Pathology - Research and Practice 251 (2023) 154905

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

The role of endoplasmic reticulum stress in promoting aerobic glycolysis in cancer cells: An overview

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ARTICLE INFO

Keywords:
Aerobic Glycolysis
Endoplasmic Reticulum Stress
Metabolic Adaptation

ABSTRACT

Aerobic glycolysis, also known as the Warburg effect, is a metabolic phenomenon frequently observed in cancer cells, characterized by the preferential utilization of glucose through glycolysis, even under normal oxygen conditions. This metabolic shift provides cancer cells with a proliferative advantage and supports their survival and growth. While the Warburg effect has been extensively studied, the underlying mechanisms driving this metabolic adaptation in cancer cells remain incompletely understood. In recent years, emerging evidence has suggested a potential link between endoplasmic reticulum (ER) stress and the promotion of aerobic glycolysis in cancer cells. The ER is a vital organelle involved in protein folding, calcium homeostasis, and lipid synthesis. Various cellular stresses, such as hypoxia, nutrient deprivation, and accumulation of misfolded proteins, can lead to ER stress. In response, cells activate the unfolded protein response (UPR) to restore ER homeostasis. However, prolonged or severe ER stress can activate alternative signaling pathways that modulate cellular metabolism, including the promotion of aerobic glycolysis. This review aims to provide an overview of the current understanding regarding the influence of ER stress on aerobic glycolysis in cancer cells to shed light on the complex interplay between ER stress and metabolic alterations in cancer cells. Understanding the intricate relationship between ER stress and the promotion of aerobic glycolysis in cancer cells may provide valuable insights for developing novel therapeutic strategies targeting metabolic vulnerabilities in cancer.

1. Introduction

Cancer, one of the most pressing challenges in modern healthcare, holds tremendous significance on multiple fronts. Its importance lies not only in its impact on individual lives but also in its broader societal and economic implications [1,2]. Cancer is a leading cause of morbidity and mortality globally. As per the World Health Organization (WHO) report, it was responsible for approximately 10 million deaths in 2020, which corresponds to nearly one in six deaths [3]. Conventional treatment methods for cancer, such as chemotherapy, and radiation therapy suffer from a lack of specificity towards cancer cells and often result in significant side effects [4,5]. The complex nature of cancer and its ability to develop resistance to conventional therapies necessitates a deeper understanding of cancer biology to devise novel and more effective treatment methods [6].

In this review, we have focused on the intriguing crosstalk between ER stress and aerobic glycolysis in cancer cells, highlighting the interplay between these two prominent features of cancer biology. The dysregulated energy metabolism characterized by enhanced aerobic glycolysis and the activation of ER stress pathways intertwine to shape the tumor microenvironment, influence cancer cell survival, and impact treatment responses. By elucidating the intricate connections between ER stress and aerobic glycolysis, this review aims to contribute to the understanding of the molecular mechanisms underlying cancer

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https://doi.org/10.1016/j.prp.2023.154905
Received 29 July 2023; Received in revised form 19 October 2023; Accepted 24 October 2023
Available online 24 October 2023

progression and to provide insights into the development of innovative therapeutic strategies targeting these interconnected pathways.

2. Endoplasmic reticulum (ER) stress

Endoplasmic reticulum (ER) stress refers to a state of disruption in the normal functioning of the endoplasmic reticulum, a cellular organelle involved in protein synthesis, folding, and quality control [7]. ER stress can be triggered by various factors such as calcium imbalance, nutrient deprivation, oxidative stress, and the accumulation of misfolded proteins [8]. The ER has a built-in mechanism called the unfolded protein response (UPR) to address and rectify ER stress [9]. The UPR is a signaling pathway that aims to restore ER homeostasis and alleviate stress. It consists of three main branches, each regulated by specific transmembrane proteins located in the ER membrane:

