OPEN ACCESS

GAVIN PUBLISHERS

Journal of Oncology Research and Therapy

Research Article

Kaladhar DSVGK. J Oncol Res Ther 6: 10106.

DOI: 10.29011/2574-710X.010106

DNA Methylation Studies and Molecular Therapy of *Helicobacter pylori* Strain for the Treatment of Gastric Cancer

Dowluru SVGK Kaladhar*

Department of Microbiology and Bioinformatics, UTD, Atal Bihari Vajpayee University, Bilaspur, Chhattisgarh, India

***Corresponding author:** Dowluru SVGK Kaladhar, Department of Microbiology and Bioinformatics, UTD, Atal Bihari Vajpayee University, Bilaspur, Chhattisgarh, India

Citation: Kaladhar DSVGK. (2021) DNA Methylation Studies and Molecular Therapy of *Helicobacter pylori* Strain for the Treatment of Gastric Cancer. J Oncol Res Ther 6: 10106. DOI: 10.29011/2574-710X.010106

Received Date: 23 July, 2021; Accepted Date: 03 August, 2021; Published Date: 10 August, 2021

Abstract

DNA methylation is a cellular process in which DNA methyltransferase regulates in addition of a methyl group to DNA, which is an epigenetic and heritable alteration that leads to cancer. About 62 genes are reported as methylated as per SCDb database and based on analysis, CDH1 (Cadherin 1) gene is showing a good characteristic relationship with gastric cancer that is caused by Helicobacter pylori. The Methylation frequency above 50 is shown in genes like APC, BRCA1, DAPK1, and RARB. Tissue-specific circular RNA induction in the human fetal development is increased from 10 week to 20 week gradually due to the genes like CDH1, PTEN, HLA-B and TIMP3. Due to CDH1 gene mutation, Beta–catenin suppresses the T-cell responses and promotes the development of tumors due to *H. pylori* infection. The selected molecules like Pravastatin, Clopidogrel, Magnesium Sulfate and Nicotine have shown control of mutated APC and CDH1 proteins. The Pravastatin has shown best activity mutated APC and CDH1 proteins. Magnesium Sulfate has shown least activity in control of CDH1 and APC proteins. Hence the present work confirms that Pravastatin is the best option for the molecular therapy in control of gastric cancer followed by drugs like Clopidogrel, Nicotine and Magnesium Sulfate.

Keywords: Gastric cancer; DNA methylation; *H. pylori*; Molecular therapy

Introduction

Gastric cancer (also known as stomach cancer) is a disease that can affect the stomach due to growth of cancerous cells in the inner lining of the stomach [1,2]. An abnormal and uncontrolled cell growth in the stomach will be observed due to gastric cancer. The symptoms may include heartburn, blood in stool, indigestion, jaundice, or trouble in swallowing nausea, vomiting, weight loss, difficulty in swallowing, loss of appetite, whites of the eyes, yellowing of the skin, upper abdominal pain and blood in the stool [3,4].

The stomach is an organ that is present between the esophagus and the small intestine. Gastric cancer is mostly affects in older people having over the age of 45 years [5]. The risk of gastric cancer is due to having *Helicobacter pylori* infection in the stomach. Most of the genetic changes (mutations) are identified in some subset of humans affected by stomach cancer due to changes in environment and lifestyle [6]. Most of the gastric cancer cases are observed due to induced by *Helicobacter pylori* infection and the other causes include eating pickled vegetables, salted and smoked foods, drinking alcohol, cigarettes smoking, and genetic syndromes [7]. The treatment options include chemotherapy, surgery, radiation or a combination, and/or targeted therapy (such as monoclonal antibody therapy) [8]. The drugs Clopidogrel and Pravastatin are mostly using in the treatment of gastric cancer [9,10].

Helicobacter pylori (H. *pylori* :plural; H. *pylorus*: singular; Synonym: *Campylobacter pylori*) is a microaerophilic, gram-negative, spiral shaped bacterium with about 3 µm long and 0.5 µm diameter [11]. *H. pylori* will be found in the stomach that causes ulcers or gastritis (stomach inflammation). In the natural stomach ecology, *H. pylorus* plays a major role in influencing the other types of gastrointestinal probiotic bacteria like *lactobacillus, Befidobacterium* etc, which increase the levels of COX2 [12]. The probiotic bacteria trigger's Helicobacter cysteine-rich proteins (Hcp), particularly HcpA (hp0211), increased genes like vacuolating toxin A (VacA) and the cytotoxin-associated gene A (CagA), tyrosine residues of host cell membrane-associated tyrosine kinase (TK), activation of protein tyrosine phosphatase/ protooncogene Shp2 and epidermal growth factor receptor (EGFR), high levels of TNF-α and/or interleukin 6 (IL-6), reduced protein expression of some of the DNA repair proteins like MLH1, MGMT and MRE11 that may be involved in gastric cancer [13].

A tumor suppressor gene produces proteins within the system that helps in regulation of cell division. Due to mutation in tumor suppressor gene like APC and CDH1, uncontrolled cell growth or apoptosis occurs and may lead to tumors [14].

