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Syndromes of Severe Insulin Resistance

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AN exceedingly large number of studies have convincingly demonstrated that insulin resistance occurs in association with a variety of physiological and pathophysiological states, including obesity, noninsulin-dependent diabetes mellitus (NIDDM), polycystic ovary syndrome (PCOS), and the constellation of central obesity, hypertension, glucose intolerance, and hyperlipidemia known as metabolic syndrome or syndrome X (1, 2) (Table 1). In addition, a number of rare, albeit very interesting, syndromes characterized by extreme insulin resistance have been described over the past 20 yr (3, 4). These syndromes are not only clinically important, but have also significantly contributed to our knowledge of the mechanisms of insulin action and resistance.

In this review, we focus on syndromes characterized by extreme insulin resistance. We present the tools and criteria for the diagnosis of severe insulin resistance and review the clinical phenotypes of type A and type B syndromes of insulin resistance, the HAIR-AN (hyperandrogenism, insulin resistance, and acanthosis nigricans) syndrome, pseudoacromegaly, Rabson-Mendenhall syndrome, leprechaunism, and lipodystrophy (3, 4). Subsequently, we discuss our current knowledge of the underlying pathophysiological mechanisms and explore the current therapeutic approach to these syndromes as well as potential future directions for research in the area.

Definition and in vivo assessment of insulin resistance

Insulin resistance has been broadly defined as "a state (of a cell, tissue, or organism) in which a greater than normal amount of insulin is required to elicit a quantitatively normal response" (3). However, insulin resistance can be selective, *i.e.* involving only certain aspects of insulin action, a fact that complicates both the definition and its characterization *in vitro* or *in vivo* (1, 3). Currently, clinical assessment of insulin resistance (or, conversely, insulin sensitivity) relies on several tests, which, in order of increasing complexity, include determination of insulin levels, either at baseline (fasting) or after oral glucose tolerance testing (OGTT) (5), assessment of sequential plasma glucose levels after the iv administration of insulin (ITT) (5), estimation of an index of insulin sensitivity (Si) by applying the minimal model technique to data obtained from the frequently sampled iv glucose tolerance test (FSIVGTT) (6), and the measurement of *in vivo* insulin-mediated glucose disposal (M) by the euglycemic hyperinsulinemic clamp procedure (7).

Although assessment of either fasting or peak insulinemia after OGTT provides a convenient, readily available means of classifying individuals into normal, mild to moderate, and severe insulin resistant (5), the results of this test must be interpreted in the context of plasma glucose levels, because the presence of any degree of hyperglycemia suggests the presence of defects in insulin secretion, further exacerbates insulin resistance, and invalidates the degree of insulinemia as an index of insulin resistance (5). Fasting insulin levels above 50–70 μU/mL or peak (post-OGTT) insulin levels above 350 μU/mL suggest severe insulin resistance, in contrast to the fasting serum insulin levels below 20 μU/mL or peak (post-OGTT) insulin levels below 150 μU/mL observed in normal individuals (5). Similarly, the rate and degree of plasma glucose fall in response to ITT are dependent not only on insulin sensitivity, but also on the presence and magnitude of the counterregulatory hormone response (including epinephrine, glucagon, cortisol, and GH) (5), thus decreasing the value of ITT in assessing insulin sensitivity *per se*.

In contrast, the assessment of an index of insulin sensitivity (Si) by employing the minimal model kinetic analysis to data obtained from the FSIVGTT appears to represent a more accurate means of quantifying insulin sensitivity (6). In this test, an iv injection of a fixed amount of glucose is followed by frequent blood sampling over 180 min and subsequent modeling of the relevant plasma glucose and insulin data to derive the indexes of insulin sensitivity (Si) and glucose effectiveness (Sg) (6). Si index values below 2×10^4 μU/mL·min typically occur in the presence of severe insulin resistance, whereas values above 5×10^4 μU/mL·min are observed in normal subjects (4). The Si correlates well with the insulin-mediated glucose disposal rate (M), as determined by the euglycemic hyperinsulinemic clamp (7). The latter, considered to be the gold standard in the assessment of insulin resistance, involves the concurrent iv infusion of

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TABLE 1. Conditions and defects associated with insulin resistance