2.1. (i) Inositol-requiring enzyme 1 (IRE1) pathway

IRE1 is an ER transmembrane protein that senses the accumulation of unfolded proteins [10]. Once activated, IRE1 acts as an endoribonuclease, which means it can cleave RNA molecules [11]. IRE1 has two major functions: splicing of the X-box binding protein 1 (XBP1) mRNA, resulting in the production of an active transcription factor (XBP1s) that promotes the expression of genes involved in ER protein folding [12], and degradation of misfolded proteins through a process known as regulated IRE1-dependent decay (RIDD) [13]. During RIDD, IRE1 recognizes and cleaves specific mRNA molecules in a sequence-specific manner. This results in the degradation of the targeted mRNA and the subsequent reduction in the corresponding protein levels. The cleavage sites in the mRNA are often located in the region encoding the protein's open reading frame, thereby preventing its translation [14]. RIDD serves as a regulatory mechanism to reduce the ER workload during stress conditions. By selectively degrading certain mRNA molecules, RIDD helps to reduce the production of proteins that may further burden the ER [15].

2.2. (ii) Protein Kinase RNA-like ER Kinase (PERK) pathway

PERK is another ER transmembrane protein [16]. Upon activation, PERK phosphorylates the alpha subunit of eukaryotic translation initiation factor 2 (eIF2α), leading to global inhibition of protein translation [17]. The primary function of eIF2α is to mediate the initiation of protein synthesis by delivering initiator tRNA (tRNAiMet) to the ribosome [18]. This is accomplished through a complex series of events that involve the binding of eIF2 to guanosine triphosphate (GTP) and the recruitment of the initiator tRNA and mRNA to the ribosome [19]. However, this selective translation inhibition enhances the translation of specific proteins, such as activating transcription factor 4 (ATF4), which regulates the expression of genes involved in antioxidant responses and amino acid metabolism [20].

2.3. (iii) Activating transcription factor 6 (ATF6) pathway

ATF6 is a third ER transmembrane protein involved in the UPR. Upon ER stress, ATF6 translocates to the Golgi apparatus, where it is cleaved by proteases to release its cytoplasmic domain [21]. This domain acts as a transcription factor, promoting the expression of genes that assist in protein folding and ER-associated degradation (ERAD) [22]. ERAD is a cellular quality control process that identifies and eliminates misfolded or unassembled proteins within the ER [23]. It involves a series of steps: recognition of aberrant proteins by ER chaperones, retrotranslocation of the proteins from the ER into the cytosol, ubiquitination of the extracted proteins with ubiquitin tags, and subsequent degradation of the tagged proteins by the proteasome [24]. Therefore, ERAD helps maintain protein quality and prevents the accumulation of dysfunctional proteins that could lead to cellular dysfunction.

Together, these pathways aim to restore ER homeostasis by reducing protein synthesis, increasing the expression of chaperones and folding enzymes, and promoting the clearance of misfolded proteins [25]. However, if ER stress persists or becomes overwhelming, the UPR can induce apoptosis to eliminate cells that cannot recover from stress and prevent further damage to the organism [26].

Cancer cells often experience conditions that cause ER stress, such as hypoxia, nutrient deprivation, and increased protein synthesis, and UPR can help tumor cells survive and adapt to these stressful conditions by restoring ER homeostasis and promoting cell survival [27]. By activating UPR pathways, cancer cells can enhance protein folding and degradation, manage oxidative stress, and adjust their metabolism to sustain their growth and survival [28]. Moreover, ER stress has been implicated in promoting various processes associated with tumor progression and metastasis. It can contribute to angiogenesis, which is crucial for tumor growth and spread, by inducing the expression of angiogenic factors [29]. Additionally, ER stress can enhance the invasive properties of cancer cells by promoting epithelial-to-mesenchymal transition (EMT), a process where cells acquire a more motile and invasive phenotype [30] (Fig. 1).

