Tropical Journal of Pharmaceutical Research October 2023; 22 (10): 2235-2241
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v22i10.27

Review Article

Nectin-3 and Nectin-4: potential prognostic biomarkers for therapeutic targeting of cancer

Aihong Yang*, Yan Ge, Panpan Yang, Yuqi Xin, Chenlu Zhang, Feixue Xu*, Jiao Yang
Department of Gynecology, The First Hospital of Lanzhou University; Lanzhou, Gansu 730000, P.R. China

For correspondence:* ***Email:* *aihongyang1@msn.com, xfx.sxq@163.com*

Sent for review: Aug 11, 2023 2019 *Revised accepted: Aug 14, 2023*

Abstract

Nectin-3 and nectin-4 belong to the immunoglobulin (Ig) superfamily, and are Ca^{2+}-independent homophilic cell adhesion molecules. Nectin-3 is ubiquitous in adult tissues, and it enhances normal levels of synaptic formation. In contrast, nectin-4 is weakly-to-moderately expressed in normal human tissues. In recent years, studies have shown that nectin-3 is highly expressed in the nervous system. Moreover, it is associated with poor prognostic factors in distant metastases and malignant tumors with high vascular invasion such as pancreatic, lung and breast cancers. In particular, nectin-4 is overexpressed in various malignant tumors, and it is associated with proliferation, angiogenesis, metastasis, drug resistance, tumor relapse, DNA repair, cancer stemness, and poor prognosis. Unlike nectin-3, nectin-4 has become a potential prognostic biomarker and specific therapeutic target for cancer as there is no consensus on the significance of abnormal expression of nectin-3 in various cancers.

Keywords: *Nectin-4; Nectin-3; Biomarker; Prognosis; Cancer; Therapeutic strategies*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Cell-cell adhesion plays an important role in maintaining the integrity of organized tissues, thereby controlling cell growth and tissue morphogenesis [1]. Cell adhesion molecules mediate adhesion on the outer surface of cells by interacting with cytoplasmic peripheral membrane proteins through homophilic or heterophilic interactions [1]. These molecules are involved in many cellular functions such as organogenesis, morphogenesis and tumor progression [2,3]. They comprise the cadherin family, integrin family, immunoglobulin (Ig) superfamily and selectin family.

Nectins belong to the immunoglobulin (Ig) superfamily, and are Ca^{2+}-independent homophilic cell adhesion molecules [1,4]. Nectins are encoded by the *PVRL* gene. They are involved in forming the cellular junctions of epithelial cells, and in the regulation of cell proliferation, movement, polarization, survival, differentiation, as well as cell-cell adhesion [5,6]. Each of these molecules consists of a single transmembrane helix, a short cytoplasmic

domain bound to afadin, and three extracellular Ig-like domains. Nectins function by binding to the actin cytoskeleton *via* afadin and cadherins [7].

Nectin-3/poliovirus receptor-like protein-3 (PVRL3) has been identified as the third in nectin family, and it is encoded by the *PVRL3* gene [8]. It is an important protein involved in synaptic abnormalities induced by chronic stress [9]. This molecule is involved in the mechanism of nectin-mediated cell-cell adhesion, and it a key gene in lens and cycloid development in mammals [10]. Normal levels of functional nectin-3 enhance normal formation of synapses in layers 2/3 of the visual cortex [11]. It regulates the maturation and differentiation of adult-derived dentate gyrus granule cells. Its selective knockout impairs long-term spatial memory. A study revealed that inhibition of its expression resulted in reduction of dendritic spines, especially thin spines [12]. The molecule is necessary for the development of structural integrity of the hippocampus and memory function after birth [13]. It is a cell surface-binding receptor which serves as a target for the prevention of TcdB-mediated cytotoxicity in *Clostridium difficile* infection [14,15]. It is ubiquitous in adult tissues and highly expressed in the nervous system. However, many studies have shown that its abnormal expression is associated with poor prognostic factors in pancreatic, breast cancers and lung with vascular invasion and high degree of distant metastasis [16-18].

