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Enhanced Transcription of the 78,000-Dalton Glucose-Regulated Protein (GRP78) Gene and Association of GRP78 with Immunoglobulin Light Chains in a Nonsecreting B-Cell Myeloma Line (NS-1)

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The 78,000-dalton glucose-regulated protein (GRP78) is a stress-inducible protein localized in the endoplasmic reticulum. It has been identified as the immunoglobulin heavy-chain-binding protein. We report here a high level of GRP78 expression in a B-cell myeloma line, NS-1, which produces only kappa light-chain proteins but is unable to secrete them. GRP78 transcription was enhanced in NS-1 cells, resulting in higher levels of GRP78 mRNA and protein than in non-immunoglobulin-producing cells. Furthermore, the nonsecreted light chains in NS-1 cells were found in specific association with GRP78. We hypothesize that in nonsecreting lymphoid cells, the presence of free, unassembled light chains in the endoplasmic reticulum could result in increased transcription of the GRP78 gene and that GRP78 can also bind to immunoglobulin light chains.

The glucose-regulated proteins (GRPs) are members of the heat shock protein (HSP) family, since the GRPs and HSPs share partial amino acid sequence identity (28, 29). However, whereas the HSPs are primarily cytoplasmic proteins, the GRPs have signal sequences which target them into the endoplasmic reticulum (ER) (29, 32). The exact physiological roles played by the stress proteins are not known. Recent evidence suggests that members of HSP70 protein family facilitate translocation of secretory and mitochondrial precursor polypeptides (5, 8). The 78,000-dalton GRP (GRP78) may be representative of a novel class of ER proteins involved in regulating transport of secreted or transmembrane proteins from the ER to the Golgi apparatus (3). It has been shown that GRP78 associates in the ER with newly synthesized proteins that have mutant structures (12) or are incorrectly glycosylated (9). It can also recognize aberrant polypeptides translocated in vitro (17). During stress, GRP78 binds to a variety of cellular proteins when protein processing is blocked in the ER (15).

From direct comparisons of amino acid sequences and immuno-cross-reactivities, GRP78 has been shown to be identical to the immunoglobulin heavy-chain-binding protein (BiP) originally observed in pre-B lymphocytes (13, 15, 29). The identification of GRP78 as BiP increases our understanding of one role of stress proteins. In lymphoid cells, GRP78 appears to associate transiently with newly synthesized immunoglobulin heavy chains. On completion of polymerization with light chains, GRP78 loses affinity and disassociates from immunoglobulin molecules (3). When light-chain assembly is inhibited, the association of heavy chains with GRP78 is prolonged and immunoglobulin secretion is blocked (14). As a first step toward understanding the regulation of GRP expression in B lymphocytes, we examined the protein and transcript levels of GRP78 in several lymphoid cell lines that had been selected in culture to alter immunoglobulin secretion.

High GRP78 transcript level in NS-1 cells. The four cell lines examined are presented in Fig. 1A. MOPC21 is a mineral oil-induced plasmacytoma from a BALB/c mouse (21). P3X63Ag8 is derived from P3K, a cell line established from MOPC21 (16). Both MOPC21 and P3X63Ag8 actively secrete immunoglobulin (gamma, kappa). NS-1 is a nonsecreting derivative of P3X63Ag8 which has lost the ability to produce functional immunoglobulin (6). It continues to synthesize kappa light chains but is unable to secrete them. SP2/0 is derived by fusion of P3X63Ag8 with a splenic B-cell line. It has lost the ability to produce heavy- and light-chain proteins (20). Total cytoplasmic RNA was isolated from exponentially growing cultures of these cells. Equal amounts of the RNA samples were applied to denaturing formalde-

