PERSPECTIVE

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Mouse models of inherited lipodystrophy

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Insulin resistance is a major factor in the pathogenesis of type 2 diabetes and underpins the strong association between obesity and diabetes. Paradoxically, the metabolic consequences of having 'too much' fat (obesity) are remarkably similar to those of having 'too little' fat (lipodystrophy): a finding that has generated considerable interest in a rare disease. In both cases, excess energy accumulates as lipid in ectopic sites such as the liver (fatty liver) and skeletal muscle, where it plays a central role in the pathogenesis of insulin resistance, dyslipidemia and type 2 diabetes. Human lipodystrophies are characterised by a total or partial deficiency of body fat, and may be inherited or acquired in origin. Genetically engineered mice with generalised lipodystrophy manifest many of the features of the human disorder, including hyperphagia, fatty liver, hypertriglyceridaemia, insulin resistance and type 2 diabetes, providing a useful tractable model of the human disorder. Partial lipodystrophy, which causes similar, albeit milder, metabolic problems in humans has been more difficult to mimic in the mouse. This review discusses key translational studies in mice with generalised lipodystrophy, including fat transplantation and the use of recombinant leptin replacement therapy. These studies have been instrumental in advancing our understanding of the underlying molecular pathogenesis of ectopic lipid accumulation and insulin resistance, and have prompted the initiation and subsequent adoption of leptin replacement therapy in human lipodystrophies. This review also considers the possible reasons for the apparent difficulties in generating mouse models of partial lipodystrophy, such as interspecies differences in the distribution of fat depots and the apparent lack of sexual dimorphism in fat mass and distribution in mice compared with the dramatic differences present in adult humans.

Introduction

What is lipodystrophy and why is it of interest?

Adipose tissue is an 'organ' with at least two essential biological roles, the first being to function as an energy storage depot for surplus energy, and the second is as an endocrine organ that is capable of synthesising and secreting hormones such as leptin and adiponectin (Kershaw and Flier, 2004). As well as storing excess energy (calories) in the form of triglycerides, adipose tissue acts as a dynamic buffer (Frayn, 2002) for postprandial lipid fluxes and as an essential source of energy in the form of non-esterified fatty acids and to a lesser extent, in times of fasting and/or sustained exercise, glycerol. Leptin, a cytokine-like peptide, is produced by adipose tissue alone and its plasma levels generally reflect the adipose tissue mass (Spiegelman and Flier, 2001). The long and most biologically active form of the leptin receptor (leptin Rb) is expressed predominantly in the hypothalamus. Signalling through this pathway regulates food intake, but also appears to modulate metabolic rate (mediated at least in part by the thyroid hormone axis), cell-mediated immunity and reproductive capacity. As might be expected from an evolutionary perspective, this axis appears to be most sensitive to a state of starvation, in which low leptin levels dramatically increase appetite, reduce metabolic rate and prevent ovulation in females (Ahima et al., 1996). Adiponectin is another cytokine-like peptide that is produced solely by adipocytes (Berg et al., 2002). Although its physiological role is less well understood than that of leptin, adiponectin plasma levels fluctuate in the opposite direction to those of leptin. Weight gain is thus associated typically with rising leptin levels and falling adiponectin levels (Table 1), whereas weight loss results in inverse changes.

Lipodystrophy is a pathological state of adipose tissue deficiency (Garg, 2004). As expected, the immediate consequences of this disorder include abnormalities in energy storage, postprandial lipid buffering and adipokine production. The lack of adipose tissue storage capacity is associated with lipid accumulation in ectopic sites such as the liver, muscle, pancreas and kidneys. In the liver, this leads to non-alcoholic fatty liver disease (NAFLD) and hepatic insulin resistance. Although lipid accumulation in skeletal muscle is more difficult to quantify accurately, several studies do suggest that lipids in skeletal muscle contribute to the development of peripheral insulin resistance and type 2 diabetes (Petersen and Shulman, 2002). Intriguingly, lipid accumulation in the pancreas (either in β cells themselves or in adipocytes within the pancreas) may impair pancreatic islet function, thereby also contributing to the pathogenesis of type 2 diabetes (Poitout, 2008). These metabolic problems are compounded by absolute or relative leptin and adiponectin deficiencies, both of which reflect the adipose tissue deficiency. Leptin deficiency is particularly disadvantageous in this setting because it induces hyperphagia and a state of positive energy balance, leading to further ectopic fat deposition. In contrast to lipodystrophy, leanness is a healthy insulin-sensitive state of

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Table 1. Adipocytokine levels in lean (healthy), obese and lipodystrophic states

	Lean	Obese	Lipodystrophy
Leptin	N	↑	↓
Adiponectin	N	↓	↓

reduced fat mass. In lipodystrophy, mature adipocyte numbers are reduced and those that are present appear to be dysfunctional, whereas leanness is characterised by 'empty adipocytes' that can be 'filled' readily. Paradoxically, lipodystrophy is, at least in terms of its metabolic consequences, more akin to obesity, a state in which adipose tissue is also dysfunctional (Savage et al., 2007). Here too, lipid accumulates in ectopic sites, leading to insulin resistance, β-cell dysfunction and, ultimately, type 2 diabetes. Proponents of the 'overflow hypothesis' suggest that the capacity to increase adipose tissue mass, a consequence of adipocyte hypertrophy and hyperplasia, is finite (Danforth, 2000; Shulman, 2000); exceeding this capacity leads to ectopic lipid accumulation, insulin resistance and type 2 diabetes (Fig. 1).

