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Review

Functional roles of fucosylated and O-glycosylated cadherins during carcinogenesis and metastasis

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ABSTRACT

Reduced cellular adhesiveness as a result of cadherin dysfunction is a defining feature of cancer and the mechanism involved in many aspects. Glycosylation is one of the most important post-translational modifications to cadherin. Major changes of glycosylation on cadherins can affect its stability, trafficking, and cell-adhesion properties. It has been reported that the different glycoforms of cadherins are promising biomarkers in cancer, with potential clinical application to constitute targets for the development of new therapies. Among the various glycoforms of cadherins, fucosylated and O-glycosylated cadherins are attracting more attention for their important roles in regulating cadherin functions during carcinogenesis. This review will discuss the most recent insights of the functional roles of fucosylated and O-glycosylated cadherins and their regulation mechanisms during carcinogenesis and metastasis. In summary, more understanding of fucosylated and O-glycosylated cadherins will lead to development of novel therapeutic approaches targeted to cancer.

1. Introduction

Cadherins are a type of cell adhesion molecule that are important in the formation of adherent junctions to bind cells with each other [1]. The cadherin superfamily comprises a set of calcium-dependent transmembrane glycoproteins that participate in cell-cell interactions and determine cell polarity and tissue architecture during embryonic morphogenesis and homeostasis [2,3]. These adhesion proteins organize into lateral clusters at cell surface where they mediate homophilic contacts between neighboring cells and participate in dynamic interactions with the actin cytoskeleton as core components of the adhere junctions [4]. For example, they are responsible for the separation of the different tissue layers and for proper cellular migration during development [5]. The cadherin superfamily is mainly composed of 1) classical cadherins, which are the major components of cell-cell adhesive junctions; Such as E-cadherin, which has been considered to be a paradigmatic classical cadherin, having five extracellular cadherin repeats, a single transmembrane domain and a cytoplasmic domain with highly conserved binding sites for the armadillo proteins p120-catenin and β-catenin. 2) non-classical cadherins, including desmosomal cadherins such as desmoglein and desmocollin; they make the desmosomes highly tension-resistant and play a role in suppressing tumors. 3) protocadherins, such as PCDH10; over-expression of PCDH10 in gastric cancer cells suppresses cell proliferation and migration; It might be a useful target for cancer therapy. 4) unconventional cadherins such as K-cadherin and T-cadherin; many results demonstrate that K-cadherin must have important functions in both the process of kidney development and tumorigenesis of some types of kidney cancer. And 5) a variety of cadherin-related molecules such as β-catenin and p-120 catenin [6–13].

E-cadherin is generally considered to be the major prototype of all the cadherin family [14]. Dysfunction of E-cadherins is an important

Abbreviations: GnT-III, *N*-acetylglucosaminyltransferase III; GnT-V, *N*-acetylglucosaminyltransferase V; GlcNAc, *N*-acetylglucosamine; O-GlcNAc, O-GlcNAcylation; FUT8, α(1,6)-fucosyltransferase; EMT, epithelial–mesenchymal transition; Asn, asparagine; Thr, threonine; NSCLC, non-small cell lung cancer; Pofuts, O-fucosyltransferases; POMT1, O-mannosyltransferases 1; POMT2, O-mannosyltransferases 1; EC, extracellular cadherin; APC, adenomatous polyposis coli; LEF-1, lymphoid enhancer factor-1

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determinant of cancer development and progression [15]. The disruption of E-cadherin-mediated cell adhesion leads to disorganized tissue architecture [10,16]. The reduced expression of E-cadherin could lead to impairment of cell-cell adhesion, which allows detachment of cells [17]. Tumor cells acquire the ability to invade and migrate when E-cadherin is suppressed. These results lead to tumor progression and metastasis [18,19]. E-cadherins can be dysregulated by multiple mechanisms including loss of heterozygosity [20,21], promoter hypermethylation [22,23], transcriptional silencing [24], inherited and somatic mutations [25,26], endocytosis [27,28], proteolysis [29], and glycosylation [30,31]. Although the specific molecular mechanism of E-cadherin's regulation of tumors has not been fully elucidated, glycosylation has been identified as the basic mechanism controlling E-cadherins' adhesion function and has been proposed to have potential in targeted treatment for cancer [32,33]. In previous studies about glycosylated E-cadherin, a large number of references are focused on the effect of N-glycosylation of E-cadherin [34]. For example, several studies have shown that the structural modifications of N-glycans of E-cadherin by *N*-acetylglucosaminyltransferase III (GnT-III) cause increased cell-cell adhesion in human colon cancer, hepatoma cells, and mouse melanoma cells [35,36]. On the other hand, structural modification of N-glycans on N-cadherin with increased branched structures by *N*-acetylglucosaminyltransferase V (GnT-V) resulted in decreased cell-cell adhesion and increased cellular motility and invasiveness in human fibrosarcoma cells [37].