Intrinsic (or primary) defects
Insulin receptor gene mutations (*i.e.* leprechaunism, Rabson-Mendenhall syndrome, type A syndrome)
?IRS-1 mutations
Putative defects in other signaling intermediates, glucose transporters
PC-1 (insulin receptor kinase inhibitor)
Secondary defects
Physiological states
Puberty
Pregnancy
Advanced age
Pathophysiological states
Fasting or starvation
Obesity
Syndrome X (metabolic syndrome)
Hyperglycemia (including diabetes mellitus)
Ketoacidosis
Cirrhosis
Uremia
Stress (e.g. trauma, sepsis)
Endocrine disorders
Acromegaly (GH)
Thyrotoxicosis (thyroid hormones)
Insulinoma and other hyperinsulinemic states (insulin)
Glucagonoma (glucagon)
Cushing's syndrome (glucocorticoids)
Pheochromocytoma (catecholamines)
Other factors
Tumor necrosis factor, other cytokines
Free (nonesterified) fatty acids (?lipodystrophy)
Adenosine
? Islet amyloid polypeptide (amylin)
Autoantibodies to insulin receptor (*i.e.* type B syndrome)

insulin at a fixed rate (usually raising plasma insulin levels to either 100 or 1000 μU/mL) and glucose at a variable rate, as necessary to maintain normoglycemia (8). Upon reaching steady state, the glucose disposal rate (M) is proportional to the exogenous glucose infusion rate (8). Patients with severe insulin resistance have M rates below 2 mg/kg·min, compared with M rates above 6 mg/kg·min in normal individuals (5). Intermediate values typify mild to moderate insulin resistance.

Clinical phenotypes

Clinical findings associated with severe insulin resistance include acanthosis nigricans (1, 3–5), consisting of velvety hyperpigmented and hyperkeratotic patches in skin fold areas, such as the nape of the neck, the axillae, and the groins, and evidence of ovarian hyperandrogenism in postpuberatal females (1, 3–5), including hirsutism, oligoamenorrhea, and infertility. These manifestations apparently involve a selective effect of insulin on skin and ovaries, respectively, mediated at least in part through activation of the insulin-like growth factor I (IGF-I) receptor (1, 3–5, 9).

All syndromes of severe insulin resistance share a number of laboratory findings. Among these, hyperinsulinemia, resulting from increased insulin secretion to compensate for the peripheral insulin resistance and (in many cases) reduced insulin clearance, is by far the most consistent finding (1, 3, 4). Additionally, impaired glucose tolerance or frank diabetes mellitus commonly, but not universally, occur at a later stage in the natural course of these syndromes (1, 3, 4). These manifestations depend on the ability of the pancreas to compensate for the peripheral insulin resistance by increasing insulin secretion (1, 3, 4).

Unique features associated with each syndrome have been recognized as a result of extensive studies and have led to the classification of patients with severe insulin resistance into several distinct phenotypes. The term type A syndrome was originally applied to lean adolescent female patients with severe insulin resistance, acanthosis nigricans, severe ovarian hyperandrogenism, and decreased insulin binding to circulating leukocytes (4) and is currently used for both female and male patients with severe inherited insulin resistance and acanthosis nigricans in the absence of autoantibodies to the insulin receptor (IR) (3, 5). Postpubertal females also have evidence of mild to severe androgen excess of ovarian origin, ranging from hirsutism, acne, oligoamenorrhea, and infertility to frank virilism with markedly elevated testosterone levels (1, 3–5). Additional, but not invariable, features of the syndrome include short stature, acral hypertrophy, accelerated linear growth, muscle cramps, and retinitis pigmentosa (1, 3–5).

In contrast to the typically early onset of the type A syndrome, patients afflicted with the type B syndrome are commonly middle-aged at presentation and, in addition to the common features of severe insulin resistance (*i.e.* abnormal glucose homeostasis, acanthosis nigricans, and ovarian hyperandrogenism), often demonstrate features associated with autoimmunity, including vitiligo, alopecia areata, arthritis, nephritis, and primary biliary cirrhosis, as well as Hodgkin's disease and ataxia-telangiectasia (1, 3–5). These patients may present with fasting hypoglycemia (with or without postprandial hyperglycemia) or may develop hypoglycemia during the course of their disease, even subsequent to a period of hyperglycemia and diabetes (1, 3–5, 10). In addition to nonspecific laboratory findings, including elevated erythrocyte sedimentation rate, leukopenia, hypergammaglobulinemia, serum antinuclear antibodies, and proteinuria, these patients demonstrate the presence of anti-IR antibodies in the plasma (1, 3, 4). Commonly, anti-IR antibody titers are in proportion to the magnitude of insulin resistance (1, 3, 4). These anti-IR antibodies are the diagnostic hallmark of the type B syndrome and explain several of its manifestations, as will be discussed later. The type B syndrome is quite distinct from the resistance to exogenous (usually of animal origin) insulin, which occurs as a result of developing antiinsulin antibodies that bind insulin and prevent its interaction with IRs (3).