Although some would argue that the applicability of observations and hypotheses based on extreme phenotypes to more common disease states is limited, the collective contribution to the advance of science that is made by the use of knockout mouse models is a worthy testament to the benefits derived from this approach. Lipodystrophic mouse models are an example of the use of an extreme phenotype to derive hypotheses that are relevant to more common forms of insulin resistance. Rather than attempting to comprehensively cover all lipodystrophic mouse models, this Perspective endeavours to highlight some of the most significant studies undertaken in lipodystrophic mouse models. Several recent reviews have comprehensively catalogued many of the existing lipodystrophic mouse models (Reitman, 2002; Reue and Phan, 2006; Asterholm et al., 2007).

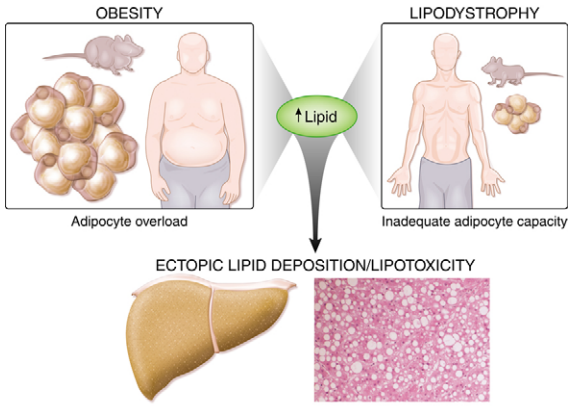

Fig. 1. Schematic illustration of the 'lipid overflow' hypothesis. The 'lipid overflow' hypothesis proposes that the capacity of adipose tissue to accommodate excess energy in the form of triglyceride is finite. Exceeding this limit leads to ectopic lipid accumulation and insulin resistance. This scenario occurs typically in obesity-associated insulin resistance. Lipodystrophy is an extreme example of reduced adipose tissue 'capacity' and is characterised by severe ectopic lipid accumulation/insulin resistance.

Features and classification of human lipodystrophy

Human lipodystrophies are a heterogeneous group of disorders, which may be genetic or acquired (Garg, 2004). They result from either the failure of adipocyte development or the immune-mediated premature destruction of adipocytes. The adipose tissue deficiency may be generalised, partial or localised. Localised forms of lipodystrophy, such as that seen in some patients who receive insulin injections, are of little metabolic consequence and are not discussed further in this manuscript. Acquired lipodystrophies may be partial (Misra et al., 2004) or generalised (Misra and Garg, 2003), and are thought to result from immune-mediated adipocyte loss. These disorders are not covered in detail here, other than a brief mention of a particularly interesting, inducible transgenic model of 'acquired lipodystrophy' that Pajvani et al. appropriately named the 'FAT-ATTAC' (fat apoptosis through targeted activation of caspase 8) mouse (Pajvani et al., 2005). In these mice, white and brown fat can be ablated within 1-2 weeks of starting treatment with a chemical dimerizer that forces dimerization of a transgenically expressed caspase 8 fusion protein specifically in adipocytes, thereby inducing apoptosis. The authors suggest that this model is particularly useful as it facilitates time course studies of the early metabolic consequences of fat loss, whereas metabolism in conventional mouse models of generalised lipodystrophy inevitably reflects a mix of primary and adaptive metabolic changes. Although short-term treatment-induced lipodystrophy in the FAT-ATTAC mouse appears to be reversible (Pajvani et al., 2005), longer term treatment apparently leads to permanent lipodystrophy, suggesting that the capacity to generate a source of adipocyte precursors is finite (Wojtanik et al., 2009).

Although human immunodeficiency virus (HIV)-associated partial lipodystrophy is now the most common cause of lipodystrophy (Koutkia and Grinspoon, 2004), few mouse models of this disorder exist and they are not discussed here.

Congenital generalised lipodystrophy (CGL), also known as Berardinelli-Seip congenital lipodystrophy (BSCL) (Garg et al., 1992; Seip and Trygstad, 1996), is an autosomal recessive condition that is characterised by a generalised absence of adipose tissue from birth, increased appetite owing to leptin deficiency (Pardini et al., 1998), accelerated growth and advanced bone age. Skeletal muscles and peripheral veins are particularly prominent owing to the paucity of subcutaneous fat. Hyperinsulinaemia from early childhood leads to acanthosis nigricans, acromegaloid features and organomegaly. Diabetes tends to develop in the second decade of life. In addition, hepatomegaly is often prominent and is caused by severe NAFLD, which generally progresses to non-alcoholic steatohepatitis (NASH) and sometimes to cirrhosis. Severe hypertriglyceridaemia, eruptive xanthomata and pancreatitis are common.

