A Review on the Molecular burden in gastric cancer caused by H. Pylori in advance stage of a global perspective.

Abdullahi Ayuba[a], Xue Jianpeng[a], Jialiang Hu[a]. Wang Ying[a], Hanmei Xu*

[a] The Engineering Research Centre for Peptide Drug Discovery & Development, China Pharmaceutical University, 24 Tongjia Xiang, Nanjing 210009, P.R China.

Main Author: Abdullahi Ayuba

Corresponding Author: Hanmei Xu

Corresponding email: 13913925346@126.com

Abstract

Background: *H. pylori* have coexisted with humans for several thousands of years, and infection with this bacterium is common. The Centers for Disease Control and Prevention (CDC) estimates that two-thirds of the world's population harbours the bacterium, with infection rates much complex in developing countries than in developed nations. *H. pylori* is a spiral-shaped bacterium that grows in the mucus layer that coats the inside of the human stomach. It survives in the harsh, acidic environment of the stomach, *H. pylori* secretes an enzyme called urease, which converts the chemical urea to ammonia. The production of ammonia around *H. pylori* neutralizes the acidity of the stomach, making it friendlier for the bacterium.

Objectives: *To access the possible effects and factors of Gastric cancer in relations to different factors e.g. Genetics, Environments etc. H. pylori* can also attach to the cells that line the inner surface of the stomach, *H. pylori* infection does not cause illness in most infected people, it is a major risk factor for peptic ulcer disease and is responsible for the majority of ulcers of the stomach and upper small intestine.

Results*: H. pylori* are thought to spread through contaminated food and water and through direct mouth-to-mouth contact. In most populations, the bacterium is first acquired during childhood. Immune cells that normally recognize and attack invading bacteria accumulate near sites of *H. pylori* infection.

Conclusions: Recent advances in this field have identified host factors which predispose to gastric cancer formation via modulation of the host immune response, the *H. Pylori* explored bacterial virulence factors which may directly cause tissue damage, and lead to gastric carcinogenesis, as well as factors responsible for an enhanced immune response. Environmental factors also associated with a predilection for gastric cancer, recognized as modifiers of key growth signalling pathways within the gastric mucosa and as such lead to growth alterations *H. pylori* have developed ways of interfering with local immune responses, making them ineffective in eliminating this bacterium

Keywords: H. Pylori, Enzymes, Gastric cancer, Stomach, Intestine, Mutations.

1.0 Introduction.

Gastric cancer, or cancer of the stomach, on other perspectives considered to be a single entity. Now, researchers divide this cancer into two main classes: gastric cardia cancer (cancer lies on the stomach lining about 1inches at the upper side of the stomach this may reach oesophagus). and non-cardia gastric cancer (cancer in some areas of the stomach).

Gastric cancer is the second most common source of cancer-related deaths in the world, of which approximately 738,000 people in 2008 Peoples death. In 1994, the International Agency for Research on Cancer classified *H. pylori* as a carcinogen, or cancer-causing agent, in humans, notwithstanding conflicting results at that time was very complex. Since then, it has been increasingly accepted that colonization of the stomach with *H. pylori* is an important cause of gastric cancer and of gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Infection with *H. pylori* is also associated with a reduced risk of oesophagal adenocarcinoma[1] Overall gastric cancer incidence is decreasing. However, this decline is mainly in the rates of non-cardia gastric cancer[2] Gastric cardia cancer, which was once very uncommon, has risen as an incidence in recent decades the distinction for cardia versus noncardia disease is important because there is evidence that the two entities have different etiologies and because several reports indicate that gastric cardia cancer and gastroesophageal[3] junction tumor are increasing in incidence and there is a parallel increased incidence in noncardia cases in the young western populations[2, 4-6] Seventy-three percent of gastric cancer cases are diagnosed in Asia; almost 50% of the world's cases are diagnosed in China alone[1, 7, 8] In general, the less developed nations carry a greater gastric cancer disease burden than developed countries. Within all afflicted nations, noncardia gastric cancer is more likely to affect persons of lower socioeconomic groups. Similarly, the risk of *H. pylori* infection is associated with lower socioeconomic status, overcrowding and unsanitary conditions. Interestingly, wealth and education have an inverse relationship to Nocardia tumours but are associated with cardia gastric cancer. In making such observations, it is important to note that other risk factors, including *H. pylori* infection, tobacco use and diet, may confound the data related to socioeconomic status. The impact of environmental factors is further supported by the fact that first-generation migrants coming from countries of the high incidence to a country of low incidence maintain the risk of the country of origin. The incidence rate decreases in the subsequent generations implicating environmental influences early in life. [1, 6, 9, 10] Europe accounts for an additional 15% and Central and South America contribute 7% of the global burden.[1, 11]

Gastric cancer is thought to result from a combination of environmental factors and the accumulation of generalized and speciWc genetic alterations and consequently affects mainly older patients often after a long period of atrophic gastritis. The commonest cause of gastritis is infection by H. pylori, which is the single most common cause of gastric cancer[3] Gastric cancer is a heterogeneous disease that demands continue attention and research with regard to prevention, early detection and novel therapeutic options.

