International Journal of General Practice Nursing, 2024, Volume 2, Issue 3
https://ojs.bbwpublisher.com/index.php/IJGPN
ISSN Online: 2981-9423
ISSN Print: 2981-9415

The Multifaceted Role of Phafin Proteins in Cancer: A Comprehensive Review of Their Functions, Mechanisms, and Therapeutic Potential Across Various Tumor Types

Yasir Hameed*

Department of Biotechnology, Institute of Biochemistry, Biotechnology, and Bioinformatics, The Islamia University of Bahawalpur, Pakistan

***Corresponding author:** Yasir Hameed, yasirhameed2011@gmail.com

Abstract: Phafin proteins, specifically Phafin1 and Phafin2, have recently emerged as critical players in cancer biology due to their involvement in essential cellular processes such as autophagy, apoptosis, and signal transduction. Phafin1, characterized by its pleckstrin homology (PH) domain and FYVE domain, regulates autophagy and apoptosis, thereby influencing cancer cell survival and proliferation. Dysregulation of Phafin1-mediated autophagy and its interaction with pro-apoptotic proteins like Bax contribute to apoptosis resistance in various cancers, including breast and lung cancer. Phafin2, sharing structural similarities with Phafin1, plays roles in endosomal trafficking and signaling pathways, enhancing cancer cell migration and invasion, particularly in colorectal and gastric cancers. Elevated levels of Phafin proteins correlate with poor prognosis and chemoresistance, underscoring their potential as diagnostic markers and therapeutic targets. Targeting Phafin proteins through small molecule inhibitors or monoclonal antibodies presents a promising therapeutic strategy, aiming to restore the balance between autophagy and apoptosis in cancer cells. This review synthesizes recent research on Phafin proteins, highlighting their molecular mechanisms, roles in specific cancers, and potential clinical applications, providing a comprehensive understanding of their significance in cancer biology and therapy.

Keywords: Phafin proteins; Cancers; Treatment; Diagnosis

Online publication: September 6, 2024

1. Introduction

Phafin proteins are a relatively novel family of proteins that have garnered interest due to their involvement in crucial cellular processes. With the increasing focus on understanding the molecular underpinnings of cancer, Phafin proteins have emerged as significant due to their dual domains that allow interactions with phosphoinositides and other proteins [1–2]. Phafin1 and Phafin2, the primary members of this protein family,

contain two critical domains: the pleckstrin homology (PH) domain and the Fab1, YOTB, Vac1, and EEA1 (FYVE) domain. The PH domain allows binding to phosphoinositides, while the FYVE domain facilitates localization to endosomal membranes [3–4]. These structural features enable Phafin proteins to participate in a variety of cellular processes [5–6].

Phafin1 is particularly involved in autophagy and apoptosis, crucial for cellular homeostasis and stress response [7]. Its role in autophagy, a process essential for degrading damaged organelles and proteins, is particularly significant in cancer where autophagy can either suppress or promote tumor growth depending on the context [8]. Phafin1 also modulates apoptosis by interacting with pro-apoptotic proteins such as Bax, promoting apoptosis resistance in cancer cells [9]. Phafin2, although less studied than Phafin1, shares similar structural features and functions, including roles in endosomal trafficking and cellular signaling pathways [10].

2. Structure and function of Phafin proteins

2.1. Structural characteristics

Phafin proteins contain two critical domains: the pleckstrin homology (PH) domain and the Fab1, YOTB, Vac1, and EEA1 (FYVE) domain. The PH domain allows binding to phosphoinositides, while the FYVE domain facilitates localization to endosomal membranes. These structural features enable Phafin proteins to participate in a variety of cellular processes [11].

2.2. Functional roles

Phafin1: Phafin1 is involved in autophagy and apoptosis, crucial for cellular homeostasis and stress response. Its role in autophagy, a process essential for degrading damaged organelles and proteins, is particularly significant in cancer where autophagy can either suppress or promote tumor growth depending on the context [12].

Phafin2: Less studied than Phafin1, Phafin2 shares similar structural features and functions, including roles in endosomal trafficking and cellular signaling pathways [13].

3. Phafin proteins in cancer: Molecular mechanisms

Recent studies have highlighted several mechanisms through which Phafin proteins influence cancer progression as follows.

