Narrative review of the molecular pathways of cholangiocarcinoma: current and future applications in management

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Abstract: Cholangiocarcinoma is responsible of 10–15% of liver cancer cases, being second most common primary liver malignancy just behind hepatocellular carcinoma. It comprises a heterogeneous group of tumors (perihilar, distal and intrahepatic carcinoma) with different cellular origins but with certain similarities among them, especially in their molecular pathways and risk factors such as cholangiopathies, metabolic diseases and even liver fluke infestations, all of them involving chronic inflammation. Said factors interact between them to induce genetic mutations, altered immune response and growth factor signaling that are constantly factors within carcinogenesis onset to a well-defined tumor with important clinical manifestations. In addition, cholangiocarcinoma has a silent clinical presentation with overly aggressive nature and refractoriness to chemotherapy. Nevertheless, with the advent of immunotherapy and genomic studies it has been proposed that novel molecular therapies act directly in oncogenic suppression or enhance immune cells activity in the tumoral microenvironment. Therefore, this review focuses on the immunogenetics of cholangiocarcinoma and the role of epigenetics in the current approach in this tumor and future applications in its management.

Keywords: Epimutations; DNA methylation; immune cells; tumoral microenvironment; cholangiocarcinoma (CCA)

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Introduction

Tumors of gastrointestinal tract account for one-third of the total global cancer incidence and mortality. In 2018, there were 18,078,957 new cases of cancer diagnosed, in which 3 of the first 6 places were occupied by colorectal, gastric, and liver cancer (1,2). In the liver, there are two main causes of cancer: hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). The latter comprises a diverse group of adenocarcinomas commonly identified depending on their location being: perihilar cholangiocarcinoma (PCC), distal cholangiocarcinoma (DCC) and intrahepatic cholangiocarcinoma (ICC), which is responsible of 10–15%...
of cases of liver cancer (1,3). Whereas CCA is not a common cause of cancer when compared with other gastrointestinal malignancies, it has a silent clinical presentation with highly aggressive nature and refractoriness to chemotherapy; as a result, this cancer has a poor prognosis representing 2% of all cancer-related deaths worldwide yearly (1,4). Furthermore, many are diagnosed at TNM stage IV and patients have a median survival time of 12 months (5).

Common signs and symptoms, such as jaundice and pain, are the consequences of a tumor that grows enough to produce a large liver mass. This only means that the cancer is probably at an advance stage. In fact, the true nature of CCA origin and the identification of risk factor and eventually population at risk are poorly understood; as result, there is a lack of screening programs. Therefore, the continuous efforts to understand the complex interactions between biology, immunology, tumor microenvironment (TME) and epigenetics are critical to develop optimum therapies, diagnosis strategies and the improvement in patient survival (6). This review focuses on role of immunogenetics and epigenetics bases of CCA and the current role of its application and future considerations in screening and therapeutic strategies in the management of this tumor.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/dmr-20-117).

**Risk factors**

There are a variety of risk factors which share at least in theory a direct link with one of the main mechanisms in the development of CCA: chronic inflammation of the biliary epithelium and bile stasis (4). Among these classic risk factors, we can distinguish primary sclerosing cholangitis (PSC), biliary-duct cysts, toxins, hepatolithiasis, diverse causes of cholelithiasis/choledocholithiasis and even parasitic infections. Besides, there are other potential risk factors that have been gaining the importance, like viral hepatitis, alcohol consumption, smoking and metabolic diseases, such as diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD) (7,8) (Table 1). Yet, it is important that epidemiology varies depending on the world regions where some risk factors play more important role than others. Regarding those variations, the incidence men-to-women ratios of ICC goes between 1.3 among white Americans to 3.3 among French population (5).

Another important factor to keep in mind when studying CCA epidemiology, is the issue of misclassification, where most cases of ICC are commonly classified as Klatskin tumors; in some cases, CCA incidence is overestimated while in others the opposite happens (7,9).

