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Role of Interleukins Pathogenesis in Cholangiocarcinoma: A Literature Review

Role of Interleukins Pathogenesis in Cholangiocarcinoma

Saira Razaqat, Hafsa Hamid, Roha Asif, Muhammad Asif, Maria Tariq, Malaika Saleem,
Hijab Abaid

Abstract

This article summarizes the role of interleukins (ILs) in the pathogenesis of cholangiocarcinoma (CCA). It discovered a negative feedback mechanism by which KRAS-mutant intrahepatic cholangiocarcinoma benefits greatly from the overexpression of interleukin 1 receptor antagonist (IL1RN)-201/203 brought about by alternative splicing. Higher levels of IL-4R are associated with a worse survival rate in CCA patients. Elevated levels of serum IL-6 have been associated with the start and progression of CCA, a common cancer generated by inflammation. IL-8 was a useful predictor of human hilar cholangiocarcinoma. Mechanistically, STAT3 signaling was used by IL-10 produced from M2-TAM to enhance the malignant characteristics of intrahepatic cholangiocarcinoma cells. It is suggested that IL-17A and IL-22 have an impact on the development of CCA associated with hepatic fluke infection. The most significant finding was the decreased expression of IL23R, a prognostic gene, in intrahepatic cholangiocarcinoma. IL-25 may be a useful prognostic biomarker as aberrant expression of the protein in CCA tissue was linked to tumor spread and a poor prognosis. Tumor cell migration and proliferation were both accelerated by homogenized liver tissue that expressed IL-33 significantly. The correlation between high IL-35 expression and aggressiveness in intrahepatic cholangiocarcinoma highlights it as a useful biomarker for assessing the course and prognosis of intrahepatic cholangiocarcinoma in clinical settings. This article concluded that IL-1, IL-4, IL-6, IL-8, IL-10, IL-17, IL-23, IL-25, IL-33 and IL-35 play significant role in the pathogenesis of CCA. Further research is required to find the association of other ILs such as IL-3, IL-5, IL-7, IL-11 and more in the pathogenesis of CCA.

Key Words: Cholangiocarcinoma; Intrahepatic Cholangiocarcinoma; Interleukins; Pathogenesis

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Core Tip: Interleukins contribute to cholangiocarcinoma pathogenesis by promoting chronic inflammation, enhancing tumor cell survival, proliferation, and invasion, and shaping a tumor microenvironment that supports cancer growth and metastasis. Interleukins, which are a group of cytokines, play a crucial role in mediating the immune response and inflammation. This article concluded that IL-1, IL-4, IL-6, IL-8, IL-10, IL-17, IL-23, IL-25, IL-33 and IL-35 play significant roles in the pathogenesis of CCA. Further research is required to find the association of other ILs such as IL-3, IL-5, IL-7, IL-11 and more in the pathogenesis of CCA.

2

INTRODUCTION

Cholangiocarcinoma (CCA) is one of the most aggressive gastrointestinal cancers with a rising worldwide incidence over the last decade. Of all primary liver malignancies, CCA accounts for 10-15% of cases, making it the second most frequent form of liver cancer. CCA also known as bile duct cancer, is a type of cancer that forms in the bile ducts[1]. In recent decades, there has been a global increase in both the incidence and fatality rates associated with this illness[2]. Although most CCA patients are discovered at an advanced stage and are thus not eligible for surgery, surgical resection is still a possible curative therapy. It is an extremely deadly hepatobiliary system adenocarcinoma with a 5-year overall survival (OS) rate of approximately 5% to 17%[3].

CCA can be categorized as intrahepatic (iCCA or ICC), perihilar (pCCA), or distal (dCCA) illness depending on the anatomy and surgery. Because iCCAs originate above the second-order bile ducts, pCCAs originate above the cystic duct and below the second-order bile ducts, and dCCAs originate below the cystic duct, surgical techniques for each entity change dramatically[4]. Multiple types of complex biological processes underlie CCA which contributes to its aggressive nature and resistance to treatment. At

the molecular level, genetic changes like mutations are essential for encouraging unchecked cell proliferation and survival, especially in intrahepatic subtypes[5].

