Roles of DEPDC1 in various types of cancer (Review)

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Received April 24, 2024; Accepted July 24, 2024

DOI: 10.3892/ol.2024.14651

Abstract. Dishevelled, EGL-10 and pleckstrin domain-containing 1 (DEPDC1) has been identified as a crucial factor in the development and progression of various types of cancer. This protein, which is largely undetectable in normal tissues but is highly expressed in numerous tumor types, serves a significant role in cell mitosis, proliferation, migration, invasion, angiogenesis, autophagy and apoptosis. Furthermore, DEPDC1 is implicated in several key signaling pathways, such as NF-κB, PI3K/Akt, Wnt/β-catenin and Hippo pathways, which are essential for cell proliferation and survival. The expression of DEPDC1 has been linked to poor prognosis and survival rates in multiple types of cancer, including hepatocellular carcinoma, lung adenocarcinoma, colorectal cancer and breast cancer. Notably, DEPDC1 has been suggested to have potential as a diagnostic and prognostic marker, as well as a therapeutic target. Its involvement in critical signaling pathways suggests that targeting DEPDC1 could inhibit tumor growth and metastasis, thereby improving patient outcomes. In addition, clinical trials have shown promising results for DEPDC1-derived peptide vaccines, indicating their safety and potential efficacy in cancer treatment. To the best of our knowledge, this is the first comprehensive review addressing the role of DEPDC1 in cancer. Through a critical analysis of existing studies, the present review aimed to consolidate existing knowledge and highlight gaps in understanding, paving the way for future research to elucidate the complex interactions of DEPDC1 in the context of cancer biology.

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Key words: cancer, dishevelled, EGL-10 and pleckstrin domain-containing 1, molecular mechanism, signaling pathway, peptide vaccine

Contents

1. Introduction

The disheveled, EGL-10 and pleckstrin (DEP) globular protein domain interacts with phospholipids and membrane receptors to recruit proteins to the plasma membrane for participation in signal transduction (1). As first described by Kanehira *et al* (2) in 2007, knockdown of upregulated DEP domain-containing 1 (DEPDC1) was shown to significantly suppress the proliferation of bladder cancer (BC) cells. Subsequent studies (3-9) have implicated DEPDC1 in multiple signaling pathways associated with tumorigenesis.

DEPDC1, also named DEPDC1A, which is located on human chromosome 1p31.3 (2), and DEPDC1B, located on chromosome 5q12.1 (10), are responsible for cell cycle regulation (4,11). There are two isoforms of DEPDC1A: DEPDC1-V1 and DEPDC1-V2. DEPDC1-V1 is composed of 5,318 nucleotides that encode 811 amino acids comprising 12 exons, while DEPDC1-V2 is composed of 4,466 nucleotides that encode 527 amino acids compromising 11 exons (DEPDC1-V2 lacks exon 8 of DEPDC1-V1) (Fig. 1).

DEPDC1 is considered a cancer-testis antigen (3), which means that other than the testes, DEPDC1 is barely detectable in normal human tissues; however, it is highly expressed in a number of tumors (2). Notably, DEPDC1 is a highly conserved protein and expression of both its isoforms is increased during mitosis (12). DEPDC1 is highly expressed in the nucleus during prophase and redistributed throughout the cell after breakdown of the nuclear membrane in the middle and late stages of mitosis (13).

DEPDC1 serves critical roles in cell mitosis, proliferation, migration and invasion, as well as angiogenesis, autophagy and apoptosis (3,12-15). Therefore, DEPDC1 may be considered a potential marker of prognosis and response to therapy. In

the present review, the roles of DEPDC1 in tumorigenesis and its related molecular mechanisms, as well as its potential as a peptide vaccine are summarized to emphasize the importance of DEPDC1 in future cancer research.

