Interleukin-6 (IL-6) Induces Insulin Resistance in 3T3-L1 Adipocytes and Is, Like IL-8 and Tumor Necrosis Factor-α, Overexpressed in Human Fat Cells from Insulin-resistant Subjects*

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Several studies have shown a relationship between interleukin (IL) 6 levels and insulin resistance. We here show that human subcutaneous adipose cells, like 3T3-L1 cells, are target cells for IL-6. To examine putative mechanisms and cross-talk with insulin, 3T3-L1 adipocytes were cultured for different times with IL-6 and tumor necrosis factor α (TNF-α). IL-6, in contrast to TNF-α, did not increase pS-307 of insulin-receptor substrate (IRS)-1 or JNK activation. However, IL-6, like TNF-α exerted long term inhibitory effects on the gene transcription of IRS-1, GLUT-4, and peroxisome proliferator-activated receptor γ. This effect of IL-6 was accompanied by a marked reduction in IRS-1, but not IRS-2, protein expression, and insulin-stimulated tyrosine phosphorylation, whereas no inhibitory effect was seen on the insulin receptor tyrosine phosphorylation. Consistent with the reduced GLUT-4 mRNA, insulin-stimulated glucose transport was also significantly reduced by IL-6. An important interaction with TNF-α was found because TNF-α markedly increased IL-6 mRNA and protein secretion. These results show that IL-6, through effects on gene transcription, is capable of impairing insulin signaling and action but, in contrast to TNF-α, IL-6 does not increase pS-307 (or pS-612) of IRS-1. The link between IL-6 and insulin resistance in man was further corroborated by the finding that the expression of IL-6, like that of TNF-α and IL-8, was markedly increased (~15-fold) in human fat cells from insulin-resistant individuals. We conclude that IL-6 can play an important role in insulin resistance in man and, furthermore, that it may act in concert with other cytokines that also are up-regulated in adipose cells in insulin resistance.

Interleukin-6 (IL-6)¹ is produced by a variety of cell types and can act both as a pro- and anti-inflammatory cytokine (1, 2). Recent studies have shown that human adipose tissue is a major site of IL-6 secretion (3, 4) accounting for 15–35% of the circulating levels (3), whereas TNF-α, in contrast, is only secreted at very low levels, if at all, by human fat cells (3).

Circulating IL-6 levels are increased in insulin-resistant states like obesity (3, 5, 6) impaired glucose tolerance (7) and Type 2 diabetes (8, 9). Significant correlations with BMI, percent fat mass, systolic and diastolic blood pressure, and fasting insulin levels have been reported (3, 5, 6) and a recent prospective study showed that circulating IL-6 levels correlate with risk for developing Type 2 diabetes irrespective of the amount of body fat (10).

A possible involvement of TNF-α in insulin resistance has been suggested in a number of studies. TNF-α has been shown to increase plasma triglycerides and very low density lipoprotein concentrations (11, 12) as well as lipolysis in mouse, rat, and human fat cells (13–17). Furthermore, the TNF-α gene is overexpressed in fat cells from both obese rodents (18) and man (19, 20) and the expression is positively correlated with degree of obesity (BMI) and hyperinsulinemia. However, immunabsorption of circulating TNF-α by specific antibodies in man did not improve insulin sensitivity (21). It was also recently reported that circulating levels of TNF-α and its receptors, s-TNF-R60 and s-TNF-R80, were not increased in patients with impaired glucose tolerance but circulating IL-6 levels were significantly elevated (7). TNF-α reduces insulin-stimulated receptor tyrosine kinase activity at low concentrations and can also decrease the expression of the insulin receptor, IRS-1 and GLUT-4 at higher concentrations (22) as well as increase the phosphorylation of serine 307 of IRS-1, thus impairing its ability to bind to the insulin receptor and initiate downstream signaling (23).

Only a few studies have addressed the potential metabolic effects of IL-6 and/or its ability to modify insulin sensitivity and action. Long term incubation with IL-6 has been shown to increase basal glucose transport in 3T3-L1 adipocytes, whereas acute stimulation had no effect (24, 25). A preliminary study suggests that IL-6 may increase lipolysis in human fat cells maintained in culture for 48 h (26). Recently, Senn et al. (27, 28) reported that IL-6 transiently (30–90 min) increased SOCS-3 expression in HepG2 cells and rat liver cells and that this was associated with an impaired effect of insulin to increase IRS-1 tyrosine phosphorylation, p85 binding, and downstream PKB/Akt phosphorylation.