Nectin-4/poliovirus receptor-related-4 (PVRL4), which has been identified as the fourth Ig-like adhesion molecules in the nectin family, is encoded by the *PVRL4* gene [19]. Moreover, it is associated with cell-cell adhesion *via* homophilic and heterophilic trans-interactions at adheren junctions [20]. Its molecular weight is 55.5 kDa, and it consists of 510 amino acid residues [19]. In contrast to nectins-1, 2 and 3 which were originally described as antigens with limited expressions in normal tissues [21], nectin-4 has been reported to be particularly enriched in placental and embryonic tissues [19]. In particular, it is overexpressed in various malignant tumors [22]. Over-expression of nectin-4 is associated with proliferation, epithelial-to-mesenchymal transition (EMT), angiogenesis, DNA repair, metastasis, drug resistance, tumor recurrence, cancer stemness, and poor prognosis [19].

This review was aimed at discussing the significance of abnormal expressions of nectin-3 and nectin-4 in different types of cancer in recent years, and their role as potential prognostic biomarkers and specific therapeutic targets in different types of cancer.

NECTIN-3 AND CANCERS

Nectin-3 promotes lymphocyte and monocyte exosmosis through trans-interaction with nectin-2 [23,24]. It is highly expressed in the cell membrane and cytoplasm in primary human lung adenocarcinoma, and the altered expression causes tumor progression and malignancy, as well as poor prognosis in affected patients [25]. However, diffuse expression of this molecule has also been reported to be associated with good prognosis in pancreatic adenocarcinoma [16]. In addition, decreased membranous expression of nectin-3 is associated with increased aggressiveness of pancreatic neuroendocrine tumors [26].

Nectin-3 acts as an oncogene in nasopharyngeal carcinoma. A study has shown that it is significantly overexpressed in nasopharyngeal carcinoma tissue samples, and it enhances the adhesion, migration and invasion of nasopharyngeal carcinoma cells [2]. Expression of the molecule is decreased in metastatic breast cancer. Moreover, it may be an inhibitor of invasion of breast cancer cells and significantly elevates the levels of TIGIT in invasive breast cancer [27]. The proteins of nectin-3 interact with TIGIT and iit has been reported that patients with high TIGIT levels exhibited positive correlations with progression-free interval and overall survival [28]. The LncRNA of PVRL3-AS1 expression is decreased in osteosarcoma tissues and osteosarcoma cells, which may be used to predict the survival of osteosarcoma patients [29].

NECTIN-4 AND CANCERS

Nectin-4 is a type I transmembrane polypeptide of adhesion molecules [21]. It has also been identified as a homolog of the poliovirus receptor (CD155/PVR) or poliovirus receptor-related (PRR) protein [30]. It plays an important role in the initiation and maintenance of adhesion connections in polarized epithelial cells [31]. The nectin-afadin-cadherin interaction system regulates cellular events such as adhesion, migration, growth and differentiation and apoptosis through the production of adherens and tight junctions [20]. The molecule possesses the endo-domain that increases DNA repair, as well as the ecto-domain that enhances the angiogenesis associated with phosphoinositide-3-kinase (PI3K)/AKT-mediated nitric oxide formation [32]. Nectin-4 and its mRNA are weakly or moderately expressed in normal

human tissues but nectin-4 is extremely highly expressed in various types of cancers. Soluble nectin-4 is a cancer biomarker when ADAM metallopeptidase domain 17 (ADAM17) and ADAM10 are cleaved from the cell surface [33]. It participates in all steps of tumor cell growth and metastatic through the angiogenesis process.

