Review

GENETICS AND ITS IMPACT ON MANAGEMENT OF DIABETES IN THE NEXT DECADE

Nicola Abate

ABSTRACT

The recent advances in our understanding of the molecular mechanisms of insulin signaling constitutes a unique opportunity to evaluate the possible genetic mechanisms involved in "predisposition" of some individuals to develop diabetes. Recent evidence suggest that common genetic polymorphisms that affect essential metabolic pathways leading to a complex disease such as diabetes, may have a major role in predisposition to diabetes. One important metabolic abnormality that increases the risk of type 2 diabetes is insulin resistance, a defect in the biochemical actions of either endogenous or exogenous insulin, frequently found in relatives of type 2 diabetic patients prior to the onset of the disease. Some ethnic groups, like the Asian Indians, are characterized by excessive prevalence of insulin resistance and excessive risk for type 2 diabetes. We are currently investigating the role of common genetic polymorphisms of genes known to affect the proximal insulin signaling, in the development of genetic predisposition to insulin resistance and type 2 diabetes.

KEY WORDS: Type 2 diabetes; Insulin resistance; genetic polymorphism; insulin signaling.

The recent advances in the understanding of the molecular basis of insulin signaling have elucidated some genetic mechanisms that could be responsible for development of insulin resistance. It appears that the genetic alterations responsible for the occurrence of complex diseases, such as insulin resistance, may more likely involve multiple point mutations that, accumulated over the course of thousands of years and may have developed as a genetic advantage (1,2). According to the thrifty genotype hypothesis (3), a predisposition to insulin resistance may have protected individuals during periods of food deprivation by reducing muscle utilization of glucose and favoring glucose utilization in organs, such as the brain that operate through an insulin-independent mechanism. The recent occurrence of excessive food availability and reduced physical activity constitute a rapid environmental change that interacts with the genetic predisposition to insulin resistance inducing a pathological decrease in glucose utilization. A genetic advantage has therefore become a genetic disadvantage and a cause of disease. Multiple mutations of genes that individually are associated with a small change in insulin sensitivity, when combined may induce a significant reduction in insulin sensitivity. Therefore, the identification of individual mutations contributing to reduced biological effects of insulin will likely provide the key to the understanding of the genetic basis of insulin resistance. The following is a summary of the known effects of genetic mutations affecting the function of specific proteins involved in the various steps of the insulin-signaling pathway.

INSULIN RECEPTOR

Several mutations of the insulin receptor that can cause insulin resistance have been described (4). However, these mutations occur infrequently in the general population and thus account only for a small portion of the genetic causes of insulin resistance.

PHOSPHOTYROSIN PHOSPHATASE (PTPase)

PTPase is responsible for dephosphorylation of the insulin receptor and its substrates, and hence, for the turning off of the insulin signal. Total membrane-bound phosphatase activity is increased in skeletal muscle of type 2 diabetic patients (5). Immunodepletion experiments in muscles from these diabetic patients and obese individuals suggest that especially two phosphatases, protein- tyrosine

From University of Texas. Southwestern Medical Center, Dallas, Texas, USA

phosphatase 1B (PTP-1B) and leukocyte antigen-related (LAR) phosphatase, are responsible for this increase (5). Plasma cell differentiation factor-l (PC-l) is a membrane glycoprotein with ectonucleotide pyrophosphatase activity that seems to act as an intrinsic inhibitor of insulin receptor tyrosine kinase activity (6). In healthy subjects with no clinically significant defects in glucose metabolism, PC-l expression in muscle negatively correlates with insulin sensitivity in intravenous insulin tolerance test and in vitro stimulation of muscle insulin receptor tyrosine kinase activity (7). Theoretically, polymorphisms of PTP-1B, LAR, PC-1 could impair insulin-signaling cascade and contribute to insulin resistance. However, no polymorphism of PTPase is described at this time.