Intracellular signaling for IL-6 is triggered by a complex consisting of the ligand-bound 80-kDa IL-6 receptor (or the soluble ~50-kDa form, sIL-6) and two homodimerized transmembrane proteins: the 55-kDa signal transducers and activators of transcription; JNK, c-Jun NH₂-terminal kinase; AEBSF, 4,2-(aminoethyl)benzenesulfonyl fluoride; PBS, phosphate-buffered saline; PPAR, peroxisome proliferator-activated receptor; GP130, glycoprotein 130.
membrane-spanning GP130 molecules. The activated tyrosine kinases Jak1, Jak2, and Tyk2 associate with GP130 followed by the phosphorylation of STAT1 and STAT3 (29). Double transgenic mice, overexpressing both sIL-6 receptor and IL-6, are smaller than their wild type littermates and have reduced body weight. These animals have markedly reduced fat depots, enlarged spleen, and shrunk disfigured livers, suggesting a role for IL-6 in cell growth (30). Furthermore, a recent study showed that mice completely lacking IL-6 became obese and that intracerebroventricular injection of IL-6 increased energy expenditure (31). An association between energy expenditure, insulin sensitivity, and the C174G polymorphism of the IL-6 promoter was also recently reported (32).

In this study, we examined if IL-6, like TNF-α, induces insulin resistance in adipose cells. We show that human subcutaneous fat cells are target cells for both IL-6 and TNF-α. Furthermore, the gene expression of IL-6 as well as TNF-α and IL-8 was markedly up-regulated (~15-fold) in fat cells from insulin-resistant subjects. Studies with 3T3-L1 adipocyte cells also showed that IL-6 impairs both insulin action and the insulin signaling pathway. IL-6, in contrast to TNF-α, does not activate JNK or increase the phosphorylation of serine 307 or of serine 612 of IRS-1. However, both of these cytokines inhibit the transcriptional activity and protein expression of several molecules related to insulin signaling and action, like IRS-1 and GLUT-4. Taken together, these data support an important role of IL-6 in insulin resistance in man and, in addition, suggest that several cytokines expressed in the adipose cells may act in concert through different mechanisms and temporal patterns.

EXPERIMENTAL PROCEDURES

Abdominal subcutaneous adipose tissue biopsies were obtained from 10 subjects, 31–56 years of age, undergoing surgery for a non-systemic abdominal disorder. In addition, adipocyte cytokine mRNA was analyzed in biopsies from 10 non-obese but insulin-resistant individuals as well as 6 insulin-sensitive control subjects. These individuals were selected on the basis of IRS-1 protein expression in the fat cells; normal or low (<50% of normal) expression, which identifies individuals with a marked insulin resistance in vivo (33–35). Low IRS-1 is also accompanied by a reduced adiponectin and GLUT-4 expression in the adipose cells (34, 35) as well as reduced circulating adiponectin levels (35). The insulin sensitivity of the individuals used to study the cytokine and S0C9-3 mRNA expression in the adipose cells (Table II) have been measured with the euglycemic clamp technique and found to differ by ~30% between groups (13.1 versus 10.3 mg/kg lean body mass × min). All procedures were approved by the Ethical Committee of Göteborg University.

Cell Isolation and Lipolysis Measurements—The tissue was cut in small pieces and treated with 0.8 mg/ml collagenase in Medium 199 with 5.5 mM glucose, 25 mM Heps, 40 mg/ml bovine serum albumin, and 0.15 mM adenosine for 60 min at 37 °C, essentially as described (36). The isolated adipocytes were filtered through a 250-μm nylon mesh and washed four times with fresh medium. The cells were diluted ~50-fold in a final volume of 500 μl and preincubated at 37 °C under slow shaking with TNF-α, IL-6 (Invitrogen, Groningen, Netherlands), or without additions (basal) for 1 or 5 h and then for an additional hour with or without 4 mM 8-bromo-cAMP (Sigma) and 6.9 mM insulin as indicated under “Results.” The samples were centrifuged through silicone oil for 5 min at 2000 rpm and glycerol was measured as described (37, 38).

