Review

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The role of the E-cadherin gene (*CDH1*) in diffuse gastric cancer susceptibility: from the laboratory to clinical practice

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Loss of function of the E-cadherin gene (*CDH1*) has been linked with diffuse gastric cancer susceptibility, and germline inactivating mutations in *CDH1* characterise the hereditary diffuse gastric cancer (HDGC) syndrome. Hypermethylation in the *CDH1* promoter region is a frequent phenomenon in poorly differentiated, diffuse gastric carcinomas and it was identified as the main mechanism for the inactivation of the remaining wild-type allele in HDGC cases. Specific criteria are used to identify patients with suspected HDGC and who should be investigated for *CDH1* germline mutations. Accurate screening is mandatory for unaffected carriers of *CDH1* mutations and selected high-risk individuals could be considered for prophylactic gastrectomy. Also, germline *CDH1* mutations may predispose to lobular breast carcinoma and prostate cancer.Germline *CDH1* mutations are not always detectable in patients who meet the HDGC criteria and the aetiological role of this gene is still under investigation. Families without recognised inactivating *CDH1* mutations may have undisclosed *CDH1* mutations or mutations in its regulatory sequences or germline mutations in unidentified genes that also contribute to the disease. In recent years, several germline missense *CDH1* mutations have been identified, some of which showed a marked negative influence on E-cadherin function in experimental models. *CDH1* promoter hypermethylation seems a key event in the carcinogenetic process of poorly differentiated, diffuse gastric cancer and it deserves further investigation as a new target for anticancer therapies with demethylating agents.
Key words: E-cadherin, gastric cancer, germline, hereditary diffuse gastric cancer

Search strategy and selection criteria

The terms 'cadherins' and 'stomach neoplasms' were used for the search in the CancerLit and the MEDLINE databases. Published articles before January 2003 were evaluated and selected if they concerned E-cadherin and diffuse gastric cancer. The reference list of these papers was carefully reviewed to look for additional information that could be relevant to this review.

The review was planned to cover the broadest information on E-cadherin and diffuse gastric cancer susceptibility, from the basic research to the clinical applications of current knowledge. Accordingly, the selected papers were subdivided and reported in the following main subjects: the E-cadherin gene (*CDH1*) and the role of the E-cadherin protein; mechanisms of *CDH1* inactivation in hereditary diffuse gastric cancer (HDGC) syndrome (germline truncating mutations and promoter hypermethylation); screening strategies and therapeutic interventions for individuals at risk for HDGC; incidence of diffuse gastric cancer and other epithelial neoplasms in *CDH1* mutation carriers; novel *CDH1* mutations and molecular mechanisms for *CDH1* inactivation which may predispose to diffuse gastric cancer susceptibility.

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The E-cadherin gene and its protein product

The E-cadherin gene (*CDH1*) is located on chromosome 16q22.1 and it contains 2.6 kb of coding sequences with 16 exons. The mature protein product belongs to the family of cell–cell adhesion molecules and it plays a fundamental role in the maintenance of cell differentiation and the normal architecture of epithelial tissues [1–7]. In fact, E-cadherin is a transmembrane homodimeric protein central to calcium-dependent adhesion in epithelial cells. E-cadherin function requires a fine interplay with the catenin–cytoskeleton complex in the cytoplasmic space and the E-cadherin dimers of neighbouring cells in the intercellular space (Figure 1). In particular, the N-terminal ends of the large extracellular domains of the dimers interact with similar E-cadherin dimers from the opposing cell surface, and the C-terminal ends of the cytoplasmic domains are associated with the catenins and the actin cytoskeleton. E-cadherin–catenin complexes from neighbouring cells cluster in specific membrane belts to form the adherens junctions, the most ubiquitous type of intercellular adhesion.

The pivotal role of E-cadherin in this transcellular network has been confirmed in various experimental data and tumour cell systems. Abrogation of the E-cadherin function induces loss of adherens junctions and impairment of cell adhesiveness and cell-proliferation signalling pathways. Abnormal morphogenesis and architecture of epithelial tissues, loss of cellular polarity and contact

inhibition, unregulated growth and invasion of adjacent tissues have been demonstrated in tumour cell systems with abolished E-cadherin expression [4–7]. On the other hand, transfection of malignant epithelial tumour cells with wild-type *CDH1* may restore the normal phenotype [6, 7]. According to these data, *CDH1* can be considered a tumour suppressor gene which may be linked with human cancer susceptibility [6–8].

