R E V I E W

The Emerging Roles and Mechanisms of PAQR3 in Human Cancer: Pathophysiology and Therapeutic Implications

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Abstract: Cancer was one of the common causes of death in the world, and it was increasing year by year. At present, Progestin and AdipoQ receptor family member 3 (PAQR3) was widely studied in cancer. It has been found that PAQR3 was down regulated in various cancers, such as the gastric cancer, osteosarcoma, glioma, hepatocellular carcinoma, acute lymphoblastic leukemia, laryngeal squamous cell carcinoma, esophageal cancer, breast cancer, non-small cell lung cancer, and colorectal cancer. The decreased expression of PAQR3 was associated with short overall survival and disease-free survival in patients with gastric cancer, hepatocellular carcinoma, laryngeal squamous cell carcinoma, esophageal cancer, breast cancer, and non-small cell lung cancer. PAQR3 could inhibit cancer progression by using the Ras/Raf/MEK/ERK, PI3/AKT, EMT and other mechanisms, and was negatively regulated by the miR-543, miR-15b-5p and miR-15b. The roles and signaling mechanisms of PAQR3, and the relationship between the expression of PAQR3 and prognosis in cancer progression are reviewed in this article, and provides new tumor marker and idea to guide cancer treatment.

Keywords: PAQR3, overall survival, disease-free survival, tumor suppressor

Introduction

Cancer has a high morbidity and mortality rate worldwide, imposing a significant burden on society.[1] Therefore, new cancer treatment methods are required to reduce the negative impact of cancer on society. In recent years, targeted therapy has given cancer patients new hope for a better prognosis.[2–6] Progestin and adipoQ receptor (PAQR) family member 3 (PAQR3) gene is located on human chromosome 4 (4q21.21) and belongs to the PAQR family, which consists of 11 members. The PAQR family is divided into three categories, namely I, II, and III, based on their physical characteristics.[7–9] PAQR3 encodes a seven-transmembrane protein that is found on the Golgi apparatus of mammalian cells. It is also known as Raf kinase trapping to Golgi and has recently been identified as a tumor suppressor. PAQR3 plays a crucial role in controlling proliferation, ERK phosphorylation, and metastasis, thereby inhibiting cancer development.[10–14] For example, PAQR3 suppresses tumor occurrence and development, as well as inhibits the proliferation and transformation of human malignant melanoma A375 cells.[10] In addition, PAQR3 expression is significantly decreased in colorectal cancer (CRC) tissues. Overexpression of PAQR3 has demonstrated an impact on the growth and migration abilities of colorectal cancer (CRC). This implies that PAQR3 could serve as a potential target for tumor treatment by promoting ERK phosphorylation and facilitating the accumulation of β-catenin in the nucleus. Conversely, the knockout of PAQR3 enhances the activity of β-catenin,[11] indicating that PAQR3 could be a new target for tumor treatment. Therefore, this review aims to offer recommendations for the clinical investigation of novel tumor markers and approaches to cancer treatment.

PAQR3 Structural Features

The PAQR3 gene is located on human chromosome 4 (4q21.21) and is highly expressed in the brain, testis, and small intestine.[15] PAQR3 has seven transmembrane domains, which have low sequence similarity to the seven transmembrane structures of G protein-coupled receptors, which are considered paralogs.[15] In addition, Luo et al found that PAQR3 is a type III membrane protein with its N-terminus facing the cytoplasm.[16] The second, fourth, and sixth rings of PAQR3 were thought to face the same direction as the N-terminus, while the C-terminus faces the Golgi apparatus. The first ring is required for the positioning of PAQR3 on the Golgi apparatus, while the third ring regulates it and interacts with Raf-1 to perform its function.