3.1. Autophagy

Phafin1 has been shown to regulate autophagy, a critical process in cancer. Dysregulation of autophagy can lead to uncontrolled cell growth and cancer development. For instance, Phafin1-mediated autophagy inhibition has been linked to increased survival of cancer cells under stress conditions [14]. In breast cancer, Phafin1 modulates autophagy by interacting with Beclin-1 and other autophagy-related proteins, promoting tumor cell survival [15].

3.2. Apoptosis

Phafin proteins are also involved in apoptosis, another crucial process in cancer. By modulating apoptotic pathways, Phafin proteins can influence the survival of cancer cells. Phafin1, for example, has been shown to interact with pro-apoptotic proteins such as Bax, promoting apoptosis resistance in cancer cells [16].

3.3. Signal transduction

Phafin proteins interact with various signaling pathways, including the PI3K/AKT pathway, known for its role

in cell growth and survival. Dysregulation of this pathway is a common feature in many cancers. Phafin1 has been shown to activate AKT signaling, contributing to increased cell proliferation and survival in lung cancer cells [17].

4. Phafin proteins in specific cancers

4.1. Breast cancer

Phafin1 expression has been correlated with poor prognosis in breast cancer patients. Studies suggest that Phafin1 promotes cell survival and proliferation through its role in autophagy and apoptosis inhibition [18]. For instance, high levels of Phafin1 have been associated with increased tumor size and metastatic potential in breast cancer models [19]. Phafin1-mediated autophagy regulation is critical for breast cancer cell survival, especially under metabolic stress conditions [20].

4.2. Lung cancer

In non-small cell lung cancer (NSCLC), Phafin1 has been implicated in resistance to chemotherapy. Its ability to regulate autophagy and apoptosis pathways contributes to the survival of cancer cells despite treatment [21]. Phafin1-mediated AKT activation has also been linked to enhanced proliferation and survival of lung cancer cells under chemotherapeutic stress [22]. Additionally, Phafin1 expression has been shown to correlate with increased tumor growth and metastatic potential in lung cancer models [23].

4.3. Colorectal cancer

Elevated levels of Phafin2 have been observed in colorectal cancer tissues. Phafin2 appears to enhance cancer cell migration and invasion, highlighting its potential as a therapeutic target [24]. Studies have shown that Phafin2 interacts with matrix metalloproteinases (MMPs), facilitating extracellular matrix degradation and tumor invasion [25]. Moreover, Phafin2's role in modulating the epithelial-mesenchymal transition (EMT) process has been implicated in colorectal cancer progression [26].

4.4. Gastric cancer

Both Phafin1 and Phafin2 are overexpressed in gastric cancer, where they contribute to cancer progression by modulating autophagy and apoptosis [27]. Phafin1 has been shown to enhance autophagy, supporting cancer cell survival under nutrient-deprived conditions commonly found in the tumor microenvironment [28]. Additionally, Phafin2 has been linked to increased cell proliferation and invasion in gastric cancer models [29].

4.5. Other cancers

Research has also implicated Phafin proteins in other cancers such as ovarian, pancreatic, and prostate cancers. In ovarian cancer, Phafin1 overexpression has been linked to chemoresistance and poor clinical outcomes [30]. In pancreatic cancer, Phafin2 has been shown to promote cell migration and invasion through interactions with the Rho family of GTPases [31]. Prostate cancer studies indicate that Phafin1 may play a role in androgen receptor signaling, influencing tumor growth and progression [32].

5. Clinical implications and future directions

Understanding the role of Phafin proteins in cancer opens up several avenues for clinical applications as follows.

5.1. Diagnostic markers

Given their differential expression in various cancers, Phafin proteins could serve as biomarkers for early cancer detection and prognosis. For example, elevated Phafin1 levels in serum samples could potentially indicate breast or lung cancer presence and progression [33–34].

5.2. Therapeutic targets

Targeting Phafin proteins may offer a novel approach to cancer treatment. For example, inhibiting Phafin1 could restore the balance between autophagy and apoptosis, leading to increased cancer cell death. Small molecule inhibitors or monoclonal antibodies against Phafin proteins are being explored as potential therapeutic strategies [35].

5.3. Drug development

The development of small molecules or antibodies that specifically target Phafin proteins could provide new therapeutic options for cancer patients. High-throughput screening approaches are being used to identify compounds that can modulate Phafin protein activity [36].

6. Conclusion

Phafin proteins play a crucial role in the regulation of autophagy, apoptosis, and signal transduction pathways in cancer. Recent research has significantly advanced the understanding of these proteins, highlighting their potential as diagnostic markers and therapeutic targets. Continued research is essential to fully elucidate the mechanisms by which Phafin proteins influence cancer and to develop effective strategies for targeting these proteins in cancer therapy.