Materials and Methods

Pubmeth

Pubmeth is a cancer methylation databased that is annotated and reviewed based on automated textmining of literature. The database includes reporting of genes that are methylated in several cancer types like Gastric cancer. The website for search for PUBMETH is http://pubmeth.biobix.be/search.html. The diseases that are related to Gastric cancer have been analyzed using pubmeth database.

SCDb

A comprehensive resource for the human Stomach Cancer database is SCDb. SCDb serves as search engines for Browse, Query, Summary and tools to know information of genes that are related to stomach cancer. The available website of SCDb is http://www.stomachcancerdb.org/dblist/query. The Gene expression levels can be quantified using RPKM (Reads Per kilobase per Million mapped reads) method from SCDb.

KEGG / Kyoto Encyclopedia of Genes & Genomes Pathway Maps

The KEGG (Kyoto Encyclopedia of Genes & Genomes) Pathway database is a collection of graphical diagrams (KEGG pathway maps) and associated text information (KEGG pathway entries) for metabolism, various other cellular processes, and human diseases.

String v11.0

STRING v11.0 is a database that is know to predicted protein-protein interactions based on physical and functional associations from databases. The search site for multiple protein interactions is https://string-db.org/cgi/input?sessionId=byDwXWOC0ymQ&input_page_active_form=multiple_identifiers.

Retrieval/ Design of ligands and proteins

Molecules are visualized from Chemical Entities of Biological Interest (ChEBI) (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=63618) (Table 1). The molecules are designed using ChemSketch from ACDLabs v10.2 and was saved as .mol file format.

S.No	Name	ChEBI	PubChem Id
1	Clopidogrel	CHEBI:37941	60606
2	Pravastatin	CHEBI:63618	54687
3	Magnesium Sulfate	CHEBI:32599	24083
4	(S)-Nicotine	CHEBI:17688	89594

Table 1: Drugs for Gastric Cancer (from DrugBank, HMDB, Dgidb, PharmGKB, IUPHAR, NovoSeek, BitterDB).

The mutated protein of tumor suppressor gene APC is retrieved from PDB database (https://www.rcsb.org/)

iGEMDOCKv2.1

iGEMDOCK v2.1 is a graphical environment that is used for recognizing pharmacological interactions and for conducting virtual screening for ligands with selected proteins. The tool is available at http://gemdock.life.nctu.edu.tw/dock/download.php.

Results and Discussion

There are 9990 genes that are involved in Human Gastric Cancer out of which 62 genes are reported as methylated genes. The 62 genes that are reported as methylated as per SCDb database are ALDH1A3, ANXA5, APC, AREG, BCL2L10, BNIP3, BRCA1, CCND2, CDH1, CDH2, CDKN2A, CDX2, CLDN3, DAB2IP, DAPK1, DKK1, DNAJC15, ESR1, F2R, FADS1, FHIT, FYN, GSTP1, HLA-B, HLTF, ID4, IGFBP3, IGFBP7, INSIG1, LOX, LZTS1, MLF1, MLH1, MTSS1, MX1, NID1, NID2, NT5E, PAX6, PGR, PPIC, PTEN, PTGS2, PYCARD, RAB32, RARB, RASSF2, RB1, RBP1, RBP4, RGS2, RPRM, SCRN1, SNAI1, SYK, TFAP2C, THBD, THBS1, TIMP3, TNFSF9, WIF1 and FGFR2. The information has been retrieved from Genecards (https://www.genecards.org/) (Table 2).

Methylated Gene	Name as on Gene Cards	Entrez Gene Summary
ALDH1A3	Aldehyde dehydrogenase enzyme	Associated with microphthalmia; detected in tumor cells
ANXA5	Annexin 5 gene	Implicated in many obstetric complications
APC	**Adenomatosis Polyposis Coli**	**Colorectal cancers**
AREG	Amphiregulin	Various types of cancers and inflammatory conditions
BCL2L10	BCL2 Like 10	Involved in many cellular activities like anti- or pro-apoptotic regulators
BNIP3	BCL2 Interacting Protein 3	Silenced in tumors by DNA methylation
BRCA1	Breast And Ovarian Cancer Susceptibility Protein 1	Modulating the subcellular localization; disease-associated mutations; transcription; recombination; DNA repair of double-stranded breaks
CCND2	Cyclin D2	Cell cycle G1/S transition; germ cell proliferation; ovarian and testicular tumors; megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 3
CDH1	**Cadherin 1**	**Gastric**, colorectal, breast, thyroid and ovarian cancer.
CDH2	Cadherin 2	Development of the nervous system; establishment of left-right asymmetry; formation of cartilage and bone.
CDKN2A	Cyclin Dependent Kinase Inhibitor 2A	Cell cycle G1 control; mutated or deleted in a wide variety of tumors; tumor suppressor gene
CDX2	Caudal Type Homeobox 2	Major regulator of intestine-specific genes; plays a major role in the early embryonic development of the intestinal tract.; associated with intestinal inflammation and tumorigenesis
CLDN3	Claudin 3	An integral membrane protein; component of tight junction strands; putative apoptosis-related protein
DAB2IP	Disabled Homolog 2-Interacting Protein	Tumor suppressor; inactivated by methylation in prostate and breast cancers

