Review Article

# Implications of epithelial-mesenchymal transition in gastric cancer

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**Abstract:** Gastric cancer phenotypes have been associated with various gene alterations. To identify the phenotypes and basis of gastric cancer, precise information about genetic mutations and molecular associations is needed. Cadherin 1, type 1, E-cadherin (epithelial) (CDH1), one of the most commonly mutated genes, is closely involved in phenotypic transitions in gastric cancer. In this review article, we intensively discuss gene alterations and molecular networks in gastric cancer focusing on both CDH1 and gastric cancer phenotypic diversity [including cancer stem cells (CSCs)] associated with the epithelial-mesenchymal transition (EMT).

**Keywords:** Cancer stem cell (CSC); Cadherin 1, type 1, E-cadherin (epithelial) (CDH1); epithelial-mesenchymal transition (EMT); gastric cancer; stem cell

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## Introduction

Gastric cancer has a variety of phenotypes (1). One of its interesting features is the differences between diffuse- and intestinal-type gastric cancers. The epithelial-mesenchymal transition (EMT) might explain these phenotypic differences. Cadherin 1, type 1, E-cadherin (epithelial) (*CDH1*) is commonly up-regulated in intestinal-type gastric cancer. In recent studies, mutations or gene alterations in *CDH1* have been associated with gastric cancer malignancy or metastatic ability. In this review, we describe the biological roles of CDH1 in gastric cancer association with EMT. Gene expression profiling of gastric cancer has revealed that both cancer grades and stages can be identified via gene signatures (2). In addition, gene and genome alterations have been examined to detect cell phenotypes. Based on a comprehensive analysis of the gastric cancer genome, a number of genes, including *CDH1*, tumor protein p53 (*TP53*), AT rich interactive domain 1A (SWI-like) (*ARID1A*), mucin 6, oligomeric mucus/gel-forming (*MUC6*), catenin (cadherin-associated protein), alpha 2 (*CTNNA2*), GLI family zinc finger 3 (*GLI3*), and ring finger protein 43 (*RNF43*) have been identified as mutated driver genes (3). These findings suggest the significance of molecular information in cancer prognosis and treatment.

In several diseases, the expression of EMT-related genes, including *CDH1*, has been demonstrated to be negatively regulated (4-8). However, the loss of CDH1 is insufficient to induce EMT, suggesting that combinations of genes are involved in the EMT process (9). In this review, we focus on the biological roles of CDH1 in gastric cancer and discuss the cellular phenotypic alterations.

## CDH1 and gastric cancer

*CDH1* is one of the frequently mutated driver genes in gastric cancer, particularly in the diffuse-type gastric

 

cancers (3,10-13). Generally, *CDH1* is up-regulated in intestinal-type gastric cancer and down-regulated in diffuse-type gastric cancers, whereas cadherin 2, type 1, N-cadherin (neuronal) (*CDH2*) is up-regulated in the diffuse-type gastric cancer (14). Analyses of *CDH1*- and *TP53*-mutated gastric cancers suggest that transforming growth factor-beta receptor 2 (*TGFBR2*) is a candidate driver gene that plays a role as a metastasis suppressor (7). Germline mutations in *CDH1* have been associated with human hereditary diffuse gastric carcinoma (15,16). Analyses using the Catalogue of somatic mutations in cancer (COSMIC) database (http://www.sanger.ac.uk/genetics/CGP/cosmic/) have revealed that *CDH1* mutations are also associated with diffuse-type gastric cancer (17). Whereas *CDH1* is mutated in approximately 40% of gastric cancer cases, germline mutations in mitogen-activated protein kinase kinase kinase 6 (*MAP3K6*) have been associated with gastric cancers without *CDH1* mutations (5). The -160C to a promoter polymorphism and haplotypes of *CDH1* have been associated with the risk of developing sporadic diffuse-type gastric cancer (18).