Nectin-4 is associated with HER2-negative luminal-B breast cancer, and its ownregulation has been correlated with improved survival [34]. Increased *PVRL4* mRNA expression confirms that its overexpression is a biomarker associated with poor prognosis and shortened life span in triple-negative breast cancer (TNBC) patients [35,36]. The molecule is a therapeutic target for TNBC [37]. Its expression is upregulated at various stages of angiogenesis and metastasis in invasive duct carcinoma samples, which make it a leading cause of tumor relapse [38]. The molecule induces lymph-angiogenesis and lymphatic metastasis by regulating the CXCR4/CXCL12-lymphatic vessel endothelial receptor-1 (LYVE-1) axis in breast cancer [39]. In breast cancer stem cells, it is also involved in activating the WNT signaling pathway through the PI3K-AKT axis [40]. The expression level of nectin-4 is elevated in 5-FU resistant metastatic cells, and it may play a prominent role in 5-FU resistance of metastatic cervical cancer [41]. The expression of this molecule is significantly high in ovarian cancer patients, and it appears to be potential marker in ovarian cancer [42,43]. Indeed, overexpression of nectin-4 is associated with low survival rate, and it may be an important prognostic marker of ovarian cancer [44]. Elevated expression of the molecule is nearly ubiquitous in urothelial carcinoma specimens, and it is often accompanied with high tumor grade and lympho-vascular invasion, as well as strong correlation with high risk of poor prognosis [45]. Nectin-4 is a new target for systemic treatment of metastatic urothelial carcinoma or locally advanced [46]. In esophageal cancer cell lines and esophageal cancer patient samples, Its overexpression is associated with tumor size, stage, invasiveness, and poor survival [47,48]. The molecule has a significant effect on gastric cancer as high levels enhance gastric cancer differentiation, lymph node metastasis, and ultimately low survival rate *via* the PI3K-AKT signaling pathway [49]. Activated Rac1 promoted lamellipodia formation and anchorage-independent growth *via* activation of β4/SHP-2/c-Src [50]. High level of nectin-4 expression mediated by AKT/PI3K pathway is correlated with shortened melanoma-specific survival, poor disease-free survival, and poor overall survival [51]. This molecule is expressed in most cutaneous squamous cell carcinoma tissues, and functions in the regulation of cell-cell interactions, migration and proliferation by regulating the expression of cyclin D1 partly through ERK signaling [52]. As an oncogene, it enhances the progression and metastasis of osteosarcoma by down-regulating miR-520c-3p, thereby activating the PI3K/AKT/NF-κB signaling pathway [53]. It is highly expressed in non-metastatic penile squamous cell carcinoma patients with high-risk human papillomavirus (HPV) infection, and it may represent a novel therapeutic target [54].

Nectin-4 is a potential therapeutic target for *de novo* anaplastic thyroid carcinoma in thyroid papillary carcinoma [55]. Enfortumab vedotin, an antibody-drug conjugate directed against nectin-4, was recently approved by US Food and Drug Administration (FDA) for patients with metastatic urothelial carcinoma in December 2019 [56-58]. A study showed that enfortumab vedotin significantly prolonged the survival, progression-free survival, and high overall response rate in patients with metastatic urothelial carcinoma or locally advanced which relapsed following a PD-1/L1 inhibitor and platinum-containing chemotherapy treatment [59]. Therefore, enfortumab vedotin may be a promising new therapy for locally advanced or metastatic urothelial carcinoma [60]. However, as reported in another study, the clinical benefit of enfortumab vedotin strongly depends on membranous nectin-4 expression. In addition, it has been reported that the expression of membranous nectin-4 is often reduced or absent in metastatic urothelial carcinoma tissue [61]. Moreover, nectin-4 has not been confirmed as a prognostic marker in renal cell carcinoma: the 5-year overall survival rates reported in patients with type 1 renal cell carcinoma who were nectin-4 positive, were higher when compared with that of nectin-4 negative patients (81.3% vs. 67.8%) [62]. Moreover, no prognostic impact was observed based on nectin-4 expression in metastatic colorectal cancer [63]. The above-mentioned cancer types and their association with nectin-3 or nectin-4, are summarized in Table 1.