PAQR3 Affects the Biological Functions

The Roles of PAQR3 in Tumorigenesis and Development

The Roles of PAQR3 in Cancer Cell Growth

Numerous studies have shown that cell proliferation and apoptosis play important roles in tumor cell growth and were closely related to cell cycle regulation.[17] Tumors develop as a result of abnormal cell cycle regulation.[17,18] Therefore, understanding tumor growth mechanisms and correcting abnormal cycle regulation may aid in the treatment of tumorigenesis. Recent studies have found that PAQR3 plays an important role by inhibiting cancer cell proliferation, colony formation and inducing cell apoptosis.[10,12,14,19–27] For example, Li et al found that overexpression of PAQR3 inhibits the proliferation of non-small cell lung cancer (NSCLC) cells, induces cell apoptosis, and promotes cell cycle arrest in the G0/G1 phase. In contrast, interference with PAQR3 gene expression promotes NSCLC cell proliferation while inhibiting apoptosis. PAQR3 may act as a tumor suppressor in NSCLC cells.[19–21] In addition, Tang et al found that increasing PAQR3 expression inhibits the proliferation of glioma cells in vitro and attenuates the growth of nude mouse tumor xenogeneic models in vivo.[14] These results demonstrate that PAQR3 functions as a tumor suppressor gene in various types of cancer cells. (Table 1).

The Roles of PAQR3 in the Metastasis of Malignant Tumors

Metastasis is the most important step in tumor progression. Metastasis of early-stage cancer via lymph nodes or blood pathways may result in a poor long-term prognosis for cancer patients, thereby increasing the economic burden on people all over the world.[35–39] The rate of early metastasis in cancer patients has a significant impact on their treatment and prognosis. Numerous studies have confirmed that PAQR3 inhibits tumor metastasis and may improve the long-term prognosis of cancer patients (Table 2). This indicates that PAQR3 overexpression is closely related to the invasion and metastasis of various cancers, including GC, glioma, and prostate cancer.

PAQR3 is Involved in Cancer-Related Mechanisms

Ras/Raf/MEK/ERK Signaling Pathway

The Ras/Raf/MEK/ERK signaling pathway is related to the cell proliferation, apoptosis, differentiation, and the cell cycle,[44] and its dysregulation is associated with the progression of various cancers, including CRC, GC, and skin cancer.[11,12,27] PAQR3 binds to Raf-1 and anchors it to the Golgi apparatus, thereby inhibiting downstream signaling.[10,45] In vitro studies confirmed that deletion of the PAQR3 gene induces ERK phosphorylation and proliferation of epidermal keratinocytes, indicating that PAQR3 acts as a tumor suppressor in skin cancer cells.[27] PAQR3 overexpression inhibits ERK phosphorylation in melanoma A375 cells, colon cancer SW-480 cells, osteosarcoma MG-63 cells, laryngeal cancer Hep2 cells, prostate cancer PC3 and DU145 cells, as well as esophageal cancer EC9706, ECA-109 and TE-1 cells.[10,11,13,24,25,29–31] Among them, PAQR3 gene silencing in prostate cancer cells increases serum-induced ERK phosphorylation.[25] U0126, a specific MEK inhibitor, has been shown in osteosarcoma, laryngeal cancer, colon cancer, and EC cells to reverse the cell proliferation effects of PAQR3 silencing.

PI3K/AKT Signaling Pathway

The PI3K/AKT signaling pathway is one of the most common pathways involved in tumor growth and metastasis. PAQR3 inhibits AKT signaling activation by inhibiting the signal transduction of the G protein Gβγ subunit and the spatial regulation of the PI3K p110a subunit.[12,46,47] Knocking out the PAQR3 gene in mouse embryonic fibroblasts (MEFs) under physiological conditions has been found to increase lysophosphatidic acid (LPA)-induced AKT phosphorylation and substrate glycogen synthase kinase 3 beta (GSK3β) phosphorylation, resulting in the increased expression of

Table 1 The Role of PAQR3 in Tumor Growth

Cancer Type	Culture Pattern	Cell level	Animal Level	Signaling Pathways	Role	Ref
Melanoma	2D culture	Growth; Colony formation	Tumor-forming ability	Raf/ERK	Antioncogene	[10]
CRC	2D culture	Growth, colony formation	Tumor-forming ability	Ras/Raf/MEK/ERK	Antioncogene	[11]
GC	2D culture	Growth; Colony formation	–	ERK, AKT, TGF-β/Smad	Antioncogene	[12,24]
Osteosarcoma	2D culture	Growth	–	ERK	Antioncogene	[13]
Glioma	2D culture	Growth	Tumor-forming ability	PI3/AKT	Antioncogene	[14]
NSCLC	2D culture	Growth: Cycle; Apoptosis; Colony formation	Tumor-forming ability	EGFR, Autophagy, NF-κB/p53/Bax, PI3/AKT	Antioncogene	[19–21]
HCC	2D culture	Growth; Colony formation	–	–	Antioncogene	[22]
Prostate cancer	2D culture	Growth; Colony formation	Tumor-forming ability	ERK, AKT	Antioncogene	[25]
ALL	2D culture	Growth; Apoptosis	–	Nrf2	Antioncogene	[26]
SC	2D culture	Cell growth; Apoptosis	–	RAF-1/ERK	Antioncogene	[27]
LSCC	2D culture	Growth	–	ERK	Antioncogene	[28]
EC	2D culture	Growth; Cycle; Colony formation	Tumor-forming ability	Raf-1/ERK, AKT, p27, p21, cyclin D1, CDK4, CDK2, Ki-67	Antioncogene	[29–31]
BC	2D culture	Growth; Colony formation	–	–	Antioncogene	[32]
Cervical cancer	2D culture	Growth	–		Antioncogene	[33]
ccRCC	2D culture	Growth	–	Raf/ERK/MEK/VEGF	Antioncogene	[34]

