Role of Nectin-4 protein in cancer (Review)

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Abstract. The Nectin cell adhesion molecule (Nectin) family members are Ca^{2+}-independent immunoglobulin-like cellular adhesion molecules (including Nectins 1-4), involved in cell adhesion via homophilic/heterophilic interplay. In addition, the Nectin family plays a significant role in enhancing cellular viability and movement ability. In contrast to enrichment of Nectins 1-3 in normal tissues, Nectin-4 is particularly overexpressed in a number of tumor types, including breast, lung, urothelial, colorectal, pancreatic and ovarian cancer. Moreover, the upregulation of Nectin-4 is an independent biomarker for overall survival in numerous cancer types. A large number of studies have revealed that high expression of Nectin-4 is closely related to tumor occurrence and development in various cancer types, but the manner in which Nectin-4 protein contributes to the onset and development of these malignancies is yet unknown. The present review summarizes the molecular mechanisms and functions of Nectin-4 protein in the biological processes and current advances with regard to its expression and regulation in various cancer types.

Contents

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1. Introduction

The disorder of cell-cell adhesion has a significant influence on tumor occurrence and development (1). Four major cell adhesion molecules, which are known as the integrins, cadherins, selectins and the immunoglobulin superfamily (IgSF), are involved in this physiological process (2). The Nectin cell adhesion molecule (Nectin) family is comprised of Nectins 1-4, which are immunoglobulin-semblable transmembrane proteins involved in the Ca^{2+}-independent adherens junctions (AJs) of cell-cell interactions via homophilic/heterophilic interplay (3-5). Moreover, Nectin family members enhance cellular viability and movement ability (6-8). Nectins 1-3 are commonly enriched in normal adult tissues, in which Nectins 1-2 are frequently expressed in immune organs (bone marrow, thymus, spleen and lymph nodes), and Nectin-3 is principally expressed in the spermary and placenta (3,4). However, several studies have revealed that Nectin-4 is specifically overexpressed in various cancer types, including breast cancer (BC), ovarian cancer (OC) and pancreatic cancer (PC) (9-14). A large number of studies have shown that Nectin-4 is closely related to tumor oncogenesis and the poor prognosis of affected patients (9-14). Fabre-Lafay *et al* (13) reported that both membranous and soluble forms of Nectin-4 were upregulated in the majority of BC tissue samples, and Nectin-4 was also confirmed as a novel biomarker associated with poor prognosis. In PC, upregulated Nectin-4 strongly stimulates cell growth and has a vital impact on intratumoral angiogenesis (14). To the best of our knowledge, the function and biological changes in Nectin-4 protein have not been

collected systematically, thereby necessitating the study of clinical significance and molecular mechanisms in different cancer types. The present review aimed to investigate the prognostic values and functions of Nectin-4 in various cancer types.

2. Molecular structures of Nectin family members

The Nectin family of proteins are Ca^{2+}-independent cell surface adhesion molecules, closely related to the formation of AJs and tight junctions (TJs) (15,16). All Nectins are members of the IgSF, initially depicted as molecules homologous to the poliovirus receptor (PVR/CD155), and can thus be described as poliovirus receptor-related proteins (PRR) or PVR-like proteins (PVRL) (3,17,18). Except for Nectin-4, Nectins 1-3 have more than one splice variant, including Nectin-1α, -1β, -1γ, -2α, -2δ, -3α, -3 and -3γ (19). Nectin-1α and -2α were firstly discovered as PRR proteins, and are also known as PRR-1 and -2, respectively (19). However, a study later confirmed the lack of correlation between Nectin-1α and Nectin-2α, and PVR (20). Moreover, they were subsequently verified to act as receptors for α-herpes virus, mediating the processes of the virus infection and diffusion Hence, the old names for these Nectins used to be HveC and HveB, respectively (20). As Nectin-4 is homologous to PVR/CD155, Nectin-4 was also known as PVRL4 (21) (Table I).

Except for Nectin-1γ, the other family members have been found to have a semblable domain structure: Three conserved immunoglobulin-like domains in the extracellular region (V-C-C domain), one transmembrane region (TM) and one short tail protein domain in the cytoplasm (Fig. 1) (5,15). Nectin-1γ is considered as a secreted protein due to the absence of a TM region (19). Furthermore, the V, C and C domains bond with several growth factor receptors, including fibroblast growth factor receptor and Erb-b2 receptor tyrosine kinase 3, which might have a significant influence on cell growth, migration and apoptosis (22-24).

The Nectin family members interact with each other via homo-cis-dimers on the surface of the cellular membrane or hetero-trans-dimers among adjacent cells for homophilic and heterophilic interactions through the extracellular region (9). The binding specificity is diverse among various Nectin family members. For example, Nectin-1 integrates with Nectin-3 and -4 to form hetero-trans-dimers. These dimers are formed between Nectin-2 and -3, but not between Nectin-1 and -2 (Fig. 2). Moreover, these hetero-trans-dimers are more tightly connected than the homo-trans-dimers (9,25). Furthermore, Nectin-2 is combined with CD226/DNAM-1 through trans-interaction. CD226/DNAM-1 contains two Ig-like domains, and is mainly enriched in T and natural killer (NK) cells, stimulating immune cells to enhance their ability of differentiation and proliferation (26,27). The Nectin-like molecule (Necl) family is another group of Ig-like cellular surface adhesion molecules consisting of five members: Necl-1, -2, -3, -4 and -5. In addition, the protein domains of Necl family members are similar to those of Nectin members. Also, Necls interact with Nectins, which jointly promote cell growth and differentiation, and inhibit cell apoptosis (20). The complicated and close interaction between Nectins and Necls is shown in Fig. 2. Several studies have revealed that the Nectin family members also serve as novel immune regulators (28-30). Reportedly, Nectin-2 (CD112, PVRL2 and CD113), Nectin-3 (PVRL3) and Necl-5 (CD155/PVR) bind to T-cell immunoreceptor via Ig and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains (TIGIT), among which, Necl-5 has the highest binding affinity (28-30). Furthermore, TIGIT has emerged as a significant molecule for immune checkpoint regulation, which consists of a type I transmembrane protein with an Ig variable extracellular domain solely enriched within a range of immune cells, including NK cells, effector cells, memory T cells and regulatory T cells (29,30). TIGIT negatively regulates the immune response via multiple steps. Following ligand interaction, TIGIT mediates the suppression of NK cell-mediated cytotoxicity and interferon (IFN)-γ production through its cytosolic immunoglobulin tail tyrosine-like phosphorylation motif and through ITIM in the cytoplasmic region, which recruits Src kinases, Grb2 and SHIP-1 (28-32). The blockade of the interaction between Nectin members and TIGIT markedly enhances the antitumor immunity mediated by reinvigorated $CD8^+$ T cells and NK cells (30,32,33).

