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Review Article

PAQR3: a novel tumor suppressor gene

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Abstract: PAQR3, also known as RKTG (Raf kinase trapping to Golgi), is a member of the progestin and adipoQ receptor (PAQR) family. The role of PAQR3 as a tumor suppressor has recently been established in different types of human cancer in which PAQR3 exerts its biological function through negative regulation of the oncogenic Raf/MEK/ERK signaling. Multiple studies have found that PAQR3 downregulation frequently occurs in human cancers and is very often associated with tumor progression and shortened patients' survival. Moreover, restoring the expression of PAQR3 could induce apoptosis and inhibit proliferation and invasiveness of cancer cells. Downregulation of PAQR3 by oncogenic microRNAs has also been reported. In this review, we summarized current knowledge concerning the role of PAQR3 in tumor development. To our knowledge, this is the first review on the role of this novel tumor suppressor.

Keywords: PAQR3, tumor suppressor, cancer, miRNAs

Introduction

Cancer, which encompasses entities of different neoplastic diseases with varying etiologic, genomic, histological and clinical characteristics, is a major public health issue, contributing to one in four deaths in the world [1-5]. Despite recent advances in its therapeutic strategies, effective management of cancer remains elusive owing to inter- and intra-tumoral heterogeneities as well as the common occurrence of drug resistance [1-3]. Therefore, it is necessary to elucidate molecular mechanisms that are commonly involved in different types of cancer in order to identify novel markers for early diagnosis and druggable targets for effective treatment.

PAQR3 was recently discovered as a novel tumor suppressor deregulated in different types of human cancer [4, 5]. PAQR3 belongs to the family of Progestin and AdipoQ Receptor (PAQR) and is a seven-transmembrane protein localized in the Golgi apparatus in mammalian cells [6, 7]. In this review, we will summarize the known function of PAQR3 as well as the causes and consequences of its deregulation in tumorigenesis.

Structural features, expression patterns and biological roles of PAQR3

PAQR family proteins include a group of transmembrane proteins broadly expressed in many species, including eubacteria, archae, *Caenorhabditis elegans* and mammals [8-10]. In mammalian genomes, PAQR family proteins are composed of 11 members-PAQR1-11 [11]. It was predicted that each PAQR protein has seven transmembrane domains with an intracellular *N*-terminus and an extracellular *C*-terminus, which is distinct from the typology of classical G-protein-coupled receptors [9, 12]. Recently, functions of some PAQR family members have been characterized. PAQR1 and PAQR2 (also known as AdipoR1 and AdipoR2) were reported to be receptors for adiponectin, which is an important adipokine with a role in glucose metabolism [13, 14]. PAQR5, PAQR7 and PAQR8 were found to be receptors for progestin [15-19].

Table 1. PAQR3 expressions in human cancers

Cancer type	Expression	Role in invasion/metastasis	References
osteosarcoma	decreased	Tumor suppressor	[10]
colorectal cancer	decreased	Tumor suppressor	[9]
gastric cancer	decreased	Tumor suppressor	[35]
hepatocellular carcinoma	decreased	Tumor suppressor	[48, 49]
bladder cancer	decreased	Tumor suppressor	[53]
renal cell carcinoma	decreased	Tumor suppressor	[29]
malignant melanoma	decreased	Tumor suppressor	[32]
skin carcinogenesis	decreased	Tumor suppressor	[57]

The Ras/Raf/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) cascade plays an important oncogenic role in human cancers [20]. This pathway regulates many cancer-related cellular functions, including cell proliferation, apoptosis, differentiation, motility and metabolism [21-24]. Dysregulation of components in the Ras/Raf/MEK/ERK pathway in cancers has been widely reported [21, 25, 26]. Recently, PAQR3, a previously uncharacterized member of the PAQR family, has bee demonstrated to be a spatial regulator of Raf-1 by sequestrating Raf-1 to the Golgi apparatus, thereby blocking the downstream signal transduction [27, 28]. Because of this unique function, PAQR3 was also named RKTG (Raf kinase trapping to Golgi) [29]. PAQR3 functions as a tumor suppressor mainly due to its inhibitory activity on the Raf/MEK/ERK signaling [24]. To this end, PAQR3 could negatively regulate proliferation and migration of cancer cells as well as sprouting and angiogenesis of endothelial cells [24]. Interestingly, PAQR3 has a functional interaction with p53 in cancer formation and, in particular, epithelial-mesenchymal transition (EMT) [30].

PAQR3 and cancer

The downregulation and tumor-suppressing functions of PAQR3 in different types of malignancy have been documented (**Table 1**).

