Cancer Letters 345 (2014) 242–248

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Chronic inflammation and gallbladder cancer

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ARTICLE INFO

Keywords:
Gallbladder cancer
Chronic inflammation
Aetiology
Pathogenesis

ABSTRACT

Gallbladder cancer (GBC) is the most common biliary tract malignancy with an extremely poor prognosis. Epidemiological data have demonstrated that chronic inflammation resulting from infection of gallbladder or gallstones predispose individuals to GBC. Recent studies have begun to elucidate molecular mechanisms underlying the development of GBC in the setting of chronic inflammation. It is possible that persistently local inflammatory reactions may contribute to the development and progression of GBC through inducing genetic alterations, and subsequent promoting survival and proliferation of mutated sells, inhibiting apoptosis, stimulating angiogenesis and metastasis. This article reviews the current understanding of the involvement of chronic inflammation in gallbladder tumorigenesis.

1. Introduction

Gallbladder cancer (GBC), first described by Maximillian de Stoll in 1777, is the most frequent malignancy of the biliary tract and the fifth most common gastrointestinal cancer worldwide [1]. There is a marked geographic variability in the incidence of GBC. Chile was found to have the highest incidence of GBC among men (12.3 per 100,000) and women (27.3 per 100,000) [2]. By contrast, its incidence in the USA is 0.82 per 100,000 for men and 1.45 for women [3]. Also, there are large racial and ethnic differences in incidence. In the USA, white men and women had significantly lower age-adjusted incidence rates of GBC compared to other racial-ethnic groups, with the highest rates in Hispanics and American Indian-Alaska Natives [3]. GBC has a peak incidence in the sixth and seventh decades of life and women are affected two to six times more often than men [4]. Generally, prognosis of GBC is extremely poor, with a 5-year survival rate of 5–10% and a median survival of only 3–6 months from the time of diagnosis in most countries [5–7]. Radical surgery was considered to offer some patients the only chance at long-term survival. Unfortunately, symptoms and signs of GBC at an early stage are vague and nonspecific; most patients are diagnosed at an advanced stage when the tumor is irresectable or metastatic [7,8]. The etiology of GBC is complex and multifactorial. Apart from age, gender, race and geographic distribution, a number of risk factors are associated with the development of GBC, such as cholelithiasis [9], obesity [10], multiparity [11], smoking [12], chronic infections of gallbladder [13], environmental exposure to specific chemicals [14], and anomalous pancreaticobiliary duct junction [15]. However, the accurate pathogenesis of GBC remains unclear.

Recently, inflammation was identified as the seventh hallmark of cancer [16]. The link between inflammation and tumorigenesis was first postulated by Virchow in the 19th century, based on the presence of leukocytes in neoplastic tissues [17]. From then on, increasing evidence demonstrated that many cancers originate from sites of chronic inflammation, which supports the view that chronic inflammation can predispose individuals to cancer. It has been suggested that at least 15% of malignancies worldwide can be attributed to chronic infections, a total of 1.2 million cases per year [18]. Moreover, up to 25% of all cancers were related to chronic inflammation irrespective of the presence or absence of infection [19]. Therefore, chronic inflammation is currently thought to be a key underlying cause for the development of many cancers. With respect to GBC, data showed that approximately 50% patients have a history suggestive of chronic cholecystitis [20,21]. The chronic inflammation of the gallbladder is triggered by a variety of factors which can be of an infectious or non-infectious nature. In addition, in a population-based study conducted in Shanghai, China, usage of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, was associated with a significant 63% reduction in the risk of GBC [22]. Therefore, chronic inflammation is probably the most common causative factor for GBC.

2. Chronic inflammation conditions

2.1. Bacterial Infections

Since the discovery that *Helicobacter pylori* (*H. pylori*) infection was associated with an increased risk of gastric adenocarcinoma,

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0304-3835/$ - see front matter © 2013 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.canlet.2013.08.034

other chronic bacterial infections are now considered to potentially have a direct role in carcinogenesis. It is becoming clear that bacteria and their products as well as resultantly chronic inflammatory reactions contribute to tumor initiation and progression in different ways. A multitude of bacteria have been identified in the gallbladders by culture or by polymerase chain reaction (PCR) of patients with cholecystitis and cholelithiasis, however, current literature suggest that only *Salmonella* Typhi (*S.* Typhi) and *Helicobacter* species might be important etiological factors for GBC [23].

The epidemiological evidence indicates a definite association between *S.* Typhi and GBC. About 3–5% of patients with acute *S.* Typhi infection become chronic carriers as the bacteria are known to persist in the biliary system, which can result in chronic infection of the gallbladder [24]. A case-control study concerning the relation between the typhoid-carrier state and maligalancies of hepatobiliary tract demonstrated that deaths due to hepatobiliary cancer were six times more often in chronic typhoid carriers than in the matched controls [13]. Consistent with the finding, a cohort study analyzing the 1964 typhoid outbreak in Aberdeen displayed that chronic typhoid carriers have an approximately 200-fold excess risk of developing hepatobiliary cancer compared with people who experienced acute typhoid and were non-carriers, and within the hepatobiliary system the main risk appears to be in the gallbladder [25,26]. Nath et al. [27] demonstrated the culture positive rate of *S.* Typhi and *S.* paratyphi-A from gallbladder bile in GBC was significantly higher than that in cholelithiasis and control groups. In the northern part of India, a significantly high Vi serology positivity was observed in patients with GBC compared to controls and patients with cholelithiasis [28]. Recently, several lines of evidence further confirmed the positive linkage between chronic typhoid carriage and GBC using nested-PCR due to its excellent sensitivity and specificity [29,30]. Collectively, these data implicate the typhoid carrier state as the crucial predisposing factor for the development of GBC.

