Mechanism of HPD-Mediated Glycolytic Reprogramming in Ovarian Cancer

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Abstract

Ovarian cancer is hard to diagnose at an early stage and has a high rate of recurrence. Because of this, its clinical treatment faces serious challenges. In recent years, studies have found that metabolic reprogramming, especially the abnormal activation of glycolysis, plays a key role in the progression of ovarian cancer. 4-Hydroxyphenylpyruvate dioxygenase (HPD) is an important molecule with two functions. It acts both as a metabolic enzyme and as an RNA-binding protein. Recent studies have confirmed that HPD is abnormally expressed in many tumors and is involved in the regulation of malignant behavior. This paper systematically reviews the molecular mechanism of HPD as an RNA-binding protein. HPD recognizes the RRACH motif on target mRNAs and promotes the translation of the key glycolytic enzymes TPI and ENO1. As a result, it increases glycolytic flux and cell proliferation in ovarian cancer cells. This paper also summarizes the potential therapeutic value of the small-molecule HPD inhibitor NTBC and its combined use with paclitaxel. These findings provide a new theoretical basis and new strategic directions for the precise treatment of ovarian cancer.

Keywords

HPD; RNA-Binding Protein; Glycolysis; Ovarian Cancer.

1. Introduction

Ovarian cancer (OC) is a major threat to women's health worldwide. It has high incidence and mortality[1]. Its early symptoms are hidden[2, 3], and it lacks specific diagnostic markers[4]. Because of this, most patients are already at an advanced stage when they are diagnosed[5]. The 5-year survival rate has stayed around 30%–40% for a long time[6, 7]. This seriously threatens women's life and health. Although surgery combined with platinum-based chemotherapy is the first-line treatment, it can only achieve some effect in the early stage. The drug resistance and recurrence rate of tumor cells remain high[8]. Therefore, finding new therapeutic targets and intervention strategies has become an urgent need.

Metabolic reprogramming is one of the main features that makes tumor cells different from normal cells. Among these, the abnormal activation of the glycolytic pathway is known as the Warburg effect[9]. It plays a key role in tumor occurrence, development, invasion, and metastasis[10]. Even when oxygen is sufficient, tumor cells still tend to get energy through glycolysis. They also produce a large number of metabolic intermediates. These products help meet the biosynthetic needs of rapid cell proliferation. In ovarian cancer, the high expression of glycolysis-related enzymes has been confirmed to be closely related to malignant tumor features and poor prognosis. These enzymes include hexokinase 2[11], phosphofructokinase [12], and pyruvate kinase M2[13]. This suggests that key enzymes in the glycolytic pathway may become potential targets for ovarian cancer treatment.

RNA-binding proteins (RBPs) are a class of proteins that can specifically bind to RNA. They regulate post-transcriptional RNA processing, including splicing, transport, translation, and degradation. They play an important role in gene expression regulation[14]. Recent studies have shown that abnormal expression or dysfunction of RBPs can affect the RNA metabolism of target genes. In this way, they take part in many biological processes. These include tumor metabolic reprogramming, cell cycle regulation, and resistance to apoptosis[15]. Therefore, studying the regulatory mechanism of RBPs in the glycolytic pathway of ovarian cancer may provide a new perspective for understanding the pathogenesis of ovarian cancer.

4-Hydroxyphenylpyruvate dioxygenase (HPD) is a key enzyme in the tyrosine metabolic pathway. It mainly takes part in tyrosine catabolism[16]. Previous studies have shown that HPD is abnormally expressed in many tumors, such as lung cancer[17], liver cancer[18], and breast cancer[19]. It is closely related to tumor proliferation, invasion, and prognosis. However, its specific role and molecular mechanism in ovarian cancer are still unclear. In particular, its regulatory role in the glycolytic pathway as an RNA-binding protein has not yet been clarified. Based on this, this paper systematically reviews the molecular mechanisms of HPD in ovarian cancer. It focuses on how HPD, as an RNA-binding protein, affects the occurrence and development of ovarian cancer. It also summarizes HPD-based targeted intervention strategies and research progress. The aim is to provide a new theoretical basis for the diagnosis and treatment of ovarian cancer.

2. Biological Function of HPD in Ovarian Cancer and Its Molecular Mechanism

2.1. The Binding Mechanism of HPD as a Non-classical RBP

HPD is a key enzyme in the tyrosine catabolic pathway. Its main role is to promote the breakdown of tyrosine and maintain the balance of tyrosine metabolism in the body [16]. However, it has not been reported whether HPD has other functions besides catalyzing tyrosine catabolism. Previous studies have confirmed that 4-hydroxyphenylpyruvate dioxygenase-like protein (HPDL), which belongs to the same group as HPD. It may have the potential to act as an RNA-binding protein[20, 21]. HPD and HPDL are highly similar in protein structure[22]. They also belong to the same enzyme family. Therefore, HPD is also very likely to have the potential to act as an RNA-binding protein.

