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Mini review

# Alcohol-induced Gastric Inflammation

Shubham Singh, Supraj Raja Sangam, Venkateswara Rao Joginapalli, Senthilkumar Rajagopal\*

**Affiliation:**

Department of Zoology, Nizam College, Hyderabad, Telangana, India

**The name of the department(s) and institution(s) to which the work should be attributed:**

Department of Zoology, Nizam College, Hyderabad, Telangana, India

**Address reprint requests to**

**\*Dr. Senthilkumar Rajagopal.**

Department of Zoology, Nizam College, Hyderabad, Telangana, INDIA or at senthilanal@yahoo.com

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**ABSTRACT:** Accumulating evidence suggests that gastrointestinal systems (GI) is more vulnerable to the oxidative stress, exposure to Reactive oxygen species (ROS) and is a prospective diseases like

fatty liver, cirrhosis, diarrhea, vomiting, and inflammatory bowel diseases (IBD). GI tract plays a particularly important role in the alcohol metabolism and absorption among the many other organ systems in the body. Alcohol/acetaldehyde is an oxidative stress inducer on gastric epithelial cells. Alcohol-induced damage to the mucosal lining of the stomach also increases the risk of gastric inflammation and gastric cancer. Moreover, increasing evidences suggests that investigating the important genes involving the gastric cancer are very intrigue. This article communicates the molecular aspects of gastritis and gastric cancer.

**KEYWORDS:** Alcohol, glycine; gut microbiota; inflammatory bowl diseases; reactive oxygen species.

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## INTRODUCTION

An approximately 500-1000 very complex micro-biota are present in human gastrointestinal (GI) tract<sup>1</sup>. The endogenous GI micro biota plays a fundamentally vital role in health and disease, yet this ecosystem remains to be completely elucidated<sup>2</sup>. The significant tasks of the commensal micro biota include protection against irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), gastric cancer, and mucosal damage, regulation of host fat storage, and stimulation of intestinal angiogenesis<sup>3-4</sup>. After consumption, the alcohol first passes through the various parts of the GI tract. In addition, alcohol may interfere with the structure as well as the function of GI-tract segments. The heartburn may occur after the alcohol consumption because of muscle malfunctioning which is separating the esophagus from the stomach. The gastric acid secretion and surrounding muscles of stomach activities are regulated by alcohol<sup>5</sup>. Similarly, diarrhea can frequently observed in alcoholics and this may due to an impaired muscle movement in

the small and large intestines. Moreover, alcohol inhibits the absorption of nutrients in the small intestine and increases the transport of toxins across the intestinal walls, effects that may contribute to the development of alcohol-related damage to the liver and other organs<sup>6</sup>.

All parts of the GI tract are interfered by alcohol. Acute alcohol ingestion induces changes in the motility of the esophagus and stomach that favor gastro esophageal reflux and, probably, the development of reflux esophagitis<sup>7</sup>. The gastric mucosa damage can occur because of alcohol abuse, including hemorrhagic lesions. The reactive oxygen species (ROS) targets the gastric mucosal proteins that are rich in sulfhydryl groups and its lead to protein de-naturation or enzyme inactivation and receptor damage or modification of the cell membrane, thus contributing to mucosal injury<sup>8</sup>.

The high alcohol content does not have any action on gastric acid secretion, but low alcohol content stimulate gastric acid secretion. Alcohol inhibits

the absorption of numerous nutrients in the small intestine<sup>9</sup>. The significant of these motility disorders for the development of nutritional disturbances in alcoholics, however, is unclear. The other digestive disorders for alcohol abuse (e.g., advanced liver disease or impaired pancreatic function); impaired digestion likely is more consequences. The mucosa in the upper region of the small intestine also damage by acute alcohol consumption and may even lead to the destruction of the tips of the villi<sup>10</sup>. This damage also leads to increase the mucosa's permeability, facilitating the transport of large molecules, such as bacterial endotoxin and/or other toxins, into the blood or lymph<sup>11</sup>.

This results in the release of potentially toxic cytokines by certain white blood cells and Kupffer cells. The release of toxic cytokines exerts multiple injurious effects on membranes and the microcirculation<sup>11</sup>. The result is possible cell damage and even cell death in the liver and other organs<sup>12-13</sup>. In addition, the results of recent epidemiological studies indicate an association between alcohol consumption and the development of gastric and other gastrointestinal cancer<sup>14-15</sup>. The hallmarks of the gastric inflammation are the surface epithelial degeneration and infiltration of the gastric mucosa by acute and chronic inflammatory cells. Gastric inflammation in severe cases may lead to the gastric cancer<sup>16-17</sup>. Gastritis in the corpus (corpus predominant and type A gastritis) and in the antrum (antrum predominant or type B gastritis) behave differently i.e. type A gastritis is more related to gastric carcinoma and type B gastritis is more related to ulcer disease. Pan-gastritis results from antrum-predominant chronic gastritis and it may also progresses to atrophic gastritis<sup>18</sup>. The hunt regarding key aspects of the pathogenesis of gastric cancer at a cellular level in order to identify novel biomarkers is on. The progression and recurrence of the gastric cancer can be easily monitored by these novel biomarkers leading to early detection of the disease. The thorough understanding of the pathogenesis of the gastric cancer will provide us potential therapeutic targets<sup>19</sup>.