3. Nectin-induced signaling during the formation of cell-cell junctions

Apart from Nectin-1β, -1γ, -3γ and -4, the remaining Nectin members share the same conserved sequence at the carboxyl terminus. In addition, there are four amino acid residues (Glu/Ala-X-TyrVal) in this conserved sequence that interact with the PDZ domain of Afadin (Fig. 1). Despite the fact that Nectin-4 does not share the conserved sequence, it can directly bind to the PDZ domain of Afadin via its carboxyl terminus (34). Interplay occurs between Nectins and the actin cytoskeleton protein via Afadin, which can activate a series of intercellular communications and signaling molecules, including AJs, TJs and inflammatory cytokines (16). A previous study reported that Nectin-4 firstly combines with Afadin and then regulates actin cytoskeleton remodeling (35). Subsequently, it induces epithelial-mesenchymal transition (EMT) and enhances the driving force for pseudopod extension in tumor cell lines (36).

The cell-cell junction is strongly influenced by the interactions among Nectins on adjacent cells. Once the interaction is established, these cadherin-catenin complexes will be recruited to the corresponding adhesion site. Subsequently, the trans-interaction of cadherins forms the AJs on adjacent cells (37-39). Synergetically, the Nectin/Afadin complex and E-cadherin/catenin complex function through Afadin and α-catenin, respectively, activating a signaling cascade (c-Src, C3G, Crk, PI3K and Vav2), thus modulating molecules such as Rap1, Cdc42 and Racs, and ultimately leading to actin cytoskeleton realignment (40-42) (Fig. 3). In conclusion, the Nectin family in co-operation with cadherin, have significant effects on the generation and maintenance of AJs and TJs, which regulate several cellular behaviors, including cell adhesion, growth, differentiation, migration and apoptosis (43,44).

4. Distribution and physiological function of Nectins

Each Nectin family member has distinct effects independently or interactively. In normal cellular conditions, Nectins 1-3 are

Table I. General characteristics and tissue distribution of Nectin family members.

Nomenclature	Old nomenclature	Splice variants	Distribution	(Refs.)
Nectin-1	PRR1/HveC	Nectin-1α Nectin-1β Nectin-1γ	Immune system organs	(3,4,19,20)
Nectin-2	PRR2/HveB	Nectin-2α Nectin-2δ	Blood cells and spermatids	(19,20)
Nectin-3	PRR3	Nectin-3α Nectin-3β Nectin-3γ	Testes and placenta	(19)
Nectin-4	PVRL4	NS	Embryonic and placental tissues	(3,4,21)

PRR, poliovirus receptor-related protein; PVRL, PVR-like protein; NS, not stated.

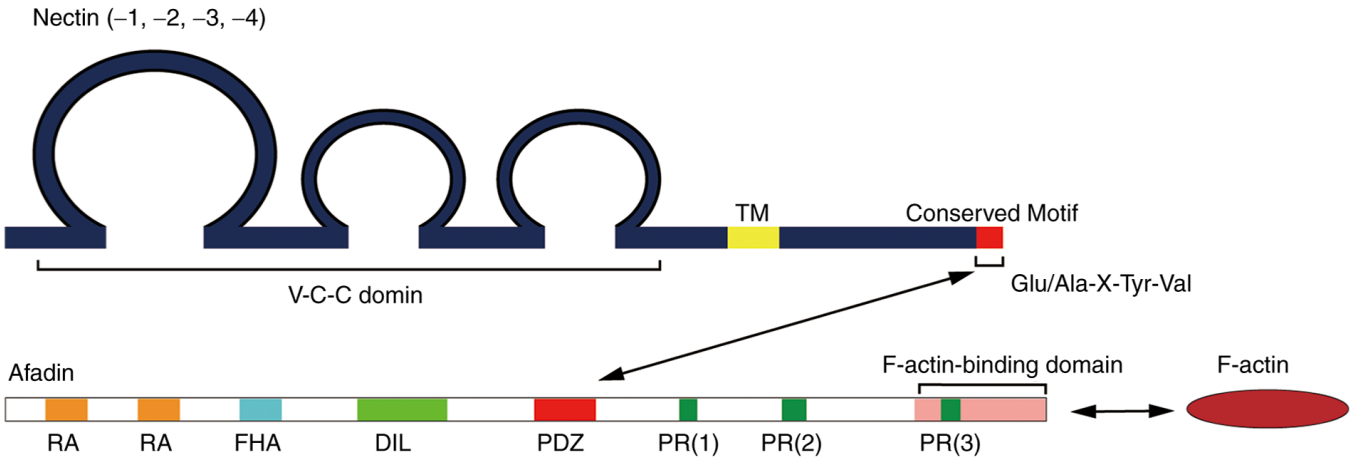

Figure 1. Molecular structures of Nectin and Afadin. Four amino acid residues (Glu/Ala-X-TyrVal) exist in the carboxyl termini of Nectin-4, which combines with the PDZ domain of Afadin. TM, transmembrane region; RA, Ras-associated domain; FHA, forkhead-associated domain; DIL, dilute domain; PR, proline-rich domain.

mainly located in neurons, fibroblasts and epithelial cells (38), where Nectin-2 and -3 are also enriched in hemocytes (B cells and monocytes) and spermatids (Table I) (19). In normal tissues, Nectin-1 and -2 are closely related to immune organs, while Nectin-4 is widely enriched in embryonic and placental tissues, including the skin, tonsils and tubular structure (trachea, esophagus and nasopharynx) (3,4). Additionally, the abnormal expression of Nectin is a cause for disease occurrence. For example, the occurrence of human Zlotogora-Ogur syndrome is the result of mutations in Nectin-1 (45). Also, Nectin-4 significantly affects the development of ectodermal organogenesis, and Nectin-4 mutations lead to a dysplasia-syndactyly syndrome characterized by webbed hands and feet (46).

5. Biological role of Nectin-4 proteins in cancer

In contrast to the distribution of Nectins 1-3, which are widely present in the tissues of a normal adult, Nectin-4 is specifically enriched in the embryonic and placental tissues, but has significantly decreased levels in adult life (4). In recent years, Nectin-4 was found to be overexpressed and served as an inducer in various malignant tumors, including BC, OC, colorectal cancer (CRC), PC and lung cancer (9-14). For example, Challita-Eid *et al* (47) collected >2,000 tumor samples from head/neck, lung, bladder, breast, pancreatic, ovarian and esophageal lesions, and approximately two-thirds were positive for Nectin-4 according to immunohistochemical (IHC) staining. In other studies, Nectin-4 was correlated with tumor occurrence and development (12,14), contributed to the occurrence of metastases in breast, lung and gallbladder tumors (48,49), was associated with advanced Tumor-Node-Metastasis (TNM) stage (III and IV) and decreased survival rates (50), and promoted cancer chemoresistance to 5-fluorouridine (5-FU) (51). Although the precise molecular mechanisms in oncogenesis and progression have not been clarified, numerous studies have reported that Nectin-4 promotes tumor angiogenesis, proliferation and migration, and triggers EMT.

