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Chapter 2

Molecular Pathogenesis of Gastric Adenocarcinoma

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Abstract

The incidence and mortality of gastric cancer (GC) rank top five and top three, respectively, among cancers around the world. It is an intricate malignancy caused by the reciprocity of intrinsically genetic, environmental, and host-related elements. The silent property, advanced clinical characterization, and potential heterogeneity have made GC a thorny disease with a high death rate. The increasing knowledge of the abundant genetic abnormalities regarding GC will definitely elongate the patients' survival. Scientists have been working hard to discover the myths beneath gastric tumorigenesis: novel biomarkers have been established, and cell transduction cascades have been well described. The study grouping GC into four molecular subtypes by The Cancer Genome Atlas (TCGA) broadens our horizon of GC etiologies. Knowledge regarding to the sophisticated networks in tumor microenvironment also bring new insights into the mechanisms assist GC development. In the future, people will strive for translating more research achievements into clinical utility. Successful translational medicine will lead to new methods for early GC diagnosis and precise medical strategies for individuals.

Keywords: gastric adenocarcinoma, molecular classification, pathogenesis

1. Introduction

Gastric cancer (GC) is the fifth most common malignancy worldwide and third leading cancer-related death. Because of poor diagnosis, 5-year survival rate of GC is rather low, ranging from 15 to 52% [1, 2]. The incident rates are higher in men than in women. GC contributes over 20% of morbidity and mortality to cancer all over the world annually, following lung and liver cancer, which account for 23 and 28%, respectively. In 2012, approximate 723,000 deaths and more than 950,000 new GC cases were reported worldwide. Despite the incidence of GC has been declining in the North American and most of the west European countries, GC remains a type of prevailing cancer with increasing risk in regions including

Asia, Eastern Europe, and certain areas of Latin America [3]. Particularly, adenocarcinomas, which developed from the glands of the most superficial layer or the mucosa, take up 90% of GC. The rest types of GC include mucosa-associated lymphoid tissue (MALT) lymphomas, which originate from the muscles surrounding mucosa areas of the stomach [4].

The risk factors include environmental factors, such as *Helicobacter pylori* infection, cigarettes smoking and high-salt diet, and host genetic alterations. Although the incidence of GC has shown a dramatic decrease in recent years due to *H. pylori* eradication, the overall survival is still quite poor due to its silent nature, late clinical presentation, and genetic heterogeneity. Thus, comprehensive understanding of the detailed molecular mechanisms and accurate pathogenesis of GC will improve patient outcome. Recently, several kinds of molecular classification of GC have been provided to reveal the genomic landscape of GC and decipher the crucial molecular changes. Among them, The Cancer Genome Atlas (TCGA) classification is a milestone for the molecular characterization of GC. Clinical translation of these molecular findings will provide novel strategies for early GC detection and promote precision therapies for GC patients.

2. The risk factors of GC

GC is defined as a tumor with multifactorial etiologies. Environmental alteration and genetic factors play major roles in GC, particularly, virus infection, dietary habits, and lifestyles are recognized to be critical factors.

H. pylori is a common human pathogen, contributing to both malignant and benign diseases. Among all the risk factors of GC, *H. pylori* is considered to be the most predominant factor, up to 80% of GC cases are led by *H. pylori* infection. At least 660,000 new diagnoses are making annually [5, 6]. Data in western countries indicated that *H. pylori* is a major risk factor for only non-cardia GC instead of cardia GC [5]. It has been noted that the death number of GC is decreasing in many developed regions, partially related to eradication therapy and improved living condition in certain populations and regions [7]. Given the worldwide aging problem and the migration trend of people from high to low prevalence regions, the mortality is very likely to increase in the future [8]. *H. pylori* infection alone is not sufficient to trigger GC. Chiba et al. suggested *H. pylori* infection contributed to GC development via two potential mechanisms, either caused chronic inflammation or directly acted on epithelial cells [9]. In general, *H. pylori* colonizes the gastric mucosal epithelium and induces chronic inflammation at the beginning of infection, while persistent inflammation resulted in GC [10, 11]. Cytokines and chemokines produced by the tumor microenvironment facilitate cell proliferation and migration, and keep cells from apoptosis and immune detection [12]. Cytokines released by different cell sources have been described as suggestive indicators in the progression of GC. The serum level of Tumor necrosis factor-α (TNF--α) in GC was found greatly reduced, however, levels of TNF-α in stage III or IV GC patients showed a significant elevation when compared to levels in earlier stage patients [13]. Besides, the secretion of Interleukin-1 (IL-1) contributes to tumor cell proliferation and progression. In addition, IL-6, IL-10, and Transforming