Nevertheless, more attention has been paid to the study of other glycosylation forms on E-cadherin. Increased levels of fucosylation have been observed in various malignancies, and fucosylation has been involved in the process of metastasis relating E-cadherin [38]. Moreover, cytoplasmic O-glycosylation is a novel, rapid mechanism for regulating cell surface transport that can down-regulate adhesion molecules in some apoptosis pathways [39]. In this review, we will only focus on the functional roles of fucosylated and O-glycosylation modified cadherins during carcinogenesis and metastasis.

2. Fucosylation of cadherins

N-glycosylation is the most common glycosylated modification in E-cadherin, contributing up to 20% of its total mass [40]. N-glycosylation is characterized by the addition of oligosaccharide structures to the asparagine (Asn) residues of nascent proteins in a consensus sequence Asn-X-Ser/Thr, where X is any amino acid other than proline [41].

Fucosylation represents the transfer of a fucose residue (from GDP-fucose) to oligosaccharide chains carried by cell-surface glycoproteins or glycolipids. Fucosylated glycans are synthesized by fucosyltransferases [42]. There are two kinds of N-fucosylation depending on their location of fucose: Core Fucosylation (α-1,6-fucosylation) and Terminal Fucosylation (α-1,2-fucosylation, α-1,3/4-fucosylation) [34]. Thirteen fucosyltransferase genes have been identified in the human genome. FUT1–11 exist in the Golgi apparatus and catalyze N-linked fucosylation, and O-fucosyltransferases (Pofuts) exist in the endoplasmic reticulum and catalyze O-linked fucosylation [41,43–47]. FUT1 and FUT2 participate in the synthesis of α-1,2-fucosylation. FUT3,4,5,6,7,9 were mainly found in mammalian cells and participated in the process of α-1,3/4-fucosylation [48]. FUT8 is an α(1,6)-fucosyltransferase that directs addition of fucose to asparagine-linked *N*-acetylglucosamine (GlcNAc) moieties, a common feature of N-linked glycan core structures [49]. Finally, two additional putative α(1,3)-fucosyltransferase genes, FUT10 and FUT11, though not yet validated by functional studies, have been identified in the human genome by comparison with fucosyltransferase sequences in the *Drosophila melanogaster* genome [50].

3. The effect of core fucosylation on E-cadherin function

Previous studies have observed that the core fucosylation of E-cadherin is increased in patients with lung adenocarcinoma and the amount of fucosylation on E-cadherin could be a potential prognostic marker of metastatic lung adenocarcinoma [51]. Chen et al. observed that low E-cadherin expression accompanied with high FUT8 expression always correlated with the lowest survival rate in clinical tumor specimens, suggesting the expression levels of E-cadherin and FUT8 could be a prognostic index for patients with non-small cell lung cancer (NSCLC) [52]. Geng et al. observed that E-cadherin was core fucosylated in highly metastatic lung cancer cells but absent of core fucosylation in low metastatic lung cancer cells. The calcium dependent cell-cell adhesion mediated by E-cadherin was strengthened with the reduction of core fucosylation on E-cadherin and was weakened with the elevated core fucosylation on E-cadherin in lung cancer cells. The proposed mechanism is that core fucosylation on E-cadherin could significantly impair three-dimensional conformation of N-glycan on E-cadherin and produce conformational asymmetry so as to suppress the function of E-cadherin [53].

However, there also have opposing views on the role of core fucosylation of E-cadherin in tumor progression. Osumi et al. observed that the expression of E-cadherin and E-cadherin dependent cell-cell adhesion in pancreatic acinar cell carcinoma cells was decreased in FUT8 knock down mice. They were able to restore the expression of E-cadherin and E-cadherin-dependent cell-cell adhesion after transfecting FUT8 into kidney epithelial cells from FUT8$^{-/-}$ mice. They suggested that core fucosylation of E-cadherin enhances cell-cell adhesion in human colon carcinoma WiDr cells by regulating the processing of oligosaccharides and turnover of E-cadherin. Tumor cells acquire the ability to invade and migrate when core fucosylation of E-cadherin is suppressed, which could lead to tumor progression and metastasis [54].