CONCLUSION

Tumor antigens represent potential drug targets expressed on the surfaces of tumor cells. Targeted therapeutics has become the standard of care in oncology for many tumor types. Nectin-3 and nectin-4 are potential biomarkers and promising targets for imaging diagnostics or theragnostics in various types of cancers, especially nectin-4. However, the significance of the abnormal expression of nectin-3 in various cancers is controversial. The detailed molecular

Table 1: Association of Nectin-3 and Nectin-4 mediated alteration of the cancer properties

Protein	Alternate names	Expression level	Types of cancer	Prognosis	References
Nectin-3	PVRL-3, PRR-3, CD113	Increased expression	Lung adenocarcinoma	Poor prognosis	25
		Diffuse expression	Pancreatic adenocarcinoma	Good prognosis	18
		Increased expression	Nasopharyngeal carcinoma	Oncogene	2
		Increased expression	Muscle invasive bladder cancer	Some cases were positive	24
		Decreased expression	Pancreatic neuroendocrine tumors	Increased tumor aggressiveness	26
		Decreased expression	Metastatic breast cancer	Good prognosis	27
		Decreased expression	Osteosarcoma	Poor prognosis	29
Nectin-4	PVRL-4, PRR-4, IgSF receptor LNIR, EDSS1	Increased expression	Triple negative breast cancer	Poor prognosis	35,36
		Increased expression	Invasive duct carcinoma	Tumor relapse	38
		Increased expression	Breast cancer	Lymph-angiogenesis and lymphatic metastasis	39
		Increased expression	Metastatic cervical cancer		41
		Increased expression	Ovarian cancer	Unfavorable survival, strong prognosis marker	42,43,44
		Increased expression	Urothelial carcinoma	Lymphovascular invasion, high tumor grade, higher risk of poor prognosis	45
		Increased expression	Metastatic urothelial carcinoma	Poor prognosis	46
		Increased expression	Esophageal cancer	Worse survival	47
		Increased expression	Gastric cancer	poor prognosis	48
		Increased expression	Melanoma	Shortened overall survival and melanoma-specific survival, poor disease-free survival	50
		Increased expression	Cutaneous squamous cell carcinoma		51
		Increased expression	Osteosarcoma	Oncogene	52
		Increased expression	Penile squamous cell carcinoma		53
		Increased expression	Metastatic colorectal cancer	No prognostic impact	62
		Increased expression	Thyroid papillary carcinoma	Poor prognosis	54
		Increased expression	Metastatic urothelial carcinoma	Poor prognosis	56,57,58
		Increased expression	Renal cell carcinoma	Not a prognostic marker	61
		Down regulation	Breast cancer	Better survival	34
		Decreased or absent	Metastatic urothelial carcinoma		60

mechanisms underlying the effect of nectin-4 on tumor angiogenesis and metastasis, and the significance of alterations in cancer properties mediated by abnormal expression of nectin-3, need further studies.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. All authors conceptualized the work, collected data and participated in the manuscript writing.