IRS-I

IRS-1 was the first insulin-receptor substrate identified and the first to be found to have multiple natural polymorphisms (8-13). Polymorphisms of IRS-1 are significantly more common in type 2 diabetic patients than in controls and include the G972R (glycine 972arginine), S892G, G819R, R1221C, and A513P variants (8,9,13). Of these, the G972R polymorphism is the most common and has been studied most extensively. This polymorphism is found in Caucasian populations, with a prevalence of 5.8% in normal and 10.7% in type 2 diabetic patients, respectively. In Caucasian populations, obese carriers of this polymorphism show decreased insulin sensitivity during an oral glucose tolerance test, and an individual homozygous for the codon 972 mutation had a diabetic response to dexamethasone challenge. The polymorphism G972R does not occur in Pima Indians (14). Diabetic Asian Indians do not seem to have increased prevalence of G972R variant as compared to diabetic Caucasians (15). However, no studies are available on the prevalence of this polymorphism in non-diabetic Asian Indians. In Japanese type 2 diabetic patients, several additional polymorphisms have been described, including P190R, M209T, and S809F polymorphisms, and silent nucleotide variants Ll42 and G625 A804 (10). While the prevalence of each of these polymorphisms alone is not different between patients and healthy controls, the combined prevalence of these polymorphisms, along with the G972R polymorphism, is threefold greater compared with healthy controls (29.5 vs. 8.5%; $p < 0.05$). In a euglycemic, hyperinsulinemic clamp, the insulin sensitivity in the carriers versus noncarriers of these polymorphism is decreased 29.5% in type 2 diabetics and 22% in healthy subjects. Recently, two polymorphisms in IRS-2 have been described in the Caucasian population: a substitution of G1057D and G879S (16). Amino acid polymorphisms of IRS-4 are also common in the Caucasian population. However, neither of these identified polymorphisms is associated with type 2 diabetes or insulin resistance (16,17).

PI3-kinase

A common polymorphism of the p85 subunit of PI3-kinase changes methionine in position 326 to isoleucine. In one study, 31% of Caucasians carried the mutation in its heterozygous form and 2% in its homozygous form. This polymorphism occurs in a region between the SH3 domain and the first SH2 domain, but the functional effects have not been studied in vitro. Although the frequency is not increased in diabetes, homozygous individuals do exhibit a 32% reduction in insulin sensitivity compared with wild type and heterozygous carriers in an intravenous glucose tolerance test (18).

Other genetic variants associated with insulin resistance involve the Rad gene – Ras associated with diabetes) (19-21). The elucidation of the mechanisms leading to the development of insulin resistance will have a major impact to better focus our therapeutic strategies for diabetes prevention and treatment. Early identification of individual at risk will be extremely useful to optimize public health efforts to halt the rampant epidemic of diabetes throughout the world.

REFERENCES

1. Lander E. S., Schork N. J.. Genetic dissection of complex traits. Science 1994;265:2037-48.
2. Chakravarti A. 1999. Population genetics—making sense out of sequence. Nat Genet 1999;21(Suppl)1 :56-60.
3. Neel J.V. Diabetes Mellitus: a thrifty genotype rendered detrimental by progress?. Am J Humn Genet 1962; 14:353-62
4. Krook A., O'Rahilly S.. Mutant insulin receptors in syndromes of insulin resistance. Bailliers Clinical Endocrinology Metabolism 1996;10:97-122.
5. Ahmad F., Azevedo J., Cortright R., Dohm G. L., Goldstein B. J.. Alterations in skeletal muscle protein-

tyrosine phosphatase activity and expression in insulin-resistant human obesity and diabetes. Journal Clinical Investigations 1997;100:449-58.

6. Maddux B. A., Sbraccia P., Kamakura S., Sasson S., Youngren J., Fisher A., Spencer S., Grupe A., Henzel W., Stewart T. A.. Membrane glycoprotein PC-1 in the insulin resistance of non-insulin dependent diabetes mellitus. Nature 1995;373:448-51.

7. Kumakura S., Maddux B. A., Sung C. K.. Overexpression of membrane glycoprotein PC-1 can influence insulin action at a post-receptor site. Journal of Cellular Biochemistry 1998;3:366-77.

8. Almind K., Bjorbaek C., Vetergaard H., Hansen T., Echwald S., Pedersen O.. Amino acid polymorphisms of insulin receptor substrate-1 in non-insulin dependent diabetes mellitus. Lancet 1993;342:828-32.

