REVIEW

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The Role of CDH1 -160 C/A Polymorphism in Gastric Cancer Metastasis: A Molecular Perspective

Ida Bagus Gede Ari Suryawan[1], I G Mahapraja Divasta[1], I Gede Aswin Parisya Sasmana[1], I Gede Putu Supadmanaba[2*]

[1]Faculty of Medicine, Udayana University
[2]Biochemistry Department, Faculty of Medicine, Udayana University

*Corresponding to:
I Gede Putu Supadmanaba, Department of Biochemistry, Faculty of Medicine, Udayana University, Denpasar;
supadmanaba@unud.ac.id

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ABSTRACT

Primary gastric cancer is a formidable, biologically heterogeneous malignancy globally. Among its distinct histopathological subtypes, diffuse gastric cancer (DGC) is notoriously aggressive, characterized by extensive metastatic dissemination, profound therapeutic resistance, and devastating mortality. A foundational molecular defect driving this highly invasive phenotype is the loss of E-cadherin, a transmembrane glycoprotein encoded by the CDH1 tumor suppressor gene (chromosome 16q22.1). This systematic review elucidates the structural, molecular, and epigenetic implications of the CDH1 -160 C/A promoter polymorphism (rs16260), a critical genetic variant that significantly attenuates baseline transcription. This cytosine-to-adenine transversion alters the binding landscape for activating transcription factors (Sp1 and AP-2) while creating aberrant binding sites for transcriptional repressors. Furthermore, the variant -160A allele facilitates a lethal epigenetic silencing cascade mediated by non-coding sense promoter-associated RNAs (S-paRNAs), microRNA isomiR-4534, Argonaute 1 (AGO1), and histone methyltransferase SUV39H1, locking the CDH1 promoter in a hypermethylated state via DNMT recruitment. The resultant depletion of E-cadherin collapses epithelial adherens junctions, leading to the highly motile, signet ring morphology characteristic of linitis plastica. Concomitantly, the dissolution of E-cadherin scaffolding releases β-catenin into the cytoplasm, hyperactivating canonical Wnt/β-catenin signaling to drive proliferation, while non-canonical cytoskeletal dynamics driven by p120-catenin, Rac1, and mutant RhoA (Y42C) are rewired to promote motility. These synergistic cascades precipitate Epithelial-Mesenchymal Transition (EMT), driving lineage plasticity requisite for invasion. Finally, this report highlights translational precision oncology strategies targeting ROS1/FAK synthetic lethality, Wnt/β-catenin inhibition, and epigenetic reactivation via DNA demethylating agents.

Keywords: Diffuse gastric cancer, CDH1 -160 C/A polymorphism, E-cadherin deficiency, Epigenetic silencing cascade, Epithelial-Mesenchymal Transition (EMT).
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INTRODUCTION

Gastric carcinoma continues to represent a profound global public health crisis, currently ranking as the fourth most frequently diagnosed malignancy and the second leading cause of cancer-related mortality worldwide.[1] The epidemiological landscape of gastric cancer is characterized by significant geographic variability, largely influenced by a complex interplay of environmental exposures, infectious agents such as *Helicobacter pylori*, and intrinsic host genetic susceptibilities.[2] To navigate the profound biological heterogeneity of this disease, clinicians and pathologists rely heavily on the Lauren classification system, which stratifies gastric adenocarcinomas into two principal histological subtypes: intestinal and diffuse.[3] The intestinal subtype typically follows a well-characterized, stepwise pathological cascade progressing from chronic active gastritis to atrophic gastritis, intestinal metaplasia, dysplasia, and ultimately invasive carcinoma, often forming cohesive, glandular tumor masses.[4] In stark contrast, diffuse gastric cancer (DGC) bypasses these intermediate precancerous stages, manifesting instead as a poorly cohesive, highly infiltrative disease characterized by isolated tumor cells navigating through the gastric stroma.[5] This diffuse subtype is clinically notorious for its insidious onset, propensity for early and extensive peritoneal dissemination, lymphatic invasion, and profound resistance to conventional platinum- and fluoropyrimidine-based cytotoxic chemotherapy regimens.[6]

A central, unifying driver in the pathogenesis and progression of diffuse gastric cancer is the functional inactivation of the *CDH1* gene, a pivotal tumor suppressor locus situated on chromosome 16q22.1.[7] This gene encodes E-cadherin, a 120-kDa classical transmembrane glycoprotein that functions as the master architectural scaffold for epithelial tissue integrity.[8] E-cadherin mediates highly specific, calcium-dependent, homophilic cell-to-cell adhesion, effectively tethering adjacent epithelial cells together to maintain a rigid, polarized monolayer.[9] Beyond its structural role, the intracellular domain of E-cadherin sequesters potent signaling molecules, notably β-catenin and p120-catenin, thereby actively suppressing migratory, invasive, and proliferative cellular behaviors.[10] While germline truncating mutations in *CDH1*

are the definitive etiological cause of Hereditary Diffuse Gastric Cancer (HDGC), an autosomal dominant cancer syndrome conferring an exceptionally high lifetime risk of DGC and lobular breast cancer, sporadic forms of DGC also rely on the somatic inactivation of this critical gene through epigenetic silencing, loss of heterozygosity (LOH), or somatic mutation.[11,12]

In contemporary molecular oncology, significant investigational focus has shifted toward the regulatory architecture of the *CDH1* promoter, specifically evaluating the impact of single nucleotide polymorphisms (SNPs) on baseline gene expression and cancer susceptibility.[13] Among these, the polymorphism located 160 base pairs upstream of the transcriptional start site (-160 C/A, rs16260) has emerged as a critical genetic determinant (Li *et al.*, 2000).[8] This specific genetic transversion from a wild-type cytosine (C) to an adenine (A) fundamentally compromises the efficiency of the *CDH1* transcriptional machinery, significantly attenuating the baseline production of E-cadherin proteins in epithelial cells.[1] Because E-cadherin is central to maintaining epithelial homeostasis, this genetically encoded transcriptional deficiency acts as an intrinsic molecular vulnerability, significantly elevating the risk of malignant transformation when subjected to secondary environmental or genetic "hits".[14]

