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PROSPECTS

Role of the Glycolytic Protein, Glyceraldehyde-3-Phosphate Dehydrogenase, in Normal Cell Function and in Cell Pathology

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Abstract The glycolytic protein glyceraldehyde-3-phosphate dehydrogenase (GAPDH) appeared to be an archtypical protein of limited excitement. However, independent studies from a number of different laboratories reported a variety of diverse biological properties of the GAPDH protein. As a membrane protein, GAPDH functions in endocytosis; in the cytoplasm, it is involved in the translational control of gene expression; in the nucleus, it functions in nuclear tRNA export, in DNA replication, and in DNA repair. The intracellular localization of GAPDH may be dependent on the proliferative state of the cell. Recent studies identified a role for GAPDH in neuronal apoptosis. GAPDH gene expression was specifically increased during programmed neuronal cell death. Transfection of neuronal cells with antisense GAPDH sequences inhibited apoptosis. Lastly, GAPDH may be directly involved in the cellular phenotype of human neurodegenerative disorders, especially those characterized at the molecular level by the expansion of CAG repeats. In this review, the current status of ongoing GAPDH studies are described (with the exception of its unique oxidative modification by nitric oxide). Consideration of future directions are suggested. J. Cell. Biochem. 66:133–140, 1997. © 1997 Wiley-Liss, Inc.

Key words: glyceraldehyde-3-phosphate dehydrogenase (GAPDH); RNA binding protein; DNA replication; DNA repair; apoptosis; triplet repeat neurodegenerative disorders; nitric oxide

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH, EC 1.2.1.12) was considered a housekeeping protein involved in basic cell catabolic processes. In particular, as a tetramer composed on identical 37 kDa subunits, its role in glycolysis was well characterized. As such, the the GAPDH protein and gene were used in numerous studies as models to understand protein and gene structure, mechanisms of enzyme action, and the control of gene expression. Considering its apparent high degree of conservation across the phylogenetic scale, conventional dogma indicated only a limited role for this housekeeping gene and protein.

However, independent studies from a number of different laboratories reported recently a variety of diverse biological properties of the GAPDH protein. These include membrane, cytoplasmic and nuclear functions in endocytosis, mRNA regulation, and tRNA export, DNA replication and DNA repair, respectively. In accord with its multidimensional nature, GAPDH gene expression is specifically regulated as a function of the cell's proliferative state [Meyer-Siegler et al., 1992; Mansur et al., 1993; Gong et al., 1996]. Further, the subcellular localization of the GAPDH protein is dependent on its growth stage [Cool and Sirover, 1989]. In noncycling normal human cells, basal levels of GAPDH are localized in the cytoplasm (Fig. 1). No immunofluorescence is detected in the nucleus. In contrast, in cycling normal human cells, an increase in antigenic GAPDH is observed (Fig. 2). However, GAPDH is now detected in the nucleus or is perinuclear.

Recent studies also indicate a role for GAPDH during neuronal apoptosis. GAPDH gene expression is increased during programmed cell death. Transfection with antisense GAPDH sequences inhibits neuronal apoptosis. Intriguingly, a specific relationship may exist in vivo between GAPDH and a number of proteins directly related to the pathology of neurodegen-

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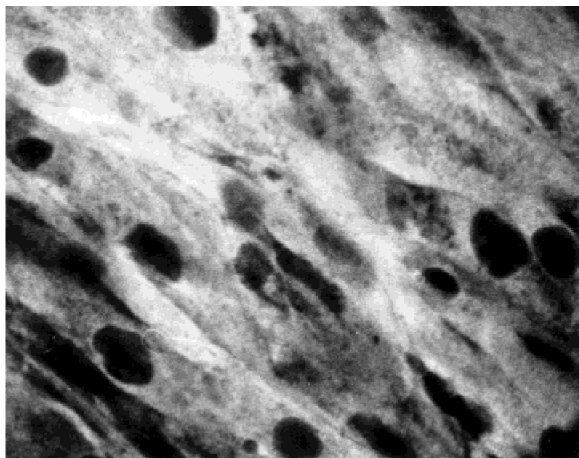
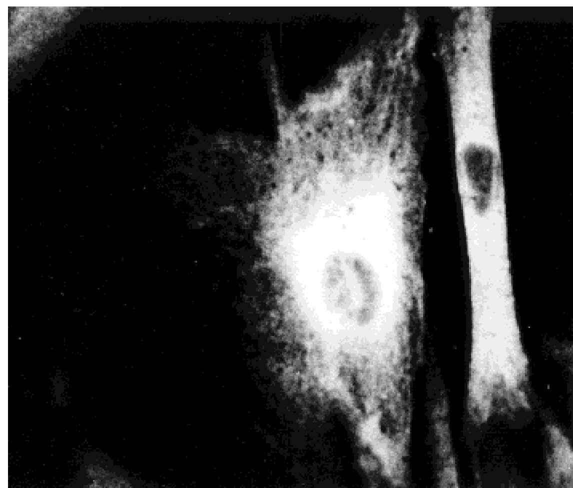