growth factor-β (TGF-β) improve survival of GC cells by promoting cell invasion and suppression of antitumor immunity. IL-11, IL-17, IL-18, IL-22, and chemokines secreted by a specific cell type also improve the progression of GC [14]. Major types of virulence factors of *H. pylori* include cytotoxin VacA, the type IV secretion system (T4SS), and the CagA effector protein. These factors are associated with multiple cellular responses, such as induction of oxidative stress and epithelial barrier disruption, in various model systems [15].

Epstein-Barr virus (EBV), also termed as human herpesvirus 4 (HHV-4), is one of the most prevalent viruses in humans. EBV was the first virus identified in human carcinoma in 1964 [16]. Approximately 95% of adults in the world are infected by EBV due to the positive detection of serological EBV markers. EBV infection may not cause severe symptoms and disease. After primary infection, EBV establishes a carrier state called latent stage. However, latent EBV infection could subsequently become high-risk oncogenic factors associated with human malignancies. EBV has been known as another significant pathogen exists in GC cells. According to worldwide data, EBV-associated GC (EBVaGC) accounts for 10%, in average, of total GC cases. Most of the EBVaGC cases were epithelial tumors, while lymphoepithelioma-like carcinomas take up 90% of the rest rare EBVaGC cases. EBVaGC presents distinct clinic properties, such as predominance among male and younger individuals and predominant proximal stomach location [17]. EBV infection can be achieved by two different entry mechanisms, either via B cell entry or fusion with epithelial cells directly [18, 19]. EBVaGC occurs in the upper and middle stomach in the majority. Fukayama et al. indicated the tumor distribution in the stomach, with the proportion that 58% in the cardia, 33% in the body, and 9% in the antrum [20, 21]. They also depicted the appearance of EBVaGC as ulcerated or saucer-like, with obvious thickened gastric wall. Moreover, the lymph node was less frequently involved during early stage within the submucosa. These characteristics are proposed to be favorable prognosis indicators. Histological studies provide evidence that immune cell infiltration was a feature of EBVaGC. For instance, infiltrating lymphocytes, containing EBV-specific cytotoxic T cells, communicate with carcinoma cells directly, in the opposite, cytokine IL-1β was upregulated to recruit noninfiltrating lymphocytes against this cell-cell contact [22, 23]. Therefore, in EBVaGC, immune responses in tumor microenvironment also accompany with the progression of EBVaGC [24].

Dietary factors: dietary risks, including salty and spicy food intake, cigarettes smoking, frequent coffee, and high-temperature drinking habits are positively associated with GC. Intriguingly, excess salt intake showed susceptibility to EBVaGC and *H. pylori*-induced GC. Habitual excess salt intake was suggested to progressively increase the risk across consumption levels of GC via a meta-analysis [25]. The association between salty food intake and *H. pylori* infection was also evaluated in a cross-sectional study of 634-middle age male cohort. The result supported habitual salt-rich Japanese food intake was prevalent in *H. pylori*-induced GC cases [26]. It is probably due to the increase of *H. pylori* colonization and persistent infection [27]. Besides salty food intake, Camargo et al. indicated that smoking was strongly associated with EBVaGC by a case-case comparison between EBV-positive tumors and EBV-negative tumors [28]. Although alcohol drinking was a suggestive risk factor of GC, heavy alcohol drinking, rather than moderate alcoholic drinks, was significantly correlated with GC development [29, 30].

3. Molecular classification and pathogenies of GC

Up to 90% of stomach malignancies are adenocarcinomas. Non-Hodgkin's lymphomas and gastrointestinal stromal tumor (GIST) make up most of the remaining 10% [31]. Even though infrequently, adenosquamous, squamous, and undifferentiated carcinomas also occur. In regard to clinical diagnosis, several pathological characterization varied from time to time. Several histological classification systems for gastric adenocarcinoma have been described, but the most frequently used are those of the World Health Organization (WHO) and Lauren [32]. In the World Health Organization (WHO) classification, there are 10 histological types [33]. The Lauren classification is commonly applied and it makes the distinction between intestinal and diffuse types. The intestinal GC consists of cohesive neoplastic cells forming gland-like structures while the diffuse type has lost cell cohesion and resulting in diffuse discohesive cellular infiltration [31]. Men and elderly are more likely to suffer intestinal type, whereas diffuse type carcinomas are relatively more common among the younger population with an equal male-to-female ratio [32]. Recently, a project named The Cancer Genome Atlas (TCGA) has proposed a brand new classification, in which GC is grouped by four subtypes: EBV-positive (EBV), microsatellite instability (MSI), genomically stable [34], and chromosomal instability [35, 36].