REFERENCES

1. *Takahashi K, Nakanishi H, Miyahara M, Mandai K, Satoh K, Satoh A, et al. Nectin/PRR: an immunoglobulin-like cell adhesion molecule recruited to cadherin-based adherens junctions through interaction with Afadin, a PDZ domain-containing protein. J Cell Biol 1999; 145(3): 539-549.*
2. *Zhao Y, Hong XH, Li K, Li YQ, Li YQ, He SW, et al. ZNF582 hypermethylation promotes metastasis of nasopharyngeal carcinoma by regulating the transcription of adhesion molecules Nectin-3 and NRXN3. Cancer Commun 2020; 40(12): 721-737.*
3. *Labernadie A, Kato T, Brugues A, Serra-Picamal X, Derzsi S, Arwert E, et al. A mechanically active heterotypic E-cadherin/N-cadherin adhesion enables fibroblasts to drive cancer cell invasion. Nat Cell Biol 2017; 19(3): 224-237.*
4. *Takai Y, Ikeda W, Ogita H, Rikitake Y. The immunoglobulin-like cell adhesion molecule nectin and its associated protein afadin. Annu Rev Cell Dev Biol 2008; 24: 309-342.*
5. *Mizutani K, Takai Y. Nectin spot: a novel type of nectin-mediated cell adhesion apparatus. Biochem J 2016; 473(18): 2691-2715.*
6. *Takai Y, Miyoshi J, Ikeda W, Ogita H. Nectins and nectin-like molecules: roles in contact inhibition of cell movement and proliferation. Nat Rev Mol Cell Biol 2008; 9(8): 603-615.*
7. *van der Kooij MA, Fantin M, Rejmak E, Grosse J, Zanoletti O, Fournier C, Ganguly K, Kalita K, Kaczmarek L, Sandi C. Role for MMP-9 in stress-induced downregulation of nectin-3 in hippocampal CA1 and associated behavioural alterations. Nat Commun 2014; 5: 4995.*
8. *Rikitake Y, Mandai K, Takai Y. The role of nectins in different types of cell-cell adhesion. J Cell Sci 2012; 125(Pt 16): 3713-3722.*
9. *Wang XD, Su YA, Wagner KV, Avrabos C, Scharf SH, Hartmann J, et al. Nectin-3 links CRHR1 signaling to stress-induced memory deficits and spine loss. Nat Neurosci 2013; 16(6): 706-713.*
10. *Lachke SA, Higgins AW, Inagaki M, Saadi I, Xi Q, Long M, et al. The cell adhesion gene PVRL3 is associated with congenital ocular defects. Hum Genet 2012; 131(2): 235-250.*
11. *Tomorsky J, Parker PRL, Doe CQ, Niell CM. Precise levels of nectin-3 are required for proper synapse formation in postnatal visual cortex. Neural Dev 2020; 15(1): 13.*
12. *Wang XX, Li JT, Xie XM, Gu Y, Si TM, Schmidt MV, Wang XD. Nectin-3 modulates the structural plasticity of dentate granule cells and long-term memory. Transl Psychiatry 2017; 7(9): e1228.*
13. *Liu R, Wang H, Wang HL, Sun YX, Su YA, Wang XD, Li JT, Si TM. Postnatal nectin-3 knockdown induces structural abnormalities of hippocampal principal neurons and memory deficits in adult mice. Hippocampus 2019; 29(11): 1063-1074.*
14. *LaFrance ME, Farrow MA, Chandrasekaran R, Sheng J, Rubin DH, Lacy DB. Identification of an epithelial cell receptor responsible for Clostridium difficile TcdB-induced cytotoxicity. Proc Natl Acad Sci U S A 2015; 112(22): 7073-7078.*
15. *Schöttelndreier D, Seeger K, Grassl GA, Winny MR, Lindner R, Genth H. Expression and (Lacking) internalization of the cell surface receptors of Clostridioides difficile toxin B. Front Microbiol 2018; 9: 1483.*
16. *Izumi H, Hirabayashi K, Nakamura N, Nakagohri T. Nectin expression in pancreatic adenocarcinoma: nectin-3 is associated with a poor prognosis. Surg Today 2015; 45(4): 487-494.*
17. *Tu HC, Ren D, Wang GX, Chen DY, Westergard TD, Kim H, Sasagawa S, Hsieh JJ, Cheng EH. The p53-cathepsin axis cooperates with ROS to activate programmed necrotic death upon DNA damage. Proc Natl Acad Sci U S A 2009; 106(4): 1093-1098.*
18. *Xu F, Si X, Wang J, Yang A, Qin T, Yang Y. Nectin-3 is a new biomarker that mediates the upregulation of MMP2 and MMP9 in ovarian cancer cells. Biomed Pharmacother 2019; 110: 139-144.*

