Tumor Necrosis Factor (TNF)-α Inhibits Insulin Signaling through Stimulation of the p55 TNF Receptor and Activation of Sphingomyelinase

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation

Peraldi, Pascal, Gökhan S. Hotamisligil, Wim A. Buurman, Morris F. White, and Bruce M. Spiegelman. 1996. “Tumor Necrosis Factor (TNF)-α Inhibits Insulin Signaling through Stimulation of the P55 TNF Receptor and Activation of Sphingomyelinase.” Journal of Biological Chemistry 271 (22): 13018–22. doi:10.1074/jbc.271.22.13018.

Citable link

http://nrs.harvard.edu/urn-3:HUL.InstRepos:41543124

Terms of Use

This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Tumor Necrosis Factor (TNF)-α Inhibits Insulin Signaling through Stimulation of the p55 TNFR Receptor and Activation of Sphingomyelinase*

(Received for publication, December 6, 1995, and in revised form, March 20, 1996)

Pascal Peraldi, Gökhan S. Hotamisligil, Wim A. Buurman†, Morris F. White, and Bruce M. Spiegelman**

From the Dana-Farber Cancer Institute and Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, §Harvard School of Public Health, Department of Nutrition, Boston, Massachusetts 02115, †Department of Surgery, University of Limburg, 6200 MD Maastricht, The Netherlands, and ‡Joslin Diabetes Center and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115

Insulin resistance is defined as a smaller than normal response to a given dose of insulin. It is also a ubiquitous correlate of obesity and a central component of non-insulin-dependent diabetes mellitus, likely representing a major causal link between these two disorders (1). Insulin resistance has been implicated in a wide range of pathological states such as dyslipidemia, atherosclerosis, and cardiovascular disorders (2).

Since as many as 30% of the adult population in the United States are obese, a better understanding of insulin resistance is an important scientific and medical goal. However, our understanding of the molecular basis of the close association between obesity and insulin resistance is very incomplete.

Several lines of evidence indicate that TNF-α plays a central role in the insulin resistance observed in obesity (3). Adipocytes from most if not all obese animals overexpress TNF-α relative to their lean counterparts (4-6). This observation has been extended to humans where expression of TNF-α is in strong positive correlation with the degree of obesity and the level of hyperinsulinemia, often taken as an indirect measure of insulin resistance (7, 8). More recently, using reverse transcriptase-polymerase chain reaction, TNF-α has also been shown to be overexpressed in muscle during obesity (9). TNF-α plays a causal role in the insulin resistance of experimental animals since neutralization of TNF-α in obese rats increases their insulin sensitivity (4), probably due to the concomitant increase in the tyrosine kinase activity of the IR in adipose tissue and muscle (10). TNF-α has been shown to interfere with insulin signaling by inhibiting IR tyrosine kinase activity in cell culture (11, 12). At the molecular level, it has recently been shown that TNF-α induces serine phosphorylation of IRS-1 (13, 14), and this modified form of IRS-1 can function as an inhibitor of the IR tyrosine kinase activity in vitro and in intact cells (13).

Despite the considerable evidence for a key role for TNF-α, the early steps by which this cytokine inhibits insulin signaling are unknown. TNF-α binds with high affinity to two receptors that possess totally different intracellular domains (15). These receptors, p55 TNFR and p75 TNFR, are glycoproteins with a single transmembrane domain. Both proteins are devoid of any enzymatic activity but can associate with several different intracellular proteins (16-20). Although it seems clear that associated proteins play a role in the signal transduction by these receptors, their precise functions are unknown.

The ability of p55 TNFR and p75 TNFR individually to mediate TNF-α signaling has been an area of active study. p75 TNFR binds TNF-α with a higher affinity and with a higher dissociation rate than p55 TNFR (Kd of 100 pM versus 500 pM and t1/2 of 10 min versus 3 h) (15). The p55 TNFR has been implicated in many biological processes including lipopolysaccharide- and D-galactosamine-induced lethality and production of interleukin-6 and granulocyte macrophage-colony-stimulat-