CDH1 mutations and diffuse gastric cancer

Several genetic alterations have been defined in human gastric carcinomas (Table 1) and their number will increase with applications of the new cDNA array technologies [8, 9]. Among those reported in Table 1, *CDH1* mutations are considered to be the commonest somatic alterations in diffuse gastric cancer and they are detectable in about 50% of cases or more. Somatic mutations in the β-catenin/APC genes occur in the diffuse histotype too, but less frequently than *CDH1* mutations. To date, only *CDH1* germline mutations have been found in the HDGC syndrome [8].

Confirmation of the potential aetiologic role of inactivating *CDH1* germline mutations was obtained from genetic analyses in gastric cancer cell lines and in gastric carcinomas [10–13]. Subsequently, further evidence for the role of E-cadherin loss in tumorigenesis comes from the study of families with an aggregation of diffuse gastric cancer [11–13].

Three germline mutations in *CDH1* were found in kindreds of Maori families from New Zealand who showed early onset, poorly differentiated diffuse gastric cancer [14]: a substitution in a donor splice consensus sequence of exon 7, a frameshift mutation in exon 15 and a premature stop codon interrupting exon 13. These findings represented the first evidence of a molecular basis for familial diffuse gastric cancer susceptibility. Since the first description in the Maori ethnic group, inactivating germline *CDH1* mutations have been demonstrated in diffuse gastric cancer families of other ethnicity [15–17]. To date, HDGC has become a recognised inherited cancer syndrome and a limited number of defined truncating germline *CDH1* mutations have been associated with the disease [18–20].

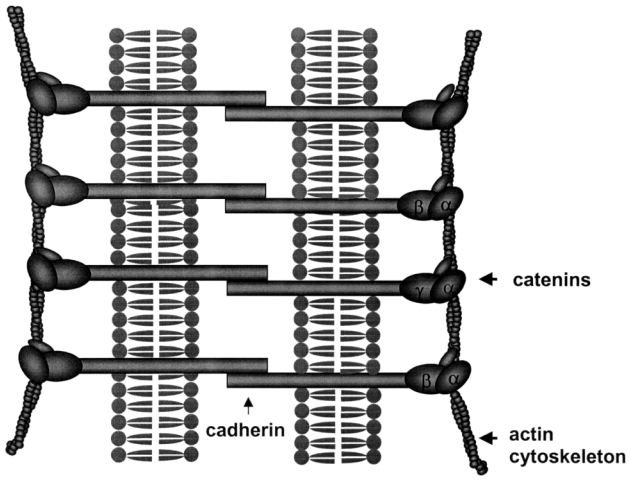

Figure 1. E-cadherin location and its role in cell–cell adhesion: each E-cadherin structure represents the protein homodimer which binds to the equivalent structure expressed on a neighbouring cell.

Table 1. Genetic abnormalities in human gastric carcinomas

Frequent	Less frequent or rare[a]	Under investigation	Promoter hypermethylation[b]
CDH1[c]	MRG[d]	Runx-3	*CDH1*[c]
TFF-1	APC	Interleukin-1a	p16
FHIT	DCC	PGFR	hMLH1
cMET	β-catenin	FGFR	p14(ARF)
HER2/neu	Bax[d]	caspases	APC
p53	TGF β I-II[d]	Killer/death receptor-5	MGMT
EGFR	STK11 (LKB1)	Fas (APO-1/CD95)	
p16/p27	k-Ras	PTEN/PIK3CA	
COX-2		p14(ARF)	
Telomerase activity		MGMT	
		Other[e]	

[a]Abnormalities that have been documented in <30% of cases, or rare abnormalities.
[b]Genes where promoter hypermethylation has been found as a frequent mechanism of epigenetic inactivation (>30% of cases).
[c]Common in tumours of the diffuse histotype.
[d]Specifically in tumours with high-frequency microsatellite instability.
[e]The role of other genes is under investigation by cDNA array technology.
APC, adenomatous polyposis coli; DCC, deleted in colorectal cancer; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FHIT, fragile histidine triad; MGMT, O[6]-methylguanine-DNA-methyltransferase; MRG, mismatch-repair genes (hMLH1, hMSH2, hMSH3, hMSH6); PGFR, platelet-derived growth factor receptor; TFF-1, Trefoil factor family I; STK11 (or LKB1) is linked to the Peutz–Jehger syndrome; TGF, transforming growth factor.

