Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

# Gastric Cancer: Gene and Gene Therapy Beyond

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**ARTICLE INFO**

**Article type**
Review article

**Article history**
Received: 23 May 2018
Revised: 22 Jul 2018
Accepted: 10 Nov 2018

**Keywords**
Gastric Cancer
Gene Therapy
Risk Factors

**ABSTRACT**

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer deaths across the world. The prevalence of GC varies in different countries and even in various regions of the same country. GC is often sporadic, and the familial type occurs in approximately 10% of the cases. The main risk factors for GC include age, family history, Helicobacter pylori infection, smoking habits, and genetic factors. One of the important altered genes in GC is p53, which is the most frequently mutated gene in this cancer type. P53 is involved in the cell cycle arrest and cell apoptosis. Moreover, it is considered to be the cellular gatekeeper for cell growth and division and it is referred as the 'guardian of genome'. Another important gene involved in GC is CDH1, which encodes the epithelial cadherin (E-cadherin) protein. E-cadherin is considered to be the main cause of familial GC. Cadherin is a type of cell adhesion molecule, which represents calcium-dependent adhesion and plays a pivotal role in maintaining adherent junctions in the areas of epithelial cell-cell contact. Furthermore, it is suspected to be a tumor suppressor gene for GC. Gene therapy has been increasingly performed on various GC cell lines, including SGC7901 and animal models, some of which will be reviewed in the present study.

Please cite this paper as:
Iravani F, Iravani R, Mojarad M. Gastric Cancer: Gene and Gene Therapy Beyond. Rev Clin Med. 2018;5(4):132-134.

## Introduction

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer deaths across the world (1,2). The incidenceof GC varies in different countries even in various regions of the same country (3). Each year, one million patients are diagnosed with GC, and the annual mortality rate has been estimated at 700,000 cases. The main cause of the high mortality rate is diagnosis at the advanced stage and delayed diagnosis (4).

Researchers have classified GC in to four main subtypes based on the molecular alterations. The most common type of GC with the highest prevalence is the diffuse subtype, which has the worst prognosis. It occurs at younger ages and accounts for 63% of all the GC cases. The second subtype, which constitutes 22% of the GC subtypes, involves microsatellite-unstable tumors. This subtype is often observed in the individuals with microsatellite instability and hyper-mutation intestinal subtype that has the best prognosis. The two other subtypes are recognized based on the mutation or lack of mutation of the p53 gene. Since p53 is the most frequently mutated gene in GC, the status of TP53 activation is considered to be the basis of these two subtypes. These patients have been shown to have a moderate prognosis since the prognosis of TP53-active group is better

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than the two other subtypes (5).

Surgery remains the only treatment option for GC and plays a key role in the management of this cancer type. During the surgical procedure of the patient, adjuvant chemotherapy, including chemoradiation, could improve the outcome of GC. Liver metastasis is one of the main challenges in the treatment of GC. Undoubtedly, GC with lymphovascular vessel metastasis is indicative of a highly aggressive biology. Therefore, liver-only deposits is an uncommon event, and higher survival rate is feasible only by invasive treatment (6).

## Literature Review

### *Risk Factors for GC and Genetic Beyond*

Similar to other cancers, GC is a multifactorial disease that is caused by genetic susceptibility and environmental factors. The environmental risk factors for developing GC include diets; high in salt and low in fruits and vegetables, increased age, family history of GC, Helicobacter pylori infection, and smoking habits. The other important factors that may be associated with the significant reduction or increase in the risk of GC are genetic factors, and genetic susceptibility plays a crucial role in the pathogenesis of GC (7,8).