Fig. 1. Intracellular localization of GAPDH in non-cycling normal human cells.



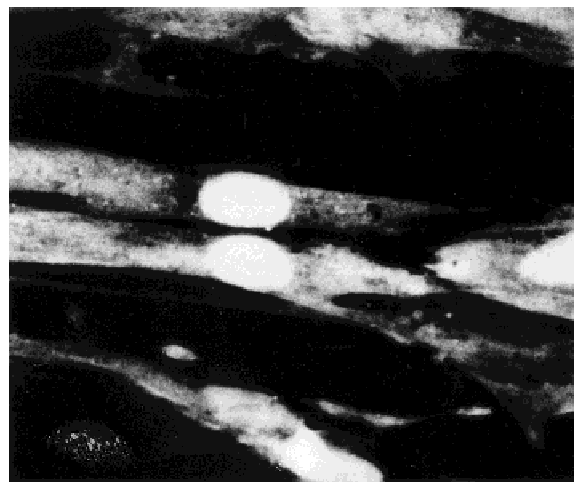


Fig. 2. Intracellular localization of GAPDH in proliferating normal human cells.

erative disorders. A series of studies indicate its specific binding to proteins identified as the primary defect in CAG expansion triplet repeat disorders. These include Huntington's disease (huntingtin), dentatorubalpallidoluysian atrophy (atrophin), spinocerebellar ataxia type-1 (ataxin), and spinobulbar muscular atrophy (androgen receptor). Further, GAPDH specifically binds to the carboxyl terminal end of the β-amyloid precursor protein (βAPP), a critical factor in Alzheimer's disease.

NEW ACTIVITIES OF MAMMALIAN GAPDH

As indicated in Table I, independent investigations detected multiple properties of mammalian GAPDH. Significantly, the identification of these new functions was proceeded by detailed experimentation, which demonstrated unique properties of an unknown protein. Subsequent to those findings, the unknown protein was identified as GAPDH.

Membrane Functions of Mammalian GAPDH

Initial studies identified the structural association of GAPDH with cell membranes [Kliman and Steck, 1980; Tsai et al., 1982; Lin and Allen, 1986; Allen et al., 1987]. In these investigations, two-dimensional gel electrophoresis detected a series of GAPDH variants. GAPDH colocalized with the band 3 anion exchanger (AE) protein [Ercolani et al., 1992]. Its glycolytic activity was diminished by this protein/protein interaction. Competition was observed with NAD^+. Other studies revealed a functional role for GAPDH in membrane fusion [Glaser and Gross, 1995]. Intriguingly, these investigations suggested that an isogenic GAPDH species, lacking its glycolytic activity, was the active species. The relationship between the former detection of GAPDH isoelectric variants and the latter identification of isogenic GAPDH species is unknown.

