Biochemical Characterization of the 94- and 78-kilodalton Glucose-regulated Proteins in Hamster Fibroblasts*

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The GRPs1 are unique sets of proteins highly conserved in animal cells. The two major and most commonly observed GRPs in the chicken, hamster, rat, mouse, and human have molecular size of 94 to 100 kDa and 78 to 80 kDa (Shiu et al., 1977; Pouyssegur et al., 1977; McCormick et al., 1979; Hightower, 1980; Lee, 1981; Melero, 1981; Welch et al., 1983). The GRPs are cellular proteins synthesized constitutively at detectable amounts under normal tissue culture conditions or in whole organs (Hightower and White, 1982), but their synthesis is markedly enhanced in response to glucose starvation and exposure to inhibitors of glycosylation such as 2-deoxyglucose, glucosamine (Pouyssegur et al., 1977; Lee, 1981), and tunicamycin (Olden et al., 1979). These proteins can also be induced following Rous sarcoma virus infection of either chicken or rat fibroblast cells (Stone et al., 1974; Isaka et al., 1975) and were originally thought to be transformation-specific. Subsequently, it was demonstrated that increased contents of these proteins are actually due to rapid depletion of glucose from the growth medium by transformed cells (Shiu et al., 1977; Peluso et al., 1978). Selective stimulation of the synthesis of these two GRPs in varying amounts has also been reported in chicken and rat cells following treatment with the calcium ionophore A23187 (Wu et al., 1981; Welch et al., 1983). While a mild increase in GRP 78/80 can be detected after heat shock or l-azetidine-2-carboxylic acid treatment, it has now been established that GRP 78/80 is a protein which is distinct from the major 72/73 kDa heat shock protein observed in mammalian cells (Hightower, 1980; Lee et al., 1981; Welch et al., 1983).

To understand better the structure and function of these GRPs, we have started to characterize the GRP94 and GRP78 in a ts hamster mutant line, K12, which overproduces these proteins 20- to 50-fold when the cells are incubated at the nonpermissive temperature, 40.5 °C (Lee, 1981; Scharff et al., 1982). Since GRP94 and GRP78, as well as their mRNAs are overproduced in this ts mutant cell line at 40.5 °C, the K12 system has provided the molecular cloning of the genes encoding these two major GRPs and discussion of their possible interrelationship with the heat shock proteins and Ca2+-binding proteins. In addition, we show that phosphate incorporation into the 78-kDa glucose-regulated protein is specifically affected in the K12 mutant cells.

This report concerns further characterization of the 94-kDa and the 78-kDa glucose-regulated proteins which are the major proteins overproduced in hamster fibroblasts when the cells are starved of glucose. Using a temperature-sensitive mutant, K12, which synthesizes high levels of these proteins at the nonpermissive temperature, we purified both proteins by two-dimensional gel electrophoresis and determined their amino acid compositions as well as the N-terminal sequences. Both proteins contain an unusual N-terminal sequence rich in glutamic and aspartic acid residues. Biochemical fractionation of these proteins demonstrated that the 78-kDa glucose-regulated protein is present in the nuclear fraction. In addition, we show that phosphate incorporation into the 78-kDa protein is specifically affected in the K12 mutant cells.

The abbreviations used are: GRP, glucose-regulated protein; DMEM, Dulbecco's modified Eagle's medium; NP40, Nonidet P-40; SDS, sodium dodecyl sulfate; LEF, isoelectric focusing.

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In Vivo Labeling and Extraction of Phosphate-labeled Proteins—
WglA or K12 cells were seeded on 60-mm diameter culture dishes in
DMEM. When the cells reached about 90% confluency, one set of
dishes was shifted to 40.5 °C while the other set was maintained at
35 °C. After 12 h, the culture medium was removed and the cells were
rinsed with phosphate-free DMEM. The cells were labeled with 140
μCi of [3H]leucine for 16 h in: A, DMEM at 35 °C; B, DMEM medium at 40.5 °C; C, glucose-free medium at 35 °C; and
D, DMEM containing 7 × 10^−4 M of Ca²⁺ ionophore A23187.
Total cell lysate was prepared, and about 5 × 10^5 cpms of [3H]leucine
protein samples were applied to each gel. The conditions for prepara-
tion of cell lysate and gel electrophoresis were as described (Lee,
1981). The autoradiograms are shown. The positions for GRP94 (A)
and GRP78 (B) 70–72 kDa heat shock protein (hs) and actin (Ac) are
indicated.