According to previous studies, about 9% of GC cases are infected by EBV [37]. All the EBV-positive GCs harbor the property of CpG island methylator phenotype (CIMP) [36, 38, 39]. EBV-positive tumors exhibited a higher incidence of whole-genomic DNA hypermethylation than any molecular subtypes. The genes with promoter hypermethylation showed most differentially silenced expression in EBV-associated GC [36]. Moreover, PI(3)-kinase inhibition was also strongly detected in EBV-positive GC, which offered a new method for the evaluation of this subtype [36]. The most highly transcribed EBV viral, message RNAs (mRNAs) and microRNAs (miRNAs), fell within the BamH1A region of the viral genome and showed similar expression patterns across tumors [36]. The mutation rate of PIK3CA is exclusively high in EBV-positive gastric cancer compared with other molecular subtypes. The mutation rate of PIK3CA in this subtype is about 80 and 68% of the mutations belongs to recurrent mutation in this dataset. In contrast, in other molecular subtypes, the mutation rates of PIK3CA are from 3 to 42%. So, this result provides a hint that using PI3K inhibitor might have the clinical therapeutic potential for this kind of molecular subtype.

The next subtypes of GC are abundant in MSI, which display increased mutation rates (in major histocompatibility complex class I genes, including B2M and HLA-B) and hypermethylation (containing hypermethylation at the *MLH1* promoter). The most obvious difference between EBV-CIMP (CpG island methylator phenotype) and MSI-associated gastric-CIMP methylation profiles is that all EBV-positive gastric tumors show promoter hypermethylation of *CDKN2A* ($p16^{INK4A}$), but the *MLH1* hypermethylation was only detected in MSI-associated CIMP [38].

In genomically stable subtype, *RHOA* mutation was detected [36]. When binding with Guanosine-5′-triphosphate (GTP), RHOA behaves through a great number of downstream effectors, such as ROCK1, mDIA, and protein kinase N. This will lead to actin-myosin-dependent cell contractility and cellular motility [40, 41] and activation of STAT3 to promote carcinogenesis [42, 43]. Except from activating mDia or ROCK1, the *RHOA* mutation Y42C has been confirmed to attenuate the

activationof protein kinase N. Because RHOA is strongly associated with cell motility, the *RHOA* mutations might contribute to the invasive growth patterns. In diffuse type GC or genomically stable GC, the lack of cellular cohesion is a hallmark for this diffuse phenotype. Apart from RHOA mutation, an inter-chromosomal translocation called CLDN18-ARHGAP26 fusion gene was identified. ARHGAP26 is a GTPase-activating protein that converts GTP-RHO to GDP-RHO and it is been reported to facilitate cellular motility. CLDN18 is a tight junction component that involves in cell adhesion. This fusion gene thus was thought to correlate with cell metastasis in this kind of molecular subtype.

With the somatic copy-number aberrations (SCNAs), the last group of GC was clustered as CIN subtype. In this subtype, a bunch of genes shows dysregulated, such as *TP53* mutations (in 71% of tumors) as well as *CDH1* somatic mutations (enriched in the genomically stable subtype, about 37% of cases).

4. The dysregulated miRNAs involved in GC

MicroRNAs (miRNAs) are one predominant category of small (roughly 20–30 nucleotides) non-coding RNAs that participate in gene expression and control [44]. Their effects are mostly lead to the degradation of message RNAs (mRNAs) or inhibitory of the translations, and subsequently affect a series of biological behaviors of cells, such as inflammation, cell proliferation, apoptosis and differentiation. In the nucleus, together with its cofactor Pasha (DGCR8), the RNase III enzyme Drosha cut out primary miRNA transcripts into a fragment of approximately 60 nucleotides named precursor miRNAs (pre-miRNAs), and initiate the biogenesis of miRNAs [45]. A cytoplasmic RNase III called Dicer will be responsible for the further processing of the pre-miRNAs and makes them mature after they are transported to the cytoplasm [46, 47]. A mature miRNA, with the length of about 18–24 nucleotides, is single-stranded, which can sometimes aim at multiple targets. These mature miRNAs always bind to the complementary sequences of targeted mRNAs directly to make mRNAs degrade or bind directly to 3′-untranslated regions (3′-UTR) of mRNAs to decrease their translation, so that miRNAs can exert their effects on regulating certain gene expression [44, 48]. Accordingly, miRNAs regulate at least 30% of genes of human as it is estimated [49].

