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Research Progress of Nectin-4 as a Targeted Therapy for Ovarian Cancer

Xinmeng Wang*, Jinzhi Lu#, Cunjian Yi#

The First Affiliated Hospital of Yangtze University, Jingzhou, China
Email: #cunjiany@163.com, #Jinzhilu2015@163.com

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Abstract

Ovarian cancer is one of the most common gynecological malignancies. The 5-year survival rate of ovarian cancer is only 50%, which is considered to be the most lethal gynecologic malignant tumor. The high mortality of ovarian cancer patients can be attributed to chemotherapy resistance, extensive intraperitoneal metastasis and other factors. Tumor antigens are expressed on the surface of tumor cells and represent potential drug targets. One of the antigens is tumor associated nectin-4, which is a member of the immune globulin superfamily. This review highlights the role of nectin-4 as a therapeutic target for ovarian cancer, and discusses the relevant research data, which is an effective new direction in the treatment of ovarian cancer.

Keywords

Ovarian Cancer, Nectin-4, Antibody Drug Conjugate (ADC), Targeted Therapy

1. Basic Characteristics of Nectin-4

Nectin-4, is a type I transmembrane 66 kDa polypeptide member of the nectin family encoded by nectin-4. It was discovered by bioinformatics in 2001. Human nectin-4 is mainly expressed in placenta [1]. As a tumor associated antigen, nectin-4 is highly expressed in a variety of cancer cells and plays a role in the development and proliferation of tumors. Blocking nectin-4 can reduce tumor proliferation and induce apoptosis in several malignant tumors. Antibody drug conjugate has been used as a potential drug target. Together with cadherin, nectin-4 participates in the formation and maintenance of adhesion. In addition, as a stimulating receptor of prolactin receptor, nectin-4 regulates the feedback in-

*First Author.
#Corresponding Authors.

hibition of SOCS1 in jak2-stat5a signaling pathway. Nectin-4 can also act as a receptor for several measles viruses, including those in humans. The mutation of nectin-4 is responsible for ectodermal dysplasia syndromia type 1, a rare autosomal recessive disorder. Recently, it has been reported that the expression of nectin-4 is high in ovarian cancer [2] and is related to tumor progression and survival [3] [4] in retrospective studies.

2. Nectin-4 as a Drug Target

Enfortumab vedotin is an ADC targeting nectin-4, which has been proved to be effective for solid tumors and malignant tumors. Enfortumab vedotin has been approved by the U.S. Food and Drug Administration for the treatment of urothelial carcinoma. In addition, preclinical studies have demonstrated the efficacy of ADCs targeting nectin-4 for solid tumors other than urothelial carcinoma. ADC was designed to target cell surface antigen, and the expression of nectin-4 in cancer cells was higher than that in normal cells. ADC consists of a monoclonal antibody against an over expressed tumor associated protein target protein and a cytotoxic drug [5] that is chemically linked to the antibody. ADC is intravenously injected [6], and their distribution in tumors is due to the long circulating half-life of the antibody. After the ADC binds to the cell target, the antigen complex is internalized, and the intracellular transportation and processing proceed along the reduced pH gradient through the endocytosome pathway. The type and location of processing is determined by the type of ADC connector. If the ADC linker is not cleavable, complete protein degradation of ADC is required, so effective lysosomal transport is needed. If the ADC linker is cleavable, the cleavage mechanisms include the hydrolysis of acid unstable bonds in acidic intracellular chambers, the cleavage of intracellular protease dependent and esterase dependent peptide and ester bonds, or the reductive decomposition of disulfide bonds in intracellular compartments. In addition, division may take place in early or late endosomes, independent of lysosome transpor payload is released [7] [8], it diffuses into the appropriate cells to trigger cytotoxicity. At present, the payloads are divided into two types, which affect DNA and tubulin formation.

Antibody drug conjugate (ADC) is a relatively new class of anticancer drugs, which aims to combine the selectivity of monoclonal antibodies with the cytotoxicity of chemotherapy. Recently, three new types of ADCs have been approved, namely trastuzumab, drutecan and savidankang, which target HER2, mandatory mAb and nectin-4, respectively.