RESULTS

Inducibility of the 94- and 78-kDa GRPs in the K12 Mutant
Cell Line—When grown at the permissive temperature, 35 °C,
in regular DMEM, K12 cells produce normal amounts of
GRP94 and GRP78 (Fig. 1A). Because of the unique ts
mutation, K12 cells grown in DMEM at 40.5 °C overproduces
the two GRPs (Fig. 1B). This induction is rapid and the
proteins accumulated to about 25-fold above the level ob-
served in the parental nonmutant WglA cell line (Lee, 1981).
Two other culture conditions also affect the level of synthesis
of these GRPs at 35 °C. When the cells are shifted at 35 °C
to glucose-free medium or DMEM containing the Ca²⁺ ion-
ophore A23187, the labeling of GRP78 is notably enhanced.
A detectable increase in the labeling of GRP94 can also be
observed (Fig. 1, C and D).

Subcellular Localization of the Hamster GRPs—In order to
determine the subcellular localization of these GRPs in ham-
ster fibroblasts, we prepared extracts from K12 cells labeled
with radioactive amino acids. The cells were incubated at
40.5 °C to maximize the yield of the GRPs. The extracts were
subfractionated into the membrane, nuclear and cytoplasmic
components using established protocols. As reported previ-
sely for rat fibroblasts cells (Pouyssegur et al., 1977), both
GRP94 and GRP78 were found in the plasma membrane
fractions purified by centrifugation in a two-phase polymer
system (Fig. 2A). Although this may indicate a membrane
localization of both GRPs, similar results would have been obtained if these abundant proteins are tightly associated and copurify with some membrane components during the isolation procedure (see under "Discussion").

Next we determined if the GRPs could be found in the nuclear fraction. For this purpose, we labeled the cellular protein with [3H]lysine and used the enrichment of the histones as an indication of the degree of purification of the nuclear fraction. The protein profiles of the unfractionated, nuclear, and non-nuclear proteins, as separated by one-dimensional gel electrophoresis, are shown in Fig. 2B. As expected, the nuclear fraction was enriched with histone proteins, while most of the actin co-purified with the cytoplasmic fraction. Although a band very close to GRP94 in molecular weight was found in the nuclear fraction, GRP94 was absent from the nuclear fraction. This point becomes clear in the two-dimensional gel electrophoresis discussed below. In contrast, GRP78 and a few other species were detected in the nuclear fraction.

Next we subjected the nuclear and non-nuclear fractions to two-dimensional gel electrophoresis. Comparing the protein profiles observed in a total cell lysate (Fig. 3A), the nuclear (Fig. 3B), and the non-nuclear fractions (Fig. 3C), we concluded that the nuclear fraction was considerably enriched with GRP78. In addition, a portion of the 72/73 kDa heat shock proteins, which were also induced in the cells during incubation at 40.5°C, were also found in the nuclear fraction. GRP94 which has pI 5.1 was clearly absent from the nuclear fraction. Since the protein slightly larger than GRP94 had been detected previously in the nuclear fraction by one-dimensional gel electrophoresis but was absent in the two-dimensional gel electrophoresis, this protein is distinct from GRP94 in electrophoretic mobility based on the net charge and is probably a basic protein which is not resolved by this gel system.

Are the GRPs Phosphorylated in Hamster Cells?—To determine if the hamster cells have the capability of phosphorylating these proteins, and if the ts mutation in K12 has any effect on the phosphorylation process, we labeled both Wg1A and K12 cells with [32P]orthophosphoric acid at 35 and 40.5°C. Equal amounts of protein sample were applied to each gel. The Coomassie brilliant blue-stained gel patterns as well as the autoradiograms are shown in parallel in Fig. 4. In both cell lines, it is clear that GRP94 is not phosphorylated, whereas some level of phosphate label is detected in GRP78.