19. Chatterjee S, Sinha S, Kundu CN. Nectin cell adhesion molecule-4 (NECTIN-4): A potential target for cancer therapy. Eur J Pharmacol 2021; 911: 174516.
20. Fabre S, Reymond N, Cocchi F, Menotti L, Dubreuil P, Campadelli-Fiume G, Lopez M. Prominent role of the Ig-like V domain in trans-interactions of nectins. Nectin3 and nectin 4 bind to the predicted C-C'-C''-D beta-strands of the nectin1 V domain. J Biol Chem 2002; 277(30): 27006-27013.
21. Reymond N, Fabre S, Lecocq E, Adelaide J, Dubreuil P, Lopez M. Nectin4/PRR4, a new afadin-associated member of the nectin family that trans-interacts with nectin1/PRR1 through V domain interaction. J Biol Chem 2001; 276: 43205-43215.
22. Challita-Eid PM, Satpayev D, Yang P, An Z, Morrison K, Shostak Y, et al. Enfortumab vedotin antibody-drug conjugate targeting Nectin-4 is a highly potent therapeutic agent in multiple preclinical cancer models. Cancer Res 2016; 76(10): 3003-3013.
23. Devilard E, Xerri L, Dubreuil P, Lopez M, Reymond N. Nectin-3 (CD113) interacts with Nectin-2 (CD112) to promote lymphocyte transendothelial migration. PLoS One 2013; 8(10): e77424.
24. Miyake M, Miyamoto T, Shimizu T, Ohnishi S, Fujii T, Nishimura N, et al. Tumor expression of Nectin-1-4 and its clinical implication in muscle invasive bladder cancer: An intra-patient variability of Nectin-4 expression. Pathol Res Pract 2022; 237: 154072.
25. Maniwa Y, Nishio W, Okita Y, Yoshimura M. Expression of nectin 3: Novel prognostic marker of lung adenocarcinoma. Thorac Cancer 2012; 3(2): 175-181.
26. Hirabayashi K, Tajiri T, Bosch DE, Morimachi M, Miyaoka M, Inomoto C, Nakamura N, Yeh MM. Loss of nectin-3 expression as a marker of tumor aggressiveness in pancreatic neuroendocrine tumor. Pathol Int 2020; 70(2): 84-91.
27. Martin TA, Lane J, Harrison GM, Jiang WG. The expression of the Nectin complex in human breast cancer and the role of Nectin-3 in the control of tight junctions during metastasis. PLoS One 2013; 8(12): e82696.
28. Guo C, Luo Z, Ismtula D, Bi X, Kong H, Wang Y, Yang Z, Mao X. TIGIT is a novel prognostic marker and correlate for immune infiltration in invasive breast cancer. Comb Chem High Throughput Screen 2023; 26(3): 639-651.
29. Liu H, Chen C, Liu L, Wang Z. A four-lncRNA risk signature for prognostic prediction of osteosarcoma. Front Genet 2023; 13: 1081478.
30. Bouleftour W, Sargos P, Magne N. Nectin-4: a tumor cell target and status of inhibitor development. Curr Oncol Rep 2023; 25(3): 181-188.
31. Takai Y, Nakanishi H. Nectin and afadin: Novel organizers of intercellular junctions. J Cell Sci 2003; 116(Pt 1): 17-27.
32. Chatterjee S, Sinha S, Molla S, Hembram KC, Kundu CN. PARP inhibitor Veliparib (ABT-888) enhances the anti-angiogenic potentiality of Curcumin through deregulation of NECTIN-4 in oral cancer: Role of nitric oxide (NO). Cell Signal 2021; 80: 109902.
33. Buchanan PC, Boylan KLM, Walcheck B, Heinze R, Geller MA, Argenta PA, et al. Ectodomain shedding of the cell adhesion molecule Nectin-4 in ovarian cancer is mediated by ADAM10 and ADAM17. J Biol Chem 2017; 292: 6339-6351.
34. Rajc J, Gugić D, Fröhlich I, Marjanović K, Dumenčić B. Prognostic role of Nectin-4 expression in luminal B (HER2 negative) breast cancer. Pathol Res Pract 2017; 213(9): 1102-1108.
35. M-Rabet M, Cabaud O, Josselin E, Finetti P, Castellano R, Farina A, et al. Nectin-4: a new prognostic biomarker for efficient therapeutic targeting of primary and metastatic triple-negative breast cancer. Ann Oncol 2017; 28(4): 769-776.