Many studies also regarded that the core fucosylation of E-cadherin affected the abnormal formation of E-cadherin complex during the epithelial-mesenchymal transition (EMT) process [55,56]. For example, the core fucosylation of E-cadherin can induce the expression of N-cadherin and Snail1to initiate EMT process [57]. During EMT initiation, decreased core fucosylation on E-cadherin leads to increased phosphorylation of Src , which is a protein kinase that is derived from a cellular gene and its activity was regulated by its tyrosine phosphorylation [58,59]. The phosphorylated Src resulted in β-catenin Y654 phosphorylation, which can effectively reduce the binding affinity of E-cadherin and β-catenin [60,61]. In FUT8 over-expressing cells, reduction of nuclear β-catenin was noted when E-cadherin was core-fucosylated, while accumulation of nuclear β-catenin was observed when FUT8 is inhibited. Furthermore, in FUT8 over-expressing cells, enhanced binding affinity of E-cadherin with β-catenin and α-catenin were observed, and reduction of Y654 phosphorylation on β-catenin was also observed. Evidence suggested that addition of 1,6-fucose on E-cadherin reduces tyrosine Y654 phosphorylation of β-catenin, leading to the reduced accumulation of nuclear β-catenin and thus increases its binding affinity to E-cadherin and the consequent enhancement of cell-cell adhesion [62]. Phosphorylation of Src can activate AKT and then increase the phosphorylated GSK-3β whose unphosphrylated form can bind with axin and APC (adenomatous polyposis coli) to induce S37 phosphorylation of β-catenin to initiate its ubiquitination and degradation [63]. During the EMT process, nuclear β-catenin is also correlated with the transcription of FUT8. Downregulation of E-cadherin leads to an increased accumulation of nuclear β-catenin which could specifically bind to lymphoid enhancer factor-1 (LEF-1) to activate FUT8 transcription [64]. Gene expression profiling analysis revealed that FUT8 was upregulated during EMT and upregulated FUT8 remodeled the core-fucosylated N-glycans on cell-surface targets such as TGF-β RI and RII complexes to enhance ligand binding and promote downstream signaling activities [65].Here we summarize the role of core fucosylated on E-cadherin during EMT in Fig. 1.

