Chapter 7
Genetic Susceptibility Markers of Gastrointestinal Cancer

M. Kiran Kumar and Pola Sudhakar

Abstract Gastrointestinal cancer is the most common type of malignant disease with high mortality and the second foremost cause of carcinoma deaths worldwide. The frequency of gastrointestinal cancer strongly depends on ethnical and geographical characteristics. For example, the prevalence of gastrointestinal cancer is significantly high in Japan and Korea, whereas in North America and Europe the occurrence of gastrointestinal cancer is very low. Generally, gastrointestinal cancers are diagnosed in late stages due to the heterogeneous nature. By considering the heterogenicity of gastrointestinal cancer, inhibition is depending on the precise diagnosis of risk factors, the underlying cause of the disease, and the management of risk factors. Therefore, this chapter aimed to review the genetic susceptible marker of gastrointestinal cancer. Molecular studies revealed that the development of GC is from the combined effect of various factors like environment, genetic and epigenetic modifications which play a crucial role in tumorigenesis and cellular immortalization. The molecular epidemiological studies revealed that some regular genetic traits act as a genetic susceptible marker to develop GC known as single nucleotide polymorphisms (SNPs). Single nucleotide polymorphisms (SNPs) are naturally occurring genetic modifications that have a different frequency in the diversified ethnic population. There are many associate studies to analyze the genetic susceptibility of GC. Genome-wide association studies are used for the identification of various single nucleotide polymorphism in genetic susceptible markers which are responsible for gastrointestinal cancer. Gene polymorphisms become an attractive biomarker of GC due to their environment-dependent alterations. Genetic susceptibility is crucial in molecular events related to the development of gastrointestinal cancers includes mucosal shielding, immune reaction to *H. pylori* infection, carcinogen detoxification, antioxidant protection, repair of DNA injury, and capability of cell propagation. The use of SNPs as prognostic markers for individual gastrointestinal cancers is very advantageous because of the availability and quality of tumor material. In this chapter, we tried to discuss some of the important genetic

M. Kiran Kumar · P. Sudhakar (✉)
Department of Biotechnology, College of Science and Technology, Andhra University, Visakhapatnam, Andhra Pradesh, India

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polymorphisms which affect gastrointestinal cancer susceptibility and how they influence malignant phenotype. The determination of genes responsible for GC susceptibility will give information for the advancement of novel GC therapeutics by studying the molecular events involved in GC carcinogenesis. This chapter includes single nucleotide polymorphisms in genes such as Cdh1, DNMT3A, PTPRCAP, PSCA, VEGF-A, XRCC1, IL-1, *HER-2*, MUC1, and MUC1.

Keywords Adenocarcinoma · Gastrointestinal cancer (GC) · Genetic susceptibility · Single nucleotide polymorphisms (SNPs) · Tumorigenesis

7.1 Introduction to Gastrointestinal Cancer

Gastrointestinal cancer is the utmost common kind of cancer with high mortality and the second foremost cause of cancer deaths worldwide (Brenner et al. 2009). Gastrointestinal carcinoma is mainly arising from the inner layer of the stomach and spread to various body parts like the liver, lungs, bones, and lymph nodes (Ruddon 2007). In Asia, gastrointestinal cancer is the most prevalent cancer, and it causes the third leading cancer deaths (Ferlay et al. 2013). Gastrointestinal carcinoma is a multifaceted disorder that is caused by the collective effect of environmental factors, host affiliated factors, genetic and biological heterogeneity. But since, several decades the incidence and mortality rates are decreased appreciably by the development of medical advancement (Ferlay et al. 2015).

7.1.1 Prevalence of GC

Cancer is considered a major cause for mortality and it increases the burden on the world due to increasing carcinogenic factors (Asombang and Kelly 2012). According to the 2012 statistics, 55% of the cancers throughout the world related to lung, breast, colon, prostate, gastrointestinal, and hepatic cancers (Zali et al. 2011). Among all the cancers gastrointestinal cancer is the fifth most common cancer around the world with 9,52,000 diagnosed cases and 7,23,000 deaths in 2012 (World Cancer Report 2014). Gastrointestinal cancer occupies the third leading cause of cancer deaths after the lung and hepatic cancer which occupies the first and second positions of cancer deaths (Lozano et al. 2012). According to the IARC 1997, large variations are observed in the incidence of gastrointestinal cancer among populations. For example, in Japan, the incidence of gastrointestinal cancer is 80 per 1,00,000 males, whereas in African states, the overall incidence of gastrointestinal cancer is only 5 per 1,00,000 people (Parkin et al. 1997). Males are more susceptible to developing stomach cancer in their lifetime which is about 1 in 95. Whereas women have a chance to develop gastrointestinal cancer which is about 1 in

154 but the risk of developing cancers for each person is affected by the other factors (American Cancer Society Cancer Facts and Figures 2019).

Gastrointestinal cancer is a predominant disease and mainly affects older people with a mean age of 60 or above. Every year out of ten about six people diagnosed with gastrointestinal cancer and it is more common in men (Parkin et al. 2005; Curado et al. 2007). The people under the age of 50 have only a 6–7% chance to develop gastrointestinal cancer, whereas less than 2% chance to develop gastrointestinal cancer for the age group below 40 (Yoshio et al. 2008). According to the American cancer society's estimations for 2019 in the United States approximately 27,510 gastrointestinal cancers are diagnosed. Among them 17,230 are men and 10,280 are women. People under 40 years of age have a chance to get stomach cancer is less than 5%. In that 5% of people under the age group, 30–39 occupies 81.1% and people under 20–29 age group occupies 18.9%. About 11,140 people have died. Among those 6800 are men and 4340 are women.