Similarly, GAPDH was identified as a tubulin binding protein, catalyzing tubulin polymerization [Kumagai and Sakai, 1983; Durrieu et al., 1987; Muronetz et al., 1994]. In skeletal muscle, GAPDH/tubulin binding resulted in triad junction formation [Caswell and Corbett, 1985]. Tubulin bundling by GAPDH was inhibited by ATP [Huitorel and Pantaloni, 1985]. The functional role of tubulin bound GAPDH was demonstrated by analysis of mutant CHO cells

TABLE I. Functions of Mammalian Glyceraldehyde-3-Phosphate Dehydrogenase

Localization	Cell function	Activity	Molecular mechanism
Membrane	Macromolecular transport	Endocytosis	Microtubule bundling protein
Cytoplasm	Energy generation	Glycolysis	ATP production
	Control of gene expression	Translational regulation	5′UTR, 3′UTR mRNA binding protein
Nuclear	Control of gene expression	Translational regulation	Nuclear tRNA export protein
	Transfer of genetic information	DNA replication	$A_{p4}A$ binding protein
	Prevention of genomic instability	DNA repair	Uracil DNA glycosylase

TABLE II. GAPDH/RNA Interactions In Mammalian Cells

RNA source	RNA probe	Sequence bound	Competitive inhibitor
Human lymphokine mRNA	3′-UTR	AUUUA	NAD^+ NADH ATP
Hepatitis A virus	5′-UTR	Stem-Loop IIIA, Pyr1 (pyrimidine rich)	NAD^+ Poly (U)
Human parainfluenza virus	3′-Genomic	UAAUUU, UUUCUUCU	NAD^+ Poly (U)
Hammerhead ribozyme	TNF-α	GCGUUGA, CGCAACU	NAD^+ ATP
Human nuclear tRNA (wild type and mutant)	$tRNA_i^{met}$ $tRNA^{phe}$ $tRNA^{tyr}$	T Stem-Loop (met: AAAGCUA; tyr: UAAGCUU)	NAD^+

deficient in endocytosis [Robbins et al., 1995]. These studies revealed that a mutation in microtubule-associated GAPDH was the causative agent. Sequence analysis of the mutant GAPDH cDNA indicated that a single amino acid change (ser^{234} to pro^{234}, C:T transition) was responsible for the endocytotic deficiency. Further, transfection of the mutant cDNA into wt cells elicited the mutant cellular phenotype.

Cytoplasmic Functions of Mammalian GAPDH

Recent studies have indicated that the translational regulation of gene expression may involve trans-acting proteins, which bind specifically to 5′-UTR or 3′-UTR mRNA sequences. As such, one may modulate parameters that control protein synthesis (i.e., rates of translation, mRNA stability). Further, investigation of RNA viruses indicated viral RNA/ribosomal association as an initial step in viral infection. This requires the use of specific host cell proteins to facilitate viral protein synthesis. Thus, cell protein/viral RNA interactions provide a basic mechanism necessary for viral infection of eucaryotic cells.

A variety of experimental protocols have been used to identify specific proteins that intereact with either cellular or viral mRNA at 5′- and 3′-UTR sequences. These include uv-crosslinking of binding proteins to the RNA of interest and electromobility gel shift assays. N-terminal sequencing is used to identify the respective binding protein. As shown in Table II, such studies identified GAPDH as a specific mRNA binding protein. It was identified as the protein that uniquely bound to AU rich 3′-UTR regions of lymphokine mRNA [Nagy and Rigby, 1995], to the 5′-UTR stem-loop IIIA region of the hepatitis A virus (HAV) [Schultz et al., 1996], and to the 3′-genome sequence element of human parainfluenza I virus type 3(HPIV3) [De et al., 1996]. In each instance, once GAPDH was identified as the RNA binding protein, anti-GAPDH antibodies or commercially available GAPDH was used to confirm its initial identification.

Common elements in these studies include the identification of pyrimidine regions in the RNA molecule as the putative GAPDH binding site. Competition experiments indicated that GAPDH/RNA binding was inhibited by poly(U) or NAD^+. These results suggest the involvement of the NAD^+ binding site within GAPDH. Such studies are in accord with the demonstration that lymphokine mRNA binds to the N-terminal 6.8 kDa GAPDH polypeptide, which contains the NAD^+ binding site.

The physiological significance of these in vitro studies was illustrated by parallel studies in vivo. In quiescent human T cells, Nagy and Rigby [1995] demonstrated the polysomal localization of GAPDH. Intriguingly, they reported a significant increase in polysomal GAPDH in mitogen-stimulated T cells. This would be in accord with immunofluorescent studies demonstrating the perinuclear localization of GAPDH in actively proliferating human cells (Fig. 2). Ribosomal salt washes were used to demonstrate GAPDH/HAV RNA binding [Schultz et al., 1996]. Lastly, double immunofluorescent studies colocalized GAPDH with HPIV3 ribonucleoprotein in the perinuclear region [De et al., 1996]. In toto, each study suggests that in vitro structural GAPDH/RNA association correlates with functional GAPDH/RNA interactions in vivo.