Abbreviations: GC, gastric cancer; HCC, hepatocellular carcinoma; CRC, colorectal cancer; ALL, acute lymphoblastic leukemia; NSCLC, non-small cell lung cancer; LSCC, laryngeal squamous cell carcinoma; EC, esophageal Cancer; ccRCC, clear cell renal cell carcinoma; SC, Skin carcinogenesis.

Table 2 The Role of PAQR3 in Tumor Metastasis

Cancer Type	Culture Pattern	Cell Level	Signaling Pathways	Role	Ref
GC	2D culture	Invasion, migration	Twist1, EMT	Antioncogene	[12,24,40,41]
Osteosarcoma	2D culture	Invasion, migration	EMT	Antioncogene	[13]
Glioma	2D culture	Invasion, migration	–	Antioncogene	[14]
HCC	2D culture	Invasion	–	Antioncogene	[22,23]
Prostate cancer	2D culture	Invasion, migration	EMT	Antioncogene	[25]
LSCC	2D culture	Invasion	–	Antioncogene	[28]
EC	2D culture	Invasion, migration	EMT	Antioncogene	[30]
BC	2D culture	Invasion, migration	–	Antioncogene	[32,42,43]
ccRCC	2D culture	Migration, angiogenesis	VEGF	Antioncogene	[34]

Abbreviations: GC, gastric cancer; HCC, hepatocellular carcinoma; BC, breast cancer; LSCC, laryngeal squamous cell carcinoma; EC, esophageal cancer; EMT, epithelial-mesenchymal transition; ccRCC, clear cell renal cell carcinoma.

tumor suppressor p53 and its downstream targets p21 and p16.[48] In addition, the upregulation of PAQR3 gene expression in prostate cancer cells inhibits AKT phosphorylation and epithelial-mesenchymal transition (EMT) characteristics. On the contrary, knocking out the PAQR3 gene has been found to increase serum-induced AKT phosphorylation and EMT characteristics.[25] Overexpression of PAQR3 in glioma cells inhibits the phosphorylation of PI3K and AKT. Wortmannin,

an AKT inhibitor, potentiates the inhibitory effect of PAQR3 on glioma cell proliferation and invasion. The AKT activator SC79 mitigates the inhibitory effect of PAQR3 on glioma cell proliferation and invasion.[14]

EMT Process

EMT process is an important biological process that allows cells derived from epithelial cells to acquire migration and invasion capabilities. It is critical to understand the molecular mechanism that regulates the EMT process of malignant tumor cells.[39] Zhao et al found that miR-15b-5p promotes the migration, invasion, and EMT process in gastric cancer (GC) cells, whereas increasing PAQR3 expression reverses this effect.[40,41] Furthermore, Ling et al found that PAQR3 overexpression negatively regulates GC cell migration and EMT.[12] Twist1 is also an important transcription factor involved in EMT and tumor metastasis.[49,50] Guo et al confirmed that PAQR3 promotes Twist1 degradation and inhibits GC cell metastasis by regulating the EMT process.[40] Tang et al found that PAQR3 overexpression inhibits glioma cell migration and invasion and prevents the EMT process.[14] Huang et al found that PAQR3 decreases the expression of EMT in prostate cancer PC3 cells and regulates prostate cancer cell invasion and metastasis.[25]