In the vast majority of cases (>95%), CGL is caused by biallelic mutations in either the gene encoding 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*) (Agarwal et al., 2002), or the gene encoding seipin (*BSCL2*) (Magre et al., 2001), an endoplasmic reticulum protein. A homozygous nonsense mutation in caveolin 1 (*CAV1*) was also identified recently in a Brazilian patient with generalised lipodystrophy (Kim et al., 2008). AGPAT2 is an essential enzyme in glycerophospholipid and triacylglycerol synthesis, providing a ready explanation for the failure of adipose tissue development in patients with genetic defects in the *AGPAT2* gene.

The mechanistic link between seipin and lipodystrophy, however, is more obscure, although recent work suggests that it is highly expressed in adipocytes and is required for adipogenesis in vitro (Payne et al., 2008). These data are supported by observations suggesting that seipin is involved in lipid droplet biology (Szymanski et al., 2007; Fei et al., 2008; Boutet et al., 2009).

It is currently not possible to distinguish clinically, with confidence, between these genetic subgroups; however, adipose tissue loss in mechanical fat pads such as the palms, soles, orbits, scalp and periarticular regions has been reported as a specific feature of BSCL that results from seipin mutations (Simha and Garg, 2003). Short stature, which is unusual in CGL where many patients manifest acromegalic features instead, was a notable feature of the homozygous carrier of the *CAV1* nonsense mutation (Kim et al., 2008).

Familial partial lipodystrophies (FPLD) are both milder and more common than CGL. In FPLD, the adipose tissue pathology appears to relate to abnormal adipose tissue topography (or fat distribution), as well as a reduction in total fat mass. Indeed, patients with these conditions can occasionally exhibit normal, or even increased, whole body adipose stores. In particular, head and neck adipose depots are often preserved (or even increased in FPLD2). Some data also suggest that the function of residual adipose tissue is abnormal (Savage et al., 2003; Tan et al., 2008). This certainly appears to be true in FPLD that is associated with peroxisome proliferator-activated receptor gamma (*PPARG*) mutations, which is not particularly surprising given the well-documented role of PPARγ in mature adipocytes.

FPLD most commonly presents in peripubertal or postpubertal women, where the loss of femorogluteal fat is particularly striking. FPLD is very difficult to detect clinically in men and in prepubertal children. Metabolic abnormalities range from asymptomatic impaired glucose tolerance and mild dyslipidaemia to severe insulin resistance with type 2 diabetes mellitus (T2DM) and severe dyslipidaemia, eruptive xanthomata and pancreatitis. NAFLD/NASH is also very common. Metabolic problems tend to present significantly earlier in women than in men with FPLD (Garg, 2000); this presumably reflects the substantial gender-related differences in human body composition – healthy women have, on average, as much as twice the amount of fat, and significantly less lean tissue, compared with healthy men. The FPLDs have been subclassified into three groups:

FPLD1 is characterised by a loss of limb fat with preserved and frequently increased truncal fat. This fat topography is almost the 'norm' in overweight/obese men, but is unusual in women in whom it appears to be associated with insulin resistance, fatty liver and dyslipidaemia. The fat distribution is reminiscent of that seen in Cushing's syndrome. Although some FPLD1 patients do have affected family members, many do not, suggesting that not all cases are inherited, and clinical observation suggests that additional factors such as the menopause and hyperandrogenism may be contributory. No specific genetic defects have been reported in this group.

FPLD2 predominantly affects the limbs and gluteal fat depots with variable truncal involvement, but with normal or excess fat on the face, neck and in the labia majora (Jackson et al., 1997). The majority of patients with FPLD2 have heterozygous loss-of-function mutations in *LMNA* (Cao and Hegele, 2000; Shackleton et al., 2000), which encodes lamin A/C, a structural component of the nuclear lamina expressed in almost all tissues. Remarkably, mutations in this gene have also been linked convincingly to several different disorders, including muscular dystrophy and dilated cardiomyopathy (Rankin and Ellard, 2006). A detailed understanding of the mechanisms underlying the tissue-selective phenotypes that are associated with *LMNA* mutations is lacking, but proposed abnormalities include structural defects in the nuclear envelope and altered binding of the nuclear lamina to chromatin or transcription factors.

FPLD3 also features a paucity of limb and gluteal fat, however, abdominal fat is generally preserved and facial fat is usually normal (Semple et al., 2006). Insulin resistance and lipodystrophy have been described in prepubertal children, although peripubertal presentation is probably most common. The very high prevalence of early-onset hypertension helps to discriminate FPLD3 from FPLD2 (Semple et al., 2006). Loss-of-function mutations in the gene encoding PPARγ, a nuclear hormone receptor that is crucial for adipose tissue development and that is targeted by thiazolidinedione (TZD) insulin sensitizers, have been described in patients with FPLD3 (Semple et al., 2006). All pathogenic mutations described to date have been heterozygous, located in the DNA- or ligand-binding domains of the protein, and most display dominant negative activity in vitro (Barroso et al., 1999; Agostini et al., 2006; Semple et al., 2006).