3. The role of aerobic glycolysis in cancer biology

Aerobic glycolysis, also known as the Warburg effect, refers to the preference of cancer cells to rely on glycolysis for energy production even in the presence of sufficient oxygen [31]. Lactate dehydrogenase (LDH) plays a crucial role in the process of aerobic glycolysis in cancer cells [32]. During aerobic glycolysis, glucose is converted into pyruvate through a series of enzymatic reactions. Instead of proceeding to the mitochondria for oxidative phosphorylation, pyruvate is converted to lactate by the enzyme LDH in cancer cells [33]. This conversion allows for the regeneration of NAD^+ from NADH, which is essential to sustain the glycolytic pathway [34]. Therefore, upregulation of LDH in cancer cells promotes the continuous conversion of pyruvate to lactate, facilitating the glycolytic flux and maintaining a high rate of glucose metabolism [32]. Several mechanistic pathways contribute to the upregulation of LDH in cancer cells. Increased activation of hypoxia-inducible factor 1 (HIF-1), a transcription factor in cancer cells directly upregulates LDH-A expression [35]. Moreover, loss of tumor suppressors like p53 can lead to glycolytic upregulation. p53 normally represses the expression of glycolytic genes, including LDH-A. When p53

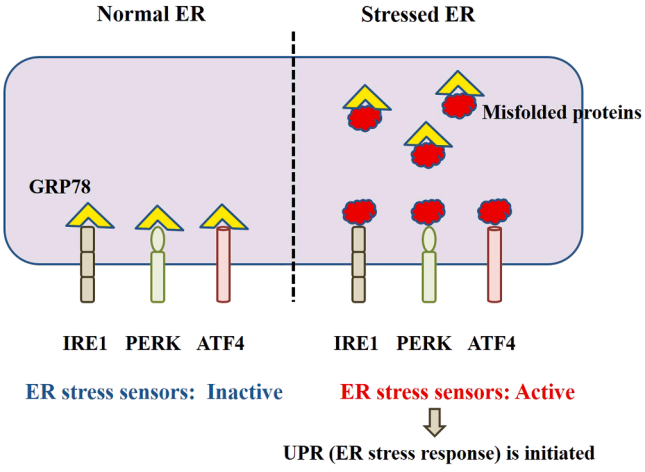

Fig. 1. ER stress occurs when there is an excessive buildup of misfolded proteins in the interior of the endoplasmic reticulum (ER). This leads to the activation of ER stress sensors, which in turn initiates a response known as the unfolded protein response (UPR). Initially, the UPR aims to rectify the ER stress by restoring protein folding. However, if the UPR is unsuccessful in resolving the issue, it can result in the induction of cell death and apoptosis.

is inactivated, LDH-A expression can increase, promoting glycolysis [36]. Additionally, c-Myc, a transcription factor frequently dysregulated in cancer, not only up-regulates LDH-A but also enhances glutaminolysis. This process involves the conversion of glutamine to pyruvate and contributes to the production of substrates for LDH [37].

It should be emphasized that the role of aerobic glycolysis in cancer biology is multifaceted and encompasses several key aspects. Despite the less efficient production of adenosine triphosphate (ATP) compared to aerobic respiration, aerobic glycolysis allows cancer cells to rapidly generate energy. This metabolic adaptation facilitates the high energy demands of proliferating cancer cells [38]. Moreover, aerobic glycolysis enables cancer cells to redirect glucose metabolites towards other biosynthetic pathways, such as the synthesis of nucleotides, amino acids, and lipids. These building blocks are essential for supporting cell growth, proliferation, and the biosynthesis of macromolecules required for tumor expansion [39]. In addition, the conversion of glucose to lactate during glycolysis leads to the accumulation of lactate and protons, contributing to the acidification of the tumor microenvironment [40]. The acidic pH promotes tumor invasion, metastasis, and immune evasion, while simultaneously impairing the function of immune cells [41]. The reliance on aerobic glycolysis provides cancer cells with a survival advantage under conditions of limited oxygen availability. This metabolic flexibility allows cancer cells to adapt to hypoxic tumor microenvironments and sustain their growth and survival [42].

4. ER stress and aerobic glycolysis in cancer

ER stress and glycolysis are highly interconnected. Multiple lines of evidence indicate that the activation of ER stress can impede aerobic glycolysis in cancer cells. Conversely, inhibiting glycolysis can induce ER stress in cancer cells. Consequently, we will address this topic in two separate sub-sections (Fig. 2).