Epigenetic changes, such as DNA methylation and non-coding RNA dysregulation, further impair gene expression and aid in the development of tumors. A pro-tumorigenic microenvironment is fostered by chronic inflammation, which activates important signaling pathways including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 3 (STAT3). While immune evasion mechanisms, such as programmed death ligand 1 (PD-L1) expression, enable CCA cells to evade immune monitoring, the epithelial-mesenchymal transition (EMT) pathway gives tumor cells invasive characteristics. The intricacy of cholangiocarcinoma is highlighted by these interrelated biological processes, which also offer potential problems for focused treatments[5].

As such, it is imperative that novel biomarkers be found as soon as possible and that treatment plans be developed for this malignancy. Prolonged inflammation is a major factor in the development and progression of CCA, a frequent malignancy carried on by inflammation. A major risk factor for CCA is a chronic inflammation of the biliary system brought on by primary sclerosing cholangitis, choledocholithiasis, or cholelithiasis[6]. Chronic inflammatory responses can also result from other risk factors for cholangiocarcinoma, such as bile duct stones and infections (hepatitis B virus, liver fluke, salmonella, *etc.*)[7].

With a 2% 5-year survival rate after metastasis, CCA also known as cancer of the biliary epithelium, is an aggressive and very uncommon type of bile duct cancer. Although a variety of risk factors have been linked to the growth and progression of CCA, the most frequent causal relationship between the risk factors and the formation of CCA is an inflammatory environment close to the biliary tree[8]. Several data show that the growth and metastasis of CCA are significantly influenced by the existence and maintenance of an inflammatory milieu at the location of the initial tumor, supporting the idea that inflammation predisposes afflicted persons to CCA. Furthermore, CCA

aggressiveness and metastasis are strongly influenced by processes that activate the tumor vasculature and promote angiogenesis and lymphangiogenesis [8],

Interleukins (ILs) are a group of cytokines (signaling proteins) that play critical roles in the immune system by regulating inflammation, immune responses, and hematopoiesis. The effect of interleukins on the inflammatory response has led to classifications of them in scientific literature. Three unique groupings are produced by this categorization. IL-1, IL-4, IL-5, IL-6, IL-8, IL-9, IL-13, IL-14, and IL-15 are among the 22 inflammatory cytokines that make up the first and biggest category. IL-7, IL-10, IL-30, and IL-37 are among the fourteen anti-inflammatory chemicals that make up the second group. IL-2, IL-3, IL-11, and IL-12 are examples of dual-function interleukins that fall into the third category. These molecules might operate as both inflammatory and anti-inflammatory agents under certain conditions [9]. However, this review article aimed to summarize the knowledge of interleukins in the pathogenesis of CCA as explained in figure 1 and table 1.

METHODS

The literature review was conducted using databases such as Science Direct, PubMed, and Google Scholar between March 01, 2025, with specific keywords like "Cholangiocarcinoma," "intrahepatic cholangiocarcinoma", "Interleukins," and "Pathogenesis." Current discoveries were prioritized, but no specific timeframe was imposed for clinical research. The English language was used for the selection of articles.

MAIN TEXT

ROLE OF INTERLEUKINS IN THE PATHOGENESIS OF CCA

A small percentage of those infected with *Opisthorchis viverrini* infection develop advanced periductal fibrosis (APF) and CCA. The infection causes persistent inflammation. These biliary diseases may be related to inflammatory cytokines and/or gene polymorphisms encoding them[10]. Pro-inflammatory cytokines, including LT- α ,

TNF- α , IFN- γ , IL-1 β , and IL-6, were shown to be considerably higher in CCA patients as compared to non-CCA (APF- and APF+) instances. PCR-RFLP or allele specific-PCR (AS-PCR) analyses were then used to look at polymorphisms in genes encoding IL-1 β -511C/T, IL-6-174G/C, IFN- γ +874T/A, LT- α +252A/G, and TNF- α -308G/A. LT- α +252A/G and TNF- α -308G/A heterozygous and homozygous variants were found to exhibit considerably greater levels of these cytokines in the CCA patients compared to the wild type. While CCA was linked to IL-6 -174G/C polymorphisms. People infected with *O. viverrini* who have many particular cytokine gene polymorphisms are vulnerable to developing fibrosis and CCA[10].