2. Association of DEPDC1 with tumorigenesis

Upregulation of DEPDC1 has been associated with poor prognosis and survival in hepatocellular carcinoma (HCC) (16-21), lung adenocarcinoma (LUAD) (22,23), colorectal cancer (CRC) (24-26), breast cancer (BrC) (27-30), ovarian cancer (31), renal cancer (32), osteosarcoma (33,34), anaplastic thyroid carcinoma (35), gastric cancer (36), cholangiocarcinoma (37), head and neck squamous cell carcinoma (38), esophageal squamous cell carcinoma (39), endometrial carcinoma (40), multiple myeloma (4,41), glioma (42), diffuse large B-cell lymphoma (43) and soft-tissue sarcoma (44). Furthermore, DEPDC1 has been reported to be significantly upregulated in 29 out of 33 types of human cancer, and to be associated with overall survival, disease-specific survival and progress-free interval prognosis in numerous tumor types (45). The upregulation of DEPDC1 may be related to apoptosis, autophagy, proliferation, migration, invasion and angiogenesis in various types of cancer (46-49). Hence, the present study reviewed the molecular mechanisms underlying the multiple functions of DEPDC1 in tumorigenesis.

3. Molecular mechanisms of DEPDC1 in tumorigenesis

BC. BC is the 10th most common cancer and the second most common cancer in men worldwide (50). The role of DEPDC1 in BC was first described in 2007. Harada *et al* (3) reported that DEPDC1 forms a complex with zinc finger protein 224 (ZNF224) that suppresses transcription of A20, resulting in inhibition of apoptosis via activation of NF-κB and the subsequent proliferation of BC cells, whereas a peptide mimic formed by coupling 11 arginine residues at the amino terminal of DEPDC1 (nucleotides 611-628) was able to inhibit formation of the DEPDC1-ZNF224 complex and induce apoptosis of BC cells both *in vivo* and *in vitro*. Wang *et al* (51) revealed that overexpression of DEPDC1 could alleviate or even reverse the inhibition of proliferation and migration of BC cells induced by knockdown of α-protein kinase 2.

Lung cancer (LC). Globally, LC remains a leading cause of cancer-related death in both men and women (52). The two main types of LC are small cell and non-small cell subtypes. Similar to BC, Wang *et al* (9) reported activation of the DEPDC1-ZNF224/A20/NF-κB axis in A549 LUAD cells. Maternal embryonic leucine zipper kinase (MELK) is a is a highly conserved serine/threonine kinase in various stages of the cell cycle (53,54). Knockout of MELK in A549 cells has been reported to significantly reduce DEPDC1 protein levels without any change to transcription levels (55). In addition, MELK-induced phosphorylation can regulate DEPDC1 protein stability (55), similar to the findings of a previous report in myeloma cells (56). Wang *et al* (15) reported that DEPDC1 could upregulate the expression of RAS and suppress autophagy via the RAS-ERK pathway in LUAD cells, thus revealing a potential relationship between DEPDC1 and autophagy.

MicroRNAs (miRNAs/miRs) are short non-coding RNAs that serve crucial roles in oncogenesis and have been investigated as potential diagnostic and prognostic markers. A study by Liu *et al* (57) found that miR-23b could downregulate DEPDC1 in non-small cell LC. Multiple miRNAs have been reported to inhibit the expression of DEPDC1 in various types of cancer, as described below.

HCC. HCC is one of the most common causes of cancer-related mortality worldwide, accounting for >800,000 deaths annually, with a 1-year survival rate of <20% (58). A study by Guo *et al* (14) revealed that upregulation of DEPDC1 induced the expression of phosphorylated (p)-Akt, c-myc and cyclin E1 in HCC cells, whereas knockdown of chemokine ligand 20 (CCL20) or chemokine receptor 6 (CCR6; receptor for CCL20) reversed these effects. In addition, knockdown of CCL20 or CCR6 reversed DEPDC1-related angiogenesis and the invasive capabilities of human umbilical vein endothelial cells. These results indicated that DEPDC1 may promote angiogenesis in HCC.