The pattern of inheritance of the disease is consistent with an autosomal-dominant susceptibility with incomplete penetrance. Tumours of patients with HDGC showed little or no E-cadherin immunoreactivity and the 'two-hit' mutational model with somatic inactivation of the second allele was proposed to explain the abrogation of *CDH1* function [14]. According to recent investigations, loss of heterozygosity did not seem to occur frequently in these tumours and an epigenetic allelic inactivation was proposed. Indeed, hypermethylation of the *CDH1* promoter was found in the majority of sporadic diffuse gastric cancer cases and this phenomenon was identified as the main cause of inactivation in the remaining wild-type allele of HDGC cases [21–25]. To date, epigenetic silencing of tumour-related genes (*APC, CDH1, p16*) due to hypermethylation of the CpG sites in the 5′ promoter regions is considered as one of the pivotal genetic alterations in cancer development [26]. According to current data, *CDH1* promoter hypermethylation is detectable in ~50% or more of HDGC cases and in 40–80% of sporadic diffuse gastric cancer cases. This phenomenon occurs significantly less frequently in gastric carcinomas of the intestinal subtype [21, 22, 25]. Given its role in reducing E-cadherin expression and its reversible nature, *CDH1* promoter hypermethylation may represent an attractive target for novel therapeutics with demethylating properties [26, 27].

A model for the development of HDGC is shown in Figure 2.

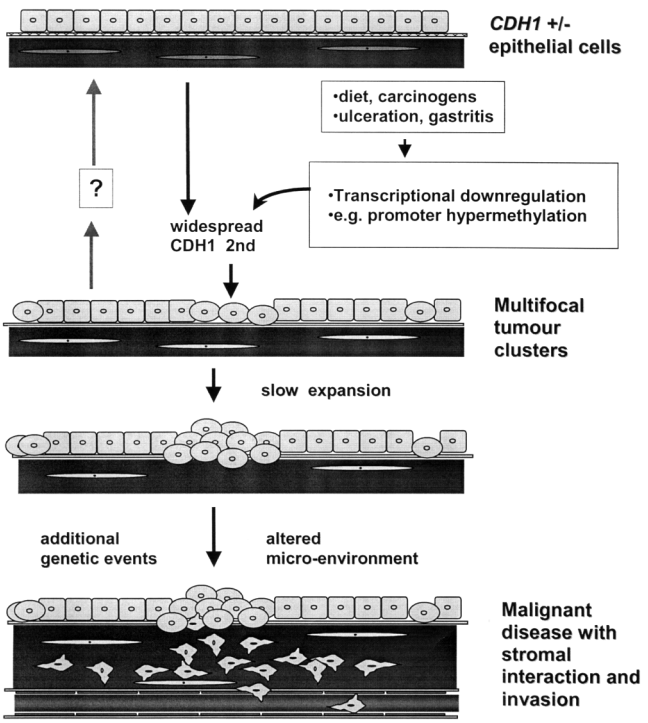

Figure 2. Model for the development of hereditary diffuse gastric cancer. The gastric mucosa in *CDH1* germline mutation carriers is normal until the second *CDH1* allele is inactivated or repressed (second hit) by transcriptional downregulation. Promoter hypermethylation represents one mechanism for downregulation, although transcription factor mediated events may also play a role. Since this downregulation would occur in multiple cells in the tissue, multifocal tumour lesions begin to develop. Environmental and physiological factors such as diet, carcinogen exposure, ulceration and gastritis may promote the downregulation event. The tumour expands slowly until additional genetic events, possibly combined with an altered microenvironment, lead to clonal expansion and disease progression. Because the second hit does not involve somatic, irreversible, mutation of the second *CDH1* allele, it is possible that the early stage lesions may be reversible.