4.1. Induction of ER stress inhibits glycolysis in cancer

Endoplasmic reticulum oxidoreductase 1 alpha (ERO1L) is an ER enzyme that contains flavin adenine nucleotide [43]. Its primary role is to promote the formation of disulfide bonds in proteins that are destined for secretion or located on the cell surface. ERO1L accomplishes this by receiving electrons from reduced protein disulfide isomerase (PDI) and subsequently transferring them to molecular oxygen [44]. Zhang *et al.*, found that ER stress induces the expression of ERO1L in pancreatic ductal adenocarcinoma (PDAC) which promotes tumor cell growth and proliferation through promoting aerobic glycolysis. The scholars found that increased expression of ERO1L shifted cancer cells from mitochondrial oxidative phosphorylation to aerobic glycolysis. This was confirmed by the finding that ERO1L inhibition reduced glucose uptake and lactate release, and genetic overexpression of ERO1L had the opposite effect [45].

Poyyakkara *et al.*, showed that thapsigargin induced ER stress in human cervical cancer cells and increased cell proliferation by promoting the expression and activity of both LDH A and LDH B. This effect was mediated through miR-23a, and specific inhibition of miR-23a abrogated ER stress induced expression of LDH in cervical cancer cells [46].

Lu *et al.*, reported that ciclopirox induced an intense ER stress in non-small cell lung cancer (NSCLC) cells. This led to the suppression of cancer cell growth, and inhibited cell migration and invasion by suppressing epithelial-mesenchymal transition (EMT). ER stress suppressed mitochondrial oxidative phosphorylation and increased the production of reactive oxygen species (ROS). While, PERK-mediated ER stress response drastically promoted aerobic glycolysis in NSCLC cells by inducing the expression of glycolytic enzymes, the overall survival of cancer cells was decreased due to highly increased apoptosis rates [47].

Glucose-regulated protein 78kD (GRP78) is a ubiquitously present ER chaperone that binds to the lumenal domains of IRE1, PERK, and ATF6 to maintain their inactive state [48]. However, this protein has a stronger affinity for the exposed hydrophobic polypeptide domains found in the misfolded proteins [49]. As a result, in situations where there are lots of misfolded proteins, the GRP78 is released from the ER stress sensors and is adsorbed onto the misfolded proteins, which puts the ER stress sensors in a state where they are ready to be activated. The UPR is then triggered as a result of the misfolded proteins acting as direct ligands for the liberated ER stress sensors [50]. Zheng *et al.*, found that betulinic acid (BA) inhibited metastasis in highly aggressive MDA-MB-231 and BT-549 breast cancer cell lines. BA inhibited both EMT and matrix metalloproteinase (MMP) secretions. The researchers found that BA inhibited the expression of GRP78, and thereby, induced ER stress and promoted PERK activity. This resulted in the decreased expression of β-catenin and its target effector c-Myc. In this manner, BA inhibited aerobic glycolysis and suppressed the expression of LDH A in breast cancer cells [51].

Transmembrane and tetratricopeptide repeat-containing (TMTC3) regulates the ER calcium levels by modulating the activity of inositol 1,4,5-trisphosphate receptors (IP3Rs) and ryanodine receptors (RyRs). These receptor channels are responsible for releasing calcium from the ER into the cytoplasm [52,53]. Hu *et al.*, demonstrated that the expression of TMTC3 was significantly lower in breast cancer tissues as compared to normal adjacent tissues. Moreover, they showed that TMTC3 overexpression in breast cancer cell lines modulated ER stress and led to the inhibition of aerobic glycolysis and lactate production, which was associated with increased apoptosis rates in breast cancer cell

