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REVIEW

Navigating the Role of E-cadherin Gene in Gastric Carcinoma

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Abstract

Gastric cancer (GC) ranks the fifth most common cancer globally. It is a profoundly aggressive neoplasm with a high mortality rate. E-cadherin encoded by the gene *CDH* is involved in the pathogenesis of different malignant tumors including gastric cancer. It is enrolled in the progression, invasion and spread of the tumor. The E-cadherin is crucial for epithelial cells adherent together and it's down regulation loosens this connection which facilitate the cellular movement and changing into the epithelial-mesenchymal transition (EMT), a fact predominant in GC. This review focuses on the structure of E-cadherin, its function and pathogenesis in the development of GC and it's correlation with different pathological factors involved in GC like *Helicobacter pylori* infection and the drug resistance of gastric malignancy.

Keywords: GC (gastric cancer), EMT (epithelial-mesenchtmal transmission), CDH (cadherin)

Introduction

Epidemiology

Incidence

Gastric Cancer (GC) is an world-wide health problem with about 1 million annual diagnosis. It still in the top 5 list of cancer worldwide (Rawla & Barsouk, 2019; Thrift & Nguyen, 2021) and regarded as the third most common causes of cancer-related deaths over the world with a survival rate less than 1 year in most cases (Bray et al., 2018; Lin et al., 2021; Thrift & El-Serag, 2020). Each year about 1.1 million cases are newly discovered with 800,000 annual deaths are recorded, so the death rate is about 75 % which renders this cancer as a horrible disease with a five year survival rate is only 20 % (Ilic & Ilic, 2022; Sung et al., 2021).

Geographical distribution

The geographical distribution of GC incidence and prevalence shows wide variation. The prevalence is still notably high in Central and South America, East Europe &East Asian countries (China and Japan). The low risk territories include Australia, North and East Africa and North America (Ang & Fock, 2014; Jemal et al., 2011; Okura et al., 2019). It was observed that the detected numbers started to decline in some world countries like in Japan, an event that may be attributed to the early methods of diagnosis depending on the endoscopic examination (Matsuda & Saika, 2013), the fight against *Helicbacter Pylori* infection and the wide usage of the refrigerator to keep the foods instead of the salt (Park & Herrero, 2021; Yang, Ying, et al., 2020). In spite of this, the death rate is still high. In the western countries the overall 5-year survival rate is about 31−33 % for all stages (Allemani et al., 2015; Chen et al., 2023) and the distant metastasis rate discovered at the time of diagnosis for cases of adenocarcinoma is still profound in spite of the recent therapeutic modalities (Dixon et al., 2016; Jemal et al., 2011; Kwee & Kwee, 2015). In the Middle East, the prevalence of GC is variable with high rate in Iran and low in Israel (Global Burden of Disease Cancer et al., 2017; Hussein, 2010). In Iraq,

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GLOBOCON study in 2020 declared that stomach cancer ranked number 9 among the cancers with 1149 new cases. It represented 3.4 % of all cancer cases (Sung et al., 2021)and it still constitutes the second common cause of cancer-related deaths in Mesopotomia (Mwafaq et al., 2022).

Gender differences

Male are two to three times affected more than female (Bray et al., 2018; Ferlay et al., 2010). Male gender and old age are two risk factors to develop gastrointestinal tract cancers including the GC (Lu et al., 2021).

Risk factors

The ***Family history*** is a pivotal risk factor in developing GC. About 90 % of cases are sporadic and the rest 10 % show some familial aggregation (Lauwers et al., 2014; Setia et al., 2015). Hereditary diffuse gastric carcinoma is the most famous form of familial stomach cancers, caused by inherited mutation of cadherin-1 gene (CDH). People with such genetic alterations are three times more susceptible to be involved with GC than those who don't carry this gene modification (Luo et al., 2018; Pinheiro et al., 2014). Not all the cases of familial GC have CDH gene mutations. Countries with high prevalence of GC like Japan and Korea have low ratio of gene clustering compared to the reduced incidence areas. This issue should lead to the thinking about the environmental effects in countries with high-recorded cases (Lee et al., 2014).

The influence of ***Diet*** as a risk factor of GC was extensively studied. It is clear that fruits and vegetables are good protectors against the evolution of malignant stomach cancer while the broiled, smoked and salt-preserved foods may enhance the figuration of this cancer (Kim et al., 2014; Muñoz et al., 2001). Food rich in nitrate and nitrite was also correlated with the elevated numbers of the cancer (Wiseman, 2008). The effect of these noxious dietary agents may be attributed to the continuous injury and regeneration of the epithelium with possible methylation of nucleic acids. This can be possibly intermingled with subsequent dysplasia and preneo-plasia (Carl-McGrath et al., 2007; Stadtländer & Waterbor, 1999).

