Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2024): 2.2
CiteScore® (2024): 5.2
www.biomolbiomed.com | blog.bjbms.org

REVIEW

Lv et al: PAQR3 in cancer molecular mechanisms

The role of PAQR3 in cancer progression – Molecular regulation, signaling pathways, and clinical implications: A review

Yan Lv[1#], Dan Li[2#], Xiao-Fei Ren[3], Qiang Guo[3*], Qiao-Ya Ren[4*]

[1]Department of Cardiothoracic Surgery, The Second Affiliated Hospital of Zunyi Medical University, Zunyi, China;

[2]Department of Oncology, Taihe Hospital, Hubei University of Medicine, Shiyan, China;

[3]Department of Cardiothoracic Surgery, Taihe Hospital, Hubei University of Medicine, Shiyan, China;

[4]Department of Oncology, The Second Affiliated Hospital of Zunyi Medical University, Zunyi, China.

[#]Equally contributed to this work: Yan Lv and Dan Li.

*Correspondence to Qiao-Ya Ren: renqya79@163.com; Qiang Guo: guoqianglidan@163.com.

DOI: https://doi.org/10.17305/bb.2026.13696

ABSTRACT

Progesterone and adiponectin receptor 3 (PAQR3) is a Golgi-localized seven-transmembrane protein that anchors rapidly accelerated fibrosarcoma kinase (Raf) and suppresses rat sarcoma/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (Ras/Raf/MEK/ERK) signaling, thereby influencing cellular proliferation, differentiation, and metastasis. This review aims to summarize the expression patterns, regulatory mechanisms, key downstream pathways, and clinical significance of *PAQR3* in cancer. We synthesized findings from published clinical and experimental studies, including in vitro assays and nude mouse xenograft models, that evaluate *PAQR3* expression, function, and signaling interactions across various tumor types. Overall, *PAQR3* is frequently downregulated in many cancers, potentially due to promoter methylation, and low expression levels are associated with adverse clinicopathologic features and reduced survival. Functionally, *PAQR3* overexpression inhibits proliferation, colony formation, migration, invasion, and tumor growth, primarily through the inhibition of extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathways and modulation of epithelial-mesenchymal transition (EMT). Additionally, PAQR3 is linked to nuclear factor kappa B/tumor protein p53 (NF-κB/p53), epidermal growth factor/beta-catenin (EGF/β-catenin) signaling, autophagy, and nuclear factor erythroid 2–related factor 2/ferroptosis (Nrf2/ferroptosis). These effects are modulated by upstream regulators, including microRNA-543 (miR-543), circular RNA 0043280/microRNA-203a-3p (circ_0043280/miR-203a-3p), microRNA-15b (miR-15b), human epidermal growth factor receptor 2 (HER2), 5-aza-2′-deoxycytidine (5-Aza-CdR), autophagy-related 7 (ATG7), and damage-specific DNA binding protein 2 (DDB2). In conclusion, PAQR3 functions as a tumor suppressor and holds potential as a prognostic biomarker. Targeting PAQR3-related pathways may provide new therapeutic opportunities.

Keywords: *PAQR3,* cancer, miRNA, prognosis, 5-Aza-CdR.

INTRODUCTION

Numerous studies have demonstrated that abnormal gene expression is linked to cancer cell growth, metastasis, and poor prognosis in cancer patients [1-6]. Progestin and AdipoQ Receptor 3 (*PAQR3*) is a gene situated on human chromosome 4, encoding a membrane protein with a distinctive seven-transmembrane domain architecture. Predominantly localized to the Golgi apparatus, this protein plays a critical role in intracellular signal transduction. It functions by anchoring Raf kinase to the Golgi membrane, thereby exerting a negative regulatory effect on the Ras/Raf/MEK/ERK signaling cascade. *PAQR3* influences essential cellular processes including proliferation and differentiation, underscoring its importance as a key regulator in maintaining normal cellular physiology using Ras/Raf/MEK/ERK signaling [6]. In recent years, extensive research has similarly confirmed the roles (such as the cell proliferation, migration, invasion) are linked to the downregulation of *PAQR3* pan-cancer [7-36]. Now, despite significant advancements in cancer treatment, the complexity of cancer cell biology, especially the role of specific genes like *PAQR3*, still poses challenges in developing more effective and targeted therapies. In addition, our review provides an update and expansion relative to existing syntheses: it not only includes recent findings from 2023 to 2025, which were not covered in the review by Guo et al., but also encompasses a broader range of literature than the meta-analysis by Zhai et al [34,35], and this review aims to summarize the roles, mechanisms, and clinical significance of *PAQR3* in cancer, providing new insights and potential therapeutic targets for clinical practitioners and researchers.

Expression levels of PAQR3 significantly decrease in cancer

The expression levels of P*AQR3* are significantly decreased in various cancer tissues and cell lines [7-27]. Specifically, compared to normal tissues, *PAQR3* expression is notably lower in tissues from osteosarcoma, thyroid cancer, glioma, lung cancer, hepatocellular carcinoma, cervical cancer, colorectal cancer, diffuse large B-cell lymphoma, acute lymphoblastic leukemia, breast cancer, esophageal cancer, gastric cancer, and renal cell carcinoma (Table 1). Furthermore, this decline in expression is observed in osteosarcoma, glioma, lung cancer, hepatocellular carcinoma, diffuse large B-cell lymphoma, breast cancer, esophageal cancer, and gastric cancer cells (Table 1). The down-regulation of *PAQR3* in cancer cells may be attributed to epigenetic modifications. DNA methylation of the *PAQR3* promoter region has been

implicated in some cancer types, leading to reduced gene transcription and subsequent lower protein expression levels [10,22]. This preliminary evidence suggests that *PAQR3* can act as a tumor suppressor gene in cancer progression.