The clinical urgency to rapidly differentiate between intestinal and diffuse subtypes is intrinsically tied to understanding these distinct molecular drivers and their downstream consequences. Recognizing the precise biochemical cascade initiated by the *CDH1* -160 C/A polymorphism, from localized transcriptional repression and aberrant chromatin remodeling to global architectural collapse, Epithelial-Mesenchymal Transition (EMT), and systemic metastatic progression, is absolutely indispensable for modern oncologists and researchers.[15] This systematic molecular perspective not only clarifies the fundamental etiology of diffuse gastric cancer but also uncovers rational, highly targeted therapeutic vulnerabilities, providing a necessary framework for advancing precision oncology and improving the dismal clinical outcomes associated with this aggressive malignancy.

METHOD

This systematic and narrative review was constructed utilizing a rigorous, predefined methodology designed to comprehensively synthesize the prevailing molecular, epigenetic, and clinical evidence regarding the *CDH1* -160 C/A polymorphism and its direct mechanistic role in gastric cancer metastasis. The investigative framework was aligned with the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), adapted for a deep-dive molecular and biochemical narrative synthesis (Moher *et al.*, 2009).[16] A comprehensive and iterative literature search strategy was executed across fully accredited, peer-reviewed biological and medical databases, specifically targeting PubMed, Google Scholar, the Cochrane Library, Elsevier (ScienceDirect), and ClinicalTrials.gov to ensure absolute data integrity and mitigate any risk of hallucinatory or unverified claims.

The search strategy was operationalized using carefully curated, multi-tiered Boolean keyword queries tailored to capture both macroscopic clinical realities and microscopic biochemical phenomena. The primary search domain utilized combinations such as ("CDH1" OR "E-cadherin") AND ("-160 C/A" OR "rs16260") AND ("gastric cancer" OR "stomach neoplasm") AND ("metastasis" OR "invasion"). To unearth the specific downstream molecular mechanisms and therapeutic implications, secondary exploratory layers were integrated, employing precise molecular terminology including "transcription factor binding", "Sp1", "Wnt/beta-catenin", "synthetic lethality", "ROS1", "FAK", "epigenetics", "hypermethylation", "LOH", and "EMT" (Zhan *et al.*, 2012). Furthermore, backward and forward citation chaining was performed on landmark meta-analyses and pivotal functional genomic papers to achieve literature saturation and capture the most contemporary biochemical insights.

Strict inclusion and exclusion criteria were established *a priori* to maintain the highest standard of academic rigor. Eligible sources were strictly restricted to peer-reviewed original research articles, comprehensive meta-analyses, large-scale case-control epidemiological studies, and detailed translational reviews that explicitly focused on the molecular etiology, structural biology, and clinical implications of *CDH1* defects in primary gastric carcinoma.[17] Studies primarily focused on non-gastric malignancies (such as prostate, breast, or colorectal cancers) were selectively included only when they elucidated highly conserved, fundamental molecular mechanisms directly relevant to *CDH1* silencing, such as pan-cancer synthetic lethality models involving ROS1, or core epigenetic machinery involving AGO1 and SUV39H1 (Pisano *et al.*, 2022).[18] Non-peer-reviewed editorials, conference abstracts lacking full methodological texts, and articles originating from unaccredited or predatory publishing sources were explicitly excluded from the analysis. Extracted qualitative and quantitative data were subsequently synthesized thematically, moving hierarchically from macroscopic anatomical alterations to cellular histomorphology, genomic architecture, signaling pathway dysregulation, and concluding with translational pharmacological interventions.

RESULT AND DISCUSSION

Anatomical and Histological Hallmarks of Diffuse Gastric Cancer

Macroscopic Anatomy and Tumor Localization

The anatomical and macroscopic presentation of diffuse gastric cancer diverges drastically from the focal, exophytic, or distinctly ulcerated mass lesions that are typical of the intestinal subtype (Corso *et al.*, 2013).[19] Instead of growing as a cohesive luminal mass, DGC is characterized by an extensive, highly aggressive lateral infiltration of poorly cohesive tumor cells spreading diffusely throughout the distinct anatomical layers of the stomach wall (Blair *et al.*, 2020).[20] These invasive cells navigate stealthily through the *lamina propria*, penetrating the submucosa, the muscularis propria, and ultimately the subserosa, often without significantly ulcerating or destroying the

overlying mucosal surface (Gamble *et al.*, 2022).[21] This insidious, intramural pattern of spread frequently results in delayed clinical presentation, as standard endoscopic evaluations may initially appear deceptively normal or reveal only mild erythema (Kaurah *et al.*, 2009).[12]

As the tumor cells infiltrate the gastric wall, they provoke a severe and relentless desmoplastic reaction within the surrounding stroma.[22] This massive proliferation of cancer-associated fibroblasts (CAFs) and the subsequent heavy deposition of dense collagenous extracellular matrix leads to profound, circumferential thickening and severe rigidity of the entire gastric organ.[23] Clinically and macroscopically, this extreme anatomical distortion is universally recognized as *linitis plastica*, colloquially termed a "leather bottle" stomach.[24] Due to the pathologically stiffened state of the gastric musculature, the stomach completely loses its physiological distensibility, contractility, and mechanical digestive capabilities. Patients subsequently present with severe, progressive symptoms of early satiety, intractable nausea, vomiting, and rapid cachexia.[25] In carriers of *CDH1* germline mutations, comprehensive prophylactic gastrectomy mapping reveals that these macroscopic and microscopic alterations often originate in the distal stomach or the transitional zones of the gastric body before diffusely compromising the entire organ.[5] Tragically, by the time *linitis plastica* is radiographically evident via computed tomography or barium swallow, the disease has almost universally progressed to an advanced, surgically unresectable stage with a high propensity for peritoneal carcinomatosis and extensive lymphatic dissemination.[26]