Infectious Agents were pointed out as an important etiology for the development of gastric cancer since long period. *Helicobacter Pylori(H.pylori)*, is considered as high carcinogenic factor in the evolution of GC and it's oncogenic role was referred by the World Health Organization (WHO) since 1994 (Ishaq and Nunn, 2015). This gram negative S-shaped bacteria is widely distributed with a prevalence more than 50 % and mostly acquired during the childhood. This infection if not treated early, it will progress into several adulthood gastropathies including chronic gastritis, peptic ulcers and gastric cancers (both adenocarcinoma and g mucosal-associated lymphoma) (Meli et al., 2019; Salama et al., 2013). The malignant-inducing role of *H.Pylori* can be attributed both to the effect of the associated inflammatory process with it's multiple cytokines secretion and the epigenetic role of bacterium on the gastric epithelium (Dincă et al., 2022; Khatoon et al., 2016; Kim et al., 2021). The impact of *H.Pylori* depends on the interaction between the bacterial virulence factors and the host immune reaction. Persons infected with *H.Pylori* strains having cytotoxic associated toxin (cagA) and vacuole associated toxin (vacA) genotypes are more susceptible to develop GC (Alzahrani et al., 2014; Matos et al., 2013; Miehlke et al., 2000).

The *Epstein-Barr virus(EBV)* is an ubiquitous viral infection with a tumor-inducing vestige and was correlated with several lymphoid and epithelial tumors. The viral proteins can be expressed by all the virally infected tumor cells (Wilson et al., 2018; Young & Murray, 2003). Since the year 1990 EBV was detected as risk agent in the development of GC (Burke et al., 1990). About 10 % of carcinomas of stomach were estimated to be related to *EBV* (Fukayama et al., 1994; Young & Rickinson, 2004). Although the GC is classified basically on the histopathological features but there is a different molecular subtyping of gastric carcinoma exist, consisted from four molecular variants*: EBV* positive tumor (9 %),microsatellite-instable tumor cells (22 %) genetically stable tumor (20 %) and chromosomal instability neoplasms (CIN) 50 % (Sun et al., 2020; Yang, Liu, et al., 2020).

It was hypothesized that smokers (both former and recent) have 1.5–2 times increased risk of developing GC than the nonsmokers. The risk increases more in male than female but dose-relation and duration is fundamental in both genders (Inoue et al., 1999; Trédaniel et al., 1997). Smokers with gastric carcinoma tend to develop more in the area of cardia more than other sites of stomach (González et al., 2003; Mao et al., 2002).

There was a contradictory about the possible risk of Alcohol consumption. Studies illustrated that drinking plenty amount of Alcohol per day may amplify the risk of getting GC, especially in the cardia (Kabat et al., 1993; Mao et al., 2002) while this link was not clarified by other authors (Franceschi & La Vecchia, 1994).

Genetic changes in gastric cancer

Variable molecular studies were conducted to investigate the possible print of different epigenetic and genetic pathways in the development and progression of GC. Discovering such changes improves the invention of new more selective targeted therapy. The main works focused on the effect of HER-2, apoptotic pathways, cell-division cycle, multidrug-resistance genes and microsatellite-instability (MSI) (Machlowska et al., 2018; Seo et al., 2019). Traditionally GC were divided (depending on the histopathology) into both intestinal and diffuse type.

Hypermethylation and 1q loss of heterozygosity (LOH) were shown to impress the progression of the intestinal variant of GC whereas chromosomal 17p LOH and mutation or loss of E-cadherin gene impacted on the evolution of the diffuse type (Nobili et al., 2011). Multiple genomic alterations interplay in both the evolution from precancerous to the frank malignant status and in the trajectory and metastasis, these changes work differently in both the intestinal and diffuse phenotypes (Ebrahimi et al., 2020).

Genomic instability

Two phenotypes of genomic instability were established in the development of gastric cancer, the microsatellite instability (MSI) and chromosomal instability (CIN), sometimes function independently with an occasional coupling between the two. The CpG island methylator phenotype (CIMP) is a newly discovered player in the carcinogenesis of gastric cancer (Hiyama et al., 2004; Ottini et al., 2006).

