Insulin regulates the expression of at least 100 genes (1). This major action of the hormone is important for normal metabolism but gains added significance in view of the fact that insulin resistance is the cornerstone of genetic diseases such as non–insulin-dependent diabetes mellitus and obesity. The possibility that faulty regulation of gene expression by insulin could result in disease is now given credence by the observations reported by Li et al. (2) in this issue of *The Journal.*

Hypertriglyceridemia (HTG) is a risk factor for coronary heart disease. Plasma triglycerides are carried mainly in VLDL and chylomicrons, both of which contain apo CIII as a major protein constituent; several studies have suggested that the overexpression of apo CIII causes some forms of HTG (3). Perhaps most convincing is the observation that overexpression of human apo CIII in transgenic mice results in HTG (4).

Chen et al. (5) showed that transcription of the hepatic apo CIII gene is increased in diabetic mice and that insulin treatment reduces apo CIII gene transcription to basal levels. In addition, a reporter gene containing the apo CIII promoter sequence from − 854 to + 22 is inhibited by insulin (5), thus the DNA sequence responsible for the insulin effect must be in that segment. Recently, Dammerman et al. (3) identified five polymorphisms in this region of the apo CIII promoter. Li et al. (2) now show that single base pair changes at either of two of the five variant sites (at − 482 and − 455) abolish the repression of apo CIII gene transcription by insulin, an observation that reveals why these mutations lead to apo CIII overexpression. The functional significance of the nucleotide changes in the other three variant sites is unclear but is not related to regulation of apo CIII gene expression by insulin. Moreover, the increased susceptibility to HTG associated with the mutation at − 482 is dependent on the presence of a particular polymorphism in the apo CIII 3′ UTR, suggesting that other factors are important in vivo.

The region containing the variant sites at − 482 and − 455 is sufficient to confer an inhibitory effect of insulin on reporter gene expression when ligated to a minimal apo CIII promoter (Leff, T., personal communication) and therefore represents an insulin response sequence (IRS) (1). This observation may have broader significance because within this region (between − 460 and − 456) is found the same T(G/A)TTT motif that has been identified as the core IRS in the phosphoenolpyruvate carboxykinase (PEPCK), insulin-like growth factor binding protein-1 (IGFBP-1), and (probably) tyrosine aminotransferase (TAT) genes (6–9). Hepatic nuclear factor-3 (HNF-3) binds to the IRS in all three genes but does not appear to be the protein through which insulin manifests its inhibitory action on gene transcription (7). Rather, HNF-3 acts as an accessory factor required for the full induction of the transcription of all three genes by glucocorticoids (7, 9). We have proposed that insulin may repress glucocorticoid-stimulated transcription via an unidentified protein, designated the insulin response factor, that either inhibits the binding or the transactivation potential of HNF-3 (7). Whether this same insulin response factor mediates the inhibitory action of insulin on apo CIII gene transcription is unclear because the mutations at − 482 and − 455 are outside the core PEPCK/IGFBP-1/TAT IRS motif. In fact, the − 455 mutation that abolishes the insulin response creates a sequence more similar to that found in the PEPCK promoter. Clearly, a detailed functional analysis of apo CIII IRS mutants is required to determine the precise core sequence necessary for the inhibitory action of insulin. The mutation at − 455 does reduce the affinity of the apo CIII IRS for binding proteins present in rat liver nuclear extract, whereas the − 482 mutation, which causes a loss of function, does not result in decreased protein binding. Obviously, much work remains to be done in this regard.

This story may soon become more interesting. It is curious that hyperlipidemia, non–insulin-dependent diabetes mellitus, obesity, and hypertension, all phenotype descriptives that represent multifactorial diseases with a strong genetic component, are also components of a syndrome in which the common denominator is insulin resistance. Could all four be explained by unique DNA regulatory sequence mutations or aberrant transcription factors?

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References

1. O'Brien, R. M., and D. K. Granner. 1991. Regulation of gene expression by insulin. *Biochem. J.* 278:609–619.

2. Li, W. W., M. M. Dammerman, J. D. Smith, S. Metzger, J. L. Breslow, and T. Leff. 1995. Common genetic variation in the promoter of the human apo CIII gene abolishes regulation by insulin and may contribute to hypertriglyceridemia. *J. Clin. Invest.* 96:2601–2605.

3. Dammerman, M., L. A. Sandkuijl, J. L. Halaas, W. Chung, and J. L. Breslow. 1993. An apolipoprotein CIII haplotype protective against hypertriglyceridemia is specified by promoter and 3′ untranslated region polymorphisms. *Proc. Natl. Acad. Sci. USA.* 90:4562–4566.

4. Ito, Y., N. Azrolan, A. O'Connell, A. Walsh, and J. L. Breslow. 1990. Hypertriglyceridemia as a result of human Apo CIII gene expression in transgenic mice. *Science (Wash. DC).* 249:790–793.

5. Chen, M., J. L. Breslow, W. Li, and T. Leff. 1994. Transcriptional regulation of the apoC-III gene by insulin in diabetic mice: correlation with changes in plasma triglyceride levels. *J. Lipid Res.* 35:1918–1924.

6. O'Brien, R. M., P. C. Lucas, C. D. Forest, M. A. Magnuson, and D. K. Granner. 1990. Identification of a sequence in the PEPCK gene that mediates a negative effect of insulin on transcription. *Science (Wash. DC).* 249:533–537.

7. O'Brien, R. M., E. L. Noisin, A. Suwanichkul, T. Yamasaki, P. C. Lucas, J.-C. Wang, D. R. Powell, and D. K. Granner. 1995. Hepatic nuclear factor-3 and hormone-regulated expression of the phosphoenolpyruvate carboxykinase and insulin-like growth factor-binding protein 1 genes. *Mol. Cell. Biol.* 15:1747–1758.

8. Suwanichkul, A., S. L. Morris, and D. R. Powell. 1993. Identification of an insulin-responsive element in the promoter of the human gene for insulin-like growth factor binding protein-1. *J. Biol. Chem.* 268:17063–17068.

9. Ganss, R., F. Weih, and G. Schütz. 1994. The cyclic adenosine 3′,5′-monophosphate- and the glucocorticoid-dependent enhancers are targets for insulin repression of tyrosine aminotransferase gene transcription. *Mol. Endocrinol.* 8:895–903.

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