Glucose Transport, Human Cells—Isolated human adipocytes were washed in glucose-free medium, packed cells were diluted ~10-fold and incubated in a final volume of 500 μl. The cells were preincubated as above and then for an additional hour with 0.15 μCi of [U-14C]glucose (Amersham Biosciences) with or without 6.9 mM insulin to measure glucose transport as described (34). The cells were centrifuged through dextran/tube 60% for 5 min at 12,000 rpm for 5 min, the supernatant was collected and stored at −80 °C. Protein concentration was measured with the bicinchoninic acid method (Pierce). Lysate proteins were separated on SDS-PAGE as described (33–35) and immunoblotted with anti-insulin receptor, anti-IRS-1, anti-p307 IRS-1, anti-p612 IRS-1, anti-IRS-2 (Upstate Biotechnology, Lake Placid, NY), anti-p-JNK, anti-JNK, anti-phospho JNK (Ser-78) (Cell Signaling Technologies, Beverly, MA) antibodies according to the recommendations of the manufacturer.

RESULTS

3T3-L1 Adipocytes—We used differentiated 3T3-L1 adipocytes to be able to study both the acute and chronic effects of IL-6 on insulin signaling and gene and protein expression of key molecules involved in insulin action.
Acute Effects on JNK and IRS-1 Serine 307 and 612 Phosphorylation—We first examined if IL-6, like TNF-α, exerts an acute (30 min) effect on serine phosphorylation of IRS-1 and JNK activation. Increased phosphorylation of serine 307 of IRS-1 impairs the tyrosine phosphorylation of IRS-1 as well as the subsequent phosphatidylinositol 3-kinase activation (23).

Fig. 1 shows that IL-6, in contrast to TNF-α, did not increase the phosphorylation of serine 307. Insulin also increased the serine phosphorylation of IRS-1 in agreement with a previous report (23). However, neither IL-6 nor TNF-α increased the phosphorylation of serine 612 of IRS-1, whereas insulin exerted a marked effect (Fig. 1).

In agreement with this finding, IL-6 did not increase the phosphorylation of JNK1/2, which was in line with TNF-α (Fig. 1). We also examined if IL-6 exposure to IL-6 reduced the insulin-stimulated tyrosine phosphorylation of the insulin receptor or IRS-1. However, no such effects were seen after 30 min (data not shown).

Long-Term Effects on IRS-1/2 Expression and Tyr(P)—Because we saw no acute inhibitory effects by IL-6 on the insulin-stimulated tyrosine phosphorylation or an increased serine phosphorylation of IRS-1, we examined potential long-term effects. As shown in Fig. 2, both cytokines induced a clear reduction in IRS-1 gene expression (~50%) after 24 h (p < 0.04) while no significant reduction in IRS-2 mRNA was seen.

Consistent with the reduced gene expression of IRS-1, there was also a ~50% decrease in IRS-1 protein expression after treatment with either IL-6 or TNF-α for 24 h (Fig. 3a), whereas there was no significant reduction of IRS-2 protein following IL-6 or TNF-α although TNF-α tended to also reduce this docking protein (Fig. 3c). Control cells showed a large increase in IRS tyrosine phosphorylation in response to insulin for 30 min, whereas preincubation with IL-6 inhibited the insulin-stimulated tyrosine phosphorylation to a similar extent as the reduced IRS-1 protein expression (Fig. 3b). Furthermore, IL-6, in contrast to TNF-α, did not inhibit the insulin receptor tyrosine phosphorylation in response to insulin in these cells (Fig. 4).

Taken together, these data show that long-term exposure to IL-6 leads to an impaired insulin signaling in 3T3-L1 adipocytes because of reduced gene and protein expression of IRS-1.

Long-Term Effects on GLUT-4 Gene Expression—We then examined if IL-6 also influenced the expression of key molecules for insulin action, like GLUT-4. GLUT-4 gene expression, measured with real-time PCR, was decreased (~35%, p = 0.04) in cells incubated for 24 h with IL-6, whereas TNF-α exerted a more powerful effect (p = 0.0001) (Fig. 5). Consistent with the decreased GLUT-4 expression, we also found a significantly decreased insulin-stimulated glucose transport in 3T3-L1 adipocytes incubated with IL-6 for 24 h (Fig. 6).