Overexpression of PAQR3 inhibits cancer cell growth and metastasis

Research has confirmed that inhibiting oncogene expression or promoting tumor suppressor gene expression can suppress cancer growth and metastasis [34-36]. *PAQR3* is frequently downregulated in cancer tissues and cells. Activation of *PAQR3* expression can inhibit cancer cell growth (Table 2). Specifically, *PAQR3* can suppress the proliferation of osteosarcoma, glioma, lung cancer, hepatocellular carcinoma, cervical cancer, colorectal cancer, diffuse large B-cell lymphoma, acute lymphoblastic leukemia, breast cancer, esophageal cancer, gastric cancer, renal cell carcinoma, colon cancer and prostate cancer cells [7,9,11-15,17-19,21,23,25-32,36]. *PAQR3* overexpression suppresses the colony formation of lung cancer, hepatocellular carcinoma, colorectal cancer, breast cancer, esophageal cancer, gastric cancer, colon cancer, and prostate cancer cells [11,14,17,21-23,26,27,29,30,32,36]. Furthermore, *PAQR3* overexpression can inhibit the cell cycle transition in lung cancer and esophageal cancer cells [11,12,23]. Moreover, *PAQR3* promotes apoptosis in lung cancer and acute lymphoblastic leukemia cells [11,12,19].

Additionally, activation of *PAQR3* expression can suppress cancer cell metastasis (Table 3). Specifically, the results from Transwell and wound healing assays indicate that *PAQR3* overexpression can inhibit the migration of osteosarcoma, glioma, cervical cancer, breast cancer, esophageal cancer, gastric cancer, renal cell carcinoma, colon cancer, and prostate cancer cells [7,9,15,20-23,25-33,36]. *PAQR3* overexpression inhibits the invasion of osteosarcoma, glioma, hepatocellular carcinoma, cervical cancer, breast cancer, esophageal cancer, and gastric cancer cells [7,9,13,15,22,23,25,31]. *PAQR3* overexpression inhibits tube formation ability in renal cell carcinoma cells [28]. Based on the above information, it can be preliminarily indicated that *PAQR3* functions as a tumor suppressor in vitro, and enhancing *PAQR3* expression may delay cancer cell growth and metastasis.

Activation of *PAQR3* expression in glioma, cervical cancer, colorectal cancer, diffuse large B-cell lymphoma, esophageal cancer, lung cancer, and gastric cancer cells, followed by the establishment of tumorigenic models in athymic nude mice,

demonstrated that *PAQR3* overexpression significantly inhibits tumor growth and proliferation in these mice [9,15,17,18,23,25,29,33]. This finding indicates that *PAQR3* functions as a tumor suppressor *in vivo* (Table 4), and enhancing *PAQR3* expression could be a viable therapeutic strategy in the clinical setting. However, further research is needed to develop safe and effective methods to specifically up-regulate *PAQR3* expression in human cancer patients without causing significant side effects.

PAQR3 INVOLVES THE SIGNALING MECHANISMS

Upstream regulation of PAQR3 in cancer

PAQR3 may be inhibited by upstream circular RNA/microRNAs (miRNAs), thereby affecting the function of the target genes of *PAQR3* [13,15,20,31]. For example, Yu et al. reported that miR-543 is overexpressed in hepatocellular carcinoma tissues, while *PAQR3* is downregulated, establishing a negative correlation and a targeted regulatory relationship between the two. miR-543 can promote the proliferation and invasion of hepatocellular carcinoma cells by specifically targeting and suppressing *PAQR3* expression [13]. Zhang et al. reported a significant decrease in circ_0043280 levels in cervical cancer. Circ_0043280 can competitively bind to miR-203a-3p, thereby promoting *PAQR3* expression and suppressing the growth and metastasis of cervical cancer [15]. Qi et al. demonstrated a targeted regulatory relationship between miR-15b and *PAQR3*. miR-15b can inhibit *PAQR3* expression, promoting progression in breast cancer and gastric cancer [20,31]. In addition, *PAQR3* may be regulated by factors such as Human epidermal growth factor receptor 2 (HER2), 5-Aza-2'-deoxycytidine (5-Aza-CdR), Autophagy related 7 (ATG7), P6-55, and Damage specific DNA binding protein 2 (DDB2) [19,21,22,23,29,32,36]. For example, Li et al. reported that *PAQR3* can inhibit the proliferation, colony formation, and migration of breast cancer cells. Trastuzumab, which inhibits HER2 expression, can promote *PAQR3* expression, thereby enhancing its inhibitory effects on breast cancer [21]. Chen et al. reported that treatment with 5-Aza-CdR significantly stimulates *PAQR3* expression in breast cancer and esophageal cancer cells, thus enhancing *PAQR3*'s efficacy against cancer cells [22,23].

DOWNSTREAM EFFECTS OF PAQR3 IN CANCER

The PAQR3/Ras/Raf/MEK/ERK signaling axis

Extracellular signal-regulated kinase (ERK) is a member of the Mitogen-Activated Protein Kinase (MAPK) family, and the ERK signaling pathway is central to the signaling network involved in cell growth, development, and division [37]. *PAQR3* can inhibit the growth and metastasis of osteosarcoma, cervical cancer, esophageal cancer, gastric cancer, renal cell carcinoma, colorectal cancer, and prostate cancer cells by suppressing the ERK signaling [7,15,17,23,25,27,28,30,32], as detailed in Table 5 and Figure 1. For instance, Ma et al. reported that *PAQR3* overexpression can suppress the phosphorylation of ERK (p-ERK) proteins and inhibit the proliferation and invasion of osteosarcoma cells. The MEK inhibitor U0126 completely abrogates the effects of *PAQR3* silencing on osteosarcoma cell proliferation and invasion [7]. Bai et al. found that *PAQR3* overexpression reduces p-ERK protein levels in esophageal cancer cells and promotes the expression of downstream ERK proteins Cyclin-dependent kinase inhibitor 1B (CDKN1B) and Cyclin-dependent kinase inhibitor 1A (CDKN1A) while inhibiting the expression of cyclin D1, Cyclin-dependent kinase 4 (CDK4), and Cyclin-dependent kinase 2 (CDK2), thereby suppressing esophageal cancer growth [23,25]. Additionally, *PAQR3* overexpression can inhibit the downstream signaling of Nuclear Factor Kappa B (Nf-kB)/Protein 53 (p53) via ERK, thereby delaying the growth of lung cancer cells [11].