Li *et al* (59) and Qu *et al* (60) reported that DEPDC1 promoted the proliferation and metastasis of HCC via activation of the Wnt/β-catenin signaling pathway. Zhou *et al* (61) also demonstrated that DEPDC1 promoted the proliferation of HCC cells and suppressed chemotherapy sensitivity via activation of the JNK signaling pathway.

Two studies reported on the regulation of DEPDC1 by non-coding RNA in HCC. Tian *et al* (49) revealed that long intergenic non-protein coding RNA, regulator of reprogramming promoted the stability of DEPDC1 mRNA via heterogeneous nuclear ribonucleoprotein K and could act as a competing endogenous RNA that affects the function of DEPDC1. Xu *et al* (62) demonstrated that certain miRNAs (including miR-96, miR-145 and miR-183) and mRNAs (including NAT2, FBXO5, CCNB1, DEPDC1 and NTN4) may be associated with the efficacy of ribavirin for treatment of HCC; among them, miR-96 and DEPDC1 constituted a miRNA-mRNA regulation pair.

CRC. CRC is the second most common malignant tumor worldwide, the incidence rate of which has increased annually (63). Wang *et al* (48) reported that DEPDC1-induced enhanced expression of suppressor of zest 12 could promote the proliferation, invasion and epithelial-mesenchymal transition of CRC cells. Sharen *et al* (64) revealed that overexpression of the large ribosomal subunit protein eL31 promoted the proliferation and migration of CRC cells by targeting DEPDC1, and upregulated the expression of p-Akt, cyclin D1, cyclin-dependent kinase 6, phosphatidylinositol-4,5-bisphosphate 3-kinase and catalytic subunit α.

Zhao *et al* (65) discovered that sirtuin 1 can bind to the promoter of miR-20b-3p and inhibit the expression of miR-20b-3p. Notably, miR-20b-3p negatively regulates DEPDC1, and DEPDC1 upregulation can enhance the resistance of CRC to oxaliplatin. Lou *et al* (66) suggested that miR-455-5p enhanced the sensitivity of CRC cells to 5-fluorouracil via negative regulation of PI3K regulatory subunit α and DEPDC1 independently.

BrC. BrC has been reported to be the most commonly diagnosed type of cancer, accounting for 2.26 million cases

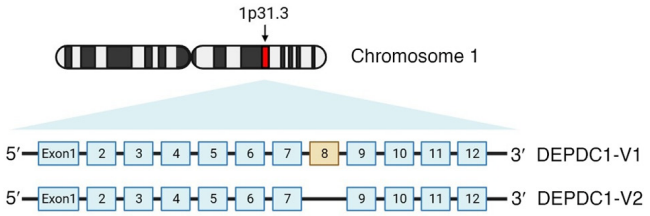

Figure 1. Chromosome mapping of the DEPDC1 isoforms. DEPDC1, dishevelled, EGL-10 and pleckstrin domain-containing 1.

worldwide in 2020, and is the leading cause of cancer-related death of women (67). Zhao *et al* (68) demonstrated that DEPDC1 promoted the proliferation, migration and invasion of BrC cells via the PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway.

Zhang *et al* (69) reported that miR-26b suppressed the expression of DEPDC1 in triple-negative BrC (TNBC), and DEPDC1 promoted the growth and proliferation of TNBC cells by increasing the expression of forkhead box protein (FOX)M1. Hao *et al* (47) reported that miR-374c-5p inhibited the progression of BrC via TATA-box binding protein associated factor 7-mediated downregulation of DEPDC1.

Prostate cancer (PC). PC is an important cause of male mortality worldwide (70). Huang *et al* (8) reported that DEPDC1 increased the activity of transcription factor E2F1, and subsequently upregulated the expression of cyclin D1 and cyclin-dependent kinase 2, leading to more frequent G_1-S phase cell cycle transition in PC. Ramalho-Carvalho *et al* (71) demonstrated that miR-130a inhibited DEPDC1 expression in PC cells.