In addition to the type A and B syndromes, the term HAIR-AN (hyperandrogenism, insulin resistance, and acanthosis nigricans) has been applied to women with all of the above features, often in association with obesity (5). However, it has not yet been fully clarified whether this syndrome represents a distinct entity from other syndromes of severe insulin resistance, such as the type A and B syndromes, or PCOS (5), and it will not be discussed in detail.

Another very rare syndrome associated with severe insulin resistance was initially described by Mendenhall (3, 11) and is currently known as the Rabson-Mendenhall syndrome. These patients present in childhood with severe in-

sulin resistance and diabetes mellitus (commonly refractory to large doses of insulin), acanthosis nigricans, abnormal nails and dentition, accelerated linear growth, precocious pseudopuberty, and, ostensibly, pineal hyperplasia (3, 11). Prognosis is generally poor, mainly due to the development of severe microvascular complications of diabetes (3).

Leprechaunism was first recognized in 1954 and is characterized by severe intrauterine and postnatal growth retardation and failure to thrive, lipoatrophy, dysmorphic features (globular eyes, large ears, and micrognathia), and acanthosis nigricans (3, 12). These infants have massive hyperinsulinemia, often associated with glucose intolerance or frank diabetes mellitus, in addition to fasting hypoglycemia (3, 12). Additionally, affected female infants commonly have hirsutism and clitoromegaly, whereas affected males commonly present with penile enlargement (3, 12). Other features of this syndrome include dysmorphic lungs, renal disease, and breast hyperplasia (3). Few of these infants live beyond the first year of life, although a few may survive until adolescence (3, 12).

The lipodystrophy syndromes represent a diverse group of disorders characterized by severe insulin resistance and associated with severe hypertriglyceridemia leading to pancreatitis, and fatty infiltration of the liver leading to cirrhosis (3, 5). These syndromes have been conveniently subclassified according to the extent and the location of the lipodystrophy and the age of onset (3, 5). Specifically, newborns or infants with congenital generalized lipodystrophy (Berardinelli-Seip syndrome), an autosomal recessive condition, lack adipose tissue completely in both sc and visceral locations and commonly manifest impaired glucose tolerance or diabetes, accelerated linear growth, precocious puberty, muscular hypertrophy, and hypertriglyceridemia (3, 13). In contrast to the Berardinelli-Seip syndrome, patients with acquired total lipodystrophy (Lawrence syndrome) appear normal at birth, but develop lipoatrophy over days to weeks, sometimes after an infectious prodrome (3). Histological evidence of panniculitis has suggested an inflammatory etiology for this syndrome, although this remains to be demonstrated (3). In addition to the above variants of generalized lipodystrophy, several forms of partial lipodystrophy have been recognized and affect specific body areas. Thus, face-sparing lipodystrophy (Kobberling-Dunnigan syndrome), an X-linked (or, rarely, autosomal dominant) condition, spares the face, which is typically full, in contrast to the lipoatrophic trunk and extremities (3, 14). Another form of partial lipodystrophy occurs in association with mandibuloacral dysplasia and joint contractures and is termed lipodystrophy with other dysmorphic features (3). Additionally, a sporadic form of partial lipodystrophy, named cephalothoracic lipodystrophy, has been described predominantly in women and occurs in association with messangiocapillary glomerulonephritis, presumably as a result of complement activation (3).

Another rare syndrome of severe insulin resistance that was recently described and characterized is insulin resistance in association with acromegaloidism (15). In addition to severe insulin resistance, these patients have features reminiscent of acromegaly, including coarse facies and bone thickening, despite a GH-IGF-I axis that appears to be normal (3, 15). However, whether these physical findings result from high insulin levels signaling through the IGF-I receptor or, alternatively, the IR *per se* remains to be established (3, 15).