Congenital generalised lipodystrophy mouse models

Several mouse models of generalised lipodystrophy have been reported. Many of these were generated in order to explore the biology of the targeted proteins and/or adipose tissue itself, rather than as models of specific genetic subtypes of human generalised lipodystrophy; the one recent exception to this is the *Agpat2* knockout mouse. Nevertheless, the metabolic consequences of almost all of these models are similar to those of human generalised lipodystrophy. They can broadly be characterised into two groups of models.

Models in which the genes encoding key adipocyte proteins were knocked out

Cebpa knockout mice

C/EBPα (CCAAT/enhancer binding protein α) is a transcription factor that is implicated convincingly in adipocyte differentiation in cultured cells (Lefterova and Lazar, 2009). *Cebpa* knockout mice develop hypoglycaemia and die shortly after birth owing to a severe defect in gluconeogenesis (Wang et al., 1995). The adipose tissue in these mice also failed to accumulate lipid, even when the mice were rescued by transgenic hepatic expression of C/EBPα (Linhart et al., 2001). The latter mice appeared to have normal amounts of brown fat and mammary adipose tissue, but lacked subcutaneous, perirenal and epididymal white fat. In addition, they had high insulin levels and postprandial hypertriglyceridaemia.

Prarg knockout mice

As with C/EBPα, the role of PPARγ, a transcription factor that is expressed most highly in adipose tissue, had been examined extensively in cultured cells prior to the generation of a knockout mouse model (Lefterova and Lazar, 2009). In fact, PPARγ knockdown and replacement studies suggested that it was essential

for adipocyte differentiation (Rosen et al., 1999). *Pparg* knockout mice die in utero, but the Mox2-Cre-floxed *Pparg* knockout mouse preserves trophoblastic PPARγ expression (Cre recombinase is expressed uniformly in epiblast-derived tissue, but not in other tissues, thereby sparing trophoblastic tissue), enabling approximately 10% of mice to reach maturity (Duan et al., 2007). Body fat was reduced significantly in these mice, and plasma leptin and adiponectin levels were low. Insulin sensitivity appeared to be impaired during an insulin tolerance test, although the females had improved glucose tolerance, possibly mediated by hyperinsulinaemia.

Agpat2 null mice

Agpat2 null mice were generated in an effort to mimic human CGL that is caused by biallelic loss-of-function mutations in *AGPAT2* (Cortes et al., 2009). Although *Agpat2*$^{-/-}$ pups were born at the expected frequency, around 80% of pups died within 3 weeks. The survivors did manifest generalised lipodystrophy, extreme insulin resistance, diabetes and hepatic steatosis. The development of hepatic steatosis was interesting given the fact that the total AGPAT activity that was measured in the livers of these mice was reduced by around 90%, despite the expression of several other putative *Agpat* genes (there are about ten putative Agpats). The dramatic upregulation of monoacylglycerol acyltransferase 1 (*Mogat1*) suggests that the alternative monoacylglycerol pathway for triglyceride synthesis compensates for the loss of AGPAT2 activity (Cortes et al., 2009).

Cav1 null mice

Caveolin-1 (*Cav1*) null mice (reviewed by Mercier et al., 2009) were first reported to manifest a hyperproliferative lung phenotype and vascular abnormalities owing to aberrant endothelial function (Razani et al., 2001). Studies in older mice later revealed a lipodystrophic phenotype (Razani et al., 2002). Mice are lean with low plasma leptin and adiponectin levels, and resist diet-induced weight gain. Adipose depots are reduced significantly (>50%) and, although glucose and insulin levels appear to be relatively normal, the mice do manifest dramatic postprandial hypertriglyceridaemia. Together with in vitro studies, this model prompted Kim et al. to screen the *CAV1* gene in humans with unexplained lipodystrophy (Kim et al., 2008). They identified a Brazilian kindred in which one patient with short stature and generalised lipodystrophy was found to be homozygous for a nonsense mutation in *CAV1*.

Models in which the aP2 promoter/enhancer was used to drive transgene expression in adipose tissue

It is important to remember that the approach of using the promoter/enhancer of the aP2 adipocyte fatty acid binding protein to drive transgene expression in adipose tissue inevitably results in transgene expression after pre-adipocytes have been induced to differentiate. Models of this type include the following:

aP2-DT-A mice

aP2-DT-A mice express modified diphtheria toxin in adipocytes (Ross et al., 1993). These mice were reportedly normal at birth but develop progressive adipocyte atrophy and necrosis from the age of around 5 months. By 9 months of age, they manifest generalised lipodystrophy, insulin resistance, hyperglycaemia, dyslipidaemia, low leptin levels and hyperphagia.

