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Mini-review

Physical and chemical insults induce inflammation and gastrointestinal cancers

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ABSTRACT

Chronic inflammation associated with viral and bacterial infections of the gastrointestinal tract (GI) and liver renders these organs susceptible to tumour development. There is also a growing body of evidence demonstrating that chemical and physical insults promote GI cancers by inducing inflammation. For example, excessive alcohol consumption and tobacco smoking induces inflammation and gastrointestinal carcinogenesis. Likewise, drinking hot beverages and intentional or accidental exposure to toxic substances leads to inflammation and GI cancer formation. However, further work needs to be undertaken using animal models to separate the direct carcinogenic effects of physical and chemical insults from the indirect effects of these insults to promote tumor formation through tissue inflammation.

1. Introduction

The initial evidence linking inflammation with cancer was reported in the 19th century by Rudolf Virchow who noted leukocytes in tumour tissue and identified tumour development at the site of chronic inflammation [1]. It is now well recognised that a range of solid tumours including tumours of the GI tract and liver have inflammatory cell components [2]. The link between both GI and liver cancers with inflammation appears to be causal, and inflammation-mediated oncogenesis is a well established paradigm [2]. For example, chronic inflammatory diseases including gastritis, esophagitis, pancreatitis and hepatitis are well-recognised risk factors for cancer development [3,4].

Chronic inflammation can mediate tumour initiation by creating genomic instability leading to mutagenesis [5,6]. The GI tract in particular is also susceptible to various physical and chemical insults, such as hot beverages, tobacco smoking, excessive alcohol consumption, and intentional or accidental intake of toxic agents. Long-term exposure to these agents may lead to chronic inflammation of the GI tract and the subsequent development of tumours [7–11]. Other chemical and physical stresses such as acid, UV exposure and excessive manual labour have also been linked with inflammation and GI cancer formation [12–14]. The physical and chemical insults for each cancer type are described in more detail in the proceeding sections.

2. General mechanisms for inflammation-induced cancer

A schematic representation of how inflammation links to cancer in the GI tract is presented in Fig. 1. Chronic inflammation triggers the production of chemokines, growth factors, reactive oxygen species (ROS) and reactive nitrogen species (RNS) [2,4,15]. These mediators activate inflammatory pathways in GI cells including COX-2, NF-κB, STAT3 and iNOS [6,15,16]. Activation subsequently promotes tumour initiation by increasing cell cycling, inhibiting tumour suppressor pathways and activating oncogenes [6,15,16]. Once tumours are established, inflammation promotes tumour progression by inhibiting apoptosis, promoting cell proliferation and angiogenesis, modulating cellular adhesion and promoting metastasis [2,5]. To date, numerous studies have linked chronic inflammation with the development of a range of solid tumours including those derived from the esophagus, stomach, gallbladder, pancreas, colon and liver [3,16–21]. There are also a large number of mouse models which demonstrate the direct involvement of chronic inflammation in the development of GI cancers [22]. For example, knockout mice for the αi2 subunit of heterotrimeric G protein (Gαi2) have defective T-cell maturation and function resulting in chronic colonic inflammation (colitis) and the development of colorectal cancer [23–25].

3. Chemical and physical insults inducing chronic inflammation and gastrointestinal cancer

3.1. Esophageal cancer

Tobacco smoking and alcohol consumption induce chronic inflammation in the esophagus and are believed to be the major

Abbreviations: GI, gastrointestinal; RNS, reactive nitrogen species; ROS, reactive oxygen species; HCC, hepatocellular carcinoma; DSS, dextran sulphate sodium; IBD, inflammatory bowel disease; TNBS, 2,4,6-trinitrobenzene sulphonic acid; DNBS, dinitrobenzene sulphonic acid; Gαi2, αi2 subunit of heterotrimeric G protein.