![Fig. 3. Two-dimensional gel electrophoresis of the hamster of glucose-regulated proteins (autoradiogram). A, total cell lysate was prepared from K12 cells labeled for 16 h at 40.5°C in the presence of 10 μCi/ml of [35S]methionine. About 4 × 10^6 cpm of the [35S]methionine-labeled protein was applied on the gel. B, the [3H]lysine-labeled nuclear fraction as shown in Fig. 2B was subjected to two-dimensional gel electrophoresis. C, the non-nuclear fraction as shown in Fig. 2B was subjected to two-dimensional gel electrophoresis. The positions of GRP94 (a), GRP78 (b), 72-73 kDa heat shock proteins (hs), and actin (Ac) are indicated.](http://www.jbc.org/)

![Fig. 4. In vivo phosphate label of hamster fibroblast proteins. Wg1A or K12 cells were labeled for 8 h in phosphate-free DMEM containing 140 μCi/ml of [32P]orthophosphoric acid. Equal amounts of each protein sample (about 40 μg) were loaded on each gel and subjected to two-dimensional gel electrophoresis. A-D, Coomassie blue staining pattern; E-H, autoradiograms of each of the gels shown at left column. A, E, Wg1A, 35°C; B, F, Wg1A, 40.5°C; C, G, K12, 35°C, and D, H, K12, 40.5°C. The slightly diffused pattern observed in the stained samples is due to treatment of the gels with fluorography enhancer.](http://www.jbc.org/)
In the case of the nonmutant line, Wg1A, from the Coomassie blue staining we estimated that there is about a 1.5-fold increase in the amount of GRP78 at 40.5 °C. The amount of 32P label in GRP78 is also slightly higher at 40.5 °C. This 1- to 2-fold increase in the amount and phosphate label incorporated into GRP78 is also observed in a derivative of a Chinese hamster ovary cell line (data not shown).

Surprisingly, for the K12 cells, even though there is a large amount of GRP78 being accumulated at 40.5 °C, the extent of phosphate label for the GRP78 is at the same level as that observed at 35 °C. Clearly, a large fraction of the GRP78 is not being phosphorylated at 40.5 °C. In addition, even at 35 °C, the level of GRP78 being phosphorylated is slightly lower than that of the Wg1A cells. Nonetheless, the levels of phosphorylation of other proteins seem to be similar for both Wg1A and K12 cells, at both 35 and 40.5 °C. Most noticeably, the 90-kDa protein, which has nearly identical pI (5.3) to GRP78, was present in similar amounts and phosphorylated equally well in Wg1A and K12 cells at both incubation temperatures. Thus, if the K12 cells are defective in some phosphorylation process, the defect appears to be specific for the incorporation of phosphate into GRP78.

**Amino Acid Composition and Partial NH2-terminal Sequence of GRP94 and GRP78**—As shown in Fig. 3, both GRP94 and GRP78 can be separated from other cellular proteins by two-dimensional gel electrophoresis. Since the mutant cell line K12 overproduces these proteins at 40.5 °C, we prepared cell extracts from K12 cells after incubation at 40.5 °C for 16 h. The protein samples, after two-dimensional gel electrophoresis, were stained briefly, and the gel spots corresponding to GRP94 and GRP78 were excised from the second dimension slab gel. After electrodialysis and extensive dialysis to remove the salts and other contaminating impurities, an aliquot of the recovered protein was analyzed by gel electrophoresis for purity and yield. No degradation of the proteins was observed (data not shown), and we obtained about 20 μg of GRP94 and 40 μg of GRP78. Using proteins purified this way, we determined their amino acid compositions and obtained a partial NH2-terminal sequence for both GRP94 and GRP78.

Table I summarizes the results of the amino acid composition analysis. It is evident that both GRPs contain a high content of aspartic acid/asparagine and glutamic acid/glutamine, as well as lysine. These results are consistent with the isoelectric pIs 5.1 and 5.3 for GRP94 and GRP78, respectively (Lee et al., 1981).

The NH2-terminal sequences of GRP94 and GRP78 are shown in Fig. 5. The striking feature of both sequences is that they are unusually rich in aspartic acid and glutamic acid. In the case of GRP94, eight out of the first thirteen amino acid residues consist of either aspartic acid (6 residues) or glutamic acid (5 residues). For GRP78, six out of the first eight amino acids are either glutamic acid (4 residues) or aspartic acid (2 residues).

**DISCUSSION**

Although considerable data exist concerning the universal induction of the GRPs by glucose starvation, the function served by these proteins under normal and induced conditions is still speculative. The controversy with respect to the role of these proteins as glucose transporters has been discussed by Olden et al. (1979) and recently reviewed by Welch et al. (1983). This important issue will certainly be examined with considerable vigor in the future. Since a variety of other stress treatments such as Ca++ influx, 1-oxoglutarate-2-carboxylic acid, viral infection, and heat shock can also induce varying amounts of the GRPs, we present here some new ideas concerning possible interrelationships between the GRPs, the heat shock proteins, and Ca++-binding proteins based on our gel electrophoresis results and the sequence data.

