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An Increased Membrane Glycoprotein PC-1 in a Werner's Syndrome Patient with Rare Compound Heterozygous Mutations

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Diabetes mellitus is known to be one of the common metabolic disorders in the Werner's syndrome (WS). It is thought that intracellular defects at the downstream of receptor signaling step cause insulin resistance in WS patients. Recently a membrane glycoprotein referred to as plasma cell differentiation antigen (PC-1) was speculated to play a role in the insulin resistance of non-insulin-dependent diabetes mellitus (NIDDM) by inhibiting the signaling mediated by the insulin receptor. Because there is no previous report showing increased PC-1 activity in WS patient, this study was undertaken to determine whether the expression of glycoprotein PC-1 is upregulated in the WS patient. The PC-1 activities of the cultured dermal fibroblasts from a 29-years-old Japanese man with WS, who had a compound heterozygous mutation consisting of mutation-4 and -6, and seven healthy controls were determined. The level of PC-1 activity of the dermal fibroblasts from the WS patient was 99.0 nmol/mg/min, and higher than that of non-diabetic healthy controls, 42.6 ± 13.8 nmol/mg/min (mean ± SD). This result suggests that glycoprotein PC-1 may play a role at least in part in the pathogenesis of insulin resistance in a patient with WS, accounting perhaps for a high frequency of diabetes mellitus in WS patients.

Introduction

In 1904, Otto Werner, an ophthalmologist in Germany, first described four patients with progeric features in his doctoral thesis "Über Katarakt in Verbindung mit Sklerodermie"[1]. Patients with Werner's syndrome (WS) prematurely appear old, with graying and/or loss of hair, a high pitched voice and/or hoarseness, and juvenile bilateral cataract. Other features are a bird-like face, a stocky trunk, slender extremities due to subcutaneous tissue atrophy, peripheral muscle atrophy and sclerodermatous skin change. Clinical features consist of arteriosclerosis, osteoporosis, diabetes mellitus and several types of benign and malignant neoplasms. The WS is an autosomal recessive genetic disease, and the gene re-

sponsible for this disease is assigned to the short arm of chromosome 8[2)3)]. In 1996, the gene responsible for the WS was identified by positional cloning[4)]. The predicted gene product is a large protein with 1,432 amino acids showing a significant similarity to RecQ type DNA helicases. Expression of the intact WS gene by a baculovirus system in insect cells showed that the WS gene produces an active ATP-dependent DNA helicase that belongs to the RecQ DNA helicase family[5)]. A total of 19 different types of gene mutations have so far been identified with the patients in Japan and other countries[6)~8)].

This report describes clinical features of a 29-years-old Japanese male patient who came to our hospital. He had juvenile cataract and graying hair that was partly being lost. He had slender extremities with atrophied peripheral muscle, and a high pitched voice characteristic of symptoms of WS. Because the patient was suspected of having WS, a genetic diagnosis, including direct nucleotide analysis, was made to investigate potential mutations in the WS gene. As described in the Results section, he had a compound heterozygous mutation consisting of mutation-4 and -6.

A high tendency to have diabetes mellitus or abnormal glucose tolerance has been reported for WS patients[9)]. Notably, increased levels of the fasting serum insulin concentration have been reported for the WS patients, suggesting that they have insulin resistance.

Insulin resistance is one of the characteristic features of non-insulin-dependent diabetes mellitus (NIDDM). Sbraccia P et al[10)] and Maddux BA et al[11)] reported that a glycoprotein extracted from the dermal fibroblasts of a patient with insulin resistance inhibited the tyrosine kinase activity of insulin receptor in vitro. This tyrosine kinase inhibitor was recently identified as a membranous protein referred to as plasma cell differentiation antigen (PC-1), and this glycoprotein is speculated to play a role in the insulin resistance of NIDDM[12)] by inhibiting the signaling mediated by the insulin receptor. There is no previous report showing increased PC-1 activity in WS patient. Together with mutation analysis for a WS patient, PC-1 activity was measured in order to determine whether the expression of glycoprotein PC-1 is upregulated in a WS patient.