Microsatellite instability (MSI) pathway

Defective DNA mistmach repair (MMR) gene system has a well-validated pathogenic role in most of the gastrointestinal cancers, including the malignant stomach tumors (Quaas et al., 2021). This MMR pathway defect is responsible for the evolution of the microsatellite instability (MSI) status and it is resulted from either mutational inactivation or epigenetic silencing of DNA mismatch repair genes (e.g., MSH2, MSH3, MSH6, MLH1 and PMS2) (Liu & Meltzer, 2017). The MSI hypermutated GC phenotype can trigger the tumor surveillance which can be a target for an immune therapy against the GC in the near future (Puliga et al., 2021). Three levels of MSI can be identified; high level MSI(MSI-H), low level MSI(MSI-L) and microsatellite stable (MSS) (Gologan et al., 2005). This variability operates on the distribution and tumor location, associated targeted genes and the prognosis. Genes regulating cell-cycle and apoptotic signaling are frequently mutated in MSI-H GC for example *TGFβ-RII,* FAS, BCL10 and *APAF* (Iacopetta et al., 1999). *Gastric carcinoma with MSI-H are of antral location, intestinal histological type and with minimal lymph node metastasis* (Zhu et al., 2015).

Chromosomal instability (CIN) pathway

CIN is a major character correlated with development of the cancer genome and it is accompanied by aberrant changes like chromosomal number, deletion, loss of heterozygosity (LOH) or gene amplification (Sansregret et al., 2018; Tanaka & Hirota, 2016). These modifications may lead to activation of the proto-oncogens or frustration of the tumor suppressor genes and a contradictory influence on the anti-cancer therapy (McClelland, 2017). Wide-scale CIN affects the survival of patient with the gastric carcinoma by influencing different prognostic factors like grade, lymph node involvement, age and metastasis (Panani, 2008). The chromosomal regions 11q23.3 and 19p13.3 participates in the age-related differences in the malignancy genomic profile and that tumors of younger patients showed gains in chromosomal regions 6p21, 9p34, 11p15, 11q23, 17p13, 19p13, and 22q13 (Buffart et al., 2007).

E-cadherin aberration in gastric carcinoma

Function of E-cadherin

E-cadherin is a superfamily of calcium-mediated membrane glycoprotein (Takeichi, 1995). It constitutes an essential components of the inter-epithelial adherent junction and it is encoded by CDH1 gene located on chromosome 16q (Schnoor, 2015). The cadherin is connected to intracellular actin, so forming a strong intercellular binding and keeping healthy cellular hemostasis (Shiozaki et al., 1996). E-cadherin is a transmembrane glycoprotein and consisted from 3 portions; extra-cellular domains (ECD),transmembrane part and the intra-cellular domain (ICD). The ICD is intermingled with α-and β-catenin and other members of catenin family. It is bonded to the cellular cytoskeleton actin so keeping the cellular frame intact and limiting the mobility of the cells (Gall & Frampton, 2013; Koirala et al., 2021).

E-cadherin normally acts as a tumor suppressor and it anchors the beta-catenin to the cell membrane, so preventing the β-catenin entrance to the nucleus with subsequent inhibition of the

epithelial-mesenchymal transition (EMT) (Lamouille et al., 2014; Y et al., 1995).

E-cadherin is present on all the epithelial cells and losing it's expression was acknowledged as a preliminary step of progression and metastasis in several cancers. Long years ago it was presumed that re-setting of the functioning cell adhesion system will reverse the malignant cells into benign phenotype in cell cultures (Birchmeier & Behrens, 1994; Chan, 2006).

E-cadherin in gastric cancer

Normally E-cadherin is a well-known tumor suppressor gene and works against the formation of GC and it has been elucidated that the promotion and spread of gastric cancer is largely related to the loss of function of E-cadherin (Shimada et al., 2011). Loss of E-cadherin is mainly noticed in the diffuse variant of GC and different studies done showed that 40–100 % of diffuse gastric carcinoma patients have E-cadherin reduced expression (García-Ruvalcaba et al., 2023).

The role E-cadherin in tumorogensis of GC

E-cadherin is a fundamental factor in the epithelial adhesion in both the physiological and pathological conditions. Down regulation of E-cadherin will facilitate the mobility of the epithelial cells and dissociation from each others whether in physiological cases, as in wound healing or in the pathological instances as in the transition from the adenoma to the invasive carcinoma (Li et al., 2012; Singh et al., 2021). Loss of E-cadherin is magnificently associated with the evolution of both sporadic and hereditary GC. Mutations that hit the *CDH* gene is a fundamental reason for the loss of expression of E-cadherin. Theses mutations can both of germline and sporadic missense or non-missense mutations (Corso et al., 2021).