DAPK1	Death Associated Protein Kinase 1	Programmed cell death; a tumor suppressor candidate; splicing results in multiple transcript variants
DKK1	Dickkopf WNT Signaling Pathway Inhibitor 1	Role in embryonic development; important in bone formation in adults; Elevated expression causes numerous human cancers; promote proliferation, invasion and growth in cancer cell lines
DNAJC15	DnaJ Heat Shock Protein Family (Hsp40) Member C15	Protein Coding gene; Cause of 3-methylglutaconic aciduria type 5; dilated cardiomyopathy with ataxia; multiple transcript variants
ESR1	Estrogen Receptor 1	Central DNA binding domain; role in growth, metabolism, sexual development, gestation, and other reproductive functions; breast cancer, endometrial cancer, and osteoporosis; have dozens of transcript variants
F2R	Coagulation Factor II Thrombin Receptor	Regulation of thrombotic response; multiple transcript variants
FADS1	Fatty Acid Desaturase 1	Conserved histidine motifs; regulate unsaturation of fatty acids
FHIT	Fragile Histidine Triad Diadenosine Triphosphatase	Involved in purine metabolism; carcinogen-induced damage; found in all esophageal, stomach, and colon carcinomas; tumor suppressor; loss of activity results in replication stress and DNA damage.
FYN	FYN Proto-Oncogene, Src Family Tyrosine Kinase	Protein-tyrosine kinase oncogene family; implicated in the control of cell growth; existence of distinct isoforms
GSTP1	Glutathione S-Transferase Pi 1	Function in xenobiotic metabolism; play a role in susceptibility to cancer and other diseases
HLA-B	Major Histocompatibility Complex, Class I, B	Central role in the immune system by presenting peptides derived from the endoplasmic reticulum lumen;
HLTF	Helicase Like Transcription Factor	Helicase and ATPase activities; regulate transcription
ID4	Inhibitor Of DNA Binding 4, HLH Protein	Regulation of diverse cellular processes; development and tumorigenesis.
IGFBP3	Insulin Like Growth Factor Binding Protein 3	Transcriptional splice variants ; altering interaction with cell surface receptors
IGFBP7	Insulin Like Growth Factor Binding Protein 7	Stimulates prostacyclin production and cell adhesion; associated with retinal arterial macroaneurysm
INSIG1	Insulin Induced Gene 1	Regulates cholesterol metabolism, lipogenesis, and glucose homeostasis; ubiquitin-mediated degradation; multiple transcript variants

LOX	Lysyl Oxidase	Multiple transcript variants; crosslinking of collagens and elastin; role in tumor suppression; predisposition to thoracic aortic aneurysms and dissections
LZTS1	Leucine Zipper Tumor Suppressor 1	Tumor suppressor protein; protein is silenced in rapidly metastasizing and metastatic tumor cells; role in cell-cycle control; Loss of heterozygosity (LOH) in the 8p arm is a common characteristic of many types of cancer.
MLF1	Myeloid Leukemia Factor 1	Phenotypic determination of hemopoetic cells; associated with myelodysplastic syndrome and acute myeloid leukemia; Multiple transcript variants
MLH1	MutL Homolog 1	DNA mismatch repair system; involved in meiosis; hereditary nonpolyposis colon cancer
MTSS1	MTSS I-BAR Domain Containing 1	Associated with Lung Giant Cell Carcinoma and Oropharyngeal Anthrax; identical protein binding *and* actin binding
MX1	MX Dynamin Like GTPase 1	Participates in the cellular antiviral response; multiple transcript variants
NID1	Nidogen 1	Basement membrane glycoproteins; role in cell interactions with the extracellular matrix
NID2	Nidogen 2	Basement membrane proteins; maintaining the structure of the basement membrane
NT5E	5'-Nucleotidase Ecto	Determinant of lymphocyte differentiation; Defects can lead to the calcification of joints and arteries
PAX6	Paired Box 6	Bind DNA and function as regulators of gene transcription; multiple transcript variants
PGR	Progesterone Receptor	Central role in reproductive events associated with the organization and maintenance of pregnancy; mediates the physiological effects of progesterone
PPIC	Peptidylprolyl Isomerase C	Accelerate the folding of proteins; can bind immunosuppressant cyclosporin A
PTEN	Phosphatase And Tensin Homolog	Tumor suppressor that is mutated in many types of cancers at high frequency; multiple transcript variants
PTGS2	Prostaglandin-Endoperoxide Synthase 2	Enzyme in prostaglandin biosynthesis; involved in inflammation and mitogenesis
PYCARD	PYRIN-PAAD-DAPIN domain (PYD) and a C-terminal caspase-recruitment domain (CARD).	Large signaling complexes in the inflammatory; undergoing apoptosis

