

Topical Issue on Cancer Signaling, Metastasis and Target Therapy

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Review Article

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The Role of *E-cadherin* - 160C/A Polymorphism in Breast Cancer

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Abstract: Breast cancer is the most prevalent cancer in women worldwide. Numerous studies have suggested that the E-cadherin adhesion system is dysregulated in cancer cells. These impaired functions of E-cadherin contribute to releasing cancer cells from the primary lesion to cell dedifferentiation. Some studies have shown that polymorphism may affect *E-cadherin* expression, and then play a role in susceptibility to breast cancer. However, the results remained controversial. In this short review, we summarize the functions of E-cadherin and the signaling pathways it regulates, and assess the association between *CDH1* polymorphisms and breast cancer susceptibility. This study suggests that genetic variation in *CDH1* and -160C/A polymorphism may have an association with breast cancer risk. The assessment of *CDH1* polymorphisms may be used for the identification of patients suitable for anti-*CDH1* therapy.

Keywords: breast cancer; E-cadherin; polymorphism

1 Breast Cancer

Breast cancer is the most common malignancy in women in the world and is the leading cause of cancer-related death [1]. Several factors contribute to initiation and progression of breast cancer [2-4]. Sustaining proliferative signaling, escaping growth inhibition and resisting cell death are hallmarks of cancers. The distinctive capacities of cancer also include inducing angiogenesis, activating

invasion and metastases. These characteristics are results of genetic deregulation. Accumulation of genetic mutations results in increasingly aggressive phenotypes [5].

2 *E-cadherin* in Breast Cancer

2.1 Structure and Functions of *E-Cadherin*

The *CDH1* gene is located on human chromosome 16q22.1 and encodes for the E-cadherin protein [6]. The E-cadherin glycoprotein is composed of three major structural domains: a single transmembrane domain, connected with a cytoplasmic domain, and an extracellular domain comprising five tandemly repeated domains called EC1–EC5, which are exclusive to cadherins [7]. The extracellular domain of E-cadherin is essential for cell to cell adhesion, as well as for the correct folding and homo/hetero dimerisation of the proteins. The cytoplasmic domain of E-cadherin interacts with the catenins (α -, β -, γ - and p120 catenin) anchored to the actin cytoskeleton, establishing cadherin-catenin complexes [8]. Conformation of E-cadherin is only stable upon Ca^{2+} binding to its highly conserved, negatively charged extracellular motifs [9]. Its stabilization at the cell membrane and accurate function occur by association to cytoplasmic p120-catenin [10]. E-cadherin forms adherens junction with its binding partner β -catenin and actin filaments. This complex is critical to inhibit individual epithelial cell motility and to provide homeostatic tissue architecture [11, 12] (Figure 1).

2.2 Signaling Pathways Regulated by *E-Cadherin*

In addition to its role in cell to cell adhesion, E-cadherin is involved in a number of signaling pathways in carcinogenesis [13]. For the Wnt/ β -catenin pathway, free β -catenins may accumulate in the cytoplasm attributed

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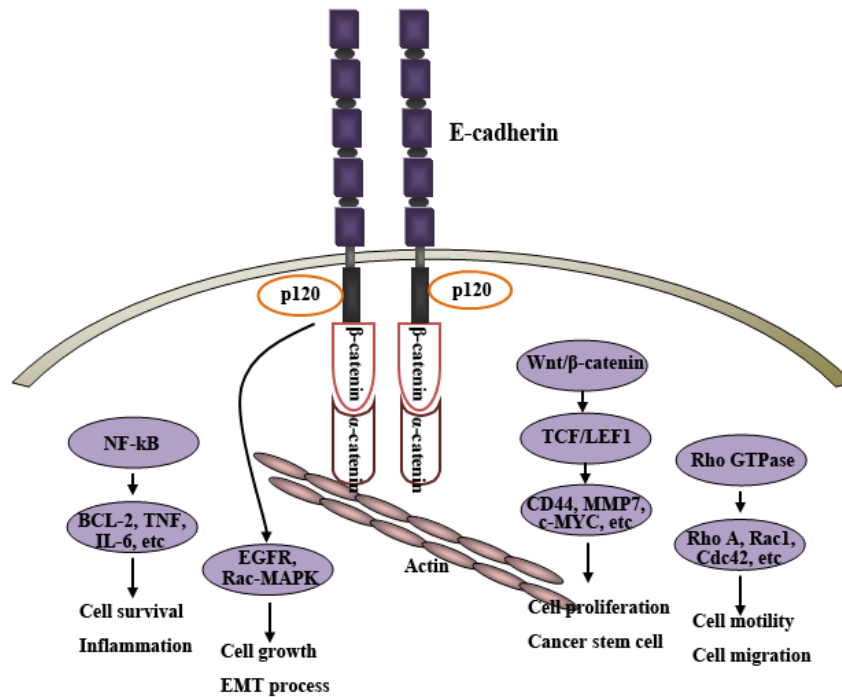