A-ZIP/F-1 (AZIP) mice

A-ZIP/F-1 (hereafter referred to as AZIP) transgenic mice express a dominant negative protein that heterodimerises with, and inactivates, members of the C/EBP and JUN families of basic region-leucine zipper (B-ZIP) transcription factors (Moitra et al., 1998). These mice lack visible fat throughout life and manifest many of the metabolic complications seen in humans with generalised lipodystrophy. Brown adipose tissue is present at birth, but involutes prematurely. Several highly informative studies have been undertaken in this model, some of which will be discussed in more detail below.

aP2-SREBP-1c mice

aP2-SREBP-1c transgenic mice express a constitutively active form of the sterol response element binding protein 1c (SREBP1c) transcription factor in adipose tissue (Shimomura et al., 1998). SREBP1c is known to upregulate several lipogenic genes, so it was something of a surprise when the mice were noted to be lipodystorphic. White adipose tissue (WAT) mass is reduced by around 70%, and the mice manifest many typical features of human generalised lipodystrophy. Brown adipose tissue mass is increased in this model.

Relevance of congenital generalised lipodystrophy mouse models for human CGL

In keeping with human CGL, all of the above models are characterised by ectopic lipid accumulation, insulin resistance and

Table 2. Metabolic features of human and mouse lipodystrophy

Metabolic feature	Human generalised lipodystrophy	Mouse generalised lipodystrophy	Human partial lipodystrophy	Mouse partial lipodystrophy
Insulin resistance	+++	+++	++	?
Diabetes	+++	++	++	?
Leptin/adiponectin	Reduced	Reduced	Reduced	?
Fatty liver	+++	+++	++	+
Dyslipidaemia	+++	++	++	+
Hyperphagia	++	++	+	?
Elevated metabolic rate	+	+	+	?
Organomegaly	++	+	+	?
PCOS*	++	?	++	?

*Many women with generalised or partial lipodystrophy manifest features of polycystic ovary syndrome (PCOS).

a tendency to develop diabetes (Table 2). Hypertriglyceridaemia, which is frequently bad enough to precipitate eruptive xanthomata and pancreatitis, is common in human CGL; it is almost always accompanied by low HDL cholesterol levels, but NEFA (non-esterified fatty acid) levels tend to be normal or even low in the fasting state. Despite the basic differences between mouse and human lipoprotein metabolism, lipodystrophic mice also tend to manifest hypertriglyceridaemia. NEFA levels are generally said to be elevated, which is not a common feature of human generalised lipodystrophy. However, in keeping with the notion that adipose tissue is an essential source of NEFAs during prolonged fasting, AZIP mice tolerate prolonged fasting poorly and tend to enter torpor prematurely (Reitman and Gavrilova, 2000).

Generalised lipodystrophy mouse models, particularly the AZIP and Srebp1c adipose transgenic (aP2-SREBP-1c) lines, have been utilised in several important studies.

Transplantation of wild-type fat into AZIP mice

In order to test the fundamental hypothesis that the metabolic abnormalities seen in patients and mice with generalised lipodystrophy are a consequence of the loss of adipose tissue mass, Gavrilova et al. reconstituted AZIP mice with fat pads from healthy wild-type littermates (Gavrilova et al., 2000) (Fig. 2). Transplantation of wild-type fat reversed the hyperglycaemia, dramatically reduced plasma insulin levels and hepatic steatosis, and improved muscle insulin sensitivity, thereby demonstrating that diabetes in this model is a consequence of the lack of adipose tissue mass. The benefits of transplantation were dose dependant. The authors went on to repeat the experiment using WAT from leptin-deficient *ob/ob* mice (Colombo et al., 2002). In this case, the fat transplants were without any metabolic benefit. At first, these data might appear to suggest that leptin secretion is the key ingredient required for these metabolic benefits; however, one might also argue that it is not particularly surprising that transplanting adipocytes which are already maximally hypertrophic ('filled to capacity') is of little metabolic benefit. More recently, Rodeheffer et al. successfully transplanted adipocyte precursors, which they had successfully identified, characterised and isolated for the first time, into AZIP mice with similarly dramatic metabolic improvements (Rodeheffer et al., 2008). As well as hinting at a potentially novel therapeutic option for lipodystrophic patients, these studies constitute a core piece of evidence in the 'lipid overflow hypothesis', which is currently one of the favoured mechanisms for obesity-induced insulin resistance.