In other words, miRNAs are capable of acting as a switch to control genes related to cell proliferation and apoptosis under pathogenic circumstances, consequently, they may have a chance to be involved in both cancer initiation and progression. It seems that no matter how clear the mechanism of malignancy behaviors or an effective therapy that might prevent tumorigenesis from the beginning, an increasing knowledge of these miRNAs is crucial. During the physiological periods, miRNAs present or absent in proper time of different stage of lives. However, they are produced abnormally in tumors, that the levels of some miRNAs are highly detected while some are lower or even none. Hence, those which are upregulated called onco-miRs, whereas the downregulated ones called tumor-suppressive miRNAs. As the names suggested, genes controlled by onco-miRs are oncogenes whose products may promote tumor cells in many aspects, whereas the opposite site of genes is tumor suppressive, which plays a role of inhibitor among the initiation or development of tumors (e.g., miR-15a

and miR-16-1, which target a member of Hippo pathway called YAP1, are downregulated in GC) [50]. Thus, identifying the target genes of these miRNAs is crucial and it may lead us to a better understanding of the miRNAs themselves.

For example, miR-21 was the first miRNA which was influenced by *H. pylori*. In tissues of both GC and *H. Pylori* infection, it was highly detected [51, 52]. Several data have reported that this miRNA can be used as a biomarker in GC diagnosis in the clinic [53–55]. And most recently, a research conducted in China suggested this miR-21 to be a GC biomarker in both diagnosis and prognosis, for the reason that, besides the high levels found in tumor tissues compared with the normal ones, miR-21 was revealed to be associated with poor survivals in clinical patients [56]. Behind the phenomena, the molecular mechanism is still unclear in GC. In other types of cancer, however, such as colorectal cancer, miR-21 decreased the tumor suppressor protein programmed cell death 4 (PDCD4) and exhibited an oncogenic function [57]. Additionally, in nonsmall cell lung carcinoma, miR-21 was found to deregulate PTEN, a tumor suppressor, to promote carcinogenesis [58].

5. The tumor microenvironment and gastric carcinogenesis

More and more evidence supported the idea that not only malignant GC cells, but also those nonmalignant cells involved in the tumor microenvironment play indispensable roles throughout GC pathogenesis. Generally, nonmalignant cells participate in various mechanisms related to GC development, such as stromal interactions, angiogenesis, and some immune responses.

Stromal components, including fibroblasts and extracellular matrix (ECM) adjacent to cancer cells, create a suitable environment for GC development. Stromal fibroblasts are known to play a central role in tumor microenvironment by interacting with cancer cells [59, 60]. However, other than ordinary fibroblasts, cancer-associated fibroblasts (CAFs) undergo a phenotypic change into myofibroblasts. Also, CAFs exhibit distinct gene expression patents that pertain to aberrant cell growth, focal adhesion, and ECM remodeling [61]. The remodeling ECM promotes the survival ability and distant colonization cancer cells by synthesizing components, such as type I and type III collagens, fibronectins, tenascin, and versican [62–64], as well as proteases like urokinase, plasminogen activator, fibroblast activation protein (FAP), and matrix metalloproteinases (MMPs) [65–67]. These characteristics are usually associated with poor prognostics. Moreover, tumor-related stromal fibroblasts secrete small molecules, such as IL-6 to stimulate cell growth, as well as factors associated with TGF-β signaling, triggering epithelial-mesenchymal transition (EMT) [68–70].