RAB32	RAB32, Member RAS Oncogene Family	Involved in autophagy; melanosome secretion; linked to leprosy
RARB	Retinoic Acid Receptor Beta	Mediates cellular signalling in embryonic morphogenesis; cell growth; differentiation; hepatocellular carcinoma; flanks a hepatitis B virus integration site; multiple transcript variants
RASSF2	Ras Association Domain Family Member 2	Located near the prion gene; Ras association
RB1	Retinoblastoma-Associated Protein	First tumor suppressor gene found; cause of childhood cancer retinoblastoma (RB), bladder cancer, and osteogenic sarcoma
RBP1	Retinol Binding Protein 1	Necessary for growth, reproduction, differentiation of epithelial tissues and vision; Multiple transcript variants
RBP4	Retinol Binding Protein 4	Carrier for retinol (vitamin A alcohol) in the blood; prevents its loss by filtration through the kidney glomeruli; deficiency of vitamin A blocks secretion of the binding protein posttranslationally; deficiency results in defective delivery and supply to the epidermal cells
RGS2	Regulator Of G Protein Signaling 2	Mediator of myeloid differentiation; play a role in leukemogenesis
RPRM	Reprimo, TP53 Dependent G2 Arrest Mediator Homolog	Related pathways are DNA Damage Response
SCRN1	Secernin 1	Regulation of exocytosis in mast cells; spliced transcript variants
SNAI1	Snail Family Transcriptional Repressor 1	Zinc finger transcriptional repressor ; critical for mesoderm formation in the developing embryo; downregulates the expression of ectodermal genes within the mesoderm;
SYK	Spleen Associated Tyrosine Kinase	Widely expressed in hematopoietic cells; mediate diverse cellular responses, including proliferation, differentiation, and phagocytosis; potential tumor suppressor in human breast carcinomas; spliced transcript variants
TFAP2C	Transcription Factor AP-2 Gamma	Activation of several developmental genes; induced during retinoic acid-mediated differentiation; plays a role in the development of the eyes, face, body wall, limbs, and neural tube
THBD	Thrombomodulin	Activation of protein C, which degrades clotting factors Va and VIIIa and reduces the amount of thrombin generated.; mutation cause of thromboembolic disease, also known as inherited thrombophilia.
THBS1	Thrombospondin 1	An adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions; play roles in platelet aggregation, angiogenesis, and tumorigenesis.
TIMP3	TIMP Metallopeptidase Inhibitor 3	Inhibitors of the matrix metalloproteinases; mutations cause autosomal dominant disorder Sorsby's fundus dystrophy; induced in response to mitogenic stimulation

TNFSF9	TNF Superfamily Member 9	Bidirectional signal transducer; generation of cytotoxic T cells; expressed in carcinoma cell lines,
WIF1	WNT Inhibitory Factor 1	Play a role in embryonic development; involved in mesoderm segmentation; epigenetically silenced in various cancers
FGFR2	Fibroblast Growth Factor Receptor 2	Interacts with fibroblast growth factors; influence mitogenesis and differentiation; associated with Crouzon syndrome, Craniosynostosis, Pfeiffer syndrome, Saethre-Chotzen syndrome, Apert syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrata syndrome, and syndromic craniosynostosis; Multiple alternatively spliced transcript variants

Table 2: Genes related to gastric cancer with methylation and its summary from Genecards.

Table 2 has shown that CDH1 (Cadherin 1) is showing characteristic relationship with gastric cancer.

Gene	Number of references	Number of references in gastric cancer	Number of samples	Methylation frequency	Details for methylation In Gastric
ALDH1A3	1	1	10	20	no subtype specified (1)
ANXA5	--	--	--	--	-
APC	**65**	**7**	**343**	**59**	**adenoma (2); adenocarcinoma (2); no subtype specified (2); Soft tissue sarcoma (1)**
AREG	1	1	10	10	no subtype specified (1)
BCL2L10	--	--	--	--	--
BNIP3	3	--	--	--	--
BRCA1	16	1	83	55	no subtype specified (1)
CCND2	9	--	--	--	--
CDH1	**81**	**13**	**597**	**52**	**carcinoma (8); no subtype specified (2); adenocarcinoma (1); adenoma (1); soft tissue sarcoma (1)**
CDH2	1	--	--	--	--
CDKN2A	205	21	1433	30	no subtype specified (8); carcinoma (6); adenocarcinoma (3); adenoma (3); soft tissue sarcoma (1)
CDX2	2	1	73	29	no subtype specified (1)
CLDN3	--	--	--	--	--
DAB2IP	--	--	--	--	--

DAPK1	68	7	660	51	adenoma (3), no subtype specified (3), carcinoma (1)
DKK1	1	1	0	0	no subtype specified (1)
DNAJC15	1	1	10	30	neuroectodermal tumour (1)
ESR1	24	1	0	0	no subtype specified (1)
F2R	1	1	10	20	no subtype specified (1)
FADS1	-	--	--	--	--
FHIT	24	--	--	--	--
FYN	--	--	--	--	--
GSTP1	56	3	200	7	adenoma (1); carcinoma (1); no subtype specified (1)
HLA-B	1	1	60	40	no subtype specified (1)
HLTF	4	1	46	20	no subtype specified (1)
ID4	4	1	76	30	adenocarcinoma (1)
IGFBP3	8	--	--	--	--
IGFBP7	2	--	--	--	--
INSIG1	1	1	22	50	no subtype specified (1)
LOX	--	--	--	--	--
LZTS1	--	--	--	--	--
MLF1	--	--	--	--	--
MLH1	69	21	1154	22	carcinoma (10); no subtype specified (5); adenocarcinoma (3); adenoma (2); intestinal (1)
MTSS1	--	--	--	--	--
MX1	--	--	--	--	--