Identification of individuals at risk

According to the Mendelian model, a healthy individual in a cancer syndrome family has a 50% chance of inheriting the mutant cancer predisposition gene. In HDGC families, carriers of germline *CDH1* truncating mutation have an estimated cumulative risk of 21% for men and 46% for women by the age of 50 years. These figures increase in the sixth and seventh decades and by the age of 80 years they have been estimated at around 67% for men and 83% for women [18, 19, 28, 29].

According to the current knowledge on HDGC, the following criteria have been adopted to identify the dominantly inherited cancer syndrome: two or more pathologically documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one diagnosed before the age of 50 years, or three or more pathologically documented cases of diffuse gastric cancer in first- or second-degree relatives of any age [28–30]. Notably, the vast majority of families with truncating *CDH1* mutations fulfil the former conditions, underlining the importance of early onset as a defining feature of inherited cancer susceptibility.

Figure 3 shows examples of families which fit the International Gastric Cancer Linkage Consortium (IGCLC) guidelines for the identification of HDGC and *CDH1* testing [28–30]. Approximately 25–50% of diffuse gastric cancer families meet these criteria, but inactivating *CDH1* mutations have been found in only 15–35% of these families [31]. In addition, recent data suggest that the frequency of *CDH1* germline mutations in featured cases of HDGC may be lower than that reported in early investigations and truncating germline mutations are under-represented [31–38]. Accordingly, unidentified *CDH1* mutations or mutations in other genes may explain diffuse gastric cancer susceptibility without known *CDH1* mutations.

Role of *CDH1* in other cancers

Lobular breast cancer is the second epithelial neoplasm which can be associated with inactivating germline mutations in *CDH1* [29, 39, 40]. In HDGC families, women carrying such *CDH1* mutations have an estimated 20–40% lifetime risk of developing lobular breast cancer. The best approach for early detection in these women is unknown; however, the adherence to current standard recommendations for the screening of *BRCA1* and *BRCA2* associated breast cancer is advisable.

New diagnostic procedures such as magnetic resonance imaging [41] and therapeutic approaches such as prophylactic mastectomy [42] and chemoprevention with tamoxifen [43] are innovative strategies which are under investigation for the management of women at risk of breast cancer due to *BRCA1* and *BRCA2* mutations. Data from early investigations seem promising and these