A previous study has shown that CDH1 expression was increased in gastric cancer cells co-expressing a putative mitogen-activated protein kinase activator with WD40 repeats (MAWD) and a MAWD binding protein (MAWBP), and they were treated with TGF-1 (19). CDH1, SMAD family member 4 (Smad4) and p53 play important roles in gastric cancer formation (20). The loss of *CDH1* and *Smad4* expression promotes diffuse-type gastric adenocarcinoma and metastasis (20).

Gastrokine 1, a molecule associated with gastric mucosal defense, is reduced in 36.4% of gastric mucosal tissues and is related to miR-185 expression (21). Considering that the Gastrokine 1-miR-185-DNA methyltransferase (DNMT) 1 axis is suggested as a suppressor of gastric carcinogenesis, the influence of gastrokine-regulated methylation on tumor progression should be investigated (21). Indeed, *CDH1* methylation was detected in more than 80% of gastric mucosal tissues examined in this study (21). CDH1, claudin-10 and claudin-17 are down-regulated in gastric cancer (22). The down-regulation of *CDH1* might be involved in cancer promotion. Germline variants of *CDH1* have been identified in sporadic gastric cancer patients, and the involvement of down-regulation in CDH1 is indicated (23). In gastric cancer, CDH1 is also regulated through cyclooxygenase-2 (COX-2) via the nuclear factor (NF)-κB pathway (24). Several somatic mutations of genes, including erb-b2 receptor tyrosine kinase 2 (*ERBB2*) (*HER2*) and *CDH1* have been detected in gastric cancer (25). Diffuse-type gastric cancer might arise from the down-regulation of *CDH1* (25). However, the expression of ERBB2 is preferentially up-regulated in intestinal-type gastric cancers, and the prognostic value of ERBB2 in gastric cancer remains controversial (25,26). The methylation status of CDH1 is altered through *Helicobacter pylori* (*H. pylori*) infection (27-29). CDH1 expression at the plasma membrane is decreased in gastroesophageal junction adenocarcinoma associated with metastasis (30). The metastasis-associated gene (*MTA3*) is also decreased in tumor tissues, suggesting that the EMT pathway is regulated via MTA3, a potential prognostic factor in gastroesophageal junction adenocarcinoma (30). Aquaporin 3 (AQP3) is overexpressed in gastric cancer tissues, whereas CDH1 is expressed in normal gastric tissues (31). It has been suggested that AQP3 induces EMT in gastric cancer cells (31). Appendiceal and intramucosal gastric signet ring cell carcinomas have been identified in diffuse-type gastric carcinoma patients with CDH1 mutations (32). Thus, whether signet ring cell carcinoma in the appendix is primary or metastatic should be carefully examined (32).

## CDH1 and EMT

EMT is a switching mechanism (33). EMT typically occurs during early embryogenesis, and the mesenchymal-epithelial transition (MET), the reverse phenomenon of EMT, might also occur during the reprogramming of fibroblasts through pluripotent factors (33). Epithelial cells convert into mesenchymal cells during EMT, which involves abundant molecular network alterations (33). Smoking reportedly induces EMT in non-small cell lung cancer through the HDAC-mediated down-regulation of *CDH1* (34). The mechanism of EMT in cancer should be investigated in correlation with CDH1 (34). As metastasis is one of the causes of cancer progression, metastatic stem cells, which initiate metastasis, are a noteworthy concept (35). Metastatic stem cells may be supported through a stem cell niche, such as hematopoietic stem cells, providing insight into the metastasis mechanism induced by EMT (35).

In EMT-related signal pathways in the neural crest, SMAD-interacting protein 1 (SIP1) is a key factor in CDH1 to CDH2 switching during development (36). CDH1 expression is regulated through snail family zinc finger 1 (SNAI1) (SNAIL) signaling, which induces EMT in gastric

 

cancer (37). The amplification of *ERBB2*, *MET*, and *FGFR2* is also involved in EMT induction in gastric cancer (37).