The PAQR3/phosphatidylinositol 3-kinase (PI3K)/AKT serine/threonine kinase (AKT) signaling axis

The PI3K/AKT pathway is a classic signaling cascade that promotes cell survival and insulin secretion [38,39]. Research has confirmed a close relationship between *PAQR3* and the PI3K/AKT signaling pathway [9,12,15,18,24,27,30,36[. For example, Li et al. reported that *PAQR3* overexpression inhibits PI3K/AKT signaling through decreases in PI3K phosphorylation (p-PI3K) and AKT phosphorylation (p-AKT), without significantly suppressing PI3K and AKT protein levels, thereby inhibiting the growth of lung cancer cells A549 and H1299 [12]. In diffuse large B-cell lymphoma U2932 cells, *PAQR3* may inhibit cell progression through the Low-Density Lipoprotein Receptor (LDLR)/PI3K/AKT signaling pathway by regulating the

expression levels of LDLR, p-AKT, and p-PI3K [19]. Furthermore, studies confirm that *PAQR3* expression is related to insulin signaling mechanisms [32]. *PAQR3* can inhibit insulin-stimulated phosphorylation of p-AKT and Glycogen Synthase Kinase 3 Beta (GSK3β), thereby participating in the growth and metastasis of gastric cancer [32].

The PAQR3/Epithelial-mesenchymal transition (EMT) signaling axis

The EMT process is closely linked to cancer metastasis [40]. *PAQR3* is involved in the metastasis of cervical cancer, esophageal cancer, gastric cancer, and prostate cancer through the EMT process [15,24,25,27,30,31,33]. For example, Huang et al. reported that *PAQR3* overexpression suppresses the expression of vimentin during the EMT process, while promoting E-cadherin and Zonula Occludens-1 (ZO-1) expression, consequently inhibiting the migration of prostate cancer cells PC3 and DU145 [30]. Bai et al. noted that *PAQR3* overexpression enhances E-cadherin expression while inhibiting N-cadherin expression, thereby reducing the migration of esophageal cancer cells [24,25]. Wu et al. showed that *PAQR3* inhibits the expression levels of snail, vimentin, Transforming Growth Factor Beta 1 (TGF-β1), Phosphorylated SMAD Family Member 2 (p-SMAD2), and Phosphorylated SMAD Family Member 3 (p-SMAD3) in the Transforming Growth Factor Beta (TGF-β)/SMAD/EMT signaling pathway, thereby promoting E-cadherin expression and inhibiting gastric cancer progression [26].

Other downstream signaling mechanisms

PAQR3 dysregulation may also participate in regulating ferroptosis using nuclear factor erythroid 2-related factor 2 (Nrf2), Epidermal Growth Factor (EGF)/β-catenin signaling, and autophagy, thereby influencing cancer progression [17-19,26,28,29,36]. For example, Wang et al. reported that *PAQR3* inhibits β-catenin nuclear accumulation in colorectal cancer SW-480 cells, thereby delaying tumorigenic capacity [17]. It may also promote ferroptosis in diffuse large B-cell lymphoma and acute lymphoblastic leukemia [18,19]. Specifically, Song et al. reported that *PAQR3* overexpression suppresses GSH levels in diffuse large B-cell lymphoma cells, while promoting Malondialdehyde (MDA), Reactive Oxygen Species (ROS), and $Fe2^{+}$ levels [18]. Jin et al. found that *PAQR3* overexpression enhances MDA, Dichlorofluorescein (DCF), and $Fe2^{+}$ levels in acute lymphoblastic leukemia cells

[19]. Additionally, *PAQR3* can inhibit the Hypoxia-Inducible Factor 1a (HIF-1α)/E1A Binding Protein p300 (p300), Beclin 1 (BECN1)/autophagy, and Epidermal Growth Factor Receptor (EGFR)/autophagy pathways to suppress lung cancer and renal cell progression [28,29].

Decreased PAQR3 expression as a biomarker for poor prognosis in cancer patients

Table 6 presents indicators related to the Prognosis and pathological features associated with *PAQR3* overexpression in cancer patients. It is better to mention that the overexpression is associated with cancer patient favourable characteristics related to metastasis, pathological stage, tumor size, and diagnosis [7,8,10,11,14,16-18,21,23,24,26,27]. Specifically, decreased *PAQR3* expression levels are significantly correlated with shorter overall survival (OS) in patients with lung cancer, hepatocellular carcinoma, diffuse large B-cell lymphoma, breast cancer, esophageal cancer, and gastric cancer [10,14,18,21,24,26]. Furthermore, reduced *PAQR3* levels significantly correlate with shorter disease-Free survival (DFS) in patients with hepatocellular carcinoma, breast cancer, esophageal cancer, and gastric cancer [14,21,24,27]. Additionally, decreased *PAQR3* expression is significantly associated with pathological staging, subtype, tissue differentiation, metastasis, tumor size, and diagnosis in lung cancer patients [10,11]. It is also related to factors such as Helicobacter pylori, venous invasion, invasion depth, lymph node metastasis, pathological stage, age, tumor size, tumor differentiation, and distant metastasis in gastric cancer patients [26,27]. The relationship between *PAQR3* expression and patient prognosis may be confounded by other factors such as co-existing genetic mutations, the patient's immune status, or the use of concurrent medications. Future studies should take these factors into account to accurately assess the prognostic value of *PAQR3*.