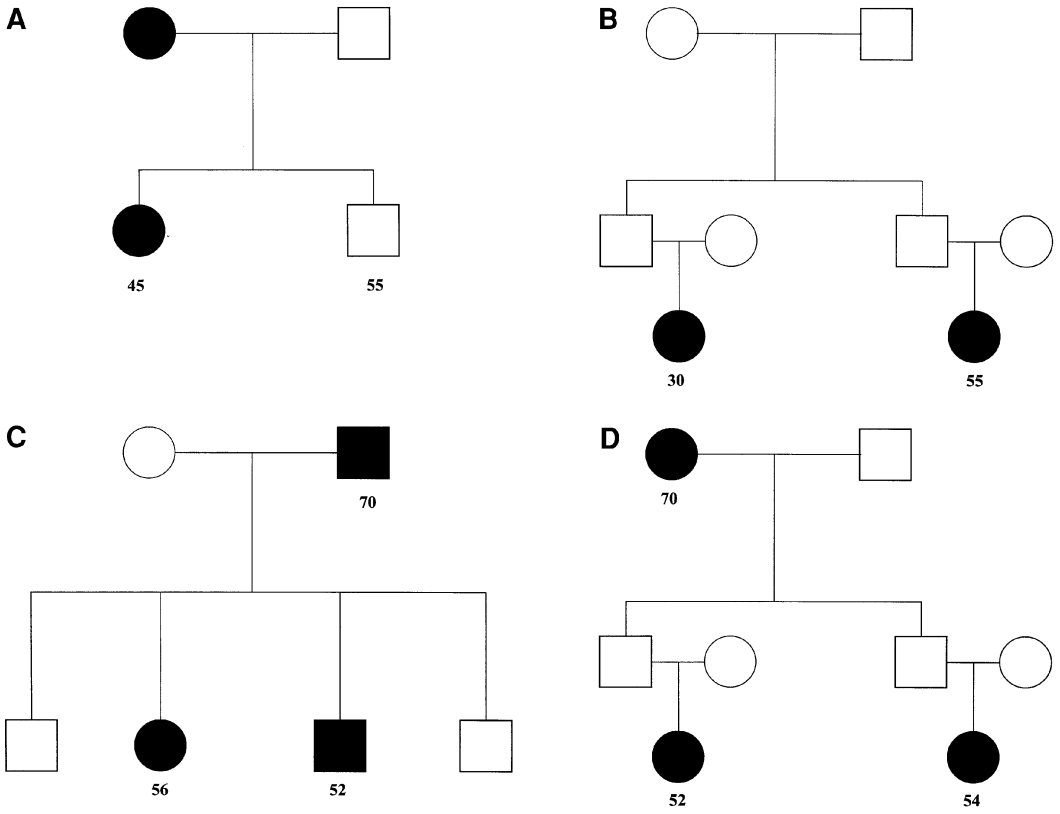

Figure 3. Examples of pedigrees that fulfil the hereditary diffuse gastric cancer criteria: two or more pathologically documented cases of diffuse gastric cancer in (**A**) first- or (**B**) second-degree relatives, with at least one diagnosed before the age of 50 years; three or more pathologically documented cases of diffuse gastric cancer in (**C**) first- or (**D**) second-degree relatives of any age. The squares represent male family members and the circles female family members. Solid symbols represent affected members with confirmed diagnosis of diffuse gastric cancer. Figures under each symbol indicate the age at diagnosis.

strategies could be effective in women with *CDH1* mutations as well, but to date, no clinical experience has been reported in this setting.

Recent data suggest that *CDH1* mutations may also be associated with the development of prostate cancer [44].

Diagnosis of HDGC

Cancer prevention efforts are warranted in individuals who are thought to have a predisposition to site-specific cancer and where early detection of those cancers may delay or prevent mortality. For this reason, more awareness of the HDGC syndrome among oncologists and family physicians may improve prevention and early detection of tumours with proven *CDH1* aetiology.

In clinical practice, the first step in the identification of the HDGC syndrome should be based on clinical clues of inherited predisposition to diffuse gastric cancer and lobular breast cancer. The family pedigree of a patient with early onset of one of these tumours and a high frequency of cancer in close relatives should be carefully investigated. The IGCLC guidelines for the identification of HDGC should be used to assess whether the cancer in the proband may be attributable to a germline *CDH1* mutation. In general, the diagnostic genetic test should only be offered to patients and members of families fulfilling the HDGC clinical criteria [28–31].

A positive genetic test can be defined as one in which the mutation is clearly deleterious to E-cadherin function. This would include all truncating mutations, frameshifts and mutations in the 100% conserved splice donor and acceptor sites (AG/CT). However, for misssense mutations and mutations in the non-transcribed regulatory regions, including the promoter and splice site consensus sequences, functional data such as increased invasiveness in *in vitro* adhesion assays, decreased transcription *in vitro*, and the identification of abnormal splice variants are required to demonstrate the effect of the mutation. These latter mutations should also be supported by demonstration of co-segregation with the disease in the family and a low frequency in the normal population.

Since there are no mutational hotspots in *CDH1*, the entire coding region, intronic splice sequences and promoter sequences need to be sequenced in each new family. If a new mutation is identified in the proband, other family members can then be tested for that mutation.

A negative test would imply either that (a) an unidentified mutation is responsible for the disease in the family or (b) that the observed familial aggregation is a chance event and family members are at general population risk for these cancers. Since (a) cannot be eliminated, continuing clinical surveillance of the family would be warranted.

More difficulties arise when testing a healthy individual with suspected family history for HDGC and no living affected relatives.