Time and Concentration Dependence—Using real-time PCR we also examined the time course and concentration dependence for the inhibitory effects of IL-6 and, for comparison, TNF-α. The effect of IL-6 on GLUT-4 and PPARγ mRNA levels was fairly slow (apparent t1/2 ~ 12 h), whereas the inhibitory effect on IRS-1 was considerably more rapid (apparent t1/2 ~ 4 h) and similar to that of TNF-α (Fig. 7, a–c). Significant inhibitory effects on IRS-1 mRNA levels were seen already after 30–60 min for both IL-6 and TNF-α (Fig. 7a). In general, TNF-α exerted a greater inhibitory effect and it was also more potent (significant inhibition generally seen for TNF-α was at 1 ng/ml and for IL-6 was at 5 ng/ml) (data not shown).

Effect of TNF-α on IL-6 mRNA and Secretion—Incubating 3T3-L1 cells with TNF-α markedly increased IL-6 gene expression in a concentration- and time-dependent manner (Fig. 7d). This effect was rapidly induced (30 min) and gradually increased for 12 h. IL-6 itself only exerted a small increase (~4-fold; Fig. 7d) while it did not change the gene expression of TNF-α (data not shown). IL-6 secretion to the incubation medium was also markedly increased by TNF-α (Table I).

Taken together, these data show that TNF-α is capable of not only exerting its effects through its own signaling molecules but it is also a powerful activator of the IL-6 gene in 3T3-L1 adipocytes. However, the long term effects of TNF-α on the
Differentiated 3T3-L1 cells were incubated without (bas) or with 20 ng/ml IL-6 or TNF-α for 24 h with or without 100 nM insulin for 30 min, proteins were extracted and analyzed by immunoblotting. a shows a representative blot of the IRS-1 protein and the scanned data below where the basal and basal + insulin are set to 1 for the respective comparisons. Results are mean ± S.E. of five experiments. *, p = 0.03; **, p < 0.01. b shows a representative blot of insulin-stimulated tyrosine phosphorylation of IRS. The insulin-stimulated samples were compared with the respective control samples = 1. Results are mean ± S.E. of four experiments. *, p = 0.02. c shows a representative blot of IRS-2 protein expression where the basal and basal + insulin are set to 1 for the respective comparisons. Results are mean ± S.E. of four experiments.
gene expression of IRS-1, PPARγ, and GLUT-4 were not dependent on the induction of IL-6 secretion because they were not inhibited by the presence of an excess amount of anti-IL-6 antibodies, immunoneutralizing ~90% of the IL-6 released to the medium, during the long-term incubations (data not shown).

**Human Adipocytes**—Because IL-6 is produced to a great extent by human fat cells (3, 4), we also examined if human subcutaneous fat cells, like breast fat cells (42), are target cells for IL-6. However, large isolated human adipocytes undergo a gradual increase in breakage, making this a less robust and dependable system for long-term incubations. Thus, these incubations were only performed for up to 6 h.

**Human Adipocytes Are Target Cells for IL-6**—We first examined if isolated human subcutaneous fat cells express a functional IL-6 signaling machinery and, thus, can be target cells for this cytokine. Both the IL-6 receptor and GP130 were clearly expressed in human fat cells both at the mRNA (data not shown) and protein level (Fig. 8A). Similarly, the p55 TNF-α receptor was present in human subcutaneous fat cells.

The likelihood that human adipocytes are target cells for both IL-6 and TNF-α was further examined by preincubating the cells for 2 h with these cytokines. IL-6, but not TNF-α, increased the phosphorylation of STAT3 on tyrosine 705 (Fig. 8a) and both cytokines increased the phosphorylation of the p42 and p44 mitogen-activated protein kinases (Fig. 8a). However, similar to the findings in the 3T3-L1 adipocytes, short-term incubations with IL-6 did not inhibit the insulin-stimulated tyrosine phosphorylation of the insulin receptor or IRS (Fig. 8b).