An uncommon primary hepatic cancer with a poor prognosis, intrahepatic cholangiocarcinoma (iCCA) is poorly understood and understudied. Another study examined 11 genetic variants (*VEGF*, *EGF*, *EGFR*, *IL-1B*, *IL-6*, *CXCL8 (IL-8)*, *IL-10*, *CXCR1*, *HIF1A*, and *PTGS2 (COX-2) genes*) involved in tumor-promoting inflammation and their relationship to disease-free survival (DFS) and overall survival (OS) in patients undergoing curative-intent surgery for iCCA to identify prognostically relevant single-nucleotide polymorphisms. The univariable and multivariable analyses revealed that the *IL-1B* +3954 C/C (73/112, hazard ratio (HR) = 1.735, $P = 0.012$) and the *IL-8* -251 T/A or A/A (53/112 and 16/112, HR = 2.001 and 1.1777, $P = 0.026$) genotypes were linked to a shorter overall survival. The multivariable model did not maintain the association between the *IL-1B* +3954 polymorphism and shorter DFS (HR = 1.983, $P = 0.012$). As a conclusion, *IL-1B* C+3954T and the *IL-8* T-251A variation have a predictive effect in iCCA patients[11].

INTERLEUKIN-1

A strong inflammatory cytokine, interleukin-1 (IL-1) can start several physiological reactions, such as lymphocyte activation, the production of acute-phase liver proteins, leukocyte infiltration at infection sites, fever, and anorexia. This highlights the critical function of cytokines in the innate immune response. All of the additional members of the IL-1 family, including IL-33, have been demonstrated to have functions in

inflammation and host defence since the finding of IL-1 α and IL-1 β sequences more than 20 years ago. IL-1 family members are generated by macrophages, as opposed to lymphocytes, which create IL-2. Blocking IL-1 receptors is one way to treat auto-inflammatory diseases which have been linked to IL-1 dysregulation in their pathophysiology[12-15].

KRAS mutations are key players in the development of tumors and are directly associated with protumor inflammation. Another study demonstrated that a particular landscape of alternative mRNA splicing linked to myeloid inflammation in intrahepatic cholangiocarcinoma was correlated with KRAS mutation, based on multiomics data collected from a large group of patients. Next, it discovered a negative feedback mechanism by which KRAS-mutant iCCA benefits greatly from the overexpression of interleukin 1 receptor antagonist (IL1RN)-201/203 brought about by alternative splicing[16]. Both IL1RN-201/203 overexpression and anakinra therapy induced a noteworthy antitumor immune response in KRAS-mutant iCCA mice *via* modifying neutrophil recruitment and behaviors. In addition, anakinra therapy in KRAS-mutant iCCA mice synergistically improved anti-PD-1 therapy to activate intratumoral GZMB⁺ CD8⁺ T cells. Clinical research revealed a substantial correlation between a better response to anti-PD-1 immunotherapy and elevated IL1RN-201/203 Levels in patients with KRAS-mutant iCCA[16].

CCA is more likely to develop and progress in people with diabetes mellitus (DM). It has been previously demonstrated that in CCA cells with unknown roles, high glucose levels upregulated interleukin-1 β (IL-1 β). With IL-1 β being proposed as a communicative cytokine, another study aimed to explore molecular pathways connecting DM to the advancement of CCA. To simulate euglycemia and hyperglycemia, respectively, CCA cells were cultivated in conditions containing either normal (5.6 mmol/L) or high (25 mmol/L) glucose. Immunohistochemistry was utilized to investigate the expression of IL-1 β and IL-1 receptor (IL-1R) in CCA tissues from people with and without diabetes mellitus[17].

Using siRNA and recombinant human IL-1R antagonist (rhIL-1RA), functional studies of IL-1 β were carried out, and the effectiveness of the knockdown was examined using Western blots. To study the effects of hyperglycemia on CCA development and the anti-tumor effects of IL-1RA, CCA xenografts were transplanted into BALB/c Rag-2⁺ Jak3⁺ (BRJ) mice. Compared to non-DM patients, individuals with hyperglycemia had CCA tumors with considerably greater levels of IL-1 β expression, and there was a positive correlation between IL-1 β and fasting blood glucose levels. When CCA cells were cultivated in high glucose, they expressed more IL-1 β , which led to faster rates of cell proliferation[17]. In vitro CCA cell proliferation was markedly inhibited by si-IL-1 β or rhIL-1RA-induced suppression of IL-1 β signaling. In vivo, the synthetic IL-1RA anakinra demonstrated noteworthy anti-tumor actions and dramatically mitigated the growth-inducing effects of hyperglycemia in CCA xenografts. In a high-glucose milieu, IL-1 β is essential to the advancement of CCA. Thus, targeting IL-1 β may aid in improving CCA's therapeutic results in patients with DM and hyperglycemia[17].

