Cholangiocarcinoma According to Different Etiologies

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This scenario is even more complex in the context of cholangiocarcinoma (CCA), which encompasses an extremely heterogeneous group of malignancies arising from the intrahepatic (iCCA) and extrahepatic (eCCA) biliary tree. The molecular heterogeneity of CCA has been observed not only when comparing iCCA and eCCA subtypes, but also among patients with the same cancer type (inter-patient heterogeneity), and even across the different topographic regions of the tumor from the same patient (intra-patient heterogeneity).

Keywords: cholangiocarcinoma ; risk factors ; genomic profiling ; liver

1. Liver Fluke Infections

Liver fluke infections with O. viverrini and C. sinensis are the leading cause of cholangiocarcinoma (CCA) development in Southeast Asia [1]. O. viverrini is endemic in Thailand, Laos, Cambodia and Vietnam, with some reported cases also in Malaysia, Singapore and the Philippines; C. sinensis is endemic in Northeast China, Southern Korea, Japan, Taiwan and Northern Vietnam [2]. These parasitic diseases represent a serious global health problem, as about 700 million people are at risk of infection worldwide, with more than 45 million people estimated to be affected in the Mekong region only [3]. In humans, infection occurs by the ingestion of raw or partially cooked fish containing encysted metacercariae, the infective stage of the parasite. Following ingestion, metacercariae are digested by gastric and intestinal juices, and juvenile flukes migrate to the intrahepatic bile ducts through the ampulla of Vater and common bile duct; here, adult flukes reproduce and, in the absence of treatment, their lifespan can be as long as 25–30 years [4]. Both O. viverrini and C. sinensis are classified as Group 1 carcinogens to humans by the International Agency for Research on Cancer (IARC) [5]. The mechanism of carcinogenesis driven by these parasites is multifactorial, and includes mechanical/chronic injury to the biliary epithelial cells, chronic tissue inflammation via reactive oxygen intermediates and nitric oxide release, and an increase in cell proliferation via parasite secretion products [6].

2. Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a rare, autoimmune cholestatic disease causing fibro-inflammatory destruction of the intra- and/or extrahepatic bile ducts, often complicated by inflammatory bowel disease, particularly ulcerative colitis [7]; although the disease course may be variable, in most cases it ultimately leads to biliary cirrhosis and liver dysfunction. In Europe and North America, the incidence rate of PSC ranges from 0.5 to 1.3 per 100,000 person-years, whereas in Asian countries this disease is less common [8]. In Western countries, PSC represents the most important risk factor for CCA, and patients with PSC carry a 400-fold higher risk of developing this malignancy compared to the general population [9]. The occurrence of CCA in these patients is higher in the first 2 years after PSC diagnosis, with 30–50% of CCAs developing within the first year [9].

3. Hepatitis Virus Infection

Hepatitis viruses are well-known risk factors for hepatocellular carcinoma (HCC), and worldwide approximately 56% and 20% of HCC cases are related to HBV and HCV infections, respectively [10]. Recent studies suggest that both HBV and HCV may also represent risk factors for CCA, particularly intrahepatic (iCCA) [11]. It seems that differences in HBV- and HCV-related CCA risk exist between Asian and Western populations. Indeed, while HBV infection represents a risk factor for CCA in some Asian countries such as China, where it is highly endemic, HCV-related CCAs mostly occur in Western countries and the United States [11]. The molecular mechanisms of HBV- and HCV-related CCA carcinogenesis still remain poorly understood, but it has been hypothesized that they may be similar to those driving HCC carcinogenesis, including a status of chronic inflammation due to the continuous presence of the virus in target tissues, and insertional mutagenesis in host cells of viral DNA, which can directly promote malignant transformation [12]. In HCC carcinogenesis, HBV-DNA

insertion is an early event after viral infection and results in DNA damage and genomic instability in infected cells; furthermore, the integration sites of HBV-DNA are not random, but target specific loci of the tumor genome [13].

4. Bile Duct Cysts

Bile duct cysts are a rare congenital disorder characterized by cystic dilatation of the intrahepatic and/or extrahepatic biliary tree, usually diagnosed during childhood or in young adults. According to Todani's classification, they can be anatomically classified into type I–V, with type I and IV accounting for about 50–80% and 15–35% of all cases, respectively [14]. The incidence of bile duct cysts is high in Asian countries, especially China and Japan (up to 100 per 100,000 person-years), while is relatively low in Western populations (1:100,000 per 100,000 person-years) [15]. The increase in CCA risk in patients with bile duct cysts is well established (up to 30-fold, compared to the general population), especially in those carrying type I and IV cysts, remaining significant even after cyst excision [16][17]. The molecular mechanisms leading to CCA development in patients with bile duct cysts still need to be fully clarified. It has been hypothesized that reflux of pancreatic enzymes, bile stasis and increased intraductal concentration of bile acids may play a central role in biliary tract carcinogenesis [18]. Indeed, the continuous stimulus of biliary epithelial cells by activated pancreatic enzymes, increased secondary bile acids and other mutagens results in chronic inflammation and increased cell proliferation, which in turn lead to oncogene and/or tumor suppressor gene mutations and cell malignant transformation [18].