Nectin-4 promotes tumor angiogenesis. Recent studies have revealed that Nectin-4 promotes tumor angiogenesis via the activated PI3K/AKT signaling pathway (52,53). Angiogenesis is the crucial foundation for tumor growth, spread, invasion and expansion (54,55). A considerable amount of vascular endothelial growth factor (VEGF) and increased microvessel density (IMD) were detected in the tumor microenvironment during angiogenesis (56,57). Zhang *et al* (52) demonstrated that the high expression of Nectin-4 protein is linked to integrin β1 (ITGB1) protein and vasculogenic mimicry (VM) formation. In PC, upregulated Nectin-4 stimulates cell growth

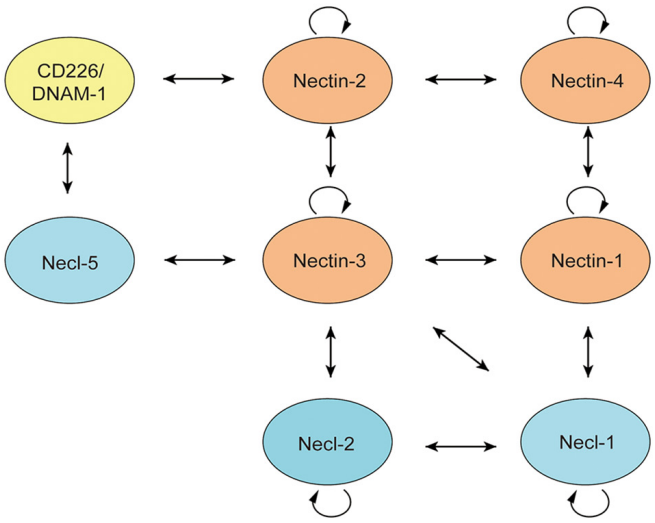

Figure 2. Homophilic and heterophilic trans-interactions among Nectins, Necls and other Ig-like molecules. Only known homophilic (looped arrows) and heterophilic (double arrows) interactions are indicated. Necl, neclin.

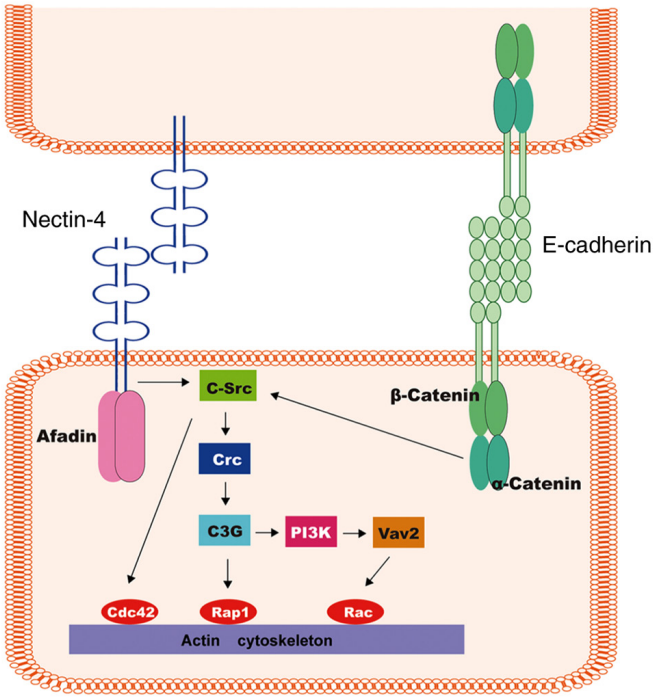

Figure 3. Nectin-induced signaling during the formation of cell-cell junctions. Nectins exert essential influence on the primary step of cell-cell junction formation. Once the interaction is established, these cadherin-catenin complexes will be recruited to the corresponding adhesion site. Subsequently, the Nectin/Afadin complex and the E-cadherin/catenin complex function through Afadin and α-catenin, respectively, activating a signaling cascade (c-Src, C3G, Crk, PI3K and Vav2), thus modulating molecules such as Rap1, Cdc42 and Racs, and ultimately leading to actin cytoskeleton realignment.

and has a vital impact on intratumoral angiogenesis (14). The downregulation of Nectin-4 inhibits the expression of VEGF and tumor angiogenesis in lung cancer and CRC (53). Further studies have shown that the interplay between Nectin-4 and endothelial ITGB4 modulates the transcriptional activity of Src, PI3K, AKT and inducible nitric oxide synthase, and ultimately induces angiogenesis (53).

Nectin-4 promotes tumor cell growth, proliferation and migration. Nishiwada *et al* (14) reported that knockdown of Nectin-4 inhibited the proliferation of human PC cells. Similarly, Zhang *et al* (48) demonstrated that the low expression of Nectin-4 restrained gall bladder cancer cell proliferation and migration *in vivo* and *in vitro*. The potential mechanism by which Nectin-4 promotes tumor cell growth, proliferation and migration is via Ras-related C3 botulinum toxin substrate 1 (Rac1) signaling activity (58,59). Rac1 is one of the members of the Rho family of GTPases, which exert a significant influence on tumor occurrence and development (60,61). Rac1 GTPase switches Rac1-GDP ('OFF' state) to Rac1-GTP ('ON' state) (62,63). Subsequently, it activates several protein kinases, including p21-activated kinases and c-Jun N-terminal kinase, thereby modulating downstream molecule signaling cascades, including the regulation of cell growth, proliferation and microtubule rearrangement (64-67). Several studies reported that elevated levels of Rac1 could be attributed to the upstream modulator of PI3K/AKT in gallbladder carcinoma, gastric cancer (GC) and BC (48,50,54).

Nectin-4 promotes EMT. EMT is the most critical cellular event before the occurrence of tumor migration, invasion and metastasis (68). A previous study demonstrated that Nectin-4 regulates cell-cell adhesion, remodels the actin cytoskeleton, triggers EMT, enhances the driving force of pseudopod extension in tumor cells, and eventually causes tumor development and spread (35). In a recent study by Hao *et al* (69), the downregulation of Nectin-4 in papillary thyroid cancer (PTC) cells suppressed EMT and inhibited PTC cell migration and invasion via the PI3K/AKT signaling pathway. Zhang *et al* (48) also reported that the upregulation of Nectin-4 regulated the formation of actin fibers by binding to Afadin and activating the PI3K/AKT pathway, which in turn activated Rac1 to regulate EMT and then control cell shape rearrangement and metastasis.

6. Nectin-4 serves as a prognostic or diagnostic marker for selected types of cancer

The biological role of Nectin-4 in promoting proliferation, migration and triggering metastasis in carcinogenesis is under intensive research focus (48-50,68,69). Despite the fact that the expression level or the positive rate of Nectin-4 are different among selected types of tumor specimens, most studies have confirmed Nectin-4 as a prognostic and diagnostic biomarker. The clinicopathological characteristics and prognostic analysis based on tumor Nectin-4 expression are summarized in Table II.

BC

Mixed BC. BC is a complicated and molecularly heterogeneous disease, presenting varied histological features (70). A total of 57 mixed BC samples were collected in the study by Fabre-Lafay *et al* (13). According to the distinction of the tumor histological type, the positive expression of Nectin-4 displayed a marked difference between the ductal carcinoma and lobular carcinomas (~60 and 5%, respectively). However, a clear difference between tumor histological types was not found in the study by Athanassiadou *et al* (71).

Table II. Clinicopathological characteristics and prognostic analysis according tumor Nectin-4 expression.