7.1.2 Global Statistics of Gastrointestinal Cancer

Worldwide the gastrointestinal cancer is the fourth most commonly occupying disease. In the western world, the incidence of gastrointestinal cancer is rapidly declining but still, GC is the second major reason of cancer-related deaths and yearly 7,40,000 deaths are recorded with the 20% 5-year survival rate. The occurrence of gastrointestinal cancer strongly depends on ethnical and geographical characteristics. For example, the prevalence of gastrointestinal cancer is significantly high in Japan and Korea, whereas in North America and Europe the occurrence of gastrointestinal cancer is very low (Crew and Neugut 2006). Japan has a more incidence of gastrointestinal cancer with an incidence of 62.7/1,00,000 than Bangladesh and India which have lower gastrointestinal cancer incidence with the incidence rates of 1.6/1,00,000 and 5.7/1,00,000, correspondingly (Fock and Ang 2010).

The occurrence of gastrointestinal cancer is different from the geographical societies. The highest prevalence of gastrointestinal cancer is found in Eastern Asia, South America, Central America, and Eastern Europe, whereas the lowermost occurrence found in Africa, North America, and Australia (Nagini 2012; Jemal et al. 2011). Hence, in high incident areas Japan, China, Korea, Eastern Europe, Central and South America, these areas are categorized into high-risk areas (Parkin et al. 2005). In North America, the major subtypes of gastrointestinal cancers are pure intestinal, pure diffuse, and mixed diffuse intestinal and their percentages are 50%, 35%, and 15%, respectively (Pisani et al. 2002). The occurrence of gastrointestinal cancer is gradually reduced in developed countries due to new inventions in medicine, but it is remaining as a serious health problem to the countries which are underdeveloped (Jahanarah et al. 2016). In the United States, the percentage of gastrointestinal cancer incidence is reduced by 1.5% per each year over the past 10 years.

In India, the occurrence rate of gastrointestinal cancer is very low when compared to the western countries and each year approximately 34,000 people diagnosed with GC with a male predominance. In India, by the end of 2020, the number of new cases will be reached to 50,000 approximately. According to the Recent Nationally Representative Survey of cancer mortality in India, the gastrointestinal carcinoma is the second common cause of cancer death among men and women (Dikshit et al. 2012). In India, the prevalence of gastrointestinal cancer is relatively high in southern areas such as Andhra Pradesh, Tamil Nadu, and Karnataka. However, recent findings demonstrate that the incidence rates of gastrointestinal cancer are increased in the North-Eastern regions of India [NCRP-2009]. Gastrointestinal cancer is the most common cancer in men than women in the Aizawl district of Mizoram (NCRP-2013). The latest reports of the National Cancer Registry Programme-2013 indicate that the incidence rates of gastrointestinal cancer for men in Aizawl and Nagaland are 64.2 and 26.2, respectively. For women, the incidence rates of gastrointestinal cancer are 31.2 in Aizawl and 12.5 in Nagaland. In Mumbai, the rates are as low as 4.2 per 1,00,000 people.

Generally, gastrointestinal cancers are diagnosed in late stages (Lee and Derakhshan 2013) due to the heterogeneous nature (Zhifang et al. 2016). The prevention and reduction of mortality rates of gastrointestinal cancers need careful attention, early detection, and proper medications (Zhifang et al. 2016). Due to the heterogenicity of gastrointestinal cancer, the prevention depends on the precise detection of risk factors, the fundamental reason of the disorder, and the management of risk factors (Yoon and Kim 2015). According to the various studies, identification and analysis of risk factors gives an effective approach for the prevention and decreasing the occurrence of GC worldwide. However, complete knowledge about the GC risk factors is essential for controlling this cancer by the plan, monitor, and evaluating national and regional states. Hence, the present study is aimed to review the genetic susceptible markers of gastrointestinal cancer.

7.2 Types of Gastrointestinal Cancer

Gastrointestinal carcinoma is a complex disorder that is categorized by the variety of different histopathological classification systems, and it is mainly classified into three pathological variants named diffuse-type, intestinal-type, and the remaining consists of mixed and indeterminate type. The diffuse-type is characterized by the development of linitis plastica which contains noncohesive single cells without gland formation and most of the times signet ring cells are existing. Hence, it is also known as signet ring cell carcinoma (Bosman et al. 2010). Diffuse GC is associated with an unfavorable prognosis due to diagnosis is often delayed until the disease advanced. *H. pylori* infection is majorly associated with intestinal-type gastrointestinal cancer. de novo diffuse-type GC is developed from the normal epithelial cells due to genetic mutations in gastrointestinal stem cells. Furthermore,

in some cases, the DGC is represented by the dedifferentiated stages of IGC and also *H. pylori* contribution is present (Pilpilidis et al. 2011).

Intestinal GC is characterized by the various degrees of differentiation in the tubular or glandular components. The major intestinal GC develops from the gastrointestinal epithelium by the inflammatory changes caused due to *Helicobacter pylori* infection, and it develops chronic gastritis which leads to atrophic gastritis and finally intestinal metaplasia and dysplasia. The sequential events in intestinal GC are in the following manner, *Helicobacter* infection-, chronic inflammation-, intestinal metaplasia-, dysplasia-, adenocarcinoma. Hence, WHO recognized *Helicobacter pylori* is a class 1 carcinogen for the pathogenesis of IGC and the eradication of H.p infection is essential for the prevention of IGC. However, in both DGC and IGC, DGC has a greater chance to develop earlier in life than IGC (Crew and Neugut 2006).

