Pluripotent PPARγ polymorphisms

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Genetic factors are associated with up to 80% of the variance in body mass index (BMI = weight in kilograms divided by the square of the height in meters) (1). In several recent papers (2–6), possible links between obesity and genetic variants of the peroxisome proliferator activated receptor type gamma (PPARγ), which has an important role in adipocyte differentiation, have been studied.

The genetic predisposition to an obese phenotype is probably multifactorial. Single gene mutations have been demonstrated only in some extremely rare cases of severe human obesity. The mutations have been associated with dysfunction of signaling systems that are crucial for the hypothalamic control of appetite and energy expenditure. The protein hormone, leptin, which is secreted from adipocytes in proportion to the amount of fat mass, acts as a negative feedback signal on the hypothalamic regulation of food intake. Defects in the genes encoding both leptin and its receptor have been demonstrated in individuals with severe obesity (7, 8). The other known monogenic causes of obesity have been linked to a disruption of melanocortin-4 receptor (MC4R) activation. MC4R is highly expressed in the hypothalamus, and the ligand for MC4R is α-melanocyte-stimulating hormone (α-MSH). The prohormone, pro-opiomelanocortin (POMC), serves as a precursor for several hormones, including α-MSH. Defects in the genes encoding both POMC and the POMC-processing enzyme, prohormone convertase 1, have been demonstrated in humans with extreme overweight, whereas inactivating mutations in the MC4R gene comprise the only known dominantly inherited form of human obesity (9–12).

In a search for genetic factors contributing to an obese phenotype, the gene encoding PPARγ has been scanned for mutations. Peroxisome proliferator activated receptors (PPARs) are members of the nuclear hormone receptor superfamily (13, 14). They are transcription factors, which form heterodimers with retinoid X receptors. The heterodimers bind to responsive elements in the regulatory regions of various genes and regulate gene expression. There are three known subtypes of PPARs (PPARα, PPARβ, and PPARγ). PPARγ exists in several isoforms, and PPARγ3 was recently described (15). PPARγ1 and PPARγ2 are identical, except for the addition of 28 amino acids in the amino-terminal region of PPARγ2.

PPARγ1 is expressed in several tissues, including fat, skeletal muscle, heart and liver. PPARγ2 is found almost exclusively in adipose tissue, and PPARγ3 expression is restricted to adipose tissue and large intestine. The receptors can be activated by polyunsaturated fatty acids and prostaglandin derivatives, which may be the endogenous ligands for PPARγ. The antidiabetic thiazolidinediones, which improve insulin sensitivity, are synthetic ligands for PPARγ and promote the differentiation of fibroblasts to adipocytes. The same induction of adipocyte differentiation has been observed in fibroblasts overexpressing PPARγ2.

The long amino-terminal region of PPARγ2 includes a domain that renders the receptor more susceptible than PPARγ1 to ligand-independent activation. However, phosphorylation of a serine residue corresponding to position 114 of the human PPARγ2 attenuates the effect of the receptor on adipocyte differentiation. The serine is part of a typical phosphorylation site for mitogen-activated protein kinase (MAP kinase), which insulin and growth factors can activate. MAP kinase activation reduces the sensitivity of PPARγ to thiazolidinediones (16). Ristow et al. (2) screened DNA from 32 obese individuals for mutations in the PPARγ gene that might affect this serine phosphorylation site. They found a missense mutation, which was predicted to change the neighboring proline at position 115 to glutamine (Pro115Gln). One-hundred and twenty-one obese and 237 normal-weight individuals were studied, and four heterozygous Pro115Gln carriers were detected among the obese group; the mutation was not observed among the normal-weight individuals. The four Pro115Gln heterozygotes were significantly more obese than the other obese individuals, and three of the four had type 2 diabetes; however, the participants were originally recruited by random selection of patients with type 2 diabetes and their spouses or employees at the institutions participating in the study. Insulin sensitivity seemed to be increased in the heterozygotes, as fasting insulin levels were lower than those of the other obese individuals. Ristow et al. (2) also studied the effect of the mutation in fibroblasts. Lipid accumulation in cells expressing the Pro115Gln variant of the receptor increased more than in fibroblasts transfected with the wild-type receptor and indicated that receptor activity was augmented by the mutation. The mutation described by Ristow et al. (2) may represent a novel form of dominantly inherited obesity.

Yen et al. (17) also screened the PPARγ gene for mutations in obese and non-obese diabetic whites and discovered a relatively common polymorphism at the
The clinical observations to date are inconclusive of any biological significance of the PPARγ agonists is generally not associated with weight gain (13).

A silent C-to-T nucleotide substitution in exon 6 of the PPARγ gene has also been described. In a study of 820 French men and women by Meihaege et al. (6) obese individuals carrying at least one T allele had greater plasma concentrations of leptin than C-allele homozygotes with a similar BMI. Those with the T allele seemed to be less obese than expected from their plasma leptin. It is not known whether the T allele affects the cellular level of PPARγ, or whether it is in linkage disequilibrium with another nearby mutation.
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PPARγ is an important target in the treatment of diabetes, but differentiating effects of thiazolidinediones have also been observed in cancer cells. The PPARγ variants have been shown to differ in their responses to thiazolidinediones in vitro. A future role of PPARγ genotyping may be to predict individual effects of treatment with PPARγ agonists.

References


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