Various mutant genes have been reported to increase the risk of GC, such as MCC (mutated in colorectal cancers, ); maps to 5q22.2,candidate tumor suppressor genes, Wnt signaling pathway regulator, APC gene (Adenomatous Polyposis Coli); a kind of tumor suppressor gene (9,10). Furthermore, epithelial cadherin (E-cadherin), also known as CDH1, is considered to be the major cause of the familial GC gene. Approximately 40% of the hereditary cases with the diffuse subtype of GC families have germline mutations in this gene,which is located on the long (q) arm of chromosome16 in band q22.1 (16q22.2) and is known as the calcium-dependent adhesion molecule (11). It is a type of cell adhesion molecule that encodes a calcium-dependent cell and cell adhesion glycoprotein, playing a key role in maintaining the adherent junctions in the areas of epithelial cell-cell contact (12). The mutation that leads to the loss of CDH1 function contributes to cancer progression through increasing proliferation, invasion, and/or metastasis (13).

The molecular dissection of gastric carcinoma has revealed the involvement of numerous other genetic alterations (14), and p53 is mutated in approximately 60% of GCs (15). P53 is one of the most frequent tumor suppressor genes that is altered in GCs in addition to SMAD4 or CDH1 (13). The mutation of p53 is not only associated with gastric cancer, but also altered in the expression of this gene has been reported in human GCs, and researchers have stated that GC with the overexpression of p53 has a high potential for metastasis to lymph nodes (16).

### *Gene Therapy for GC*

Gene therapy is a novel therapeutic approach to become the alternative choice for the successful treatment of any diseases with complicated treatment (e.g., cancers). Despite the similarity of Gastric cancer to other cancer types and the advancement in the current treatment modalities, the clinical outcomeof GC remains discouraging (17), leading to poor prognosis with an estimated five-year survival rate of lower than 20% (15). Since the basic molecular alterations in cancers involve the extreme activity of oncogenes or inactivation of tumor suppressor genes, gene therapy involves the reintroduction of wild-type tumor suppressor function to the cells lacking the function of that gene. Another strategy in this regard is to silence oncogenes (18) for the augmentation of the tumor response to chemotherapy or radiotherapy, conferring resistance to the toxic effects of such treatments (19).

In a study, Yuan-Gen Fuet al. (2003) introduced caspases-3, which plays a key role in cell apoptosis, to GC cell line SGC7901 by the eukaryotic expression vector pcDNA/Rev-caspase-3. After performing antisense therapies in the mentioned studies, the authors concluded that gene therapy using this vector could significantly induce the apoptosis of gastric cancer cell line SGC7901, which may become a potential approach to gastric cancer gene therapy (20). Consistently, Shi-Ying Zheng (2005) induced apoptosis on SGC-7901 cells by infecting Ad-FasL (a member of the tumor necrosis factor), reporting a significant reduction in cell growth and colony-forming activity compared to the control adenovirus-infected cells. In addition, they observed the retardation in the growth of SGC-7901 xenografts in nude mice after intra-tumoral injection with Ad-FasL, and the researcher suggested that this target gene might have the potential value in genetic treatment for gastric cancer (21).

In this regard, Zhang J et al. (2009) conducted a research regarding gene therapy for GC through constructing a short-hairpin RNA (shRNA) adenovirus vector, which was the antisense of Akt1 (protein kinas B1, PKB1/Akt1) and cyclooxygenase-2 (COX-2) then transfected into the SGC-7901 cell line. Following that, the tumor volume in the treatment group was reported to be less than the controls, and the difference was considered statistically significant. Finally, the researcher concluded that Akt1 and COX-2 shRNA could suppress the growth of SGC-7901, providing a new strategy for

GC gene therapy (22).

In another study, Hui Zhang et al. (2015) investigated the effects of Twist gene silencing on the both mRNA and protein levels of human malignant gastric SGC7901 cells. According to the findings, testing this strategy led to cell cycle arrest at the G0/G1 phase, apoptosis, proliferation suppression, and reduced ability of cell invasion and migration (23). Several other studies have also proposed similar results through gene silencing or introducing other tumor suppressor genes, while they are still in the early phases of treatment.

## Conclusion

According to the results, the number of ongoing or completed clinical trials regarding gene therapy reached 1,274 from 1996 until 2014, and 63.8% of these studies have been focused on human cancers (24). However, further investigations are still required in order to determine the most effective methods to approve a curative and proper medication for GC.

## Acknowledgements

None.

## Conflict of Interest

The authors declare no conflict of interest.

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