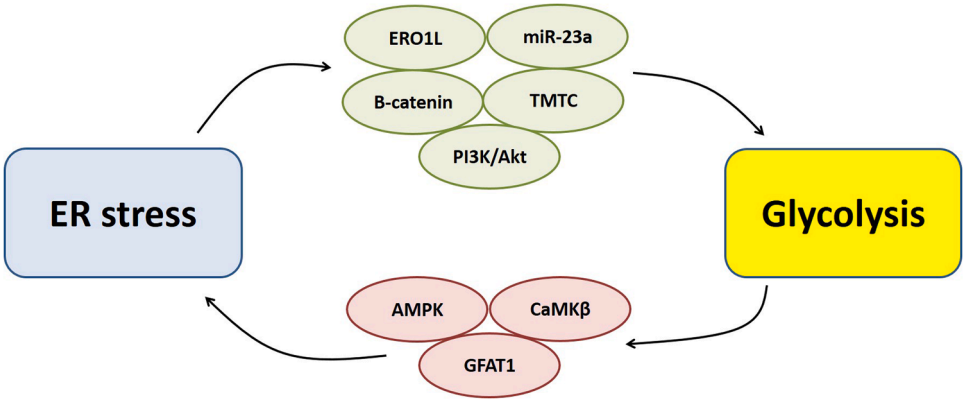

Fig. 2. An overview of the interplay between endoplasmic reticulum (ER) stress and the glycolytic pathway. ER stress affects glycolysis through ERO1L, miR-23, β-catenin, TMTC, and PI3K/Akt. On the other hand, glycolysis affects ER stress through AMPK, CaMKβ, and GFAT1. AMPK, AMP-activated protein kinase; CaMKβ, calcium/calmodulin dependent protein kinase beta; ERO1L, endoplasmic reticulum oxidoreductase alpha; GFAT1, glutamine-fructose-6-phosphate transaminase 1; PI3K, phosphoinositide 3-kinase; TMTC, transmembrane and tetratricopeptide repeat containing protein.

lines [54]. TMTC3 has a significant impact on protein folding and quality control within the endoplasmic reticulum (ER), possibly resulting in the buildup of misfolded proteins and subsequent ER stress [55]. This influence stems from TMTC3's role in modulating calcium signaling within cells, ultimately causing calcium dysregulation in the ER, thereby contributing to ER stress [56]. Additionally, TMTC3 affects the expression and function of chaperone proteins, which in turn affects the ER's capacity to effectively fold and process proteins [57].

Likewise, Garaham and colleagues reported that the induction of ER stress in neuroblastoma cells activated the IRS-1/PI3K/AKT signaling pathway; and thereby, suppressed the expression of key glycolytic enzymes. This effect culminated in reduced cell proliferation and increased cell apoptosis [58]. Another study on HepG2 hepatocellular carcinoma cells revealed that canagliflozin, a sodium/glucose cotransporter 2 inhibitor, was cytotoxic to these cells and increased apoptotic rates. Canagliflozin augmented UPR as evidenced by increased activities of IRE-1α, ATF-6, and XBP-1. While it increased the activity of PI3K/AKT/mTOR signaling pathway, the activity of Wnt/β-catenin signaling pathway was diminished. Moreover, canagliflozin attenuated glucose uptake, glycolytic pathway, and ATP production in HepG2 cells [59]. It should be emphasized that canagliflozin directly inhibits glucose uptake; therefore, it can cannot be concluded that this agent inhibits aerobic glycolysis by solely inducing UPR.

4.2. Inhibition of glycolysis activates ER stress in cancer

2-deoxy-D-glucose (2-DG) is a glucose-like compound that not only hinders glycolysis but also disrupts N-linked glycosylation. It has been reported that 2-DG suppresses the cell growth in 1420 pancreatic cancer cell line, MDA-MB-435 melanoma cell line, and SKBR3 breast cancer cell line by reducing ATP production. Moreover, it has been evidenced that the ER stress is induced in all cell lines after treatment with 2-DG [60]. Moreover, it has been shown that 2-DG, but not glucose starvation, activate ER stress in 1420 pancreatic cancer cell line. 2-DG activates AMP-activated protein kinase (AMPK) via inducing Ca^{2+}/Calmodulin-dependent protein kinase β (CaMKβ). Either inhibition of AMPK or CaMKβ obviates ER stress in cancer cells even in the presence of 2-DG [61]. It is worth noting that in earlier reports, 2-DG was initially introduced as an anti-cancer agent [62]. This apparent shift in its role may raise questions about its potential dual effects in cancer. The evolving understanding of 2-DG's mechanisms in cancer research has highlighted the complexity of its actions. While it was initially investigated for its potential to target the high glucose demands of cancer cells, subsequent research has revealed that 2-DG can also induce endoplasmic reticulum (ER) stress, which may promote tumor growth [63]. This duality underscores the intricate interplay of factors in cancer biology, and the context in which 2-DG is applied is crucial to determining its ultimate impact on cancer cells.