RBPs are a class of protein molecules with key functions in cells[23]. They are characterized by special RNA-binding domains. These include zinc finger domains, double-stranded RNA-binding domains, and RNA recognition motifs. These domains allow them to specifically bind to RNA or to specific motifs in RNA secondary structures[24]. Based on these structures and binding abilities, RBPs widely take part in many post-transcriptional regulatory processes. These include RNA splicing, transport, and translation control[14, 25]. Because RBPs have strong and broad RNA-binding ability, they are important regulatory factors. They play an essential role in cell growth, differentiation, material and energy metabolism, and the occurrence and development of many diseases[23, 26]. Therefore, it is significant to further study whether HPD has additional functions in cancer progression and drug response regulation[20]. Studies have shown that the T382 phosphorylation site of HPD is regulated by the kinase STK33 and the molecular chaperone TTC36. This modification affects the PELI1-mediated ubiquitin degradation pathway of HPD[27]. This suggests that its protein stability may be related to its RNA-binding function. In lung cancer, HPD increases G6PD activity through the LKB1-AMPK/HDAC10 signaling axis. It significantly increases the flux of the pentose phosphate pathway and directly drives tumor cell proliferation[17]. In liver cancer, loss of HPD activates mTOR-mediated glutamine anaplerosis. This reshapes intracellular metabolic homeostasis and then supports tumor growth and survival[18]. In breast cancer,

HPD overexpression is closely related to invasive phenotypes and poor clinicopathological parameters. This is an important basis for HPD to be an independent marker of poor prognosis[19]. These findings suggest that HPD may act as an RBP across different cancer types and play a role in many cancers.

In recent years, Xie first directly confirmed a new function of HPD in cancer. They mainly used experiments such as RNA immunoprecipitation sequencing (RIP-seq). These studies showed that HPD acts as a non-classical RNA-binding protein (RBP). Xie etc. found that HPD, as an RNA-binding protein, targets many RNA molecules involved in cancer progression. These include the glycolytic enzymes triosephosphate isomerase (TPI) and enolase 1 (ENO1). They play key roles in tumor growth processes[29, 30], such as cell cycle regulation and glycolytic metabolic reprogramming[28].

In addition, this research group used experimental data analysis to show that HPD can bind to the CDS regions of cancer-related mRNAs, such as TPI and ENO1. Specifically, it binds to CDS1 of TPI and CDS2 of ENO1. HPD achieves specific binding by recognizing the RRACH motif[20]. This finding goes beyond the traditional understanding of HPD function. It reveals a new mechanism. In this mechanism, HPD takes part in gene expression regulation through its RNA-binding activity. It also provides a typical example of the cross-talk between metabolic enzymes and RNA regulatory networks. Because HPD is specifically associated with RNAs related to tumor progression, it may become a potential molecular target for cancer diagnosis, prognosis evaluation, and targeted therapy. It also provides a new direction for mechanistic research and clinical translation in related diseases.

Analysis of the HPD binding motif provides a basis for its specific recognition of RNA. However, it is also important to identify the structural domains and mechanism by which HPD binds RNA. This is the key to fully revealing the molecular basis of their interaction. Studies have found that the secondary and tertiary structures of the HPD protein contain a pair of double-stranded RNA-binding domains (dsRBDs). These domains have an α-β-β-β-α folding pattern[31]. It is worth noting that the RNA regions around the RRACH motifs in TPI-CDS1 and ENO1-CDS2 show double-stranded structural features. This is highly consistent with the known targets of dsRBDs, which are double-stranded mRNA structures[20]. Therefore, this provides structural support for their specific interaction. Further functional studies showed that the two dsRBDs of HPD, namely RBD1 and RBD2, play key roles in RNA binding. HPD binds directly to mRNA through these domains. When RBD1 or RBD2 is deleted, its ability to bind mRNA is greatly reduced[20]. Based on these findings, it can be inferred that targeting the RBD domains of HPD may disrupt its RNA-binding activity. This may further block glycolytic flux, inhibit tumor growth, and improve drug response[20].

In summary, existing studies have revealed a new functional role of HPD as a non-classical RNA-binding protein. It recognizes the RRACH motif in the coding sequence (CDS) of target mRNAs through its double-stranded RNA-binding domains (dsRBDs). In this way, it achieves specific binding. This targeted binding to the CDS region of mRNA is the key first step for HPD to exert its regulatory function. It can then affect the translation efficiency of target mRNAs. The specific mechanism and biological effects are described below. These findings provide a theoretical basis for the translational study of HPD as a potential target for cancer diagnosis and treatment.