*The abbreviations used are: TNF, tumor necrosis factor; IR, insulin receptor; IRS, insulin receptor substrate; TNFR, TNF receptor; PDGF, platelet-derived growth factor; PAGE, polyacrylamide gel electrophoresis.
TNF-α Inhibits Insulin Signaling in 3T3-L1 Adipocytes and Myeloid Cells—

In order to investigate the TNF receptors involved in insulin resistance, we wanted to make use of agonist antibodies that have been used as specific activators of p55 TNFR and p75 TNFR. However, our previous work in 3T3-F442A adipocytes indicated that a robust effect on insulin receptor signaling took several days to develop in these cells (11). Since antibodies applied to the cells can be taken up via Fc receptors or destroyed, many cell lines were surveyed to find those that show a relatively rapid effect of TNF-α on insulin signaling. Fig. 1 shows that 6 h of treatment of 3T3-L1 adipocytes with murine TNF-α strongly inhibits the insulin-stimulated tyrosine phosphorylation of the IR and IRS-1 at doses from 10 to 50 ng/ml. We have also investigated this effect in myeloid 32D-IR/IRS-1 cells. The parent 32D cells have low levels of IR and no IRS-1 or IRS-2 and have been used as a model system where these components have been genetically engineered into cells to study specific biochemical mechanisms related to insulin action (22, 23). Fig. 1 illustrates that 4 h of TNF-α treatment (from 1 to 25 ng/ml) inhibits IR and IRS-1 tyrosine phosphorylation stimulated by insulin in these cells. In both cell lines, the absolute quantities of IR and IRS-1 were not affected, indicating that TNF-α induces a specific defect in the stoichiometry of tyrosine phosphorylation.

Stimulation of p55 TNFR Is Sufficient to Inhibit Insulin-Induced Tyrosine Phosphorylation of IR and IRS-1—It is now well established that human TNF-α binds to murine p55 TNFR but not murine p75 TNFR (24). Thus, using human versus mouse TNF-α has provided a tool to compare the effect of stimulation of only one type of receptor with the activation of both receptors. As a first step we verified that mRNA encoding both receptors was present in 32D-IR/IRS-1 cells and 3T3-L1 adipocytes (data not shown). Mouse and human TNF-α were titrated on both cell lines, and IR and IRS-1 were analyzed by anti-phosphotyrosine Western blot. As observed in Fig. 2, human and mouse TNF-α inhibit IR and IRS-1 phosphorylation with a very similar potency in both cell lines. This result suggests that stimulation of p55 TNFR by itself is sufficient to mimic the full effect of TNF-α on IR tyrosine kinase inhibition.

It has recently been shown that polyclonal antibodies directed toward p55 TNFR or p75 TNFR can act as agonist on these receptors, with no cross-reaction (25). Thus, these agents provide a means to activate both of these receptors individually. 32D-IR/IRS-1 and 3T3-L1 cells were incubated with 5 and 15 μg/ml polyclonal antibodies directed toward p55 TNFR (Ab55) or p75 TNFR (Ab75), or both. Cells were then treated with insulin, and IR and IRS-1 were immunoprecipitated and analyzed by anti-phosphotyrosine Western blot. As observed in Fig. 3, Ab55 inhibits IR and IRS-1 tyrosine phosphorylation in a dose-dependent way in 32D-IR/IRS-1 (7 and 49% for IR and 10 and 45% for IRS-1) and in 3T3-L1 adipocytes (5 and 55% for

**RESULTS**

**Cell line**

| Western Blot | IP |
|--------------|----|
| 32D IR/IRS1  | p-tyr protein |
| 3T3-L1      | p-tyr protein |