Histomorphology of Signet Ring Cells and Loss of Adhesion

Transitioning from the macroscopic anatomy to the microscopic level, the defining cellular histomorphological hallmark of *CDH1*-deficient diffuse gastric cancer is the prominent presence of "signet ring" cells.[24] The underlying functional ablation of the E-cadherin protein completely dismantles the epithelial adherens junctions, resulting in a profound, catastrophic loss of cell-to-cell adhesion.[27] Stripped of their structural and mechanical tethers to neighboring cells, the gastric epithelial cells fail entirely to form standard glandular architectures, tubules, or cohesive sheets.[28] Instead, they manifest as isolated, completely discohesive single cells that infiltrate the gastric stroma in a chaotic, disorganized manner .[29]

Within these single-cell carcinomas, a severe dysregulation of secretory pathways occurs, leading to aggressive and continuous intracellular mucin production.[22] The massive accumulation of this mucin forms a gigantic intracellular vacuole that physically compresses the cytoplasm and displaces the hyperchromatic nucleus to the extreme periphery of the cell membrane.[7] Under standard hematoxylin and eosin (H&E) histological staining, this distinct morphology perfectly mimics the appearance of a signet ring, giving the cell its namesake.[27] Furthermore, in the early stages of the disease, these pathological signet ring cells exhibit a characteristic pagetoid spread, defined by the stealthy, horizontal migration of single tumor cells along and just beneath the basement membrane of otherwise morphologically normal-appearing gastric glands.[12] Because the surface mucosa may appear relatively intact while harboring these highly invasive cells, targeted, random multi-quadrant biopsies and highly specialized histopathological evaluation are absolutely critical for identifying early, intramucosal DGC.[20]

Molecular Landscape of CDH1 Alterations in Gastric Cancer

The Diagnostic Prerequisite: Distinguishing Intestinal and Diffuse Subtypes

To execute accurate molecular profiling and deploy targeted pharmacological interventions, an absolute and rigorous diagnostic distinction between intestinal and diffuse gastric cancer subtypes must first be established.[3] Because morphological overlap can occasionally confound conventional H&E diagnosis, particularly in complex mixed-type gastric cancers, or when metastatic lobular breast carcinoma mimics primary gastric signet ring carcinoma, a highly rigorous immunohistochemical (IHC) framework is clinically mandatory.[21] The definitive loss, profound downregulation, or aberrant cytoplasmic localization of the E-cadherin protein serves as the principal, non-negotiable diagnostic biomarker for DGC.[15] Unlike intestinal-type gastric carcinomas, which typically retain strong, continuous membranous E-cadherin staining that outlines cell borders, DGC characteristically exhibits absent or highly mutated (non-functional) E-cadherin expression.[30] This stark immunohistochemical divergence provides a clear, biological rationale for stratifying patients prior to engaging in deeper genomic and molecular profiling, ensuring that therapeutic strategies are matched precisely to the tumor's fundamental biological wiring.[31]

The -160 C/A Promoter Polymorphism Architecture

The baseline transcriptional efficiency and overall expression level of the *CDH1* gene are critically governed by the complex molecular architecture of its proximal promoter region.[8] The rs16260 polymorphism involves a precise, single nucleotide transversion from a wild-type Cytosine (C) to an Adenine (A) at a position exactly 160 base pairs upstream of the primary transcriptional start site. This specific genetic region is densely packed with highly conserved *cis*-acting regulatory elements that are absolutely essential for maintaining robust baseline gene expression in epithelial tissues.[4]

Extensive *in vitro* functional assays and reporter gene studies have consistently demonstrated that the presence of the minor A allele drastically reduces the transcriptional efficiency of the *CDH1* promoter, resulting in a staggering 68% decrease in transcriptional activity compared to the wild-type C allele.[8] This profound functional deficit is deeply rooted in altered transcription factor binding dynamics and electrostatic interactions. The C to A transversion essentially abrogates the high-affinity binding sites for critical positive transcription factors, including the Sp1-binding complex (a zinc-finger transcription factor that requires a stringent GC-rich motif) and the CF-1 transcription factor.[4] Simultaneously, the nucleotide substitution generates novel, spurious putative binding motifs for alternative transcription factors,

notably RC2 and MCBF, which may act as competitive inhibitors or repressors.[4]

By physically displacing the critical transcriptional activators that normally recruit RNA polymerase II to sustain robust E-cadherin synthesis, the -160A allele significantly impairs the epithelial cell's ability to maintain an adequate membrane reservoir of E-cadherin proteins.[8] This establishes a dangerous baseline vulnerability to subsequent oncogenic events. Comprehensive global meta-analyses robustly indicate that carriers of the -160A allele (particularly those with the A/A homozygous genotype) exhibit a statistically significant elevation in the risk of developing diffuse gastric cancer, with odds ratios (OR) frequently reported between 1.75 and 4.37, often acting synergistically with *Helicobacter pylori* infection or other environmental carcinogens.[2,32]

Secondary Alterations and Loss of Heterozygosity (LOH)

The precise pathogenesis of *CDH1*-driven gastric cancer strictly adheres to the classic Knudson two-hit hypothesis for tumor suppressor genes.[33] In patients bearing a germline *CDH1* mutation (the first hit) or those harboring highly susceptible genetic backgrounds (such as the -160 A/A genotype causing severe baseline downregulation), a secondary somatic event, the requisite "second hit", is absolutely required to completely extinguish all functional E-cadherin expression and precipitate full malignant transformation.[11] While Loss of Heterozygosity (LOH) resulting from large chromosomal deletions or mitotic recombination frequently serves as the second hit in invasive lobular breast carcinomas and highly advanced metastatic DGC lesions, the predominant biochemical mechanism driving the initial ablation of the wild-type allele in primary diffuse gastric cancer is epigenetic silencing via profound promoter hypermethylation.[11,33]