The global distribution of gastric cancer varies substantially across geographical regions which illustrate the multitude of

factors that are associated with the incidence, survival and mortality of the disease. The Asian countries account for the majority of the world's cases while Europe and the Americas combined make up less than a quarter of the world disease burden[7, 11, 12] the two main histologic subtypes of the disease, intestinal and diffuse type, as classified by Lauren, define [13] two distinct entities that have different epidemiology, etiology, pathogenesis and behavior. The last several decades have demonstrated a gradual decline in the rates of gastric cancer in most populations and across subtypes. Perhaps, the decline can be attributed in part to improved food preservation with the advent of electric refrigeration,[14]

2.0. Helicobacter pylori.

Gastric cancer is one of the few neoplasms that is directly linked to an infectious organism. *H. pylori* is a spiral Gram-negative bacterium that colonizes the stomach of about half of the world's population and is associated with chronic gastritis, peptic ulcer disease, gastric lymphomas and noncardia adenocarcinomas and is Class I human carcinogen.[6, 15, 16] *H. pylori* infection is the strongest known risk factor for the development of gastric cancer, however, only a small minority of the infected population develops a malignancy. *H. pylori* infections are more strongly associated with intestinal-type adenocarcinoma than the diffuse subtype of gastric cancer but can be causal in either histology. It is estimated that the infection with the bacterium is responsible for almost 80% of distal gastric cancer cases, but has little association with cardia gastric carcinoma [16, 17]. The infection is typically acquired during infancy and will remain present for life if left untreated. The inflammation caused by a chronic infection may generate reactive oxygen species which are capable of inducing DNA damage.[18] *H. pylori* are also capable of inducing hypermethylation, particularly of CpG islands, thereby inactivating tumour suppressor genes. Different strains of the bacteria have variable carcinogenicity. The more aggressive strains carry the cytotoxin-associated gene A (CagA) which encodes an oncogenic protein that can be injected directly into gastric epithelial cells via type IV secretion precipitating a cascade of molecular events linked to [19] carcinogenesis [20]. CagA appears to induce disruptions of intracellular junctions, loss of epithelial polarity, increased proliferation, reduced apoptosis leading to carcinogenesis. Most strains in the high-risk areas of East Asia and the Colombian Andes are CagA positive, which helps to explain the increased incidence of the malignancy in this area [19]. The vacA protein is another virulence factor that causes intracellular vacuoles and membrane channels in epithelial cells.[21]
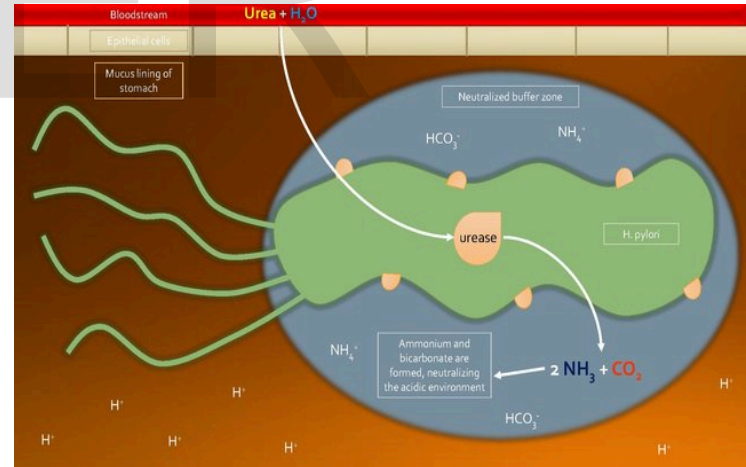

Figure. 1. How H. Pylori secretes an enzyme in the bloodstreams, Urease is produced by all strains of H. pylori and functions to hydrolyze urea into CO_2 and NH_3. NH_3 effectively buffers the acid environment immediately surrounding the bacterium permitting survival in the acid environment of the stomach. Urease enzyme activity is tightly controlled by a pH-gated urea channel, UreI, which is open at low pH and closed at neutral pH conditions.

2.1. *H. pylori* infection associated with any other cancer?

Whether *H. pylori* infection is associated with risk of other cancers remains unclear.