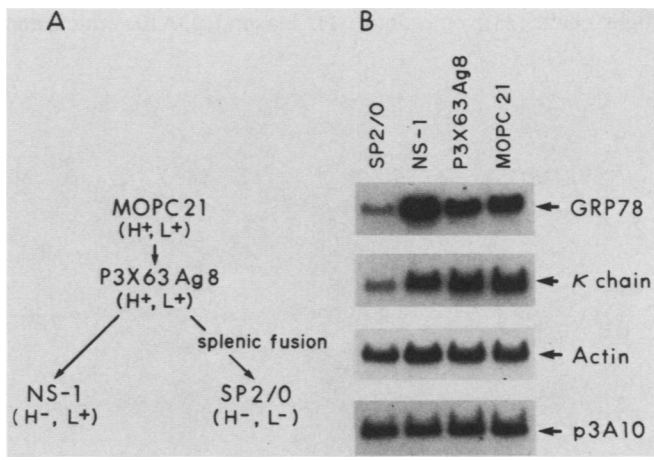

FIG. 1. Relative transcript levels in B-lymphocyte cell lines. (A) Description of B-cell myelomas. (B) Relative transcript levels. The cell lines are indicated at the top. RNA (10 μg) from each sample was applied to denaturing formaldehyde-formamide gels, electrophoresed, and blotted onto nitrocellulose filters (26). The filters containing transferred RNA were hybridized at 42°C for 16 h with hexamer-labeled (11) cDNA plasmids (specific activities, 10^8 cpm/μg) encoding GRP78, kappa light chain, α-actin, and p3A10. The autoradiograms are shown.

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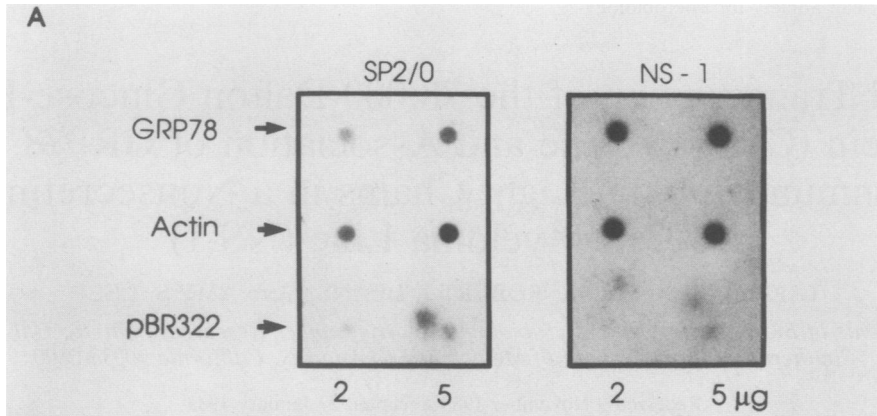


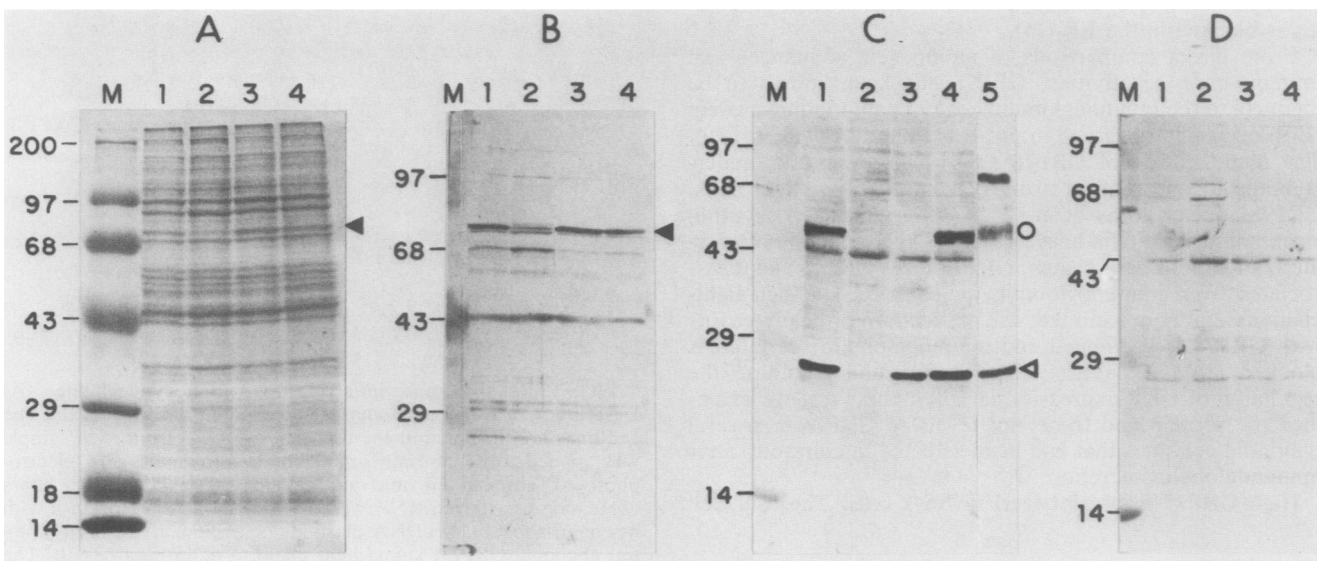
B

	SP2/0			NS-1		
	Avg Peak area	Avg (-pBR)	% actin	Avg peak area	Avg (-pBR)	% actin
GRP78	6.6	4.0	(31)	40.3	38.1	(113)
Actin	15.3	12.7	(100)	36.0	33.8	(100)
pBR322	2.6	0		2.2	0	