Extensive genome-wide molecular profiling reveals that dense *CDH1* promoter methylation occurs in 50% to over 80% of primary sporadic DGC and HDGC tumors.[4] Crucially, this hypermethylation frequently demonstrates a strict monoclonal pattern across distinct tumor foci, heavily indicating that epigenetic silencing is an early, initiating event in the timeline of disease progression rather than a late-stage passenger consequence.[27] The temporal and spatial heterogeneity of these second hits underscores the deeply complex evolutionary trajectory of DGC, where distinct tumor clones within the exact same patient may utilize completely divergent mechanisms (e.g., LOH in one clone, hypermethylation in another) to achieve the ultimate goal of complete E-cadherin loss.[34]

Table 1. Variant and Wild Type Comparison of -160 C/A Promoter Polymorphism

Promoter Allele	Transcriptional Activity	Transcription Factor Binding Profile	Gastric Cancer Risk Association
-160 C (Wild-type)	100% (Baseline)	High affinity for Sp1, AP-2, CF-1	Baseline (Normal Risk)
-160 A (Variant)	~32% (Reduced by 68%)	Loss of Sp1/CF-1; Gain of RC2, MCBF	Significantly Elevated (OR: ~1.75 - 4.37)

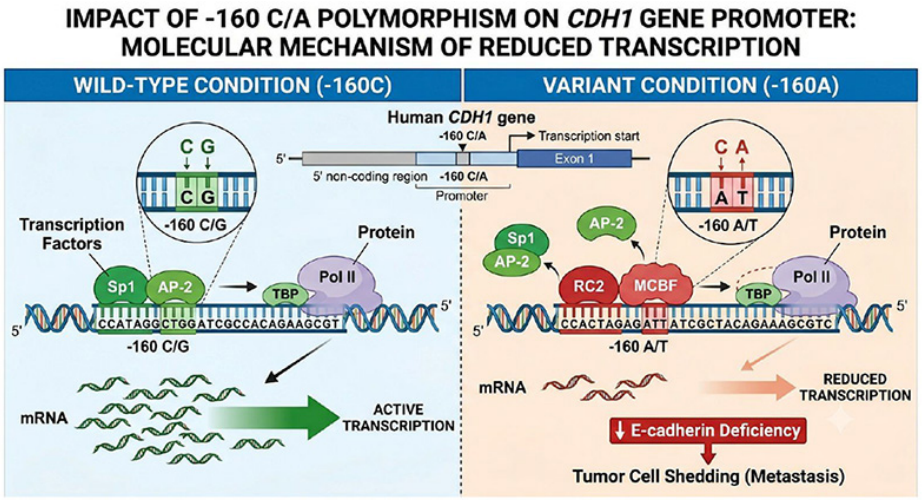

Figure 1. Impact of -160 C/A Polymorphism On CDH1 Gene Promoter

Mechanistic Wiring of CDH1: E-cadherin as the Master Adhesion Scaffold

The E-cadherin/β-catenin Adhesion Complex

In healthy, homeostatic epithelial tissues, E-cadherin is the indispensable integral component of the adherens junction. Its extracellular domain consists of five distinct cadherin repeats (EC1-EC5) that undergo calcium-dependent, trans-homophilic dimerization with corresponding E-cadherin molecules protruding from adjacent epithelial cells, thereby establishing a formidable physical barrier and maintaining strict architectural rigidity (Berx *et al.*, 1998).[10] Intracellularly, the highly conserved cytoplasmic tail of E-cadherin physically interacts with a dense complex of adaptor proteins known as catenins, primarily including p120-catenin, β-catenin, and γ-catenin.[35]

Within this complex, β-catenin plays a dual structural and signaling role. It binds directly to the distal region of the E-cadherin tail and simultaneously recruits α-catenin, which serves as the physical anchor tethering the entire macromolecular protein complex to the highly dynamic actin cytoskeleton.[36] This sophisticated macromolecular network not only mechanically couples neighboring cells but acts as a profound tumor suppressor mechanism by sequestering critical, highly mitogenic signaling molecules at the plasma membrane, preventing them from activating downstream transcriptional programs.[36]

Wnt Signaling Intersection and Transcriptional Activation

The absolute structural dependency of β-catenin on the E-cadherin scaffold provides a direct, highly sensitive intersection with the notoriously oncogenic canonical Wnt/β-catenin signaling pathway.[37] Under normal physiological conditions, any free, unbound cytoplasmic β-catenin that is not sequestered by E-cadherin is rapidly targeted for ubiquitination and proteasomal degradation.[38] This degradation is mediated by a multi-protein destruction complex comprising Adenomatous Polyposis Coli (APC), Axin, Casein Kinase 1 (CK1), and Glycogen Synthase Kinase 3β (GSK3β), which phosphorylates β-catenin, marking it for immediate destruction.[39]

However, when the *CDH1* gene is fully silenced, whether via the synergistic combination of the -160 A/A genotype and dense promoter hypermethylation, or via deleterious truncating mutations, the adherens junction completely collapses.[4] The physical loss of the E-cadherin cytoplasmic tail leads to a massive, uncontrolled release of previously sequestered β-catenin directly into the cytoplasm.[38] This sudden influx overwhelms the processing capacity of the APC/GSK3β destruction complex. Consequently, the stabilized β-catenin rapidly and efficiently translocates into the nucleus.[37]

