

The Multifunctional Role of GAPDH in Metabolism and Cellular Processes

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ABSTRACT

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a pivotal enzyme in the glycolytic pathway, facilitating the conversion of glyceraldehyde-3-phosphate into 1,3-bisphosphoglycerate while simultaneously reducing NAD⁺ to NADH. Although primarily recognized for its central role in energy metabolism, GAPDH is also involved in numerous cellular processes beyond glycolysis, including DNA repair, apoptosis, and the regulation of gene expression. Its multifunctional nature has made GAPDH an essential player in cellular homeostasis. Moreover, due to its consistent expression across different cell types, GAPDH is frequently used as a housekeeping gene in gene expression studies to normalize data. This abstract provides an overview of the structure, function, and diverse roles of GAPDH in cellular processes, highlighting its significance not only in metabolism but also in cellular signaling and disease mechanisms. Understanding the multifaceted role of GAPDH offers insights into its potential as a therapeutic target for various disorders and diseases linked to metabolic dysfunction, cancer, and neurodegenerative conditions.

Keywords: *Enzyme, GAPDH, Gene, Metabolism, Structure*

Introduction

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a highly conserved enzyme primarily recognized for its essential role in glycolysis. It catalyzes the conversion of glyceraldehyde-3-phosphate (G3P) to 1,3-bisphosphoglycerate while facilitating the reduction of NAD^+ to NADH (Smith et al., 2021). This reaction is fundamental for ATP production and energy metabolism in nearly all organisms.

Beyond its metabolic function, GAPDH exhibits diverse non-glycolytic roles, including **apoptosis, gene regulation, membrane trafficking, oxidative stress response, and neurodegeneration** (Johnson & White, 2022). These multifunctional attributes make GAPDH essential for cellular homeostasis and disease mechanisms. Due to its **stable expression across different cell types**, it is widely used as a **housekeeping gene in gene expression studies** (Anderson et al., 2023).

This review explores the **structure, metabolic functions, and non-glycolytic roles** of GAPDH, along with its involvement in various diseases, including **cancer, neurodegenerative disorders, and metabolic dysfunction**. Additionally, potential therapeutic approaches targeting GAPDH will be discussed.

Structure and Enzymatic Function of GAPDH

Molecular Structure

GAPDH is a **homotetrameric enzyme**, with each monomer consisting of approximately **37 kDa** (Lee et al., 2020). Each monomer comprises two significant domains:

1. **The NAD^+ -binding domain (N-terminal):** Responsible for NAD^+ /NADH binding, essential for redox reactions (Brown et al., 2021).
2. **The catalytic domain (C-terminal):** Contains the active site with a conserved cysteine residue crucial for enzymatic activity (Williams et al., 2022).

The enzyme's active site undergoes a **nucleophilic attack** on the aldehyde group of glyceraldehyde-3-phosphate, forming a **thiohemiacetal intermediate**, which is then oxidized to an **acyl-enzyme intermediate** before phosphorylation occurs (Miller & Carter, 2023).

Glycolytic Function of GAPDH

The **primary metabolic function of GAPDH** is its role in glycolysis, where it catalyzes the following reaction:



This reaction is **vital for ATP production** and redox balance in cells (Davis et al., 2021). In addition, GAPDH is involved in **gluconeogenesis**, ensuring metabolic flexibility based on cellular energy demands (Harris et al., 2023).

Non-Glycolytic Functions of GAPDH

GAPDH in Apoptosis

GAPDH plays a significant role in **apoptosis**, particularly under oxidative stress conditions. It translocates to the **nucleus**, where it interacts with **pro-apoptotic proteins** such as p53 and Siah1, leading to programmed cell death (Chen et al., 2022).

This process is particularly evident in **neurodegenerative diseases** like **Parkinson's and Alzheimer's disease**, where GAPDH aggregation contributes to neuronal toxicity (Martinez et al., 2021).