2.2. HPD Affects Glycolytic Flux by Regulating mRNA Translation

Glycolysis is the most typical core process in cancer metabolic reprogramming. Its main feature is that cancer cells still prefer glycolysis under aerobic conditions. This is called the Warburg effect[32]. Glycolytic metabolic reprogramming plays a key role in the malignant progression of ovarian cancer. High expression of the key glycolytic enzymes hexokinase 2 (HK2) and pyruvate kinase M2 isozyme (PKM2) can quickly produce ATP and biosynthetic

precursors. This supports the unlimited proliferation of tumor cells[33]. At the same time, HK2 can also increase the resistance of ovarian cancer to chemotherapeutic drugs such as cisplatin through autophagy[11]. PKM2 can enhance the migration and invasion ability of cancer cells by regulating epithelial-mesenchymal transition[34]. In addition, glycolysis can produce NADPH through the pentose phosphate pathway and maintain redox homeostasis[35]. It also forms a positive feedback loop with the hypoxia signal HIF-1α and continuously drives tumor progression[36]. Therefore, glycolysis has become an important metabolic feature that makes cancer different from normal cells.

RBPs precisely control tumor glycolysis through post-transcriptional regulation. For example, the HuR protein increases PKM2 expression by binding to and stabilizing PKM2 mRNA. This directly promotes glycolytic flux[37]. hnRNPA2/B1 promotes glucose uptake by regulating the level of GLUT1 mRNA[38]. At the splicing level, hnRNPA1/A2 and PTB mediate the selective splicing of the PKM gene. This promotes the production of the glycolysis-related PKM2 isoform[39]. In addition, LIN28A/B inhibits the maturation of let-7 miRNA. In this way, it indirectly removes the inhibition of glycolytic genes such as HK2. This forms a cascade amplification effect[40]. These mechanisms together form a multi-level regulatory network and drive tumor metabolic reprogramming.

Previous studies have confirmed that HPD is a non-classical RBP. It can bind to many kinds of mRNAs and promote global mRNA translation[20]. Glycolysis is a core feature of cancer metabolic reprogramming. The expression of key glycolytic enzymes is also closely related to malignant tumor phenotypes. Therefore, studying the mRNAs of glycolytic enzymes may further reveal how HPD specifically acts on these functional mRNAs during global translation regulation. It may also help explain its biological significance in abnormal cancer metabolism.

Studies have shown that HPD can significantly regulate the protein levels of the key glycolytic enzymes TPI and ENO1[20]. This effect mainly depends on its RBD domains. When HPD is knocked down, the protein levels of these two enzymes decrease. Conversely, when HPD is overexpressed, their protein levels increase. This indicates that HPD regulates their protein levels by promoting the mRNA translation of TPI and ENO1. It does not rely on transcription or protein degradation pathways.

Further studies found that HPD knockout can significantly reduce global translation efficiency in cells. It also clearly reduces the accumulation of TPI and ENO1 mRNAs in the polysome fractions. HPD loss or reduced HPD expression can suppress glycolysis in ovarian cancer cells. It can also reduce cell proliferation and inhibit tumor growth in vivo. At the same time, the protein levels of TPI and ENO1 are reduced in tumor tissues. Exogenous expression of ENO1 or TPI can partly reverse these inhibitory effects[20]. These results clearly show that HPD affects the glycolytic pathway and cell proliferation in ovarian cancer cells by regulating ENO1 and TPI. In addition, in HPD knockout cells, exogenous expression of wild-type HPD can partly restore the decreased related indicators. However, this effect is not seen when HPD mutants lacking RBD1 or RBD2 are expressed. This confirms that the promoting effect of HPD on glycolysis and cell proliferation depends on its function as an RNA-binding protein, especially the RBD1 and RBD2 domains.

In summary, glycolysis is a typical feature of cancer metabolic reprogramming. In ovarian cancer, it promotes malignant tumor phenotypes through key enzymes. RBPs affect tumor glycolysis through post-transcriptional regulation. In this way, they promote tumor metabolic reprogramming. HPD, as an RBP, uses its RBD domains to bind RNA. It specifically regulates the translation of TPI and ENO1. As a result, it increases glycolytic flux in tumor cells. This helps meet the energy needs of cancer cells and provides materials for biosynthesis. It also promotes glycolysis and cell proliferation in tumor cells. This mechanism supports the idea that the RBD domains of HPD may be a potential target for cancer treatment. It also provides an important theoretical basis for later studies on its clinical application.