Some studies have found a possible association between *H. pylori* infection and pancreatic cancer, but the evidence is conflicting [12, 22] . Studies investigating the possibility that *H. pylori* are a risk factor for colorectal[23] adenocarcinoma or lung cancer have found no evidence that it is associated with the risk of either type of cancer[2, 24] infection with *H. pylori* is the primary identified the cause of gastric cancer. Other risk factors for gastric cancer include chronic gastritis; older age; male sex; a diet high in salted, smoked, or poorly preserved foods and low in fruits and vegetables;[25, 26] tobacco smoking; pernicious anemia; a history of stomach surgery for benign conditions; and a family history of stomach cancer
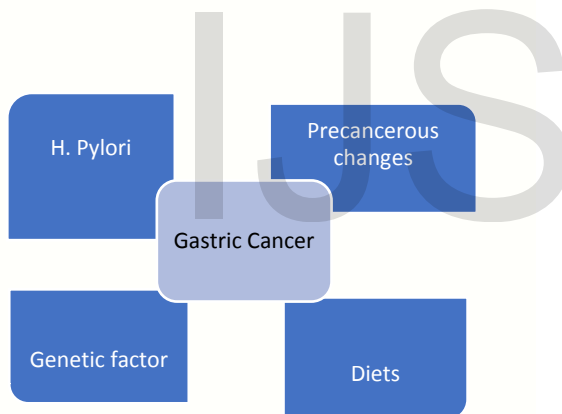

Figure. 2. Different factors associated with gastric cancer

2.2. H. pylori bacterial factors causes Gastric cancer.

H. pylori are well adapted to the gastric environment, withstanding low pH to gain entry to its preferred niche, the mucus layer of the stomach. Once there, the bacterium evades local and systemic immune responses which are ineffective at eliminating the organism. In the absence of antibiotic therapy, colonization persists for the life of the host. The H. pylori genome is 1.65 million base pairs and codes for approximately 1500 genes[27] . Of these, only 2/3 of the genes have been assigned biological roles. The function of the remaining 1/3 of the genome remains obscure. A modified signature-tagged mutagenesis approach, used to detect the genes essential for colonization and survival of H. pylori identified 47 genes, including several previously known factors such as urease and motilin, thereby validated this method [28] bacterial factors, which contribute to carcinogenesis, including those that enable the bacteria to effectively colonizes the gastric mucosa, incite a more aggressive host immune response and direct virulence factors of the organism.

3.0. Genetic predisposition to gastric cancer.

Most cases of gastric cancer are sporadic and not linked to germ line mutations. An exception to this is mutations within the E-cadherin gene, which has been linked to a familial diffuse form of gastric cancer. E-cadherin codes for a calcium-dependent protein involved in cell-cell adhesion. Continues expression E-cadherin in the correct cellular location is required for tight cell-cell association within the epithelium layer. Loss of function is thought to contribute to invasion and metastatic spread of gastric cancer. E-cadherin also plays a major role in mucosal integrity and tissue differentiation. Germ-line mutations of the E-cadherin gene have been identified in several kind who suffer from a marked increase in diffuse-type gastric carcinoma [29] the first cytokine studied in detail in humans was interleukin-1 beta, a pro-inflammatory cytokine shown to induce gastrin release, inhibit acid secretion, and promote apoptosis. Studies by many scientists looking at single nucleotide

polymorphisms (SNPs) within the IL-1h gene suggested that high-expressing IL-1h genotypes increase the risk of developing both atrophy and gastric cancer secondary to Helicobacter infection [30] . Moreover, recently a combination of IL-1h, TNF-h and IL-10 SNPs which potentially result in a phenotype of elevated IL-1h and TNF-a and decreased IL-10 has been shown to confer a 50-fold increased risk of gastric cancer[31].

3.0. Alterations in gastric mucosal signaling: regulation of apoptotic and proliferative pathways

The host response to infection induces multiple changes within the gastric mucosa leading to the formation of adenocarcinoma. The balance between apoptosis and proliferation is severely altered and the cellular composition distorted as parietal and chief cells are depleted and metaplastic lineages emerge. These changes are likely due to effects of Th1 type cytokines which act at several levels including induction of hypochlorhydria and atrophy the host response to infection induces multiple changes within the gastric mucosa leading to the formation of adenocarcinoma. The balance between apoptosis and proliferation is severely altered and the cellular composition distorted as parietal and chief cells are depleted and metaplastic lineages emerge. These changes are likely due to effects of Th1 type cytokines which act at several levels including induction of hypochlorhydria and atrophy [32] direct cytokine signaling, or secondary effects through modulation of other growth-promoting signaling cascades. H. pylori in humans has been associated with both an increase and a decrease in apoptosis, dependent upon the population studied [33] increase in proliferation is seen in all cases of mucosal damages due to infection. Apoptosis and proliferation are intimately associated, and regulations of these pathways are more effectively discussed together. Apoptosis is a physiological safeguard against perpetuating acquired DNA damage. While increased apoptosis in the setting of Helicobacter infection may contribute to ulcer formation and cell lineage depletion, inhibition of apoptosis may lead to transformation of cells leading to gastric adenocarcinoma. Mouse models of infection combined with human and rat cell culture systems have provided a great deal of insight into the interactions of the bacterium with various host cell proliferation and apoptotic pathways and have allowed detailed study of individual signaling cascades not possible in human systems [33].