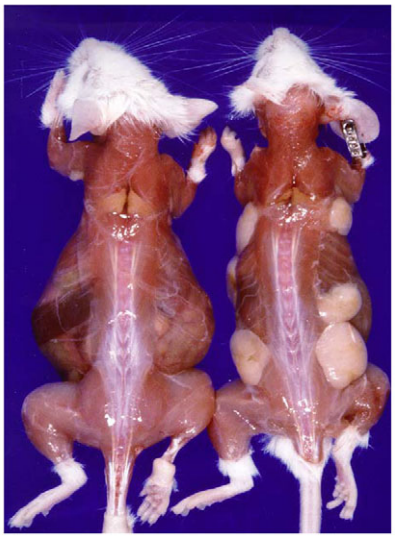

Fig. 2. Fat transplantation from a wild-type mouse to an AZIP lipodystrophic mouse. A-ZIP/F-1 mice at 13 weeks after transplantation. The skin was dissected from a sham-operated mouse (left) and from a mouse that received 900 mg of parametrial fat (right) in seven grafts (a ventral graft is not visible). The reduction in abdominal girth reflects the dramatic improvement in hepatic steatosis that is seen post-transplantation. Figure reproduced with permission from the American Society for Clinical Investigation (Gavrilova et al., 2000).

Infusion of leptin into aP2-SREBP-1c mice

In addition to providing a physical depot for triglyceride storage, adipocytes secrete leptin in proportion to their size. Leptin deficiency, whether it is the result of a primary genetic change or secondary to lipodystrophy, is perceived by the brain as a state of 'starvation', prompting efforts to increase food intake and limit energy expenditure. Hyperphagia in the setting of generalised lipodystrophy is particularly disadvantageous and tends to exacerbate ectopic lipid accumulation, insulin resistance and hyperglycaemia. Shimomura et al. were the first to address this problem by infusing leptin into aP2–SREBP-1c transgenic mice (Shimomura et al., 1999). The authors documented dramatic changes in plasma insulin and glucose levels, and in hepatic steatosis, in response to leptin infusion. They also suggested that the metabolic improvements that were noted could not be explained by a reduction in food intake alone, suggesting instead that leptin had additional therapeutic benefits. A low dose of centrally administered (intracerebroventricular) leptin was as effective as high-dose peripheral leptin (Asilmaz et al., 2004). Central leptin also reduced the expression of mRNA encoding hepatic stearoyl-CoA desaturase-1 (SCD1) and enzyme activity to levels seen in wild-type mice. SCD1 is a core component of the de novo lipogenesis pathway in hepatocytes, which is increased in insulin-resistant states. These data suggested that the primary site of action for leptin is central rather than peripheral, and that centrally mediated repression of hepatic SCD1 contributes to the antisteatotic effects of leptin. In addition, leptin was later shown to induce metabolic benefits in AZIP mice (Colombo et al., 2002). These studies prompted therapeutic trials of leptin replacement in patients with CGL (Oral et al., 2002). Here too, dramatic metabolic benefits were documented and leptin replacement is now used in the treatment of human CGL.

Ablation of PPARγ expression in the liver

PPARγ is expressed most highly in adipose tissue but is also detectable in many other tissues. In the liver, PPARγ expression is increased in several mouse models of fatty liver, including the AZIP and other lipodystrophic mice. Gavrilova et al. ablated liver PPARγ expression by crossing mice with a floxed *Pparg* allele with mice expressing Cre recombinase under the control of the liver-specific albumin promoter (Gavrilova et al., 2003). This led to a significant reduction in hepatic steatosis, suggesting that, in this model, PPARγ in the liver was involved directly in the pathogenesis of fatty liver.

These observations have led to concerns about the use of TZDs in patients with lipodystrophy, despite accumulating evidence in favour of TZD use in people with fatty liver who are not lipodystrophic (Belfort et al., 2006). AZIP mice with a liver-specific deletion of Pparg were also noted to have increased serum lipids, impaired triglyceride clearance and more severe muscle insulin resistance, suggesting that the liver serves a primary buffering role in states characterised by adipose tissue dysfunction (Gavrilova et al., 2003).

A model of selective postreceptor hepatic insulin resistance

Insulin resistance is typically defined in terms of the effects of insulin on hepatic glucose production and glucose disposal in peripheral tissues (skeletal muscle and fat). However, insulin has pleiotropic effects on glucose, lipid and protein metabolism. Thus, the potential for selective defects in the insulin signalling cascade, with different effects on glucose, lipid and protein metabolism, exists and has long been mooted as a possible explanation for some otherwise unexplained features of insulin resistance syndromes (Taylor et al., 1992). The observation that both insulin-resistant aP2–SREBP-1c transgenic mice and insulin-resistant *ob/ob* obese mice exhibit impaired insulin-stimulated suppression of hepatic gluconeogenesis, but enhanced insulin-stimulated hepatic lipogenesis, prompted Brown and Goldstein to propose a model featuring selective postreceptor hepatic insulin resistance (Shimomura et al., 2000; Brown and Goldstein, 2008). According to this model, the canonical insulin-signalling pathway through insulin receptor substrate (IRS)–phosphoinositide 3-kinase (PI3K)–protein kinase B–forkhead box O transcription factor 1 (IRS-PI3K-AKT-FOXO1) is selectively downregulated in the presence of hyperinsulinaemia. By contrast, a parallel pathway linking activation of the insulin receptor to transcriptional upregulation of the crucial lipogenic transcription factor SREBP1c remains fully functional and thus mediates enhanced lipogenesis in the presence of hyperinsulinaemia (Fig. 3). The molecular components of this signalling pathway have yet to be elucidated fully. Increased liver fat owing to activation of the INSR-SREBP1c pathway is, in turn, associated with excess hepatic production of large triglyceride (TG)-rich very low-density lipoprotein (VLDL) particles. Cholesteryl ester transfer protein (CETP) exchanges cholesterol esters from high- and low-density lipoprotein (HDL and LDL, respectively) particles with TGs from VLDL, lowering HDL cholesterol levels and facilitating the accumulation of atherogenic, small dense LDL particles (Ginsberg, 2000). This hypothesis, stating that the prevalent form of insulin resistance is a specific and incomplete intracellular defect, is supported in part by recent observations in liver insulin receptor knockout (LIRKO) mice (Biddinger et al., 2008). These animals manifest low liver and plasma TG levels despite being hyperglycaemic and hyperinsulinaemic, a finding that is in keeping with a genetic deficiency in the first step of insulin signalling, which is common to the pathways leading to AKT and SREBP. The notion that selective postreceptor defects in insulin signalling might contribute to the pathogenesis of fatty liver and dyslipidaemia also appears to be true in both lipodystrophic (Semple et al., 2009) and obese insulin-resistant humans (Donnelly et al., 2005).