Figure 1. E-cadherin regulated signaling pathways involved in breast cancer, including Rho GTPases, Wnt/ β -catenin pathway, NF- κ B pathway, EGFR, and Rac-MAPK signaling. Activation of these pathways leads to an increase in cell proliferation, decrease in cell apoptosis, cell migration, and inflammation associated gastric cancer development. Abbreviations: Rho GTPases, Ras homolog guanosine 5'-triphosphates; NF- κ B, nuclear factor kappa B; EGFR, epidermal growth factor receptor; MAPK, Mitogen-activated protein kinases.

to nonfunctional APC (adenomatous polyposis coli) or GSK-3 β (glycogen synthase kinase3 β) [14]. Subsequently, a high level of β -catenins in the cytoplasm translocates into the nucleus, binds to members of the TCF/LEF1 (Transcription Factor/Lymphoid enhancer-binding factor 1) family, and activates the expression of Wnt target genes, including *CD44*, *c-MYC*, and *MMP7* [15]. Activation of these genes contributes to increased cell proliferation and tumor progression. Hence, it is supposed that by sequestering β -catenin at sites of cell to cell contact, E-cadherin expression can suppress Wnt/ β -catenin signaling.

Another pathway frequently overexpressed in breast cancer involves Rho GTPases, with Rho A, Rac1, and Cdc42 extensively studied [16,17]. In addition, activation of RhoA through an E-cadherin dependent pathway involves the role of EGFR (epidermal growth factor receptor) [18]. Mutations at the E-cadherin extracellular domain may impair the interaction of E-cadherin and EGFR, lead to EGFR activation, and further enhance cell motility through activating RhoA [19]. Moreover, loss of E-cadherin and release of p120-catenin activate the Rac1-MAPK (mitogen activated protein kinase) signaling pathway and promote transformed cell growth [20]. Interestingly, the E-cadherin/catenin complex appears to possess the ability to down modulate NF- κ B activity [21]. In mammals, the canonical NF- κ B activation pathway

mainly applies to p65: p50 dimers, which is released after I κ B phosphorylation by the IKK complex and subsequent degradation of this inhibitor. Finally, the heterodimer is translocated to the nucleus and activates the transcription of various target genes including *Bcl-2*, *IL-6*, and *TNF* [22]. To summarize the above, dysregulation of E-cadherin leads to dysfunctions of E-cadherin-mediated signaling pathways, which alters cell polarity, increases cell survival, and promotes EMT process as well as cell invasion and migration [23]. These effects induce cancer initiation and progression, including breast cancer.

3 Genetic Mutations and Variants of *E-Cadherin* in Breast Cancer

Genetic mutation is one major mechanism for silencing tumor suppressor genes. E-cadherin acts as a tumor suppressor and downregulation of E-cadherin is observed in various cancers. Frequent E-cadherin gene (*CDH1*) inactivating mutations have been identified in lobular breast cancers. The lifetime risk of breast cancer in *CDH1* gene mutation carriers is on the order of 40% to 50% [24]. E-cadherin has been postulated to function as a potent breast tumor suppressor [25]. E-cadherin downregulation or loss is associated with poor prognosis in breast cancer

patients across different histologic and molecular subtypes [26-28]. Invasive lobular breast cancers in most cases do not express E-cadherin [29-31], and in a smaller proportion they show only atypical expression. This latter subtype often shows loss of heterozygosity of the wild type allele of *CDH1*, combined with inactivating mutations of the remaining copy.