Oral squamous cell carcinoma (OSCC). OSCC is a major public health concern, accounting for >90% of all oral malignancies worldwide (72). Guo *et al* (46) indicated that the tobacco-specific nitrosamine carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone could lead to DNA methyltransferase 1-regulated DNA methylation, which may promote DEPDC1 expression; this upregulated DEPDC1 expression can stimulate the proliferation of OSCC cells by inhibiting the expression of cytochrome P450 family 27 subfamily B member 1. Qiu *et al* (73) suggested that DEPDC1 may positively regulate the expression of FOXM1, resulting in nuclear localization of β-catenin, which is the most important indicator of Wnt pathway activation. Huang *et al* (74) revealed that DEPDC1 promoted activation of the Wnt/β-catenin signaling pathway in OSCC.

Nephroblastoma (NB). NB, or Wilms tumor, is the most common renal cell malignancy and the second most common extracranial solid tumor in children after neuroblastoma, (75). Geng *et al* (76) demonstrated that, in NB cells, overexpression of FOXO3a inhibited the protein expression of p-GSK-3β, Wnt3a and β-catenin, whereas overexpression of DEPDC1 had the opposite effects. In addition, FOXO3a inhibited the transcription of DEPDC1, which was associated with NB-like proliferation, migration and invasion. This previous study also revealed that knockout of S100 calcium-binding protein A16 (S100A16) inhibited the migration, invasiveness and angiogenesis of NB cells, which was partially reversed by overexpression of DEPDC1. Furthermore, a study by Geng *et al* (77) demonstrated that S100A16 and DEPDC1 promoted the progression and angiogenesis of NB through the PI3K/Akt/mTOR pathway.

Other types of cancer. A study by Yang *et al* (7) showed that downregulation of DEPDC1 reversed the inhibitory effect of protocadherin-10 (PCDH10) against the proliferation of endometrial endometrioid carcinoma cells, and knockdown of DEPDC1 blocked progression of the cell cycle and promoted apoptosis, thus replicating the effects of PCDH10 overexpression and indicating that PCDH10 may be upstream of DEPDC1.

Feng *et al* (78) demonstrated that knockout of DEPDC1 inhibited the cell cycle progression of nasopharyngeal carcinoma and the occurrence of nasopharyngeal carcinoma tumor formation in nude mice. However, the expression levels of cell cycle-related genes were measured in nasopharyngeal carcinoma cells after knockout of DEPDC1, without exploring the specific molecular mechanisms. Meanwhile, Kikuchi *et al* (79) revealed that DEPDC1 inhibited the apoptosis of glioma cells via the NF-κB signaling pathway.

Yang *et al* (80) demonstrated that downregulation of DEPDC1 activated the Hippo signaling pathway by overexpressing p-large tumor suppressor kinase 1 and p-yes-associated protein 1, thereby inhibiting the proliferation, invasion, migration and angiogenesis of osteosarcoma cells. Furthermore, overexpression of kinesin family member 4A reversed the effects of DEPDC1 on downregulation of the Hippo signaling pathway.

These studies have indicated that DEPDC1 serves a complex and critical role in several important signaling pathways in various types of cancer (Fig. 2; Table I); however, the molecular mechanisms require further clarification.

4. DEPDC1 antisense long non-coding (lnc)RNA (DEPDC1-AS1)

LncRNAs are involved in a variety of cell signaling pathways. Some lncRNAs act as carcinogens in tumors, whereas others act as tumor suppressors (81). Antisense lncRNAs are transcribed from the DNA lagging strand as complementary sequences to the leading strand (82).

DEPDC1-AS1 is considered a reliable prognostic marker of LUAD (83) and ovarian cancer (84). DEPDC1-AS1 has been reported to be associated with ferroptosis and to have the highest hazard ratio among the 12 best prognostic markers of LUAD (85). Xu *et al* (86) reported that DEPDC1-AS1 may be considered a reliable marker for the detection and prognosis of gastric cancer, where it can bind to human antigen and increase the stability of F11 receptor mRNA, which is associated with the proliferation and metastasis of gastric cancer cells.

