Neoplasma 2022; 69(6): 1270–1276

doi:10.4149/neo_2022_220529N571

The role of SPDEF in cancer: promoter or suppressor

Minireview

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Received May 29, 2022 / Accepted August 1, 2022

SPDEF, as a member of the ETS transcription factor family, was found to play important roles not only in some normal organs but also in some cancers. Scientists found that the significant increase of SPDEF in some cancers promotes tumor development, while some others found that the expression of SPDEF is lost in some cancers, and the loss of SPDEF is related to the proliferation, invasion, and metastasis. In this review, we summarized the function of SPDEF in normal tissues and its dual behaviors in different cancers, which may become a novel target in the diagnosis and therapy of cancers in the future. Besides, the multi-upstream regulatory mechanism of SPDEF plays different regulatory roles in different tumors, deserving further study. Moreover, there is one research, reporting that SPDEF plays a role in promoting mucus production during viral infection, and this may provide new ideas for future research about virus-associated cancer.

Key words: SPDEF, dual behaviors, cancer, upstream regulation, viral infection

Cancer, as one of the most common diseases with high deadly potential, threatens human health worldwide. Cancer pathogenesis and development are considered to be the results of multiple factors, including functional mutations of oncogenes and the inactivation of tumor suppressor genes [1]. Despite people having made great efforts on the molecular mechanisms, they are still not fully uncovered. The existence of tumor heterogeneity makes the diagnosis and treatment of tumors great challenges. It is necessary and important to identify novel molecular pathways to improve cancer treatment outcomes.

E26 transformation specific (ETS) transcription factor family is defined by a conserved DNA-binding domain from Drosophila to humans. The ETS domain has been identified as a DNA binding domain and binds specifically to a sequence containing the common core trinucleotide GGA. It is involved in protein-protein interactions and cofactors, in which it exerts its biological activities including growth control, maturation, differentiation, and other biological programs [2]. SAM pointed domain containing ETS transcription factor (SPDEF) is known as a member of the family, and the role of SPDEF in the human body is widely reported. In this review, present understandings of SPDEF are summarized with a specific emphasis on its significant role in cancer.

Molecular characterization of SPDEF

SPDEF, also called prostate-derived ETS factor (PDEF), was first isolated from the human prostate. SPDEF gene is located on chromosome 6p21.31 and contains the highly conserved DNA binding domain, the ETS domain, so it is considered a member of the ETS transcription factor family. SPDEF gene includes 6 exons that control the synthesis of SPDEF protein and consist of 335 amino acids. In the upstream region of the ETS domain, there is a significant homology with the point domain of some other ETS family members and weak homology with the SAM interaction domain of Eph receptor and polycomb protein. However, compared with other members of the ETS family, SPDEF has a significantly different sequence of ETS DNA binding domains, which also results that the ETS domain of SPDEF protein uniquely prefers to bind to a GGAT core than a GGAA core [3].

SPDEF in the development and physiological function of some organs

In initial studies, SPDEF is expressed almost exclusively in the prostate, and low levels of transcription in the breast, ovaries, and salivary glands, which may be related to androgens or steroids [3]. Later studies show that SPDEF has also physiological expression in tissues of the brain [4], lung [5], respiratory tract [5], and gastrointestinal tract [6], which have a high epithelial cell component. More and more studies have found that SPDEF is an important molecule in the physiological function of various tissues of the human body (Table 1).

SPEDF is closely related to the growth and development of the prostate. SPDEF was first found clearly expressed in the prostate, and its expression is mainly located in prostate epithelial cells. The expression of SPEDF is closely related to the expression of androgen receptor, which plays an important role in the androgen-dependent proliferation and differentiation of prostate epithelium [3]. Some scientists consider that it is reasonable to assume that SPDEF has an important function in normal prostate tissue [7].

In addition, SPDEF promotes the expression of the PSA gene in normal prostate tissue and prostate cancer, which is particularly evident in prostate cancer. On the one hand, SPDEF is a direct positive regulator of PSA gene transcription, which can bind to the PSA promoter and enhance the activity of the PSA promoter. On the other hand, activation of the androgen receptor can upregulate the level of SPDEF, and then regulate the function of the androgen receptor in a positive feedback way. SPDEF and androgen receptor jointly activate the promoter of the PSA gene and promote the expression of the PSA gene [3].