36. Zeindler J, Soysal SD, Piscuoglio S, Ng CKY, Mechera R, Isaak A, Weber WP, Muenst S, Kurzeder C. Nectin-4 expression is an independent prognostic biomarker and associated with better survival in triple-negative breast cancer. Front Med 2019; 6: 200.
37. Shao F, Pan Z, Long Y, Zhu Z, Wang K, Ji H, et al. Nectin-4-targeted immunoSPECT/CT imaging and photothermal therapy of triple-negative breast cancer. J Nanobiotechnology 2022; 20(1): 243.
38. Sethy C, Goutam K, Nayak D, Pradhan R, Molla S, Chatterjee S, Rout N, Wyatt MD, Narayan S, Kundu CN. Clinical significance of a pvrl 4 encoded gene Nectin-4 in metastasis and angiogenesis for tumor relapse. J Cancer Res Clin Oncol 2020; 146(1): 245-259.
39. Sethy C, Goutam K, Das B, Dash SR, Kundu CN. Nectin-4 promotes lymphangiogenesis and lymphatic metastasis in breast cancer by regulating CXCR4-LYVE-1 axis. Vascul Pharmacol 2021; 140: 106865.
40. Siddharth S, Goutam K, Das S, Nayak A, Nayak D, Sethy C, et al. Nectin-4 is a breast cancer stem cell marker that induces WNT/β-catenin signaling via Pi3k/Akt axis. Int J Biochem Cell Biol 2017; 89: 85-94.
41. Nayak A, Das S, Nayak D, Sethy C, Narayan S, Kundu CN. Nanoquinacrine sensitizes 5-FU-resistant cervical cancer stem-like cells by down-regulating Nectin-4 via ADAM-17 mediated NOTCH deregulation. Cell Oncol 2019; 42(2): 157-171.
42. Nabih ES, Abdel Motaleb FI, Salama FA. The diagnostic efficacy of nectin 4 expression in ovarian cancer patients. Biomarkers 2014; 19(6): 498-504.
43. DeRycke MS, Pambuccian SE, Gilks CB, Kalloger SE, Ghidouche A, Lopez M, et al. Nectin 4 overexpression in ovarian cancer tissues and serum. Am J Clin Pathol 2010; 134: 835-845.
44. Bekos C, Muqaku B, Dekan S, Horvat R, Polterauer S, Gerner C, Aust S, Pils D. NECTIN4 (PVRL4) as putative therapeutic target for a specific subtype of high grade serous ovarian cancer-an integrative multi-omics approach. Cancers 2019; 11(5): 698.
45. Tomiyama E, Fujita K, Rodriguez Pena MDC, Taheri D, Banno E, Kato T, et al. Expression of Nectin-4 and PD-L1 in upper tract urothelial carcinoma. Int J Mol Sci 2020; 21(15): 5390.
46. Heath EI, Rosenberg JE. The biology and rationale of targeting nectin-4 in urothelial carcinoma. Nat Rev Urol 2021; 18(2): 93-103.
47. Deng H, Shi H, Chen L, Zhou Y, Jiang J. Over-expression of Nectin-4 promotes progression of esophageal cancer and correlates with poor prognosis of the patients. Cancer Cell Int 2019; 19: 106.
48. Lin X, Hu H, Pan Y, Gao S. The prognostic role of expression of Nectin-4 in esophageal cancer. Med Sci Monit 2019; 25: 10089-10094.
49. Zhang Y, Chen P, Yin W, Ji Y, Shen Q, Ni Q. Nectin-4 promotes gastric cancer progression via the PI3K/AKT signaling pathway. Hum Pathol 2018; 72: 107-116.
50. Pavlova NN, Pallasch C, Elia AEH, Braun CJ, Westbrook TF, Hemann M, et al. A role for PVRL4-driven cell-cell interactions in tumorigenesis. Elife 2013; 2: e00358.
51. Tanaka Y, Murata M, Shen CH, Furue M, Ito T. NECTIN4: A novel therapeutic target for melanoma. Int J Mol Sci 2021; 22(2): 976.
52. Tanaka Y, Murata M, Oda Y, Furue M, Ito T. Nectin cell adhesion molecule 4 (NECTIN4) expression in cutaneous squamous cell carcinoma: A new therapeutic target? Biomedicines 2021; 9(4): 355.
53. Liu Y, Li G, Zhang Y, Li L, Zhang Y, Huang X, et al. Nectin-4 promotes osteosarcoma progression and metastasis through activating PI3K/AKT/NF-κB signaling by down-regulation of miR-520c-3p. Cancer Cell Int 2022; 22(1): 252.
54. Grass GD, Chahoud J, Lopez A, Dhillon J, Eschrich SA, Johnstone PAS, Spiess PE. An analysis of Nectin-4 (PVRL4) in penile squamous cell carcinoma. Eur Urol Open Sci 2023; 49: 1-5.