Relatively few studies (83-86) have investigated the role of DEPDC1-AS1 in tumorigenesis; therefore, the specific molecular mechanisms remain unclear. It has been suggested that antisense lncRNAs may act through RNA-DNA hybridization (87). Notably, the effect of DEPDC1-AS1 on DEPDC1 expression remains unknown; however, DEPDC1-AS1 has

Table I. Molecular mechanism of DEPDC1 in various tumors.

Cancer type	Possible mechanisms	(Refs.)
BC	DEPDC1-ZNF224 complex inhibits A20 transcription, thereby activating the NF-κB pathway to inhibit apoptosis; 11R-DEP: 611-628 peptide induces apoptosis by inhibiting the formation of the aforementioned complex	(3)
	ALPK2 promotes proliferation and migration by positively regulating DEPDC1	(51)
Lung cancer	DEPDC1-ZNF224 complex inhibits A20 transcription, thereby activating the NF-κB pathway to inhibit apoptosis; 11R-DEP: 611-628 peptide induces apoptosis by inhibiting the formation of the aforementioned complex	(9)
	MELK enhances DEPDC1 protein stability	(55)
	DEPDC1 suppresses autophagy via the RAS-ERK pathway	(15)
	STAT1 induces upregulation of KTN1-AS1, which inhibits the expression of miR-23b and thus upregulates DEPDC1	(57)
HCC	DEPDC1 upregulates CCL20/CCR6 to promote angiogenesis	(14)
	DEPDC1 activates the Wnt/β-catenin pathway	(59,60)
	DEPDC1 activates the JNK pathway	(61)
	Linc-ROR upregulates DEPDC1 by competitively binding to miR-130a-3p, inducing EMT and angiogenesis	(49)
	miR-96 and DEPDC1 constitute a miRNA-mRNA regulation pair	(62)
CRC	DEPDC1 upregulates SUZ12 and H3K27Me3 to promote EMT	(48)
	eL31 promotes proliferation and migration by targeting DEPDC1	(64)
	SIRT1 mediates DEPDC1 upregulation by inhibiting the expression of miR-20b-3p	(65)
	miR-455-5p inhibits DEPDC1 expression	(66)
Breast cancer	DEPDC1 activates the PI3K/AKT/mTOR pathway	(68)
	miR-26b negatively regulates the expression of DEPDC1, and DEPDC1 positively regulates the expression of FOXM1	(69)
	miR-374c-5p downregulates DEPDC1 by inhibiting TAF7 expression	(47)
PC	DEPDC1 interacts with E2F1 and increases its transcriptional activity to upregulate cyclin D1 and CDK2 to promote the cell cycle	(8)
	DEPDC1 is suppressed by miR-130a	(71)
OSCC	NNK promotes the expression of DEPDC1 through DNMT1, thereby inhibiting the expression of CYP27B1	(46)
	DEPDC1 activates the Wnt/β-catenin pathway through FOXM1	(73)
	DEPDC1 activates the Wnt/β-catenin pathway	(74)
NB	FOXO3a inhibits the Wnt/β-catenin pathway by downregulating DEPDC1	(76)
	S100A16 acts upstream of DEPDC1 and promotes angiogenesis through the PI3K/Akt/mTOR pathway	(77)
EEC	PCDH10-induced downregulation of DEPDC1 induces apoptosis	(7)
Glioma	DEPDC1 activates the NF-κB signaling pathway by inhibiting A20	(79)
Osteosarcoma	DEPDC1 inhibits the Hippo signaling pathway by upregulating KIF4A	(80)

DEPDC1, dishevelled, EGL-10 and pleckstrin domain-containing 1; EMT, epithelial-mesenchymal transition; BC, bladder cancer; HCC, hepatocellular carcinoma; CRC, colorectal cancer; PC, prostate cancer; OSCC, oral squamous cell carcinoma; NB, nephroblastoma; EEC, endometrial endometrioid carcinoma.

potential for the detection and prognosis of various types of cancer, although further studies are needed to elucidate the underlying mechanisms.