CDH1 is a major marker of epithelial cell states. In BGC823 human gastric cancer cells, *CDH1* was up-regulated through the siRNA-based gene knockdown of N-acetylglucosaminyltransferase V (GnT-V) (38). When considering the expression of other EMT markers, GnT-V might contribute to the metastasis and invasion of gastric cancer (38). *CDH1* is down-regulated during EMT and has been implicated in the induction of pluripotency (39,40). *CDH1* is also down-regulated in human cancer and has been correlated with increased *WNT* expression (41).

## CDH1 and cancer stem cells (CSCs)

*CDH1* expression is decreased during the EMT process, which might represent an essential mechanism for CSC maintenance (42). Considering that CSCs and EMT are strongly related, the CDH1 function might also be involved in CSC development (43). A decrease in *CDH1* expression in hepatocellular carcinomas has been correlated with early recurrent disease (44). CDH1 network created by cBioPortal may be useful to reveal the cancer mechanism (*Figure 1*, *Table 1*) (45,46).

## Conclusions

In conclusion, CDH1 is a key molecule for the phenotypic transition of gastric cancer cells into mesenchymal states. CDH1 is up-regulated in epithelial cells, and the down-regulation of CDH1 leads to EMT. The role of CDH1 as a marker for EMT detection and the mechanism of EMT via CDH1 and other molecular signaling should be further investigated to understand gastric cancer and CSCs.

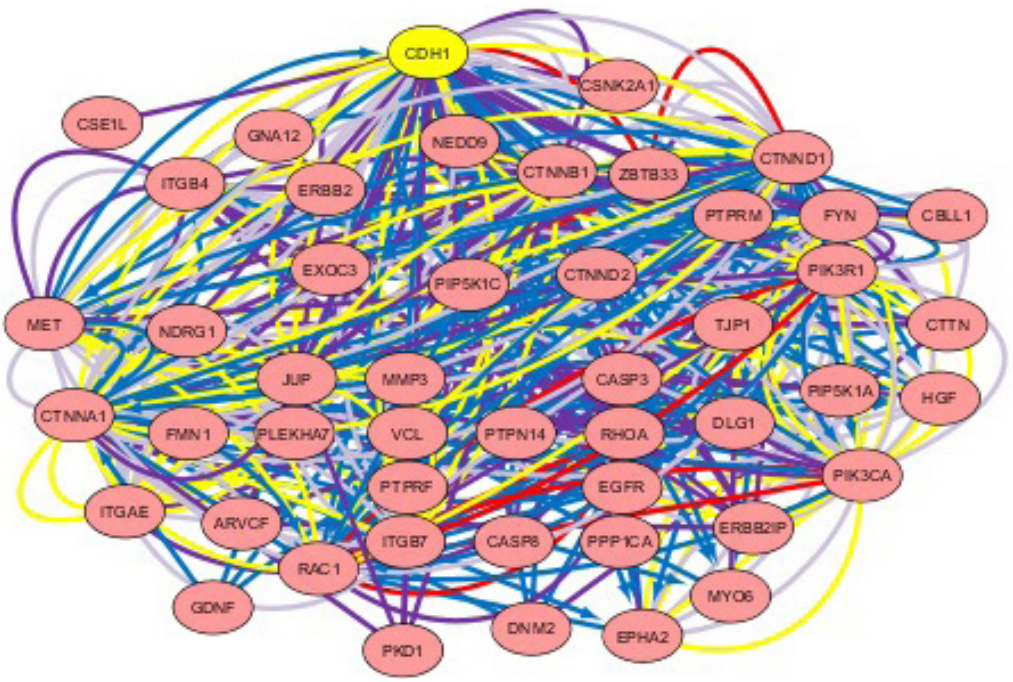


**Figure 1** Network of CDH1 (analyzed with cBioPortal and cytoscape). Gene network of CDH1 is shown. The network was analyzed with cBioPortal and cytoscape (http://www.cbioportal.org/; http://www.cytoscape.org/).

