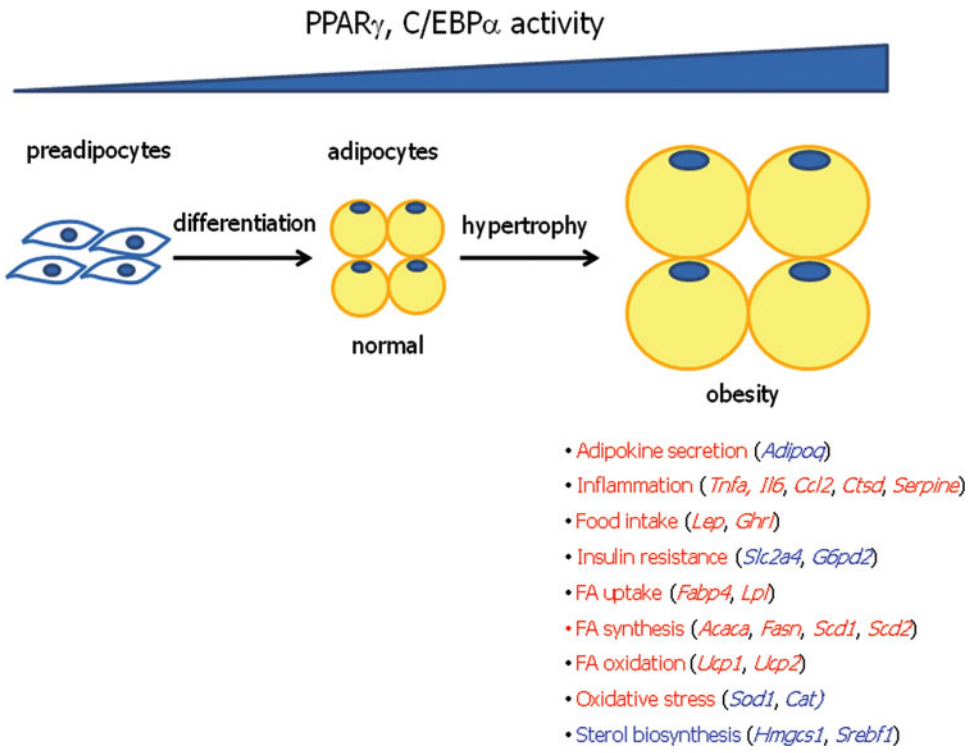

Figure 2 The schematic diagram of gene expression and regulation in the adipose tissue of obese mice. The expression of genes and the effect of gene expression is color coded. Red color: upregulation. Blue color: downregulation. (Color figure available online.)

help oxidize stored FFA in obese individuals, reducing lipid droplet and adipose tissue size.

Some obesity candidate genes were also associated with oxidative stress. In adipose tissue, increased influx of FFAs, glucose, and inflammatory cytokines leads to increased oxidation of energy substrates and ceramide formation, which can lead to generation of mitochondrial reactive oxygen species (ROS) causing oxidative stress (Evans et al., 2002; Evans et al., 2005; Eriksson, 2007). Emerging evidence suggests that intracellular accumulation of ROS is associated with insulin resistance and metabolic syndrome (Evans et al., 2002; Robertson, 2004; Evans et al., 2005). Furthermore, oxidative stress is also reported to be increased in patients with abdominal obesity (Fujita et al., 2006). *Sod1* is one of the three superoxide dismutases and converts harmful superoxide radicals to molecular oxygen and hydrogen peroxide. Hydrogen peroxide is also a harmful byproduct of normal metabolism and it must be quickly converted into less harmful substances (Zelko et al., 2002). *Cat*, a commonly found enzyme in nearly all aerobic organisms, degrades hydrogen peroxide to water and oxygen. Since the expression of both *Sod1* and *Cat* is downregulated, it is thought that this further exacerbates existing oxidative stress and insulin resistance. Whether obesity candidate genes associated with oxidative stress are useful therapeutic targets has not yet been established. It would be interesting to observe whether transgenic or knockout mice have altered responses to diet-induced obesity.