**Fig. 1.** TNF-α inhibits IR and IRS-1 tyrosine phosphorylation in adipocytes and myeloid cells. Upper panels, 32D cells were incubated in serum-free complete Cellgro medium and treated for 4 h with 1.5, and 25 ng/ml (lanes C, D, and E, respectively) or without (lanes A and B) recombinant mouse TNF-α. Cells were treated for 3 min with (lanes B-E) or without (lane A) insulin (10^{-8} m), and IR and IRS-1 were immunoprecipitated (IP) for 90 min at 4 °C. After washes, proteins were analyzed by Western blot using anti-phosphotyrosine (p-tyr), anti-IR, or anti-IRS-1 (protein) antibodies. Lower panels, 3T3-L1 cells were starved in complete Cellgro medium for 48 h and treated for 6 h with 10, 25, and 50 ng/ml (lanes C, D, and E, respectively) or without (lanes A and B) TNF-α. IR and IRS-1 were then analyzed as described above. Results are representative of experiments performed at least three times.
In the presence of 5 and 15 F and 6
to 63 S.E. of three different experiments. Incubations of cellsin
incubated with Ab55 and Ab75 as described above and were
inhibition of all the receptors endowed with tyrosine kinase
action of the IR by agonist antibodies might be due to a general
the ability of insulin to stimulate IR and IRS-1 tyrosine
the presence of non-immune antibodies (Ni) did not modify
additivemanner (from 49 6 4% for IR, and from 45 6 6% for IRS-1 at the higher concentration, mean
of p55 TNFR or p75 TNFR. This indicates that inhibition of
the production of ceramides and phosphocholine (15). Ceramides
induce the activation of ceramide-activated kinases and phos-
phorlation was analyzed (Fig. 4 A). C2 and C6 reduce IR
equivalently (about 50%), while sphingosine (C2) and
IR and 15 and 60% for IRS-1). In 32D cells and 3T3-L1 adipocytes,
reduce IR and IRS-1 phosphorylation by antibody activation of p55 TNFR and p75
Panel A, 32D-IR/IRS-1 cells and 3T3-L1 adipocytes were treated in the presence of 5 and 15 g/ml Ab55 (lanes C and D), Ab75 (lanes E and F), Ab55 and Ab75 (lanes G and H), or 30 g/ml non-immune antibodies (NI, lane I) for 4 and 6 h, respectively. Ab, antibody. Cells were then treated without (lane A) or with (lanes B–I) insulin for 3 min, rinsed in ice-cold phosphate-buffered saline, and lysed. IR and IRS-1 were immunoprecipitated (IP) and analyzed by anti-phosphotyrosine Western blot. All these results are representative of experiments performed three (3T3-L1) to six (32D cells) times with similar results.
films were scanned on an Abaton scanner and were quantified using NIH-image v.1.44.
immunoprecipitated and analyzed by anti-phosphotyrosine Western blot. As observed in Fig. 3B, the tyrosine phosphorylation of the PDGF b receptor was not altered after stimulation of p55 TNFR or p75 TNFR. This indicates that inhibition of tyrosine kinase activity by Ab55 is accomplished with some specificity for the IR.
Ceramides and Sphingomyelinase Mimic the Effect of TNF-α on Insulin Signaling—Among the many activities of the p55 TNFR is the activation of sphingomyelinase, which leads to the production of ceramides and phosphocholine (15). Ceramides induce the activation of ceramide-activated kinases and phosphatases (26, 27). To ask whether this pathway may be relevant to insulin signaling, 3T3-L1 adipocytes were treated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phospho-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
teated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phos-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
treated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phos-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
treated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phos-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
treated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phos-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
treated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phos-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
treated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phos-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
treated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phos-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
treated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phos-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
treated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phos-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
treated with sphingomyelinase and two cell-permeant ceramides (N-acetylsphingosine (C2) and N-hexanoylsphingosine (C6)). Cells were then stimulated with insulin, and IR and IRS-1 tyrosine phos-
phorylation was analyzed (Fig. 4 A). C2 and C6 reduce IR and IRS-1 phosphorylation equivalently (about 50%), while sphingomyelina
TNF-α Inhibits Insulin Signaling

**FIG. 5.** TNF-α, sphingomyelinase, and ceramide convert IRS-1 but not IRS-2 into an inhibitor of the IR tyrosine kinase activity. 3D-IR/IRS-1 and 3D-IR/IRS-2 were treated for 4 h with TNF-α (10 ng/ml), C2 (1 μM), C6 (1 μM), or sphingomyelinase (1 unit/ml). IRS-1 and IRS-2 were then immunoprecipitated and after several washes were incubated in the presence of wheat germ agglutinin-purified IR, which has been stimulated by insulin (10^{-6} M) for 30 min at 4 °C. The kinase reaction was initiated by the addition of [γ-32P]ATP, MgCl_2, and MnCl_2, and continued for 1 h at room temperature. The IR was then analyzed by SDS-PAGE. These results are representative of experiments performed three times with comparable results.