CONCLUSION

Research has established that *PAQR3* functions as a tumor suppressor gene in cancer, and activation of *PAQR3* expression may improve patient prognosis. This is associated with various signaling mechanisms, including PI3K/AKT, EMT, ferroptosis, and Ras/Raf/MEK/ERK pathways, and is regulated by miR-543, miR-203a-3p, miR-15b, HER2, and 5-Aza-CdR, thereby influencing cancer cell growth

and metastasis (Table 5). The anti-tumor mechanism of *PAQR3* shows significant heterogeneity. In certain cancer types (such as diffuse large B-cell lymphoma), *PAQR3* enhances ferroptosis in Diffuse large B-cell lymphoma through the PI3K/AKT [18]. However, in other cancers (such as stomach cancer), it may function through different pathways. This difference may be related to the cancer-specific expression of tissue-specific microenvironments, mutation backgrounds, and upstream regulatory factors. In addition, although epigenetic drugs such as 5-Aza-CdR can demethylate and activate the expression of *PAQR3*, their clinical transformation faces limitations such as strong toxicity and prominent drug resistance, and there is an urgent need to develop more precise epigenetic intervention strategies.

However, studies on *PAQR3* are still in their early stages. Future research should focus more closely on the upstream and downstream mechanisms of *PAQR3* to better understand the pathogenesis and ultimately block disease progression. Additionally, the anti-cancer treatment targeting *PAQR3* still faces multiple challenges. Firstly, the heterogeneity of the mechanism requires the design of specific treatment strategies for different cancer types, and it is necessary to precisely regulate the *PAQR3* pathway in combination with the molecular typing and microenvironment characteristics of the tumor. Secondly, the development of drugs targeting *PAQR3* needs to overcome the urgent problems such as low delivery efficiency and poor stability. In addition, the *PAQR3* pathway interacts with multiple signaling networks. Targeted therapy may cause off-target effects, and the safety of treatment needs to be enhanced through highly selective delivery systems (such as nanocarriers or conditionally activated gene editing tools). Ultimately, the combined targeting of upstream regulatory factors (such as HER2 inhibitors) of *PAQR3* or downstream effector pathways (such as ferroptosis inducers) may be an important direction for enhancing efficacy and overcoming drug resistance. Future research could utilize patient-derived organoids to more accurately recapitulate the in vivo tumor microenvironment and study the roles of *PAQR3*. Overall, this review summarizes the mechanisms and clinical significance of *PAQR3*, providing a new theoretical foundation and direction for cancer treatment.

Conflicts of interest: Authors declare no conflicts of interest.

Funding: This work was funded by Zunyi City Joint Fund (Zun Shi Ke He HZ Word (2024) No. 441).

Data availability: All data were obtained from published literature, open-access resources, or the corresponding author.

Submitted: December 8, 2025

Accepted: January 18, 2026

Published online: January 29, 2026

REFERENCES

1. Xu J, Zhang Z, Qian M, Wang S, Qiu W, Chen Z, et al. Cullin-7 (CUL7) is overexpressed in glioma cells and promotes tumorigenesis via NF-κB activation. *J Exp Clin Cancer Res*. 2020;39(1):59–59. https://doi.org/10.1186/s13046-020-01553-7
2. Lin C, Wu Y, Qian Y, Li J, He Y, Yu H, et al. SATB2 promotes radiation resistance of esophageal squamous cell carcinoma by regulating epithelial-to-mesenchymal transition via the Wnt/β-catenin pathway. *Front Oncol*. 2025;15:1543426. https://doi.org/10.3389/fonc.2025.1543426
3. Zhang Z, Mei Y, Hou M. Knockdown RBM15 inhibits colorectal cancer cell proliferation and metastasis via N6-methyladenosine (m6A) modification of MyD88 mRNA. *Cancer Biother Radiopharm*. 2022;37(10):976–986. https://doi.org/10.1089/cbr.2021.0226
4. Yan Q, Sun Q, Feng Y, Hu Q, Zhu J. ATP1B3 may promote glioma proliferation and migration through MAPK/NF-κB signaling pathway. *Front Oncol*. 2025;15:1537687. https://doi.org/10.3389/fonc.2025.1537687
5. Guo Q, Ke XX, Liu Z, Gao WL, Fang SX, Chen C, et al. Evaluation of the prognostic value of STEAP1 in lung adenocarcinoma and insights into its potential molecular pathways via bioinformatic analysis. *Front Genet*. 2020;11:242. https://doi.org/10.3389/fgene.2020.00242
6. Lei L, Ling ZN, Chen XL, Hong LL, Ling ZQ. Characterization of the Golgi scaffold protein PAQR3, and its role in tumor suppression and metabolic pathway compartmentalization. *Cancer Manag Res*. 2020;12:353–362. https://doi.org/10.2147/CMAR.S210919
7. Ma Z, Wang Y, Piao T, Li Z, Zhang H, Liu Z, et al. The tumor suppressor role of PAQR3 in osteosarcoma. *Tumour Biol*. 2015;36(5):3319–3324. https://doi.org/10.1007/s13277-014-2964-z
8. Gao J, Ma XP, Deng FS, Jiang L, Jia WD, Li M. Associations of the BRAF V600E mutation and PAQR3 protein expression with papillary thyroid carcinoma

clinicopathological features. *Pathol Oncol Res*. 2020;26(3):1833–1841. https://doi.org/10.1007/s12253-019-00779-x