SPDEF promotes the maturation of goblet cells and Paneth cells to keep the function of the gastrointestinal tract. SPDEF is essential for mucosal production and reparation in digestive tract tissues. In the intestine tissues, SPDEF mRNA and protein expression are localized in Paneth cells, goblet cells, and early crypt progenitor cells. It plays a significant role in the maturation of goblet cells and Paneth cells [8], inhibiting the proliferation of intestinal progenitor cells and inducing their differentiation into goblet cells [9]. SPDEF is considered a transcriptional co-regulator of BHLH transcription factor 1, a key transcription factor that controls cell differentiation and maturation of intestinal epithelial cells [10]. Similarly, in the stomach, SPDEF RNA and proteins are mainly expressed in mucous adenosine cells in the antrum and mucous neck cells in corpus glands and play roles in the terminal maturation of gastric antrum mucous adenosine cells [6].

SPDEF is associated with mucus formation in the respiratory tract and plays an essential role in some chronic respiratory diseases. SPDEF is also found expressed in the lungs and respiratory tract tissues [5]. SPDEF is required for the differentiation from non-ciliated secretory epithelial cells into goblet cells in normal trachea-laryngeal submucosal glands, as well as for goblet cell differentiation in some human lung diseases. SPDEF regulates a group of genes involved in goblet cell differentiation, mucin synthesis, and secretion [11]. SPDEF interacts with the C-terminal domain of thyroid transcription factor 1 (TTF1) to activate promoters of selectively expressed genes in respiratory epithelial cells, including Sftpa, Scgb1a1, Foxj1, and Sox17. Together with ERM, another member of the ETS family, it regulates the selective gene expression and cell differentiation of airway

Table 1. The role of SPDEF in the development and physiological function of some organs.

Organ	Targets/Regulators and signaling pathways	Function	References
prostate	androgen receptor	promote prostatic epithelial cell proliferation and differentiation, promote the expression of the PSA gene	[3]
small intestine	Creb3l4, Ccl6, Hgfac, Cryptdins ↑	promote the maturation of goblet cells and Paneth cells	[8]
	Mmp7 and Ang4 ↓		
intestine	goblet cell genes AGR2, MUC2, RETLNB, and SPINK4 ↑	inhibit the proliferation of intestinal progenitor cells and induces their differentiation into goblet cells	[9]
pig intestine	PI3K/Akt, ERK1/2, P38, and JAK/STAT signaling pathways	regulate TFF3-mediated intestinal barrier and wound healing function	[10]
	BHLH transcription factor 1	control cell differentiation and maturation of intestinal epithelial cells	[10]
stomach		promote the terminal maturation of gastric antrum mucous adenosine cells, and avoid gastric inflammatory hyperplasia	[6]
lungs and respiratory tract	thyroid transcription factor 1 (TTF1) ↑	promote the differentiation from non-ciliated secretory epithelial cells into goblet cells	[5]
	Sftpa, Scgb1a1, Foxj1, and Sox17 ↑		
	FOXA3 ↑	induce goblet cell metaplasia and Th2 inflammatory response	[12]
	AGR2 and CLCA1 ↑, MUC5AC ↑, STAT6 ↑	promote mucus production in some chronic respiratory diseases	[14]

epithelial cells and their precursors in early lung development [5]. What's more, SPDEF and FOXA3 activate each other to induce goblet cell metaplasia and Th2 inflammatory response in airway epithelial cells in postnatal exposure to gas allergens and viruses, which influences response patterns to environmental exposure later [12]. In summary, SPDEF plays an important role in the growth and development of the respiratory system, especially in early development.

In many chronic airway inflammatory diseases like chronic obstructive pulmonary disease (COPD) and chronic rhinosinusitis with nasal polyps (CRSwNP), SPDEF was found significantly upregulated and increases the expression of a major gel-formed mucin MUC5AC through various cytokines [13]. SPDEF can co-activate AGR2 and CLCA1 gene promoters to increase MUC5AC gene expression and protein production with the presence of IL-13. This process is also found related to STAT6. Besides, the promoting effect of SPDEF on IL-13-induced mucus hypersecretion may be related to the inhibition of Foxa2, which is a key transcription factor known to inhibit mucus production [14]. Therefore, SPDEF can promote mucus production in some chronic respiratory diseases and play a driving role in the occurrence and development of diseases.