GRP94/100 from rat and human cells has been reported to be associated with the plasma membrane by subcellular fractionation and with the perinuclear membrane by indirect immunofluorescence (Pouyssegur et al. 1977; Welch et al., 1983). We observed a similar association of hamster GRP94 with the membrane fraction; however, since the purity of the membrane fraction is difficult to access, the possibility that co-purification of GRP94 with the membrane fraction is due to its tight association with a membrane component cannot be eliminated. Relevant to this speculation is the fact that hamster GRP94 has a native molecular size of 192 kDa, suggesting that the protein either forms a dimer or is covalently linked with another protein. Such a difference in native and denatured molecular size was also observed in human cells (McCormick et al., 1979; Welch et al., 1983). Thus, GRP94/100 is likely to form some form of complex in vivo. While it can be converted to a glycosylated form (Pouyssegur et al., 1977; Welch et al., 1983), the significance of the glycosylation is unclear.

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* A. Lin and A. S. Lee, unpublished observation.

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**TABLE I**

Amino acid composition of the hamster 94- and 78-kDa glucose-regulated proteins

| Amino acid | 94 kDa mol % | 78 kDa mol % |
|------------|-------------|-------------|
| Asp*       | 12.9        | 17.6        |
| Thr         | 5.2         | 8.6         |
| Ser         | 4.4         | 4.0         |
| Glu*        | 18.9        | 17.3        |
| Gly         | 5.9         | 3.9         |
| Ala         | 6.4         | 3.1         |
| Val         | 6.9         | 7.9         |
| Met         | 1.3         | 1.2         |
| Ile         | 5.1         | 7.0         |
| Leu         | 9.6         | 9.2         |
| Tyr         | 2.7         | 1.8         |
| Phe         | 4.1         | 3.9         |
| His         | 1.5         | 1.2         |
| Lys         | 10.2        | 9.1         |
| Arg         | 4.9         | 4.1         |
| Pro         | ND         | ND          |
| Cys         | ND         | ND          |
| Trp         | ND         | ND          |

* Represents both Asp and Asn.
* Represents both Glu and Gln.
* ND: not determined.

![Fig. 5](http://www.jbc.org/)

**Fig. 5. Partial NH2-terminal sequences of hamster 94- and 78-kDa glucose-regulated proteins.**
Although hamster GRP94 and glycogen phosphorylase (EC 2.4.1.1), the enzyme responsible for glycogen degradation when the levels of glucose are low, have nearly identical subunit molecular sizes, very similar amino acid compositions, and similar native molecular sizes of 192 kDa, a comparison of the NH\textsubscript{2}-terminal sequences of GRP94 and rabbit muscle glycogen phosphorylase shows no similarity. Since a high degree of sequence homology exists between species near the NH\textsubscript{2} terminus and in the catalytic sites of this enzyme (Fletterick and Madsen, 1980), it is unlikely that GRP94 is related to glycogen phosphorylase. In nonmutant hamster cells, GRP94 is not inducible by incubation at 40.5 °C; thus it is not a member of the hamster heat shock stress proteins (Lee, 1981).

In the hamster system, GRP78 is the most abundant glucose-regulated protein. Its synthesis is enhanced at least 50-fold by the K12 ts mutation, and following glucose starvation it accumulates to 2- to 3-fold higher levels than observed for GRP94. In contrast to GRP94, GRP78 is slightly heat inducible in nonmutant hamster cells (Lee, 1981). In rat and human cells, GRP78 is found to incorporate phosphate label but is not glycosylated (Welch et al., 1983). A recent report further shows that the same protein (designated SP83) in rat and chick embryo fibroblasts is modified by ADP ribosylation (Carlsson and Lazarides, 1983). Our data on this phosphorylation analysis show that GRP78 is also labeled by phosphate in the hamster cells. Furthermore, we note that while other cellular proteins incorporate equal amounts of phosphate label at 35 and 40.5 °C, the large amount of GRP78 overproduced at 40.5 °C is not being modified. This specific effect on GRP78 as observed in the K12 cells can be due to some specific defects in the phosphorylation process of this protein involving ATP and protein kinases. Alternatively, if GRP78 is indeed a major acceptor of ADP ribosylation, then a specific defect in this process in K12 cells can lead to the same observation. The fact that the mutant K12 cells appear to be specifically deficient in the phosphate labeling of GRP78 may allow us to examine the molecular basis for its overproduction at 40.5 °C and the functional aspects of the nonphosphorylated GRP78 in fibroblast cells.