**Metabolic Effects of IL-6**—Having established that human fat cells express a functional signaling machinery for IL-6, we then incubated isolated human fat cells for 2 and 6 h with IL-6 to examine possible effects on lipolysis and glucose transport. However, only small effects were found; no significant differences were seen in basal or insulin-stimulated glucose transport after 2 h nor was basal or cAMP-stimulated lipolysis significantly changed after 2 or 6 h (data not shown). Thus, IL-6 does not exert an acute lipolytic effect in human subcutaneous fat cells.
IL-6, IL-8, TNF-α, and SOCS-3 mRNA in Fat Cells from Insulin-resistant Subjects—We have previously shown that IRS-1/GLUT-4 gene and protein levels are markedly reduced in adipocytes from both Type 2 diabetic (43) as well as in a cohort of non-diabetic individuals who are characterized by a marked insulin resistance in vivo (33–35). This group, thus, provides an excellent opportunity to investigate the potential relevance in human fat cells of our findings in 3T3-L1 cells where IL-6 is capable of reducing both IRS-1 and GLUT-4 expression.

As shown in Table II, IL-6 gene expression was low in the control insulin-sensitive group, whereas it was markedly (15-fold) higher in the insulin-resistant subjects. Importantly, all these individuals were non-obese (BMI < 30 kg/m²) and the difference remained significant also after matching the groups for BMI (p < 0.04).

We also examined if cytokines other than IL-6 showed a differential expression in the fat cells from insulin-resistant individuals. Human fat cells are known to express both TNF-α and IL-8 (19, 44) and, as shown in Table II, both TNF-α and IL-8 mRNA levels were increased in the insulin-resistant subjects. Furthermore, both IL-6 (r² = 0.28, p = 0.03) and IL-8 (r² = 0.41, p = 0.007) mRNA levels correlated with TNF-α expression. We also examined if SOCS-3 mRNA levels were up-regulated in these cells but, although the expression was higher in...
this occurs, in part, through different mechanisms. That IL-6, like TNF-α, rodents and human subjects (6–10) had mean BMI 26.3 ± 0.9 kg/m² and low IRS-1 subjects (age range 33–55 y) had mean BMI 26.3 ± 0.9 kg/m².

### Table II

| IRS-1 expression | IL-6 mRNA | Normalized RQ |
|------------------|-----------|---------------|
| Normal           | 0.038 ± 0.012 | 1             |
| Low              | 0.069 ± 0.100 | 16.1          |
| RQ TNF mRNA      | 0.063 ± 0.029 | 1             |
| Low              | 0.385 ± 0.098 | 6.1           |
| RQ IL-6 mRNA     | 0.114 ± 0.053 | 1             |
| Low              | 0.628 ± 0.241 | 5.5           |
| RQ SOCS-3 mRNA   | 0.493 ± 0.112 | 1             |
| Low              | 0.586 ± 0.098 | 1.5           |

*R* p < 0.05.

the insulin-resistant group, this difference was not statistically significant (Table II).

### DISCUSSION

Several studies have documented a role of proinflammatory cytokines, in particular TNF-α, in insulin resistance in both rodents and human subjects (6–12). The present study shows that IL-6, like TNF-α, can induce insulin resistance and that this occurs, in part, through different mechanisms.

TNF-α rapidly increases the phosphorylation of serine 307 of IRS-1 through JNK activation (23, 45) that, in turn, negatively modulates the insulin-stimulated interaction with the insulin receptor and the subsequent tyrosine phosphorylation of IRS-1. We here show that IL-6 does not activate this pathway nor did we find any increase in the phosphorylation of serine 612 of IRS-1 following preincubations with either IL-6 or TNF-α. Insulin, however, markedly increased the phosphorylation of serine 612 of IRS-1.

In HepG2 cells, it was recently shown that IL-6 induced a rapid reduction in the effect of insulin to increase the binding of p85 to IRS-1 and to activate PKB/Akt (27, 28). However, this effect of IL-6 was not associated with a reduced autophosphorylation of the insulin receptor but was attributed to the rapid and transient (30–90 min) induction of SOCS-3 that, in turn, leads to a reduction in IRS-1 phosphorylation and phosphatidylinositol 3-kinase activation (28). This mechanism can also lead to an increased ubiquination and degradation of the IRS molecules (46) although this was not found in HepG2 cells or primary rat liver cells after 90 min (28).