PAQR3 and osteosarcoma

Osteosarcoma is the most common type of primary malignant bone tumor [31-33]. Ma et al. found that PAQR3 expression was downregulated in osteosarcoma tissues compared with the adjacent normal regions in 80 paired samples. Moreover, low expression of PAQR3 was associated with metastasis in osteosarcoma patients [5]. Furthermore, restored expression of PAQR3 in osteosarcoma cell line MG-63 inhibited cell proliferation, migration, and invasion through inhibition of ERK phosphorylation [5].

PAQR3 and colorectal cancer

Colorectal cancer is one of the most common digestive tract malignancies worldwide, with over 1.2 million new cases and estimated 608,700 deaths in 2008 [34-37]. Wang et al. reported that PAQR3 expression was significantly decreased in colorectal cancer samples as compared with adjacent non-cancer tissues [4]. In addition, PAQR3 expression was inversely associated with tumor grade. By crossing PAQR3-depleted mice with $Apc^{Min/+}$ mice that have a germ-line mutation in the tumor suppressor gene *APC*, the *in-vivo* function of PAQR3 in colorectal cancer development was analyzed. It was found that the survival time and the tumor area in the small intestine of the $Apc^{Min/+}$ mice was significantly aggravated by PAQR3 deletion. Furthermore, the cell proliferation rate, anchorage-independent growth, epidermal growth factor (EGF)-stimulated ERK phosphorylation and EGF-induced nuclear accumulation of β-catenin were all inhibited by PAQR3 overexpression and enhanced by PAQR3 knockdown in SW-480 colorectal cancer cells [4].

PAQR3 and gastric cancer

Gastric cancer is one of the most common cancers and the fourth most leading cause of cancer-related mortality worldwide [38, 39]. PAQR3 has been shown to be frequently downregulated in gastric cancer compared with para-cancerous histological normal tissues at both mRNA and protein levels. PAQR3 expression was negatively correlated with tumor size, stage, venous and lymphatic invasion, metastasis, and survival of patients with gastric cancer. In addition, downregulation of PAQR3 was highly correlated with increased EMT. Functionally, restored expression of PAQR3 negatively modulated proliferation, migration and EMT of gastric cancer cells [30].

PAQR3 and hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the ten top malignancies in the world, with extremely high morbidity and mortality [40-42]. The expression of PAQR3 was significantly decreased in liver cancer tissues [43]. Clinicopathological correlation analyses showed that PAQR3 downregulation was significantly associated with the tumor size, histological grade and recurrence of HCC. In addition, the downregulation of PAQR3 was associated with the expression of serum alpha-fetoprotein and mitotic count [43]. Kaplan-Meier survival curves showed a correlation between decreased expression of PAQR3 and poor prognosis of HCC patients. Importantly, PAQR3 expression predicted overall and disease-free survival of HCC patients independent of other clinicopathological parameters. Furthermore, restored PAQR3 expression in Hep3B HCC cells significantly diminished cell proliferation and colony formation whereas silencing PAQR3 expression in the normal hepatic cell line LO2 significantly enhanced cell proliferation [43]. Yu et al. also reported that PAQR3 was significantly downregulated in HCC tissues as compared with the adjacent tissues in which lower levels of PAQR3 were associated with metastasis status of HCC patients [44]. In conclusion, PAQR3 plays an important role in the development of HCC and serves as a potential biomarker for prognostication in HCC patients.

PAQR3 and bladder cancers

Bladder cancer is the most common type of urogenital cancers and is the ninth leading cause of deaths among men [45-47]. Xiu et al. reported that enforced expression of PAQR3 significantly inhibited the proliferation and invasive capabilities of bladder cancer cells. However, the expression of PAQR3 in the bladder cancer remains unknown [48].

PAQR3 and renal cell carcinoma

Renal cell carcinoma (RCC) is the third most common urological cancers with a high mortality rate of >40% [49]. Clear-cell RCC (ccRCC) is a highly vascularized tumor in which an autocrine vascular endothelial growth factor (VEGF) signaling is required for maintaining the homeostasis of vasculature. PAQR3 has been shown to negatively regulate cell proliferation, migration, sprouting and angiogenesis of endothelial cells [24]. Mechanistically, PAQR3 suppresses mitogen-activated protein kinase (MAPK) signaling and thereby negatively regulating the transactivation activity of hypoxia-inducible factor 1α (HIF-1α) and the downstream VEGF transcription [24]. The expression of PAQR3 is significantly downregulated in ccRCC tumor samples, with an inverse correlation with VEGF expression levels. These results highlighted the functional roles of PAQR3 and its regulated Raf/MEK/ERK signaling cascade in angiogenesis and autocrine VEGF signaling in ccRCC.