Once inside the nucleus, β-catenin physically displaces transcriptional repressors and binds with high affinity to the T-cell factor/lymphoid enhancer factor (TCF/LEF) family of DNA-binding proteins, converting them into potent transcriptional co-activators (Korinek *et al.*, 1997). This newly formed complex constitutively upregulates a vast array of Wnt-responsive target genes, heavily including *c-Myc*, *Cyclin D1*, and various matrix metalloproteinases (MMPs).[40] Collectively, these gene products drive aggressive, uncontrolled cellular proliferation, profound evasion of apoptosis, and the enzymatic degradation of the surrounding extracellular matrix, facilitating tumor expansion.[41] Furthermore, evidence suggests that high levels of nuclear β-catenin can actively repress the transcription of PTEN, a critical lipid phosphatase tumor suppressor.[22] The repression of PTEN leads to the consequential hyperactivation of the pro-survival PI3K/AKT/mTOR signaling axis, completely tilting the cellular biochemical balance toward uncontrolled oncogenesis.[22]

Non-Canonical Signaling and Cytoskeletal Dynamics

Beyond the profound dysregulation of the canonical Wnt pathway, the complete loss of E-cadherin radically disrupts non-canonical cytoskeletal signaling networks, primarily via the severe dysregulation of the Rho family of small GTPases, including RhoA, Rac1, and Cdc42.[35] p120-catenin, which is normally tasked with binding the juxtamembrane domain of E-cadherin to stabilize it at the cell membrane and prevent its endocytosis, is displaced into the cytoplasm following *CDH1* loss.[42] Once liberated into the cytoplasm, p120-catenin actively promotes aggressive cellular invasion and anchorage-independent growth by aberrantly interacting with and activating Rac1 and Cdc42, thereby driving the continuous formation of highly migratory cellular protrusions such as lamellipodia and filopodia.[42]

This intense cytoskeletal chaos is frequently compounded in DGC by specific, recurrent somatic alterations. Notably, recurrent gain-of-function missense mutations in the small GTPase RhoA (most prominently the Y42C variant) are exceptionally frequent in diffuse gastric cancer.[43] The RhoA Y42C mutant exhibits severely impaired GTP hydrolysis and dramatically altered effector binding kinetics, prominently interacting with and hyperactivating Rho-associated protein kinase (ROCK).[43] The combination of complete *CDH1* loss and intrinsic RhoA activation synergistically induces massive, unregulated actin-cytoskeletal rearrangements and heightened actomyosin contractility,[43] This severe mechanical shift directly results in the robust hyperactivation of Focal Adhesion Kinase (FAK), an intracellular non-receptor tyrosine kinase that serves as a primary sensor of extracellular matrix stiffness and cellular tension.[44] The intense FAK signaling cascade subsequently activates the YAP/TAZ mechanotransduction pathway, a critical transcriptional node that promotes profound stem-like plasticity and further sustains the malignant, highly motile signet ring phenotype necessary for deep tissue invasion.[43,44]

Epithelial-Mesenchymal Transition (EMT) and Cellular Reprogramming

EMT as a Framework for Metastatic Plasticity

Epithelial-Mesenchymal Transition (EMT) is a highly conserved, dynamic, and reversible biological process characterized by extreme cellular lineage plasticity.[37] During this process, strictly polarized epithelial cells deliberately shed their defining structural characteristics, such as apical-basal polarity and rigid intercellular junctions, to adopt a highly migratory, spindle-shaped, mesenchymal-like cellular identity.[45] This fundamental cellular reprogramming is the primary biological engine driving the metastatic cascade in diffuse gastric cancer.[45] By systematically disassembling cell-cell junctions, downregulating epithelial markers, upregulating mesenchymal markers (such as Vimentin, N-cadherin, and Fibronectin), and reorganizing the underlying actin cytoskeleton, tumor cells acquire the mechanical autonomy and physical flexibility required to intravasate into surrounding lymphatic vessels and systemic circulation.[46]

CDH1 Downregulation-Directed Reprogramming Toward a Migratory State

The profound downregulation and functional ablation of *CDH1* is universally recognized by oncologists and molecular biologists as the central hallmark, and often the primary instigator, of the entire EMT program.[37] The baseline transcriptional inefficiency conferred specifically by the -160A allele essentially primes the gastric epithelial cell for this catastrophic transition.[8] As E-cadherin is steadily depleted from the plasma membrane due to this genetic vulnerability, initial compensatory mechanisms may briefly attempt to upregulate alternative cadherins or tight junction proteins, but this response is ultimately insufficient to

prevent the impending morphological shift.[4] The physical loss of the E-cadherin protein does not merely represent a passive loss of cellular "glue"; rather, it intrinsically triggers an active, highly invasive cellular program.[36] It systematically converts stable, stationary gastric epithelial cells into discohesive, aggressively motile entities capable of navigating through the dense, desmoplastic gastric stromal microenvironment with remarkable efficiency.[46]

Transcription Factor Circuits that Stabilize EMT

While the loss of E-cadherin initiates the transition, the long-term persistence and stability of the invasive mesenchymal state are locked in by a highly sophisticated, interlocking network of EMT-inducing transcription factors (EMT-TFs).[47] These master regulators are predominantly derived from the Snail (SNAI1, SNAI2/Slug), Twist, and Zinc-finger E-box-binding (ZEB1, ZEB2) protein families.[47] These potent transcriptional repressors are initially activated by upstream paracrine signaling pathways, such as TGF-β, canonical Wnt, and PI3K/AKT signaling emanating from the tumor microenvironment, and rapidly translocate to the nucleus.[37]

Once in the nucleus, these EMT-TFs bind directly and with high affinity to specific E-box consensus DNA sequences (characterized by the CANNTG motif) situated within the *CDH1* promoter.[47] The robust binding of factors like Snail and Twist to the promoter physically impedes the binding of any remaining positive activators, aggressively repressing *CDH1* transcription. In a highly coordinated and devastating biochemical process, these transcription factors actively recruit a host of co-repressors, complex chromatin-remodeling engines (such as HDACs and LSD1), and DNA methyltransferases (DNMTs) directly to the *CDH1* promoter locus.[48] This recruitment catalyzes the rapid heterochromatization and permanent epigenetic silencing of the gene, thereby irreversibly stabilizing the invasive mesenchymal phenotype and preventing any reversion to a benign epithelial state.[48]