7.2.1 Adenocarcinoma

Adenocarcinomas are the most frequent malignancies (90%) of the stomach which arise from the inner layer of gastrointestinal epithelium. The development of malignancies is rare from tissues like connective tissue and lymphatic tissues. Different body parts have different frequency to develop adenocarcinomas. For example, gastrointestinal cardia has a chance to develop the highest percentage of adenocarcinomas (31%), whereas the antrum and body of the stomach have only 26% and 14% chance to develop gastrointestinal cancer, respectively. Based on the histology and location, adenocarcinomas is classified and histological tumors exhibit heterogeneous appearance. Hence, the classification is mainly based on the prominent structures of tumors. Based on the gland formation and mucus secretion ability, malignancies are divided into two types. They are well-differentiated and poorly differentiated types. The majority of tubular cancers are well-differentiated and signet carcinomas are poorly differentiated. The other less common types of carcinomas are mucinous, papillary, and undifferentiated carcinomas.

7.2.2 Early Gastrointestinal Cancer

In early gastrointestinal cancer, the tumor cells restrict the stomach superficial mucosal layer and the tumors have less than 2 cm diameter, which appears as subtle lesions. The diagnosis of early gastrointestinal cancer is very crucial because the potential treatment of EGC requires endoscopic therapy is followed by an excellent diagnosis.

7.2.3 Hereditary (Familial) Gastrointestinal Cancer

Familial gastrointestinal cancer describes the chance to develop diffuse-type gastrointestinal cancer in the family members below the age of 40. The international gastrointestinal cancer linkage consortium (IGCLC) gives the measures for diagnosis. According to the IGCLC, two or more cases of diffuse-type gastrointestinal cancer in first- or second-level generation with minimum one member diagnosed before 50 years of age or pathologically identified three or more cases in the first- and second-level family members irrespective of the age. Among the family, one-third members have a germline mutation of the CDH1 gene. The affected family members also have a greater risk to develop breast and colon cancer.

7.2.4 Lymphoma

Gastrointestinal lymphomas are two types; they are B or T cell types. The B cell gastrointestinal lymphomas are developed primarily from the stomach particularly in the mucosal-associated lymphoid tissue (MALT), and these are considered as low-grade tumors. These lymphomas are highly favorable for clinical therapies, but they have a high frequency of transformation.

7.3 Causes of Gastrointestinal Carcinoma

GC is considered as a complex disease because both the environmental and genetic factors have a major part in the growth of GC. Gastrointestinal carcinoma is highly prevalent in the lower socioeconomic classes and is frequently detected in the advanced conditions (Carcas 2014). Diverse environmental factors that enhance gastrointestinal cancer risk include *Helicobacter pylori* and EBV infection, more salt and more nitrogen foods, tobacco, pre-malignant stomach lesions and genetic factors. All the described factors are referred to as gastrointestinal cancer risk factors (González and Agudo 2012). Among all the above-mentioned cases, the *Helicobacter pylori* infection is the major cause for developing gastrointestinal cancer which accounts for approximately 60% of cases (Fiona and Martin 2011). Other common causes for gastrointestinal cancers are packed vegetables, smoking, and genetic mutations (World Cancer Report 2014). Molecular studies revealed that the development of GC is from the combined effect of various factors like environment, genomic, and epigenetic modifications which show a vital role in tumorigenesis and cellular immortalization (World Cancer Report 2014).

Single nucleotide polymorphisms (SNPs) are naturally occurring genetic modifications that have a different frequency in the diversified ethnic population. Researchers focus on the identification of novel genetic susceptibility markers for

all the types of gastrointestinal carcinomas. SNPs can modify the expression pattern of genes and can alter the function of a gene, which leads to an increased risk of diverse diseases, including cancer. There are numerous examples for the existence of polymorphic genes which increase susceptibility to GC (Pinheiro et al. 2010). Nowadays, there is a possibility of identification and getting information of unexplored SNPs within a large number of genes by using advanced technologies like Genome-Wide Association Studies (GWAS) and high-throughput genomic investigation. These new methods for the detection of SNPs simultaneously give perceptions for the pathogenesis of GC. The development of the malignant disease is mainly by the cumulative effect, particularly by the genetic polymorphism, ethnicity, and exposure to environmental risk factors (Saeki et al. 2011).

In recent years, genetic markers show a significant role in the identification and management of patients with gastrointestinal carcinomas especially colorectal cancer, gastrointestinal stromal tumors, gastrointestinal and gastro-esophageal junction cancers. In 2003 and 2007, the European Group of Tumour Markers (EGTM) establish guidelines for the use of biomarkers in CRC (McLean and El-Omar 2014). This chapter provides new inventions on the use of biomarkers in gastrointestinal and gastro-esophageal junction cancers and gastrointestinal stromal tumors.

7.4 Genetic Susceptible Markers of Gastrointestinal Cancers

The development of gastrointestinal cancer is associated with multiple factors such as gastritis, gastrectomy (Duffy et al. 2007), *Helicobacter pylori* infection (Rugge et al. 2014), and genetic susceptibility factors (Gatti et al. 2004). Genetic factors play an important role in the development of gastrointestinal cancer. The familial clustering phenomenon of gastrointestinal cancer reveals that only a small fraction of people is affected after they exposed to the same environment. This phenomenon indicated that environmental exposure plays a major role in genetic susceptibility which leads to gastrointestinal cancer development in individuals (Xie et al. 2014). The epidemiological studies also reveal that only a small percentage of people who exposed to an environment with high incidence rates of gastrointestinal cancer are affected. These studies suggested that the chance of an individual to get gastrointestinal cancer depends on the individual's genetic susceptibility. In this chapter, we aimed to summarize the relationship between genetic polymorphisms and gastrointestinal cancer susceptibility.