3. Clinical Studies of ADC Drugs

Antibody drug conjugates are monoclonal antibodies against surface proteins of cancer cells. These antibodies are associated with an effective cytotoxic drug. By preferentially delivering cytotoxic drugs to tumors, ADC can achieve high tumor drug concentration and efficient cancer cell killing, and has low systemic distri-

bution and miss target effect. ADC has three basic components—antibody, linker and cytotoxic payload [9] [10] [11]. Compared with the corresponding traditional cytotoxic drugs, the structural effectiveness and tolerance of ADC depend on the specificity of monoclonal antibody and the stability of linker. The best target antigen should be highly expressed in tumor cells and lowest in other parts of the body. Unlike typical targeted therapies that usually act to inhibit carcinogens, ADC may play an anti-tumor role, even targeting surface proteins that do not directly promote cell growth and proliferation, as long as they are highly and selectively expressed in the tumor microenvironment and can promote internalization. In addition to antigen selection and antibody design, the properties of chemical linkers are keys to the stability of ADC structure and the release of cytotoxic payloads into tumors. The linker can be divided into pyrolytic and non cleavable. The non cleavable linkers are usually very stable in circulation, and maintain physical connectivity between warheads and amino acid residues after lysosome degradation in ADC structure cells, both of which promote very accurate delivery to antigen expressing cells [12]. On the other hand, although cleavable linkers are usually unstable in circulation, they allow the release of small cytotoxic loads within the cell and then spread to the tumor microenvironment to play an anti-cancer effect on adjacent cells, regardless of the target antigen expression. This phenomenon is called bystander effect. Ongoing work on the biomolecular engineering of ADC focuses on further optimizing the linker to maintain circulatory stability—thereby minimizing systemic toxicity—while allowing cytotoxic release within the tumor and bystander killing. In addition to technological advances that allow the development of more effective ADC linkers, the properties of cytotoxic agents have also been developed. Previous generations of ADCs using conventional chemotherapy drugs failed to produce sufficient efficacy at tolerable doses. However, the recent development of ADC relies on more efficient cytotoxins that cannot be systematically used. Since there are a limited number of target antigens on any given cancer cell, and each ADC constitutes a limited number of cytotoxic molecules, the effective intratumoral drug concentration is quite low. Cytotoxic drugs must be able to overcome MDR1 mediated efflux, which is an established mechanism of ADC resistance.

A drug called gituzumab ozogamycin was the first ADC approved by FDA in 2000 [13] [14] [15] omycin is composed of monoclonal antibodies against CD33. CD33 is highly expressed in most acute myeloid leukemia (AML) cells. It is coupled to calicamycin, an effective anti-tumor antibiotic, through acid hydrolyzable hydrazine conjugate, a drug that acts by inducing double stranded DNA cleavage of specific motifs. The number of patients in phase II who received an accelerated response to doxorubicin in the phase III trial was subsequently increased due to the addition of doxorubicin. However, continued efforts to modify the dosing regimen and minimize toxicity have led to more encouraging survival data. On this basis, the US FDA re-approved gittuzumab oxazogamycin for AML in 2017.

4. Relationship between Nectin-4 and Ovarian Cancer

Abnormal expression of nectin-4 has been observed in several cancer types, including bladder cancer, breast cancer, lung cancer, pancreatic cancer and ovarian cancer. The activation of WNT in PI3K-Akt signaling pathway by nectin-4-β-Catenin and Rac small G protein promote the proliferation and metastasis of cancer cells. In addition, nectin-4 interacts with the tyrosine kinase receptor erbB2 to promote its activation, thus stimulating PI3K-Akt signaling pathway. However, overexpression of nectin-4 itself does not provide sufficient evidence of its pathogenicity. Neither the protein expression nor the genomic evidence itself is the evidence of driving oncogenes; there is still a lack of direct evidence that nectin-4 is a driving gene for cancer. Although nectin-4 has been proved to be a prognostic marker for various cancers, a prognostic marker is expected to prove its analytical and clinical validity, as well as its clinical utility; nectin-4 has not yet met these criteria and may need to be supplemented by other predictors of outcome to provide sufficient accuracy and practicality in clinical practice.