3.1. The Fas Ag pathway.

The Fas Ag pathway of apoptosis is recognized as a leading cause of tissue destruction during Helicobacter infection. More recently, however, a role for Fas Ag signaling in proliferation has been recognized [22] H. pylori can both directly and indirectly (through cytokine production) induce Fas Ag and Fas ligand expression [34] in transformed cell lines, H. pylori can directly induce and activate the Fas pathway [35] in nontransformed cell cultures, direct bacterial contact does not appear sufficient for induction and activation, but requires components of the immune responses. One laboratory has shown IL-1h, TNF-a and IFN-g produced during infection increase surface Fas Ag expression on gastric mucosal cells resulting in increased proliferation at low receptor abundance and increased susceptibility to FasL-induced apoptosis at high receptor abundance[36].

3.2. Other apoptotic pathways.

The majority of published data focuses on Fas-mediated apoptosis; however, TNF-a and IFN-g can directly induce apoptosis [37] Nitric oxide, while usually discussed in the

context of DNA damage and mutagenesis, can directly influence mitochondrial pathways of apoptosis [38] and potentially plays a role in multiple levels of cell signal transduction during infection. Additionally, bacterial factors may directly induce apoptosis. VacA has been reported to insert directly into the membrane of mitochondria, inducing cytochrome c release and apoptosis[39].

3.3. Major histocompatibility class II (MHCII) signalling.

Expression of MHCII has been implicated in gastric carcinogenesis. Cells that express MHCII molecules regulate the host immune response by binding to Helicobacter organisms, processing antigens and presenting them to lymphocytes to initiate/perpetuate the immune response. MHCII molecules are not usually expressed on gastric epithelial cells but are upregulated during *Helicobacter* infection as a result of IFN-g exposure [37] these gastric mucosal cells acquire the ability to weakly present antigen [37].

3.4. Induction of stress pathways.

CagA protein interacts with several major growth regulating signal transduction pathways including the Ras/ MEK/ERK pathway [40] and the Src family of protein tyrosine kinases [41] these interactions may explain the substantial variation in levels of apoptosis/proliferation between individuals infected with different strains of *H. pylori* [37] with higher proliferation/lower apoptosis rates in patients infected with CagA$^+$ isolates compared to those infected with cagA strains, or uninfected controls[37].

3.5. Endocrine regulation of proliferation.

Helicobacter infection induces hypergastrinemia which has been causally linked to increased proliferation and cancer.

Gastrin is a peptide hormone produced primarily by G cells located in the gastric antrum. Gastrin is potent in vitro [42] mitogen acting through the CCK-beta receptor which regulates gastric acid secretion, oxyntic gland proliferation, and may directly synergize with *Helicobacter* to induce cell growth alterations and gastric tissue damage. The insulin– gastrin (INS-GAS) transgenic mouse has a pattern of gastrin expression which mimics the serum G-17/G-gly profile seen in patients who develop gastric atrophy and cancer. Infection in the conducted shown mice produce an early increase in acid secretion and over time progress through atrophy, achlorhydria, hyperplasia, metaplasia, dysplasia and invasive gastric cancer by 8 months of age [43].

4.0. DNA damage and repair pathways.

Oxidative DNA damage and repair Persistent inflammation is associated with the generation of mutagenic substances such as reactive oxygen species (superoxide anions, hydrogen peroxide, hydroxyl and hydroperoxyl radicals) [44] and reactive nitrogen species (nitric oxide, peroxynitrite, nitrogen dioxide, nitrosoperoxy carbonate) [45] which may act to directly damage the host cell DNA resulting in mutation, or may alter cell growth and cell death pathways [37] In addition, *H. pylori* infection has also been implicated in decreasing the antioxidant properties of the gastric mucosa [46] further leading to damage by these reactive species. Infection with CagA.strains significantly lowers the gastric juice vitamin C levels in comparison with CagA H. pylori strains[47].

