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

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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

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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 is 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 adherens 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 it 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 a 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 promotes lamellipodia formation and anchorage-independent growth via activation of β4/SHP-2/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

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

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Availability of data and materials

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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.

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