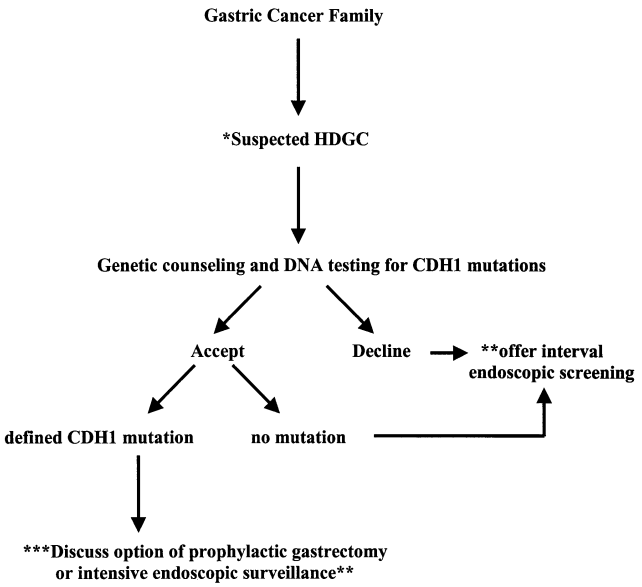

Figure 4. Schema to guide the management of familial gastric cancer kindreds. *Consider the IGCLC guidelines for the identification of patients with suspected hereditary diffuse gastric cancer (HDGC) (see text). **Chrome endoscopy with methylene blue or indigo carmine/congo red staining can be used to improve the efficacy of upper endoscopy for early diagnosis. ***Carriers of featured *CDH1* mutations with highly penetrant phenotypes.

In this case, the counselling should stress that a negative test does not exclude the diagnosis of HDGC in that family. In some cases, however, it may be possible to identify a mutation in DNA extracted from archived paraffin-embedded tissue from an affected relative.

Figure 4 summarises current attitudes toward the screening and the management of familial gastric cancer kindreds.

Surveillance strategies in HDGC

Surveillance strategies in healthy individuals within an HDGC family can lead to the diagnosis of early stage diffuse gastric cancer, which allows radical surgery with potential curative intent. Upper endoscopy is considered the best available approach, even if the diagnosis could be difficult in the case of early lesions, which are small and tend to infiltrate rather than ulcerate or form exophytic masses. Multiple biopsies of gastric mucosa [45] or chrome endoscopy with methylene blue or indigo carmine/congo red staining could improve the efficacy of upper endoscopy for early diagnosis of HDGC.

Among known HDGC families, the median age of diagnosis has ranged between 30 and 40 years and the youngest subject was 14 years. Due to this broad range and the poor understanding of the contributing factors that initiate disease, the age of disease onset is highly unpredictable in *CDH1* mutation carriers. To date, there are no clear guidelines for the timing of surveillance strategies. However, chrome upper endoscopy every 6–12 months beginning from the time of a positive test (regardless of age) or beginning at an age that is 5–10 years earlier than the youngest affected patient in the family has been proposed [20, 30].

A role for prophylactic gastrectomy?

In recent years, prophylactic gastrectomy has been considered for early detection and curative resection of diffuse gastric cancer in carriers of germline *CDH1* mutations [46–49]. In these studies, baseline endoscopic examination did not reveal diffuse gastric cancer but, notably, it was diagnosed in all cases after careful pathological examination of the resected stomach. In the majority of cases, the examination revealed multifocal disease with up to >200 microscopic lesions identified per stomach.

The role of prophylactic gastrectomy in *CDH1* mutations carriers deserves further investigation and this intervention should be carefully discussed with individuals who ask for it [50]. The limited number of patients enrolled in available studies and the lack of studies comparing prohylactic gastrectomy versus intense surveillance strategies, together with the short follow-up and the lack of data on the incidence of second tumours do not allow any firm conclusion on the efficacy of this approach for improving survival. Also, total gastrectomy is still associated with a risk of mortality and postoperative complications in 2–4% and 10–20% of patients, respectively. Almost all of the patients who have undergone total gastrectomy have experienced one or more morbidity-related symptoms [51]. Thus, data on the survival benefit of prophylactic gastrectomy in carriers of *CDH1* mutations are insufficient, but the early and long-term complications of this procedure are clearly defined and they are likely to be detrimental to the quality of life of these subjects. Intensive surveillance, as described in the previous section, should be proposed to *CDH1* mutation carriers not desiring gastrectomy (Figure 4).