4.1. Cell-cell crosstalk and signal disruption.

Parietal cell loss is temporally associated with atrophy, mucous cell metaplasia and initiation of dysplastic changes [48]

suggesting a cause and effect relationship. In addition to the production of acid, the parietal cell regulates key differentiation decisions in the fundic oxyntic glands with ablation of parietal cells associated with the appearance and expansion of undifferentiated cell types. Dysregulated proliferation of poorly differentiated precursor cells is often associated with the appearance of a mucous neck cell lineage expressing trefoil factor 2 (TFF2) or spasmolytic polypeptide (SP). TFF2 is felt to have a physiological a role in cytoprotection and maintenance of mucosal integrity and repair because it is usually expressed at the edges of healing ulcers, with downregulation of expression once restitution and healing are complete and continues expression, as seen in mucous cell metaplasia was associated with dysplasia and progression to cancer; however, causality has not been shown. Another effect of parietal cell loss is hypochlorhydria, hypergastrinemia, and bacterial overgrowth, which may contribute independently to tissue damages and abnormal cell signalling [49].

5.0. Dietary factors contributing to gastric cancer.

Diets that are high in salt and nitroso-compounds (contained in such products as pickled foods, soy sauce, dried and salted fish and meats) are associated with a 50–80% increased gastric cancer risk [50] C57BL/6 mice infected with *H. pylori* and fed a high salt diet (7.5% sodium) develop more pronounced gastric atrophy, hyperproliferation, foveolar hyperplasia and maintain higher bacterial colonization rates compared to mice maintained on a normal diet [51], many dietary components have been shown to have a protective effect against *Helicobacter*-induced damage, ulcer formation and incidence of gastric cancer. Green tea catehins (epigallocatechin and epicatechin) have been shown to inhibit the growth of H. pylori in vitro, and this effect is synergistic with amoxicillin [52], resveratrol and other red wine extracts inhibit the growth of Cag$^+$ strains of *H. pylori* in vitro [53] Garlic oil, garlic powder and their diallyl sulfur constituents have a substantial anti-*Helicobacter* effect in vitro [54] as well as High intake of selenium, beta-carotene, and vitamins A, C and E inhibit the growth of *H. pylori* in a guinea pig model of infection [55] methanolic extract from plantain banana (Musa sapientum var. paradisiaca) has a significant antiulcer and antioxidant activity on the gastric mucosa. Intake of this extract decreases lipid peroxidation and superoxide dismutase induced by ulcer-causing agents [56].

6.0. Genetic alterations in gastric cancer progression.

While atrophy and intestinal metaplasia have been linked to progression to adenocarcinoma, direct cell progression through these stages has not been conclusively shown. Investigators have tried to unravel the mutations responsible for gastric cancer initiation and progression in an attempt to uncover a logical progression of acquired damage akin to what is seen in colorectal cancer. Unfortunately, gastric cancer does not follow a pattern similar to colorectal carcinoma progression [57], what scientists observes is that p53 is most commonly mutated (60–70% of cancers) **[58]** Other genetic abnormalities found at high frequency include deletions or suppression of the fragile histadine triad gene (FHIT) (60%), adenomatous polyposis coli gene (APC) (50%) and deleted in colorectal cancer gene (DCC) (50%), while overexpression/amplification of cyclooxygenase 2 (COX-2) (70%), HGF/SF (60%), VEGF (50%), c-met (45%), AIB-1 (40%), h-catenin (25%), microsatellite

instability (25–40%) and DNA aneuploidy (60–75%) have also been demonstrated [59] there is not a clear cut up pattern of mutations in gastric cancers with most mutations studied to date accumulating once the cell has undergone malignant transformation [60]. Therefore, the precise role, if any, they play in initiating malignant transformation is not clear. More recently, gastric-specific tumor suppressor genes TFF1 [60] and RUNX3 [61] have been identified and may represent gatekeepers of the gastric cancer pathway, and represent logical targets for further study. Investigations into these genes and their contributions to the gastric cancer phenotype will prove valuable to our understanding of disease progression. Recent studies have pay more attention which has been given to activation and silencing of developmental pathways in cancer initiation and progression [62] inappropriate activation of specific developmental pathways may be involved in the development of intestinal metaplasia—a candidate precursor of intestinal-type gastric carcinomas. To this end, CDX2 has been investigated as it plays an important role in small bowel development and differentiation. CDX2 is expressed normally in the proximal intestine, not the distal, and is not expressed in the stomach. Intestinal metaplasia is characterized by the trans-differentiation of gastric epithelial cells to an intestinal phenotype. Ectopic expression of CDX2 in the gastric mucosa in transgenic mice induces intestinal metaplasia[63] drase I. Ectopic expression of CDX2 successfully produces ectopic intestinal tissue skin to metaplasia; however, progression to dysplasia and cancer has not been noted. These findings suggest that additional factors in the infected gastric milieu which favor intestinal cell development are responsible for transformation.