Table 1 Hormone levels of the WS patient

T_3	133 ng/dl	serum-E	0.01 ng/ml
T_4	6.0 μg/dl	NE	0.33 ng/ml
TSH	5.0 μU/ml	DA	0.02 ng/ml
free T_3	2.96 pg/ml	DOPA	1.8 ng/ml
free T_4	0.76 ng/dl	urine-E	6.2 μg/day
testosterone	636.0 ng/dl	NE	68.2 μg/day
free testosterone	31.8 pg/ml	DA	710 μg/day
ACTH	20.4 pg/ml	DOPA	40 μg/day
cortisol	9.2 μg/dl	MN	0.06 mg/day
		NMN	0.13 mg/day

E: epinephrine, NE: norepinephrine, DA: dopamine, MN: metanephrine, NMN: normetanephrine.

Patient and Methods

1. A patient with Werner's syndrome

The patient in this study was a 29-years-old Japanese man, who had characteristic features of WS, including premature senility, early graying of and loss of hair, juvenile cataract with a history of onset at 15-years-old. He was 170.1 cm tall, and 63.3 kg in weight (body mass index: 21.2). He had slender extremities with subcutaneous tissue and peripheral muscle atrophy, and a bird-like face. He had a high pitched voice. His parents were known to be consanguineous. His mother died from brain tumor at 34-years-old. He had hypothyroidism, free T_4 was 0.76 ng/dl and TSH was 5.1 μU/ml. Hypogonadism was not found, and the adrenal function was within the normal range (Table 1).

2. Metabolic study

We calculated a homeostasis model assessment for insulin resistance (HOMA-R), which was a simple index of insulin resistance by Matthews et

al[13], of the levels of fasting serum glucose and insulin concentration (fasting glucose (mmol/L) × fasting insulin (μU/ml)/22.5). A 75g-oral glucose tolerance test and a glucagon intravenous injection test were carried out. An euglycemic glucose clamp study at an infusion rate of 1.12 mU of insulin per kg body weight per minute was performed according to the method by DeFronzo et al[14]. The clamp study was continued until the glucose infusion rate was maintained at a steady state for at least 60 minutes, and the plasma glucose concentration remained at 80 mg/dl. The mean glucose infusion rate (GIR) in healthy control subjects was 6.81 ± 1.61 mg/kg/min (mean ± SD: n=46) and that in NIDDM patients was 3.59 ± 2.06 mg/kg/min (n=130) in our hospital.

3. Gene mutation analysis

The patient was informed about the aim of the study and his informed consent was obtained. DNA was extracted from peripheral blood leukocytes. A polymerase chain reaction (PCR) was carried out using this DNA, as a template, and specific primers designed to detect the mutation sites. The nucleotide sequences of DNA fragments amplified by the PCR were determined as described by Matsumoto T et al[7].

4. PC-1 activity of cultured fibroblasts

Dermal fibroblasts taken from the patient and seven healthy controls by forearm skin biopsy were cultured in DMEM medium with 10% FCS. The PC-1 activity of the dermal fibroblasts was determined as described by Maddux BA et al[12]. Briefly, the cells were grown until confluent, washed three times with phosphate-buffered saline (PBS) and were solubilized in 150 mM NaCl, 1% Triton X-100, 1mM phenylmethylsulfonyl fluoride and 20 mM imidazole (pH 7.8) for 1 hour at 4℃. Supernatants containing 0.05～3 μg protein were then incubated with 9 nmol [^{35}S] 3'-phosphoadenosine-5'-phosphosulphate (PAPS) in the presence of 0.1 μmol $MgCl_2$ in 20 μl buffer (0.1 M 2-amino-2-methyl-1-propanol-HCl, pH 9.4; Sigma, Tokyo) for 30 min at 37℃. Twenty five μl of 0.1 M sodium acetate (pH 5.5) was added and samples were boiled for 1 min. Then 0.5 ml of activated charcoal (40 mg charcoal per ml in 20 mM sodium sulphate) was added. After 10 min on ice, the tube mixture was centrifuged, and the radioactivity in the supernatant was counted by liquid scintillation counter.