Germline alterations in sequence of DNA are supposed to represent the main feature of a tendency to most complex traits, such as cancer (Milne et al. 2009). Genetic diseases triggered through the gradual accumulation of modifications in genes that regulate the differentiation, growth, and DNA repair can lead to the development of gastrointestinal cancer (Kelly et al. 2009). A small percentage of people only develop GI cancers based on their hereditary component and it is proved

through the well-studied genetic disorders and the family history associated risk factors (Grady and Markowitz 2002). Approximately 5% of hereditary genetic disorders are due to strong mutations evident with well-studied experimental demonstrations (Garber and Offit 2005). 20–25% of genetic disorders are associated with a hereditary component, which is not established until now (Jasperson et al. 2010). Several gastrointestinal cancers develop due to mutations in one gene, and this type of cancers are less carrying but develop persistently than the other cancers which are developed by combination with well-studied genetic disorders (Kelly et al. 2009). The single gene polymorphisms (SNPs) in genes which are participated in the regulation of metabolic pathways or the genes can be controlled by environmental influences (Jasperson et al. 2010). Mutations in multiple susceptible loci can also lead to the development of cancers by inducing additive effects (Grady and Markowitz 2002). This chapter discourses the genomics of the well-studied hereditary cancers of the GI tract.

The molecular epidemiological studies revealed that some common genetic traits act as a genetic susceptible marker to develop GC known as single nucleotide polymorphisms (SNPs) (Oliveira et al. 2006). Gastrointestinal carcinogenesis is also depending on the host genetic risk factors. Hence, gene polymorphisms become an attractive biomarker of GC due to their environment-dependent alterations. Genetic susceptibility crucial in molecular events related to the development of gastrointestinal cancers includes mucosal shielding, immune reaction to *H. pylori* infection, carcinogen detoxification, antioxidant protection, repair of DNA injury, and capability of cell propagation (Yin et al. 2009). The use of SNPs as prognostic markers for gastrointestinal cancers is very advantageous because of the accessibility and quality of tumor material, and they can be determined independently and easily evaluated from individual blood samples. There are many associate studies to analyze the genetic susceptibility of GC. For example, genome-wide association studies are used for the identification of various single nucleotide polymorphism in genetic susceptible markers which are responsible for gastrointestinal cancer. HDGC is a sporadic autosomal dominant disease, and it is produced by the germline mutations in the CDH1 gene, which translates cell adhesion molecule known as E-cadherin. 70–80% of gastrointestinal cancers are developed by the mutations in the CDH1 gene.

GC also develops other types of familial cancers, including Lynch syndrome, familial adenomatous polyposis, Peutz–Jeghers syndrome, and Li–Fraumeni syndrome. The prevalence of gastrointestinal cancer is 2.9 times higher in individuals who are having germline mutations in the MLH1 gene. A study by Hansford et al. (Gonzalez et al. 2002) reported that 12% of CDH1-negative HDGC families have germline mutations in tendency genes including CTNNA1, BRCA2, STK11, PALB2, ATM, MSR1, and SDHB. All these genes can sense the development of gastrointestinal cancer in families and provide molecular evidence of tumorigenesis (Hansford et al. 2015). DNA methyltransferase 3A is responsible for the genomic methylations and also essential for the differentiation of stem cells during development in mammals (Ding et al. 2008). Fan et al. (Yurgelun and Boland 2017) reported that the polymorphism of gene DNMT3A-448 A>G is involved in the development

of gastrointestinal cancer by acting as a genetic susceptible marker for GC. Ding et al. (Fan et al. 2010) reported that gastrointestinal carcinogenesis involves the de novo expression of the DNMT3A gene.

Protein Tyrosine Phosphatase Receptor Type C-Associated Protein (PTPRCAP) is participated in the stimulation of Src family kinases (SFKs) (Motoya et al. 1999) and the activated SFks play a key role in the interruption of the epithelial adherin junctions by dislocating the E-cadherins in membranes (Avizienyte et al. 2002). PSCA gene also reported as a genetic susceptible marker for gastrointestinal cancer (Sakamoto et al. 2008a). PSCA is overexpressed in differentiating gastrointestinal epithelial cells to inhibit the cell proliferation and its silenced form mostly found in gastrointestinal carcinomas. Lu et al. (Lu et al. 2010) reported that two polymorphisms (rs 2976392 and rs 2294008) in the PSCA gene lead to gastrointestinal carcinogenesis. The VEGF (Vascular Endothelial Growth Factor) gene has been identified in many genome-wide association studies as a genetic susceptible marker. VEGF is important for the progression of various tumors including GC by acting as a key factor in angiogenesis (Ke et al. 2008). Several studies reported that the VEGF 634 G>C polymorphism involved in the increasing risk to form GC (Guan et al. 2009).

The polymorphism 1612 G>A in the 3′-UTR of VEGF is associated with the deregulation of affected genes and thereby increasing the risk of gastrointestinal cancer (Tahara et al. 2009). The gene XRCC1 (X-ray Repair Cross-Complementing Group 1) is involved in the maintenance of integrity and DNA nucleotide composition, and it is important for the normal functioning of the cell. XRCC1 is participated in the base excision repair mechanism that repairs the single nucleotide changes produced by the ionizing radiations, alkylating agents, and metabolic toxins (Caldecott et al. 1995). The XRCC1-77 T>C polymorphism in promoter region is correlate with human cancer known as non-small cell lung cancer (Hao et al. 2006). Corso et al. (2009) reported that the relation between the XRCC1 77 T>C polymorphism and the increased risk of gastrointestinal carcinoma. Hence, the polymorphism of XRCC1 can be used as a host genetic susceptible factor for gastric carcinoma.