**DISCUSSION**

Several recent lines of evidence now indicate that TNF-α is a very important link between insulin resistance and obesity. In addition to the data showing overexpression of TNF-α from adipose tissue of obese and insulin-resistant rodents (4–6), new evidence indicates a tight correlation between obesity, insulin resistance, and TNF-α expression in humans (7, 8). That the relationship between TNF-α and insulin resistance is causal has been shown directly in animal neutralization studies. Using a soluble TNF receptor-IgG fusion protein designed to neutralize TNF-α, it has been shown that insulin resistance could be greatly reduced in obese Zucker fatty rats, along with an improvement in hyperglycemia, hyperinsulinemia, and hyperlipidemia (10). This correlated with a large increase in the tyrosine phosphorylation of both the IR and IRS-1, which are known to be affected during obesity and insulin resistance (10). Reciprocally, treatment of adipocytes in culture with TNF-α induces a decrease in the tyrosine kinase activity of IR (11). An inhibition of insulin-induced tyrosine phosphorylation of IR and IRS-1 has also been shown in cultured hepatoma cells (12).

It is very likely that this inhibition of IR tyrosine kinase activity by TNF-α is a major mechanism by which TNF-α induces insulin resistance in obesity. Indeed, although several defects located at a postinsulin receptor level have been detected in obese animals, such as a decrease in the quantity of IR and of the insulin-sensitive glucose transporter Glut4, it has been noted that none of them can explain the extent of insulin resistance in this disease (1, 28). On the other hand, reduced tyrosine kinase activity of the IR, such as occurred under the action of TNF-α, has been noted in both animals and human non-insulin-dependent diabetes mellitus (29, 30). Clearly, induced tyrosine kinase activity would be expected to affect all subsequent actions of insulin (31). Understanding the molecular mechanisms by which TNF-α inhibits IR tyrosine kinase activity and subsequent tyrosine phosphorylation of IRS-1 will provide insight into the molecular basis of TNF-α-induced insulin resistance in obesity.

One mechanism by which TNF-α interferes with the function of the IR appears to involve TNF-α-induced serine phosphorylation of IRS-1 (13, 14). This serine-phosphorylated IRS-1 acts as an inhibitor of IR in vitro and is also associated with reduced IR activity in intact cells (13). On the other hand, the first steps stimulated by TNF-α, which lead to the inhibition of IR tyrosine phosphorylation, were unknown. By using human TNF-α, we observed that stimulation of p55 TNFR alone was sufficient to inhibit IR and IRS-1 tyrosine phosphorylation with the same potency of stimulation of both TNF receptors. Agonist antibodies to p55 TNFR induced a very similar effect. Activation of p75 TNFR alone by specific agonist antibodies also resulted in an inhibition of the IR signaling, though this effect is smaller compared with that induced by antibodies to p55 TNFR. Of course, it is possible that the difference in the magnitude of the effects of p55 TNFR and p75 TNFR antibodies resides in differences in their respective affinities for their ligands or in their stability. However, the fact that the two approaches yield similar results strongly suggests that stimulation of p55 TNFR alone is mainly responsible for the effect of TNF-α on IR and IRS-1 tyrosine phosphorylation in these cells. However, it is important to note that there is some reason to believe that p75 TNFR could play some role in vivo. First, the mRNA for p75 TNFR is dramatically increased (4.5-fold) (5) in the adipose tissue of obese/insulin-resistant mice. Second, since the absolute levels of TNF-α are rather low in obesity (less than 100 pg/ml) (4) and the p75 TNFR has a higher affinity for TNF-α, it could play a relatively more important role. The definitive role of these two receptors must include an analysis of insulin resistance in obese mice containing appropriate null alleles for both receptors (32–34).
nase convert IRS-1 into an inhibitor of IR tyrosine kinase activity, as does TNF-α. These compounds have some specificity for IR signaling since they do not inhibit PDGF tyrosine phosphorylation in adipocytes nor do they modify IR and IRS-2 tyrosine phosphorylation in 32D-IR/IRS-2 cells. These data indicate that activation of sphingomyelinase and production of ceramides is likely to be a major pathway used by p55TNFR to mediate IR inhibition. Ceramides directly activate various enzymes such as PKC-ζ, a membrane-associated kinase (37) that phosphorylates and activates Raf-1 (38), and a cascade of phosphatases that dephosphorylates and activates PTP-2C (40, 41). Moreover, IRS-2 has been shown to be the alternative substrate of the IR in IRS-1-deficient mice (41). However, it is clear from Figs. 4 and 5 that IRS-2 cannot replace IRS-1 in this inhibition. This is the first important difference observed in the function of IRS-1 and IRS-2, and this could be an important tool to understand the mechanism by which IRS-1 inhibits the IR upon TNF-α treatment of the cells.