First author	Year of publication	Country	Cancer	Cases, n	Age (range), years	Follow-up (range), months	Nectin-4 protein level	High Nectin-4 expression on IHC, % (n/total n)	OS, months	OS Univariate analysis, HR (95% CI); P-value	OS Multivariate analysis, HR (95% CI); P-value	Nectin-4- related clinicopathological parameters	(Refs.)
Zeindler *et al*	2019	Switzerland	TNBC	168	Mean, 62 (47-77)	50.40	↑	58.00% (86/148)	NA	0.0271 (0.0077-0.0952); P<0.001	0.0220 (0.0055-0.0889); P<0.001	Lower tumor stage (P=0.025); pN0 lymph node stage (P=0.034)	(74)
Rajc *et al*	2017	Croatia	Luminal-B BC	147	Mean, 62 (53-70)	80.70 (35.70-103.50)	↑	NA	NA	P<0.001	2.92 (1.8-4.75); P<0.001	Tumour size (P<0.05)	(72)
M-Rabet *et al*	2017	France	TNBC	61	NA	83	↑	62.00% (38/61)	NA	1.65 (1.1-2.47); P=0.0154	1.53 (1.02-2.30); P=0.039	TN (P<0.05); Basal subtypes (P<0.05)	(73)
Lattanzio *et al*	2014	Italy	Luminal A-BC	197	Median, 54.90	95 (6-298)	↑	m-Nectin-4: 13.70%; c-Nectin-4: 61.90%	NA	NA	m-Nectin-4: 4.0 (1.5-10.8) P=0.007; c-Nectin-4: 3.5 (1.1-11.6) P=0.038	m-Nectin-4: PR (P=0.045); c-Nectin-4: ER (P=0.038)	(75)
Athanassiadou *et al*	2011	Greece	BC	140	Mean, 55.72 (28-85)	60	↑	64.30% (90/140)	Mean 36.71; Median 37.5	P>0.05	P>0.05	Grade (II and III) (P<0.0001); tumor size (P<0.0001)	(71)
Fabre-Lafay *et al*	2007	France	BC	57	NA	NA	↑	61%	NA	NA	NA	Number of metastases (P=0.038)	(13)
Erturk *et al*	2019	Turkey	LC	74	Median, 60 (28-78)	NA	↑	NA	NA	NA	P=0.758	Disease stage; history of surgery; tumor size; presence of metastasis (all, P<0.05)	(83)
Takano *et al*	2009	Japan	NSCLC	422	Median, 55 (31-83)	NA	↑	58.10% (245/422)	NA	2.116 (1.551-2.887); P<0.0001	2.145 (1.558-2.954); P<0.0001	Histological type (P=0.0059)	(10)
Tomiyama *et al*	2020	Japan	UTUC	99	NA	NA	↑	65.70% (65/99)	NA	2.69 (0.90-6.50); P=0.072	2.10 (0.64-5.81); P=0.179	Higher risk of progression (P=0.031); CSM (P=0.036)	(85)
Zhang *et al*	2019	China	CRC	68	Median, 56 (26-81)	NA	↑	70.60% (48/68)	Median, 25.0	NA	NA	ITGB1 expression (P<0.01); VM formation (P<0.05); DMS (P=0.031); TNM stage; (P=0.033)	(52)
Deng *et al*	2019	China	EC	NA	NA	NA	↑	NA	NA	1.704 (1.027-2.825); P=0.039	1.795 (1.042-3.092); P=0.035	Tumor size (P=0.012); tumor stage (P=0.016)	(55)
Lin *et al*	2019	China	EC	94	NA	NA	↑	37.80% (31/82)	NA	1.747 (1.003-3.044); P<0.05	P<0.05	Tumor size (P=0.012); depth of tumor invasion (P=0.008)	(12)

Table II. Continued.

First author	Year of publication	Country	Cancer	Cases, n	Age (range), years	Follow-up (range), months	Nectin-4 protein level	High Nectin-4 expression on IHC, % (n/total n)	OS, months	OS Univariate analysis, HR (95% CI); P-value	OS Multivariate analysis, HR (95% CI); P-value	Nectin-4-related clinicopathological parameters	(Refs.)
Zhang *et al*	2018	China	GC	64	NA	NA	↑	70.30% (45/64)	NA	NA	NA	LNMets (P=0.025); TNM stage (P=0.006)	(50)
Zhang *et al*	2018	China	GC	212	Median, 55.30	NA	↑	60.40% (128/212)	NA	3.815 (2.243-6.490); P<0.001	2.402 (1.364-4.232); P=0.002	Differentiation (P=0.004); primary tumor (P=0.001); LNMets (P<0.001); TNM stage (P<0.001)	(49)
Nishiwada *et al*	2015	Japan	PC	123	Median, 66 (33-82)	NA	↑	51.4%	Median, 14.20	1.628 (1.105-2.398); P=0.014	1.721 (1.085-2.730); P=0.021	Ki-67 expression (P<0.001); VEGF expression (P<0.001)	(14)
Izumi *et al*	2015	Japan	PC	49	Median, 67 (50-87)	27.20 (2.40-117.20)	↑	NA	NA	NA	NA	Tumor size (P=0.035)	(86)
Zhang *et al*	2016	China	GBC	68	NA	NA	↑	63.20% (43/68)	Mean, 6.82	3.150 (1.788-5.552); P<0.001	2.704 (1.527-4.788); P=0.001	Pathological T stage (P=0.029); LNMets P=0.041)	(48)
Ma *et al*	2016	China	HCC	87	NA	23 (2-60)	↑	67.82% (59/87)	Median, 21.92	2.054 (1.202-3.507); P=0.008	2.085 (1.216-3.574); P=0.008	Tumor size (P=0.029); status of metastasis (P=0.023); vascular invasion (P=0.018); TNM stage (P=0.003).	(87)

BC, breast cancer; TNBC, triple-negative BC; LC, lung cancer; NSCLC, non-small cell lung cancer; CSM, cancer-specific mortality; DMS, distant metastasis stage; HGSOC, high-grade serous ovarian cancer; CRC, colorectal cancer; EC, esophageal cancer; GC, gastric cancer; PC, pancreatic cancer; GBC, gallbladder cancer; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; m-Nectin-4, membranous-Nectin-4; c-Nectin-4, cytoplasmic-Nectin-4; ITGB1, integrin β1; VM, vasculogenic mimicry; TN, tumor and node; TNM, Tumor-Node-Metastasis; VEGF, vascular endothelial growth factor; LNMets, lymph node metastases; OS, overall survival; PR, progesterone receptor; ER, estrogen receptor; NA, not available; ↑, increase.

Approximately two-thirds of samples were found to be positive for Nectin-4 protein expression and have a correlation with tumor size, grade and lymph node infiltration. Thus, the correlation between the expression of Nectin-4 and the histological types is controversial. Perhaps, the definition of Nectin-4 positive or negative expression may not be consistent, and the expression might be influenced by the antibody titer. Furthermore, the limited tumor specimens from each cohort might affect the final results. Hence, additional studies with a large number of samples are essential to verify the connection between Nectin-4 and the histological type.

Luminal $B^{HER2\ negative}$ BC. Rajc *et al* (72) analyzed results from 147 patients who suffered from luminal $B^{HER2\ negative}$ BC to determine the correlation between Nectin-4 protein expression and clinicopathological parameters. The results revealed that Nectin-4 expression was not correlated with Ki-67 and the hormone and growth factor receptors. In addition, the downregulation of Nectin-4 may improve the survival rate, including disease-free survival (DFS), overall survival (OS) and distant relapse-free survival (RFS) rates.