Autophagy

PAQR3 induces autophagy during starvation via the AMPK and MTORC1 signaling pathways.[20] During the growth and proliferation of NSCLC cells, PAQR3 promotes autophagy in cancer cells by EGFR inhibitor (erlotinib), blocking the interaction between BECN1 and the activated form of EGFR, and inhibiting BECN1 tyrosine phosphorylation. This indicates that PAQR3 regulates autophagy via the EGFR and inhibits NSCLC progression.[20]

Other Signaling Pathways

Abnormal hypermethylation of the CPG island in the promoter region of the tumor suppressor gene could cause its own transcription inactivation, thereby silencing it, which was involved in the occurrence and development of cancer. Lounglaithong et al found that the methylation of the PAQR3 promoter region is increased in prostate cancer. The rate of PAQR3 hypermethylation is associated with nerve infiltration.[51] Chen et al found that PAQR3 overexpression or silencing had no effect on HER2 mRNA expression in breast cancer (BC) cells, whereas inhibiting HER2 gene expression increases PAQR3 gene expression in BC cells and inhibits BC cell growth and migration.[32,42] The demethylating agent 5-Aza-dC increases PAQR3 gene expression in BC cells while inhibiting clonal formation and invasion.[42] Therefore, reducing abnormal methylation of the PAQR3 promoter region may play a direct or indirect role in the development of BC, CRC, and prostate cancer.

In addition, miRNA mainly regulates the expression of target mRNAs by binding to the 3' untranslated region (UTR), thus playing an important role in human development and various pathological conditions.[52,53] Figure 1 shows that miR-543, miR-203a-3p, miR-15b-5p, and miR-15b can inhibit PAQR3 mRNA and protein expression, thereby promoting the proliferation, migration, and invasion of liver cancer, GC, and BC.[23,24,33,40,43]

Decreased Expression of PAQR3 is Associated with the Poor Prognosis of Cancer Patients

In general, the expression of PAQR3 is low in pan-cancer tissues, and the levels of PAQR3 expression are associated with the prognosis of EC, HCC, GC, and others (Table 3). Ling et al reported that PAQR3 mRNA and protein expression decreased in GC tissues while the methylation rate increased. PAQR3 expression has been linked to *Helicobacter pylori* infection, tumor size, tumor stage, vein and lymphatic invasion, distant metastasis, and lymph node metastasis. In GC patients, the rate of PAQR3 methylation has been linked to the depth of tumor invasion, lymph node metastasis, and TNM staging. GC patients with elevated PAQR3 expression were found to have better overall survival (OS) and disease-free survival (DFS).[12,24] Wu et al found that the expression of PAQR3 in HCC tissues is significantly decreased and is associated with tumor size, grade, and recurrence. The Kaplan–Meier survival curve revealed a relationship between low PAQR3 expression and poor prognosis in HCC patients. PAQR3 expression is an independent prognostic marker for OS and DFS in HCC patients.[22] Liang et al found that the expression of PAQR3 in lung cancer is decreased and is associated with TNM stage, lymph node metastasis, pathological type, and degree of differentiation in lung cancer patients. PAQR3 expression is associated with a poor prognosis.[19,21] Bai et al found that the expression of PAQR3 is significantly
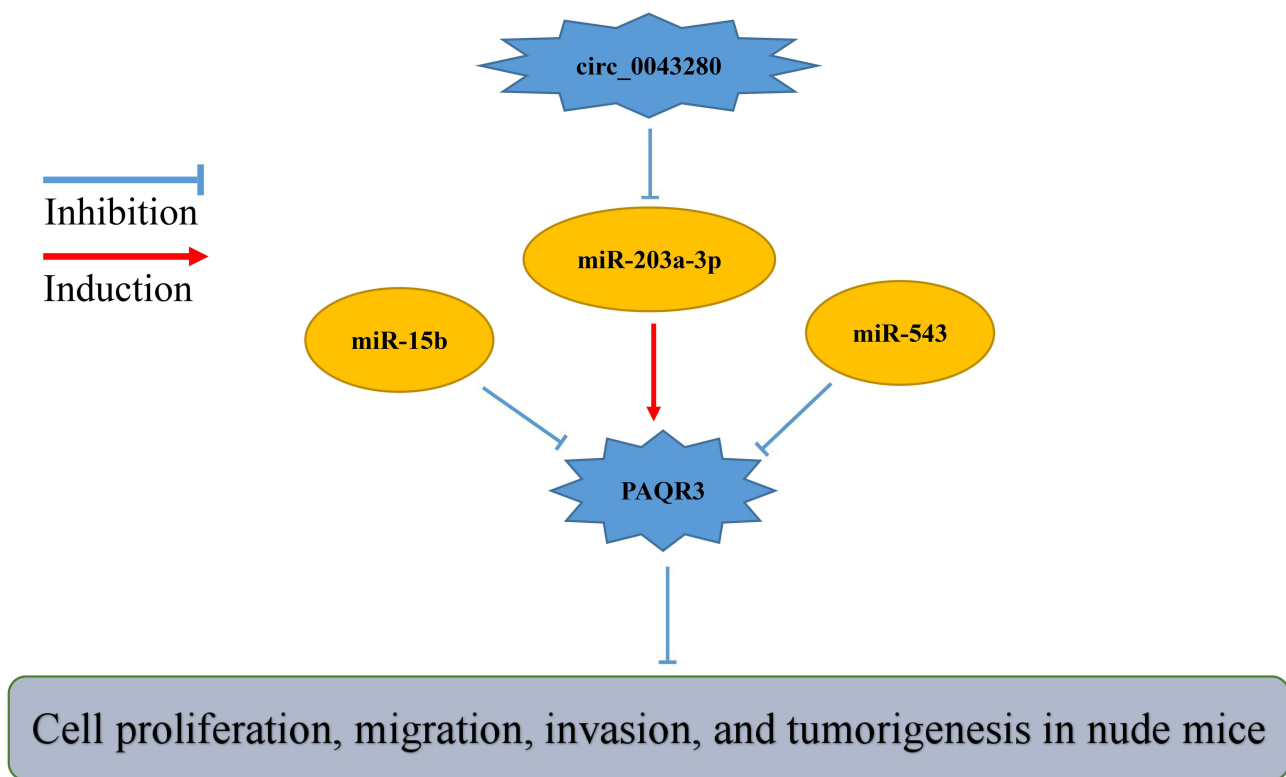
Figure 1 The miRNAs-PAQR3 signaling pathway in cancer progression.