**Classic risk factors**

Regarding parasitic infections, *Opisthorchis viverrini* and *Clonorchis sinensis* infestations are well-known risk factors for CCA, especially for ICC by inducing chronic inflammation, cholangitis, and fibrosis of the periportal system. In fact, those organisms were designated as group 1 carcinogens by the World Health Organization. For instance, in Thailand, fluke infestation is highly related with CCA which is the most common cause of primary liver cancer (89%) (9,10). Less common, infestation of *Ascaris lumbricoides* and *Clonorchis sinensis* can cause hepatolithiasis (present in 30% of patients with such infestations). Nevertheless, most cases are reported in endemic areas for those parasites, mainly in East and Southeast Asia (7-11).

With respect to biliary tract disease, they follow the same mechanism of chronic damage and inflammation of biliary epithelium. PSC also induces a dysregulated progenitor cell proliferation increasing the risk for ICC. Furthermore, patients with PSC have an incidence of 5–10% of CCA (7,11). In the case of cholelithiasis, the presence of calculi has been associated with chronic biliary tract inflammation and increased cancer risk both in Western and Asian population (11). A meta-analysis revealed that choledocholithiasis alone or choledocholithiasis accompanied by hepatolithiasis was associated with the risk of ICC [odds ratio (OR) 17.64, 95% confidence interval 11.14–27.95] (12).

In addition, while lithiasis can cause chronic physical damage to biliary epithelium by a gallstone, other cholestasis diseases, such as Caroli’s disease (15% of lifetime incidence) and bile-duct cysts (6–30% of lifetime incidence of CCA) (12,13), can induce damage through bile stasis (7,12). Indeed, bile acids (BAs) due to their detergent action on lipid component can induce damage to cell membranes, generating reactive oxygen species (ROS) and ultimately can cause necrosis and apoptosis (14). Moreover, BAs are capable to activate growth factors in CCA cell lines by inducing cyclooxygenase-2 (COX-2) and sphingosine 1-phosphate receptor 2 (S1PR2) activation (15,16).

**Metabolic risk factors**

Obesity and diabetes have emerged in past years as...
important risk factors for many types of cancer. In the gastrointestinal tract, both diseases play a key role by interfering with normal metabolic functions in cells and by activating inflammatory cells and growth factors after a complex cascade of cell signaling and damage. Furthermore, after a tumor is set, obesity and diabetes, but specially obesity can dysregulate cellular and non-cellular processes within the TME (17). In the UK, a case-control study found a significant association of diabetes and obesity with CCA, and it was especially notorious in patients with BMI ≥30 kg/m² who had 1.5 times more risk of CCA when compared with those with BMI <25 kg/m² (18). Previously, a larger study in the United States reported a significant association between metabolic syndrome and ICC (OR 1.56) (19).

Nonetheless, while there is important evidence regarding the role and association of obesity and diabetes in many gastrointestinal cancers, there is still few evidences for CCA and metabolic alterations. For instance, several meta-analyses revealed a strong association of obesity with HCC, but there is few information for ICC and in the case of extrahepatic cholangiocarcinoma (ECC), most studies were inadequate to determinate a real correlation (8,20,21). Likewise, evidence about diabetes and CCA suffers a lack of consistency among different studies bringing just modest association between both conditions (8,18).

### Genetic factors

In CCA, experimental models have showed the role of epigenetics in CCA which can be summarized in two main processes (involving each one a series of multistep); a preneoplastic lesion due to different factors that induce DNA alteration generating epimutation on progenitors, and then, a tumorigenesis and progression of cancer after clonal expansion of mutated progenitor cells (22). Several studies have been shown that genetic