Triple-negative BC (TNBC). A large retrospective study of ~6,000 patients with BC was conducted by M-Rabet *et al* (73). The upregulation of Nectin-4 was observed in the majority of specimens. Furthermore, the results confirmed that Nectin-4 was a novel biomarker associated with the poor prognosis for TNBC. Among the ~60 patients with TNBC, those with upregulated Nectin-4 were more likely to have a shorter life span compared to those with downregulated Nectin-4. In the established animal models of TNBC, M-Rabet *et al* (73) used antibody-drug conjugates (ADCs) targeting Nectin-4 to evaluate the curative effect, with satisfactory results. The results revealed that this ADC induced rapid, complete and durable responses in Nectin-4-positive xenograft TNBC samples, including primary tumors, metastatic lesions and local relapses. However, another study by Zeindler *et al* (74) collected nearly 200 samples of TNBC, and the results showed that the elevated level of Nectin-4 was the protective factor in TNBC. Moreover, the results demonstrated that upregulated Nectin-4 expression was correlated with low-grade malignancy, improved survival and no lymph node involvement (LNI). The relationship between Nectin-4 overexpression and the prognosis of TNBC is controversial. It may be that the final adjuvant treatment results were not unified and that there was a lack of complete clinical information for the aforementioned cohorts utilized. Therefore, high-quality evidence from a large number of patients with TNBC is needed to clarify the uncertainties.

Luminal-A BC. Nectin-4 exists in the cytoplasm and membrane of malignant cells, which has been termed cytoplasmic-Nectin-4 (c-Nectin-4) and membranous-Nectin-4 (m-Nectin-4), respectively (13). Approximately 200 luminal-A patients were incorporated in the study by Lattanzio *et al* (75). The distribution of high Nectin-4 differed markedly between the cytoplasm and membrane (18 and 75%, respectively). Both m-Nectin-4 and c-Nectin-4 were shown to be closely related to the DFS, as assessed by Cox proportional hazards model. Furthermore, the upregulated level of the protein could be considered as an adverse biomarker and therapeutic target for luminal-A BC (75).

Nectin-4 occurs in soluble form in the plasma. Soluble-Nectin-4 (s-Nectin-4) is formed from the ectodomain of Nectin-4, which is cleaved by a disintegrin and metalloproteinase 17 (76). s-Nectin-4 could also be regarded as a diagnostic indicator of BC. Fabre-Lafay *et al* (13) demonstrated that s-Nectin-4 in serum increased the accuracy rate of clinal diagnosis for BC. Compared to a single indicator (CEA/CA15-3), the diagnostic accuracy was increased by 10% using a combination of Nectin-4/CEA/CA15-3. Furthermore, s-Nectin-4 was significantly connected with the number of metastases (Table II).

Reproductive system cancer

OC. Hibbs *et al* (77) and Derycke *et al* (11) reported that Nectin-4 is upregulated in OC at both mRNA (OC cell lines) and protein (OC tissues) levels, respectively. In the study by Nabih *et al* (78), 25 patients with OC were included. The majority of patients presented with high expression of Nectin-4. Furthermore, several studies demonstrated that Nectin-4 overexpression facilitates cell aggregation and formation of spheroids in OC cell lines using functional assays and real-time digital photographs (79-82). In addition, these multicellular spheroids were resistant to chemotherapy drugs that lead to tumor growth and metastasis (81).

Previous studies have shown that s-Nectin-4 might serve as a marker of disease relapse and metastasis in breast carcinoma (10,15). Derycke *et al* (11) also found that s-Nectin-4 was upregulated in OC. Nabih *et al* (78) further revealed a close correlation between s-Nectin-4 and tumor stages and disease progression. In addition, the studies by Nabih *et al* (78) and Derycke *et al* (11) agreed that Nectin-4 is a valuable diagnostic predictor to differentiate between benign and malignant ovarian tumors. Furthermore, Nectin-4 combined with CA-125 had a higher sensitivity and specificity compared with Nectin-4 or CA-125 alone. As a consequence, a Nectin-4 and CA-125 combination is able to monitor the treatment effect and relapse of patients with OC.

Respiratory system tumors

Lung cancer. Approximately 420 patients with non-small cell lung cancer (NSCLC) were included in the study by Takano *et al* (10). Nearly two-thirds of patients presented with upregulation of Nectin-4 and poor survival. The results also demonstrated that the upregulation of Nectin-4 was one of the most crucial independent prognostic factors of OS for NSCLC (Table II). The underlying mechanism involved Nectin-4 acting on Rac1 and stimulating the extension of lamellipodia, and improvement to the movement capacity of lung cancer cells. In addition, s-Nectin-4 was upregulated in patients with NSCLC. Notably, patients with high expression of s-Nectin-4 had a short survival time and undesirable tumor metastasis. In contrast to CEA and CYFRA21-1, Nectin-4 had the advantages of high accuracy and specificity for lung cancer diagnosis (10). In the recent study of 77 lung cancer samples, Erturk *et al* (83) assessed the correlation between Nectin-4 and clinicopathological parameters. The results showed that Nectin-4 was involved in tumor size, tumor stage and distant metastasis.

Urinary system tumors

Urothelial carcinoma (UC). Recently, in a study investigating predominantly bladder cancer cases, a study showed that more than half of UC samples were positive for Nectin-4 protein expression (84). Another study showed that the majority of patients with bladder cancer (83%) were Nectin-4-positive, as assessed by IHC, and ~50% of specimens exhibited moderate or high levels of staining of Nectin-4 (48). Similar results were found in the study by Tomiyama *et al* (85), where ~66% of bladder cancer samples tested were moderately or highly positive for Nectin-4. Furthermore, upregulated Nectin-4 expression was correlated with tumor progression.

In one study of UC, Nectin-4 was upregulated in 95% of metastatic samples (48). In addition, Tomiyama *et al* (85) reported that ~66% of patients presented with high Nectin-4 levels in upper tract urothelial carcinoma (UTUC). The upregulation of Nectin-4 was often accompanied by poor prognostic markers, such as lymphovascular invasion and high tumor grade. Moreover, UTUC with upregulated Nectin-4 was associated with a risk of poor progression-free survival (PFS) (Table II).

Digestive system cancer

CRC. A total of 370 CRC samples were obtained from The Cancer Genome Atlas database (https://www.genome.gov/Funded-Programs-Projects/Cancer-Genome-Atlas). The results demonstrated that Nectin-4 was connected with TNM stage and LNI (52). To further substantiate these findings, Zhang *et al* (52) collected a different cohort encompassing 68 CRC samples. Upregulated Nectin-4 was observed in >70% of patients, and its expression was strongly linked to ITGB1 protein, VM formation and TNM stage (Table II). The study suggested that Nectin-4 promoted angiogenesis and facilitated the progression of CRC. It was also reported that Nectin-4 had a crucial impact on colon cancer chemoresistance to 5-FU. The cell culture tests showed that Nectin-4 overexpression in CRC cells facilitated the growth, proliferation and movement of cells, and enhanced the resistance to chemoradiotherapy via the PI3K/AKT signaling pathway. Nectin-4 silencing mediated by si-Nectin-4 reversed chemotherapeutic drug resistance and improved the effect of treatment in the CRC cells, thereby indicating that gene silencing could be considered as a novel therapeutic strategy for CRC (51).