9. Tang SL, Gao YL, Hu WZ. PAQR3 inhibits the proliferation, migration and invasion in human glioma cells. *Biomed Pharmacother*. 2017;92:24–32. https://doi.org/10.1016/j.biopha.2017.05.046
10. Liang X, Sun B, Han J, Zhao X, Liu Z. Expression and clinical significance of progesterone and adiponectin receptor family member 3 in lung cancer. *Zhongguo Fei Ai Za Zhi*. 2017;20(4):259–263.
11. Guo Q, Ke XX, Fang SX, Gao WL, Song YX, Chen C, et al. PAQR3 inhibits non-small cell lung cancer growth by regulating the NF-κB/p53/Bax axis. *Front Cell Dev Biol*. 2020;8:581919. https://doi.org/10.3389/fcell.2020.581919
12. Li X, Li M, Chen D, Shi G, Zhao H. PAQR3 inhibits proliferation via suppressing PI3K/AKT signaling pathway in non-small cell lung cancer. *Arch Med Sci*. 2018;14(6):1289–1297. https://doi.org/10.5114/aoms.2017.72220
13. Yu L, Zhou L, Cheng Y, Sun L, Fan J, Liang J, et al. MicroRNA-543 acts as an oncogene by targeting PAQR3 in hepatocellular carcinoma. *Am J Cancer Res*. 2014;4(6):897–906.
14. Wu HG, Zhang WJ, Ding Q, Peng G, Zou ZW, Liu T, et al. Identification of PAQR3 as a new candidate tumor suppressor in hepatocellular carcinoma. *Oncol Rep*. 2014;32(6):2687–2695. https://doi.org/10.3892/or.2014.3532
15. Zhang C, Liu P, Huang J, Liao Y, Pan C, Liu J, et al. Circular RNA hsa_circ_0043280 inhibits cervical cancer tumor growth and metastasis via miR-203a-3p/PAQR3 axis. *Cell Death Dis*. 2021;12(10):888. https://doi.org/10.1038/s41419-021-04193-7
16. Li RH, Zhang AM, Li S, Li TY, Wang LJ, Zhang HR, et al. PAQR3 gene expression and its methylation level in colorectal cancer tissues. *Oncol Lett*. 2016;12(3):1773–1778. https://doi.org/10.3892/ol.2016.4843
17. Wang X, Li X, Fan F, Jiao S, Wang L, Zhu L, et al. PAQR3 plays a suppressive role in the tumorigenesis of colorectal cancers. *Carcinogenesis*.

2012;33(11):2228–2235.
https://doi.org/10.1093/carcin/bgs245

18. Song X, Zhang W, Yu N, Zhong X. PAQR3 facilitates the ferroptosis of diffuse large B-cell lymphoma via the regulation of LDLR-mediated PI3K/AKT pathway. *Hematol Oncol*. 2024;42(1):e3219.
https://doi.org/10.1002/hon.3219
19. Jin L, Tong L. PAQR3 inhibits proliferation and aggravates ferroptosis in acute lymphoblastic leukemia through modulation Nrf2 stability. *Immun Inflamm Dis*. 2021;9(3):827–839.
https://doi.org/10.1002/iid3.437
20. Qi LQ, Sun B, Yang BB, Lu S. MiR-15b facilitates breast cancer progression via repressing tumor suppressor PAQR3. *Eur Rev Med Pharmacol Sci*. 2020;24(2):740–748.
21. Li Z, Ling ZQ, Guo W, Lu XX, Pan Y, Wang Z, et al. PAQR3 expression is downregulated in human breast cancers and correlated with HER2 expression. *Oncotarget*. 2015;6(14):12357–12368.
https://doi.org/10.18632/oncotarget.3657
22. Chen J, Wang F, Xu J, He Z, Lu Y, Wang Z. The role of PAQR3 gene promoter hypermethylation in breast cancer and prognosis. *Oncol Rep*. 2016;36(3):1612–1618.
https://doi.org/10.3892/or.2016.4951
23. Bai G, Chu J, Eli M, Bao Y, Wen H. PAQR3 overexpression suppresses the aggressive phenotype of esophageal squamous cell carcinoma cells via inhibition of ERK signaling. *Biomed Pharmacother*. 2017;94:813–819.
https://doi.org/10.1016/j.biopha.2017.07.154
24. Bai G, Yang M, Zheng C, Zhang L, Eli M. Suppressor PAQR3 associated with the clinical significance and prognosis in esophageal squamous cell carcinoma. *Oncol Lett*. 2018;15(4):5703–5711.
https://doi.org/10.3892/ol.2018.8004
25. Zhou F, Wang S, Wang J. PAQR3 inhibits the proliferation and tumorigenesis in esophageal cancer cells. *Oncol Res*. 2017;25(5):663–671.
https://doi.org/10.3727/096504016X14761384026719
26. Wu YL, Hong LL, Ling ZN, Hu XY, Liu Z, Li P, et al. Golgi scaffold protein PAQR3 as a candidate suppressor of gastric cardia adenocarcinoma via regulating

TGF-β/Smad pathway. *J Clin Lab Anal*. 2022;36(9):e24617. https://doi.org/10.1002/jcla.24617

27. Ling ZQ, Guo W, Lu XX, Zhu X, Hong LL, Wang Z, et al. A Golgi-specific protein PAQR3 is closely associated with the progression, metastasis and prognosis of human gastric cancers. *Ann Oncol*. 2014;25(7):1363–1372. https://doi.org/10.1093/annonc/mdu168
28. Zhang Y, Jiang X, Qin X, Ye D, Yi Z, Liu M, et al. RKTG inhibits angiogenesis by suppressing MAPK-mediated autocrine VEGF signaling and is downregulated in clear-cell renal cell carcinoma. *Oncogene*. 2010;29(39):5404–5415. https://doi.org/10.1038/onc.2010.270
29. Cao Q, You X, Xu L, Wang L, Chen Y. PAQR3 suppresses the growth of non-small cell lung cancer cells via modulation of EGFR-mediated autophagy. *Autophagy*. 2020;16(7):1236–1247. https://doi.org/10.1080/15548627.2019.1659654
30. Huang W, Guo W, You X, Pan Y, Dong Z, Jia G, et al. PAQR3 suppresses the proliferation, migration and tumorigenicity of human prostate cancer cells. *Oncotarget*. 2016;8(33):53948–53958. https://doi.org/10.18632/oncotarget.9807
31. Zhao C, Li Y, Chen G, Wang F, Shen Z, Zhou R. Overexpression of miR-15b-5p promotes gastric cancer metastasis by regulating PAQR3. *Oncol Rep*. 2017;38(1):352–358. https://doi.org/10.3892/or.2017.5673
32. Qiao S, Guo W, Liao L, Wang L, Wang Z, Zhang R, et al. DDB2 is involved in ubiquitination and degradation of PAQR3 and regulates tumorigenesis of gastric cancer cells. *Biochem J*. 2015;469(3):469–480. https://doi.org/10.1042/BJ20150253
33. Guo W, You X, Xu D, Zhang Y, Wang Z, Man K, et al. PAQR3 enhances Twist1 degradation to suppress epithelial-mesenchymal transition and metastasis of gastric cancer cells. *Carcinogenesis*. 2016;37(4):397–407. https://doi.org/10.1093/carcin/bgw013
34. Guo Q, Liu XL, Zhai K, Chen C, Ke XX, Zhang J, et al. The emerging roles and mechanisms of PAQR3 in human cancer: pathophysiology and therapeutic implications. *Int J Gen Med*. 2023;16:4321–4328. https://doi.org/10.2147/IJGM.S422523