There are several *Helicobacter* species that are known to colonize the hepatobiliary tract in humans and animals which usually result in chronic inflammation [31,32]. Several PCR-based studies showed that *Helicobacter* species was identified in resected gallbladder tissue and bile collected from patients with cholecystitis or cholelithiasis [31,33]. More importantly, a study conducted in Japanese and Thai populations revealed that the incidence of *H. bilis* in GBC patients was significantly higher than in patients with gallstones and cholecystitis [34]. Similarly, Murata et al. [35] reported that *H. bilis* infection rate was 2–3 times higher in cases with biliary tract cancer than in those without. *H. bilis* infection could activate transcript factors such as nuclear factor-kappa B in human bile duct cancer cells, thereby stimulating production of vascular endothelial growth factor (VEGF) and leading to enhancement of angiogenesis [36]. *H. pylori*, classified as a class I carcinogen by the World Health Organization, is a well-established cause of gastric cancer and recently proved to be responsible for GBC. The presence of *H. pylori* in the bile was 9.9 times more frequent in patients with biliary tract carcinoma compared with patients in the control group [37]. Boonyanugomol et al. [38] demonstrated that in patients with cholangiocarcinoma, the gallbladder mucosa exhibited a significantly higher inflammatory grade and cell proliferative index in the *H. pylori*-PCR-positive samples compared with the negative ones. A similar linkage was found between *H. hepaticus* and GBC [39,40]. However, other several studies failed to demonstrate any increase in risk of GBC in presence of *H. bilis* [41] or *H. pylori* [42]. The disparities of the above findings may be partly due to small sample sizes and various detecting methods that have different sensitivity and specificity. Therefore, although epidemiological and experimental studies suggest a possible role of *Helicobacter* species in the development of GBC, further research, especially multicenter prospective studies using more standardized protocols for detecting *Helicobacter* species in biliary system, should be conducted to clarify whether these bacteria are capable of causing the formation of GBC.

2.2. Noninfectious factors

Although it has been proposed that various etiopathological agents may be associated with the development of GBC, the primary risk factor of GBC as reported in all studies is the presence of gallstones. Indeed, gallstones are present in 75–90% of patients with GBC [43,44]. In an autopsy study from Chile, the researchers reported that the incidence of GBC is seven times higher in patients with gallstones than in those without [45]. Furthermore, the risk of developing GBC seems to correlate with size, volume and weight, and number of the gallstones. For patients with stone diameters of 2.0–2.9 cm, the odds ratio (versus stone size less than 1 cm) is 2.4, whereas for stones 3 cm or larger, the ratio is 10.1 [46]. Similar figures were found in another report from 1676 subjects that large stones (>3 cm) are found in 40% of the patients with GBC and the relative risk for GBC in subjects with stones $\geqslant$3 cm is 9.2 compared with subjects with stones <1 cm [47]. However, the mechanism by which cholelithiasis predisposes to GBC has yet to be established. It is postulated that the repeated physical trauma or irritation caused by the long term presence of stones to the gallbladder mucosa leads to a state of chronic inflammation [9]. The chronic inflammation combined with bacterial infections could promote epithelial hyperplasia, dysplasia and ultimately progressin to carcinoma. For example, Albores-Saavedra et al. [48] reported that in gallbladder specimens excised for cholelithiasis or cholecystitis, 83% exhibited epithelial hyperplasia, 13.5% atypical hyperplasia and 3.5% *in situ* carcinoma, suggesting cholelithiasis and cholecystitis could produce a series of epithelial pathologic changes. Mathur et al. [49] demonstrated that the average volume and weight of the stone progressively increase from cholecystitis, hyperplasia, metaplasia to carcinoma in cholecystectomy specimens with gallstones. Therefore, cholelithiasis is a well-established risk factor for GBC although only 1–3% of patients with gallstones develop GBC [4].

3. General mechanisms of inflammation-associated neoplasia and progression

It has been proposed that chronic inflammation increases the risk of cancer and plays an important role in tumor initiation, progression and the metastatic process. However, the general mechanism by which chronic inflammation affects the development of human cancer including GBC still has not been fully elucidated. Acute inflammation is a self-limiting process as pro-inflammatory and anti-inflammatory cytokines are induced in a tightly regulated sequence. Chronic inflammation, by contrast, may be associated with persistence of low-grade initiating agents or failure to completely resolve an acute inflammatory response [50]. The cancer-associated inflammation is characterized by the presence of host leukocytes, primarily macrophages, and inflammatory mediators in the local microenvironment.

During chronic inflammation, a variety of inflammatory mediators, such as cytokines, chemokines, reactive oxygen species, prostaglandins (PGs) and growth factors, could induce genetic and epigenetic alteration in oncogenes and/or tumor suppressor genes, DNA methylation and post-translational modifications [51]. It has been reported that the rate of mutation is much higher in the inflamed microenvironment than in normal tissues, with a mutation frequency of 4×10^{-8} and $< 1 \times 10^{-8}$ per base pair, respectively [16]. On the other hand, activation of oncogenes and/or inactivation of tumor suppressor genes affect the expression of various