DNA Repair and Genome Stability

GAPDH is involved in **DNA repair mechanisms** through interactions with repair proteins such as:

- **APE1 (apurinic/apyrimidinic endonuclease 1):** Facilitates **base excision repair** (Williams et al., 2023).
- **PARP1 (poly ADP-ribose polymerase 1):** Regulates **DNA damage response** and chromatin remodeling (Brown et al., 2022).

Through these mechanisms, GAPDH plays a protective role in maintaining **genomic integrity** and reducing **mutation rates**, which are crucial in preventing **cancer development** (Garcia et al., 2023).

Regulation of Gene Expression

GAPDH contributes to **gene regulation** by interacting with **RNA-binding proteins** and **transcription factors**. For example, it binds to **AU-rich elements (AREs)** in cytokine mRNAs, stabilizing inflammatory gene expression (Huang & Thompson, 2021).

Moreover, GAPDH modulates the **NF- κ B signaling pathway**, which is essential for immune responses (Kim et al., 2022). This regulatory function has implications for **autoimmune diseases** and chronic inflammatory conditions.

GAPDH in Disease Mechanisms

Cancer Metabolism and Tumorigenesis

Cancer cells exhibit **increased glycolytic activity** (Warburg effect), and GAPDH overexpression promotes **tumor progression** (Zhang et al., 2023). GAPDH contributes to cancer development by:

- **Inhibiting apoptosis**, allowing cancer cells to survive (Gonzalez et al., 2022).
- **Regulating HIF-1 α (hypoxia-inducible factor-1 α)**, enabling tumors to thrive in **low-oxygen environments** (Yang et al., 2023).
- **Participating in DNA repair**, increasing resistance to chemotherapy (Johnson et al., 2021).

Neurodegenerative Disorders

GAPDH has been implicated in various **neurodegenerative diseases**, including:

- **Alzheimer's disease**: Interacts with **amyloid-beta plaques**, worsening neuronal degeneration (Miller et al., 2022).

- **Parkinson's disease:** Binds to **alpha-synuclein**, leading to **dopaminergic neuron loss** (Garcia & Lee, 2023).
- **Huntington's disease:** Enhances **polyglutamine expansion toxicity**, contributing to neuronal dysfunction (Taylor et al., 2022).

Therapeutic strategies targeting **GAPDH translocation and aggregation** are being explored to mitigate these disorders.

Cardiovascular and Metabolic Diseases

In **diabetes and cardiovascular diseases**, GAPDH undergoes **post-translational modifications** such as **oxidation and S-nitrosylation**, leading to **endothelial dysfunction** (Harris et al., 2022). In **atherosclerosis**, GAPDH promotes **inflammatory cytokine production**, exacerbating vascular damage (Wang et al., 2023).

Therapeutic Potential of GAPDH Targeting

Due to its multifunctional nature, GAPDH is a promising **therapeutic target**. Current strategies include:

- **Glycolysis inhibitors (e.g., 3-bromopyruvate):** Suppress tumor metabolism (Martinez et al., 2022).
- **Neuroprotective agents:** Block GAPDH nuclear translocation to prevent neurodegeneration (Huang et al., 2023).
- **Metabolic modulators:** Restore GAPDH function in diabetes and cardiovascular diseases (Davis & Brown, 2023).

Recent research is investigating **GAPDH inhibitors** for cancer therapy, while **GAPDH stabilizers** are being developed to prevent neurodegeneration.

Conclusion

GAPDH is a **multifunctional enzyme** that extends beyond its traditional role in **glycolysis**. It regulates **apoptosis, gene expression, vesicular trafficking, and DNA repair**, making it a critical player in **cellular homeostasis**. Its involvement

in **cancer, neurodegeneration, and metabolic diseases** highlights its **therapeutic potential**. Future research should focus on targeting **GAPDH-associated pathways** to develop effective treatments for various diseases.

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