55. Toda S, Sato S, Saito N, Sekihara K, Matsui A, Murayama D, et al. TROP-2, Nectin-4, GPNMB, and B7-H3 are potentially therapeutic targets for anaplastic thyroid carcinoma. Cancers 2022; 14(3): 579.
56. US Food and Drug Administration (FDA). FDA grants accelerated approval to sacituzumab govitecan for advanced urothelial cancer. FDA; 2021.
fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sacituzumab-govitecan-advanced-urothelial-cancer
57. Chang E, Weinstock C, Zhang L, Charlab R, Dorff SE, Gong Y, et al. FDA approval summary: Enfortumab vedotin for locally advanced or metastatic urothelial carcinoma. Clin Cancer Res 2021; 27(4): 922-927.
58. McGregor BA, Sonpavde G. Enfortumab vedotin, a fully human monoclonal antibody against nectin 4 conjugated to monomethyl auristatin E for metastatic urothelial carcinoma. Expert Opin Investig Drugs 2019; 28: 821-826.
59. Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee JL, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021; 384(12): 1125-1135.
60. Yu EY, Petrylak DP, O'Donnell PH, Lee JL, van der Heijden MS, Loriot Y, et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2021; 22(6): 872-882.
61. Klümper N, Ralser DJ, Ellinger J, Roghmann F, Albrecht J, Below E, et al. Membranous NECTIN-4 expression frequently decreases during metastatic spread of urothelial carcinoma and is associated with enfortumab vedotin resistance. Clin Cancer Res 2023; 29(8): 1496-1505.
62. Zschäbitz S, Mikuteit M, Stöhr C, Herrmann E, Polifka I, Agaimy A, et al. Expression of nectin-4 in papillary renal cell carcinoma. Discov Oncol 2022; 13(1): 90.
63. Moretto R, Germani MM, Giordano M, Conca V, Proietti A, Niccoli C, et al. Trop-2 and Nectin-4 immunohistochemical expression in metastatic colorectal cancer: searching for the right population for drugs' development. Br J Cancer 2023; 128(7): 1391-1399.