7.0. PATHOLOGIC SUBTYPES AND CHARACTERISTICS

Several classification systems exist to define gastric cancer but the most frequently used is the Lauren classification. The Lauren classification defines two main histologic subtypes: Intestinal-type and diffuse type.[13] Each subtype represents distinct clinical and epidemiologic characteristics. There are rare cases of gastric carcinomas that display features of both histologic subtypes. The morphologic differences between the two subtypes are related to intercellular adhesion molecules, which are preserved in intestinal type disease and defective in diffuse gastric carcinoma. Both subsets can have targetable protein expressions such as human epidermal growth factor receptor 2 (HER2) expression.

Gene amplification is a frequent mode of gene alteration in gastric cancer. Such protein overexpression can be detected by IHC. Amplification of HER2 has been observed in colorectal, lung, gastric and ovarian tumors [2] in gastric cancer, HER2 overexpression is reported in 7–34% of tumors, particularly at the G-E junction and in the intestinal type [64] lesions. Epidermal growth factor receptor (EGFR) overexpression has been shown to be a marker for poor prognosis in gastric [65] cancer Expression of both vascular endothelial growth factor A (VEGFA) and its receptor is reported in about 40% of gastric cancer cases and increased expression of VEGFA is associated with a poor prognosis and advanced [66] diseases. All the above proteins are targets for biological therapeutic options and have been studied for impact on survival. The details of the therapeutic trials will be discussed later in this review. New biomarkers for targeted therapy are being explored, such as fibroblast growth factor receptor (FGFR), hepatocyte growth factor receptor, and the

mammalian target of rapamycin. Some of the new targets are in clinical trials.

7. 2. INTESTINAL SUBTYPES

The intestinal subtype is the most frequently diagnosed histology in high-risk populations and is more likely to be sporadic than inherited. It [67] is diagnosed in older individuals, males more than females, and the tumors tend to have the gross appearance of ulcerated masses. Tumorgenesis is strongly associated with *H. pylori* infection. As such, the intestinal subtype is linked to the decreasing incidence in gastric cancer seen globally over the last several decades [68] Chronic infection with *H. pylori* bacterium leads to a sequence of histologic changes that result in a malignant lesion. The cascade of events begins with sustained bacterial infection with *H. pylori* that leads to nonatrophic gastritis that transforms into multifocal atrophic gastritis without metaplasia then into intestinal metaplasia and finally dysplasia [69, 70] develops. The prolonged gastric inflammation resulting from chronic *H. pylori* infection may cause epithelial damage that leads to gastric atrophy characterized by loss of parietal cells and chief cells and glandular atrophy. [68] Chronic infection with *H. pylori* bacterium leads to a sequence of histologic changes that result in a malignant lesion. The cascade begins with sustained bacterial infection with *H. pylori* that leads to nonatrophic gastritis that transforms into multifocal atrophic gastritis without metaplasia then into intestinal metaplasia and finally, dysplasia develops. [70] The prolonged gastric inflammation resulting from chronic *H. pylori* infection may cause epithelial damage that leads to gastric atrophy characterized by loss of parietal cells and chief cells and glandular atrophy [68] the gastric epithelium is replaced by intestinal metaplasia, particularly in the lesser curvature of the stomach, but it can be seen anywhere in the stomach. [68] Alterations in tumor suppressor genes are found in many intestinal-type gastric cancers. The P53 tumor suppressor gene (TP53) is an important regulator of the cell cycle. Loss of heterozygosity or mutational inactivation of TP53 expression occurs in more than 60% of invasive gastric [3] cancers. Abnormalities in TP53 expression have also been observed in *H. pylori*-associated chronic gastritis, metaplasia and dysplasia; however the relationship between TP53 and *H. pylori* remains unclear [71, 72] Mutations in the adenomatous polyposis coli gene have also been identified in intestinal and diffuse type gastric tumors and are also linked to *H. pylori* and gastric tumor initiation and proliferation Hypermethylation and microsatellites are also observed.[73]

7. 3. DIFFUSE SUBTYPE.