5. Hormone assays

The serum immuno-reactive insulin (IRI) was measured by a commercially available enzyme immunoassay kit (Japan Roche Co, Tokyo, Japan). The serum C-peptide immunoreactivity (CPR) level was measured by the RIA kits (Shionogi Pharmacia Co, Osaka, Japan).

Results

1. Gene mutation

We found that the patient has two different gene mutations, each on one of the two WS gene alleles (data not shown). One was mutation-4, a base substitution (G→C at splicing junction 3370 th base), which resulted in the deletion of 95 bp corresponding to exon 264). Another was mutation-6, which was a nonsense mutation converting the codon CGA (at nucleotide 1336 of the cDNA) to a stop codon TGA[7]. The protein generated by mutation-6 is predicted to be truncated at amino acid residue 368 and does not contain the helicase domain essential for the DNA helication.

2. Metabolic study

Fasting levels of both IRI (43.8 μU/ml) and CPR (5.2 ng/ml) were elevated when the fasting plasma glucose of the patient was 137 mg/dl. The insulin resistance index of HOMA-R was 14.8. During a 75 g-oral glucose tolerance test, plasma glucose concentrations were 188 mg/dl at fasting, and 381 mg/dl at 120 min. The plasma IRI concentrations were 61.3 μU/ml at fasting, 98.5 μU/ml at 30 min, 129.1 μU/ml at 60 min, 156.0 μU/ml at 120 min (Fig. 1). In the glucagon test, the

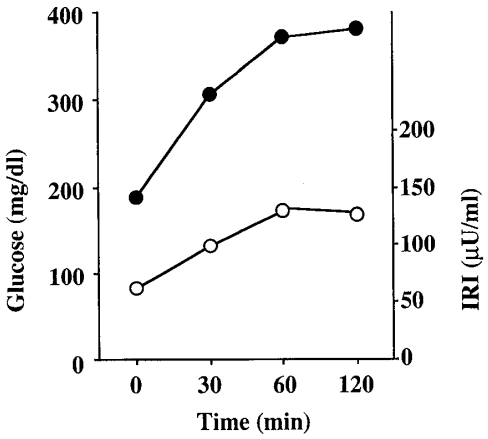

Fig. 1 Profile of plasma glucose level and insulin level during a 75g-oral glucose tolerance test in the WS patient
●: plasma glucose concentration (mg/dl), ○: immuno-reactive insulin (μU/ml).

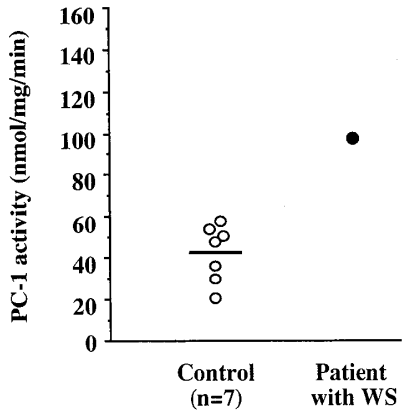

Fig. 2 A high PC-1 activity in fibroblasts from the WS patient
The level of PC-1 activity of the WS patient was 99.0 nmol/mg/min, higher than that of non-diabetic healthy controls, 42.6 ± 13.8 nmol/mg/min (mean ± SD).

Table 2 Glucagon test

Time (min)	0	6
Glucose (mg/dl)	124	134
CPR (ng/ml)	4.2	6.7

CPR : C-peptide immunoreactivity.

plasma CPR concentrations were 4.2 ng/ml at fasting, 6.7 ng/ml at 6 min after 1 mg glucagon injection (Table 2). The hyperinsulinemic euglycemic glucose clamp study in the patient showed that the GIR was 1.21 mg/kg/min at a plasma glucose level of 80 mg/dl.

3. PC-1 activity

The level of PC-1 activity of the WS patient was 99.0 nmol/mg/min, and was higher than that of non diabetic healthy controls (42.6 ± 13.8 nmol /mg/min, mean ± SD; n=7, Fig. 2)[15].