From in vitro translation analysis, we observed that GRP78 is synthesized in vitro as a slightly larger species, possessing a slightly more basic charge than the in vivo protein (Lee et al., 1981). The charge differences can now be explained by the lack of phosphorylation or ADP ribosylation in the in vitro translation system. We speculate that GRP78 is first synthesized and then a short peptide is cleaved away to yield the mature GRP78 with the NH\textsubscript{2}-terminal sequence which is presented here. The significance of this prepeptide as well as the modification by phosphate observed in the mature protein remains to be determined.

The localization of GRP78 is less well defined than that of GRP94. Our results based on cell fractionation suggest that while GRP78 is synthesized in the cytoplasm, it can also be found in the membrane and nuclear fractions. The highly acidic NH\textsubscript{2} terminus of the protein can possibly interact with some basic chromosomal proteins. It is interesting to note that some heat shock proteins, upon induction, can also be found localized inside the nucleus (Velasquez et al., 1980).

The fact that GRP78 and the cytosolic form of phosphoenolpyruvate carboxykinase (EC 4.1.1.32) have similar sizes for their protein subunits and mRNA prompted us to determine if they are related. The synthesis of phosphoenolpyruvate carboxykinase in rat liver is markedly altered by the availability of glucose in the diet (Lamers et al., 1982). In addition, this enzyme is the rate-limiting enzyme in lactate gluconeogenesis in fasted rats. However, we failed to detect any increase in cytosolic phosphoenolpyruvate carboxykinase activity in our cell extracts at either 35 or 40.5 °C and no cross-hybridization of the cDNA coding for phosphoenolpyruvate carboxykinase (Yoo-Warren et al., 1982) with pC5, the cDNA likely to encode for GRP78, was observed.

An unusual feature of the NH\textsubscript{2}-terminal sequences of both GRP94 and GRP78 is the relatively high abundance of the acidic amino acids, in particular aspartic acid and glutamic acid. Although a search for homologous NH\textsubscript{2}-terminal sequences among known identified proteins has not yielded any positive results, the high content of Asp/Asn and Glu/Gln is shared by the 72-kDa heat shock protein reported for Hela cells (Welch et al., 1982), as well as the 72-kDa protein from Drosophila melanogaster deduced from the nucleotide sequence of the gene (Ingolia et al., 1980). In addition, recently the sequence of the yeast 90-kDa heat shock protein (Hsp 90) has been deduced from its nuclear acid sequence (Finkelman et al., 1983). Although yeast Hsp 90 has a different NH\textsubscript{2}-terminal sequence from that of the hamster GRPs, a block of the yeast Hsp 90 internal amino acid sequence (position 200-242) bears a striking resemblance to the NH\textsubscript{2} terminus of hamster GRP94 and GRP78. Within this 21-amino acid residue block, a repeat unit consisting of alternating Gly-Glu-Lys-Gln or Asn-Glu-Lys is found. In view of this homology and the similarities in amino acid composition with hamster and Drosophila heat shock protein, it may be a general characteristic for stress proteins to be highly acidic, and some of the shared peptides may have evolved from a common ancestral protein sequence.

On the other hand, the acidic residues of GRP94 and GRP78 may form a highly negatively charged environment that will effectively bind Ca\textsuperscript{2+}. The amino acid composition of several Ca\textsuperscript{2+}-binding protein such as calmodulin and troponin C is also rich in glutamic and aspartic acid. In addition, if we compare the proposed Ca\textsuperscript{2+}-binding sequences of different Ca\textsuperscript{2+}-binding proteins (Dedman et al., 1978) with that of the NH\textsubscript{2}-terminal sequence of GRP94 and GRP78, some limited homology can be detected. Whether this in fact reflects a structural or functional relationship between the GRPs is currently unknown. Since the calcium concentration within the cell may have a major impact on glycosylation, cell division, and other cellular metabolism, there may exist a fundamental interrelationship among these cellular processes, as manifested by the synthesis of the same set of proteins under stress conditions.

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