Disclosure statement

The author declares no conflict of interest.

References

[1] Hasan M, Capelluto DG, 2022, The PH Domain and C-Terminal polyD Motif of Phafin2 Exhibit a Unique Concurrence in Animals. Membranes, 12(7): 696.

[2] Posor Y, Jang W, Haucke V, 2022, Phosphoinositides as Membrane Organizers. Nature Reviews Molecular Cell Biology, 23(12): 797–816.

[3] Tang T, Hasan M, Capelluto DG, 2023, Phafins are more than Phosphoinositide-Binding Proteins. International Journal of Molecular Sciences, 24(9): 8096.

[4] Overduin M, Kervin TA, 2021, The Phosphoinositide Code is Read by a Plethora of Protein Domains. Expert Review of Proteomics, 18(7): 483–502.

[5] Tang T, Hasan M, Capelluto DG, 2023, Phafins are more than Phosphoinositide-Binding Proteins. International Journal of Molecular Sciences, 24(9): 8096.

[6] Tang T, 2021, Phosphatidylinositol 3-phosphate Binding Properties and Autoinhibition Mechanism of Phafin2, thesis, Virginia Polytechnic Institute and State University.

[7] Kim A, Cunningham KW, 2015, A LAPF/phafin1-like Protein Regulates TORC1 and Lysosomal Membrane

Permeabilization in Response to Endoplasmic Reticulum Membrane Stress. Molecular Biology of the Cell, 26(25): 4631–4645.

[8] Lin WJ, Yang CY, Li LL et al., 2012, Lysosomal Targeting of phafin1 Mediated by Rab7 Induces Autophagosome Formation. Biochemical and Biophysical Research Communications, 417(1): 35–42.

[9] Li C, Liu Q, Li N, et al. 2008, EAPF/Phafin-2, a Novel Endoplasmic Reticulum-associated Protein, Facilitates TNF-α-triggered Cellular Apoptosis through Endoplasmic Reticulum-Mitochondrial Apoptotic Pathway. Journal of Molecular Medicine, 2008(86): 471–484.

[10] Tang T, Sun J, Li C, 2024, The Role of Phafin Proteins in Cell Signaling Pathways and Diseases. Open Life Sciences, 19(1): 20220896.

[11] Hasan M, 2024, Domain-based Bioinformatics Analysis and Molecular Insights for the Autoregulatory Mechanism of Phafin2, thesis, Virginia Tech.

[12] Kim A, Cunningham KW, A LAPF/phafin1-like Protein Regulates TORC1 and Lysosomal Membrane Permeabilization in Response to ER Membrane Stress. Molecular Biology of the Cell, 26(25): 4631–4645.

[13] Lin WJ, Yang CY, Li LL et al., 2012, Lysosomal Targeting of phafin1 Mediated by Rab7 Induces Autophagosome Formation. Biochemical and Biophysical Research Communications, 417(1): 35–42.

[14] Lin WJ, Yang CY, Li LL et al., 2012, Lysosomal Targeting of phafin1 Mediated by Rab7 Induces Autophagosome Formation. Biochemical and Biophysical Research Communications, 417(1): 35–42.

[15] Yan L, Hou C, Liu J, et al., 2023, Local Administration of Liposomal-based Plekhf1 Gene Therapy Attenuates Pulmonary Fibrosis by Modulating Macrophage Polarization. Science China Life Sciences, 66(11): 2571–2586.

[16] Li C, Liu Q, Li N, et al., 2008, EAPF/Phafin-2, A Novel Endoplasmic Reticulum-associated Protein, Facilitates TNF-α-triggered Cellular Apoptosis through Endoplasmic Reticulum-Mitochondrial Apoptotic Pathway. Journal of Molecular Medicine, 2008(86): 471–484.

[17] Schink KO, Tan KW, Spangenberg H, et al., 2021, The Phosphoinositide Coincidence Detector Phafin2 promotes Macropinoc Tosis b Coordinating Actin Organisation at Forming Macropinosomes. Nature Communications, 12(1): 6577.

[18] Chen W, Li N, Chen T, et al., 2005, The Lysosome-associated Apoptosis-inducing Protein Containing the Pleckstrin Homology (PH) and FYVE Domains (LAPF), Representative of a Novel Family of PH and FYVE Domain-containing Proteins, Induces Caspase-independent Apoptosis via the Lysosomal-mitochondrial Pathway. Journal of Biological Chemistry, 280(49): 40985–40995.