 

**Table 1** Genes in CDH1 network created by cBioPortal

| Gene symbol | Gene title |
|---|---|
| *ARVCF* | Armadillo repeat gene deleted in velocardiofacial syndrome |
| *CASP3* | Caspase 3, apoptosis-related cysteine peptidase |
| *CASP8* | Caspase 8, apoptosis-related cysteine peptidase |
| *CBLL1* | Cbl proto-oncogene-like 1, E3 ubiquitin protein ligase |
| *CDH1* | Cadherin 1, type 1, E-cadherin (epithelial) |
| *CSE1L* | CSE1 chromosome segregation 1-like (yeast) |
| *CSNK2A1* | Casein kinase 2, alpha 1 polypeptide |
| *CTNNA1* | Catenin (cadherin-associated protein), alpha 1, 102kDa |
| *CTNNB1* | Catenin (cadherin-associated protein), beta 1, 88kda |
| *CTNND1* | Catenin (cadherin-associated protein), delta 1 |
| *CTNND2* | Catenin (cadherin-associated protein), delta 2 |
| *CTTN* | Cortactin |
| *DLG1* | Discs, large homolog 1 (Drosophila) |
| *DNM2* | Dynamin 2 |
| *EGFR* | Epidermal growth factor receptor |
| *EPHA2* | EPH receptor A2 |
| *ERBB2* | Erb-b2 receptor tyrosine kinase 2 |
| *ERBB2IP* | Erbb2 interacting protein |
| *EXOC3* | Exocyst complex component 3 |
| *FMN1* | Formin 1 |
| *FYN* | FYN proto-oncogene, Src family tyrosine kinase |
| *GDNF* | Glial cell derived neurotrophic factor |
| *GNA12* | Guanine nucleotide binding protein (G protein) alpha 12 |
| *HGF* | Hepatocyte growth factor (hepapoietin A; scatter factor) |
| *IGF1R* | Insulin-like growth factor 1 receptor |
| *IQGAP1* | IQ motif containing GTPase activating protein 1 |
| *IRS1* | Insulin receptor substrate 1 |
| *ITGAE* | Integrin, alpha E (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide) |
| *ITGB4* | Integrin, beta 4 |
| *ITGB7* | Integrin, beta 7 |
| *JUP* | Junction plakoglobin |
| *MET* | MET proto-oncogene, receptor tyrosine kinase |
| *MMP3* | Matrix metallopeptidase 3 |
| *MYO6* | Myosin VI |
| *NDRG1* | N-myc downstream regulated 1 |
| *NEDD9* | Neural precursor cell expressed, developmentally down-regulated 9 |
| *PIK3CA* | Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha |
| *PIK3R1* | Phosphoinositide-3-kinase, regulatory subunit 1 (alpha) |
| *PIP5K1A* | Phosphatidylinositol-4-phosphate 5-kinase, type I, alpha |
| *PIP5K1C* | Phosphatidylinositol-4-phosphate 5-kinase, type I, gamma |
| *PKD1* | Polycystic kidney disease 1 (autosomal dominant) |

**Table 1** *(continued)*

 

**Table 1** *(continued)*

| Gene symbol | Gene title |
|---|---|
| *PLEKHA7* | Pleckstrin homology domain containing, family A member 7 |
| *PPP1CA* | Protein phosphatase 1, catalytic subunit, alpha isozyme |
| *PTPN14* | Protein tyrosine phosphatase, non-receptor type 14 |
| *PTPRF* | Protein tyrosine phosphatase, receptor type, F |
| *PTPRM* | Protein tyrosine phosphatase, receptor type, M |
| *RAC1* | Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1) |
| *RHOA* | Ras homolog family member A |
| *TJP1* | Tight junction protein 1 |
| *VCL* | Vinculin |
| *ZBTB33* | Zinc finger and BTB domain containing 33 |

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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