Finally, a number of rare genetic syndromes are associated with severe insulin resistance. Among them, Alstrom syndrome, an autosomal recessive disorder, presents with retinitis pigmentosa, sensorineural deafness, hypogonadism, and obesity and is commonly associated with severe insulin resistance and acanthosis nigricans (3). Myotonic dystrophy, an autosomal dominant condition that presents with progressive muscular dystrophy, myotonia, mild mental retardation, baldness, cataracts, and postpubertal testicular atrophy, has been associated with severe insulin resistance (3). Werner's syndrome, a progeria syndrome, presents with bird-like facies, gray hair, cataract formation, slender extremities, and severe insulin resistance (16).

Pathogenesis of severe insulin resistance

Insulin binds to the extracellular (α) subunits of its heterotetrameric receptor, consisting of two (α) and two (β) subunits and activates the intracellular tyrosine kinase in the transmembrane (β) subunits (17) (Fig. 1). Insulin receptor autophosphorylation and subsequent tyrosine phosphorylation of critical intracellular signaling intermediates ensue, including insulin-like substrates 1 and 2 (IRS-1 and -2), Shc, and Gab1 (17, 18). These activated intermediates bind to and activate other signaling molecules, including the adapter proteins Grb2 and Nck, the tyrosine phosphatase Syp, and the phosphoinositide 3-kinase, amplifying and diversifying the initial signal generated by the insulin binding to its receptor (17). A host of protein intermediates are subsequently activated, including the *ras* (Grb2-mSOS-Ras)-mitogen-activated protein kinase pathway, the pp70 kinase, the PKB/Akt (protein kinase B), and possibly other unidentified pathways, and ultimately lead to the well characterized insulin

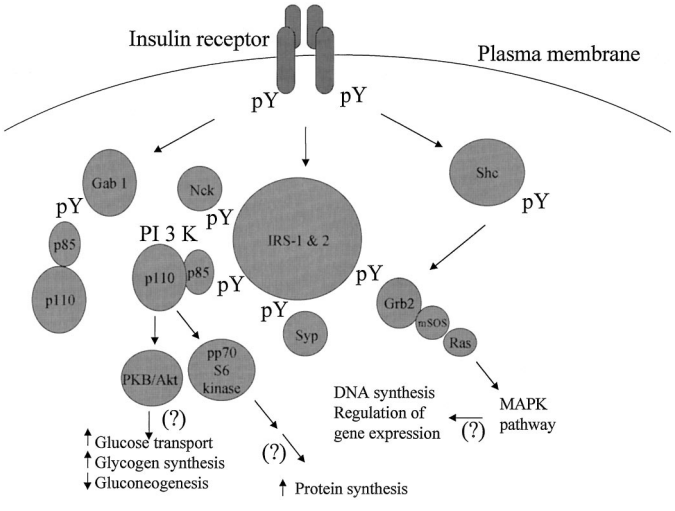

FIG. 1. Overview of the insulin signaling cascade. Abbreviations used in text and figures: ESR, Erythrocyte sedimentation rate; IGT, impaired glucose tolerance;pY, phosphotyrosine; Shc, *src* homology 2 (SH2)-containing protein; Syp, SH2 protein tyrosine phosphatase; PI 3 K, phosphoinositide 3-kinase; GRB2, growth factor receptor-bound protein 2; GAB1, GRB2-associated binder 1; mSOS, mammalian son of sevenless; MAPK, mitogen-activated protein kinase; PKB/Akt, protein kinase B.

effects, such as stimulation of cellular glucose and amino acid uptake, glycogen synthesis, lipogenesis, and mitogenesis by mechanisms that have not been completely elucidated and are currently the focus of intense research (17).

Abnormalities in any of the entire insulin signaling pathway molecules, from the IR until the final effectors, could potentially be implicated in the pathogenesis of severe insulin resistance (Fig. 1). Following the chronology of discovery of the messenger molecules involved in insulin signaling, the researchers' attention was initially turned toward the IR, the first characterized and most obvious such candidate. Since 1988, over 50 mutations of the IR gene have been described, and have been shown to decrease IR synthesis (class I), interfere with intracellular trafficking of the IR (class II), decrease insulin binding (class III), impair IR tyrosine kinase activity (class IV), or lead to accelerated IR degradation (class V). IR mutations (in homozygous or compound heterozygous form) have been found in all patients with leprechaunism or the Rabson-Mendenhall syndrome (17, 18). In patients with the former condition, such IR mutations markedly curtail the availability of IR on the plasma membrane by interfering with IR synthesis or trafficking or by accelerating IR degradation (18). Similarly, in patients with the latter syndrome, the presence of severe defects of the IR gene results in defective IR synthesis and, thus, markedly impaired insulin binding to the IR (18).