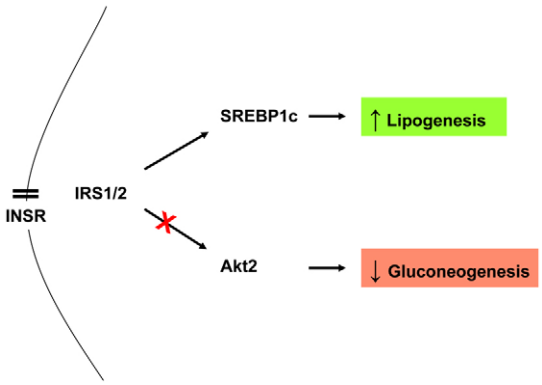

Fig. 3. Schematic representation of selective postreceptor (partial) hepatic insulin resistance. Under normal circumstances, an increase in insulin levels suppresses hepatic gluconeogenesis and stimulates de novo lipogenesis. In insulin-resistant states, the ability of insulin to suppress hepatic gluconeogenesis is impaired (red cross), whereas insulin-stimulated de novo lipogenesis is increased. Selected signalling intermediaries only are shown. INSR, insulin receptor; IRS, insulin receptor substrate; AKT, serine-threonine kinase AKT (also known as protein kinase B); SREBP1c, sterol regulatory element binding protein 1c.

Familial partial lipodystrophy mouse models

Numerous mouse models with reduced fat mass have been generated and some of these do indeed appear to manifest a lipodystrophic rather than lean phenotype, e.g. perilipin knockout mice (Tansey et al., 2001). Such models would appear to provide candidate genes that are worth considering in efforts to identify the genetic basis of otherwise unexplained human FPLD. However, the lean phenotype of several lean mouse models is a consequence of a primary increase in energy expenditure rather than adipocyte dysfunction (Reitman, 2002). These models should be distinguished from lipodystrophic models, where the apparent increase in metabolic rate is almost certainly an adaptive response to excess energy intake in the context of reduced adipose tissue storage capacity. Although folklore would suggest that this is a common human phenotype, robust scientific evidence supporting the idea is lacking. Many of these lean models were reviewed recently by Reitman (Reitman, 2002) and are not considered here. Instead, the focus herein is on mouse models of specific subtypes of human FPLD.

In humans, FPLD tends to present with stereotypic patterns of fat loss, for which the molecular/physiological basis remains poorly understood. Autosomal dominant mutations in *LMNA* are currently the most common cause of human FPLD (FPLD2). This, together with the interest generated by the heterogeneity of phenotypes associated with *LMNA* mutations, promptly lead to efforts to generate an *Lmna* knockout mouse. Homozygous $Lmna^{-/-}$ mice manifest severe muscular dystrophy and die within approximately 8 weeks of birth (Sullivan et al., 1999). Although these mice were reported to be lean, this appeared to be a consequence of their myopathic disease rather than lipodystrophy (Cutler et al., 2002). As approximately 90% of the *LMNA* mutations that are associated with FPLD in humans occur in exon 8, with the majority affecting amino acid 482, Wojtanik et al. recently generated a transgenic mouse model in which they expressed human wild-type, or R482Q mutant, *LMNA* in mouse adipose tissue (using the aP2 promoter) (Wojtanik et al., 2009).