9. Laakso M., Malkki M., Kekalainen P., Kuusisto J., Deeb S. S.. Insulin receptor substrate-1 variants in non-insulin-dependent diabetes. Journal of Clinical Investigation 1994;94:1141-6.

10. Ura S., Araki E., Kishikaua H., Shirotani T., Todaka M., Isami S., Shimoda S., Yoshimura R., Matsuda K., Motoyoshi S., Miyamura N., Kahn C. R., Shichiri M.. Molecular scanning of the IRS-1 gene in Japanese patients with non-insulin-dependent diabetes mellitus: identification of five novel mutations in IRS-1 gene. Diabetologia 1996;39.

11. Hager J., Zouali H., Velho G., Froguel P.. Insulin receptor substrate (IRS-1) gene polymorphism in French NIDDM families. Lancet 1993;342:1430

12. Imai Y., Frusco A., Suzuki Y., Lesniak M. A., D'Alfonso R., Sesti G., Bertoli A., Lauro R., Accili D., Taylor S. I.. Variant sequences of insulin receptor substrate-1 in patients with noninsulin dependent diabetes mellitus. Journal of Clinical Endocrinology and Metabolism 1994;79:1655-8.

13. Yoshimura R., Araki E., Ura S., Todaka M., Tsuruzoe K., Furukawa N., Motoshima H., Yoshizato K., Kaneko K., Matsuda K., Kishikaua H., Shichiri M.. Impact of natural IRS-1 mutations of insulin signals: mutations of IRS-1 in the PTB domain and near SH2 protein binding sites result in impaired function at different steps of IRS-1 signaling. Diabetes 1997;46:929-36.

14. Celi F. S., Silver K., Waltson J., Knwler W. C., Bogardus C., Shuldiner A. R.. Lack of IRS-1 codon 513 and 972 polymorphism in Pima Indians. J Clin Endocrinol Metab 1995;80:2827-9.

15. Hitman G. A., Hawrami K., Mckarthy M. I., Viswanathan M., Snehalatha C., Ramachandran A., Tuomilehto J., E. Tuomilehto-Wolf, Nissinen A., Pedersen O.. Insulin receptor substrate-1 gene mutations in NIDDM; implications for the study of polygenic disease. Diabetologia 1995;38:481-6

16. Kalidas K., Wasson J., Glaser B., Meyer J. M., Duprat L. J., White M. F., Permutt M. A.. Mapping of the human insulin receptor substrate-2 gene, identification of a linked polymorphic marker and linkage analysis in families with type II diabetes: no evidence for a major susceptibility role. Diabetologia 1998;41:1389-91

17. Almind K., Frederiksen S. K., Ahlgren M. G., Urhammer S., Hansen T., Clausen J. O., Pedersen O.. Common amino acid substitutions in insulin receptor substrate-4 are not associated with type II diabetes mellitus or insulin resistance. Diabetologia 1998;41:969-74.

18. Hansen T., Andersen C. B., Echwald S. M., Urhammer S., Clausen J. O., Vestergaard H., Owens D., Hansen L., Pedersen O.. Identification of a common amino acid polymorphism in the p85alpha regulatory subunit of phosphatidylinositol 3-kinase: effects on glucose disappearance constant, glucose effectiveness, and the insulin sensitivity index. Diabetes 1997;46:494-501.

19. Reynet C., Kahn C. R.. Rad: a member of the ras family overexpressed in muscle of type II diabetic humans. Science 1993;262:1441-4.

20. Doria A., Caldwell J. S., Reynett C., Rish S.S., Weremowicz S., Morton C. C., Warram J. H., Kahn C. R., Krolewski A. S.. Trinucleotide repeats at the rad locus. Allele distribution in NIDDM and mapping to a 3-cM region on chromosome 16q. Diabetes 1995;44:243-7.

21. Moyers J. S., Bilan P. J., Reynet C., Kahn C. R.. Overexpression of Rad inhibits glucose uptake in cultured muscle and fat cells. Journal of Biological Chemistry 1996;271:23111-6.