Biomedicine & Pharmacotherapy 103 (2018) 1212–1216

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Emerging role of sperm-associated antigen 9 in tumorigenesis

Jun Pan[a,1], Haiyuan Yu[a,1], Zhicheng Guo[a], Quhe Liu[a], Meng Ding[a], Kai Xu[a], Lijun Mao[a,b,*]

[a] Department of Urinary Surgery, The Affiliated Hospital of Xuzhou Medical University, Xuzhou 221000, China
[b] Jiangsu Key Laboratory of Biological Cancer Therapy, Xuzhou Medical University, Xuzhou 221002, China

ARTICLE INFO

Keywords:
SPAG9
Cell cycle
Tumor
Diagnosis
Therapy

ABSTRACT

Sperm-associated antigen 9 (SPAG9) is a new member of cancer testis antigen and belongs to c-Jun NH2-terminal kinase (JNK) interacting protein (JIP) family. SPAG9 is highly expressed in a variety of tumors patients, and induces immune response in the host. SPAG9 regulates JNK and mitogen-activated protein kinases (MAPKs) signaling pathways which promote the growth, metastasis and drug resistance of tumors. In addition, SPAG9 modulates cell cycle progression and upregulates matrix metalloproteinases during the progression of tumors. Silencing SPAG9 expression could suppress the development of tumors. This review summarizes recent progress in our understanding of the emerging role of SPAG9 in tumorigenesis and highlights the potential of SPAG9 as a novel target for cancer diagnosis and therapy.

1. Introduction

The expression of cancer testis (CT) antigens is normally restricted to human germ line but CT antigens are aberrantly expressed in various malignancies [1]. Therefore, CT antigens are ideal antigens for immunologic therapy of tumors, and CT antigens such as NY-ESO-1 and MAGE were tested as cancer vaccines in clinical trials [2,3]. SPAG9 is a new member of CT antigens family. Shankar et al. first cloned *SPAG9* gene encoding human sperm surface protein (HSS) from a human testis cDNA library [4]. *SPAG9* gene was mapped to the 17q21.33 in human chromosome [4]. The protein structure of SPAG9 is shown in Fig. 1a. SPAG9 has structural homology with c-Jun NH2-terminal kinase (JNK) interacting protein 3 (JIP3) and is classified as JIP4 [5]. SPAG9 has a specific expression in acrosomal compartment of the sperm and participates in spermatozoa-egg interaction [5]. With structural homology of JNK, SPAG9 is involved in MAPK signaling pathway to regulate cellular activities (Fig. 1b) [5,6]. Interestingly, recent studies have shown that SPAG9 is expressed at high level in a variety of human tumors (Fig. 1c) [7]. Below we will summarizes recent progress in our understanding of the emerging role of SPAG9 in tumorigenesis.

1.1. SPAG9 and prostate cancer

Prostate cancer (PCa) has a high mortality in the male worldwide [8]. The surgery and radiotherapy can cure the early and Localized PCa. However, clinical therapy would be a challenge once PCa develops to advanced stage [9].

SPAG9 is overexpressed in PCa patients and could promote the proliferation of PCa cells via the upregulation of cyclin D1 and cyclin E [10]. Cyclin D1 would form a complex with cyclin-dependent kinase (CDK) 4/6 to regulate cell proliferation [11]. The overexpression of cyclin D1 was reported in several cancers, associated with the proliferation of cancer cells [12,13]. SPAG9 may promote the growth of PCa via the control of cell cycle.

Matrix metalloproteinases (MMPs) are known to promote the metastasis of tumors [14]. The abilities of motility and invasion are required for cancer cells to detach from primary mass, migrate through extracellular matrix (ECM) and colonize in other sites to achieve metastasis [15]. MMP-2 and MMP-9 play an important role in promoting PCa cell invasion and lymph node metastasis [16]. The tissue inhibitor of metalloproteinases (TIMPs) could suppress the activity of MMPs, and the imbalance of TIMPs and MMPs would induce the metastasis of cancer [17,18]. In PCa cells, the depletion of SPAG9 led to the inhibition of MMP-2 and MMP-9 due to the upregulation of TIMP-1 and TIMP-2 [19].