FIG. 2. In vitro transcriptional rates of the GRP78 gene. (A) Nuclei isolated from 10^8 SP2/0 and NS-1 cells were labeled in vitro with 250 μCi of [α-^{32}P]UTP in 100 μl of reaction mixture as described previously (2, 30). Both yielded about 10^7 cpm of labeled nuclear RNA, which was hybridized to 2 and 5 μg of plasmids encoding GRP78, actin, and pBR322 as described elsewhere (2). (B) Summary of relative transcriptional rates. The peak areas from two experiments were determined by densitometry of the autoradiograms exposed to a linear range of film, using a Hoefer GS300 scanner. After subtraction of background hybridization to the blank filters and the nonspecific binding due to pBR322, the average peak areas were standardized against that of actin, which was set at 100%.

hyde-formamide gels and electrophoresed (26). The RNA was then transferred to nitrocellulose filters for blot hybridizations with the cDNA probes encoding GRP78 (31), kappa light chain (23), or α-actin (1). Plasmid p3A10, which encodes a non-glucose-regulated transcript (27), was included as a control.

We observed an unusually high level of GRP78 transcripts in the nonsecreting NS-1 myeloma cells (Fig. 1B). Relative



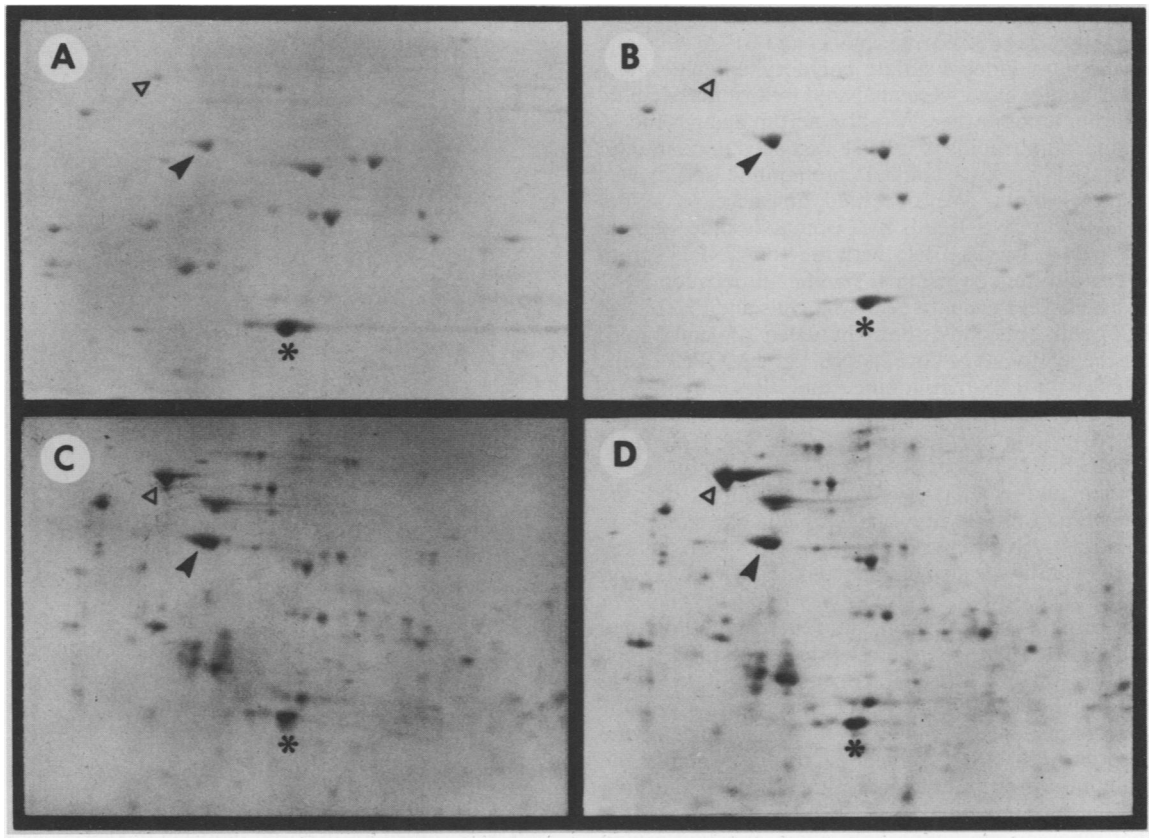


FIG. 4. Two-dimensional gel electrophoresis of GRP78. (A) [^{35}S]methionine-labeled protein lysate prepared from mouse L cells labeled for 3 h in methionine-free Dulbecco modified Eagle medium containing 4.5 mg of glucose (GIBCO Laboratories, Grand Island, N.Y.) supplemented with 0.5% dialyzed calf serum (Biocell, Carson, Calif.); (B) mouse L-cell lysate prepared from cells grown for 24 h in glucose-free Dulbecco modified Eagle medium before labeling for 3 h; (C) MOPC21 and (D) NS-1 cell lysates prepared from cells labeled for 16 h in Dulbecco modified Eagle medium. The protein lysates were prepared and subjected to two-dimensional gel electrophoresis as described previously (18). Positions of GRP78 (◀), GRP94 (◁), and actin (*) are indicated.

to the mRNA levels of actin and p3A10, there was a sixfold increase for GRP78 mRNA in NS-1 cells compared with the level in SP2/0 cells and a twofold increase compared with levels in the immunoglobulin-secreting MOPC21 and P3X63Ag8 cells. The levels of kappa light-chain mRNA were similar in the two immunoglobulin-secreting lines, slightly lower in NS-1 cells, and fivefold lower in SP2/0 cells.