New perspectives

Inactivating *CDH1* germline mutations are not always detectable in cases meeting the HDGC criteria. Possible explanations for familial aggregation of diffuse gastric cancer should consider chance clusters of sporadic cancer. Also, genetic differences between ethnic groups may contribute to variability in the frequency of inactivating *CDH1* germline mutations in HDGC cases. Alternatively, the families without recognised inactivating *CDH1* mutations may have undisclosed *CDH1* mutations or mutations in the regulatory sequences or germline mutations in unidentified genes that also contribute to the disease [52]. Current investigations are studying missense *CDH1* mutations [53–59] and polymorphisms in the *CDH1* promoter [59–65] and molecular interactions involving E-cadherin and contributing to tumorigenesis [66–70].

New *CDH1* mutations with potential aetiologic role

According to recent figures, the total number of discovered truncating mutations in *CDH1* is 24 and the total number of missense mutations is four [31, 59]. These missense mutations, together with other *CDH1* genetic variants [53–59], are currently under investigation for their putative aetiologic role.

The *CDH1* promoter region has been screened for genetic variants with potential effects on the transcriptional activity of the gene. Indeed, studies *in vitro* showed that single nucleotide polymorphisms might reduce the transcriptional efficiency of *CDH1* and thereby reduce levels of functional protein [60, 61]. One of these putative functional polymorphisms consists of the C/A nucleotide change at position –160 in the *CDH1* promoter [61]. Recent investigations have evaluated its frequency *in vivo* [62] and its putative aetiologic role in case–control studies [63, 64]. To date, the largest case–control analysis [64] did not find a significant association between this germline change and diffuse gastric cancer susceptibility, but this result should be looked at with caution given the marked difference in the median age between diffuse gastric cancer cases (>60 years) and controls (<35 years). An additional analysis of the –160 C/A change together with an intronic polymorphism (48+6T/C; *CDH1* intron 1) and a silent exonic polymorphism (2076C/T; *CDH1* exon 13) suggested the presence of functionally distinct haplotypes at *CDH1*: a susceptibility haplotype (marked by A-T-T), a protective haplotype (C-T-T) and one or more neutral haplotypes [65]. These preliminary data are of particular interest and they may clarify the role of functional polymorphisms in the *CDH1* promoter; however, they must be confirmed in large epidemiological studies. Additional *CDH1* variants which may cause functional amino-acid substitutions in the E-cadherin protein have been described recently. Handschuh et al. [53] and Suriano et al. [58] found *CDH1* germline mutations in exons 8, 9 and 12 which may result in abnormal localisation of the E-cadherin protein and/or its decreased capability to bind calcium ions which are necessary to stabilise the protein and likely to protect it from protease degradation. Indeed, these *CDH1* variants caused loss of adhesiveness, altered morphology, and increased motility and invasion in experimental models [53, 58]. Data in support of these hypotheses have been found in immunohistochemistry analyses of the E-cadherin protein which showed abnormal cytoplasmic localisation and 'dot-like' staining patterns in the presence of germline *CDH1* mutations [53, 71].

Finally, these genetic variants alone could not be sufficient to abrogate *CDH1* function and they should be investigated in combination with other molecular mechanisms. Promoter hypermethylation, *Helicobacter pylori* infection, gastritis or reparative processes in the gastric epithelium may cause downregulation of E-cadherin that can contribute to the ultimate development of the cancer phenotype [66, 67].

Molecular mechanisms for E-cadherin inactivation

As part of adherens junctions, E-cadherin not only provides a physical link within tissues, but orchestrates proper adhesion, cell division and the maintenance of the differentiation programme, implicating it as a component of the cellular signalling network [1–7]. Abrogation of the fine interplay between molecules regulating cell motility and differentiation and E-cadherin may represent a novel mechanism for tumorigenesis [68–70].

The main positive regulators of proliferation and tissue expansion are receptor tyrosine kinases (RTKs), which are activated upon growth factor binding [69]. Downstream pathways include the ras-MAPK cascade and the PI3K system, which transduce incoming signals to promote division and to protect from apoptosis. Activation of RTKs can negatively act on E-cadherin function, leading to disassembly of adherens junctions and the acquisition of an invasive phenotype [69]. Experimental evidence suggests that RTK-mediated downregulation/disassembly of the E-cadherin–catenin complexes can be achieved on several levels: transcriptional repression of *CDH1* (e.g. via snail) [72, 73], post-translationally by direct or indirect phosphorylation of adherens junction components (e.g. β-catenin) [74], or RTK-associated endocytosis and degradation of E-cadherin [75]. In turn, functional E-cadherin complexes appear to antagonise the growth-promoting RTK activities as has been observed during contact inhibition [76]. Suppression of RTK signalling might be mediated by the activation of specific phosphatases (e.g. LAR) [77], which could reverse growth factor induced phosphorylation events or directly inactivate RTK pathway components.