In the present study using 3T3-L1 adipocytes or isolated human fat cells, we saw no acute (30–120 min) inhibitory effect of IL-6 on the insulin-stimulated tyrosine phosphorylation of the insulin receptor or IRS-1 nor was the serine phosphorylation of p85 reduced. Reduced these results are clearly different from the findings of Senn et al. (27) in HepG2 cells and may indicate that the induction of SOCS-3 by IL-6 either follows a different time course in fat cells or that the major effect of IL-6 is exerted through other mechanisms such as the transcriptional regulation identified in the present work. These possibilities are currently under investigation. However, our recent finding (47) that a high IL-6 infusion for 2 h in rats did not reduce the insulin effect during a euglycemic clamp clearly supports that any acute inhibitory effects of IL-6, mediated through a transient activation of SOCS-3, are of less importance for whole body insulin sensitivity. Similar results have recently been reported in man (47). However, because a fairly high insulin concentration was used during the euglycemic clamps, these data cannot exclude the possibility that the liver, in contrast to peripheral tissues, exhibited a modest reduction in insulin sensitivity.

The salient novel findings in the present study are that: IL-6 and TNF-α clearly exert different effects on JNK activation and phosphorylation of serine 307 of IRS-1; both IL-6 and TNF-α reduce the expression of IRS-1, GLUT-4, and PPARγ; IL-6, like TNF-α, decreases insulin-stimulated glucose transport; TNF-α markedly increases IL-6 mRNA and protein secretion; and IL-6 mRNA levels, like those of IL-8 and TNF-α, are increased in human fat cells from non-obese but insulin-resistant subjects. Taken together, these data clearly support a role of IL-6 in insulin resistance and this is further underscored by the fact that the adipose tissue is a major source of IL-6 production in man (3, 4). IL-6 secretion by 3T3-L1 cells was only minor in the absence of TNF-α. However, already a low concentration of TNF-α (1 ng/ml) increased IL-6 secretion ~30-fold, whereas a higher concentration further increased IL-6 release ~200-fold. Thus, TNF-α may exert an important autocrine regulation of cytokine release as also proposed recently by Hotamisligil and co-workers (48).

Because TNF-α markedly increases IL-6 release from fat cells, a distinct possibility was that the effects of TNF-α, at least in part, were attributable to a concomitant release of IL-6. However, the inhibitory effects of TNF-α on gene expression in 3T3-L1 cells was not significantly prevented by the presence of an excess of anti-IL-6 antibodies in the medium, supporting direct effects of TNF-α. In addition, TNF-α was more potent...
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and inhibited the gene expression of, in particular, GLUT-4 and PPARγ to a greater extent than IL-6. However, the effect of these cytokines on IRS-1 was similar and was rapidly induced (30–60 min).

The effect of IL-6 on gene transcription was selective because no effect was seen on IRS-2 mRNA levels. Insulin-stimulated tyrosine phosphorylation of IRS-1 was markedly reduced by IL-6 and this effect could be entirely attributable to the reduced protein expression. This is also supported by the finding that IL-6 did not inhibit the insulin receptor phosphorylation or IRS-2 protein expression.

A novel and interesting finding was that IL-6 gene expression, together with IL-8 and TNF-α, was markedly increased in cells from non-obese but insulin-resistant subjects. This finding was true whether or not the insulin-resistant subjects were lean or overweight.

The insulin-sensitive and -resistant groups were selected on the basis of having normal or low (=50% of normal) IRS-1 protein expression. A reduced IRS-1 and GLUT-4 gene and protein expression is seen in fat cells from Type 2 diabetic subjects (43) as well as in ~30% of non-diabetic subjects with a genetic predisposition for Type 2 diabetes (33–35). Furthermore, adiponectin mRNA levels in the adipose cells as well as circulating adiponectin levels are also reduced in these subjects (35). Both IL-6 and TNF-α reduce IRS-1 and GLUT-4 in 3T3-L1 adipocytes, a causal relationship between the cellular phenotype and cytokine expression is a distinct possibility.

In conclusion, these data provide clear evidence that IL-6 is not only produced by the fat cells but it is also capable of inducing insulin resistance in these cells. Its potential role in whole body insulin resistance in man is further supported by the observation that insulin-resistant individuals also showed evidence of a marked up-regulation of the IL-6 gene. The adipose tissue can play an important role in modulating whole tissue can play an important role in modulating whole

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