Enhanced transcription of GRP78 in NS-1 cells. To determine whether the difference in GRP78 transcript levels in NS-1 and SP2/0 cells resulted from differences in transcriptional initiation, rates of transcription of the GRP78 genes in these cells were compared. Nuclei were isolated from SP2/0 and NS-1 cells and labeled in vitro with [α-^{32}P]UTP (2). The radiolabeled nuclear RNA was hybridized with excess amounts of cDNA plasmids encoding GRP78 and actin. Plasmid pBR322 was included to monitor nonspecific binding. The autoradiograms (Fig. 2A) were quantitated by densitometry and standardized to actin transcription. The rate of GRP78 mRNA synthesis was about 3.5-fold higher in NS-1 cells than in SP2/0 cells (Fig. 2B). Similarly, the rate of GRP78 transcription was about 1.5- to 2-fold higher in NS-1 cells than in a secreting myeloma line, S194 (heavy- and light-chain producing), which showed a GRP78 mRNA level 2-fold lower than that of NS-1 (data not shown). Therefore, the rate of GRP78 transcription correlated with the steady-state level of the GRP78 mRNA in these cells (Fig. 1), and the increase in the GRP78 mRNA level in NS-1 cells can be accounted for in part by a higher rate of GRP78 transcription.

Accumulation of GRP78 protein in NS-1 cells. The results from transcript measurements predicted that the NS-1 cells would show an increase in GRP78. To examine GRP78

FIG. 3. Immunoblot analysis of GRP78 and kappa light chains. Proteins (80 μg) from each cell sample was electrophoresed on 10% sodium dodecyl sulfate-polyacrylamide gels, transferred to Hybond-C membranes (Amersham Corp., Arlington Heights, Ill.) with the Polyblot apparatus (American Bionetics Inc.), and probed with the indicated antisera as previously described (4) except that the substrate used was 4-chloro-1-naphthol (Sigma Chemical Co., St. Louis, Mo.). In all panels, lanes 1, 2, 3, and 4 contained protein lysates from P3X63Ag8, SP2/0, NS-1, and MOPC21, respectively. Prestained protein molecular size standards (in kilodaltons) are shown in lane M. (A) Coomassie blue stain of B-cell protein lysates; (B) immunoblot with the anti-GRP78 peptide serum (1:500 dilution); (C) immunoblot with the anti-kappa light-chain serum (1:200 dilution; ICN Pharmaceuticals Inc., Irvine, Calif.) (lane 5 contained purified mouse myeloma protein [immunoglobulin M kappa chain; Bionetics]); (D) immunoblot with preimmunized rabbit serum (1:500 dilution). Positions of GRP78 (◀), kappa-chain bands (◁), and heavy-chain bands (○) are indicated.