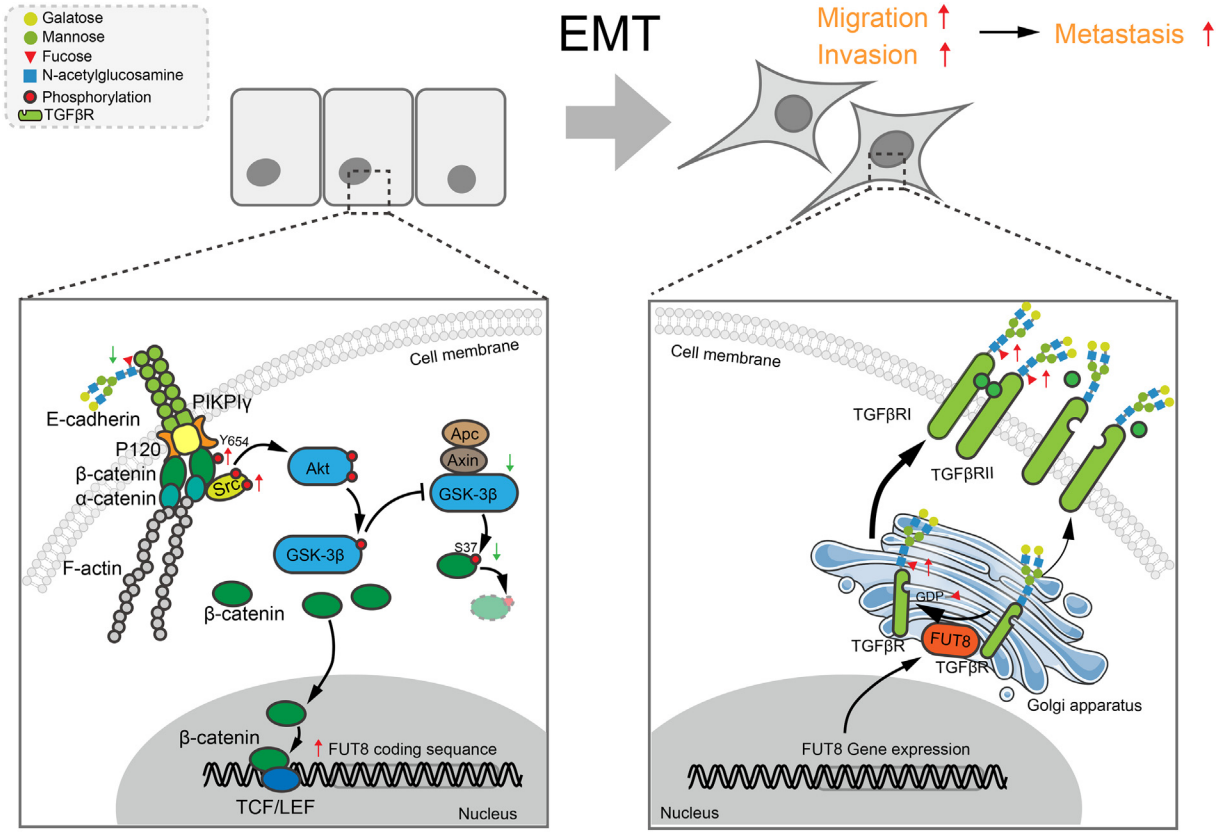

Fig. 1. Schema of core fucosylation on E-cadherin during EMT progression. In early stage of EMT, the decreased level of core fucosylation of E-cadherin activates Src, then inactivates GSK-3β by activating Akt , which leads to the accumulation of nuclear β-catenin. β-catenin can further combine with LEF1 and promote the transcription of FUT8. In the late stage of EMT, FUT8-mediated receptor core fucosylation that promotes TGF-β signaling and EMT, thus stimulating cancer cell invasion and metastasis [59–65].

4. Terminal fucosylation glycotransferases regulate E-cadherin

In addition to core fucosylation, there are few research papers about terminal fucosylation on cadherins. However, several terminal fucosylation related glycotransferases were associated with the expression of E-cadherin during the process of EMT [66]. FUT1 and FUT2 are alpha 1, 2-fucosyltransferases which can catalyze the addition of alpha 1, 2-linked fucose to glycans [67]. It has been shown that the increased expression of E-cadherin after FUT1/2 knockdown and the opposite results were noted in breast cancer by overexpression of FUT1/2 suggested an indirect effect of E-cadherin expression upon FUT1/2 modification [68]. Mc Conkey et al. revealed that the expression of two enzymes (FUT1 and GALNT14) correlates closely with E-cadherin expression in bladder cancer cells from the public gene expression profiling datasets (W. Choi, unpublished observations) [69]. Inhibition of FUT3/6 expression by siRNAs suppressed the terminal fucosylation of type I TβR, the other type of cadherin superfamily, and the phosphorylation of downstream molecules, thereby inhibiting the invasion and migration of colorectal cancer cells by EMT [70,71].

5. O-glycosylation of cadherins

O-linked glycosylation is the attachment of carbohydrate moieties to the oxygen atom of serine (Ser) or threonine (Thr) residues. O-glycosylation occurs as a post-translational modification in the Golgi apparatus after the protein has been produced [72]. The reported O-glycosylation types of cadherins mainly include O-GlcNAcylation and O-mannosylation. O-GlcNAcylation (O-GlcNAc) consists of the attachment of *N*-acetylglucosamine (GlcNAc) structures to Ser or Thr residues, which occurs on cytoplasmic and nuclear proteins remaining in the cell [73]. In recent years, increasing study suggests that O-GlcNAc modified E-cadherin correlates with cellular features and tumors relevant to metastasis. For example, the O-GlcNAcylation could enhance ovarian cancer cell migration and decrease the expression of E-cadherin in ovarian cancer [74]. The possible reason is addition of O-GlcNAc structures to E-cadherin directly prevents its binding to p120-catenin. Newly synthesized cadherins are trafficked from the trans-Golgi network to the plasma membrane in association with β-catenin. At the plasma membrane, p120-catenin binds to cadherin juxta membrane domain, stabilizing and preventing the entry of cadherin into degradative endocytic pathways. P120-deprived cadherin is prone to interact with other proteins, promoting E-cadherin internalized by clathrin-dependent pathways. After internalization, E-cadherin can be recycled back to the plasma membrane or targeted for degradation [39]. The other mechanisms induce multiple modifications of E-cadherin that prevent trafficking to the plasma membrane. O-GlcNAcylation of the cytoplasmic domain of E-cadherin prevents the binding of PIPKIγ, and the O-GlcNAcylated E-cadherin is retained in the endoplasmic reticulum [75]. We summarized the possible mechanisms of O-GlcNAc modified E-cadherin during metastasis in Fig. 2.