Host genetic features act as a key element in the increased risk for the development of cancer, and the associations of various polymorphisms on diversified genes and their products interact with environmental factors and provide important information to explain the multiple risks in diversified populations. EI-Omar et al. (2000a) reported that the interaction of precise gene variants increases the risk of gastric carcinoma. The meta-analysis of individual cytokine gene polymorphism in GC susceptibility reveals that the association between specific variants of IL1RN VNTR, IL1B-511, and IL10-1082 gene polymorphisms increase the GC risk. The interleukin-1 beta IL1B-31T (rs 1143627) and IL-1 receptor antagonist IL1RN2/2 genes are linked with an enhanced risk of both chronic hypochlorhydria and GC by altering IL-1 concentration in the stomach. Genetic polymorphism along with the susceptibility of cancer also affects the tumor phenotype. Total genome expression studies are useful for the identification of new genes involved in invasion, metastasis, and potential prognostic factors. Sequential analysis of gene expression studies

identifies the several genetic susceptibility genes such as CDH1, APOE, FUS, COL1A1. COL1A2, GW112, and MIA.

7.4.1 CDH1 Gene

The CDH1 gene is present on the 16q 22.1 chromosome of human and it contains 16 exons, which transcribed into 4.5 kb m-RNA and translates into E-cadherin (Bussemakers et al. 1994). E-cadherin is a calcium-dependent cell adhesion molecule which plays an important role in maintaining polarity and differentiation of cells by forming adherin junctions and desmosomes (Stemmler 2008). E-cadherin is a glycoprotein which contains three domains known as small cytoplasmic domain, transmembrane domain, and large extracellular domain. Five tandemly repeated domains are present in the extracellular domain and they are named as EC1- EC5 (Takeichi 1995). The extracellular domains of cadherins involved in cell–cell interactions by forming homophilic dimerization.

The cytoplasmic domain of E-cadherin contains three different types of catenins known as α, β, and γ. These catenins are involved in the anchoring of cadherins by establishing the interaction between the cytoplasmic domain of cadherin and the actin in cytoskeleton (Gumbiner and Mccrea 1993). E-cadherin is predominantly expressed in the epithelial cells and makes strong adherin junctions thereby; suppress the invasion (Yagi and Takeichi 2000). Germline mutations of CDH1 allele produces diffuse-type gastric carcinoma by the inhibition of E-cadherin second allele is by the methylations, mutations. Furthermore, researchers reported that the cancer cells migrate to various body parts and make changes among the cancer cells and the constituents of extracellular matrix (Valastyan and Weinberg 2011). This leads to tumor progression by altering the cell–cell adhesions and cell–matrix adhesions. E-cadherin and the cadherin–catenin complex in the cytoplasmic side of the epithelial cells involved in the various signalling pathways include Wnt signalling, Rho GTPases, and NF-κB. Hence, mutations in E-cadherin affect these signalling pathways by influencing the cell polarity, cell survival, invasion, and migration in gastric carcinogenesis.

E-cadherin also exhibits various partners for making interaction in the cytoplasmic adhesion complex with the actin filament. The Epithelial Mesenchymal Transition (EMT) process is by the several signalling pathways such as Wnt signalling, Rho GTPases, and EGFR (Cavallaro and Christofori 2004). The inhibition of E-cadherin expression on epithelial cells leads to decreasing the polarity of a cell and enhances the migratory and invasive development characteristics by the initiation of active signals for EMT (Garcia de Herreros and Baulida 2012). The WNT gene family proteins are involved in a signalling pathway for embryonic development and oncogenesis. This signalling can be subdivided into two types: β-catenin-dependent signalling or canonical Wnt signalling. Another type of signalling is β-catenin-independent signalling, known as non-canonical Wnt signalling. The WNT gene family involves glycogen synthase kinase-3beta (GSK-3beta) molecules, beta-

and gamma-catenins, and APC. Beta-catenin binds directly to the intracellular domain of E-cadherin and alpha-catenin by interacting with cytoskeletal actin through the APC protein. Beta-catenin is also a transcriptional coregulator and is persistently targeted for proteasomal degradation by the APC/Axin/GSK3b complex when the pathway is inactive. In the canonical pathway, the Wnt protein subtype binds to receptors on the cell membrane and inactivates the APC/Axin/GSK3b; thereby degradation of b-catenin is prevented which leads to increased levels of free cytoplasmic beta-catenin. The free b-catenin migrates into the nucleus where it forms a complex with LEF-1/TCF which is capable of promoting transcription of other genes involved in proliferation (Staal et al. 2008).

Maximum level concentration of β-catenins in the cytoplasm immediately translocate into the nucleus and binds to the TCF/LEF1 elements. Furthermore, stimulates the Wnt target genes expression, including CD44, c-MYC, cyclin D1, and MMP7 (Moon et al. 2004). Activation of these genes enhances the rate of cell proliferation and induces tumor formation. E-cadherin expression on cell membrane inhibits the Wnt β-catenin signalling pathway by sequestering the β-catenin at the sites of cytoplasmic domain and cytoskeleton junction. Hence, the cytoplasmic domain is important for the inhibition of Wnt β-catenin-mediated expression of gene (Gottardi et al. 2001). Various cellular systems demonstrated that the sequestration of β-catenin by E-cadherin can compete with the β-catenin/TCF-mediated transcriptional activity of the canonical Wnt signalling pathway (Cavallaro and Christofori 2004).