The dysregulated expression of SPDEF in some cancers

By searching the distribution of SPDEF in normal and tumor tissues of human adults in cDNA library databases, it was found that SPDEF was present at a relatively high frequency in the brain, breast, lung, and ovarian tumors compared to normal tissues [4]. Similarly, according to data from Cancer Bioportal, SPDEF was found to be elevated in a small number of melanomas, esophageal, ovarian, uterine, lung, and liver cancers [15]. However, some studies have shown that the expression of SPDEF is decreased in hepatic carcinoma [16], head and neck squamous cancer [17], and colon cancer [18].

Prostate cancer is the widely investigated tumor for SPDEF mechanisms, the findings of which are controversial at present. Compared with normal prostate tissue, the expression of SPDEF in prostate cancer is significantly increased. Meanwhile, the increased SPDEF expression is associated with high Gleason grade, advanced stage, rapid cell proliferation, and early prostate cancer recurrence [19]. SPDEF is believed to interact directly with androgen receptors and act as a coactivator of androgen receptors to induce prostate-specific antigen (PSA) expression in prostate tumor cells [3]. However, in some advanced prostate cancers, SPDEF expression is lost [20]. Some studies have also shown that SPDEF expression is decreased in the process of prostate cancer from low grade to high grade, and the decreased expression of SPDEF in prostate cancer may be associated with poor prognosis [21].

Some researchers believe that the different performances of SPDEF in different studies may be related to the experimental reagent and the selection of the study population [19]. It seems that the increased expression of SPDEF is more related to tumorigenesis and cell proliferation, while the loss of SPDEF is to promoting the invasion and metastasis of advanced cancer tumor cells. More studies are needed to uncover its role in the occurrence and development of cancer.

The overexpressed SPDEF in cancer tissue is always associated with pathogenesis or poor prognosis in some cancers. In non-triple-negative breast cancer, a high level of SPDEF mRNA transcription and protein expression were found and were positively correlated with TNM stage and lymph node status, tumor invasion, and lymphatic metastasis in different subtypes of breast cancer. The overall survival of breast cancer patients with high expression of SPDEF is relatively poor [22]. A study on ER(-) breast cancer found that AR(+)SPDEF(+) patients showed shorter overall survival or disease-free survival, and the expression of SPDEF could be one of the important independent factors influencing overall survival [23].

In lung mucinous adenocarcinoma, SPDEF is one of the top 50 genes highly expressed, and the co-induction of SPDEF and $KRAS^{G12D}$ in transgenic mouse models led to malignant mucinous lung tumors [24]. In ovarian cancer, high SPDEF mRNA was detected in 71% of ovarian carcinoma tissues [4], and SPDEF protein is frequently expressed in low malignant potential ovarian tumors, serous ovarian carcinoma, and peritoneal metastases, but barely in normal ovary and cystadenoma tissues [25]. While in gastric cancer tissues both SPDEF mRNA and protein were significantly higher compared to adjacent tissues, the elevated SPDEF expression was closely related to the poorly differentiated situation [26].

These studies suggested that SPDEF overexpressed in some cancer tissues and its expression was closely associated with the genesis and progression of cancers. SPDEF can work as an important and valued prognostic-related molecule in these cancers.

The loss of SPDEF in cancer is related to the poor prognosis in some other cancers. The expressions of SPDEF were downregulated in human hepatocellular carcinoma, squamous cell carcinoma of the head and neck, and colon cancer tissues compared with corresponding non-neoplastic tissues. The common characteristic of several cancers was that the lower expression of SPDEF was related to poorer differentiation, poorer prognosis and poorer clinical outcomes [16–18]. In lung adenocarcinoma, while SPDEF expression was upregulated compared with normal lung tissue samples, the patients with overexpression of SPDEF were related to longer relapse-free survivals, especially the patients in stage I [27]. SPDEF was considered an independent prognostic indicator for patients with these carcinomas.