In HCC (hepatocellular carcinoma), the expression of nectin4 was over expressed in 68% of HCC tissues. The positive expression of nectin4 was significantly correlated with tumor size, metastasis status, vascular invasion and lymph node metastasis stage. The expression of nectin-4 was also associated with poorer relapse free and overall survival, univariate and multivariate. In gastric cancer, the expression of nectin-4 in cancerous tissues is higher than that in normal gastric tissues, and it is associated with poor prognosis. Previous studies have shown that nectin-4 is overexpressed in 51.5% of high-grade serous ovarian cancer tissues, but has no effect on survival in heterogeneous populations with different histology (serous, mucus, uterine fluid like and clear cells), grading and FIGO staging. The abnormal expression of nectin4 showed several cancer entities, and the expression rate was 47% in primary serous tumor and 79% in metastasis of serous ovarian cancer. In a study that evaluated the expression of nectin-4 in 39 patients with ovarian cancer, 21 patients with benign ovarian pathology, and 25 healthy controls, increased expression of nectin-4 mRNA was found in 97.4% of ovarian cancer samples. In human ovarian cancer cells, the significance of nectin-4 in cell-cell adhesion, proliferation and migration has been confirmed by experiments [16].

However, one of the peptides n4-p10 significantly inhibited the formation of spheroids. The ability of peptide n4-p10 to prevent ovarian cancer cell aggregation can improve the efficacy of chemotherapy by maintaining cell aggregation as single or small cells [17] [18] [19]. Two steps in the previous studies of spheroid formation and spheroid formation were described. Studies have shown that ovarian cancer cell lines with dense spheroids are more aggressive than loose aggregates, suggesting that the inhibition of globular formation by nectin-4 peptide can reduce the metastasis of ovarian cancer. Targeting cell adhesion molecules involved in globular formation can improve the sensitivity to chemothera-

peutic drugs. Similarly, the use of peptides to block laminin induced globular formation can improve the efficacy of cisplatin in ovarian cancer cells [20]. The formation of multicellular globules is a key component of the progression of ovarian cancer, and may play a role in metastasis and chemotherapy resistance [21]. It is suggested that the use of peptide to inhibit cell adhesion and spheroid formation may be a new method to increase chemotherapy response of ovarian cancer. In addition to nectin-4, other cell adhesion molecules, such as cadherin and Mucin-4, are also involved in the spheroid formation and metastasis of ovarian cancer [22] [23] [24]. Targeting cell adhesion molecules involved in globular formation can improve the sensitivity to chemotherapeutic drugs. Using polypeptides to block laminin induced spheroid formation can improve the efficacy of cisplatin in ovarian cancer cells.

5. Conclusion and Prospect

Tumor associated antigen nectin-4 is selectively overexpressed in ovarian cancer and other types of cancer, which represents a feasible target for anticancer therapy of ADC. Therefore, the results of ongoing and future studies on the combination of immunotherapy and other new drugs are expected. It is mainly used as a binding platform for ADC to force the mAb vidodin to deliver the payload MMAE and destroy the cancer cells containing nectin-4. The function of nectin-4 is not over correlated with the payload effect. The reason for choosing tumor associated antigen nectin-4 as a target of ovarian cancer is that there are a large number of discoveries in ovarian cancer. Although the expression of nestin-4 in normal human tissues is significantly lower than that in ovarian cancer tissues, the presence of nestin-4 in normal tissues contributes to the target effect of mandatory monoclonal antibodies in the toxic characteristics of drugs. In order to reduce target toxicity, other methods are being used to further optimize the ADC. Although ADC is an effective anticancer drug, resistance to ADC can be produced. It is necessary to further evaluate the primary and secondary mechanisms of drug resistance. It is necessary to fully understand the mechanism of ADC resistance through effective preclinical experiments, so as to make ovarian cancer patients live longer.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Timmermans, M., Sonke, G.S., van de Vijver, K.K., van der Aa, M.A. and Kruitwagen, R. (2018) No Improvement in Long-Term Survival for Epithelial Ovarian Cancer Patients: A Population-Based Study between 1989 and 2014 in the Netherlands. *European Journal of Cancer*, **88**, 31-37. https://doi.org/10.1016/j.ejca.2017.10.030