ETS-like gene 1 tyrosine kinase (ELK1) is an effector of p38 signaling pathway, and regulates the expression of the genes implicated in migration, invasion, and metastasis of prostate cancer [20,21]. The depletion of ELK1 would suppress the migration of androgen-independent PCa cells [21]. SPAG9 can be a scaffold protein of protein kinase C-related kinase 1 (PRK1) to engage p38 signaling pathway initiated by cytokine TGFβ1 and activate transcriptional regulator ELK1 [9]. Furthermore, the depletion of SPAG9 would suppress the formation of blood-vessel in PCa by the control of VEGF activity [19].

* Corresponding author at: Department of Urinary Surgery, The Affiliated Hospital of Xuzhou Medical University, Xuzhou 221000, China.
E-mail address: maolijunxz@163.com (L. Mao).
[1] Equal contributors.

https://doi.org/10.1016/j.biopha.2018.04.168
Received 25 January 2018; Received in revised form 23 April 2018; Accepted 23 April 2018

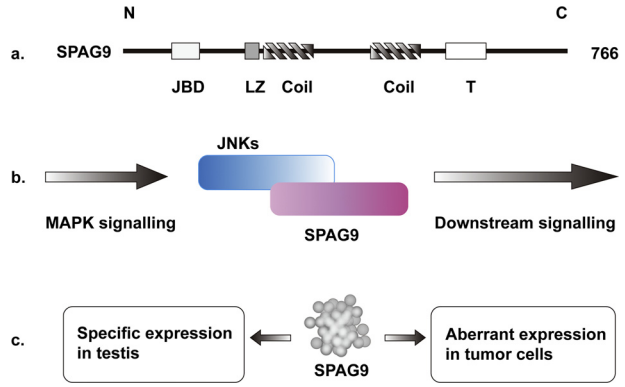

Fig. 1. (a) The protein structure of SPAG9. SPAG9 is a protein of 766 amino acids in length and contains JNK binding domain (JBD), coiled coil domain (coil), leucine zipper motif (LZ) and transmembrane binding site (T). (b) SPAG9 can be a scaffold protein to work with JNK in MAPK signaling. (c) SPAG9 has a specific expression in the testis and is aberrantly expressed in different tumor cells.

1.2. SPAG9 and hepatocellular carcinoma

The histological subtype of 70–85% of liver cancer cells is hepatocellular carcinoma (HCC) [22]. SPAG9 is overexpressed in HCC [23]. The overexpression of SPAG9 was associated with enhanced proliferation of HCC cells, while silencing of SPAG9 led to the downregulation of cyclin D1, cyclin E and the upregulation of p16 and p21, leading to G1 phase arrest of HCC cells [24].

In addition, overexpression of ELK1 was reported in HCC cells, and the expression levels of SPAG9 and ELK1 in metastatic cells are higher than in low-metastatic cells [23]. The migration and invasion induced by SPAG9 are dependent on the expression of ELK1. SPAG9 may interact with ELK1 to promote the migration and invasion of HCC cells.

SPAG9 also induced a strong humoral response in HCC patients. The serum levels of the antibodies against SPAG9 in HCC patients are higher than in control people [25]. The antibodies against SPAG9 are valuable in the diagnosis of HCC.

Interestingly, SPAG9 expression had an inverse correlation with miR-141 expression in HCC cells [26]. SPAG9 was validated as the direct target gene of miR-141 by Dual-luciferase reporter assay. The overexpression of miR-141 could suppress SPAG9 in HCC cells, while the suppression of miR-141 caused the upregulation of SPAG9 and promoted the proliferation, invasion and migration of HCC cells [26]. c-jun and MMP-9 are the downstream molecules of JNK signaling pathway which promotes the growth and metastasis of tumors [27]. As expected, the downregulation of c-jun and MMP-9 was found in HCC cells with miR-141 overexpression [26]. Thus miR-141/SPAG9 axis could be exploited for HCC therapy.