expression at the protein level, protein extracts were prepared from MOPC21, P3X63Ag8, NS-1, and SP2/0 cells and resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Parallel blots were analyzed by Coomassie blue staining and immunoblotting. A rabbit serum against the 15 amino-terminal amino acids of GRP78 was used to quantitate the level of GRP78. As a control, preimmune serum was used in parallel blots. We observed an increase in the amount of GRP78 in NS-1 cells by Coomassie blue staining (Fig. 3A) as well as by reactivity with the anti-GRP78 serum (Fig. 3B). The difference was most significant between NS-1 and SP2/0. The difference between NS-1 cells and P3X63Ag8 and MOPC21 cells was consistently between 1.5- and 2-fold. To monitor the synthesis of GRP78, NS-1 and MOPC21 cells were labeled with [^{35}S]methionine, and the protein was analyzed on two-dimensional gels. GRP78 was one of the major labeled protein species in NS-1 and MOPC21 cells (Fig. 4C and D). GRP78 in the B-cell line had the same molecular size and isoelectric focusing point as did the GRP78 inducible in mouse fibroblasts by glucose starvation (Fig. 4A and B). Synthesis of another glucose-regulated protein, GRP94 (25), was also enhanced in these B cells (Fig. 4C and D).

Next, the protein extracts from the four B-lymphoid cell lines immunoblotted with a rabbit serum against the kappa light chain (Fig. 3C). Light-chain protein was detected in NS-1, MOPC21, and P3X63Ag8 cells in quantities proportional to the kappa mRNA level (Fig. 1). The size of the light-chain protein in NS-1 was similar to that found in the immunoglobulin-secreting myelomas; therefore, if the light chain in NS-1 cells is mutated, it is not a large deletion. It is notable that whereas the kappa light-chain constant-region cDNA probe hybridized at a low level to RNA samples from SP2/0 (Fig. 1B), no mature light-chain protein was observed in SP2/0 cells (Fig. 3C). The faint band at the light-chain position was an unrelated protein present in similar quantities in all four cell lines and cross-reacted with the preimmune serum (Fig. 3D). Since the anti-mouse kappa light-chain serum contained contaminating anti-heavy-chain activities, it also detected the ~55,000-dalton heavy chains in the immunoglobulin-secreting myelomas P3X63Ag8 and MOPC21. As expected, NS-1 cells were devoid of heavy chains. Therefore, in NS-1 cells, a pool of free light chains apparently accumulated intracellularly.

Association of GRP78 with the kappa light chain in NS-1 cells. GRP78 has been shown to associate with newly synthesized or abnormally processed immunoglobulin heavy chains (3, 14). GRP78 is also known to bind other cellular proteins with a mutant structure (12). The presence of malfolded protein in the ER correlated with an increased transcript level of GRP78 (22). One explanation for the high-level expression of GRP78 in NS-1 cells may be related to the production of nonsecreted immunoglobulin light chains inside these cells. Consistent with this view, SP2/0, which no longer produced either heavy- or light-chain molecules, exhibited the lowest level of GRP78. To test this hypothesis, we determined the association of GRP78 with the kappa light chain produced in NS-1 cells. For this purpose, [^{35}S]methionine-labeled protein extracts from NS-1 cells were immunoprecipitated with the anti-BiP (GRP78) and the anti-kappa light-chain antibodies. The immunoprecipitates were treated in reducing conditions and analyzed on denaturing polyacrylamide gels to resolve the protein species. GRP78 coimmunoprecipitated with the kappa light chain produced in NS-1 cells (Fig. 5A and B). The GRP78 and the kappa light-chain complex could be immunoprecipitated with either antibody preparation. Therefore, we discovered that GRP78 could, in addition to interacting with the immunoglobulin heavy chains, interact with immunoglobulin light chains in NS-1 cells. Our results are in agreement with those of a recent independent survey of a large number of B-cell myelomas which demonstrate that GRP78 is found only in association with the light chains in nonsecreting light-chain myelomas such as NS-1 and that GRP78 is not associated with light chains in secreting myelomas (J. Ma, J. Kearney, and L. M Hendershot, manuscript in preparation). It is possible that the kappa light chains produced by the NS-1 cell line harbor subtle mutations that allow them to bind to GRP78. Alternatively, the association of GRP78 with light chains may be a lower-affinity interaction than that of GRP78 with heavy chains. Therefore, the accumulation of the normal kappa light chains in the absence of immunoglobulin heavy-chain expression in the ER of NS-1 cells may allow a more prolonged and stable association of the two proteins.