Acknowledgments—We thank Drs. M. Myers, B. Chesterman, T. Roberts, and C. Stiles for the gift of antibodies and cells. We thank members of the B. Spiegelman laboratory for their scientific and technical advice.

REFERENCES
1. Olefsky, J., and Molina, J. (1990) in Diabetes Mellitus (Rifkin, H., and Porte, D., eds) pp. 121–153, Elsevier Science Publishing Co., Inc., New York
2. Bennet, P. (1990) in Diabetes Mellitus (Rifkin, H., and Porte, J. D., eds) pp. 357–377, Elsevier Science Publishing Co., Inc., New York
3. Hotamisligil, G. S., and Spiegelman, B. M. (1994) Diabetes 43, 1271–1278
4. Hotamisligil, G. S., Sharlight, N. S., and Spiegelman, B. M. (1993) Science 259, 87–91
5. Hofmann, C., Lorenz, K., Brathwaiite, S. C., Cola, J. R., Palazuk, B. J., Hotamisligil, G. S., and Spiegelman, B. M. (1994) Endocrinology 134, 264–270
6. Hannon, A., Benedek, H., Le Marchand-Brustel, Y., Susulic, V. S., Lowell, B. B., and Flier, J. S. (1995) Diabetes 44, 1266–1273
7. Hotamisligil, G. S., Arner, P., Caro, J. F., Atkinson, R. L., and Spiegelman, B. M. (1995) J. Clin. Invest. 95, 2409–2415
8. Kern, P., Saghizadeh, M., Ong, J., Bosch, R., Deen, R., and Simoslo, R. (1995) J. Clin. Invest 95, 2111–2119
9. Saghizadeh, M., Ong, J. M., Garvey, T. W., Henry, R., and Kern, P. A. (1996) J. Clin. Invest. 97, 1111–1116
10. Hotamisligil, G. S., Budavari, A., Murray, D., and Spiegelman, B. M. (1994) J. Clin. Invest. 94, 1543–1549
11. Hotamisligil, G. S., Murray, D. L., Choy, L. N., and Spiegelman, B. M. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 4854–4858
12. Feinstein, R., Kanety, H., Papa, M. Z., Lunenfeld, B., and Karasik, A. (1993) J. Biol. Chem. 268, 26025–26028
13. Hotamisligil, G. S., Erladi, P., Budavari, A., Ellis, R., White, M., and Spiegelman, B. M. (1996) Science 271, 665–668
14. Kanety, H., Feinstein, R., Papa, M., Henri, R., and Karasik, A. (1995) J. Biol. Chem. 270, 23780–23784
15. Vandenebade, P., Diederick, W., Beyer, R., and Fiers, W. (1995) Trends Cell Biol 5, 392–399
16. Song, H., Dunbar, J., Zhang, Y., Guo, D., and Donner, D. (1994) J. Biol. Chem. 270, 3574–3581
17. Hsu, H., Xiong, J., and Goeddel, D. (1995) Cell 81, 495–504
18. Stanger, B., Leder, P., Lee, T., Kim, E., and Seed, B. (1995) Cell 81, 513–523
19. Rothe, M., Song, H., Henzel, W., and Goeddel, D. (1994) Cell 78, 681–692
20. Mosialou, G., Birkenbach, M., Yalamanchili, R., Van Arsda, T., Ware, C., and Kieff, E. (1995) Cell 80, 389–399
21. Garcia de Herreros, A., and Brimbaum, M. (1989) J. Biol. Chem. 264, 19994–19999
22. Wang, L. M., Keegan, A. D., Li, W., Lienhard, G. E., Pacini, S., Gutkind, J. S., Myers, M. G., Sun, X. J., White, M. F., Aaronson, S. A., Paul, W. E., and Piero, J. H. (1993) Proc. Natl. Acad. Sci. U. S. A. 90, 4032–4036