It is fixed that β-catenin is essential for E-cadherin cell–cell connection and the Wnt-signaling pathway. The modified E-cadherin level can adjust the Wnt-signaling system by altering the concentration of free β-catenin level (Kuphal & Behrens, 2006). Motivation of the Wnt-pathway results in stabilization of β-catenin while Wnt-genes dysregulation is accompanied by the development of several types of cancer, including gastric cancer (Bienz & Clevers, 2000; Koushyar et al., 2020). The deletion of E-cadherin is coordinated with modifications of several factors including the gene and mRNA levels (Oliveira et al., 2004). Multiple site mutations of *CDH1* gene is pointed out as a risk factor for the development of hereditary GC. It has been elucidated that 50–80 % diffuse GC are accompanied by minimized or lost E-cadherin expression (Choi et al., 2020). Diffuse GC with *CDH1* mutation have more aggressive signs like elevated Ki67 index and p53 mutation (Muzashvili et al., 2020). Studying the possibility of getting *CDH1* gene mutation in a person with family history of diffuse GC may indicate several modalities like recurrent gastroscopy or even prophylactic partial gastrectomy (Shenoy, 2019).

About 80 % of diffuse GC cases are accompanied by hypermethyelation of the CpG promoter of the *CDH1* gene, leading to its inactivation (Ushijima & Sasako, 2004).

Role in tumor metastasis

E-cadherin is a tumor suppressor protein and its downregulation was synchronized with the detachment of tumor intercellular junctions and subsequently in tumor growth and metastasis. It is also accused in the epithelial-mesenchymal transition (EMT) process (Na et al., 2020). EMT is an axial step in the development of metastatic cancer where the malignant cells lose their epithelial phenotype and get mesenchymal properties, aiding their separation from each others and having mobility. Several transcriptional markers related to EMT like Twist, Zeb and Snail families were implicated to promote cancer metastasis (Lu & Kang, 2019). Snail transcriptional factors largely suppress E-cadherin gene transcription. Epithelial cells with Snail expression clarify fibroblastic phenotype and show high capacity of invasion and metastasis (Cano et al., 2000).

Epidermal Growth factor Receptor (EGFR) is a product of the proto-oncogen ErbB1 gene and it was found out to be highly expressed in GC. EGFR expression in stomach cancer is coordinated with poor prognosis including the recurrence and metastasis (Al-Obaidie et al., 2016; Nagatsuma et al., 2015). A significant relationship between the down-regulation of E-cadherin and EGFR expression was illustrated in this awful tumor (Jones et al., 1996).

It was proved that CD73 overexpression was correlated with poor prognosis of gastric cancer via it's role in EMT. The CD73 is correlated to RICS/RhoA signaling pathway and the drug-inhibition for CD73 could minimize experimental metastasis (Xu et al., 2020). Missense mutation of E-cadherin in diffuse gastric cancer can potentiate RhoA activity and thereby promoting tumor progression and metastasis (Shenoy, 2019).

Matrix metalloproteinases (MMP) are group of zinc-dependent endopeptidase that have the power

to degrade the extra-cellular components. MMP may be enrollled in many pathological conditions such as tumor invasion and metastasis (Kähäri and Saarialho-Kere, 1999). MMP-1 amd MMP-2 can participate in the degradation of E-cadherin and subsequently in the progression of GC (Kumar et al., 2021).

Role of E-cadherin in chemotherpay resistance in GC

It's well known that chemotherapy is the main management option for the advanced GC. Resistance to chemotherapy is a serious condition that can be seen in several cases. Variable mechanisms of chemo-resistance (MOC) stand behind the poor response to the treatment (Marin et al., 2016). EMT stimulation grants the gastric epithelial to get more mesenchymal characters and less epithelial features and thereby more malignant dedifferentiation and accelerated insensitivity to the chemotherapy. It is well known that EMT activation can arise in E-cadherin downregulation (Peng et al., 2014). E-cadherin can minimize the resistance of modulating drugs by negatively controlling the expression of BCL-2 through the modulation of the nuclear β-catenin level (Sasaki et al., 2000). E-cadherin upregulates P27, an inhibitor of mitosis and increases the expression of PTEN (Yang et al., 2008). The HSP90AA1 is a well documented gene that is expressed well both in the primary and metastatic GC through the stimulation of EMT that counteracts the role of E-cadherin in maintaining the inter-epithelial tight junctions (Chang et al., 2009).

E-cadherin and Helicobacter Pylori-related gastric cancer

H.pylori infection is a famous risk agent in the development of GC. *H.pylori* motivates a hypermethylation status of the *CDH-1* gene, an important event in chronic gastritis and intestinal metaplasia. With the subsequent down regulation of E-cadherin, *H.pylori* infection will induce cancer development and progression (Liu & Chu, 2014). Cytotoxic associated gene A(Cag A) of the *H.pylori* can stimulate the EMT while Vac A stimulates the Wnt/β-catenin signaling pathway with a subsequent final induction of CCND1 gene (Alipour, 2021). After enrolling in the gastric epithelium bacterial CagA dissociates the complex of E-cadherin & catenin, leading to accumulation of β-catenin in the cytoplasm and nucleus (Zhang et al., 2017).