1.3. SPAG9 and bladder transitional cell carcinoma

Bladder transitional cell carcinoma (TCC) is one type of genitourinary malignancies with a high morbidity and mortality. Kanojia et al. investigated SPAG9 expression and humoral response against SPAG9 in bladder TCC patients. SPAG9 was expressed in 82% superficial non-muscle invasive bladder TCC patients, and there was a significant association of superficial non-muscle invasive stage, low grade tumors and high SPAG9 expression [28]. In addition, SPAG9 silenced UM-UC-3 cells were arrested in G0–G1 phase of cell cycle, with the upregulation of p16 and p21 and the downregulation of CDK1, CDK4, cyclin B, cyclin D and cyclin E [28]. SPAG9 may promote bladder TCC through the regulation of cell cycle. SPAG9 may be implicated in the tumorigenesis of bladder TCC and is a potential biomarker in early diagnosis of bladder TCC cancer.

1.4. SPAG9 and ovarian cancer

The demethylation of SPAG9 gene promotor region contributes to the tumorigenesis of ovarian cancer [29]. Cui et al. found that the demethylation of SPAG9 gene promotor region in ovarian epithelial cancer was high compared with the non-ovarian cancer tissues. Consistently, SPAG9 expression in lymph node metastasis patients was higher than that in non-lymph node metastasis patients, and SPAG9 expression in TNM stage III - IV patients was higher than that in TNM stage I - II patients. SPAG9 may promote the tumorigenesis of ovarian cancer [30].

JNK-associated leucine-zipper protein (JLP) is also encoded by SPAG9 gene [31]. SPAG9 gene generates three splice variants, JLP (1307 amino acids), JIP4 (1142 amino acids), and SPAG9 (766 amino acids). Recent study indicated high JLP expression in ovarian cancer tissues and cells [32]. Normal fallopian tube-derived epithelial cells would gain the clonogenic and long-term survival potential with JLP overexpression. JLP is involved in the activation of JNK pathway stimulated by lysophosphatidic acid (LPA), which can promote the proliferation and migration of ovarian cancer cells [32]. Furthermore, Garg et al. reported humoral immune response against SPAG9 in 67% of patients with epithelial ovarian cancer [7]. SPAG9 can be used in the diagnosis and immunotherapy of epithelial ovarian cancer.

1.5. SPAG9 and breast cancer

Targeted hormone therapy is effective for breast cancer patients positive for estrogen receptor (ER) and progesterone receptor (PR) [33]. The trastuzumab can achieve good efficacy in the patients expressing human epidermal growth factor receptor 2 (HER2) [34]. However, 15% of breast cancer patients without the expression of the above three receptors are diagnosed as triple-negative breast cancer (TNBC) [35]. While Taxol is an anti-mitotic drug often used in the treatment of breast cancer, Yang et al. found that the patients with increased expression of SPAG9 were not sensitive to chemotherapy by Taxol [36]. The expression of SPAG9 is associate with Taxol resistance in breast cancer, and could be an indicator in the selection of treatment.

Kanojia et al. detected the expression of SPAG9 and humoral immune response against SPAG9 in early stages (I and II) and in low-grade (grade 1) patients with breast cancer, and found that high SPAG9 immunoreactivity score (IRS) was associate with lymphovascular invasion and predicted risk of recurrence of breast cancer [37]. Thus SPAG9 can be used to diagnose early breast cancer and monitor the recurrence of breast cancer.

SPAG9 is involved in the progression of TNBC. Jagadish et al. found that the depletion of SPAG9 in TNBC MDA-MB-231 cells caused cell cycle arrest and cell senescence [38]. In addition, they detected the upregulation of p21 and pro-apoptotic molecules as well as the downregulation of anti-apoptotic molecules, MMPs and epithelial to mesenchymal transition (EMT) markers in SPAG9 depleted MDA-MB-231 cells [38]. Thus SPAG9 can inhibit apoptosis, enhance cell cycle progression and promote EMT to facilitate the growth, invasion and survival of TNBC.

Sinha et al. employed gene silencing approach to downregulate SPAG9, and reported the reduction of growth and invasion potential of TNBC [39]. Taken together, these studies suggest that SPAG9 is involved in the progression of breast cancer and can be used in early diagnosis, immunotherapy, and predicting the risk of recurrence of breast cancer.

1.6. SPAG9 and renal cell cancer

Renal cell cancer (RCC) is a common malignant urological carcinoma. SPAG9 expression level was high in RCC [40]. Garg et al. employed small interfering RNA (siRNA) targeting SPAG9 to treat RCC cells and found the reduction of the proliferation and migration of RCC