NID1	--	--	--	--	--
NID2	--	--	--	--	--
NT5E	--	--	--	--	--
PAX6	1	--	--	--	--
PGR	6	--	--	--	--
PPIC	--	--	--	--	--
PTEN	15	1	66	39	carcinoma (1)
PTGS2	20	7	653	19	carcinoma (3); no subtype specified (3); adenoma (1)
PYCARD	9	1	10	0	no subtype specified (1)
RAB32	1	1	48	27	adenocarcinoma (1)
RARB	48	4	246	51	carcinoma (2); no subtype specified (2)
RASSF2	1	--	--	--	--
RB1	15	--	--	--	--
RBP1	2	--	--	--	--
RBP4	--	--	--	--	--
RGS2	1	1	10	0	no subtype specified (1)
RPRM	8	1	0	0	no subtype specified (1)
SCRN1	--	--	--	--	--
SNAI1	1	1	10	0	no subtype specified (1)
SYK	8	2	61	34	carcinoma (1); no subtype specified (1)
TFAP2C	--	--	--	--	--

THBD	--	--	--	--	--
THBS1	19	6	625	38	no subtype specified (3); carcinoma (2); adenoma (1)
TIMP3	34	4	254	25	adenoma (3); no subtype specified (1)
TNFSF9	--	--	--	--	--
WIF1	8	--	--	--	--
FGFR2	--	--	--	--	--

Table 3: methylated frequency and detils in Gastric cancer genes using Pubmeth.

Table 3 has shown that Methylation frequency above 50 is shown for APC, BRCA1, CDH1, DAPK1 and RARB.

S.No	Related Disease	Top Affiliating Genes (text searches by Pubmeth)
1	Sarcoma	APC, CDH1, CDKN2A, DAPK1
2	Adenoma	APC, CDH1, CDKN2A, DAPK1 , GSTP1, MLH1, PTGS2, THBS1, TIMP3
3	Neuroectodermal tumour	DNAJC15
4	Adenocarcinoma	APC, CDH1, CDKN2A, ID4, MLH1, RAB32, ID4
5	Carcinoma	CDH1, CDKN2A, GSTP1, MLH1, PTEN, PTGS2, RARB, SYK, THBS1
6	Intestinal	MLH1
7	No subtype specified	ALDH1A3, APC, AREG, BRCA1, CDH1, CDKN2A, CDX2, DAPK1 , DKK1, ESR1, F2R, GSTP1, HLA-B, HLTF, NSIG1, MLH1, PTGS2, PYCARD, RARB, RGS2, RPRM, SNAI1, SYK, THBS1, TIMP3

Table 4: Diseases related to Gastric Cancer.

Table 4 and Figure 1 have shown that CDH1 is related to several diseases related to gastric cancer.

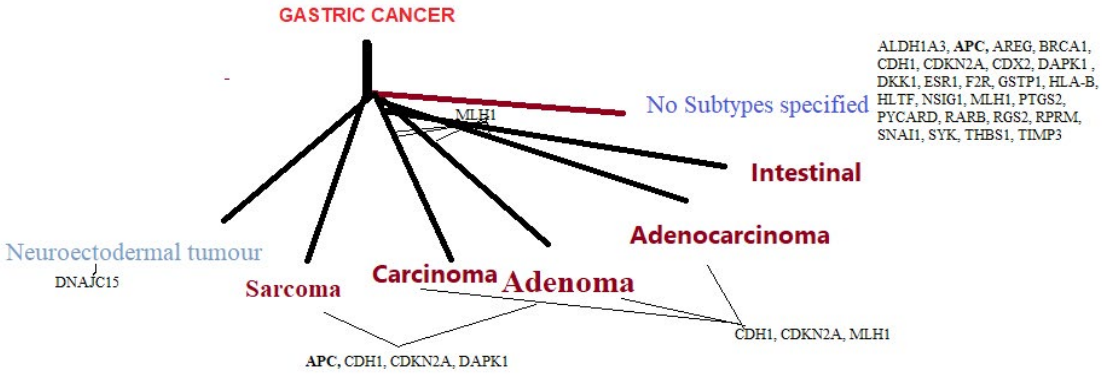

Figure 1: Graphical network of the top 7 diseases related to Gastric Cancer.