The diffuse subtype of gastric cancer appears to be more aggressive than the intestinal type. It is generally diagnosed in younger patients and no gender bias exists. [68] While it can be associated with *H. pylori* infection it is more frequently associated with loss of expression of E-cadherin and no precancerous lesions have been defined [74]. The E-cadherin gene (CDH1) encodes a homodimeric transmembrane cellular adhesion protein that aids in assembling the cell: Cell adhesion complex [65]. The gene appears to function as a tumour suppressor gene requiring a "two-hit" model if inactivation [75]. The hereditary form of diffuse gastric cancer (HDGC) has an autosomal dominant pattern of inheritance. The disease presents early in life and has a lifetime cumulative risk of developing gastric cancer of more than 80% by age 80 [76] Patients with HDGC often present with multifocal tumours under an intact mucosal surface

making diagnosis difficult. Patients with CDH1 germline mutations and family history of gastric cancer are referred for prophylactic gastrectomy [77], Sporadic diffuse gastric carcinomas have also been linked to abnormalities in CDH1. Mutations and loss of heterozygosity in the CDH1 gene and promoter hypermethylation are observed in sporadic diffuse type gastric tumours [75, 78].
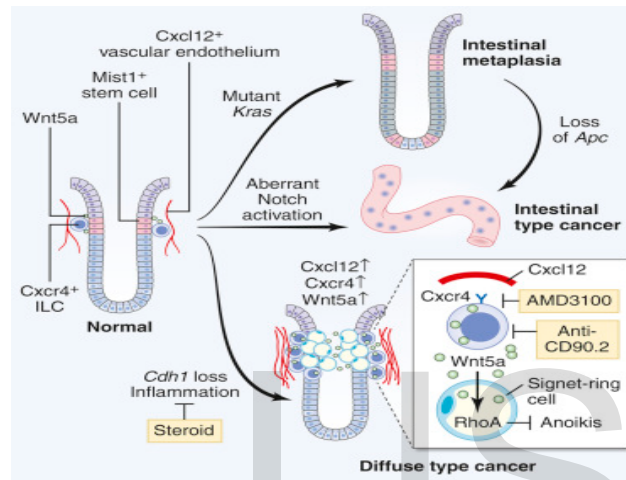

Figure. 3. The diffuse types cancer penetrated via Wnt5a with Cxcr4 ILC which activate cdh 1 and lost inflammations.

8.0. The "Nature" component of the role of CDH1, encoding E-cadherin

The existence of a familial form of GC has been known since the 1800s when multiple cases of GC were noted in the Napoleon Bonaparte family [79], approximately 1–3% of GCs arise as a result of inherited GC predisposition syndromes, such as hereditary diVuse GC (HDGC), caused by a germline mutation in the CDH1 gene, encoding E-cadherin, a molecule central in the processes of development, cell diVerentiation, and maintenance of epithelial architecture [80] GC in its hereditary form can also be caused by germline mutations of the TP53 tumors suppressor gene which occurs in the Li–Fraumeni syndrome [81] and new germ line mutations in this gene continues to be

discovered [82] BRCA2 gene mutations are associated with familial aggregations of not only breast but also of gastric, ovarian, pancreatic, and prostate cancers (The Breast Cancer Linkage Consortium [83].

8.1. The cag pathogenicity island

The most important feature which distinguishes strains of H. pylori is the presence or absence of the cag island. The cag pathogenicity island is approximately 40 kb and contains 31 genes. The terminal gene of this island, cagA, is often times used as a marker for the entire cag locus. Several genes within the island have homology to genes that encode a type IV secretory system. Once the bacteria adhere to the gastric epithelial cell, the type IV secretion system functions to export bacterial DNA and/or proteins into the host cell cytoplasm. In vitro experiments suggest that once in the cytoplasm, CagA undergoes kinase-mediated phosphorylation. Phosphorylated CagA, in turn, dephosphorylates host cell proteins, activating intracellular signalling pathways. Alterations in host cell proteins lead to actin cytoskeleton reorganization and morphological changes [84] described in cultured cells as the "hummingbird phenotype. A similar phenotype has not been described in vivo, and the impact of these potential signalling pathways in gastric cancer development remains to be clarified. Compared to cagA strains, cagA$^+$ strains are associated with more severe inflammation, higher degrees of atrophic changes and a greater chance of progressing to gastric adenocarcinoma [85] Other genes within the pathogenicity island are felt to be important for disease (cagE or picB, cagG, cagH, cagI, cagL, cagM) as they appear to be required for in vitro epithelial cell cytokine release.

8.2. Polymorphisms, including IL1B

Countless research articles focus on the role of polymorphism as a risk factor or protective factor for gastric carcinogenesis. Continuing advances in genotyping technologies and the inclusion of DNA collection in observational studies have resulted in an increasing number of genetic association studies. Polymorphisms in genes from diverse molecular pathways have been significantly associated with GC, such as *MTHFR* C677T, involved in folate metabolism [86] Genetic susceptibility to cancer: the role of polymorphisms in candidate genes [86] and the DNA repair genes *XPA, XPC, ERCC2* [87] which play an important role in repairing DNA damage related to *H. pylori*-induced inflammatory process, the role of the activation and detoxification of polycyclic aromatic hydrocarbons, by genes such as *GSTT1, SULT1A1, NAT2* and the *EPHX1* gene.