Further studies suggested the therapeutic significance of RNA/GAPDH interactions. In these studies, Sioud and Jespersen [1996] reported that GAPDH increased the activity of the tumor necrosis factor alpha (TNF-α) ribozyme. This enhancement was observed both in vitro and in vivo. In accord with the mRNA studies described above, the GAPDH binding site was contained within pyrimidine regions of the TNF-α ribozyme. Competition experiments demonstrated that both NAD^+ and ATP inhibited GAPDH/ribozyme binding. Thus, in toto, these studies demonstrate a variety of GAPDH/RNA interactions. Further, they suggest that GAPDH/RNA binding involves pyrimidine regions in RNA (especially uracil residues) and the NAD^+ binding site in GAPDH.

Nuclear Functions of Mammalian GAPDH

Initial structural investigations identified GAPDH as a DNA binding protein [Tsai and Green, 1973; Perucho et al., 1977] as well as a non-histone nuclear protein [Morgenegg et al., 1986]. Recent studies have indicated three new nuclear functions of GAPDH in mammalian cells. First, in accord with investigations demonstrating cytoplasmic RNA/GAPDH interactions, Singh and Green [1993] identified GAPDH as a nuclear tRNA export protein. These studies used normal and export-defective tRNA in mobility shift assays. The purification of the unknown export protein included poly(U) affinity chromatography. N-terminal sequencing identified the unknown protein as GAPDH. Commercially purchased human erythrocyte GAPDH exhibited tRNA binding. Competition was observed using NAD^+. Sequence analysis indicated the significance of the G57 uracil as an important residue for GAPDH binding.

Second, Baxi and Vishwanatha [1995] investigated the role of $A_{p4}A$ in DNA replication and DNA repair. In their studies, photoaffinity probes were used to identify $A_{p4}A$ binding proteins. These studies detected unique binding of a 37 kDa nuclear protein. This interaction was Mg^{++} dependent. The nuclear protein was identified as GAPDH by sequence analysis of tryptic peptides. The physiological significance of this structural interaction is indicated by previous studies demonstrating the physical association of mammalian GAPDH with replicating DNA [Lee and Sirover, 1989]. In those studies, the procedures of Reddy and Pardee [1980] were used to isolate DNA replication complexes. Immunological analysis using anti-GAPDH monoclonal antibodies identified GAPDH/DNA interactions. Treatment with DNase dissociated the complex. Radiolabeling with (^{35}S)methionine demonstrated that the biosynthesis of nuclear GAPDH paralleled its DNA association.

Third, three different laboratories reported the role of human GAPDH in DNA repair. Initially, nuclear human GAPDH was identified as a uracil DNA glycosylase (UDG) based on its ability to release uracil from a poly (dA)-poly (dU) substrate [Meyer-Siegler et al., 1991]. Subsequently, this report was confirmed by Baxi and Vishwanatha [1995]. They demonstrated that their $A_{p4}A$ binding protein, purified to homogeneity, exhibited UDG activity. The physiological significance of these in vitro findings was indicated by McNulty and Toscano [1995]. They demonstrated in vivo that human cells, treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), increased GAPDH gene transcription and translation. Intriguingly, they reported a significant increase in cytoplasmic GAPDH activity, which was paralleled by a noticeable decrease in nuclear UDG activity. Control experiments indicated that TCDD treatment did not affect the integrity of the nuclear membrane. They suggested that these results indicated that human cells may modulate the subcellular localization of GAPDH.