Besides the Wnt signalling, there is another pathway induced by the E-cadherin extracellular domain (Suriano et al. 2003) which is mediated by the enhanced RhoA activity and leads to acquire high migration ability. EGFR (Epidermal Growth Factor) plays a major role in the stimulation of RhoA by an E-cadherin-mediated pathway (Bremm et al. 2008). Hence, mutations in the extracellular domain of E-cadherin lead to wrong interaction with EGFR and activate the EGFR, which leads to increase the motility of cell by RhoA activation (Mateus et al. 2007). However, loss of E-cadherin also releases P120-catenin which activates the Rac1-MAPK (Mitogen-Activated Protein Kinase) signalling pathway and induces the overexpression of RhoA, Rac1, and Cdc42 (Pan et al. 2004). The above signalling molecules are thought to play a critical role in the organization of cytoskeleton, motility of cell, and promotion of cell growth (Heasman and Ridley 2008).

H. pylori infection induces the gastric cancer by inflammation-associated carcinogenesis during inflammation of epithelial cells is regulated by the NF-κB (Karin and Greten 2005). In mammals, activation of canonical NF-κB signalling pathway is mainly by the dimerization of P65:P50. Under normal conditions the NF-κB is inactivated by the IFK. Upon inflammation, the mediators such as cytokines and microbial or endogenous molecules induce the release of P65:P50 by phosphorylation of IKB by the IKK complex. The free P^{65}:P^{50} heterodimer moves into the nucleus and triggers the expression of response-specific genes includes Bcl-2, IL-6, and TNF (Ben-Neriah and Karin 2011). The expression of these genes increases the proliferative ability and decreases the apoptosis ability, thereby enhancing the chance to develop inflammation-associated tumour growth. In a cell, it is evident

that the hyperexpression of E-cadherin can decrease the NF-κB stimulation, whereas loss of E-cadherin induces the activity of NF-κB (Kuphal et al. 2004). NF-κB suppression is mediated by the catenin and E-cadherin complex (Solanas et al. 2008). Hence, the stimulation of NF-κB through the down regulation of E-cadherin gives information for the *H. pylori* infection-related gastrointestinal cancer development.

7.4.2 DNMT3A Gene

Eukaryotes have three types of DNA methyltransferases called as DNMT1, DNMT2, DNMT3A, and DNMT3B. DNMT1 is involved in the maintenance of the pre-existing methylation patterns on DNA during replication; hence, it is called maintenance methyltransferase (De Carvalho et al. 2012). Whereas the DNMT3A and DNMT3B are involved in the formation of new methylation patterns during embryogenesis; hence, they are called de novo methylases (Liu et al. 1998). Among all other DNA methylases DNMT3A is crucial for the development of several cancers including gastrointestinal cancer (Li 2002). DNA methylation plays an important role in epigenetic inheritance of DNA. If there are any abnormalities in DNA methylation, that will lead to the development of cancer (Robertson et al. 1999). Abnormal DNA methylation in gastric epithelial cells leads to alter the expression of tumor suppressor genes which are involved in the carcinogenesis (Park et al. 2006).

The cell proliferation and differentiation in gastrointestinal epithelium are controlled by the intracellular factors called cell cycle regulators (Kang et al. 2008). The cell division is negatively controlled by the inhibition of CDK4 (INK4)-CDK4/6 Cyclin D-Rb-E2F pathway (Neureiter et al. 2006). The inactivation of INK4 enhances the formation of active CDK4/6-cyclin D complex, which is involved in cell proliferation. The INK4 family includes P16INK4A, P15 INK4B, and P18 INK4C (Canepa et al. 2007). The risk of developing cancer in gastric intestinal epithelial cells significantly increases with the P16 deregulation (Sherr and Roberts 1995) and Rho A-mediated inactivation of INK4 family members. This leads to the loss of cell cycle regulation particularly at G1-S transition, and it indicates that the INK4 family proteins have a significant role in gastrointestinal epithelial cell proliferation (Sun et al. 2004). In addition to the silencing of INK4 members, RhoA also involves in the development of cancers by inducing promoter hypermethylation (Zhang et al. 2009). DNMT3A induces the gastrointestinal carcinoma by methylating the P18 INK4C gene product and decreases the expression of P18 INK4C; it leads to the dysregulation of G1-S check point. The loss of G1-S regulation leads to unregulated cell proliferation and induces gastrointestinal carcinoma. All these findings are useful for the development of new drugs and therapies to treat gastrointestinal cancer by specifically target DNMT3A.

7.4.3 PTPRCAP Gene

The Protein Tyrosine Phosphatase Receptor Type C Associated Protein (PTPRCAP) also called as CD45-AP is involved in the carcinogenesis by acting as a positive regulator for the protein tyrosine phosphatase. The PTPRC carries signals intracellularly by activating the Src family kinases such as SFK. The protein tyrosine phosphatase activity of PTPRC can dephosphorylate the inhibitory phosphate groups leading to activation of SFK (Takeda et al. 2004). The phosphatase activity of PTPRC is activated by the interaction with PTPRCAP transmembrane domain. The inactivation of SFK is by the phosphorylation of inhibitory tyrosine residues at carboxy terminal (Barraclough et al. 2007). Both the protein tyrosine kinases and phosphatases interact with each other and regulate the signal transduction cascades for cell proliferation (Hyoungseok et al. 2009). The deregulated protein tyrosine phosphatase is involved in the progression of carcinoma (Hunter and Cooper 1985). The diffuse-type gastrointestinal cancer is associated with the polymorphism in the promoter of PTPRCAP gene at the position of −309 (Kirsch et al. 2009); hence, it can be used as genetic susceptible marker for the gastrointestinal cancer. Human epithelial cell carcinomas are characterized by the overproduction of SFK protein (Matsuda et al. 1998).