The analysis of exon 1 to exon 16 of *CDH1* gene mutations have been implicated in breast cancer (Table 1). As the genomic transcription is critically dependent on the exact sequence of these elements, the nucleotide changes of these mutations can lead to transcriptional alterations by modifying the affinity of the DNA-binding proteins [32, 33]. These mutations lead to truncated proteins of E-cadherin, abnormal alterations of the E-cadherin's calcium binding sites, or increases in its proteolytic

degradation, which inactivate its functions. Inactivation of E-cadherin decreases cell to cell adhesion and induces aberrant alternations of E-cadherin-associated signaling pathways involved in cell proliferation, EMT process, inflammation, and so forth. These aberrant changes trigger breast cancer development.

4 The Role of *E-cadherin* Polymorphisms in Breast Cancer Risk

Genetic polymorphisms are the change of the common DNA sequence in the general population. In contrast with mutations, this type of change does not cause obvious disease. This slight difference occurs in the promoter region, exon or coding sequence, and may affect gene expressions or protein function, leading to different characteristics among individuals. Single-nucleotide polymorphisms (SNPs) are the most common type of variation in the human genome. SNPs provide powerful tools for a variety of medical genetic studies. SNPs occur about once every 1000 base pairs. In recent years there has been an enormous effort by numerous laboratories worldwide to identify the role of genetic mutations in genetic predisposition and disease progression in particular cancers.

A study by Li et al. [32] suggested that interindividual variation in E-cadherin expression may be a result of SNPs in the E-cadherin (*CDH1*) gene promoter region and in turn lead to individual susceptibility to carcinoma. The literature with regard to *CDH1* polymorphisms and breast cancer is limited but increasing. Several studies [39-41] found a relationship between the -160 C/A polymorphism and the risk of cancer, results are summarized in Table 2. Restriction fragment length polymorphism was used to analyse germline DNA samples that were extracted from breast cancer patients or controls. Most of these studies comprise of small sample sizes and may be prone to sampling bias.

Cattaneo et al. [42] investigated a sample of the Italian population and found no association between the -160 C/A SNP and breast cancer risk (OR = 1.35, 95 % CI = 0.84–2.17). Lei et al. [37] found the same result among the Swedish as well as Czech populations. But in some studies [39-41], positive associations between the -160 C/A polymorphism and breast cancer susceptibility and/or progression were detected. Yu et al. [39] found a significant increase (30% more likely) in risk among *CDH1*- 160A allele carriers.

Table 1: *CDH1* gene exon 1–16 mutations in breast cancer.

Exon	Codon	Nucleotide change	Predicted protein change	References
Ex_1	-	48+1G>A	Donor splice site	[34]
Ex_2	17	49del115	Frameshift	[35, 36]
	17	50insAG	Stop codon at 67	
	20	59G>A	W20X	
	23	67C>T	Q23X	
	30	88C>A	Pro30Thr	
Ex_3	55	164del224	Frameshift	[35-37]
	123	367C>T	H123Y	
	127	372insC	Stop codon at 136	
Ex_4	157	469del63	In-frame deletion	[35]
Ex_5	204	612del9	In-frame deletion	[35]
Ex_6	261	G>T	Stop codon	[6]
Ex_7	-	846G>A	Met282Ile	[36-38]
	288	862–867delCG	Stop codon at 292	
	315	944A>G	D315S	
Ex_9	386	G>T	Stop codon	[6]
	399	1197del4	Stop codon at 416	
Ex_10	463	1387G>C	E463Q	[6, 35, 36]
	504	G>T	Stop codon	
	507	1519del7bp	Stop codon at 519	
Ex_12	598	1793G>A	R598Q	[35, 36]
	613	1836delA	Stop codon at 630	
	626	1876T>G	Phe626Val	
	627	g. 1881del8	Frameshift	
Ex_13	-	1942G>T	E648X	[34-36]
	677	2029delC	Frameshift	
	683	2047delGT	Stop codon at 686	
Ex_14	742	2223insA	Stop codon at 747	[34]
Ex_15	-	2398delC	p.P799fs	[34]

–: Numbering is according to the cDNA, starting at the A in the start codon (Genbank accession n° Z13009); g: genomic DNA; Ex: Exon; del: delete; ins: insert; p.: protein.

Table 2: Studies of *CDH1* polymorphisms and risk of breast cancer.