Gene	Methylation frequency	Reads Per Kilobase of transcript, per Million mapped reads (RPKM)					
		HPA RNA-seq normal tissues	RNA sequencing of total RNA from 20 human tissues	Tissue-specific circular RNA induction during human fetal development			
				10Wk	16WK	18 wk	20Wk
ALDH1A3	20	6.493± 2.886	1.571	1.339±0.081	2.585	1.949	3.325 ± 0.504
APC	**59**	**2.171 ± 0.773**	**1.521**	**4.506±0.49**	**6.645**	**6.024**	**5.741±0.485**
AREG	10	8.789±4.535	0.942	0.017±0.017	0.041	0.026	0.03±0.025
BRCA1	55	0.869±0.342	0.445	1.771±0.082	1.591	1.755	1.783±0.173
CDH1	**52**	**49.374±13.587**	**13.78**	**9.971±0.239**	**18.684**	**18.918**	**18.719±0.886**
CDKN2A	30	0.344±0.347	0.042	0.01±0.001	0.012	0	0.015±0.021
CDX2	29	0	0.091	0.215±0.215	0	0.085	0
DAPK1	51	7.785±2.725	2.608	6.396±0.123	6.713	6.067	6.288±0.184
DNAJC15	30	5.177±1.071	2.408	2.767±0.01	4.014	5.941	5.12±0.65
F2R	20	5.02±0.927	1.867	5.496±0.098	5.181	6.161	5.509±0.637
GSTP1	7	173.829±89.126	37.927	21.165±8.309	33.007	61.985	48.063±6.079
HLA-B	40	269.516±86.645	36.153	3.013±1.096	6.595	8.141	14.092±9.148
HLTF	20	4.47±1.498	1.457	4.334±0.426	5.186	5.527	5.13±0.415
ID4	30	8.625±5.243	1.802	5.459±0.884	7.885	10.285	9.941±0.693
INSIG1	50	17.359±1.653	4.373	2.492±0.185	6.034	8.679	5.683±0.157
MLH1	22	5.409±0.706	2.826	4.326±0.235	5.227	5.89	5.68±0.526
PTEN	39	8.303±1.828	3.666	6.643±0.678	11.059	11.206	11.494±0.971

PTGS2	19	1.905±1.847	1.158	0.599±0.084	1.136	3.143	1.986±0.983
RAB32	27	6.901±1.864	1.066	1.934±0.385	2.3	3.832	3.441±0.61
RARB	51	1.228±0.535	0.828	3.651±0.649	5.523	6.791	4.949±1.07
SYK	34	9.23±1.112	3.317	2.41±0.271	2.485	4.019	3.064±0.169
THBS1	38	22.886±16.861	11.345	13.62±1.188	23.401	28.878	21.43±0.933
TIMP3	25	19.121±2.647	16.301	14.244±2.006	30.908	32.44	35.32±5.48

Table 5: Million mapped reads (RPKM) for Gastric cancer genes.

Table 5 has shown that Tissue-specific circular RNA induction during human fetal development has been increased from 10week to 20 week gradually due to CDH1, HLA-B, PTEN and TIMP3.

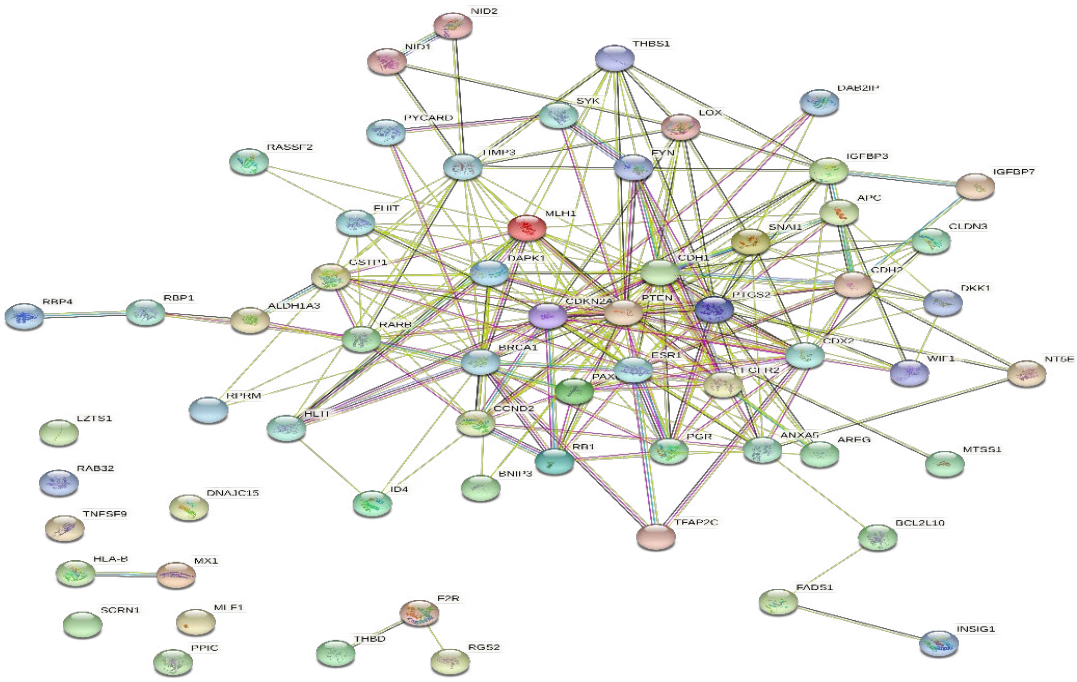

Figure 2: Protein-Protein interaction analysis.

Figure 2 has shown that CDH1 is related to several other cancer causing genes like PTEN, BRCA1, MLH1, APC etc.