PAQR3 and malignant melanoma

Malignant melanoma remains a life-threatening malignancy, accounting for 80% of skin cancer deaths [50, 51]. Fan et al. have shown that PAQR3 could bind and sequester B-Raf to the Golgi apparatus [27]. When overexpressed in A375, a human malignant melanoma cell line with mutant *BRAF* (V600E), PAQR3 could inhibit ERK activation, proliferation and transformation. In addition, the tumorigenicity of PAQR3-overexpressing A375 cells was suppressed in nude mice with reduced cell proliferation in the tumor xenografts [27]. Collectively, these data suggest that PAQR3 could suppress human melanoma that harbors an oncogenic *BRAF* mutation via its antagonistic action on B-Raf.

PAQR3 and skin carcinogenesis

Xie et al. described a suppressive role of PAQR3 in skin carcinogenesis by analyzing chemical carcinogen-induced tumorigenesis [52]. Epidermis hyperplasia and proliferation were increased in PAQR3-deficient mice after acute treatment with 7,12-dimethylbenz (a) anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA). Using a two-stage DMBA/TPA carcinogenesis protocol on mouse skin, both the number and size of papillomas were increased upon PAQR3 knockout, accompanied by shortened tumor latency and enhanced keratinocyte proliferation. The regression of the carcinogen-induced tumors was also prolonged in PAQR3-deficient mice upon cessation of DMBA/TPA treatment. Consistently, the levels of Raf-1 and ERK phosphorylation in primary keratinocytes as well as skin tumors were elevated when PAQR3 was genetically ablated. Collectively, PAQR3 plays a suppressive role in chemical carcinogen-induced mitogenesis and tumor formation in skin.

MicroRNA-mediated PAQR3 downregulation in cancers

MicroRNAs (miRNAs) are evolutionarily conserved, endogenous, non-coding, and single-stranded RNAs that regulate biological functions by targeting multiple messenger RNAs (mRNAs) [53-55]. MiRNA can bind to the 3'-untranslated regions (UTRs) of target mRNAs and induce mRNA cleavage or translational repression depending on the degree of complementarity [56, 57]. MiRNAs play significant roles in several fundamental biological processes, including apoptosis, cell proliferation, differentiation, development, and metabolism through regulating critical signaling molecules, including cytokines, growth factors, transcription factors, and pro-apoptotic and anti-apoptotic proteins [58-60]. MiRNAs have been shown to function as oncogenes or tumor suppressor genes through regulating their mRNA targets in many cancers, such as gastric cancer, breast cancer, glioblastoma, osteosarcoma and HCC [38, 61-65].

There was complementarily between the seed region of miR-137 and the 3'-UTR of PAQR3. Enforced expression of miR-137 could reduce both PAQR3 protein and mRNA levels in bladder cancer cells. Overexpression of miR-137 also remarkably reduced the luciferase activity of the reporter gene with the wild-type construct but not with the mutant PAQR3 3'-UTR construct, indicating that miR-137 directly targeted the PAQR3 3'-UTR. Moreover, restored expression of PAQR3 could significantly reverse the proliferation and invasion promoted by miR-137 [48]. Another study showed that overexpression of another miRNA, miR-543, inhibited PAQR3 expression in HCC [44]. To this end, enforced expression of miR-543 significantly decreased the luciferase activity of wild-type but not mutant PAQR3 3'-UTR. MiR-543 also significantly reduced PAQR3 protein levels in HepG2 cells [44].

Conclusions and future perspectives

Taken together, PAQR3, a member of PAQR family, is a novel tumor suppressor. PAQR3 exerts its anticancer effects by inhibiting the Raf/MEK/ERK signaling cascade, which is a central oncogenic axis in human cancers. Previous studies have established the tumor suppressive role of PAQR3 in colorectal, gastric, bladder and skin cancers as well as osteosarcoma, HCC, RCC and melanoma. However, the expression and function of PAQR3 in other common cancer types remain unclear. In addition, aside from miRNAs, relatively little is known about the mechanism underlying PAQR3 downregulation in human cancers in which genetic and epigenetic susceptibility as well as environmental factors might play a role in this process. A better understanding of the upstream regulation of PAQR3 could provide critical insights into strategies that could potentially restore the tumor suppressor function of PAQR3.

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Disclosure of conflict of interest

None.

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