7.4.4 PSCA Gene

Prostate-Specific Cell Surface Antigen (PSCA) is a glycoprotein made up of 123 amino acids, and the PSCA gene is present on the 8q24.2 chromosome (Sakamoto et al. 2008b). PSCA protein used for the intracellular signal transduction due to the presence of GPI-anchored proteins. The extracellular domain of PSCA has a microdomain which contains high amounts of glycolipids, cholesterol, and lipidate proteins; hence, it exists on the extracellular lipid rafts of the cell membrane (Reiter et al. 1998). The PSCA gene is a tumor suppressor gene, and it is associated with susceptibility of gastrointestinal carcinomas by altering the properties of cell–cell adhesion and proliferation (Sharom and Radeva 2004). Hence, the PSCA gene can be used as genetic susceptible marker for gastrointestinal cancer (Summy and Gallick 2003). The polymorphism in PSCA gene such as rs2294008 makes the gene more expressive; this leads to the carcinogenesis (Hruska et al. 2009). The polymorphism changes the first amino acid of PSCA methionine into threonine; this change leads to the premature termination of the 9 amino acid length truncated PSCA protein (Fu et al. 2012). The down regulation of PSCA enhances the cell growth inhibitory properties in gastrointestinal epithelial cells (Summy and Gallick 2003).

7.4.5 VEGF-A Gene

Vascular endothelial growth factor A (VEGF-A) is the most formidable factor for the neoangiogenesis. Neoangiogenesis is the process of formation of new blood vessels from the pre-existing precursor endothelial cells, and this is the pathological symptom of inflammation, epithelial ulcers, and the carcinogenesis and metastasis (Yancopoulos et al. 2000). VEGF is a secreted protein and it also plays an important role in increasing the permeability of blood vessels (Senger et al. 1983). Carcinogenic tissue is characterized by the high presence of VEGF-A. This high content of VEGF is due to secretion by the cancer cells and also from the fibroblast and inflammatory cells which constitute the stroma of a tumor (Senger et al. 1983).

The elevated levels of VEGF expression in stomach primarily indicated the peptic lesion healing (Fukumura et al. 1998). In addition, high levels of VEGF also indicate the presence of gastrointestinal adenocarcinoma, which is accomplished by the increased intra-tumoral microvessel density (Jones et al. 2001). Furthermore, VEGF overexpression in gastric malignant lesions like chronic atrophic gastritis and intestinal metaplasia suggests that the alterations of VEGF expression may also involve in the process of gastric carcinogenesis (Maeda et al. 1999). The intestinal-type of gastric cancers is mere dependent on the angiogenesis compared to diffuse-type gastric cancer. The levels of VEGF-A and the number of blood vessels are correlated significantly in the gastrointestinal carcinomas (Feng et al. 2000).

A polymorphism in VEGF gene 3′ UTR sequences associated with the elevated VEGF levels in serum (Yamamoto et al. 1998). The 3′ UTR sequences of VEGF involved in the stabilization of m-RNA, and it is also involved in the induction of VEGF in hypoxic condition. Researchers identify the genes named as Hu family; their products bind to the 3′ UTR AU-rich sequences of several m-RNAs including VEGF m-RNA (Renner et al. 2000). The Hu protein to 3′ UTR alters the confirmation of m-RNA and makes it resistant to RNAase attack. These alterations in 3′ UTR leads to VEGF gene polymorphism which affects the respective functions of the gene (Awata et al. 2002). The polymorphism in the VEGF-A 3′ UTR sequence induces m-RNA conformational integrity and causes overexpression of VEGF; finally, it leads to gastrointestinal cancers.

7.4.6 XRCC1 Gene

The X-ray repair cross-complementing group (XRCC) is the major protein involved in the repair mechanisms of DNA. The XRCC1 acts as a scaffolding protein, which directly interacts with the DNA polymerase β, ADP-ribose polymerase (PARP), DNA ligase III and forms a complex which is involved in the base excision repair mechanism (Ramamoorti et al. 2001). Several external and internal mutagens such as ionizing radiations, alkylating agents, deaminating agents, and reactive oxygen radicals cause the DNA damage, and this type of DNA damages are repaired by the

base excision repair mechanism (Caldecott et al. 1996). The XRCC1 protein independently recognizes the nicks or gaps in the damaged DNA and induces the repair mechanism by recruiting DNA polymerase β (Christmann et al. 2003). The DNA repair mechanisms might play a key role in the development of gastrointestinal cancer. Hence, it can be referred as genetic susceptible markers of gastrointestinal cancers. Two different point mutations in the XRCC1 gene conserved sites make the gene polymorphic. The two-point mutations are substitution type. One of the mutations is C to T substitution is located at 194 codon in exon 6 and other mutation is G to A substitution located at 399 in exon 10 which leads to the alteration of amino acids arginine to tryptophan and arginine to glutamine, correspondingly. These alterations induce the carcinogenesis in gastrointestinal track (Butkiewicz et al. 2000). The amino acid alterations change the repair capacity of XRCC1 and increase the chance of DNA damage which leads to carcinogenesis (Marintchev et al. 1999).