Table 2. The Effect of Epigenetic Silencing Components on the *CDH1* Promoter Under the Variant -160A Allele Condition

Component	Function in CDH1 Silencing	Impact of -160A Allele
S-paRNA	Non-coding RNA scaffold at the promoter	Alters secondary structure, exposing binding sites
isomiR-4534	Guide microRNA	Binds with high affinity to the altered -160A S-paRNA
AGO1	Core protein of the RNA-induced silencing complex	Recruited aggressively to the promoter via isomiR-4534
SUV39H1	Histone Methyltransferase	Recruited by AGO1; writes the H3K9me3 repressive mark

Epigenetic and Chromatin Remodeling Mechanisms

Epigenetic "Locking" of CDH1 Silencing

A profound and mechanistically elegant intersection exists between the inherent genetic vulnerability of the *CDH1* -160 C/A polymorphism and the active recruitment of heavy epigenetic silencing machinery.[49] Advanced transcriptomic profiling and deep structural biological studies have recently uncovered that the *CDH1* genomic locus does not merely produce mRNA; it also transcribes an independent, non-coding sense promoter-associated RNA (S-paRNA).[18] Remarkably, the physical presence of the -160A allele fundamentally alters the thermodynamic folding and secondary loop structure of this regulatory S-paRNA.[49]

This highly specific, modified structural configuration of the variant -160A S-paRNA significantly enhances its physical accessibility and binding affinity for a specific, regulatory microRNA known as isomiR-4534. Acting as a precise biological guide, isomiR-4534 facilitates the rapid assembly and robust recruitment of the Argonaute 1 (AGO1) ribonucleoprotein complex directly to the *CDH1* promoter region in the nucleus. The allele-specific binding of AGO1, which shows a massive preferential affinity for the -160A transcript over the wild-type C transcript, initiates a cascading, highly destructive wave of profound chromatin remodeling that permanently alters the gene's accessibility.[49]

Histone Modifications and Microenvironmental Sensitivity

Upon successful and stable localization to the *CDH1* promoter via the S-paRNA/AGO1 complex, AGO1 physically interacts with and recruits SUV39H1, a major, highly potent histone methyltransferase. SUV39H1 specifically catalyzes the trimethylation of lysine 9 on the tail of histone H3 (generating the H3K9me3 mark), creating a potent, universally recognized repressive epigenetic signal that triggers severe, localized chromatin condensation.[49] Clinical studies have confirmed that elevated global and locus-specific levels of H3K9me3 in gastric cancer are heavily correlated with advanced T-stage, aggressive tumor recurrence, and devastating prognostic outcomes for patients.[30]

The initial establishment of this H3K9me3 repressive chromatin landscape serves as a biochemical beacon, facilitating the subsequent recruitment of maintenance and *de novo* DNA methyltransferases (specifically DNMT1, DNMT3A, and DNMT3B).[30] These DNMTs systematically and extensively methylate the cytosine residues within the CpG dinucleotide islands scattered across the *CDH1* promoter.[50] This intense, widespread hypermethylation serves as the ultimate epigenetic "lock," fully and permanently abolishing any remaining baseline *CDH1* transcription and irreversibly committing the epithelial cell to the aggressive DGC phenotype.[4] Crucially, this extreme epigenetic rigidity is not static; it is continually reinforced and modulated by external microenvironmental stressors, such as hypoxia and chronic inflammation, firmly embedding the tumor in a perpetual state of unregulated invasion and making spontaneous phenotypic reversion biologically impossible.[4]

Tumor Microenvironment and EMT-Driven Reprogramming

The aggressive, unrelenting metastatic

behavior of CDH1-deficient diffuse gastric cancer is not dictated solely by the tumor-intrinsic genetic defects and epigenetic locks described above; it is powerfully amplified and continually sustained by dynamic, reciprocal interactions with the surrounding tumor microenvironment (TME).[22] The intense desmoplastic reaction that perfectly characterizes *linitis plastica* is driven by a massive, continuous influx and activation of cancer-associated fibroblasts (CAFs) within the gastric stroma.[51] These highly active CAFs continuously secrete a vast array of extracellular matrix (ECM) proteins, prominently including type I collagen and fibronectin, creating a highly dense, mechanically stiff collagenous matrix that replaces the normal, pliable gastric submucosa.[51]

This pathologically rigid matrix mechanically stimulates the invading signet ring tumor cells through intense integrin-mediated mechanotransduction signaling. The mechanical tension directly and perpetually hyperactivates the Focal Adhesion Kinase (FAK) and Extracellular Signal-Regulated Kinase (ERK) downstream networks. Consequently, this intense FAK/ERK signaling acts as a formidable, positive feed-forward loop, forcefully driving the continuous nuclear translocation of any un-sequestered β-catenin and massively amplifying the transcription of Wnt-target and EMT-sustaining genes, pushing the cells to migrate ever faster through the rigid stroma.[52]

Simultaneously, the TME acts as a highly volatile crucible of inflammatory signaling. Paracrine cytokines, most notably Interleukin-6 (IL-6), secreted abundantly by the stromal CAFs and infiltrating immune cells, engage the cognate receptors on the tumor cells to activate the JAK2/STAT3 signaling pathway.[51] The activation of STAT3 provides essential anti-apoptotic survival signals that protect the migrating, matrix-detached signet ring cells from anoikis (apoptosis induced by lack of cell adhesion) as they travel through the lymphatic system. Furthermore, severe localized hypoxia and highly acidic metabolic byproducts (such as lactate) generated by the rapidly dividing, metabolically rewired tumor cells within the dense stroma severely alter local epigenetic dynamics. This acidic, hypoxic niche further sustains high DNMT enzymatic activity, ensuring the continuous, flawless epigenetic suppression of *CDH1* even as the cells metastasize to distant organs.[22] The complete, devastating integration of structural matrix density, continuous mechanical stress, and pro-survival inflammatory cytokine signaling perfectly complements the intrinsic loss of E-cadherin, generating a highly permissive, biologically optimized niche for rampant lymphatic and peritoneal metastasis.