Our network analysis revealed interplay between obesity candidate genes with a variety of functions apparently coordinated by *Pparg* and *Cebpa*. Excessive fat intake increases the size and mass of adipose tissue and increases FA uptake (*Fabp4* and *Lpl*) (Fig. 2). Enhanced secretion of inflammatory cytokines (*Tnfa*, *Il6*, *Ccl2*, *Ctsd*, and *Serpine*) and decreased secretion of adipokine (*Adipoq)* affect food intake (*Lep* and *Ghrl*), insulin sensitivity (*Slc2a4* and *G6pd2*), FA synthesis (*Acaca*, *Fasn*, *Scd1*, *and Scd2*), FA oxidation (*Ucp-1* and *Ucp-2*), glucose metabolism (*Gpd1*), and inflammation. Oxidative stress is increased as a byproduct and this is further exacerbated by downregulation of detoxifying genes (*Sod* and *Cat*). In future studies, it may be worthwhile to use a similar approach to identify tissue specific obesity candidate genes.

The present meta-review of obesity candidate genes in adipose tissue is based on genes altered in diet-induced obesity, rather than genes underlying genetic predisposition to obesity. Fat mass- and obesity-associated gene (FTO) was one of the earliest obesity candidate genes identified by large genome-wide association studies (Frayling et al., 2007), but is primarily associated with genetic predisposition to obesity rather than diet induced obesity. Studies have shown in humans whom have at least one FTO risk allele, increased intake of food, impaired satiety, and increased susceptibility to T2DM (Speakman et al., 2008; Haupt et al., 2009; Tanofsky-Kraff et al., 2009). Furthermore in mice the expression of FTO gene is also modulated by food intake, body weight, and fat mass (Fischer et al., 2009; Church et al., 2010). However, the interactions between FTO and other obesity candidate genes still remain to be elucidated.

CONCLUDING REMARKS

Despite the enormous amount of microarray data obtained from diet induced obesity models, systematic approaches for interpreting findings from these studies are still lacking. In this review, we discussed findings using a literature-driven network analysis approach to search for obesity candidate genes in published microarray studies, which revealed the following:

1. Upregulated genes were associated with FA synthesis (*Acaca, Fasn, Lpl, Scd1,* and *Scd2*), inflammation (*Tnfa, Il6, Ccl2, Ctsd,* and *Serpine*), signal transduction and transporters (*Fabp4, Cfd, Lep, Pparg,* and *Cebpa*), and energy homeostasis (*Gpd1, Ucp-1,* and *Ucp-2*).
2. Downregulated genes include Adipoq and genes associated with sterol biosynthesis (*Hmgcs1* and *Srebf1*), insulin sensitivity (*Slc2a4* and *G6pd2*), and oxidative stress (*Sod* and *Cat*).
3. Pparg appeared to be a core obesity gene, which interacts with lipid metabolism and inflammation genes.

An important drawback using the literature-driven network analysis approach described is it will tend to identify only genes which have strong evidence of differential expression in diet-induced obesity. Nevertheless, it can help identify interactions between genes with strong evidence of dysregulation in diet induced obesity. If we assume that the next generation of obesity drug, functional food, or food components will be designed to inhibit an obesity gene/protein, it is really essential to look at how gene products (e.g., proteins) interact. So we know the potential side-effects of blocking a gene or protein to prevent an individual developing obesity. On top of that, it is also essential to develop better ways to coordinately interpret findings from past and future microarray studies, which will help identify therapeutic targets for the treatment of obesity.

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ABBREVIATIONS

Acaca	Acetyl-Coenzyme A carboxylase
Adipoq	Adiponectin
Cat	Catalase
Ctsd	Cathepsin D
Cebpα	CCAAT/enhancer binding protein alpha
Ccl2	Chemokine (C-C motif) ligand 2
Cfd	Complement factor D
Fabp4	Fatty acid binding protein 4
Fasn	Fatty acid synthase
G6pd2	Glucose-6-phosphate dehydrogenase 2
Slc2a4	Glucose transporter 4
Gpd1	Glycerol-3-phosphate dehydrogenase 1
Hmgcs1	3-hydroxy-3-methylglutaryl-coenzyme A synthase 1
Il6	Interleukin 6
Lep	Leptin
Lpl	Lipoprotein lipase
Pparg	Peroxisome proliferator activated receptor gamma
PAI-1	Plasminogen activator inhibitor type 1
Scd1	Stearoyl coenzyme A desaturase 1
Srebf1	Sterol regulatory element binding transcription factor 1
Sod1	Superoxide dismutase 1
Tnfa	Tumor necrosis factor alpha
Ucp1	Uncoupling protein 1
Ucp2	Uncoupling protein 2

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