#### PROPHYLAXIS OF THE ALCOHOL-INDUCED GASTRIC INJURY

Walaa reported that pre-treatment with *P. macrocarpa* fruit extract has protective effects against ethanol-induced gastric ulcers in rats by significantly stimulating inflammatory mediators PGE<sub>2</sub>, TGF- 1 and reducing TNF- which effect in the

increase production of mucus and stomach pH to provide a protective environment against the offensive factors<sup>20</sup>. Thalidomide<sup>21</sup> and Resistance Starch<sup>22</sup> have been shown to have protective effect against alcohol-induced mucosal damage by down-regulating genes like inducible nitric oxide synthase (iNOS), cytochrome oxidase-2 (COX2), Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), Interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-6, etc..  $\alpha$ -lipoic acid has been reported to enhance the healing of gastric ulcers by its radical scavenging and anti-apoptotic activity<sup>23</sup>. In contrast, the recent report stated that the oral pretreatment of menthol displayed a gastro protective activity against ethanol-induced gastric inflammation<sup>24</sup>.

#### GENES FREQUENTLY MUTATED IN GASTRIC CANCER

Acetaldehyde the metabolic product of the alcohol is found to be the carcinogenic agent. In human cells, it may cause sister chromatid exchanges and chromosomal aberrations. The acetaldehyde forms DNA-adducts like N<sub>2</sub>-ethyl-2'-deoxyguanosine (which is increased in the DNA from the WBC from the alcoholic abusers) and 1, N<sub>2</sub>-propano-2'-deoxyguanosine (responsible for the genotoxic and mutagenic effects of crotonaldehyde)<sup>25</sup>.

The genes frequently mutated in the gastric cancer are APC, BRAF, CDKN2A, CTNNB1, ERBB2, HRAS, KRAS, NRAS, PGDFRA, REGIV, COL1A1, CDH17, APOC1, COL1A2, YF13H12, CEACAM6, APOE, REGIV, FUS, S100A11 and p53. The mutations at downstream of the RTKs, KRAS has been found to be associated with about 9-15% of gastric carcinoma cases<sup>26,27</sup>. CDH17 is a candidate marker gene for tumor progression<sup>28</sup>. CDH1 is a marker of an epithelial phenotype and is often lost in gastric tumors due to the process of epithelial to mesenchymal transformation (EMT) and is a negative prognostic marker<sup>29</sup>. Thyrotropin receptor (TSHR) has been shown to be lost at the DNA level, in some gastric cancers<sup>30</sup>.

#### GENES REGULATES THE GASTRIC FUNCTION

1.ADENOMATOUS POLYPOSIS COLI (APC): encodes protein Adenomatous polyposis coli which is a negative regulator for the  $\beta$ -catenin concentrations. APC interacts with E-cadherin which is involved in the cell adhesion. Mutations in APC gene may lead to the gastric cancer<sup>31</sup>. APC mutation is involved in carcinogenesis of intestinal type of gastric cancer and is independent of microsatellite instability (MSI) phenotype but related to the loss of heterozygosity (LOH) pathway in gastric cancer<sup>32</sup>. The inactivation of

APC plays a role in development of some gastric cancers, particularly very well differentiated adenocarcinomas and signet-ring cell carcinomas<sup>33</sup>.

2. B-Raf (*BRAF*) gene makes B-Raf protein which is involved in the intracellular signalling for the cell growth. Drugs to treat *BRAF* mutations have been developed including vemurafenib and dabrafenib. The frequency of *BRAF* mutations in gastric cancer is reported to be 5%<sup>34</sup>. Seven *BRAF* mutations in 319 primary stomach cancers were reported. Despite the low frequency of *BRAF* mutation in stomach cancer compared with that of malignant melanoma, the experimental data suggest that alteration of RAS-RAF kinase pathway by *BRAF* mutation together with RAS mutation may play an important role in gastric carcinogenesis<sup>35</sup>.

3. CDKN2A: CDKN2A gene encodes cyclin-dependent kinase inhibitor 2A (also called p16) – a tumour suppressor protein. CDKN2A promoter methylation is found to be associated with gastric carcinogenesis but only about 30% of gastric cancer cases were found to be methylated. CDKN2A methylation may be specific to a subset of gastric cancer and probably plays a significant role in the beginning of intestinal-type gastric cancer<sup>36</sup>. The expression loss of P16 protein related to the gastric carcinogenesis, gastric carcinoma. The mutation of p16 gene in *exon 2* is not involved in gastric carcinogenesis. But the deletion of p16 gene in *exon 2* might be involved in gastric carcinogenesis<sup>37</sup>.

4. REGIV: It is frequently overexpressed in Gastric carcinoma and restriction to its expression is narrow in noncancerous tissue. In addition, the amino acid sequence of the REGIV protein seems to be secretive protein from its amino acid sequence. The over-expression of the REGIV was reported in Gastric carcinoma by Naohide et al.<sup>28</sup>

## CONCLUSION

In conclusion, more studies have to be done in the genes are involved in humans on diseases where free radicals, pro-inflammatory cytokines, inflammation are formed. The underlying mechanisms are not totally clear. Several mechanisms have been proposed and genes that are regulates the gastric cancer can be investigated.

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