ROLE OF GAPDH IN APOPTOSIS

Apoptosis, or programmed cell death, is defined by a specific pattern of gene expression

and regulation. Recently, a series of investigations indicated an intrinsic role for GAPDH in neuronal apoptosis [Sunaga et al., 1995; Ishitani and Chuang, 1996; Ishitani et al., 1996a,b]. In those studies, programmed cell death was examined using rat cerebellar granule cells (CGCs) in short-term culture. During the first 14 days in vitro (DIV), the death rate was undetectable. However, in the following 3 days, a burst of neuronal cell death was observed. Electron microscopic and DNA degradation analysis revealed a characteristic apoptotic pattern of chromosomal condensation and internucleosomal cleavage. Treatment with actinomycin D (Act-D) or cycloheximide (CHX) at 7 DIV prevented apoptosis as indicated by a reduction of dead cells at 17 DIV.

SDS-PAGE was used to examine protein synthesis during apoptosis. At latter stages (17 DIV), the increased expression of a 38 kDa protein was detected. Its synthesis was eliminated by treatment with Act-D or CHX. N-terminal microsequencing of the eluted protein identified it as GAPDH. Subsequently, Northern blot analysis demonstrated increased GAPDH gene expression at 11 DIV, which reached its maximum at 15 DIV. Treatment of CGCs with Act-D or with CHX blocked the observed increase in steady state GAPDH mRNA levels. This diminution in GAPDH gene expression paralleled the reduction in neuronal apoptosis.

The physiological significance of GAPDH expression as a basic requirement for programmed neuronal cell death was then examined. These investigations used transfection of antisense and sense GAPDH sequences into CGCs at 7 DIV. A 3–8-fold reduction in programmed neuronal cell death was observed at 17–19 DIV after transfection of the antisense GAPDH sequences. Subsequently, the generality of GAPDH expression and its role in regulating apoptosis was examined using cytosine arabinoside (AraC) to induce programmed neuronal cell death. GAPDH mRNA and protein levels sequentially increased after AraC exposure. As expected, in these studies, treatment with Act-D or CHX reduced the extent of apoptosis. Treatment with antisense GAPDH constructs diminished AraC induced neuronal cell death. Intriguingly, a complete blockage of apoptosis was observed. Further, the extent of this protection surpassed that detected with Act-D or with CHX. In toto, these studies suggest that GAPDH is not a "passive" component of neuronal apoptosis. Instead, they provide initial evidence suggesting that GAPDH expression may comprise an intrinsic requirement for programmed neuronal cell death.

GAPDH AND THE CELLULAR PHENOTYPE OF NEURODEGENERATIVE DISEASE

Recent molecular and biochemical studies have identified striking, perhaps interrelated, characteristics of a series of age-related, autosomal dominant, neurodegenerative disorders [Albin and Tagle, 1995; Gusella and MacDonald, 1996; Nasir et al., 1996]. Termed trinucleotide repeat neurodegenerative diseases, each is characterized by the expansion of CAG repeats in the primary gene defective in the respective disorder. The triplet repeat is present in coding regions of the gene. This results in the production of a mutant protein containing polyglutamine tracts in its N-terminal region. The respective proteins are detected in a wide variety of cells although only neurodegenerative symptomology is observed. Synthesis of the mutant protein is required for clinical manifestation of the disorder. Further, disruption or ablation of the respective gene does not result in the abnormal phenotype [Ambrose et al., 1994; Mangiarini et al., 1996].

Based on this evidence, it was postulated that the molecular mechanisms that underlie each disease may be based on a gain of function that specifically characterizes the mutant protein. However, the respective proteins do not display structural similarities and have disparate intracellular localizations. Accordingly, it was hypothesized that this gain of function may involve specific protein-protein interactions. In this manner, each defective protein could affect one or more basic cellular processes. As such, identification of such protein-protein interactions may provide insight into the molecular basis for CAG expansion disorders.

As shown in Table III, these recent studies identify GAPDH binding as a specific protein-protein interaction in each disorder. These include its binding to huntingtin, the gene product deficient in Huntington's disease [Burke et al., 1996]; atrophin, the gene product deficient in dentatorubalpallidoluysian atrophy (DRLPA) [Burke et al., 1996]; ataxin, the molecular defect in spinocerebellar ataxia type-1 [Koshy et al., 1996]; and the androgen receptor, the gene