| Table 1 Risk factors and their role in cholangiocarcinoma carcinogenesis |
|-----------------------------|-------------------------------------------------|-----------------------------------|
| **Risk factor**             | **Mechanism**                                   | **Essential references**          |
| Fluke infestations          | Parasites such as may lead to chronic damage y biliary cells due to local inflammation caused by immune response against the parasite and the mechanical damage by the parasite itself | Sripa B, et al. PLoS Med, 2007    |
| Chronic cholestasis/        | A stone in the biliary duct will caus mechanical damage and as consequence inflammation (due to COX-2 synthesis in the bile ducts) and cell proliferation. An increased rate of cellular DNA synthesis may lead to mutations. In addition, stones alter biliary flow which may alter bile acid composition that are capable to induce cellular damage | Gupta A. Hepatobiliary Surg Nutr, 2017 |
| Obesity                     | The main mechanism is related with a proinflammatory state that comes from adipose tissue which releases cytokines into the bloodstream, mainly TNF-α and IL-6 | Lauby-Secretan B, et al. N Engl J Med, 2016 |
|                             |                                                 | Khan SA, et al. Liver Int, 2019   |
|                             |                                                 | Tyson GL and El-Serag HB. Hepatology, 2011 |
|                             |                                                 | O’Sullivan J, et al. Nat Rev Gastroenterol Hepatol, 2018 |
| Diabetes                    | Hyperglycemia and the adaptation of cell to metabolic alterations are related with DNA methylation or mutation, mainly due to mitochondrial dysfunction. In addition, diabetes is highly related with obesity and cholelithiasis | Welzel TM, et al. Clin Gastroenterol Hepatol, 2007 |
| NAFLD                       | Patients with this condition express a proinflammatory state since Kupffer cells response to the oxidative stress, adipokines and damage-associated molecular pattern from hepatocytes. Also, NAFLD may progress to fibrosis and cirrhosis | Khan SA, et al. Liver Int, 2019    |
|                             |                                                 | O’Rourke CJ, et al. Trends Cancer, 2019 |

COX-2, cyclooxygenase-2; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; NAFLD, non-alcoholic fatty liver disease.
polymorphisms may modulate CCA risk (3,7,23). This can be seen in the common mutations of isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) genes that are present in ICC (24) or the association between glutathione S-transferases (GSTs) and CCA (25). Furthermore, most of gene polymorphisms in CCA are directly related to DNA repair and inflammation, for example the human oxoguanine glycosylase 1 (hOGG1) and MutY homolog (MUTYH, MYH) genes, which codify vital proteins to DNA repair pathways or the natural killer (NK) cell receptor G2D (NKG2D) (7).

Likewise, since the most studied epigenetic changes that occur in cancer include DNA methylation and histone modification, it has been identified that epimutations of methylenetetrahydrofolate reductase (MTHFR) gene is involved in folate metabolism and DNA methylation in patients with Opisthorchis viverrini (7). In addition, epigenetic silencing by promoter hypermethylation over tumor suppressor gene (TSG) is a hallmark of CCA, hence, the identification of signaling pathways in silencing those genes and even the regulation of oncogenes and microRNAs responsible of silencing have been proposed as promising therapies (26-28).

Pathogenesis

The molecular set of CCA is a mix of multiple mechanisms, such as cell damage, DNA injury and reparation, epimutations, inflammation, and abnormal cellular growth (“hits”) leaving aside the two hits theory. Yet, we can mention two major processes as a response and consequence to DNA alteration: proliferation and inflammation (3). Moreover, the DNA cells mutation may be the result of adaptation either against chronic inflammation by extrinsic factors like PSC or de novo epimutations in response to metabolic disturbances within the cell. In fact, the presence of the variant allele rs3197999 of the macrophage stimulating 1 gene (MST1) results in p.R689C amino acid substitution within the β-chain of MSP (MSPβ) and as a consequence, induces chemotaxis and macrophage activation. Therefore, immune response without inflammation is possible in the context of CCA (29). Nevertheless, despite the complex interaction between all factors mentioned above in CCA, there is still an important challenge to extrapolate these findings to the clinical scenarios. The understanding of these molecular pathways is critical for the development of better strategies in CCA management.