8.3. Stem cells in gastric cancer

Given the current hypothesis that cancer arises from cancer stem cells (CSCs), the mechanism by which chronic inflammation leads to the emergence of CSCs needs to be addressed. It has been presumed that the gastric stem or progenitor cell is located in the isthmus of the gastric glands in the corpus and gives rise to differentiated daughter cells via bidirectional migration patterns. In the gastric antrum, the stem or progenitor cells are located at the bottom of the glands, and descendants migrate toward the surface unidirectionally Bjarke's et al. provided the evidence for the existence of multipotent stem cells in the adult mouse gastric epithelium using chemical mutagenesis to label random epithelial cells by loss of transgene function in transgenic mice (Bjerknes and Cheng 2002). This work revealed that many gastric glands showed a loss of transgene function in all major epithelial cell types, consistent with the clonal expansion of a single mutation, therefore indicating the existence of multipotent gastric stem cells. For many years, resident tissue stem cells have been viewed as the best candidate for CSCs, because the simplest model is one in which a tumour arises from the stem or progenitor cells at the existing site. In the intestine, mutations in long-lived (Lgr5+) stem cells located at the crypt bottoms are believed to be the precursor to intestinal cancer. Barker et al. reported that the G-protein coupled receptor Lgr5 was expressed in the bottom of gastric glands, and ongoing lineage tracing experiments implied that the entire gastric gland-derived.
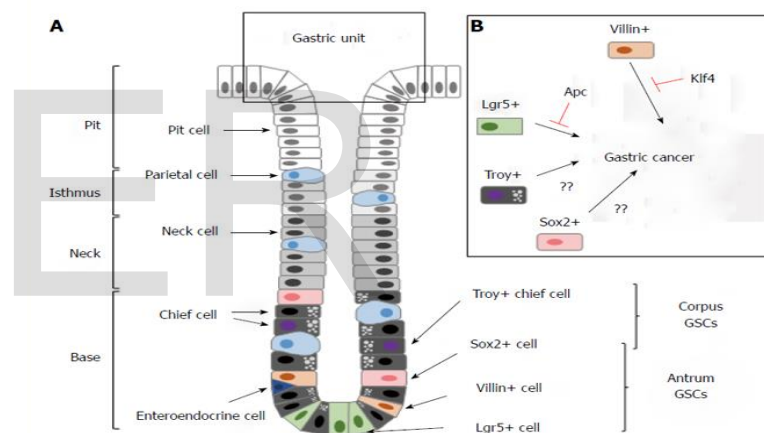

Figure. 4. Stem cell in Gastric cancer been tortured with other areas of cell lining.

9.0 Contradictory increase incidence of Gastric cancer in a Global Subpopulations.

Although the overall incidence of gastric cancer is declining both globally and in the United States, a recent observational analysis from the SEER Program reveals increasing rates of noncardia, intestinal type gastric cancer in white US residents ages 25–39 over the last three [2] decades. The same trend has been observed in Spain and

six other European countries [4, 5]. The cause of this trend is unclear. The frequent use and possibly abuse, of H2 blockers and proton pump inhibitor, has been implicated as a precipitating factor but is also unlikely given the young age of the affected population. Another possible hypothesis is the increased frequency of antibiotic use during childhood [88]. The cause of this concerning trend warrants further epidemiological evaluations in order to prevent further increase in disease burden.

10.0. Conclusion.

Gastric cancer remains a significant threat to global health. Although there has been a consistent and measurable decline in the incidence of the disease over the last several decades, there is still significant room for improvement with regard to prevention, early detection and intervention and life-extending therapies. Clear recommendations for screening and intervention exist in the high-risk populations like those with CDH1 mutations and a family history of gastric [77] cancer. It is less clear whether all high-risk areas should undergo routine screening and treatment of the infectious and carcinogenic organism, *H. pylori*. No clear recommendations have been made in support of screening for atrophic or dysplastic changes in asymptomatic patients in high-risk regions. It is known that patients found to have atrophic or dysplastic changes in the gastric mucosa are at an increased risk of developing invasive cancer. In this population of patients, endoscopic surveillance is recommended [89] In Japan, any lesions that are clearly identified are endoscopically resected, which has yielded a 5-year survival rate up to 90% in this [90] population. The encouraging results from the Japanese observational analysis serve as a foundation upon which screening guidelines could be established for high-risk patient populations around the world.

Consent for publication

All the authors are agreed for the publication of this manuscript

Availability of data and material

All the relevant data is available upon request by the corresponding authors

Competing interest

None of the authors has any competing interest

Animal studies and ethics approval

Not applicable.

Human studies and ethics approval

Not applicable.

Funding statement

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