Esophageal cancer (EC). In a recent study by Deng *et al* (55), results revealed that Nectin-4 was upregulated in human EC samples. The study further confirmed a close connection between Nectin-4 protein expression and tumor size and stage. Moreover, patients with upregulated Nectin-4 had a worse survival time than those with downregulated expression, as assessed by the Cox model analysis [hazard ratio (HR), 1.795; P=0.035] (Table II). Also, Nectin-4 was shown to enhance cell viability and migration in EC cell lines, as well as to facilitate tumor formation *in vivo* (55). These findings were consistent with a recent study by Lin *et al* (12), wherein ~40% of patients presented with increased Nectin-4 expression in EC. The study also revealed that increased Nectin-4 was markedly involved in tumor size and depth of tumor invasion. In addition, Nectin-4 expression was an unfavorable risk factor for EC, as shown by the multivariate Cox model (P<0.05; Table II).

GC. In the study by Zhang *et al* (50), over two-thirds of GC samples presented upregulated Nectin-4. In addition, Nectin-4 upregulation was closely correlated with LNI and TNM stage (Table II) and an increased risk of decreased 5-year survival rate. The study also showed that the overexpression of Nectin-4 specifically targets the downstream molecule PI3K/AKT and then acts on Rac1 to facilitate cell proliferation and movement. In another study (49), high expression of Nectin-4 was detected in 60.4% (128/212) of GC tumors and was deemed to be an adverse biomarker for survival in patients with GC (HR, 2.402; P=0.002).

PC. Nishiwada *et al* (14) reported that >50% of PC tissues are Nectin-4-positive, and upregulated Nectin-4 has been shown to be associated with an unfavorable prognosis of PC. The patients with upregulated Nectin-4 expression showed a significantly shorter survival time compared with those in the low expression group (P<0.01). The study also demonstrated a vital connection between Nectin-4 and Ki-67 expression (P<0.001). Patients with upregulated Nectin-4 were more likely to have a high expression level of Ki-67. Hence, Nectin-4 could be considered as a novel proliferation marker and was also confirmed as a crucial biomarker associated with poor survival (P=0.021). Moreover, the findings also revealed that Nectin-4 in PC was positively and prominently associated with IMD and VEGF expression. In a similar study, Izumi *et al* (86) reported that upregulated Nectin-4 might be an undesirable risk factor for PC. Also, patients with upregulated Nectin-4 expression exhibited a larger tumor size compared with those with low expression.

Hepatocellular carcinoma (HCC). In the study by Ma *et al* (87), a total of 87 HCC samples were collected. Approximately 68% of HCC samples presented noticeably higher expression of Nectin-4 protein than normal samples. Moreover, upregulated Nectin-4 was correlated with TNM stage, tumor size, spread and metastasis, and vascular involvement. Patients in the Nectin-4-positive group exhibited a worse prognosis compared with those in the negative expression group. Moreover, Nectin-4 was a valuable biomarker for predicting RFS and OS. Also, Nectin-4 targeted PI3K/AKT via the Nectin-Afadin complex to regulate various cellular processes, including increased cell growth, inhibited apoptosis, and increased local infiltration and transfer in HCC tumor cells (23).

Gallbladder cancer (GBC). A total of 68 patients with GBC were enrolled in a study by Zhang *et al* (48), and positive Nectin-4 expression was observed in ~65% of samples. In contrast to normal tissues, GBC samples exhibited a higher expression level of Nectin-4 (P<0.01). The study also showed that Nectin-4 was closely associated with the pathological stage and LNI (Table II). Notably, patients with upregulated Nectin-4 were likely to have a short survival time. Thus, upregulated Nectin-4 can be considered as a novel biomarker associated with poor prognosis, as assessed using Cox model

Table III. Clinical trials using EV in advanced or metastatic urothelial carcinoma.

Factor	EV-101	EV-201	EV-103	EV-301	EV-302
NCT (clinicaltrials.gov) no.	NCT02091999	NCT03219333	NCT03288545	NCT03474107	NCT04223856
(Refs.)	(93,94)	(95)	(96)	(97)	(95,97)
Phase	I	II	I	III	III
Line of treatment	Later-line	Later-line	First-line	Later-line	First-line
Prior treatment	CT	CT or ICI	NO	Both platinum-based CT and ICI	NO
Comparison	NA	Once accepted, platinum-based CT and ICI vs. ICI	Comparing EV in combination with ICI(P) and/or CT	EV vs. CT (except platinum)	Comparing EV in combination with P with or without CT vs. CT
EV dose	1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle.	1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle.	1.25 mg/kg on days 1 and 8 of a 21-day cycle.	1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle.	1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle.
Population	112	125	45 (preliminary)	301	1,095 (aim)
ORR (95% CI), %	43 (33.6-52.6)	52 (41-62)	73.3 (58.1-85.4)	40.6 (34.9-46.5)	NA
CR, %	5	20	15.6	4.9	NA
PR, %	38	31	58	NA	NA

CT, chemotherapy; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; P, pembrolizumab; ORR, overall response rate; CR, complete response; PR, partial response; NA, not available.

analysis (HR, 2.704; P=0.001). Furthermore, Nectin-4 was identified to regulate GBC cell growth, movement and spread by stimulating the PI3K/AKT signaling cascade, and the process could be suppressed by RNA interference *in vitro* and *in vivo* (48).

7. Enfortumab vedotin (EV)

As aforementioned, Nectin-4 may be a prognostic marker specifically upregulated in various cancer types, which promotes tumorigenesis and progression (49,52,58,61). Thus, it could be a promising novel molecular target for developing therapeutic strategies for cancer. EV is a new type of ADC targeting Nectin-4 in clinical practice (88,89). ADCs are novel monoclonal antibodies coupled with robust biological drugs via a labile crosslinker. Importantly, the antibody links with a specific antigen only found on target tumor cells. Therefore, ADCs have an advantage over traditional drugs in the aspect of drug specificity (88). When the monoclonal antibody binds to antigen receptors of tumor cells, it triggers the internalization of the antibody and mediates drug release that could be viewed as 'targeted chemotherapy' (89). The effectiveness of ADC therapy depends on the specificity of the antibody (90). Typically, two classical ADCs, Adcetris and Kadcyla, have been widely utilized in clinical practice to treat Hodgkin's lymphoma$^{CD30\text{-}positive}$ and BC$^{HER2\text{-}positive}$, respectively (88). Moreover, as a novel ADC, EV comprises the monoclonal antibody targeting Nectin-4 and is coupled with a microtubule-disrupting agent, known as monomethyl auristatin E (MMAE), via a protease-cleavable maleimidocaproyl valine-citrulline linker (91). After EV is linked to the V-C-C domain of Nectin-4 antigen, it triggers complex internalization and translocates to the lysosome to cleave the valine-citrulline linker and release MMAE in target cells. Subsequently, MMAE combines with tubules and accelerates microtubule disassembly, ultimately playing an efficient role against cancer (88,90,91) (Fig. 4). Clinically, EV was approved by the US Food and Drug Administration (FDA) in 2019 for treating locally advanced or metastatic UC (mUC) after the failure of previous chemotherapy regimens and immune checkpoint inhibitors (ICIs) (85).