7.4.7 IL-1 Gene

Interleukin-1 (IL-1) is involved in the cell proliferation and differentiation by acting as a pro-inflammatory chemokine (Huang et al. 2005). The IL-1 family have three types of interleukins known as IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1RA). IL-1α and IL-1β are synthesized from the various genes but they show functional similarities by binding with the same receptor and elicit same biological responses (England et al. 2014). IL-1 is present in cytoplasm, and it regulates the expression of several genes which are involved in the tumor induction, metastasis, and angiogenesis (Fanjul-Fernández et al. 2010; Rahim et al. 2014; Akdis et al. 2011; Liacini et al. 2002). 1α and IL-1RA have structural homology with both IL-1α and IL-1β, and it binds to the IL-1 receptor type 2 without delivering an activation signal. IL-1 acts as an antagonist to the IL-1α and IL-1β. The binding of IL-1RA induces the molecular reorganization of receptor and acts as an inhibitor for IL-1 (Wei et al. 2015). IL-1RA involves in the down regulation of IL-6 and IL-8 in pancreatic carcinomas (Apte and Voronov 2002) and VEGF in gastrointestinal carcinoma (Matsuo et al. 2004). The polymorphism in the IL-1β and IL-1RN increases the risk of gastrointestinal carcinogenesis. Two linked IL-1β polymorphism such as 511 C>T and 31 T>C induces the overexpression IL-1 h, and it enhances the risk of gastrointestinal carcinoma (Ma et al. 2009).

7.4.8 HER-2 Gene

The Human Epidermal Growth Factor Receptor 2 (HER) is a 185 KDa, transmembrane glycoprotein receptor. The HER-2 acts as proto-oncogene, and it is encoded by gene ERBB2 which is located on 17q11.2-12 chromosome (El-Omar et al. 2000b). The epidermal growth factor receptor family includes four types of proteins. They

are HER-1, HER-2, HER-3, and HER-4. The HER-1 is also called as EGFR, HER-2 and HER-3 are called as ErbB-3, and HER-4 is called as ErbB-4. All the HER family members have a similar molecular and structural organization. HERs are transmembrane proteins that consist of an extracellular ligand binding domain, cytoplasmic domain with tyrosine kinase activity, and a transmembrane domain. The binding of ligands with the extracellular domains induces the signal transduction through the activation of activated mitogen-protein kinase, phosphoinositide-3 kinase, phospholipase-C, protein kinase-C, signal transducers, and transcription factors. The activation of transcription factors involves in the induction of several responses such as proliferation, apoptosis, adhesions, migration, and differentiation (Baselga et al. 1996). The abnormal HER-2 expression induces the cell proliferation and inhibits the apoptosis, which leads to carcinogenesis (Olayioye 2001). This abnormal HER-2 can induce cancers in different types of tissues including breast, kidneys, heart, and gastrointestinal tract (Baselga et al. 1996).

7.4.9 MUC1 Gene

The mucin genes are mainly involved in the protective function of gastric mucosa. There are different subtypes of mucin genes, such as MUC1, MUC2, MUC5AC, MUC6, and trefoil peptide family (Bafna et al. 2010). MUC1 gene product is a 2000 kDa transmembrane glycoprotein which interacts with the bicarbonate ions to protect gastric mucosa by forming mucus-bicarbonate barrier (Wang and El-Bahrawy 2015). During post-translational modifications, the MUC1 peptide is fragmented by self-proteolysis into N-terminal and C-terminal subunit named as MUC1-N and MUC1-C, correspondingly. These two subunits are non-covalently attached to each other and present on the external side of the epithelial cell membrane. The transmembrane MUC1-N has several sites for glycosylation, and it gives protection to the cells non-specifically (Nath and Mukherjee 2014). The MUC1-C has a transmembrane domain and a cytoplasmic domain and it is involved in intracellular signal transduction. The cytoplasmic domain of MUC1-N contains many phosphorylation sites and a single β-catenin binding site. The formation of MUC1-N cytoplasmic tail and β-catenin complex is induced by the phosphorylation of Thr residues in the TDRSPYEKV sequence of cytoplasmic tail, and it leads to the activation of cell cycle regulating gene p53 by nuclear localization of the complex (Sandra 2001). Several studies demonstrate that the expression of MUC1 is significantly increasing with prognosis of cancer. Hence, MUC1 is considered as an oncoprotein, and it can be used as a genetic susceptible marker for the gastrointestinal carcinomas.

7.5 Conclusions and Future Perspectives

Gastrointestinal carcinoma is a complex disease that is caused by the combined effect of environmental factors, host affiliated factors, genetic and biological heterogenicity. The lifestyle and dietary habits of individuals, associated with genetic susceptibility and molecular changes developed throughout the lifetime, are the basis for the carcinogenesis of GC. Abundant research has been accomplished to find molecular markers for GC. Understanding the consequences of these mutations in susceptibility is attaining importance in cancer research to develop new therapeutic and preventive measures. Furthermore, the molecular pathways are required to know the causes of GC and make a possibility to achieve the best clinical methods to assure an accurate diagnosis and effective treatment. Attaining a comprehensive molecular understanding of the several genomic abnormalities related to GC will be crucial to enhance the results of patients. Recent research has seen significant improvement in decoding the genetic information of GC by finding novel molecular mechanisms involved in cellular pathways that are associated with gastrointestinal carcinoma and development. The identification and analysis of GC susceptibility risk factors give an effective approach for the prevention and decrease the occurrence GC in the future. The prevention and the development of new therapeutics for GC are possible by a systematic unveiling of novel molecular pathways involved in GC carcinogenesis, and it is the vital program in medical research to overcome the socioeconomic burden of cancer deaths.

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