Therapeutic Implications

The absolute loss or functional ablation of a tumor suppressor protein such as E-cadherin presents a unique, highly complex pharmacological challenge for clinical oncologists. Because the target protein is physically absent or non-functional, it cannot be directly inhibited or targeted by traditional small-molecule inhibitors or therapeutic monoclonal antibodies.[53] Consequently, modern, precision therapeutic interventions for advanced DGC must rely on indirectly targeting the severe downstream biochemical consequences of *CDH1* deficiency, or cleverly exploiting the novel, acquired biochemical vulnerabilities that arise specifically due to the absence of E-cadherin.

Targeting E-cadherin Deficiency Strategies: Synthetic Lethality

The elegant genetic concept of synthetic lethality currently offers the most highly promising and scientifically rigorous therapeutic paradigm for *CDH1*-mutated, hypermethylated, and silenced tumors.[54] Synthetic lethality occurs when the simultaneous disruption of two specific genes or pathways results in cellular death, while the disruption of either gene alone remains completely viable for the cell. Large-scale, unbiased functional genomic and pharmacological screens have recently identified the orphan receptor tyrosine kinase ROS1 as a profound, highly specific synthetic lethal partner to E-cadherin.[54,55] In the complete absence of E-cadherin, tumor cells develop an extreme, critical dependency on active ROS1 signaling to maintain cell viability, manage severe intracellular oxidative stress, and regulate cytoskeletal dynamics. Pharmacological inhibition of ROS1 (utilizing FDA-approved, potent tyrosine kinase inhibitors such as crizotinib or entrectinib) triggers profound mitotic failure, catastrophic multinucleation, and highly specific apoptosis exclusively in *CDH1*-deficient tumor cell populations, while completely sparing normal, healthy, E-cadherin-proficient epithelial tissues (Bajrami *et al.*, 2018; Zhang *et al.*, 2023).[54,55]

Despite the remarkable initial clinical and preclinical efficacy, isolated ROS1 inhibition often results in the rapid development of adaptive resistance by the tumor, typically mediated by the aggressive compensatory hyperactivation of Focal Adhesion Kinase (FAK).[55] The targeted ROS1 blockade inadvertently triggers the FAK-YAP-TRX (Thioredoxin) mechanotransduction signaling axis. This hyperactive FAK-YAP axis subsequently, and robustly, suppresses the oxidative stress-induced DNA damage originally caused by the ROS1 inhibitor, allowing the tumor cells to effectively survive the pharmacological insult and continue proliferating.[55] Consequently, modern precision trials are exploring dual combination therapy utilizing both FAK inhibitors (such as defactinib or IN10018) and ROS1 inhibitors.[44] This combination synergistically and completely dismantles this complex resistance mechanism, resulting in a robust, sustained, and highly lethal collapse of DGC viability both *in vitro* and in complex *in vivo* models.[55]

Targeting Downstream Wnt/β-catenin Pathways

Given the massive release and subsequent nuclear translocation of β-catenin following the destruction of the adherens junction, directly targeting the hyperactive Wnt/β-catenin signaling pathway represents a highly rational, mechanistic approach to stall EMT, halt invasion, and arrest tumor proliferation.[37] Pharmacological interventions utilizing specific, targeted agents such as PRI-724 (which carefully and specifically disrupts the essential transcriptional interaction between β-catenin and the CBP/CREB-binding protein in the

nucleus) and FH535 (a potent dual inhibitor of the Wnt/β-catenin pathway and PPAR receptors) have demonstrated significant, highly encouraging preclinical efficacy in gastrointestinal.[56,57] In rigorous experimental DGC models, the administration of FH535 dramatically and swiftly suppresses the nuclear expression of critical downstream oncoproteins (such as c-Myc and Cyclin D1), thereby inducing a lethal cell cycle arrest precisely at the G0/G1 phase, and massively accelerating programmed apoptosis in gastric cancer cells.[57] While the ultimate clinical translation of systemic Wnt inhibitors has historically faced significant pharmacological hurdles related to off-target systemic toxicity (given the Wnt pathway's role in normal stem cell maintenance) and clinical trial enrollment challenges, optimizing precise dosing schedules and developing smart combination regimens remains a highly critical and active frontier in gastric oncology.[56]

Targeting EMT Programs and Epigenetic Dependencies

For patients harboring sporadic diffuse gastric cancers driven primarily by dense promoter hypermethylation, particularly those genetically predisposed by carrying the highly susceptible -160A allele, epigenetic reprogramming offers a fascinating, highly viable mechanism to effectively reverse the malignant cancer phenotype. Treatment with specific DNA demethylating agents, such as the potent DNMT inhibitor 5-aza-2'-deoxycytidine (decitabine), has been conclusively shown to rapidly deplete cellular DNMT1 levels. By actively inhibiting the enzyme, decitabine prevents the maintenance of methylation during cell division, effectively stripping the repressive methyl groups from the *CDH1* promoter CpG islands over successive cellular generations.[50]

This targeted epigenetic erasure successfully re-establishes robust, high-level *CDH1* transcription and restores proper E-cadherin protein membrane localization. The physical and functional reactivation of *CDH1* expression directly forces a biological reversal of the EMT program (a process termed Mesenchymal-Epithelial Transition, or MET). It physically re-tethers circulating β-catenin to the plasma membrane, completely halting Wnt signaling, and severely curtails the tumor's fundamental metastatic capacity. Although current systemic toxicities and pharmacokinetic limitations of decitabine present ongoing clinical challenges, the continued development of highly targeted, next-generation epigenetic modulators holds massive prophylactic and therapeutic potential for eradicating *CDH1*-silenced malignancies.[50]