The origin and progression of CCA

In CCA, multiple models and investigations established the origin of gene mutations in biliary progenitors’ cells residing in canals of Hering; here, these cells may differentiate into abnormal neoplastic cells for the three main types of CCA (22). However, according to the type of cancer cells which are originated from biliary progenitors’ cell, the presentation will be one of the three main types of CCA. For PCC, the cell of origin may be originated from mucin-secreting cholangiocytes. In the case of ICC, it will be divided into the two main different histological subtypes. Therefore, the cell of origin is the largest intrahepatic bile ducts for large bile duct (mucinous) type, and the mucin-negative cuboidal cholangiocytes for small bile duct type (30). Furthermore, they are susceptible to develop a premalignant lesion, such as biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm of the bile ducts (IPNB) (31-33). In fact, IPNBs have an estimated risk of 40–80% to transform into CCA (34).

Main molecular signaling and genetic changes in CCA

The modifications in cellular DNA begin after several and chronic insults against hepatobiliary cells that may be induced by cholestatic diseases or metabolic dysfunction in the context of metabolic diseases. Chronic inflammation leads to increased exposure of cholangiocytes to the inflammatory mediators’ interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), COX-2 (34). Among them, stand out COX-2 induced by BAs and inflammatory cytokines, promoting the formation of nitric oxide which causes DNA damage and inhibition of DNA repair (29). As a consequence, the transformation into precancerous cells and cancer stem cells is driven by two transcriptomic profiles; an inflammatory class and a proliferative class, characterized by oncogenic activation and induction of pro-inflammatory pathways (Table 2). Besides, epimutations of hepatobiliary cells can contribute to those mechanisms through silencing of TSGs (4,26).

Meanwhile, the most important oncogene alterations in CCA are those related to KRAS, BRAF, EGFR, PIK3CA and TP53, of which all are very important in DNA repair. Most of them encode key proteins that are part of signaling pathway in cancer proliferation, even in CCA. For instance, KRAS gene encodes K-Ras protein for Ras-MAPK pathway which may transduce extracellular signals into the nucleus to active genes responsible of growth factors (26,29,35).
Even more, the ErbB-family of receptors, including the epidermal growth factor receptor (EGFR), are the most affected pathways in ICC (26). On the other hand, while uncontrollable cell proliferation is important in CCA pathogenesis, it is important to mention that those new cells are highly resistant to hypoxia and are capable of inducing vascularization due to ERK signaling pathway which may activate vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) (3,35).

Regarding the inflammatory class, a series of immune-related signaling pathway play a major role where the pathway of the signal transducer and activator for the transcription 3 (STAT3) by Ras-MAPK is the most significant. Besides, STAT3 modulate survival IL-6/STAT3 tumor propagation by upregulation of Mcl-1 (an apoptosis inhibitor) (20,29,34). In addition, CCA TME is rich in immune cells, and in this context, P13K/AKT and MAPK pathways increase neutrophil migration, while IL-6/STAT3 stimulates recruitment of macrophages which can be transformed into fibroblast and tumor-associated macrophages (TAMs) (Figure 1) (34-38).

Other important genetic alterations include mutation of SMAD4 that dysregulates the transforming growth factor beta (TGF-β) signaling in metastatic CCA (36) and the WNT-β-catenin signaling pathway involved in the losing of cell to cell adhesion by misfunction of E-cadherin and β-catenin (37,39).

**Immunobiology and TME**

Except for genetic alterations, the crosstalk between immune mechanism and TME may impact in the progression and even response to treatment of CCA (Figure 1). In fact, with the advent of immunotherapy, the role of immune cells is even more important for new CCA therapies. TME contains abundant immune cells, such as TAMs and myeloid-derived suppressor cells (MDSCs) that compete for nutrients against cancer cells (37,40). To complicate that situation further, cancer cells exhibit an immune suppression activity due to metabolic competition with T cells; the Warburg effect has been widely studied in cancer, and explains how cancer cells dramatically increase their glucose uptake and lactate production alongside ROS (37,40). The latter becomes important since the competition for metabolic substrates can activate the response for certain immune cells. Furthermore, glucose restriction in TME can affect tumor-infiltrating lymphocytes (TILs); for instance, CD4+ and CD8+ are antitumor effector cells that may be activated in the context of aerobic glycolysis (41). Moreover, CD8+ suppress tumor growth and induce apoptosis while increased levels of CD4+ were associated with longer overall survival (41,42). Besides, dendritic cells (DCs), which are responsible in many cases of initiate adaptive immune responses, seem to be decreased in patients with CCA; evidence suggests that DCs play a role in containing growth expansion and metastasis (43).