3. Potential Therapeutic Value of Targeting Glycolysis-RBP

3.1. The Effect and Mechanism of NTBC Targeting HPD in Ovarian Cancer

In ovarian cancer, some RNA-binding proteins (RBPs) have been confirmed as potential therapeutic targets[41-43]. These include MEX3A, QKI5, and RBM24/ESRP1, which play key roles in disease progression. These RBPs affect ovarian cancer progression and chemotherapy resistance through post-transcriptional regulation. This includes the regulation of mRNA stability, alternative splicing, and translation efficiency. RNA-binding proteins play a central role in post-transcriptional regulation in ovarian cancer. The clinical value of the targets above has also been confirmed. Therefore, we have reason to infer that HPD, as an RNA-binding protein, also has great potential to become a therapeutic target for ovarian cancer.

Recent studies have shown that targeting the RNA-binding protein HPD can inhibit tumor occurrence and progression. This provides a new idea for the treatment of ovarian cancer. The small-molecule compound 2-(2-Nitro-4-(trifluoromethyl)benzoyl)cyclohexane-1,3-dione (NTBC) has been confirmed to significantly inhibit the activity of 4-hydroxyphenylpyruvate dioxygenase (HPD)[44]. Its mechanism is to bind precisely to the RBD functional domains of HPD. It specifically interacts with key amino acid sites such as His266 and Glu349. In this way, it inhibits HPD function and blocks the proliferation of ovarian cancer cells[20].

Further studies showed that NTBC inhibits the interaction between HPD and mRNA. It also suppresses overall cellular translation and reduces the levels of key energy metabolism proteins, such as TPI and ENO1. In this way, it reprograms tumor metabolism and finally inhibits cell proliferation. This effect is highly specific. It does not affect RNA stability or the cellular localization of HPD. In in vivo experiments, NTBC significantly inhibited xenograft growth in an A2780 ovarian cancer CDX mouse model. It also reduced the expression of TPI and ENO1 in tumor tissues. This was consistent with the in vitro results[20]. These results together reveal the core pathway of "HPD regulation - translation inhibition - metabolic reprogramming - restricted proliferation" at the molecular, in vitro, and in vivo levels. They confirm the key role of HPD in maintaining the malignant phenotype of ovarian cancer.

Taken together, these studies show that HPD plays a key regulatory role in the occurrence and development of ovarian cancer. HPD can also be specifically inhibited by NTBC. This means that HPD has the potential to become a therapeutic target. An intervention strategy centered on HPD provides a new research direction for the precise treatment of ovarian cancer. It also lays an experimental foundation for the clinical translation of small-molecule inhibitors. This may open a new therapeutic path to improve the prognosis of patients with ovarian cancer in the future.

3.2. Application of NTBC Combined with Paclitaxel in the Treatment of Ovarian Cancer

NTBC can specifically regulate HPD by targeting it. In this way, it shows anti-tumor effects. At the same time, by regulating the related functions of HPD as an RNA-binding protein, NTBC can significantly increase the sensitivity of tumor cells to paclitaxel. Based on this feature, recent studies have explored the combined use of NTBC and paclitaxel in the treatment of ovarian cancer. The synergistic anti-tumor effect of this combination was significant in a CDX mouse model established with A2780 cells. The inhibitory effect of the combination treatment on ovarian cancer growth was significantly better than that of NTBC or paclitaxel alone[20].

These findings suggest that a treatment strategy targeting HPD has unique value because it regulates the function of an RNA-binding protein. It has potential for use as an independent treatment for ovarian cancer. It also shows a strong synergistic effect in combination therapy. In the future, the therapeutic effect may be further improved by optimizing the combined treatment plan. This may provide two treatment choices for ovarian cancer: single-drug

intervention and combination therapy with enhanced effects. In addition, this combined treatment model may reduce chemotherapy-related side effects by lowering the dose of a single drug. Therefore, it not only provides a solid theoretical basis for improving current ovarian cancer treatment strategies, but also shows broad clinical potential for improving patient prognosis, treatment safety, and tolerance.

4. Discussion

HPD is a dual-function molecule: a tyrosine metabolic enzyme and a non-classical RBP. It drives ovarian cancer glycolysis and proliferation by binding TPI/ENO1 mRNA via dsRBDs and promoting translation. Current limitations include unclear regulation of other glycolytic molecules, interactions with other RBPs, and roles in non-coding RNA networks. Future studies should explore HPD's interactome and regulatory pathways to refine its oncogenic network.

NTBC specifically inhibits HPD's RBP activity, suppressing glycolysis and tumor growth. Combination with paclitaxel enhances efficacy, highlighting HPD as a viable therapeutic target. Further development of HPD-targeted drugs and optimized combination strategies will improve ovarian cancer treatment. HPD's diagnostic value and roles in early detection also warrant investigation.

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