Authors	Year	Population	Case/control	Risk factor
Goode et al. [43]	2002	East Anglian	-/-	N.S.
Lei et al. [37]	2002	Stockholm	576/348	N.S.
Sarrió et al. [36]	2003	Spain	45/20	N.S.
Cattaneo et al. [42]	2006	Central Italy (Lazio)	99/246	N.S.
Yu et al. [39]	2006	Taiwan	468/470	Minor allele carriers (<i>rs16260 A</i>) were 30% more likely to be breast cancer cases than women with only the major allele (C).
Tipirisetti et al. [40]	2013	Indian	202/250	The frequencies of -160A/A genotypes ($p = 0.038$) and -160A alleles ($p = 0.046$) were significantly higher in patients compared to controls.
Shabnaz et al. [41]	2015	Bangladesh	310/250	A significant association was found between -160 C/A (<i>rs16260</i>) polymorphisms and breast cancer risk. In case of <i>CDH1</i> <i>rs16260</i> polymorphism, C/A heterozygote and combined C/A + A/A genotypes were found to be strongly associated ($P = 0.005$, $OR = 1.67$; $P = 0.0037$, $OR = 1.68$) with increased risk of breast cancer. The variant A allele also increased the breast cancer risk ($P = 0.0058$, $OR = 1.52$).

N.S.: not significant

Tipirisetti et al. [40] depicted that *CDH1* -160A/A genotype is responsible for the occurrence of breast cancer among Indian women. In the recent study, Shabnaz et al [41] found a significant association of *CDH1* -160 C/A polymorphism and breast cancer risk in Bangladeshi women for the first time. Taken together, these apparently conflicting data may reflect the important biological function of *CDH1* polymorphisms. Due to the small sample sizes of most of the studies, limited numbers of *CDH1* polymorphisms examined, and differing ethnicity of the study groups, all of the above findings are considered to be preliminary.

5 Discussion

This short review focuses on the evidence for a role for *E-cadherin* in breast cancer predisposition and prognosis. It has an emphasis on studies of the role of the *CDH1* gene polymorphisms in breast cancer. Seven studies are included. Additional studies are still needed to evaluate the association between *CDH1* gene polymorphisms and breast cancer susceptibility.

Many studies have suggested that SNPs in the *E-cadherin* (*CDH1*) gene promoter region contribute to interindividual variation in the production of E-cadherin. Difference in individual E-cadherin level lead to variations in individual susceptibility to cancer [32]. Germline mutations in *CDH1* are highly penetrant, with a risk of up to 70% of symptomatic diffuse gastric cancer by the age of 75 years [44]. *CDH1* constitutive mutations also account for some familial clustering of lobular breast cancers [45]. In

this study, we found significant association between the *CDH1* -160 C/A polymorphism and breast cancer in recent studies. -160C/A SNP within the *CDH1* promoter region is a functional polymorphism that may affect transcription efficiency *in vitro* [42]. There is no doubt that E-cadherin inactivation plays an important role in the development of breast cancers. A large number of investigations indicate complete and irreversible inactivation of E-cadherin in lobular breast cancer. These findings implicit E-cadherin's role as a genuine tumor suppressor role in this subclass of breast cancer.

Adjuvant chemotherapy decreases the risk of breast cancer recurrence in patients with breast cancer. In addition, it increases the rate of survival [46-48]. Despite the limitations of most published studies, the preliminary research described in the literature indicates that *E-cadherin* polymorphism assessment may be used to evaluate breast cancer susceptibility and aggressiveness. Methods for selection of the patients who are suitable for anti-E-cadherin therapy should be developed and established. Further clinical trials involving the study of *E-cadherin* polymorphisms should be completed that comprise a large number of patients of different ethnicities. In summary, E-cadherin and its associated signaling pathways play important roles in maintaining functions of breast cancer. In contrast, dysregulation of these factors contributes to breast cancer initiation and progression. Detection of the expression and aberrant alterations of E-cadherin are promising for clinical applications for diagnosis, prognosis and therapy for breast cancer. However, care should be taken due to the tumor promoting

role of E-cadherin in specific cell context in order not to render development of other tumors during reactivation of E-cadherin for therapy of breast cancer. Further studies of the functions of E-cadherin and the mechanisms of its tumor suppressing and tumor promoting roles are still in need before it can be used for wide application in clinic.

Conflict of Interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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