35. Zhai K, Miao XP, Ai SG, Guo Q, Zha RZ. Downregulation of PAQR3 expression predicts poor prognosis of patients with pan-cancer: a meta-analysis. *Front Oncol*. 2025;15:1574150. https://doi.org/10.3389/fonc.2025.1574150
36. You X, Gai Y, Wang Z, Wang Y, Ye J, Cao Y, et al. Transcriptomic and functional validation reveals PAQR3/P6-55 as potential therapeutic targets in colon cancer. *Biology (Basel)*. 2025;14(7):780. https://doi.org/10.3390/biology14070780
37. Ullah R, Yin Q, Snell AH, Wan L. RAF–MEK–ERK pathway in cancer evolution and treatment. *Semin Cancer Biol*. 2022;85:123–154. https://doi.org/10.1016/j.semcancer.2021.05.010
38. Huang X, Liu G, Guo J, Su Z. The PI3K/AKT pathway in obesity and type 2 diabetes. *Int J Biol Sci*. 2018;14(11):1483–1496. https://doi.org/10.7150/ijbs.27173
39. Glaviano A, Foo ASC, Lam HY, Yap KCH, Jacot W, Jones RH, et al. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. *Mol Cancer*. 2023;22(1):138. https://doi.org/10.1186/s12943-023-01827-6
40. Saitoh M. Involvement of partial EMT in cancer progression. *J Biochem*. 2018;164(4):257–264. https://doi.org/10.1093/jb/mvy047

TABLES AND FIGURES WITH LEGENDS

Table 1. Expression of PAQR3 in cancer

Type	N	Tissues	Cells	Cancer cells	Normal cell	Ref
Osteosarcoma	60	Down	Down	SOSP-9607, SAOS-2, MG63, U2OS	hFOB	7
Thyroid cancer	60	Down	-	-	-	8
Glioma	11	Down	Down	U251, U87, LN-18	1800	9
Lung cancer	106	Down	-	-	-	10
Lung cancer	60	Down	-	-	-	11
Lung cancer	20	Down	Down	SK-MES-1, A549, SPCA-1, H1229	BEAS-2B	12
Hepatocellular carcinoma	60	Down	Down	HepG2, Hep3B, Bel7402, SMMC-7721	HL-7792	13
Hepatocellular carcinoma	194	Down	-	-	-	14
Cervical cancer	40	Down	-	-	-	15
CRC	54	Down	-	-	-	16
CRC	62	Down	-	-	-	17
DLBCL	46	Down	Down	SUDHL4, OCI−LY19, U2932, OCI−LY10	HMy2.CIR	18
ALL	43	Down	-	-	-	19
Breast cancer	60	Down	Down	MDA-MB-231, BT474, SKBR3, MCF7	MCF-10A	20
Breast cancer	82	Down	-	-	-	21
Breast cancer	46	Down	-	-	-	22
ESCA	40	Down	Down	KYSE150, ECA-109, TE-1	HEsEpiCs	23
ESCA	80	Down	-	-	-	24

ESCA	-	-	Down	EC9706, TE13, ECA109	HEEC	25
Gastric cancer	166	Down	Down	HGC27, SGC7901	GES-1	26
Gastric cancer	300	Down	-	-	-	27
RCC	31	Down	-	-	-	28

Abbreviations: CRC: Colorectal cancer; RCC: Renal cell carcinoma; ESCA: Esophageal cancer; ALL: Acute lymphoblastic leukemia; DLBCL: Diffuse large B-cell lymphoma.

Table 2. The role of PAQR3 in cancer cell growth *in vitro*

Type	Cancer cells	Proliferation	Clone formation	Cycle	Apoptosis	Ref
Osteosarcoma	MG63	Inhibition	-	-	-	7
Glioma	U251, U87	Inhibition	-	-	-	9
Lung cancer	A549, H1299	Inhibition	Inhibition	Inhibition	Promotion	11
Lung cancer	A549, H1299	Inhibition	-	Inhibition	Promotion	12
Hepatocellular carcinoma	HepG2	Inhibition	-	-	-	13
Hepatocellular carcinoma	Hep-3B	Inhibition	Inhibition	-	-	14
Cervical cancer	MS751, HeLa	Inhibition	-	-	-	15
Colorectal cancer	SW-480	Inhibition	Inhibition	-	-	17
DLBCL	SUDHL4, U2932	Inhibition	-	-	-	18
ALL	CEM-C1, Jurkat	Inhibition	-	-	Promotion	19
Breast cancer	MCF7, SKBR3,	Inhibition	Inhibition	-	-	21

	MDA-MB-231, MDA-MB-468, MDA-MB-453					
Breast cancer	MCF-7	-	Inhibition			22
ESCA	ECA-109, TE-1	Inhibition	Inhibition	Inhibition	-	23
ESCA	ECA-109	Inhibition				25
Gastric cancer	HGC27	Inhibition	Inhibition	-	-	26
Gastric cancer	AGS	Inhibition	Inhibition	-	-	27
RCC	HUVEC	Inhibition	-	-	-	28
Lung cancer	HCC827	Inhibition	Inhibition	-	-	29
Prostate cancer	PC3, DU145	Inhibition	Inhibition	-	-	30
Gastric cancer	BGC-823, SGC-7901	Inhibition	-	-	-	31
Gastric cancer	AGS	Inhibition	Inhibition	-	-	32
Colon Cancer	HCT116, HCT115	Inhibition	Inhibition	-	-	36

Abbreviations: CRC: Colorectal cancer; RCC: Renal cell carcinoma; ESCA: Esophageal cancer; ALL: Acute lymphoblastic leukemia; DLBCL: Diffuse large B-cell lymphoma.