H.pylori also can induce GC through the nuclear factor kB (NF-kB) signaling system which can induce several cytokines, interlukines and MMP. The infection activates the NF-kB-and AKT-mediated MMP9 induction with subsequent gastric cell migration (Maubach et al., 2013). Both NF-kB and ERK pathways can dowregulate E-cadherin with a later on loss of cell–cell junction and starting invasion (Shibata et al., 2005).

Clinical applications of E-cadherin in gastric cancer

A-Clinical significance of soluble E-cadherin in gastric cancer

The extracellular domain of the E-cadherin can be cleaved in some pathological conditions such as gastric H.pylori infection by several proteolytic enzymes such as MMP and ADAMs (a disintigerin metaloproteinases). This will generate 80KD piece which is released from mucosal cells into circulation (David & Rajasekaran, 2012). It was documented that serum level of E-cadherin is higher in gastric cancer than normal tissue and also in the profound metastatic conditions and in the lymph node involvement. Thus soluble E-cadherin can be considered as a biomarker for diagnosis, metastasis, recurrence and prognosis of GC (Liu & Chu, 2014).

B-E-cadherin is a biomarker for gastric cancer ferroptosis

Preserved function of E-cadherin prevent the bioactivity of the ferroptosis (non-apoptotic, iron-dependent cell death) through the activation of Hippo pathway. Down –regulation of E-cadherin gene reverse the above process and amplifies the sensitivity of tumor cells for ferroptosis (Minikes et al., 2023).

C-genetic mutation of E-cadherin in diffuse gastric cancer (DGC)

It is well known than mutation of E-cadherin is highly associated with the development of DGC which supposed a guideline to ask for E-cadherin genetic counceling for any patient involved with DGC (Guilford et al., 2010).

In normal condition, *CDH* gene will be transcribed into pre-mRNA. The pre-mRNA will mature into mRNA by a process of splicing. The operation of *CDH* gene splicing can be disordered, leading to the formation of abnormal E-cadherin, so targeting the process of splicing and the whole gene can be a future therapeutic weapon against GC (Guilford et al., 2010).

E-cadherin activators

As mentioned above that E-cadherin dysregulation is associated with EMT and poor prognosis of GC, so re-establishing of its function can improve the outcome Of GC. The usage of demethylating drugs like 5-aza-2-deoxycytidine and DNA methylation transferase can reactivate the E-cadherin function (Murgo, 2005). The application of histone deacytelase inhibitors, like oxamflatin improved the E-cadherin expression and reduced the cancer cells viability in GC (Faghihloo et al., 2016). Non-steroidal ant-inflammatory drugs, especially COX-2 inhibitors can be of chemo-preventive and therapeutic effect of GC with or without *H.pylori* infection (Wang et al., 2014). COX-2 inhibitors is closely associated with the increased expression of E-cadherin and downregulation of NF-kB and Snail pathways (Chen et al., 2013). The anti-diabetic drug metformin can prevent the EMT formation of GC by a glucose-independent basis (Valaee et al., 2017).

Summary

Gastric carcinoma (GC) is an aggressive cancer and it's ordinarily diagnosed at an advanced stage. It is of high mortality rate world-wide. Early diagnosis reduces the mortality rate. GC can be of sporadic and familial. The familial cases present at earlier age than the sporadic cases. Variable molecular classifications in addition to the classical Lauren histological one have been designed. Different molecular pathways of the carcinogenesis were discovered in a hope of decoding this monster cancer and finding proper management. The influence of E-cadherin protein and its encoding gene, *CDH* has been elucidated in different tumors including gastric cancer. It is present in both the sporadic and familiar cases of GC. It's primary physiological function is keeping the epithelial cells tightened together and can function as a tumor suppressor gene and thereby down-regulation of E-cadherin can encourage the local invasion and distant metastasis of GC. The reduced expression of E-cadherin occur in different mechanisms as a defect in the whole or part of its genome. This in discovering different targets for gene and molecular therapy of gastric cancer.

Author contributions

All authors took part in selecting the topics of the research and involved in revision and writing.

Ethics information

This is an observational study and no humans nor animals were involved in this study.

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Conflict of interest

The authors declare that the research was done in the absence of any commercial or financial relationship that could be explained as a potential conflict of interest.

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