Angiogenesis is also a pivotal process contributes to tumor progression. Cell population in GC tumor microenvironment regulates the density and architecture of new blood vessels by stimulating the proliferation and differentiation of myofibroblasts and vascular endothelial cells [71, 72]. The growing number of new vessels was reported to facilitate GC metastasis [73, 74]. To promote angiogenesis, GC cells provide numerous angiogenic factors, including VEGF, FGF-2, CXCL1, and Ang-2, to microenvironment [75–78]. It has been noted that high level of VEGF-A contributed to endothelium-dependent angiogenesis. VEGF-A signaling increased both the new blood vessel number and permeability in GC [79]. VEGF-A strongly

promotes the angiogenesis and aggressive phenotype of human intestinal-type GC [80]. Bevacizumab is a specific antibody against VEGF-A, and dominantly regulates normal and pathological angiogenesis. Clinical trials of bevacizumab in phase II advanced GC suggested a satisfied curative effect [81]. Unfortunately, in the randomized phase III Avastin in Gastric Cancer (AVAGAST) study, the combination of chemotherapy and bevacizumab did not show a better overall survival extension in the first-line treatment when compared to advanced GC patients, who only subjected chemotherapy [82]. Intriguingly, REGARD and RAINBOW trials using VEGFR2 targeting antibody ramucirumab have also shown a significant increase in the overall survival of patients with advanced GC [83]. It can be partially explained by the geographical differences of GC patients.

Immune reactivity in GC development is based on various types of immune cells in different stages [84]. First, in eliminating stage, macrophages and dendritic cells recruit to secrete chemokines and cytokines, such as IL-12 and IFN-γ, to phagocytize and remove apoptotic cancer cells [85]. Cancer cells survived from elimination subsequently under equilibrium stage and adapted to immune-suppression. The number of tumor-infiltrating lymphocytes (TILs) was noted as independent predictors to evaluate lymph node metastasis and GC patient survival in this stage. Interestingly, TILs exert either oncogenic or tumor-suppressive influence in GC cells, attributing to their unique functions. In a recent report, tumor-associated macrophages with high levels of CD163 expression exhibited aggressive characteristics and expression of cancer stem cell markers in recurrent GC cases. $CD163^+$ macrophages might, therefore, related to independent worse prognosis [86]. T-lymphocyte subsets are also significant cell types associated with both early onset of tumor and tumor progression. It has been reported that the high ratio of $CD8^+$ cytotoxic TILs/$FOXP3^+$ regulatory T cells (Treg) correlated with high overall survival rate and good prognosis, especially in MSI gastric cancer [87, 88]. Eventually, cancer cells escape from immune responses.

Immunogenicity could be blunted by releasing cytokines including TGF-β, TNF-α, and IL-10. Therefore, cancer cells can evade the detection by immune effectors in the tumor microenvironment [89]. PD-1 is one of the most important receptors expressed by T cells and monocytes. PD-1 negatively regulates the effectors by binding to its ligands PD-L1 and PD-L2. Blocking PD-1/PD-L1 has been suggested as a promising immune-therapeutic option [90, 91]. The relationship between PD-L1 level and prognosis remains under debate, however, a recent meta-analysis pooled all present data and suggested PD-L1 to be a valuable prognostic indicator of GC patients by dividing patients into different groups [92].

Collectively, tumor microenvironment composed of multiple subjects, such as tumor stromal fibroblasts, lymphocytes, and angiogenic factors. All these components cooperate together, configuring a context for GC development.

6. Conclusion

There is still a large realm of the unknown area about GC pathogenies even though the related research studies have been going deeper and our horizon has been broadened in the past few years. Epigenetically, we are seeking to unravel the mechanisms of gastric tumorigenesis

affected by chromatin remodeling. Besides, there are miRNAs, lncRNAs, and some other classic molecules that are involved in GC development, which requires a more detailed investigation regarding these aspects. The most crucially and urgently, we are struggling to explore specific and precise therapies for patients who are suffering or likely to suffer from GC, especially genomically stable GC (a type of GC with a high mortality).

When it comes to the novel small entities, there are even more issues waiting to be addressed, such as how lncRNAs interact with chromatin alterations during gastric carcinogenesis. Moreover, in addition to *H. pylori* and EBV, scientists have identified a wild variety of bacteria in the stomach through DNA sequencing. These uncultivatable bacteria have formed a complicated community and there are few clues about how they interact with *H. pylori* and host immunity during GC initiation and progression. In the early detection field, molecular findings may facilitate new approaches for diagnosing GC early, by identifying high-risk potential sufferers via the molecular features of precancerous lesions. Finally, therapeutic strategies need to be designed precisely for each GC subtypes, according to their somatic driver change of genome or tumor-associated cell compartments, such as stromal cells and tumor-infiltrating immune cells.

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