Typically, the metastatic conversion includes the epithelial–mesenchymal transition (EMT) [78]. EMT is manifested as a switch from a stationary epithelial to a migratory fibroblastoid phenotype. At a molecular level, this switch involves the Rho family GTPases (Rho, Rac, Cdc42) system, which regulates distinct changes in the actin cytoskeleton required for adhesion, migration and invasion [79]. Rho and Rac appear to have opposing roles in the rearrangement of actin filaments. Downstream elements of RTK signalling have been shown to interact and activate the GTPases, which can interfere with cadherin-mediated adhesion [80]. However, the Rho–Rac system also appears to be regulated by E-cadherin. This regulation may be mediated by p120-catenin, a part of the E-cadherin complex, but may also involve phosphatidylinositol 3-kinase [81–85].

Abrogation of the fine interplay between E-cadherin, the RTK pathway and the Rho–Rac system may severely compromise the differentiated epithelial phenotype and lead to enhanced proliferation and induction of EMT (Figure 5). Genetic or other alterations in the molecules interacting with E-cadherin might thus represent novel mechanisms which could contribute to gastric carcinogenesis. However, the *in vivo* relevance of these findings has yet to be determined in diffuse gastric cancer. For a more detailed insight, the reader may refer to the reviews by Thiery and Chopin [70] and Conacci-Sorrell et al. [68].

Conclusions

Standardised clinico-pathological criteria are used to identify patients and families with HDGC and available techniques in molecular biology allow *CDH1* analysis. Accurate screening is essential for unaffected carriers with deleterious germline *CDH1* mutations and selected high-risk individuals could be considered for prophylactic gastrectomy.

Missense germline mutations in the *CDH1* coding sequences and its promoter region may represent additional genetic lesions for diffuse gastric cancer susceptibility. Also, their pathogenic role should be investigated with concomitant conditions that may reduce E-cadherin expression. Eradication of *H. pylori,* treatment of gastritis and the reversion of *CDH1* promoter hypermethylation could represent future chemopreventive strategies.

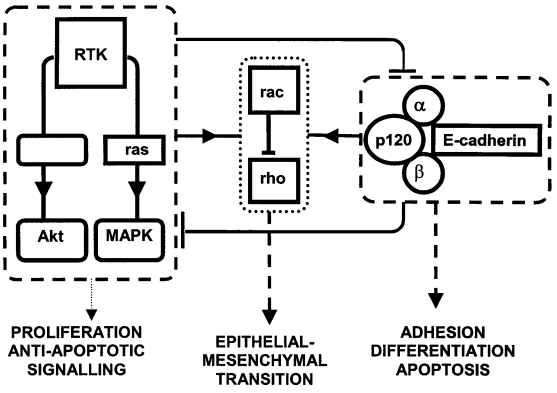

Figure 5. Main positive regulators of proliferation and tissue expansion are receptor tyrosine kinases (RTKs). Downstream pathways include the ras-MAPK cascade and the PI3K system. RTKs can negatively act on E-cadherin function leading to disassembly of adherens junctions. The Rho family GTPases (Rho, Rac, Cdc42) system regulates changes in the actin cytoskeleton. Downstream elements of RTK signalling have been shown to interact and activate Rho-Rac GTPases which can interfere with the cadherin-mediated adhesion. Catenin p120 was found to act as an inhibitory regulator of cadherin function either promoting or repressing E-cadherin-dependent adhesion. More details on these molecular interactions are reported in the text.

CDH1 promoter hypermethylation is a major mechanism for E-cadherin silencing. Potentially, this is a reversible process that could be the target of demethylating agents. These novel compounds are currently under investigation in phase I/II trials and they represent new, and hopefully effective drugs in the treatment of human neoplasms.

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