5. Clinical significance of DEPDC1

DEPDC1 as a diagnostic and prognostic marker. As aforementioned, high DEPDC1 expression is associated with the poor prognosis of various types of cancer. Therefore, DEPDC1 may have potential as a diagnostic and prognostic marker for clinical diagnosis and response to treatment. For example, a significant proportion of LUAD cases are caused by mutations to epidermal growth factor receptor, K-Ras or anaplastic lymphoma kinase; however, these three genes are not suitable as markers of triple-negative LUAD. Alternatively, high expression of DEPDC1 has been associated with the poor prognosis of triple-negative LUAD (5) and may thus be a promising target for cancer prognosis.

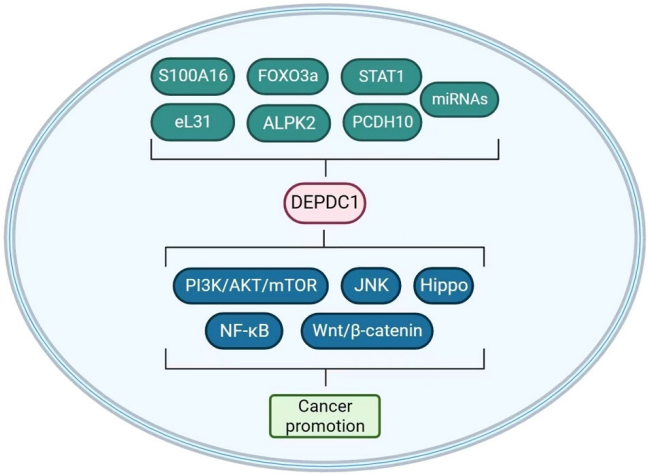

Figure 2. Summary of upstream and downstream molecules and pathways associated with DEPDC1. The green boxes include upstream regulators of DEPDC1 and the blue boxes include the downstream pathways regulated by DEPDC1. These molecular regulatory mechanisms have not been demonstrated in the same cell type. Therefore, this diagram is only intended to show that DEPDC1 is involved in multiple signaling pathways. Created with BioRender.com. DEPDC1, dishevelled, EGL-10 and pleckstrin domain-containing 1; S100A16, S100 calcium-binding protein A16; FOX, forkhead box protein; miRNAs, microRNAs; ALPK2, α-protein kinase 2; PCDH10, protocadherin-10; mTOR, mammalian target of rapamycin.

Potential therapeutic targets. DEPDC1 is related to multiple signaling pathways and may be a signaling hub for tumor development, and could thus be considered a promising new therapeutic target. Arumugam *et al* (88) suggested that DEPDC1, as a consistently differentially expressed gene in TNBC, may interact well with doxorubicin and anethole, which is a phytocompound, suggesting that DEPDC1 could be a possible therapeutic target of TNBC.

DEPDC1 is also a potential marker of the response to medications. Microtubule-targeted chemotherapy induces apoptosis of cancer cells by promoting phosphorylation and degradation of induced myeloid leukemia cell differentiation protein Mcl (MCL1), a member of the anti-apoptotic Bcl-2 family (89). Sendoel *et al* (6) concluded that DEPDC1 may regulate vincristine (a tubulin-targeted chemotherapy drug)-induced cell death by promoting JNK-dependent degradation of MCL1, whereas knockdown of DEPDC1 mediated resistance to vincristine-induced cell death, suggesting that vincristine may serve an antitumor role through DEPDC1. Therefore, whether the expression levels of DEPDC1 can predict the efficacy of anti-tubulin drugs on tumors may be a meaningful research direction.

As aforementioned, multiple miRNAs can inhibit the expression of DEPDC1 and enhance the sensitivity of tumors to chemotherapy drugs to address drug resistance. Therefore, the use of miRNAs targeting DEPDC1 may be a promising research direction to reduce chemotherapy resistance.