decreased in esophageal squamous cell carcinoma (ESCC) tissue than in adjacent tissues and is associated with race, tumor size, lymph node metastasis, and local recurrence. Decreased PAQR3 expression has been linked to a poor prognosis and is an independent prognostic indicator in ESCC patients.[29] An increase in the methylation rate of the gene promoter region decreases the expression of tumor suppressor genes, resulting in tumor development. Chen et al found that the degree of methylation in the PAQR3 promoter region is increased in BC tissues, and the probability of a poor prognosis in BC patients increases with the rate of methylation.[42] These findings indicate that the PAQR3 expression

Table 3 The Prognostic Value of PAQR3 in Clinical Patients

Cancer	Tissue Expression	Prognosis	Ref
GC	Down	DFS, OS	[12,24]
Osteosarcoma	Down	NA	[13]
Glioma	Down	NA	[14]
HCC	Down	OS, DFS	[22,23]
ALL	Down	NA	[26]
LSCC	Down	NA	[28]
EC	Down	OS, DFS	[29,31]
BC	Down	OS, DFS	[32,42,43]
NSCLC	Down	OS	[19,21,54]
CRC	Down	Survival time	[11,55]
ccRCC	Down	NA	[34]

Abbreviations: GC, gastric cancer; HCC, hepatocellular carcinoma; LSCC, laryngeal squamous cell carcinoma; EC, esophageal cancer; BC, breast cancer; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; ALL, acute lymphoblastic leukemia; OS, overall survival; ccRCC, clear cell renal cell carcinoma; DFS, disease-free survival; NA, Not Applicable.
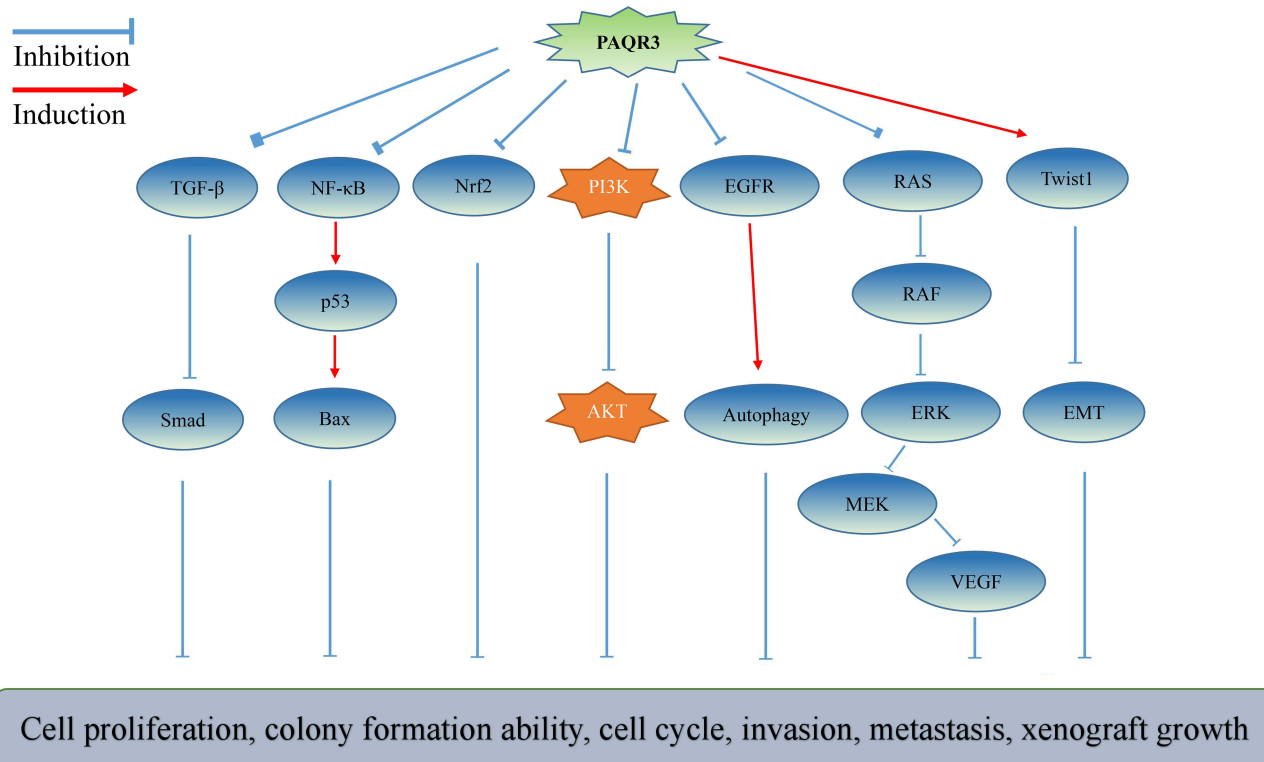
Figure 2 Downstream signaling of PAQR3 in cancer progression.

level is closely linked to the prognosis of cancer patients and that increasing PAQR3 expression may improve the prognosis of patients. Therefore, PAQR3 is a potential biomarker for cancer prognosis as well as a target for anti-tumor therapy.