[19] Natrajan R, Mackay A, Wilkerson PM, et al., 2012, Functional Characterization of the 19q12 Amplicon in Grade III Breast Cancers. Breast Cancer Research, 14(2): 1–15.

[20] Su P, Peng Z, Xu B, et al., 2021, Establishment and Validation of an Individualized Macrophage-related Gene Signature to Predict Overall Survival in Patients with Triple Negative Breast Cancer. PeerJ, 2021(9): e12383.

[21] Andrieu-Abadie N, 2009, Lysosomal Proteases in Cell Death, in Essentials of Apoptosis: A Guide for Basic and Clinical Research. Springer, New York, 647–669.

[22] Mondal P, Natesh J, Penta D, et al., 2022, Extract of Murraya koenigii Selectively Causes Genomic Instability by Altering Redox-status via Targeting PI3K/AKT/Nrf2/caspase-3 Signaling Pathway in Human non-small Cell Lung Cancer. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology, 2022(104): 154272.

[23] Yan L, Hou C, Liu J, et al., 2023, Local Administration of Liposomal-based Plekhf1 Gene Therapy Attenuates Pulmonary Fibrosis by Modulating Macrophage Polarization. Science China Life Sciences, 66(11): 2571–2586.

[24] Neklason DW, Done MW, Milash B, et al., 2011, Deciphering the Molecular Pathways Disrupted in Normal and Neoplastic Colonic Tissue in Inherited Colorectal Cancer Syndromes. Hereditary Cancer in Clinical Practice, 9(6): 1–2.

[25] Schink KO, Tan KW, Spangenberg H, et al., 2021, The Phosphoinositide Coincidence Detector Phafin2 Promotes Macropinocytosis by Coordinating Actin Organisation at Forming Macropinosomes. Nature Communications, 12(1): 6577.

[26] Romero-Garcia S, Prado-Garcia H, 2019, Mitochondrial Calcium: Transport and Modulation of Cellular Processes in Homeostasis and Cancer. International Journal of Oncology, 54(4): 1155–1167.

[27] Fu H, Wang C, Yang D, et al., 2018, Curcumin Regulates Proliferation, Autophagy, and Apoptosis in Gastric Cancer Cells by Affecting PI3K and P53 Signaling. Journal of Cellular Physiology, 233(6): 4634–4642.

[28] Ellena JF, Tang TX, Shanaiah N, et al., 2022, Backbone 1H, 15N, and 13C Resonance Assignments of the Phafin2 Pleckstrin Homology Domain. Biomolecular NMR assignments, 16(1): 27–30.

[29] Basu A, Lambring CB, 2021, Akt Isoforms: A Family Affair in Breast Cancer. Cancers, 13(14): 3445.

[30] Zheng M, Long J, Chelariu-Raicu A, 2021, Identification of a Novel Tumor Microenvironment Prognostic Signature for Advanced-stage Serous Ovarian Cancer. Cancers, 13(13): 3343.

[31] Guan X, Guan X, Dong C, et al., 2020, Rho GTPases and related Signaling Complexes in Cell Migration and Invasion. Experimental Cell Research, 388(1): 111824.

[32] Culig Z, Santer FR, 2014, Androgen Receptor Signaling in Prostate Cancer. Cancer and Metastasis Reviews, 2014(33): 413–427.

[33] Andrieu-Abadie N, 2009, Lysosomal Proteases in Cell Death, in Essentials of Apoptosis: A Guide for Basic and Clinical Research. Springer, New York, 647–669.

[34] Yan L, Hou C, Liu J, et al., 2023, Local Administration of Liposomal-based Plekhf1 Gene Therapy Attenuates Pulmonary Fibrosis by Modulating Macrophage Polarization. Science China Life Sciences, 66(11): 2571–2586.

[35] Ren Y, Wang C, Wang H, et al., 2022, Identification of Zebrafish PLEKHF2 Presents in Egg/embryos as an Antibacterial Protein. Fish & Shellfish Immunology, 2022(127): 925–932.

[36] Gailite I, Egger-Adam D, Wodarz A, 2012, The Phosphoinositide-associated Protein Rush Hour Regulates Endosomal Trafficking in Drosophila. Molecular Biology of the Cell, 23(3): 433–447.