[2] Brancati, F., Fortugno, P., Bottillo, I., Lopez, M., Josselin, E., Boudghene-Stambouli, O., Agolini, E., Bernardini, L., Bellacchio, E., Iannicelli, M., *et al.* (2010) Mutations in PVRL4, Encoding Cell Adhesion Molecule Nectin-4, Cause Ectodermal Dysplasia-Syndactyly Syndrome. *The American Journal of Human Genetics*, **87**, 265-273. https://doi.org/10.1016/j.ajhg.2010.07.003

[3] DeRycke, M.S., Pambuccian, S.E., Gilks, C.B., Kalloger, S.E., Ghidouche, A., Lopez, M., Bliss, R.L., Geller, M.A., Argenta, P.A., Harrington, K.M., *et al.* (2010) Nectin 4 Overexpression in Ovarian Cancer Tissues and Serum: Potential Role as a Serum Biomarker. *American Journal of Clinical Pathology*, **134**, 835-845. https://doi.org/10.1309/AJCPGXK0FR4MHIHB

[4] Buchanan, P.C., Boylan, K.L.M., Walcheck, B., Heinze, R., Geller, M.A., Argenta, P.A. and Skubitz, A.P.N. (2017) Ectodomain Shedding of the Cell Adhesion Molecule Nectin-4 in Ovarian Cancer Is Mediated by ADAM10 and ADAM17. *Journal of Biological Chemistry*, **292**, 6339-6351. https://doi.org/10.1074/jbc.M116.746859

[5] Takano, A., *et al.* (2009) Identification of Nectin-4 Oncoprotein as a Diagnostic and Therapeutic Target for Lung Cancer. *Cancer Research*, **69**, 6694-6703. https://doi.org/10.1158/0008-5472.CAN-09-0016

[6] Zhang, Y., *et al.* (2016) A Novel PI3K/AKT Signaling Axis Mediates Nectin-4-Induced Gallbladder Cancer Cell Proliferation, Metastasis and Tumor Growth. *Cancer Letters*, **375**, 179-189. https://doi.org/10.1016/j.canlet.2016.02.049

[7] Pavlova, N.N., *et al.* (2013) A Role for PVRL4-Driven Cell-Cell Interactions in Tumorigenesis. *eLife*, **2**, e00358. https://doi.org/10.7554/eLife.00358

[8] Siddharth, S., *et al.* (2017) Nectin-4 Is a Breast Cancer Stem Cell Marker That Induces WNT/beta-Catenin Signaling via Pi3k/Akt Axis. *The International Journal of Biochemistry & Cell Biology*, **89**, 85-94. https://doi.org/10.1016/j.biocel.2017.06.007

[9] Rabet, M., *et al.* (2017) Nectin-4: A New Prognostic Biomarker for Efficient Therapeutic Targeting of Primary and Metastatic Triple-Negative Breast Cancer. *Annals of Oncology*, **28**, 769-776. https://doi.org/10.1093/annonc/mdw678

[10] Nishiwada, S., *et al.* (2015) Nectin-4 Expression Contributes to Tumor Proliferation, Angiogenesis and Patient Prognosis in Human Pancreatic Cancer. *Journal of Experimental & Clinical Cancer Research*, **34**, Article No. 30. https://doi.org/10.1186/s13046-015-0144-7

[11] Ma, J., *et al.* (2016) Expression and Clinical Significance of Nectin-4 in Hepatocellular Carcinoma. *OncoTargets and Therapy*, **9**, 183-190. https://doi.org/10.2147/OTT.S96999