Discussion

WS is an autosomal recessive genetic disease. Its causative gene was assigned to the short arm of chromosome 8 p 11–12, and was recently identified to code for a RecQ type DNA helicase[2)3)]. Despite these findings, nothing is known about the exact biological function of WS helicase in the cells of normal individuals, although data are accumulating that cells from WS patients show a hyper DNA recombination, resulting in chromosomal instability[16]. At least 19 different types of mutations have been found in WS patients worldwide, and 8 types of mutations have been identified in WS patients in Japan where WS patients are most frequently found[6)~8)]. Mutation-4 causes a deletion of 95 bp corresponding to a single exon 26 by a single base change at the splice donor sequence[4]. By contrast, mutation-6 is a nonsense mutation converting an arginine codon CGA to a stop codon TGA. Mutation-6 results in the production of a truncated, and an apparently inactive, helicase consisting of 369 amino acids, while mutation-4 generates a truncated and deficient helicase that is unable to migrate from the cytoplasm to the nucleoplasm[17)18)].

In the Japanese patient population analysis, mutations-4 and -6 are most popular, while other mutations are rare[6]. Our epidemiological studies showed that mutations-4 and -6 are two major mutations in Japan; among the total of 126 chromosomes examined, mutations-4 and -6 comprised 50.8% and 17.5% of the total[7]. Curiously, those patients with mutations-4 and -6 apparently

share a same genetic background. Whereas, it is rare that WS patients have a compound heterozygosity with mutation-4 and -6 (4.8% of the total of Japanese WS patients). We identified this type of compound heterozygosity in our patient. A rapid and reliable procedure of genetic diagnosis to identify the mutated WS gene will be important in the future, because the carriers of the mutated WS gene are predicted to be one out of 200～400[4]. Japan is considered to be unique in the epidemiology of WS, representing the highest frequency of this syndrome in the world.

Diabetes mellitus is known to be one of the most common metabolic disorders in the WS, especially insulin resistance, with 44% of WS patients being complicated by diabetes mellitus[9]. The hyperinsulinemic euglycemic clamp study revealed a decreased sensitivity in the WS patients to the exogenously administered insulin[19]. In our patient, a higher fasting insulin level, excessive secretion of insulin during the glucose loading test and a lower glucose disposal rate upon the hyperinsulinemic euglycemic glucose clamp were observed, indicating that he had a severe insulin resistance. Having hyperglycemia despite the pronounced hyperinsulinemia suggested that a biologically ineffective insulin, or high concentrations of anti-insulin hormones exist, or alternatively, the subnormal insulin effects are ongoing at the cellular level. No anti-insulin antibody and anti-insulin receptor antibody was, however, present in our WS patient. Furthermore, normal or subnormal concentrations of serum cortisol, growth hormone, glucagon and thyroxin contribute to the argument against antagonism by anti-insulin hormones. There were previous reports that autophosphorylation of insulin receptors in erythrocytes was within the normal range, and insulin binding was also normal in WS patients[19)~22)]. However, glycogen synthase activity and glucose uptake are reduced when stimulated by insulin[20)22)]. Thus, an intracellular defect at the downstream receptor signaling step is possible.