These mice did manifest age-dependant partial lipodystrophy, hepatic steatosis and insulin resistance. However, the pattern of lipodystrophy differed from that seen in humans with *LMNA*-associated FPLD insofar as all fat pads were smaller in transgenic mutant mice than in transgenic wild-type mice, whereas humans with FPLD typically lack femorogluteal, limb and truncal fat but have an excess of facial/neck fat. In humans, the mechanism for this particular pattern of fat loss, as well as its tendency to manifest at puberty, is still unknown. These discrepancies highlight the fact that mouse fat depots do not precisely mirror those of humans. The dramatic differences in fat distribution and total fat mass between men and women are also not seen in mice, and mice do not appear to replicate the marked changes in fat mass/distribution that are seen in humans at the time of puberty. In humans with the FPLD2 phenotype, metabolic complications occur significantly earlier and more frequently in women than in men (Garg, 2000), whereas the phenotype of transgenic *LMNA* R482Q mice was more prominent in males (Wojtanik et al., 2009).

Wojtanik et al. also attempted to explore the molecular mechanisms that are responsible for the lipodystrophy that is associated with *LMNA* mutations. Measurements of lipolysis in isolated adipocytes were similar in cells from the transgenic wild-type *LMNA* and mutant *LMNA* mice, but the capacity to differentiate into mature adipocytes was reduced in pre-adipocytes that were isolated from the stromovascular fraction of *LMNA* R482Q transgenic mutants. The authors suggest that the reason for partial lipodystrophy in this mouse model is a reduced ability to recruit a new pool of adipocytes when the existing adipocytes reach their maximum capacity for storing lipid (Wojtanik et al., 2009).

Heterozygous loss-of-function mutations in *PPARG* constitute the second most common cause of human FPLD (FPLD2). Given the wealth of in vitro data indicating that PPARγ is essential for adipocyte differentiation, several mouse models have addressed the role of PPARγ in adipose tissue. These models have been the subject of several papers, including a recent review (Gray et al., 2005), so will not be discussed in detail here. This review will, however, highlight a few key observations. Firstly, as with the *LMNA* transgenic model discussed above, none of these models accurately mimic the stereotyped pattern of fat loss that is seen in humans with FPLD3. At least two independent groups generated P465L *Pparg* knock-in mice (Tsai et al., 2004; Gray et al., 2006). This mutation is homologous to the first human *PPARG* mutation (P467L) associated with partial lipodystrophy (Barroso et al., 1999; Savage et al., 2003). Although fat mass is reduced to some extent in these mice, they appeared to be insulin sensitive. Interestingly they did, however, manifest hypertension, which is common in FPLD3. It was only when these mice were crossed with leptin-deficient obese *ob/ob* mice that extreme insulin resistance was noted (Gray et al., 2006). The same group observed a similarly exaggerated insulin resistance phenotype in *Pparg2* isoform-specific knockouts when crossed with *ob/ob* mice (Medina-Gomez et al., 2007). The authors argue that loss-of-function mutations in *Pparg* limit the 'expandability' of adipose tissue or, to put it another way, the capacity of adipose tissue to accommodate excess energy as lipid.

Akt2 knockout mice are certainly insulin resistant (Cho et al., 2001) and appear to manifest age-dependant partial lipodystrophy (Garofalo et al., 2003). One human family with fairly typical FPLD features (most similar to FPLD3) has been reported with a loss-of-function mutation in *AKT2* (George et al., 2004).

Concluding remarks

Although mouse models of generalised lipodystrophy do not necessarily replicate the genetic basis for human CGL, they do appear to manifest almost all of the key metabolic changes that are seen in the human condition (Table 2). They have, therefore, been of considerable use as a tractable model in which to explore the molecular mechanisms underpinning many of the metabolic complications associated with CGL. The paradoxical similarities between lipodystrophy-associated insulin resistance and obesity-associated insulin resistance have meant that concepts such as the 'lipid overflow' hypothesis are in many ways crucially dependent on observations made in these mouse models. Studies in these mice have also led to the use of novel therapies with immediate practical benefits for patients, as well as the promise of future options such as transplantation of adipocyte precursors.

Mouse models of partial lipodystrophy do not appear to mimic the human disorders as closely and have thrown up some surprising results (Table 2). These discrepancies relate in part to: (1) the differences between human and mouse fat distribution, (2) the dramatic gender-related differences in fat distribution and mass that are seen in humans but not mice, and (3) the well-known metabolic variation between different mouse strains. Although very recent data suggests that adult humans do retain brown adipose tissue (Cypess et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009), this may be another source of mouse-human metabolic differences. The ambient temperature in most mouse facilities is around 21-23°C, which is well below the thermoneutral temperature for mice (~30°C). This means that brown adipose tissue remains very active in adult mice, whereas most adult humans ensure that their immediate environment is close to thermoneutrality for most of the time. Brown adipose tissue may thus be another source of mouse-human metabolic differences in partial lipodystrophy phenotypes, and it may be worth studying more of these models in thermoneutral environments. The relevance of this intervention was highlighted in the uncoupling protein 1 (UCP1) null mouse model that, when first studied, did not appear to be obese (Feldmann et al., 2009). However, when housed at 30°C, these mice do become obese on a chow diet. An alternative approach may be to provide a more extreme caloric challenge to adipose tissue by crossing lipodystrophic mouse strains with *ob/ob* mice.

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COMPETING INTERESTS

The author declares no competing financial interests.

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