Family studies indicate an autosomal dominant or autosomal recessive pattern of transmission of the type A syndrome, with variable penetrance (1, 3–5). Furthermore, *in vivo* studies of such patients show increased hepatic glucose output and diminished insulin-mediated glucose disposal rates (1, 3–5). Such findings are further corroborated by *in vitro* evidence of impaired insulin binding and action at the cellular level (1, 3–5, 19, 20). Although several IR mutations have been previously associated with the type A syndrome (18, 21), it currently appears that most patients with this syndrome do not possess such mutations, implying the presence of other critical primary defects in insulin signaling (22, 23), as seems to be the case in patients with NIDDM (24). Moreover, it appears that the correlation between genotype and phenotype of patients with severe insulin resistance is imprecise, as suggested by the presence of the same (Leu 193 Pro) mutation of the IR gene in a patient with the type A syndrome and in another with the Rabson-Mendenhall syndrome (24).

In addition to mutations of the IR gene, a transmembrane protein named PC-1 has been proposed as the cause of the type A syndrome in one patient (18, 25), possibly by interfering with IR tyrosine kinase activity (18). However, its significance in the pathogenesis of severe insulin resistance has not been conclusively demonstrated (18). Additionally, excessive IR serine phosphorylation has been implicated as a potential mechanism for insulin resistance in a subset of PCOS patients (2).

As mentioned above, anti-IR antibodies occur in association with the type B syndrome, presumably as a result of either loss of immune tolerance or generation of an immune response to an exogenous antigen and autoantibody formation through molecular mimicry (3). These antibodies can lead to insulin resistance by sterically interfering with insulin binding (3), although some anti-IR antibodies appear to lead to IR activation, explaining the fasting hypoglycemia that may occur in these patients (1, 3–5, 10). Additionally, defects of signaling intermediates distal to the IR are increasingly being demonstrated in a minority of patients with severe insulin resistance, including the presence of an IRS-1 mutation in such a patient, although its etiological significance remains unclear (18). More recently, selective impairment of insulin-stimulated phosphoinositide 3-kinase activity was demonstrated in three patients with severe insulin resistance and pseudoacromegaly (26).

Although an autosomal recessive mode of transmission has been suggested for the Berardinelli-Seip syndrome (3, 5), the pathogenesis of associated insulin resistance is poorly understood, and it remains unclear whether insulin resistance is primary or occurs secondary to lipodystrophy. Linkage analysis in 10 families with congenital lipodystrophy failed to implicate 14 candidate genes, the IR, IRS-1, and IGF-I genes among them (27). According to Randle's hypothesis (or cycle), excessive plasma FFA may lead to insulin resistance by decreasing peripheral glucose utilization and increasing hepatic gluconeogenesis (3). In addition, the recent demonstration of insulin resistance in white and brown adipose tissue-diphtheria toxin A-ablated (αBP2-DTA) mice, whose adipose tissue was completely absent (28), suggests that insulin resistance may indeed be secondary to the lack of adipose tissue and raises the hope that the etiologies for human lipodystrophy may be elucidated soon.

The pathogenesis of severe insulin resistance in patients with the previously mentioned rare genetic syndromes is unclear, although impaired insulin binding has been demonstrated in insulin target tissues from patients with myotonic dystrophy (3), and impaired postreceptor insulin signaling has been shown in patients with Werner's syndrome (16).