Glutamine-fructose-6-phosphate amidotransferase 1 (GFAT1) is an enzyme that plays a key role in the first and rate-limiting step of the hexosamine biosynthesis pathway (HBP). The HBP is a metabolic pathway that branches off from glycolysis and produces a molecule called UDP-N-acetylglucosamine (UDP-GlcNAc) [64]. GFAT1 catalyzes the conversion of fructose-6-phosphate and glutamine into glucosamine-6-phosphate, which is an essential precursor for the synthesis of UDP-GlcNAc. UDP-GlcNAc is involved in various cellular processes, including protein glycosylation. GFAT1 is therefore critical for regulating the levels of UDP-GlcNAc and influencing protein glycosylation [65]. Ishino *et al.*, found that 2-DG dose-dependently reduced the expression of GFAT1 in pancreatic ductal adenocarcinoma cell via activating the AMPK pathway. Accordingly, protein N-glycosylation was suppressed which led to the activation of ER stress and increased number of annexin V-positive apoptotic cells. The researchers found that metformin, the potent AMPK activator, had a synergistic effect with 2-DG in suppressing the growth of cancer cells [66]. Moreover, it was demonstrated that PFK158, the potent chemical inhibitor of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), inhibited the glycolytic pathway in malignant pleural mesothelioma (MPM), leading to the inhibition of proliferation and increased apoptosis due to cell cycle arrest at G0/G1 phase. Inhibition of glycolysis was associated with increased rates of micropinocytosis and induction of ER stress, as evidenced by increased expressions of GRP78, IF4E, XBP-1, and Hsp70 in MPM cells [67].

5. Conclusion

The association between ER stress and the induction of aerobic glycolysis in cancer cells presents a fascinating area of research with significant implications for cancer biology and therapy. The Warburg effect, characterized by increased glucose uptake and lactate production even under normoxic conditions, is a metabolic adaptation commonly observed in cancer cells. While the Warburg effect has been extensively studied, the precise mechanisms driving this metabolic shift remain incompletely understood. Recent investigations have unveiled a potential connection between ER stress and the promotion of aerobic glycolysis in cancer cells. ER stress, triggered by various cellular stressors, leads to the activation of the unfolded protein response (UPR). However, severe or prolonged ER stress can activate alternative signaling pathways that impact cellular metabolism, including the upregulation of aerobic glycolysis. Transcription factors such as ATF4 and XBP1, along with key signaling pathways including PERK, IRE1, and ATF6, have been implicated in ER stress-induced metabolic reprogramming. The intricate interplay between ER stress and metabolic alterations in cancer cells suggests a potential avenue for therapeutic intervention. Targeting the vulnerabilities associated with ER stress-induced metabolic rewiring may offer new opportunities for developing effective anti-cancer strategies. Furthermore, understanding the crosstalk between ER stress and other oncogenic pathways, such as the PI3K/AKT/mTOR pathway, could provide insights into combinatorial treatment approaches. In summary, investigating the relationship between ER stress and aerobic glycolysis in cancer cells contributes to our understanding of cancer metabolism and highlights potential therapeutic targets. Continued research in this field holds promise for the development of innovative strategies to selectively disrupt the metabolic adaptations of cancer cells and improve clinical outcomes for cancer patients.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to publish

This article does not contain any studies with human participants or animals performed by any of the authors.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Declaration of Competing Interest

We would like to submit a review article entitled "The Role of Endoplasmic Reticulum Stress in Promoting Aerobic Glycolysis in Cancer Cells: An Overview" by Abduladheem Turki Jalil, Mohanad Ali Abdulhadi, Sami Awad Alkubaisy, Sara Hamed Thejeel, Israa M. Essa,

Muna S. Merza, Rahman S. Zabibah, Raad Al-Tamimi for possible publication in Pathology – Research and Practice; and the authors declare that they have no conflict of interest.

Data Availability

This article does not contain any studies with human participants or animals performed by any of the authors.

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