Notably, a variety of Chinese herbal extracts, such as paeoniflorin (90), a compound found in *Paeonia lactiflora* and *Paeonia* x *suffruticosa*, and platycodin D (91), a bioactive component of the roots of *Platycodon grandifloras*, have been reported to exhibit anticancer effects via multiple signaling pathways. Therefore, it may be possible to explore whether there are natural drugs that can inhibit DEPDC1. Therefore, future studies are warranted to verify the feasibility of DEPDC1-targeted anticancer therapies.

6. Peptide vaccines

Peptide-based anticancer vaccines use tumor-associated or tumor-specific peptides to induce and activate T cells. These peptides are present on human leukocyte antigen (HLA) molecules on the cell surface and are recognized by T-cell receptors. Peptide vaccines have the advantages of low side effects, but must be optimized prior to clinical application (92).

Shortly after being described in BC, DEPDC1 was investigated as a new target for peptide vaccines. Obara *et al* (93) conducted a clinical trial of possible peptide fragments that would bind to the HLA-A*2402 molecule, and administered the M phase phosphoprotein 1 (MPHOSPH1)-278 and DEPDC1-294 peptides to six patients with BC. Four of the six patients vaccinated with DEPDC1-294 achieved cytotoxic T lymphocyte (CTL)-positive responses to DEPDC1-294, with one achieving a partial response. This sample was expanded in a further study to 32 patients who received this combined peptide vaccine, and the study concluded that the 2-year survival rate was slightly better than in response to treatment with vinflunine (94). However, this previous study did not include a control group, but rather compared the efficacy of vinflunine with other studies, which may lead to errors due to different backgrounds of the patients (94). In addition, the ability of the peptide vaccine to prevent recurrence of non-muscular-invasive BC was evaluated after transurethral resection of bladder tumors in 127 patients (95). Combined with intravesical Bacillus Calmette-Guerin (BCG), the overall 2-year recurrence-free survival rate was 74% for patients in the HLA-A*2402-positive group, which was higher than the negative control group (95). However, both groups received the BCG vaccine, which might have masked the therapeutic effect of the peptide vaccine. Therefore, an additional study with three groups (peptide alone, BCG alone and peptide combined with BCG vaccine) is required.

Fujiwara *et al* (96) conducted a clinical trial of 35 patients with gastric cancer treated with a HLA-A24-binding peptide vaccine, which comprised a mixture of multiple peptides derived from DEPDC1, upregulated LC 10 (URLC10) epitope peptide, FOXM1, kinesin family member 20A (KIF20A) and vascular endothelial growth factor receptor-1 (VEGFR1). The study found that this peptide vaccine treatment was safe and promising to induce a specific T-cell response in patients with advanced gastric cancer. The study further demonstrated that the peptide vaccine was well tolerated in combination with S-1; however, this study, as an early exploratory study, did not show a clear clinical benefit of this combination therapy over S-1 alone due to sample size limitations (97). Although no notable antitumor effect or survival benefit was observed due to the small sample size and short duration, these trials demonstrated that the vaccine was safe with no serious adverse reactions, except for minor skin reactions, and patients with injection site reactions tended to achieve better outcomes. All of the tested peptide vaccines induced a specific T-cell response, and the patients who responded to CTL achieved better survival than those who did not, especially those who responded to the DEPDC1 peptide.

A clinical trial conducted by Daiko *et al* (98) of 13 patients with esophageal cancer treated with five peptides revealed that at least one peptide induced a response to CTL in all patients, although the CTL initiation rate of the DEPDC1 peptide was only 26.7%, and the efficacy was not analyzed, as only safety was addressed.