TABLE III. GAPDH/Protein Interactions in Neurodegenerative Disorders

Genetic disorder	Gene product	Expansion of CAG repeats	Method of detection	GAPDH binding site
Huntington's Disease	Huntingtin	Yes	Polyglutamine affinity chromatography	N.D.
Dentatorubalpall-idoluysian atrophy	Atrophin	Yes	Polyglutamine affinity chromatography	N.D.
Spinocerebellar ataxia type-1	Ataxin	Yes	Yeast two-hybrid system	N-terminal polyglutamine containing domain (amino acids 1–300)
Spinobulbar muscular atrophy	Androgen receptor	Yes	Yeast two-hybrid system	N-terminal polyglutamine containing domain (amino acids 13–156)
Alzheimer's Disease	β-Amyloid precursor protein	No	Affinity chromatography	C-terminal βAPP

product which may underlie spinobulbar muscular atrophy [Koshy et al., 1996]. In each case, the specificity of GAPDH binding was demonstrated by the high affinity of the respective protein for GAPDH. These studies include confirmation of the yeast two hybrid studies by in vitro analysis of GAPDH binding, the requirement of formic acid elution of GAPDH from affinity columns, and negative control studies demonstrating the inability of myoglobin affinity columns to bind GAPDH.

Recent studies have also indicated specific protein-protein interactions between the β-amyloid precursor protein (βAPP) and GAPDH [Schulze et al., 1993]. Although it may not be the primary genetic defect in Alzheimer's Disease (AD), βAPP has been the subject of intensive study in its etiology [Slekoe, 1994; Checler, 1995]. βAPP is a membrane-bound protein containing a cytoplasmic tail. Its improper cytoplasmic processing results in the formation of the β-amyloid protein (βAP), a 4 kDa protein derived from the carboxyterminal end of βAPP. βAP is implicated as a major factor in the formation of senile plaques in AD.

In these studies, recombinant rat C-terminal βAPP was produced by PCR amplification (nucleotides 1,789–2,088), plasmid ligation, and subsequent bacterial overexpression. The purified protein was used in affinity chromatography to identify brain binding proteins. A single protein of 35 kDa was tightly bound, eluted from the C-terminal βAPP affinity column only by 3M NaSCN. N-terminal sequencing analysis identified it as GAPDH. Sephacryl gel filtration using commercial GAPDH confirmed C-terminal βAPP/GAPDH binding. Accordingly, in toto, these cumulative findings suggest that molecular modeling may prove useful to determine the presence or absence of common structures in each protein, which define its GAPDH binding.

FUTURE DIRECTIONS

As indicated in this review, our knowledge of GAPDH function in mammalian cells is still developing. This is in accord with earlier suggestions that we are at the beginning phase of our understanding of the multiple functions of this protein in eucaryotic cells [Sirover, 1996]. However, we still lack sufficient data to define the molecular mechanisms that underlie these new activities. We need to define the methods through which normal cells regulate the intracellular localization of GAPDH. Further, although it is clear that GAPDH is involved in apoptosis, its specific role is unknown. It may be a matter of energy utilization. Alternatively, one or more GAPDH activities (especially mRNA regulation) may be required. Similarly, the role of GAPDH in the cellular phenotype of neurodegenerative disorders may involve its structural properties (i.e., membrane or microtubule association) or its functional activities (energy utilization, apoptosis, translational control of gene expression, DNA replication, or DNA repair). Finally, new functions of GAPDH have been identified in mammalian cells. One needs to know whether GAPDH in other, highly developed, cells or organisms may display similar properties.

Although not discussed in this review, GAPDH is a specific target of nitric oxide (NO), which catalyses the non-enzymatic covalent modification of GAPDH by NAD^+ [McDonald

and Moss, 1994; Brune and Lapetina, 1995]. In terms of extent, this effect of NO would not be considered as major. However, this degree of modification may be reminiscent of previous investigations, which examined DNA alkylation by chemical agents. In those studies, the major DNA products are phosphotriesters and N^7-alkylguanine. However, further analysis demonstrated that those adducts were not the critical lesions. Minor in terms of extent, O^6-alkylguanine is highly significant due to the consequences of this modification. Similarly, by affecting one or more of its activities, the unique NO-induced modification of GAPDH could induce pleiotropic effects in eucaryotic cells. Thus, the cumulative studies described in this review indicate the need for further investigations not only of the role of GAPDH in normal cell function but also its role in cell pathology.

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