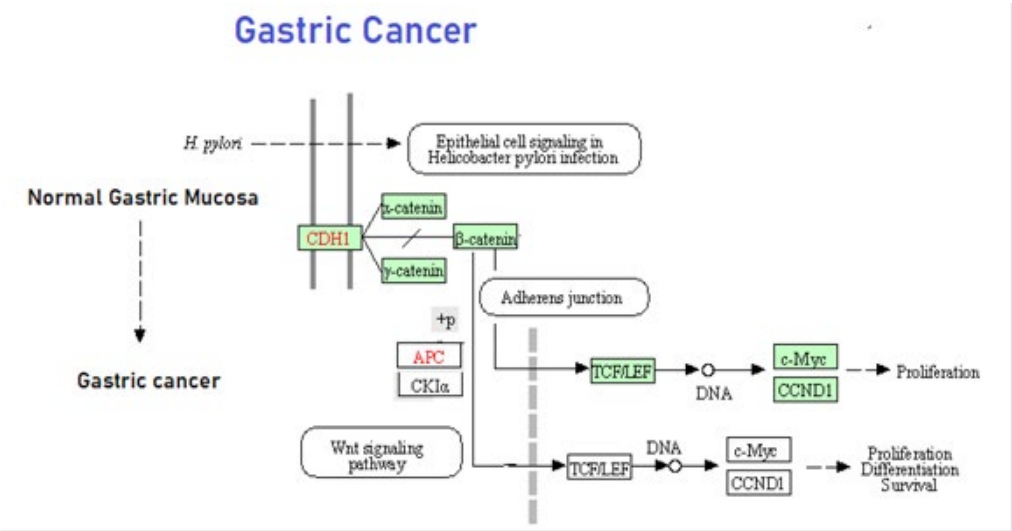

Figure 3: Mechanism of CDH1 in Gastric cancer.

Figure 3 has shown that CDH1 acts on Beta-catenin that is important in transcription of Wnt-specific genes. Due to CDH1 gene mutation, Beta –catenin suppresses T-cell responses and promotes the progression of tumors.

S.No	Name of Drug	APC		CDH1	
		Total energy in Kcal/mol	Active site	Total energy in Kcal/mol	Active site
1	Clopidogrel	-72.66	V-M-LEU-37-V-M-GLU-40-V-S-GLU-40-V-M-ALA-41-V-S-MET-44-V-M-ALA-41-V-S-MET-44	-63.8	H-S-GLN-23-V-M-PRO-5 -V-S-PRO-6-V-S-LYS-73-V-M-GLN-23-V-S-GLN-23
2	Pravastatin	-92.21	H-S-ASN-22-H-S-GLU-26-H-M-LEU-27-V-S-GLU-19-V-S-LEU-23-V-S-GLU-26-V-S-ASN-30-V-M-LEU-27-V-S-LEU-27-V-M-GLU-28-V-S-GLU-28	-94.32	H-M-VAL-3-H-S-THR-97-H-M-GLN-23-H-M-LYS-25-V-S-VAL-3-V-M-ILE-4-V-M-PRO-5-V-S-PRO-6-V-S-LYS-73-V-S-VAL-95-V-S-THR-97-V-S-GLN-23-V-S-LYS-25
3	Magnesium Sulfate	-39.85	H-S-ASN-20-H-S-ARG-24-V-S-LYS-17	-36.23	H-M-VAL-3-H-M-GLU-93
4	Nicotine	-57.33	H-M-LEU-37-H-S-GLU-40-V-M-GLU-40-V-S-GLU-40-V-M-ALA-41-V-M-ALA-41-V-S-MET-44	-51.95	H-M-VAL-3-H-M-ILE-4-H-M-GLN-23-V-S-VAL-3-V-M-ILE-4-V-S-PRO-6-V-S-VAL-95-V-S-GLN-23

Table 6: Activity of drugs against CDH1 gene as molecular therapy for Gastric cancer.

The selected molecules like Clopidogrel, Pravastatin, Magnesium Sulfate and Nicotine have shown control of mutated CDH1 and APC proteins. The Pravastatin has shown best activity and Magnesium Sulfate has shown least activity in control of CDH1 and APC proteins. Hence Pravastatin is the best option molecular therapy in control of gastric cancer followed by Clopidogrel, Nicotine and Magnesium Sulfate (Table 6). Figure 4 and 5 has shown the docking poses and active site of drugs against CDH1 and APC proteins respectively.

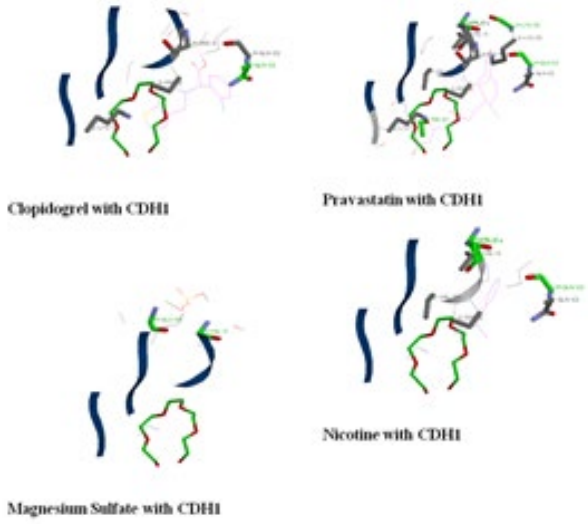

Figure 4: Docking of molecules with CDH1 protein.