Currently, the mutational pattern of CCA associated with bile duct cysts has not been investigated in large population studies. Recently, the case of a 16-year-old girl who developed an extrahepatic (eCCA) after two years from choledochal cyst resection has been reported [19]. Tumor sequencing showed the occurrence of de novo somatic mutations in TP53 and RBM10 genes, along with KRAS amplification; however, these genetic alterations were likely sporadic in this patient, as they occurred shortly after cyst resection [19].

Bile duct cysts are frequently associated with pancreaticobiliary maljunction, a congenital malformation where pancreatic and bile ducts join anatomically outside the duodenal wall [20]. Pancreaticobiliary maljunction is widely recognized as an important risk factor for biliary tract cancer [21]. Biliary tract carcinogenesis associated with pancreaticobiliary maljunction is characterized by a hyperplasia–dysplasia–carcinoma sequence induced by the status of chronic inflammation in the biliary epithelium [21]. A molecular study on cancerous and noncancerous biliary tract epithelium from 37 patients with pancreaticobiliary maljunction reported a high incidence rate of KRAS and TP53 mutations both in cancerous and noncancerous lesions, suggesting that in this patient setting the occurrence of these mutations may represent an early event in biliary carcinogenesis [22]. Despite these findings, no definitive conclusion can be drawn about the genetic profile of CCA associated with bile duct cysts, and further molecular studies on a larger patient population are needed.

5. Liver Cirrhosis

Cirrhosis represents the final stage of liver fibrosis and is characterized by profound changes in the hepatic architecture, with the formation of fibrous septae and regenerative nodules in response to chronic liver injury, which progressively leads to liver disfunction. Cirrhosis represent the main risk factor for HCC, but epidemiological studies have proven evidence that it also represents a risk factor for CCA, especially iCCA [23]. A recent large-scale retrospective study on 1312 iCCA Asian patients reported that 23.0% of iCCA cases occurred on a cirrhotic liver, a much higher percentage than in Western countries [24]; furthermore, 90.1% of cirrhotic patients showed HBsAg positivity, indicating that liver cirrhosis is mostly associated with HBV infection in China [24].

6. Hepatolithiasis

Hepatolithiasis refers to the presence of stones within the intrahepatic bile ducts. The incidence of hepatolithiasis is low in Western countries (from 0.6% to 1.3%), but relatively high in China, Taiwan, Hong Kong, Korea and Japan (from 2% to 25%), where it is frequently related to liver fluke infection with C. sinensis [25]. The association between hepatolithiasis and CCA development is well-documented [1], with an overall CCA incidence of 5–13% in patients with this pathological condition [26]. The link between hepatolithiasis and CCA development is not fully understood, but chronic inflammation (mainly related to recurrent cholangitis, bile stasis, biliary stricture and bacterial infection, which often occur in patients with hepatolithiasis), likely plays a central role in biliary carcinogenesis [25].

CCA carcinogenesis associated with hepatolithiasis is thought to follow a stepwise progression from a precancerous lesion, namely biliary intraepithelial neoplasia (BilIN), to invasive CCA [27]. BilIN is classified as BilIN-1 (corresponding to low-grade dysplasia), BilIN-2 (corresponding to high-grade dysplasia) and BilIN-3 (corresponding to carcinoma in situ) [27].

A study on patients with hepatolithiasis, including 3 cases without BilIN lesions, 12 cases with BilIN-1, 16 cases with BilIN-2, 10 cases with BilIN-3 and 38 cases with iCCAs, detected KRAS mutations in 48% of patients with BilIN (but not in those without BilIN lesions) and in 31.5% of iCCAs [28]. Furthermore, the prevalence of KRAS mutations was highest in BilIN-2 lesions (43.8%), compared to BIIIN-1 (25%) and BilIN-3 (30%), suggesting that this genetic alteration likely occurs early during the progression from BilIN to iCCA [28].