<table>
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<tr>
<th>Signal pathway</th>
<th>Putative roles</th>
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<td>ERK</td>
<td>Activation of VEGFR and PDGFR</td>
<td>Chen C, et al. Cells, 2019</td>
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<tr>
<td>P13K/AKT</td>
<td>Neutrophil migration</td>
<td>Labib PL, et al. BMC Cancer, 2019</td>
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<td>IL-6/STAT3</td>
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<td></td>
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The most common pathways are related to somatic mutations that dysregulate genomic stability, cell cycle control, proinflammatory signals and growth factors. Ras-MAPK, Ras-mitogen activated protein kinase; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; ERK, extracellular-signal-regulated kinase; P13K/AKT, phosphatidylinositol 3-kinase; IL-6/STAT3, interleukin-6-mediated JAK/STAT3; TGF-β, transforming growth factor-beta.
On the contrary, TAMs infiltration in TME is related to angiogenesis and poor outcomes and recurrence (44). In two studies, it was clear that macrophages release Wnt ligands for Wnt-β-catenin signaling pathway, but also that this mechanism can be inhibited and then serves as a potential therapeutic target (39,45). In addition, mitochondrial dysfunction and oxidative stress lead to Kupffer cells (KCs) recruitment; as a consequence, KCs activates the protein kinase JNKs (mediators of oncogenic transformation and CCA proliferation) by TNF (46). Moreover, TNF-α exhibits other mutagenic mechanism over DNA, such as upregulation of activation-induced cytidine deaminase (AID), that mutates DNA by converting cytosine to uracil and resulting in mutation of P53 and MYC proto-oncogene (29).

Likewise, MDSC are also related to negative outcomes by suppressing immune activity of T cells (41). While immunogenically suppression explains the lack of response against cancer, TAMs are capable to promote cancer cell invasion and metastasis due to secretion of TNF, IL-6, TGF-β, VEGF and PDGFR, of which all are tumor growth-promoting factors. In addition, the cascade of signals mentioned above promote epithelial-to-mesenchymal transition (EMT) (35). On the other hand, NK cells can identify and eliminate cancer cells. One *in vitro* study in human cells and another *in vivo* study in a nude mouse model showed that infusion of NK cells induces cytotoxicity against CCA cells and inhibits tumor growth (44,47,48).

In general, the immune systems can play in both sides CCA, some of innate immune systems seem to promote growth factors for cancer cells as well as a myriad of ligands for signaling pathways in cells migration and cell differentiation, which can contribute to CCA progression. Even more, TAMs and neutrophil express mechanism of immunosuppression against other immune cells, allowing cancer cells to escape from immune-mediated apoptosis. Nonetheless, decreasing the population of these cells and
increasing others such as T cells, may be a resourceful target alongside adjuvant therapies in CCA.

**Implementing new strategies**

As it was mentioned early, genomic heterogenicity is a hallmark in CCA, and different genes altered by epigenetic factors are important within carcinogenesis, eventually leading to a dysregulated immune response. Some of those epigenetic changes are in fact closely related to well-known and putative risk factors; thus, knowing those epigenetic changes is possible to implement screening strategies. To illustrate the latter, it was previously reported an association of *BRCA2* mutation with CCA which remains as uncommon, but due to the success of some therapies in other BRCA-associated malignancies, a new proper approach to understand the role of BRCA mutation in CCA may be useful to use BRCA a potential therapeutic target and prognostic biomarker (49).

The elucidation of certain mechanism between some conditions and CCA has helped in the identification of risk factors. Besides, those risk factors stated above, and in the context of the growing epidemy of metabolic diseases, obesity is widely associated with cancer, mainly by the action of adipokines and growth factors derived from adipose tissue. Furthermore, obesity increases 1.5–2.0 times the relative risk of developing gastrointestinal cancers (50). On the other hand, NAFLD, which is associated with obesity at the same time that encourages for investigations regarding genetic polymorphisms (recommendation grade AI) (51).