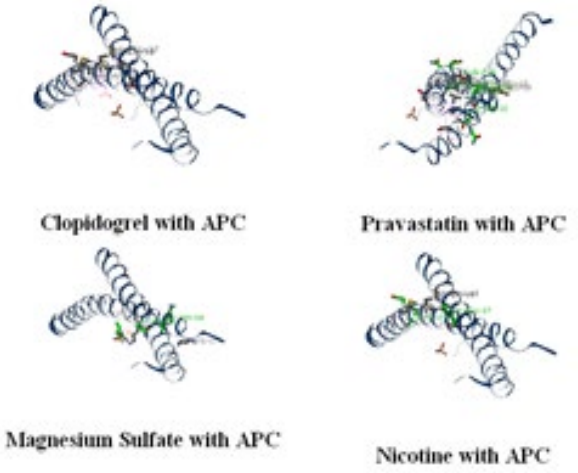

Figure 5: Docking of molecules with APC protein.

DNA methylation is an epigenetic mechanism that is most favorable eukaryotes, an important regulator of the gene transcription and play key role in carcinogenesis [15-18]. Alterations in the process of DNA methylation are common in the development of a wide variety of tumors. Helicobacter pylori (H. pylori) infection can induce epigenetic changes and involve most important risk factor for the development of gastric cancer [19]. Chemoprevention with pravastatin may be important in molecular therapy of gastric cancer.

Conclusion

Due to CDH1 gene mutation, Beta–catenin suppresses the T-cell responses and promotes the progression of tumors due to H.pylori infection. The Pravastatin has shown best activity and Magnesium Sulfate has shown least activity in control of CDH1 and APC proteins. Hence Pravastatin is the best option molecular therapy in control of gastric cancer followed by Clopidogrel, Nicotine and Magnesium Sulfate.

Acknowledgments

The author likes to thank administration of Atal Bihari Vajpayee University for providing assistance and support.

Disclosure statement

The authors declare no conflicts of interest.

References

1. Burlaka AP, Ganusevich II, Gafurov MR, Lukin SM, Sidorik EP. (2016). Stomach cancer: interconnection between the redox state, activity of MMP-2, MMP-9 and stage of tumor growth. Cancer Microenvironment, 9: 27-32.
2. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. (2016). Gastric cancer. The Lancet, 388: 2654-2664.
3. Aoun G, Sharrouf W, Aoun P. (2019). Gastrointestinal Disorders: What the Dental Practitioner Should Know. Int J Biomed Healthc, 7: 95-100.
4. Maconi G, Manes G, Porro GB. (2008). Role of symptoms in diagnosis and outcome of gastric cancer. World journal of gastroenterology: WJG, 14: 1149.
5. Sitarz R, Skierucha M, Mielko J, Offerhaus GJA, Maciejewski R, et al. (2018). Gastric cancer: epidemiology, prevention, classification, and treatment. Cancer management and research, 10: 239.
6. Rawla P, Barsouk A. (2019). Epidemiology of gastric cancer: global trends, risk factors and prevention. Przeglad gastroenterologiczny, 14: 26.
7. Nagini S. (2012). Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World journal of gastrointestinal oncology, 4: 156.
8. Song Z, Wu Y, Yang J, Yang D, Fang X. (2017). Progress in the treatment of advanced gastric cancer. Tumor Biology, 39: 1010428317714626.
9. Lee CH, Franchi F, Angiolillo DJ. (2020). Clopidogrel drug interactions: a review of the evidence and clinical implications. Expert Opinion on Drug Metabolism & Toxicology, 16: 1079-1096.
10. Konings IR, van der Gaast A, van der Wijk LJ, de Jongh FE, Eskens FA, Sleijfer S. (2010). The addition of pravastatin to chemotherapy in advanced gastric carcinoma: a randomised phase II trial. European journal of cancer, 46: 3200-3204.
11. Oleastro M, Ménard A. (2013). The role of Helicobacter pylori outer membrane proteins in adherence and pathogenesis. Biology, 2: 1110-1134.
12. Serban DE. (2014). Gastrointestinal cancers: influence of gut microbiota, probiotics and prebiotics. Cancer letters, 345: 258-270.
13. Wu WK, Cho CH, Lee CW, Fan D, Wu K, et al. (2010). Dysregulation of cellular signaling in gastric cancer. Cancer letters, 295: 144-153.
14. Pećina-Šlaus N. (2003). Tumor suppressor gene E-cadherin and its role in normal and malignant cells. Cancer cell international, 3: 1-7.
15. Singal R, Ginder GD. (1999). DNA methylation. Blood, The Journal of the American Society of Hematology, 93: 4059-4070.

16. Moore LD, Le T, Fan G. (2013). DNA methylation and its basic function. Neuropsychopharmacology, 38: 23-38.

17. Bird A. (1992). The essentials of DNA methylation. Cell, 70: 5-8.

18. Das PM, Singal R. (2004). DNA methylation and cancer. Journal of clinical oncology, 22: 4632-4642.

19. Cheung KS, Leung WK. (2018). Risk of gastric cancer development after eradication of Helicobacter pylori. World journal of gastrointestinal oncology, 10: 115.