In 1990, platinum-based chemotherapy was the first choice for the treatment of mUC. Although the survival of patients was prolonged, the tolerance to intensive chemotherapy was poor (85). Since 2016, several ICIs, including atezolizumab, nivolumab, pembrolizumab, durvalumab and sacituzumab govitecan antibodies, targeting programmed cell death protein-programmed death ligand 1 (PD-1/PD-L1) and tumor-associated calcium signal transducer 2, achieved outstanding results. However, despite better drug tolerance and fewer adverse drug reactions, the response rates to PD-1/PD-L1 were low (91). In 2019, targeted EV therapeutics showed promising results in terms of response rates for patients who had undergone heavy treatment, including ICI and/or platinum-containing chemotherapy (91,92). The approval process timeline for treatments for mUC is shown in Fig. 5. Owing to the encouraging nature of existing data, several clinical trials based on EV treatment are underway. The current review presents the clinical efficacy data for patients treated with EV.

EV-101 trial. A total of 155 patients with mUC who suffered from drug (chemotherapy or ICI) failure or did not meet the requirements of chemotherapy were recruited in the phase I trial (EV-101, NCT02091999) between June 23, 2014, and October 25, 2018 (93). Subsequently, 112 patients were treated with a recommended phase II dose (1.25 mg/kg EV once a week over a 4-week cycle). Prior to EV treatment, ~96% of these patients experienced chemotherapy failure, and 72% of patients accepted anti-PD-1/PD-L1 treatment. The overall response rate (ORR), complete response (CR) rate and partial response (PR) rate was 43, 5 and 38%, with a median PFS time of 5.4 months and a median duration of response (DOR) of 7.4 months. In patients

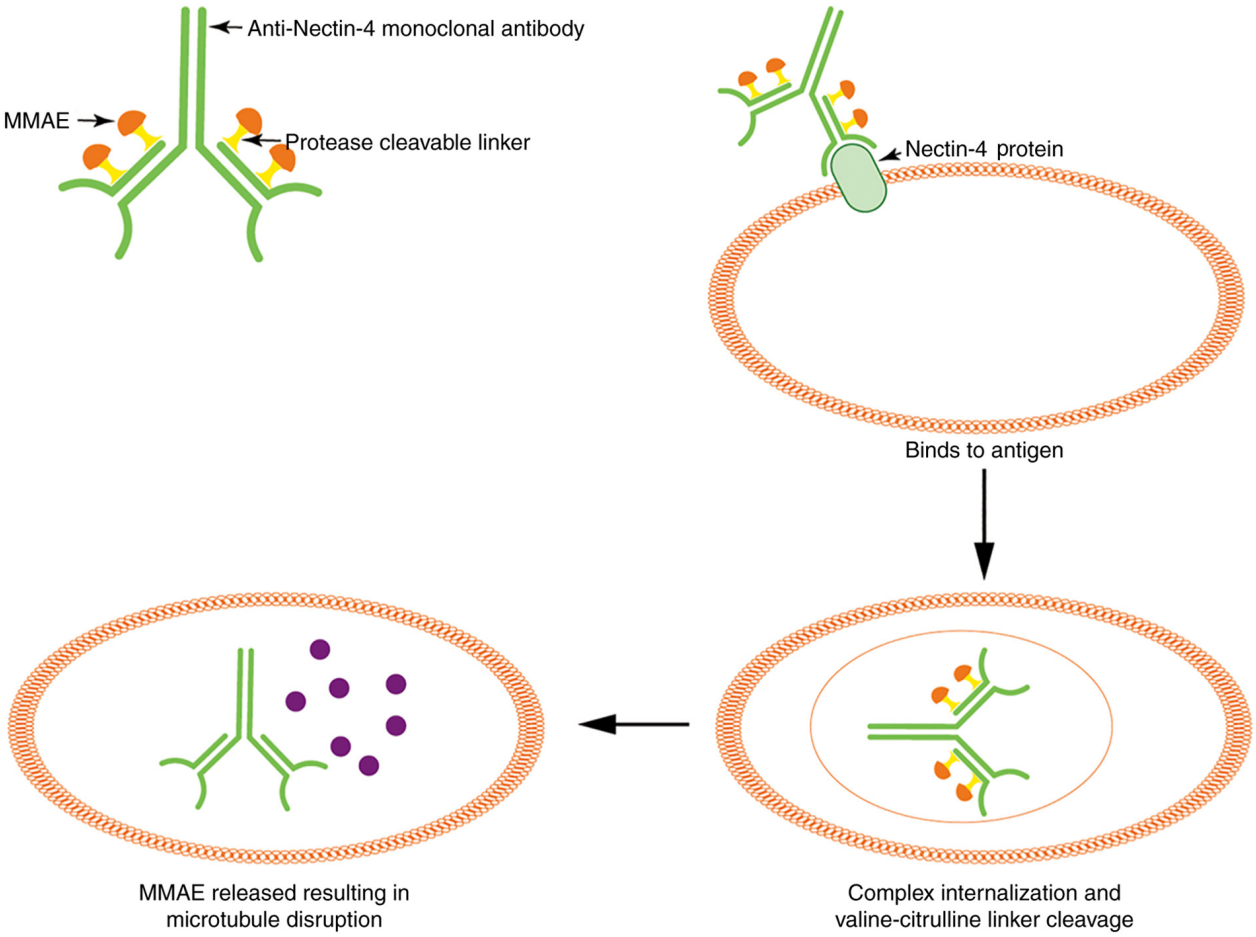

Figure 4. Mechanism of action for EV. Once EV unites to the V-C-C domain of Nectin-4 antigen, triggering the complex internalization, it is then transferred to the lysosome, which cleaves the valine-citrulline linker and causes the release of MMAE into target cells. Subsequently, MMAE could combine with tubules and accelerate microtubule disassembly, ultimately play an efficient role in against cancer. MMAE, monomethyl auristatin E; EV, enfortumab vedotin.