Treatment

Currently available therapies for the syndromes of severe insulin resistance are nonspecific, as the pathogenesis of these syndromes is incompletely understood. Diet and exercise, in addition to drug therapy, have been the traditional tenets of treatment for diabetes mellitus. Clearly, caloric restriction ameliorates glucose intolerance in patients with diabetes mellitus by improving both peripheral insulin resistance and insulin secretion (29). However, short term severe caloric restriction did not improve the response to exogenous insulin in a small study of women with severe insulin resistance (29). Additionally, although regular exercise may improve the glucose tolerance of patients with NIDDM (29), it is unknown whether exercise improves the peripheral insulin sensitivity in patients with severe insulin resistance. Thus, the roles of diet and exercise in patients with these syndromes require further investigation, although it appears unlikely that the commonly lean, severely insulin-resistant individuals will significantly benefit from caloric restriction and exercise alone.

Moreover, drug therapy for patients with severe insulin resistance syndromes is currently unsatisfactory. Insulin is often administered in very high doses, but usually fails to

provide adequate glycemic control (3, 29). Similarly, administration of sulfonylureas to patients with severe insulin resistance has failed to show significant benefits, probably because these agents act primarily by augmenting insulin secretion, which is already increased in patients with severe insulin resistance (29).

Administration of IGF-I, which may act by binding to either the IGF-I receptor or a functioning IR, has been attempted in patients with several syndromes of severe insulin resistance, including the type A or B syndromes, the Rabson-Mendenhall syndrome, leprechaunism, and lipodystrophy (29–31) (Mantzoros, C. S., and A. C. Moses, unpublished observations) and has led to improvement in glycemic control and decrease in fasting insulin levels in short term studies (29) (Mantzoros, C. S., and A. C. Moses, unpublished observations). However, some of these beneficial effects were not maintained in a 10-week trial (30). Moreover, IGF-I administration is occasionally associated with acute side-effects, such as fluid retention, carpal tunnel syndrome, and jaw pain. In addition, there is concern that IGF-I administration may exacerbate the development of microvascular complications, particularly retinopathy, in patients with diabetes (29), and endogenous IGF-I has recently been associated with breast and prostate cancer (32, 33). Thus, its efficacy-safety profile in patients with severe insulin resistance remains unclear.

Agents that improve insulin sensitivity present attractive candidates for the treatment of individuals with severe insulin resistance. Specifically, metformin, a biguanide that suppresses hepatic glucose output and increases insulin-mediated glucose disposal, has been shown to improve glycemia in patients with the type B syndrome or lipoatrophic diabetes (29), but did not improve the insulin resistance in patients with myotonic dystrophy (29). More recently, troglitazone, a thiazolidinedione that improves insulin sensitivity in NIDDM, was shown to improve insulin resistance in patients with Werner's syndrome (34) and is currently being studied in individuals with other syndromes of severe insulin resistance, including the HAIR-AN syndrome. Furthermore, administration of vanadate or vanadium salts to patients with NIDDM has led to improvement in glycemic profile and peripheral insulin resistance (29, 35), although the roles of these compounds in patients with severe insulin resistance remain unclear. Limited data suggest an improvement in insulin sensitivity in response to administration of phenytoin to patients with the type A syndrome (29). Additionally, functional activation of a mutant IR, obtained from a patient with the Rabson-Mendenhall syndrome, by a monoclonal antibody *in vitro* led to improved IR autophosphorylation and glycogen synthesis *in vitro*, raising hopes that such therapy may benefit patients with severe insulin resistance (36). Small studies suggest improvement in insulin sensitivity of patients with lipodystrophic diabetes in response to administration of bezafibrate (37) or dietary supplementation with ω-3 fatty acid-rich fish oil (29), possibly by interfering with Randle's cycle (3). Finally, immunosuppressants and plasmapheresis have been tried in some patients with the type B syndrome with beneficial results (3).

Future directions

Although significant progress has been made in our understanding of the syndromes associated with severe insulin resistance, much remains to be accomplished. Thus, the critical defects in insulin signaling responsible for the severe insulin-resistant syndromes remain to be elucidated. Additionally, the clinical description of syndromes, such as the HAIR-AN syndrome, must be clearly distinguished from more common phenotypes associated with moderate insulin resistance. On-going studies must clarify the role of currently available therapies aiming at ameliorating insulin resistance, such as troglitazone and vanadate, and the efficacy-safety profile of other treatments, such as IGF-I (29). Undoubtedly, novel therapies targeted at correcting the underlying defects in a specific manner are very much needed. It is hoped that the rapid advances in our understanding of insulin signaling will lead to such novel drug design, including gene therapies for both the common entities associated with insulin resistance as well as these rare but debilitating disorders.

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