Table 3. The role of PAQR3 in cancer cell metastasis *in vitro*

Type	Cancer cells	Migration	Invasion	Wound healing	Tube formation	Ref
Osteosarcoma	MG63	Inhibition	Inhibition	-	-	7
Glioma	U251, U87	Inhibition	Inhibition	-	-	9
Hepatocellular carcinoma	HepG2	-	Inhibition	-	-	13

Cervical cancer	MS751, HeLa	Inhibition	Inhibition	Inhibition	-	15
Breast cancer	MDA-MB-231	Inhibition	Inhibition	-	-	20
Breast cancer	MCF7, SKBR3, MDA-MB-231, MDA-MB-468, MDA-MB-453	Inhibition	-	Inhibition	-	21
Breast cancer	MCF-7	-	Inhibition	-	-	22
ESCA	ECA-109, TE-1	-	Inhibition	-	-	23
ESCA	ECA-109	Inhibition	Inhibition	-	-	25
Gastric cancer	HGC27	Inhibition		Inhibition	-	26
Gastric cancer	AGS	Inhibition	-	Inhibition	-	27
RCC	HUVEC	Inhibition	-	Inhibition	Inhibition	28
Prostate cancer	PC3, DU145	Inhibition	-	Inhibition	-	30
Gastric cancer	BGC-823, SGC-7901	-	Inhibition	Inhibition	-	31
Gastric cancer	AGS	Inhibition	-	Inhibition	-	32
Gastric cancer	AGS	Inhibition	-	-	-	33
Colon Cancer	HCT116, HCT115	Inhibition	-	-	-	36

Abbreviations: RCC: Renal cell carcinoma; ESCA: Esophageal cancer.

Table 4. The role of PAQR3 in the tumorigenic potential of cancer cells in nude mice *in vivo*

Type	Cancer cells	Roles	Ref
Glioma	U251	Inhibition	9
Cervical cancer	-	Inhibition	15
CRC	SW-480	Inhibition	17
DLBCL	U2932	Inhibition	18
ESCA	ECA109	Inhibition	23
ESCA	ECA109	Inhibition	25
Lung cancer	HCC827	Inhibition	29
Gastric cancer	AGS	Inhibition	33

Abbreviations: CRC: Colorectal cancer; ESCA: Esophageal cancer; DLBCL: Diffuse large B-cell lymphoma.

Table 5. Molecular mechanisms involved in PAQR3 signaling

Type	Downstream pathways	Upstream pathways	Ref
Osteosarcoma	p-ERK	-	7
Glioma	PI3K/AKT	-	9
Lung cancer	Nf-kB/p53	-	11
Lung cancer	PI3K/AKT	-	12
Hepatocellular carcinoma	-	miR-543/PAQR3 ↓	13
Cervical cancer	EMT, p-AKT, p-ERK	circ_0043280/miR-203a-3p/PAQR3↑	15
CRC	EGF/p-ERK, EGF/β-catenin	-	17
DLBCL	LDLR/PI3K/AKT, ferroptosis	-	18
ALL	Nrf2/ferroptosis	-	19
Breast cancer	-	miR-15b/PAQR3 ↓	20
Breast cancer	-	HER2/PAQR3 ↓	21

Breast cancer	-	5-Aza-CdR/PAQR3↑	22
ESCA	P27/p21/CYCLD, p-ERK	5-Aza-CdR/PAQR3↑	23
ESCA	EMT, p-AKT	-	24
ESCA	EMT, p-ERK	-	25
Gastric cancer	TGF-β/Smad/EMT	-	26
Gastric cancer	p-AKT, p-ERK, EMT	-	27
RCC	VEGF/ERK, HIF-1α/p300	-	28
Lung cancer	BECN1/Autophagy, EGFR/Autophagy	ATG7/PAQR3↑	29
Prostate cancer	p-AKT, p-ERK, EMT	-	30
Gastric cancer	EMT	miR-15b-5p/PAQR3 ↓	31
Gastric cancer	EGF/ERK, AKT, insulin	DDB2/PAQR3 ↓	32
Gastric cancer	Twist1/EMT	-	33
Colon Cancer	PI3K/AKT	P6-55/PAQR3↑	36

Abbreviations: CRC: Colorectal cancer; RCC: Renal cell carcinoma; ESCA: Esophageal cancer; ALL: Acute lymphoblastic leukemia; DLBCL: Diffuse large B-cell lymphoma; EMT: Epithelial-mesenchymal transition.

Table 6. Clinicopathological features related to PAQR3 in cancer

Type	PAQR3 expression	Prognosis	Clinical characteristics	Ref
Osteosarcoma	Down	-	Metastasis↑	7
Thyroid cancer	Down	-	Extrathyroidal-extension	8
Lung cancer	Down	OS↓	Pathological stages↑, tissue differentiation ↓ , metastasis↑	10
Lung cancer	Down	-	Tumor size↑, diagnosis	11
Hepatocellular carcinoma	Down	OS↓, DFS↓	AFP↑, tumor size↑, tumor grade ↓ , recurrence↑	14
CRC	Down	-	Tissue differentiation↓, lymph node metastasis↑, depth of invasion↑	16

CRC	Down	-	Gender, tumor grade↓	17
DLBCL	Down	OS↓	-	18
Breast cancer	Down	OS↓, DFS↓	Tissue differentiation↓, pathological stage↑, Her2 status	21
ESCA	Down	-	Pathological stage↑, lymph node metastasis↑	23
ESCA	Down	OS↓, DFS↓	Nationality, tumor size↑, lymph node metastasis↑, recurrence↑	24
Gastric cancer	Down	OS↓	Helicobacter pylori, venous invasion↑, invasion depth↑, lymph node metastasis↑, pathological stage↑	26
Gastric cancer	Down	DFS ↓	Age, Helicobacter pylori, tumor size↑, tumor differentiation↓, venous invasion↑, lymph node metastasis↑, invasion depth↑, pathological stage↑, distant metastasis↑	27

Abbreviations: CRC: Colorectal cancer; ESCA: Esophageal cancer; DLBCL: Diffuse large B-cell lymphoma.