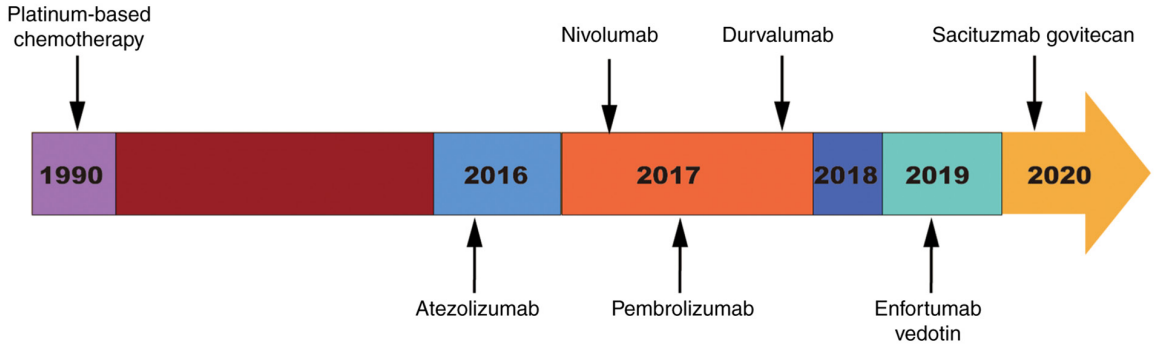

Figure 5. US Food and Drug Administration approval timeline for chemotherapy, ICIs and EV against mUC. In 1990, platinum-based chemotherapy was first used to treat mUC. Since 2016, ICIs, including atezolizumab, nivolumab, pembrolizumab, durvalumab and sacituzumab govitecan antibodies, which targeted programmed cell death protein 1 and tumor-associated calcium signal transducer 2, successively came on the market against mUC. In 2019, EV was approved for treating patients with mUC. ICIs, immune checkpoint inhibitors; mUC, metastatic urothelial carcinoma; EV, enfortumab vedotin.

with a history of liver metastasis and treatment with PD-1/PD-L1 inhibitor, the ORR was 42 and 36%, respectively (Table III). The median OS time with 1.25 mg/kg EV was 12.3 months (95% CI, 9.3-15.3), and the OS rate at 1 year was 51.8%, with a median follow-up time of 16.4 months (94).

EV-201 trial. A total of 125 patients undergoing chemotherapy or PD-1/PD-L1 inhibitor treatment for advanced mUC were enrolled in the phase II trial (EV-201 trial, NCT03219333) between October 8, 2017, and February 11, 2020. Prior to EV treatment, these enrolled patients were categorized into two groups as follows: Group 1, once received combination treatment of platinum-based chemotherapy and PD-1/PD-L1 inhibitor; and group 2, only once received PD-1/PD-L1 inhibitor. In group 2 of EV-201, the enrolled 89 patients were treated with EV at a dosage of 1.25 mg/kg once a week over a 4-week

cycle. At data cutoff (September 8, 2020), the ORR, CR rate and PR rate were 52% (46/89 patients), 20% (18/89 patients) and 31% (28/89 patients), respectively, with a median follow-up time of 13.4 months (Table III). The median PFS time was 5.8 months (95% CI, 5.03-8.28) (95).

EV-103 trial. The EV-103 trial (NCT03288545) is another phase I, multicenter clinical trial in progress. All patients received a combination treatment of EV plus PD-1 inhibitor (pembrolizumab) and/or chemotherapy as the first choice for treating advanced UC or mUC. Prior to combination treatment, the trial collected 45 mUC patients unsuitable for chemotherapy. In addition, these patients were treated with EV (at a dosage of 1.25 mg/kg once a week over a 3-week cycle) combined with a PD-1/PD-L1 inhibitor (at a dose of 200 mg on days 1, 8 and 15 over a 3-week cycle). At the recent 2020 American Society of Clinical Oncology (ASCO) virtual meeting, Rosenberg reported that these combined therapies showed encouraging and durable activity, with an ORR of 73.3%, a CR rate of 15.6%, a PR rate of 58% and a median PFS time of 12.3 months, while 93% had a decline in target lesions (96). Due to these results, on February 18, 2020, the FDA granted a breakthrough therapy designation for the combination of EV and pembrolizumab for cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma as the first-line treatment (96).

EV-301 trial. Patients with previous platinum-based chemotherapy and PD-1/PD-L1 inhibitor treatment were enrolled in the phase III trial of EV-301 (NCT03474107) between June 2018 and July 2020. A total of 608 patients were randomly assigned to two groups in a 1:1 ratio. A total of 301 patients accepted EV alone (at a dosage of 1.25 mg/kg once a week over a 4-week cycle) and 307 patients accepted a chemotherapy regimen, excluding platinum (given on days 1, 7 and 15 over a 3-week cycle) (Table III). The ORR and CR rate were lower in the chemotherapy group than in the EV group (17.9 vs. 40.6% and 2.7 vs. 4.9%, respectively). In addition, the OS and PFS times were longer in the EV group than those in the chemotherapy group, with a median follow-up time of 11.1 months (HR, 0.70; P=0.001; and HR, 0.62; P<0.001, respectively) (97).

EV-302 trial. The EV-302 trial (NCT04223856) is a phase III study enrolling patients with mUC who have not received any prior treatment. This trial aims to observe and compare the therapeutic effect between chemotherapy alone and the combination of EV and PD-1/PD-L1 inhibitors with or without chemotherapy. The study is divided into three groups: Group A, pembrolizumab plus EV; group B, cisplatin/carboplatin plus gemcitabine; and group C, pembrolizumab plus EV plus cisplatin/carboplatin. The PFS and OS are the main observation indexes. ORR, DOR and disease control rate are secondary observation indexes. This trial is open for registration and aims to enroll 1,095 patients by November 2023 (Table III) (95,97).

8. Oncolytic virus

As aforementioned, Nectin-4 is a tumor cell marker highly expressed on the apical surface of a number of adenocarcinoma cell lines and correlated with tumor progression and worse prognosis (49-55,66,71). Unexpectedly, Nectin-4 can also serve as another receptor for measles virus (MV) oncolytic therapy (98). In the past decades, MV, as a member of the Paramyxoviridae family, was found to be likely to infect the respiratory system (99). Importantly, MV can serve as an oncolytic virus, characterized by the ability to attack and dissolve cancer cells, but to not hurt normal cells. Previously, several studies have shown that MV could act as a 'natural cancer cell-killer' for Burkitt's lymphoma and Hodgkin's disease during natural virus infections. This phenomenon could be attributed to the fact that MV recognizes and binds to CD150/SLAM receptors that are explicitly expressed in these tumors, inducing a cascade of immune responses (100,101). However, accumulating evidence over the past decade has shown that MV infects several cell lines independently of the CD150/SLAM receptors, leading to the discovery of new receptors for MV therapy. Noyce *et al* (21) reported that cells that synthesized Nectin-4 became susceptible to MV infection, identifying this membrane protein as the elusive epithelial receptor. The interaction between MV and Nectin-4-positive cancer cells triggers MV internalization and exerts an oncolytic effect (21). In addition, some synthetic MVs carry therapeutic substances, such as the sodium iodide symporter, which trigger the internalization and aggregation of radioactive iodine to enhance cell killing (102). In conclusion, advantage could be taken of the natural killing effect of MV for the treatment of Nectin-4-induced cancer.

9. Conclusion

The present review has shown that Nectin-4 expression has been altered in numerous cancer types, and that it is crucial in regulating tumor occurrence and development. This review also revealed that the overexpression of Nectin-4 is correlated with the poor prognosis of patients. However, the exact mechanism underlying increased levels of Nectin-4 and its role in transcriptional and protein control during carcinogenesis is yet to be elucidated. The putative association between Nectin-4 proteins and cancer would open a novel avenue for identifying potential therapeutic targets to improve patient outcomes.

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Availability of data and materials

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Authors' contributions

GW, YangZ, and XL conceptualized and designed this present review. YantingZ, XH and GL performed the literature search for this article. LL and MY collected and analyzed the relevant

data. YL and XH wrote the manuscript. CX and PZ designed and finalized the tables and figures. FS and ZY reviewed and corrected the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

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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