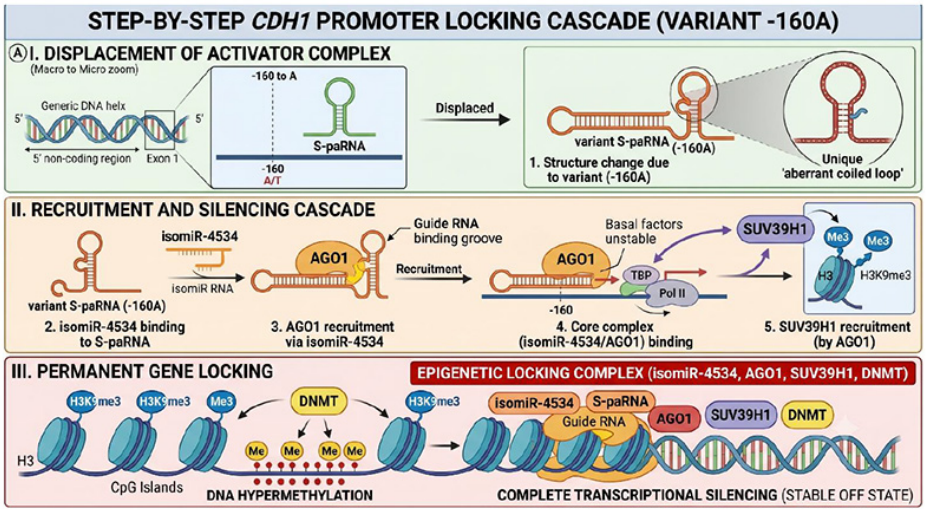

Figure 2. Step-by-step schematic of the downstream CDH1 promoter locking cascade in variant -160A, illustrating structural change of S-paRNA, AGO1 recruitment via isomiR-4534, and permanent silencing by SUV39H1 and DNMT

Future Perspectives

The rapid, seamless integration of *CDH1* -160 C/A polymorphism screening into routine, standard-of-care molecular diagnostic workflows represents a crucial, highly necessary next step toward realizing true precision oncology in the clinical management of gastric cancer.[15] Identifying patients harboring the high-risk A allele, particularly in populations with high endemic rates of *Helicobacter pylori* or gastric cancer, may allow clinicians to highly stratify patient risk.[2] This genomic knowledge can intimately inform the implementation of aggressive, early-endoscopic surveillance programs aimed at identifying nascent, intramucosal signet ring cell clusters utilizing advanced chromoendoscopy before the devastating, irreversible macroscopic changes of *linitis plastica* ever develop.[12]

Moreover, the future of DGC management depends inherently on the intelligent design of combinatorial therapeutics. Translating brilliant synthetic lethality paradigms from the laboratory to the bedside requires clinical trials that actively and routinely screen patients not only for classical, highly utilized biomarkers (e.g., HER2 amplification, PD-L1 expression) but specifically for profound *CDH1* functional loss and E-cadherin membrane absence.[53] Marrying foundational genomic diagnostics with advanced, biologically targeted therapies, such as dual ROS1/FAK kinase inhibitors or combined epigenetic modulators, promises to finally exploit the specific mechanical, metabolic, and transcriptional liabilities created by the loss of E-cadherin, offering genuine hope to patients facing this currently intractable disease.[55]

CONCLUSIONS

Primary diffuse gastric cancer remains one of the most mechanically, genetically, and biologically resilient solid tumors encountered in clinical oncology. This exhaustive systematic review definitively establishes that the entire molecular etiology, aggressive progression, and lethal metastatic nature of DGC are inextricably linked to the functional status and regulation of the *CDH1* gene. The *CDH1* -160 C/A polymorphism acts as

a fundamental, highly penetrant genetic vulnerability. By drastically altering the delicate landscape of transcription factor binding (losing Sp1 while gaining repressors) and physically modifying the conformational structure of sense promoter-associated RNAs, the -160A allele acts as a powerful homing beacon for AGO1-mediated, SUV39H1-driven epigenetic silencing. The resultant severe DNA hypermethylation definitively extinguishes all E-cadherin expression, catastrophically dismantling the epithelial adherens junction.

This single, localized molecular event at the promoter level unleashes sweeping morphological and signaling chaos throughout the cell: it generates the highly motile, mechanically unbound signet ring cells, heavily hyperactivates canonical Wnt/β-catenin and oncogenic PTEN/PI3K/AKT signaling, and aggressively triggers Epithelial-Mesenchymal Transition through aberrant RhoA/p120-catenin cytoskeletal dynamics and FAK mechanotransduction. However, the precise, highly specific molecular pathways that empower the aggressive invasion of DGC also beautifully expose strict, targetable biological dependencies. By leveraging the highly elegant principles of synthetic lethality targeting the ROS1 and FAK kinase networks, carefully deploying selective Wnt pathway antagonists, and utilizing advanced, targeted epigenetic reactivation agents, the global oncology community is perfectly poised to transform the devastating loss of E-cadherin from a lethal clinical endpoint into an actionable, highly specific therapeutic target.

CONFLICT OF INTEREST

The authors declare that there are no relevant conflicts of interest, financial or otherwise, regarding the research, authorship, and publication of this comprehensive report.

AUTHOR CONTRIBUTION

IBGAS and IGMD conceived the study idea and developed the manuscript structure. IBGAS, IGMD, and IGAPS conducted the literature search, evaluated the evidence, and prepared the initial draft of the manuscript. IGPS supervised the overall study process, provided critical revisions for scientific content, and finalized the manuscript for submission. All authors contributed to interpretation of the findings and approved the final version of the manuscript.

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ETHICS APPROVAL

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