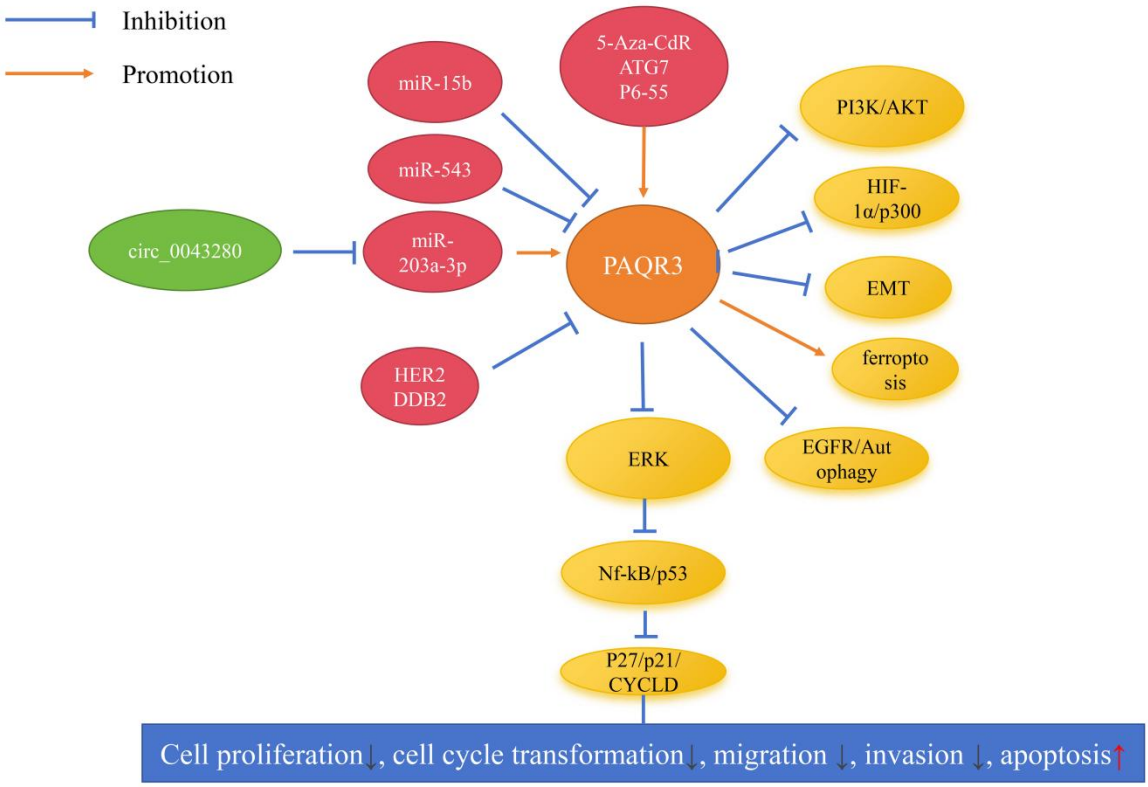

Figure 1. PAQR3-centered signaling network. Schematic summary of reported upstream regulators and downstream effectors of PAQR3 in cancer, with emphasis on the PAQR3/Ras/Raf/MEK/ERK axis discussed in the text. Upstream non-coding RNAs (circ_0043280; miR-15b, miR-543, miR-203a-3p) and protein/epigenetic regulators (HER2/ERBB2, DDB2; 5-Aza-2′-deoxycytidine (5-Aza-CdR), ATG7, p6-55) modulate PAQR3 expression/activity. Functionally, PAQR3 attenuates ERK signaling (including reduced ERK phosphorylation reported in multiple tumor models) and influences downstream modules such as NF-κB/p53 and cell-cycle regulators (p21/CDKN1A, p27/CDKN1B, cyclin D1), thereby restraining tumor cell proliferation, cell-cycle progression, migration and invasion, while promoting apoptosis. PAQR3 also intersects with additional pathways implicated in tumor biology, including PI3K/AKT, HIF-1α/p300, EMT, EGFR-linked autophagy, and ferroptosis (context-dependent). Blue blunt-ended lines indicate inhibition; orange arrows indicate activation/promotion. **Abbreviations:** PAQR3: Progestin and adipoQ receptor family member 3; circ_0043280: Circular RNA circ_0043280; miR: MicroRNA; HER2/ERBB2: Human epidermal growth factor receptor 2; DDB2: Damage-specific DNA binding protein 2; 5-Aza-CdR: 5-Aza-2′-deoxycytidine; ATG7: Autophagy related 7; EGFR: Epidermal growth factor receptor; ERK: Extracellular

signal-regulated kinase; NF-κB: Nuclear factor kappa B; p53: Tumor protein p53; CDKN1A/p21: Cyclin-dependent kinase inhibitor 1A; CDKN1B/p27: Cyclin-dependent kinase inhibitor 1B; PI3K: Phosphatidylinositol 3-kinase; AKT: AKT serine/threonine kinase; HIF-1α: Hypoxia-inducible factor-1 alpha; EP300/p300: Histone acetyltransferase p300; EMT: Epithelial–mesenchymal transition.