There have also been more successful treatments. For example, a 2016 study conducted by Murahashi *et al* (99) enlisted 18 patients treated with five HLA-A*2402 restricted tumor-associated antigen epitope peptides from the novel chloroplast outer membrane kinase KOC1, threonine tyrosine kinase, URLC10, DEPDC1 and MPHOSPH1 vaccines. A total of 4 days before vaccination, the patients received increasing dosages of cyclophosphamide. In this study, the overall survival of nine patients with CRC was 9.4 months, which was better than the effect of cetuximab in another study (6.1 months) (100), indicating the advantage of peptide vaccines with DEPDC1 as one of the epitope peptides. In addition, a 40-year-old male patient with esophageal cancer (celiac lymph node metastasis) achieved a complete response with no disease recurrence after 5 years.

In a 2019 study conducted by Kikuchi *et al* (101), 19 patients with grade III or IV glioma were treated with a peptide vaccine that included peptide epitopes from four glioma oncoantigens (lymphocyte antigen 6 family member K, DEPDC1, KIF20A and FOXM1) and two glioma angiogenesis-associated antigens (VEGFR1 and VEGFR2). Not only were there no serious adverse reactions, but a 33-year-old woman with anaplastic oligoastrocytoma (grade 3) was cured; their tumor shrank 3 months after vaccination and disappeared 9 months later with no tumor recurrence after 38 months. Although the sample size was small and there was no significant increase in overall survival, the fact that a patient was cured is encouraging, and further emphasizes the potential of DEPDC1 as a peptide vaccine target.

Some *in vitro* studies have reported that DEPDC1-derived peptides can induce activation of CTL and T helper (Th) cells (102,103). Furthermore, Yatsuda *et al* (104) demonstrated that the $DEPDC1_{191-213}$ peptide induced a strong Th cell response in HLA-DR4 transgenic mice. As compared with CTL epitopes alone, co-inoculation of CTL and Th cell epitopes has also been reported to achieve clinical benefits in patients with melanoma (105). Therefore, co-vaccination with multiple CTL and Th epitope peptides containing DEPDC1 may induce a better immune response and result in better efficacy against tumors, although further clinical studies are needed.

7. Conclusion and future prospects

DEPDC1 is a newly discovered tumor-related gene that is upregulated in various malignant tumors and may be involved in tumorigenesis as a marker of poor prognosis. Therefore, the potential of DEPDC1 for detection and prognosis of cancer should be considered.

DEPDC1 is involved in the regulation of tumor cell proliferation, metastasis, autophagy, apoptosis and angiogenesis by mediating different signaling pathways. Some of these signaling pathways (NF-κB, PI3K/Akt, Wnt/β-catenin and Hippo) may promote cell proliferation and survival. However, since intracellular signal transduction is complex and there is cross-dialogue between different pathways, further studies are needed to clarify the signal transduction mechanism of DEPDC1.

Future studies may also focus on: i) Comparing the sensitivity and specificity of DEPDC1 with other common diagnostic and prognostic markers in different types of tumors; ii) investigating the unique role of DEPDC1 in predicting therapeutic response; and iii) evaluating the practical effectiveness of DEPDC1 as a marker in clinical applications.

Owing to the multifaceted characteristics and effects of cancer-testis antigens (3,102), DEPDC1 is a potential therapeutic target. Treatment targeting DEPDC1 could inhibit the proliferation and metastasis of tumor cells and improve patient outcomes. Furthermore, the efficacy of DEPDC1-derived peptides in immunotherapy as cancer vaccines has been confirmed in clinical trials, thus warranting further studies to identify effective peptide segments, determine appropriate dosages and assess efficacy in combination with other peptide vaccines, as well as radiotherapy and chemotherapy. DEPDC1 also provides a direction for the study of the molecular mechanisms of antitumor drugs. Clarification of the mechanism of DEPDC1 could provide a new therapeutic target for the prevention and treatment of malignant tumors.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 82104603) and the Peking University People's Hospital Research and Development Fund (grant nos. RS2021-12 and RDX2021-08).

Availability of data and materials

Not applicable.

Authors' contributions

DL performed the literature review and wrote the draft. HL was responsible for reviewing the literature, and reviewed and revised the draft. JO conceived and designed the study, acquired funding, and reviewed and revised the draft. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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