23. Wang, L. M., Myers, M. G., Sun, X. J., Aaronson, S. A., White, M. F., and Piero, J. H. (1993) Science 263, 1591–1594
24. Lewis, M., Tartaglia, L., Lee, A., Bennett, G., Rice, G., Wong, H. W. H., Chen, E., and Goeddel, D. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 2830–2834
25. Paleolog, E. M., Defasale, S. J., Burman, W. A., and Feldman, M. (1994) Blood 84, 2578–2590
26. Kolsevnsen, R., and Golde, D. (1994) Cell 77, 325–328
27. Heller, R. A., and Körnke, M. (1994) J. Biol. Cell 126, 5–9
28. Sheperd, P., and Khan, B. (1993) in Insulin Resistance (Moller, D., ed) pp. 253–300, John Wiley & Sons, Inc., New York
29. Saad, M. J. A., Araki, E., Miralpeix, M., Rothenberg, P. L., White, M. F., and Kahn, C. R. (1992) J. Clin. Invest. 90, 1839–1849
30. Thies, R. S., Molina, J. M., Ciaraldi, S., Freidenberger, G. R., and Olefsky, J. M. (1993) Diabetes 42, 250–259
31. White, M. F., and Kahn, C. R. (1994) J. Biol. Chem. 269, 1–4
32. Pfeffer, K., Matsuyama, T., Kundig, T. M., Wakeham, A., Kishihara, K., Shahinian, A., Vignaimen, K., Ohashi, P., Körnke, M., and Mak, T. (1993) Cell 73, 457–467
33. Roth, J., Leslauer, W., Lottsch, H., Lang, Y., Koebel, P., Korteng, F., Althage, A., Zinkenagel, R., Steinmetz, M., and Blumthelm, H. (1993) Nature 364, 798-802
34. Erickson, S. L., de Sauvage, F. J., Kikly, K., Carver-Moore, K., Pitts-Meek, S., Gillett, N., Sheehan, K. C., Schreiber, R., Goeddel, D. V., and Moore, W. M. (1994) Nature 372, 560–563
35. Muller, G., Ayoob, M., Storz, P., Rennec, J., Fabbro, D., and Pfenzhaier, K. (1995) EMBO J. 14, 1156–1165
36. Lucano, J., Berra, E., Municio, M., Diaz-Meco, M., Dominguez, I., Sanz, L., and Moscat, J. (1994) J. Biol. Chem. 269, 19200–19202
37. J. Joseph, C., Byun, H., Bittman, R., and Kolesnick, R. (1993) J. Biol. Chem. 269, 3047–3052
38. Yiao, B., Zhang, Y., Delikat, S., Mathias, S., Basu, S., and Kolesnick, R. (1995) Nature 378, 307–310
39. Dobrowolski, R., and Hannun, Y. (1992) J. Biol. Chem. 267, 5048–5051
40. Sun, X. J., Wang, L.-M., Zhang, Y., Yenush, L., Myers, M. G., Glauser, E., Lane, W. S., Piero, J. H., and White, M. F. (1995) Nature 377, 173–177
41. Patty, M.-E., Sun, X.-J., Bruening, J. C., Araki, E., Lipes, M. A., White, M. F., and Kahn, C. R. (1995) J. Biol. Chem. 270, 24670–24673
Tumor Necrosis Factor (TNF)-α Inhibits Insulin Signaling through Stimulation of the p55 TNF Receptor and Activation of Sphingomyelinase

Pascal Peraldi, Gökhan S. Hotamisligil, Wim A. Buurman, Morris F. White and Bruce M. Spiegelman

J. Biol. Chem. 1996, 271:13018-13022.
doi: 10.1074/jbc.271.22.13018

Access the most updated version of this article at http://www.jbc.org/content/271/22/13018

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 38 references, 20 of which can be accessed free at http://www.jbc.org/content/271/22/13018.full.html#ref-list-1