O-mannosylation is initiated by the covalent attachment of mannose to Ser or Thr residues of secretory and membrane proteins in the ER lumen, and catalyzed by the protein O-mannosyltransferases 1 and 2 (POMT1 and POMT2) [76]. The cadherin superfamily carries O-linked mannose (O-Man) glycans at highly conserved residues in specific extracellular cadherin domains, and it was suggested that the function of E-cadherin was dependent on their O-Man glycans [77]. The cadherins have multiple repeats of an extracellular cadherin (EC) domain and mediate cell-cell adhesion by trans homodimerization between the most distal EC1 and EC1–2 domains on apposed cells [78]. Interestingly, the

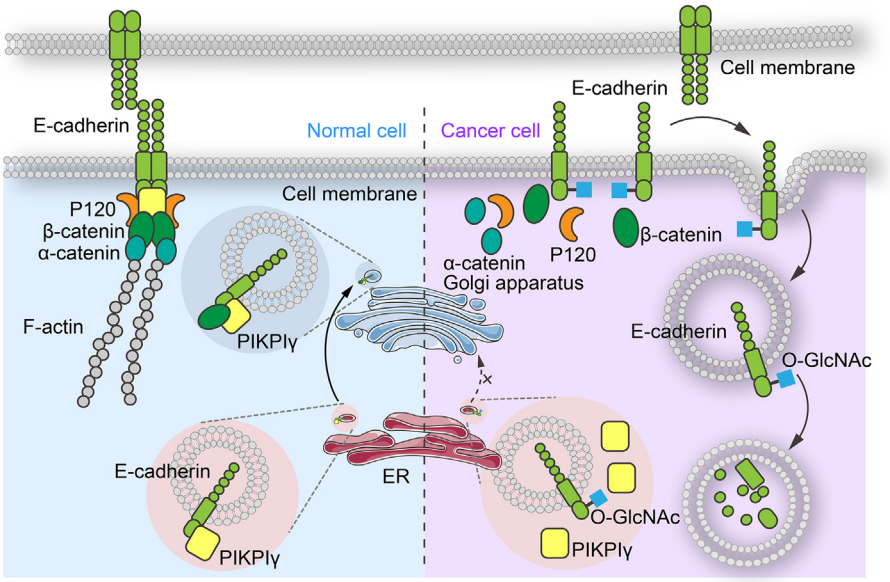

Fig. 2. The O-GlcNAc modified E-cadherin that prevents trafficking of E-cadherin to the plasma membrane in cancer cells. The trafficking of E-cadherin in normal cells was shown on the left. The distribution of E-cadherin to plasma membrane disrupted through two possible mechanisms in cancer cells were shown on the right [9,75].

latest research demonstrated that EC1 and EC2 domains of cadherin are not O-mannosylated. However, the O-Man-modified sites are confined to EC3–5 domains of both classic type 1 and 2 cadherins and appear to have been evolutionarily conserved. The presence or absence of O-Man-modified glycans or alterations in their structure could have an impact on the presentation of EC1 and EC2 domains of cadherins during trans homodimerization or alter homo or hetero dimerization during cis interactions in the membrane [79]. The latest research demonstrated that initiation of cadherin/protocadherin O-Man glycosylation is not dependent on the evolutionary conserved POMT1/ POMT2 [80]. Disruption of O-Man on E-cadherin reduced cellular adhesion, suggesting O-mannosylation is required for E-cadherin-mediated adhesion [81]. There is still much to be learned about the role of O-Man glycans in its contribution to malignant transformation.

6. Conclusions

Numerous human diseases including cancer are associated with changes in glycan structures. The clinical relevance of glycans recruits intensive interests for their crucial roles in the development, regulation and progression of cancer [82]. Dysfunction or inactivity of cadherin families always leads to cancer initiation and progression [83]. Aberrantly modified glycans in cadherin has been proved to participate in carcinogenesis. In the past decades, regulation of N-fucosylated and O-glycosylated E-cadherin in cancer and its contribution to tumor-microenvironment interactions remain poorly understood. In this review, we have comprehensively summarized the most recent insights of the functional roles of fucosylated and O-glycosylated cadherins during carcinogenesis and metastasis. Moreover, we elaborated on the regulation mechanism of fucosylation and O-glycosylation on cadherins in invasion and metastasis of cancer cells. E-cadherin dysregulation is a common event that occurs during cancer progression as well as a causative event in the cases of some carcinomas; it is essential to elucidate the molecular mechanisms underlying its post-transcriptional modifications such as fucosylation and O-glycosylation. We envision that identifying targeted cadherin as well as determining the functions of specific oligosaccharide structures in cadherin are equally important. With this knowledge, we are able to seek the novel therapeutic perspectives targeting functional cadherin in cancer.

Author contributions

XL and MXM proposed the study and co-wrote the manuscript. XMZ partly designed and performed the animations. YW, FG and YTF critiqued the manuscript and were involved in the conception and design of the study. All authors have read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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