The dual behaviors of SPDEF in cancers

SPDEF shows different functions in the regulation of tumor cell proliferation. The overexpression of SPDEF in

several human cancers is considered correlated with tumor cell proliferation. In estrogen receptor-negative breast cancer cells, the activation of SPDEF directly downregulates the expression of MAD1, and also promotes the degradation of it and separates it from MAX. With MAD1 decreasing, MYC competitively binds to MAX and forms a heterodimer, which upregulates MYC-mediated gene transcription and further promotes the proliferation of cancer cells [28].

There are also several studies showing that SPDEF expression is lost and the loss of SPDEF promotes tumor progression and tumor cell proliferation. It is found that overexpression of SPDEF inhibits the mRNA and protein levels of Foxm1, a key transcription factor for tumor cell proliferation. SPDEF binds to an automatic regulatory site located in the –745/–660bp mouse Foxm1 promoter region and interferes with the ability of Foxm1 to activate its own promoter, thereby inhibiting Foxm1 transcription [29].

In prostate cancer cells, the decreased expression of SPDEF in prostate cancer patients with androgen deprivation therapy increases the production of TGFBI, resulting in promoting the proliferation and metastasis of the cancer cells [30]. This goes some way toward explaining metastatic castration-resistant prostate cancer, which is that most patients develop resistance after receiving androgen deprivation therapy [31].

SPDEF can regulate the cell cycle progression. It can induce the cell into a quiescent state in colorectal cancer cells. The central pointed domain of SPDEF acts on ARM repeat 4–6 of β-catenin, which partially overlaps the binding region to TCFs. Thus, SPDEF disrupts the binding through competitive protein interactions and displaces β-catenin from the promoter or enhancer region of several cell cycle genes, so it induces tumor cells to enter the G0 phase of the cell cycle and inhibits cells proliferation [32]. Besides, SPDEF binds to the functional ETS DNA binding site at the –2118 bp promoter of the p21 gene promoter and modulates its inhibitory cell cycle activity in breast cancer [33]. SPDEF can also bind to the microRNA-448 promoter in hepatocellular carcinoma cells, and inhibit cell cycle progression by negatively regulating DOT1L expression [34].

Loss of SPDEF is associated with tumor invasion and metastasis through various pathways. It has been suggested that the ability of tumor cells to invade and metastasize may be related to the activation of specific pathways associated with EMT, with which epithelial cells acquired mesenchymal characteristics of reduced intercellular contact and enhanced cell motility and invasiveness [35].

The studies found that SPDEF can negatively regulate the transcription of key molecules of EMT in different kinds of cancer, such as CCL2 [36], E-cadherin [37, 38], and SLUG [39], and resulted in dysregulation of the migration and invasion activity of tumor cells. It is also found that SPDEF is a regulatory repressor of uPA expression by directly binding to the 2.4 KB ETS binding site upstream of the uPA transcription start site [20]. uPA can catalyze surface plasminogen into plasmin and degrade various extracellular matrices directly, usually promote the invasion and metastasis of cancer cells [40, 41]. In addition, MMP9 and MMP13 have also been reported to be important downstream participants in SPDEF-mediated tumor invasion [42]. Besides, SPDEF could inhibit GRIK3 which would enhance cell migration and invasion in breast cancer cells. With the recovery of SPDEF expression, the migration and invasion activity of tumor cells enhanced by GRIK3 was reduced [43].

SPDEF inhibits apoptosis in tumor cells by inhibiting the expression of some apoptotic factors. SPDEF has been found to be an inhibitor of FAS expression and plays a role in inhibiting apoptosis. FAS mRNA was found to be overexpressed in SPDEF knockout MCF7 breast cancer cells under hormone depletion [44]. Meanwhile, a PDEF binding region was found upstream of the FAS gene locus in prostate cancer cells, which means that SPDEF can directly inhibit the expression of the pro-apoptotic gene FAS [45]. SPDEF may be a direct negative regulator of apoptosis inhibitor survivin. SPDEF can bind to the functional ETS binding site of the survivin promoter and inhibit the transcription of survivin in prostate cancer cells and MCF-7 breast cancer cells. SPDEF silencing leads to survivin upregulation, increasing growth of the breast cancer cells *in vitro*, and tumor formation *in vivo* [20, 46].