[12] Deng, H., Shi, H., Chen, L., Zhou, Y. and Jiang, J. (2019) Over-Expression of Nectin-4 Promotes Progression of Esophageal Cancer and Correlates with Poor Prognosis of the Patients. *Cancer Cell International*, **19**, Article No. 106. https://doi.org/10.1186/s12935-019-0824-z

[13] Teutsch, S.M., *et al.* (2009) The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: Methods of the EGAPP Working Group. *Genetics in Medicine*, **11**, 3-14. https://doi.org/10.1097/GIM.0b013e318184137c

[14] Febbo, P.G., *et al.* (2011) NCCN Task Force Report: Evaluating the Clinical Utility

of Tumor Markers in Oncology. *Journal of the National Comprehensive Cancer Network*, **9**, S1-S32. https://doi.org/10.6004/jnccn.2011.0137

[15] Challita-Eid, P.M., *et al.* (2016) Enfortumab Vedotin Antibodydrug Conjugate Targeting Nectin-4 Is a Highly Potent Therapeutic Agent in Multiple Preclinical Cancer Models. *Cancer Research*, **76**, 3003-3013. https://doi.org/10.1158/0008-5472.CAN-15-1313

[16] Birrer, M.J., Moore, K.N., Betella, I. and Bates, R.C. (2019) Antibody-Drug Conjugate-Based Therapeutics: State of the Science. *Journal of the National Cancer Institute*, **111**, 538-549. https://doi.org/10.1093/jnci/djz035

[17] Lambert, J.M. and Berkenblit, A. (2018) Antibody-Drug Conjugates for Cancer Treatment. *Annual Review of Medicine*, **69**, 191-207. https://doi.org/10.1146/annurev-med-061516-121357

[18] Boylan, K.L.M., Buchanan, P.C., Manion, R.D., Shukla, D.M., Braumberger, K., Bruggemeyer, C. and Skubitz, A.P.N. (2017) The Expression of Nectin-4 on the Surface of Ovarian Cancer Cells Alters Their Ability to Adhere, Migrate, Aggregate, and Proliferate. *Oncotarget*, **8**, 9717-9738. https://doi.org/10.18632/oncotarget.14206

[19] Rosso, M., Majem, B., Devis, L., Lapyckyj, L., Besso, M.J., Llaurado, M., Abascal, M.F., Matos, M.L., Lanau, L., Castellvi, J., *et al.* (2017) E-cadherin: A Determinant Molecule Associated with Ovarian Cancer Progression, Dissemination and Aggressiveness. *PLOS ONE*, **12**, e0184439. https://doi.org/10.1371/journal.pone.0184439

[20] Usui, A., Ko, S.Y., Barengo, N. and Naora, H. (2014) P-cadherin Promotes Ovarian Cancer Dissemination through Tumor Cell Aggregation and Tumor-Peritoneum Interactions. *MCR*, **12**, 504-513. https://doi.org/10.1158/1541-7786.MCR-13-0489

[21] Yoshida, Y., Kurokawa, T., Nishikawa, Y., Orisa, M., Kleinman, H.K. and Kotsuji, F. (2008) Laminin-1-Derived Scrambled Peptide AG73T Disaggregates Laminin-1-Induced Ovarian Cancer Cell Spheroids and Improves the Efficacy of Cisplatin. *International Journal of Oncology*, **32**, 673-681. https://doi.org/10.3892/ijo.32.3.673

[22] Teo, M.Y. and Rosenberg, J.E. (2018) EMA and FDA Prune the Checkpoint Inhibitor Treatment Landscape. *Nature Reviews Urology*, **15**, 596-597. https://doi.org/10.1038/s41585-018-0074-1

[23] Diamantis, N. and Banerji, U. (2016) Antibody-Drug Conjugates—An Emerging Class of Cancer Treatment. *British Journal of Cancer*, **114**, 362-367. https://doi.org/10.1038/bjc.2015.435

[24] Thomas, A., Teicher, B.A. and Hassan, R.T. (2016) Antibody-Drug Conjugates for Cancer Therapy. *The Lancet Oncology*, **17**, E254-E262. https://doi.org/10.1016/S1470-2045(16)30030-4