Conclusions

PAQR3 has been extensively studied in the past decades, particularly its roles in cancer initiation, progression, metastasis, and clinical outcomes. PAQR3 may act as a tumor suppressor and is related to the poor prognosis for various cancers, such as NSCLC, EC, and HCC, which are associated with hypermethylation of the PAQR3 promoter region and negative regulation of overexpression of miR-543, miR-15b-5p, and miR-15b (Figure 1). PAQR3 can further suppress cancer progression by inhibiting Raf/MEK/ERK, PI3K/AKT, TGF-β/Smad, and autophagy pathways (Figure 2). Although the mechanisms mentioned above have been identified, some questions remain unanswered. Are there, for example, other factors that decrease PAQR3 expression levels? Does PAQR3 play the same tumor suppressor role in cancer resistance? In general, it is essential to conduct comprehensive research on the upstream and downstream mechanisms of PAQR3, as well as its interactions with other molecules. This research holds paramount importance in understanding the role of PAQR3 in cancer, evaluating its correlation with prognosis in cancer patients, and advancing the potential application of PAQR3 in cancer treatment.

Abbreviations

PAQR3, progestin and adipoQ receptor family member 3; EMT, epithelial-mesenchymal transition; GC, gastric cancer; HCC, hepatocellular carcinoma; ALL, acute lymphoblastic leukemia; LSCC, laryngeal squamous cell carcinoma; EC, esophageal cancer; BC, breast cancer; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; OS, overall survival; DFS, disease-free survival.

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