The regulation of SPDEF

SPDEF, like other molecules, is precisely regulated by upstream genes. The molecular regulatory mechanisms are different, including 1) binding to transcription elements of transcription promoters to regulate mRNA expression; 2) post-transcriptional level regulation, affecting protein expression; 3) regulation by protein-protein interactions. The multi-directional upstream regulatory mechanism of SPDEF plays different regulatory roles in different tumors, which is closely related to its function in different tumors. An in-depth understanding of SPDEF provides a basis for the use of new targets for tumor therapy.

In estrogen receptor-negative breast cancer, the expression level of SPDEF is closely related to the androgen receptor expression. Androgen receptors can be recruited at the enhancer of the SPDEF gene and directly upregulate SPDEF expression, leading to its activation in estrogen receptor-negative breast cancer cells [28]. It was also discovered that Gata6 directly inhibits SPDEF gene expression by binding to the cis-regulatory region located 40 kb upstream of the human SPDEF transcription start site in mice, and human Caco-2 intestinal cell culture model [47]. Notch signaling induces HES1 expression and further inhibits the expression of ATOH1, which binds to the core promoter regions of the SPDEF gene and directly regulates its expression in mouse intestinal and human colon cancer cells [48]. Some other scientists also hold the opinion that ATOH1 silencing causes the loss of SPDEF in human colon cancer

[49]. lncRNA NKX3-1, as a kind of lncRNA, can promote SPDEF expression by targeting FEM1B, thus promoting the proliferation, invasion, and migration of glioma cells and inhibiting apoptosis [50]. MiRNA 204 (miR-204) can regulate endogenous SPDEF mRNA at the post-transcriptional level to regulate SPDEF protein level [56].

In addition, CDK11p58 and CDK11B can promote the degradation of SPDEF through protein interactions. In prostate cancer studies, SPDEF was phosphorylated by CDK11p58 and subsequently ubiquitinated and degraded, thus promoting tumor cell migration and invasion. However, overexpression of GADD45 could inhibit the activity of CDK11p58, as well as the CDK11p58-mediated degradation of SPDEF [51]. In addition, CDK11B, another CDK11 protein family member, can degrade SPDEF through the ubiquitin-proteasome pathway in hepatocellular carcinoma [34].

SPDEF expression with the human rhinovirus infection

There are very few studies on SPDEF and viral infection-related diseases. Human rhinovirus (HRV) is commonly associated with exacerbations of COPD [52] and asthma [53] and can cause excessive mucus levels. It was shown that the infection of HRV-A16 or HRV-1B caused a dose-dependent increase in MUC5AC gene expression, but also resulted in an increase in goblet cell markers and a decrease in ciliary cell markers and ciliogenesis-associated transcription factors. It is found that the expression of SPDEF, FOXA3, and AGR2 genes was significantly increased in human bronchial epithelial cells 48 h after infection with HRV-A16, while SPDEF was involved in mucin production by regulating the expression of several genes, including FOXA3, FOXA2, and AGR2 [54]. It is reasonable to assume that viral infection may cause the elevation of SPDEF and participate in the regulation of mucus production-related gene expression.

So far, no more studies have been able to clearly explain the direct or indirect relationship between SPDEF and viral infection, and due to the lack of relevant studies, more *in vivo* and *in vitro* studies are needed to further confirm this conclusion.

Summary and prospects

SPDEF, as a member of the ETS transcription factor family, has gradually entered the limelight in recent years, and its role in cancers has also gradually attracted the attention of scientists. In some cancers, SPDEF is found to be significantly elevated and promote tumor development through various pathways, while in some cancers the expression of SPDEF is significantly decreased and the loss of SPDEF also plays a role in promoting the proliferation, invasion, and metastasis of tumor cells. However, why SPDEF plays a dual role in tumors needs to be further studied and may help to uncover the mechanism of how SPDEF works in the occurrence and development of cancers. SPDEF may provide a novel target for early detection, treatment, and prognosis of tumors in the future. In decades of research, scientists have found seven cancer-related viruses, such as HPV related to cervical cancer and hepatitis virus related to liver cancer [55]. There is one research reporting that SPDEF plays a role in promoting mucus production during viral infection. Whether the emergence and the function of SPDEF are associated with cancer-related viral infection is something that needs deeper study in the future, and this may provide new ideas for future cancer research.

Acknowledgments: This work was supported by the Zhejiang Natural Science Foundation (LY21H160032).

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