Indeed, identification of such potential risk factors may allow to identify patients at risk, but more importantly, the epigenetic interplay can be also a therapeutic target. Moreover, in the most recent guidelines of CCA, the European Association for the study of the Liver (EASLD) recommends to keep in mind risk factors like cirrhosis, chronic viral hepatitis, alcohol excess, diabetes, and obesity at the same time that encourages for investigations regarding genetic polymorphisms (recommendation grade AI) (51).

There are also interesting findings related to the application of proteomics in certain diseases as biomarkers for malignancy. For example, the determination of matrix metalloproteinase-7, tumor type M2 pyruvate kinase and IL-6 in ICC (52).

On the other hand, identification of genetic alteration may be used for biomarkers, especially in early stages where imaging studies lack the utility. In this scenario, novel techniques have been the subject for many investigations; this is the case of circulating tumor DNA (ctDNA) sequencing that can detect the presence of circulating free DNA in plasma. Furthermore, liquid biopsy allows to determinate nucleic acids of tumor cells in bloodstream (53). Finally, there are extracellular vesicles released by cancer cells containing RNA, proteins, and metabolites. These methods have already been tested in patients with HCC, CCA and PSC (54).

Even more, it is believed that the role of extracellular vesicles may be far beyond by driving away chemotherapeutic agents out of cancer cell and even more by carrying ligands for EMT for other in tissues, hence promoting metastasis (55).

Detection of DNA methylation biomarkers is also possible. The most common genes that suffer from DNA methylation are TSG; in CCA, the hypermethylation of the proteins p16 and p14 encoded by the INK4a-ARF locus on chromosome 9p21 results in cell cycle dysregulation (54). Likewise, detection of *IDH1* methylation can serve as a biomarker, which was patented in a recent study where *IDH1* R132x mutation was present in the tumor and plasma of patients with ICC (56). Moreover, there are two novel drugs, ivosidenib and enasidenib, that inhibit IDH1, both are still in different phases of their clinical trials (57).

The above lead to therapeutic strategies related to epigenetic changes (DNA methylation). For instance, Hatano et al. conducted a study were DNA demethylation induce tumor-suppressive effect in colon cancer cells (58). In contrast, inducing DNA methylation over oncogenes can be a possible option (27). It is important to mention the importance of such efforts since the first-line therapy for CCA (gemcitabine plus cisplatin) conferring a median survival time of 1 year while no other therapies have been currently approved (51).

Regarding the role of immune cells in novel therapies, Jung and colleagues conducted an *in vivo* study in mouse where it was seen that infusion of NK cells increases their cytotoxic activity against human HuCCT-1 cells (48). In another study the combination of NK cells infusion with cetuximab blockaded EGFR activation and inhibits human CCA cells (47).

Besides, molecular therapies include the inhibition of signaling pathways. For instance, we previously described the important role of MAPK pathway, in this case vemurafenib, dabrafenib and trametinib were the subjects of study in clinical trials. Nevertheless, three of them showed partial response. On the contrary, the inhibition by larotrectinib and entrectinib of the neurotrophic tyrosine
kinase receptor (TRKA), involved in cell growth and proliferation, has demonstrated favorable responses in patients with cancer, including CCA (57).

Conclusions

The management of CCA is complex due to its very own nature that it is excessively aggressive and eminently silent. In fact, poor prognosis and bad response to treatment is in part due to a late diagnosis. To complicate further, current diagnostic tools are capable of detecting CCA in early stages; even if the tumor is recognized in stages that allow to perform surgery, the odds of metastasis and relapse are high. Accordingly, it is imperative to development noninvasive biomarkers in early stages but also new therapeutic targets. To accomplish it, understanding the molecular pathways and immunobiology of CCA, especially because of its heterogenicity, is crucial.

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