A membrane glycoprotein that inhibits the insulin receptor tyrosine kinase in vitro was isolated from the fibroblasts of NIDDM patients. This glycoprotein inhibitor was recently identified as the glycoprotein PC-1[10)~12)]. Additional evidence that the PC-1 is upregulated in the fibroblasts from eight out of ten NIDDM patients examined, and that the insulin receptor kinase activity is inhibited in the PC-1-transfected cells[12)], strongly support a potential involvement of PC-1 protein in the insulin resistance. In the whole body, adipose tissues and muscle are the tissues most uptaking glucose[23)]. The PC-1 levels in muscle is inversely correlated to the insulin-stimulated glucose transport of skeletal muscle[24)25)] and the PC-1 content in adipose tissue correlates with the insulin sensitivity of the whole body[26)]. These findings indicate that PC-1 may have a role in insulin resistance both in vivo and in vitro, and reduced insulin stimulation of insulin receptor tyrosine kinase activity in vitro. The findings prompted us to examine the PC-1 content expressed in patient fibroblasts less invasively. The PC-1 activity in the cultured fibroblasts of our patient was higher than that of normal subjects. This result indicates that glycoprotein PC-1 may be one of causes of insulin resistance in our patient. Several mechanisms have been postulated to understand the early steps of the insulin receptor signaling. One of the mechanisms is based on the idea that autophosphorylation of the receptor β-subunit facilitates interactions between the receptor molecule to other cellular proteins. Glycoprotein PC-1, however, is not expressed in erythrocytes, the autophosphorylation of the insulin receptor and the insulin binding is within the normal range. Two hypotheses explain the insulin resistance in WS, one is the defect in the in-

tracellular signaling of insulin, and the other is the inhibition of the autophosphorylation of the insulin receptor by PC-1.

Glycoprotein PC-1 was originally described as a cell surface marker of the immunogloblin secreting B lymphocytes[27]. However, this protein is also expressed in fibrobrasts, placenta, cartilage, the distal convoluted tubules of the kidney, ducts of the salivary grand, epididymis, chondrocytes, skeletal muscle and adipose cells[10)28)29)]. Glycoprotein PC-1 is a 115～135 kDa transmembrane protein and forms a dimer by disulfide-bonded polypeptide chains, depending on the cell type. It is a type II transmembrane protein containing a short cytoplasmic NH_2-terminal domain and a large COOH terminal extracellular domain that shows enzymatic activity cleaving phosphosulphate, pyrophosphate, and phosphodiester bonds[30)31)]. A cysteine-rich region is adjacent to the extracellular surface domain of the molecule[29]. In situ hybridization showed that the human PC-1 gene is in chromosome 6q22 q23[32]. The PC-1 contains extracellular phosphodiesterase and pyrophosphatase activity that decreased the extracellular adenosine triphosphate[33]. The mutated PC-1 lacking the phosphodiesterase and pyrophosphatase activity is able to inhibit the autophosphorylation of the insulin receptor[34]. How the PC-1 exerts an inhibitory effect on the insulin receptor remains to be not clarified, although it is plausible that the extracellular domain of the PC-1 protein may form a complex with the insulin receptor.

In conclusion, we identified a rare compound heterozygous mutation consisting of mutation-4 and -6 in our WS patient. A significant increase in glycoprotein PC-1 level was found in our WS patient who carried this compound heterozygous mutations. It suggested that an increased level of glycoprotein PC-1, and its inhibitory effect on the tyrosine kinase of the insulin receptor, may have a role in the pathogenetic insulin resistance of the WS, accounting perhaps for a high frequency of diabetes mellitus in WS patients.

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Werner Syndrome における遺伝子変異の同定とチロシンキナーゼ阻害物質 PC-1 活性の上昇

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ウェルナー症候群（WS）はインスリン抵抗性を高率に合併する早老症である．本症疑診例の遺伝子変異を検索し，さらにインスリン受容体チロシンキナーゼ阻害物質 PC-1 活性の面からインスリン抵抗性を検討した．

症例は 29 歳男性で，インスリン抵抗性糖尿病（FPG：137 mg/dl，IRI：44 μU/ml，GIR：1.21 mg/kg/min）と特徴的な身体所見から WS が疑われた．

末梢血白血球 DNA より WS 遺伝子の変異を調べたところ，WS 遺伝子の mutation-4, -6 の複合変異を同定した．また，患者由来の培養皮膚線維芽細胞における PC-1 活性を測定したところ，PC-1 活性は 99.0 nmol/mg/min と正常人（42.6±13.8）に比し上昇していた．

WS 遺伝子の稀な変異を有する WS の 1 例を見出し，PC-1 活性の上昇を確認した．膜糖蛋白 PC-1 が WS におけるインスリン抵抗性の一因となっている可能性も示唆された．