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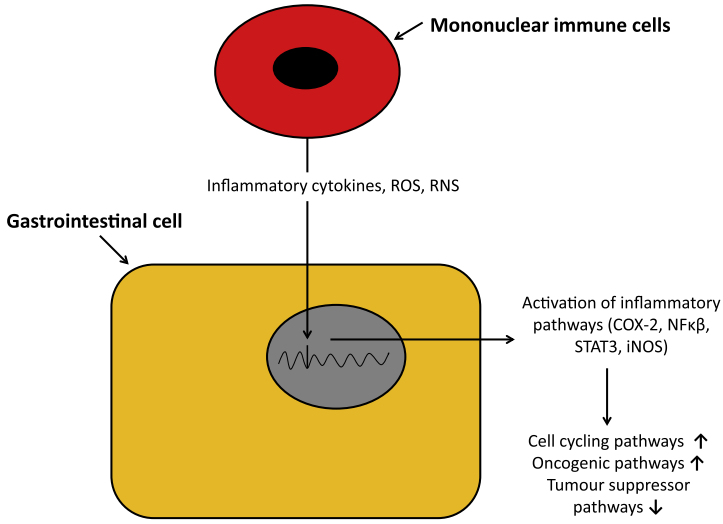

Fig. 1. Schematic illustration of the link between inflammation and cancers of the gastrointestinal tract.

risk factors for developing esophageal cancer (see Table 1) [26–29]. Both alcohol and tobacco smoking are independent risk factors for esophageal cancer, however, when both factors are combined, the risk of cancer is compounded. For example, a meta-analysis of 5 hospital based studies of 2609 participants showed that moderate tobacco smoking or moderate drinking alone was not associated with an increase in esophageal cancer risk. However, when participants were both heavy drinkers and smokers, the risk of esophageal cancer was increased 12- and 19-fold in men and women respectively [26]. People who drink mate (an infusion of the herb *Ilex paraguayensis*) and cachaea (a sugar cane spirit) also have an increased risk of esophageal cancer (see Table 1) [12,14]. Likewise, polycyclic aromatic hydrocarbons may increase the risk as shown in studies from North Eastern Iran where the levels of aromatic hydrocarbons in the urine of 99 participants mirrored the incidence of esophageal squamous cell carcinoma [30].

Heat is a physical insult that is a recognised risk factor for esophageal cancer. In high risk area areas of South America, drinking hot beverages significantly increased the risk of esophageal cancer with a relative risk ratio of 2.07 (see Table 1) [12]. Similarly in high risk esophageal cancer regions of Iran, more than 50% of people drink their tea at temperatures of 60 °C or higher [31]. In Japan and China, boiled rice gruels are regularly consumed at high temperatures in high risk esophageal cancer regions [32].

Physical irritation of the esophagus is a major risk factor for esophageal cancer. In the Caspian littoral region of Iran were there is a high prevalence of esophageal cancer, bread is the main staple food and people in this region eat their food 3–4 times faster [31,33]. Eating a large hard-to-digest portion of bread creates a larger and more abrasive bolus inflicting physical damage on the esophagus and increasing the risk of cancer [31,33]. In China and Iran, fine particles have also been found in the esophagus of people who live in these high risk regions [34]. Thus, physical and chemical insults can promote esophageal cancer by inducing chronic inflammation.

3.2. Gastric cancer

Studies in the US and Russia have shown that tobacco smoking increases the risk of developing gastric cancer (see Table 2) [29,35] by inducing chronic inflammation [8,11]. Nicotine, the major toxic component in cigarettes induces chronic gastritis and epithelial damage thereby stimulating the proliferative potential of the gastric epithelium and favouring malignant transformation [3].

Table 1
Chemical and physical insults that increase the risk of esophageal cancer.

Number of participants	Risk type	Risk factor	Region	Relative risk	References
476,606	Chemical	Tobacco smoking	US	9.27	[29]
2609			Not specified	5.1 (men) 3.1 (women)	[26]
476,606			US	4.04	[29]
Not specified			Not specified	2.5	[57]
2454			Shanghai, China	2.1 (men) 1.6 (women)	[28]
474,606		Alcohol	US	4.93	[29]
120,852			Netherlands	4.61	[85]
7239			Not specified	4.2	[86]
2609			Not specified	4.4 (men) 2.2 (women)	[26]
2454			Shanghai, China	1.4 (men)	[28]
513		Cachaea	South eastern South America	1.83	[14]
2609		Mate' drinking	South America	1.47	[26]
513			South eastern South America	1.47	[14]
99		Polycyclic aromatic hydrocarbons	North Eastern Iran	Not specified	[30]
2609	Physical	Hot beverages	South America	2.07	[12]