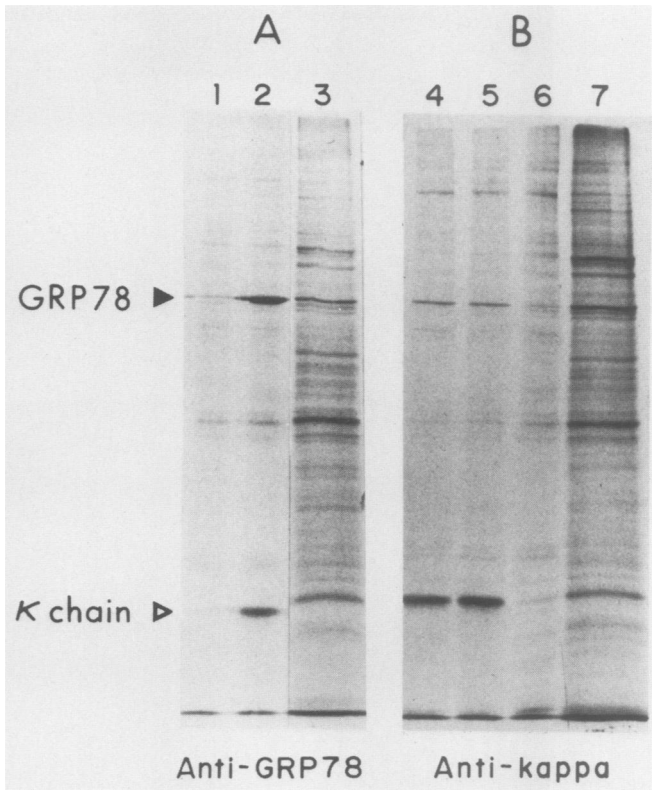


FIG. 5. Immunoprecipitation of NS-1 cell lysate. About 10^7 NS-1 cells were labeled for 16 h with 10 μCi of [^{35}S]methionine per ml of Dulbecco modified Eagle medium. The cells were suspended in 1 ml of lysis buffer containing 0.5× phosphate-buffered saline, 0.5% deoxycholate, 0.5% Nonidet P-40, and 1 mM phenylmethylsulfonyl fluoride. About 1.5×10^6 cpm of cell lysate was immunoprecipitated with 50 μl of anti-GRP78 (lane 2) and 1 μl (lane 4) and 4 μl (lane 5) of anti-kappa light-chain antibodies as described previously (7). Lanes 1 and 6 are control immunoprecipitation reactions with the antibodies omitted; lanes 3 and 7 are contained 2×10^5 cpm of NS-1 total cell lysate. Immunoprecipitated proteins and cell lysates were reduced and resolved on 10% sodium dodecyl sulfate-polyacrylamide gels as described previously (24). The autoradiograms are shown. Positions of GRP78 and kappa light-chain proteins are indicated.

Although the immunoprecipitation experiments clearly demonstrated the association of GRP78 with kappa light

chains, the binding is not quantitative for several reasons. For example, the antibody preparations against the kappa light chain may not be able to recognize the antigenic site within the complex as efficiently as do the free molecules. In the case of the association of GRP78 (BiP) with the heavy chain in RD3-2 and J558 cells, the anti-heavy-chain antibody cannot immunoprecipitate the complex, whereas the anti-GRP78 (BiP) antibody can (3). In addition, light-chain protein that is not in the ER compartment would immunoprecipitate and contribute to kappa light-chain levels.

The results presented here on the expression of GRP78 and its mRNA levels in these B-lymphoid cell lines yielded two new observations. First, we showed enhanced transcription of the GRP78 gene in the NS-1 cell line, which continues to synthesize light chains but has lost the ability to synthesize functional heavy chains. Second, using antibodies against GRP78 (BiP), we could detect specific association of GRP78 with the kappa light chains produced in NS-1 cells. Although we cannot rule out the possibility that a fortuitous mutation in NS-1 cells is involved in transcriptional activation of the GRP78 gene, on the basis of this and other recent investigations (10, 15, 19, 22, 25) we postulate that in fibroblast cells as well as in B lymphocytes, a sensory device apparently exists which transmits the state of ER activity to the nucleus. The recurring observation is that transcription of the GRP78 gene is most correlated with the presence of abnormal proteins in the ER. GRP78 production may not be related simply to level of secretion. More likely, it is related to the extent of malfolded or unassembled protein present in the ER. Our studies provide further evidence that GRP78 (BiP) has a larger repertoire of proteins to which it can associate in vivo than was originally described (13). Further investigations into the domain of GRP78 that binds to the kappa light-chain protein will provide more information on the structural and functional relationship of these protein complexes.

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