7. Thorotrast

Thorotrast is a radioactive colloidal suspension of thorium dioxide that has been used from the 1930s to the 1950s as a radiographic contrast agent. Once intravascularly injected, it remains in the reticuloendothelial system for many decades, thus accumulating in different organs, mainly the liver [29]. Thorotrast is a well-known risk factor for primary liver cancers, particularly iCCA [1]. Subjects exposed to this agent have indeed a 300-fold increase in iCCA risk [30]. The molecular mechanisms of Thorotrast-induced carcinogenesis have not been fully elucidated; however, as it has a very long half-life in target organs (up to 400 years) and emits alpha-radiations, it is biologically conceivable that the mechanisms may be linked to mutagenic events in oncogenes and tumor suppressor genes. A study on 22 Thorotrast-associated iCCAs reported a high occurrence of TP53 mutations (27.2% of cases), most commonly A-G transitions, in these patients; of note, *TP53* mutations tended to accumulate in advanced tumors [31]. Interestingly, TP53 mutations were also detected in the surrounding normal liver parenchyma where Thorotrast accumulated during the years [31]. Overall, these findings show that Thorotrast continuously damages the DNA of hepatocytes, resulting in A-G transitions of the *TP53* gene; however, as this compound has been banned since 1969, currently the number of iCCAs linked to exposure to Thorotrast is negligible.

8. Aflatoxins

Aflatoxins are mycotoxins produced by Aspergillus fungi, which contaminate food. The risk of exposure to afloxins is high in areas where food preservation is sub-optimal, as occurs in several West African countries [32]. The most toxic aflatoxin detected in contaminated food is aflatoxin-B1 (AFB1), classified as a Class 1 carcinogen by the IARC [33]. The liver is the major site of AFB1 detoxification, where it is metabolized into highly reactive epoxides able to form AFB1-DNA adducts, mainly G:C → T:A transversions [34]. It has been shown that the third base of codon 249 (AGG to AGT) in the TP53 gene is a preferential site for AFB1-DNA adduct formation, which results in the aminoacidic substitution of Arginine for Serine (R249S) [34][35]. Chronic exposure to AFB1 is strongly associated with HCC development, and the detection of the TP53 R249S mutation is considered a molecular hallmark of HCC carcinogenesis induced by aflatoxins [35]. In high aflatoxin-exposed areas of Southeast Asia, China and sub-Saharan Africa, this mutation occurs in up to 75% of HCCs, whereas in regions where aflatoxin exposure is low, such as Europe and the USA, TP53 R249S mutation drops down to <6% of HCCs [35].

Conversely, when compared to HCC, the role of aflatoxin exposure in iCCA development still remains unsettled. Sequencing analysis on iCCA Asian patients negative for liver fluke infection reported the occurrence of TP53 mutations in 39 (38.2%) out of 102 cases, a frequency much higher than that reported in other cohorts of iCCA fluke-negative patients from other countries (ranging from 6% to 9.8% of cases) [36][37]. Interestingly, although most of the TP53 mutations identified were truncating, 10 occurred at the codon 249 (R249S) [37]. This represents the first study reporting the occurrence of TP53 R249S mutations in iCCA patients, suggesting that aflatoxin exposure could represent a risk factor not only for HCC, but also for iCCA development in Chinese patients. Despite this hypothesis being consistent with the widespread aflatoxin contamination in Southern China, it requires further studies to be confirmed.

9. Organic Solvents

To date, the role of environmental risk factors in CCA development has been little investigated. An increased iCCA incidence has been reported among workers of a printing company in Osaka, following chronic exposure to high concentrations of volatile organic solvents, mainly 1,2-dichloropropane (1,2-DCP) and dichloromethane (DCM) [38]. Among the 111 workers, 17 developed an iCCA at a younger age than the general population (from 25 to 45 years old), and none of them resulted in being exposed to other known risk factors for this disease [38]. Notably, it was observed that iCCA incidence increased with cumulative exposure to 1,2-DCP (adjusted RR = 14.9, 95% CI 4.1–54.3 for middle-exposure category, and adjusted RR = 17.1, 95% CI 3.8–76.2 for high-exposure category), suggesting an exposure–response relationship [39]. The potential association between CCA development and 1,2-DCP and/or DCM exposure has been reinforced by further epidemiological studies reporting the occurrence of this malignancy in an additional 13 printing workers of other Japanese companies [40][41] and in 6 out of 11 Thai workers occupationally exposed to these substances [42].

10. Asbestos

Asbestos is a natural mineral that has been widely used in industry during the past century and is classified by IARC as carcinogenic to humans (category 1) [43]. Despite being banned in 52 countries, the health risks continue to be relevant, since about 125 million people worldwide are still environmentally exposed to this carcinogen and the growth rate of asbestos-related cancers is expected to increase in the coming years [44], due to the long latency period between exposure and disease development.

Asbestos-induced carcinogenesis is complex, and involves different mechanisms, including chronic inflammation, reactive oxygen/nitrogen species production, induction of chromosomic/genomic aberrations, immune response reduction, absorption of carcinogens and ionizing radiations, and binding to nucleic acids and nuclear proteins [45]. The susceptibility to asbestos-induced carcinogenesis seems to vary among the different tissue types, making some organs at a higher cancer risk compared to others [46]; as for the liver, the accumulation of asbestos fibers can be facilitated by the high microvascular permeability of the hepatic sinusoids [47].

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