INTERLEUKIN-4

Interleukin-4 (IL-4) is recognized as a cytokine that holds a central position in regulating the immune response. Investigations into the signal transduction of cytokines have elucidated the mechanism through which IL-4 carries out its functions. The two cytoplasmic proteins that are active during IL-4 signal transduction are IL-4-induced phosphotyrosine substrate/insulin receptor substrate 2 (4PS/IRS2) and ¹⁶signal transducer and activator of transcription (STAT) 6[18]. STAT6 plays a crucial role in modulating the biological activities of IL-4, as demonstrated by recent investigations employing STAT6-deficient animals. Moreover, cytokine IL-13 which is connected to IL-4, requires STAT6 to perform its tasks. Evidence suggests that both IL-4 and IL-13 can promote the synthesis of immunoglobulin E (IgE), a key mediator of allergic reactions [18].

Numerous cancer cells have overexpressed the interleukin-4 receptor (IL-4R), which is essential for the growth of tumors and the development of medication resistance. Phage display allowed for the identification of IL4RPep-1, an IL-4R-binding peptide that is utilized to target tumors[19]. It utilized IL4RPep-1 to direct the delivery of a proapoptotic peptide to chemoresistant CCA that is unique to the tumor, therefore preventing the development of the tumor. Higher levels of IL-4R are associated with a worse survival rate in CCA patients, according to immunohistochemistry analysis of human primary CCA tissues. It revealed that IL-4R levels were elevated in moderately to poorly differentiated types. It was shown that IL4RPep-1 bonded more strongly to human CCA cells with high IL-4R expression, KKU-213 than it did to KKU-055 cells with low IL-4R expression[19].

In KKU-213 cells, a combination of IL4RPep-1 and the proapoptotic peptide (KLAKLAK)₂, known as IL4RPep-1-KLA, increased the levels of cytotoxicity and apoptosis induced by 5-fluorouracil (5-FU). After internalizing in the cells, IL4RPep-1-KLA colocalized with mitochondria. The homing of IL4RPep-1-KLA and IL4RPep-1 to the KKU-213 tumor in mice was shown by whole-body fluorescence imaging and immunohistochemistry examination of tumor tissues[19].

Treatment with 5-FU alone did not significantly suppress tumor development in mice, but systemic delivery of IL4RPep-1-KLA effectively inhibited KKU-213 tumor growth. During peptide therapy, mice did not exhibit any notable systemic adverse effects, such as immunotoxicity or liver toxicity. These results imply that IL4RPep-1-KLA has promise as a targeted therapeutic agent to treat CCA that is resistant to chemotherapy[19].

The interleukin-4 receptor α (IL-4R α) is known to be abundantly expressed on the surface of several types of solid tumors in humans. Previously, it designed a novel IL-4R α -lytic hybrid peptide that was composed of cell-lytic peptide and binding peptide to IL-4R α . It reported that the designed IL-4R α -lytic hybrid peptide demonstrated both *in vitro* and *in vivo* antitumor activity against human pancreatic cancer cells that expressed IL-4R α [20].

As a new molecular targeted treatment for human biliary tract cancer (BTC), it assessed the anticancer effect of the IL-4R α -lytic hybrid peptide here. Six BTC cell lines were exposed to cytotoxic action from the IL-4R α -lytic hybrid peptide at concentrations as low as 5 μ M, which was shown to kill 50% of all cells[20]. Additionally, it demonstrated that gemcitabine and IL-4R α -lytic hybrid peptides have synergistic cytotoxic action in vitro. Furthermore, in a human BTC xenograft model in vivo, intravenous injection of IL-4R α -lytic hybrid peptide markedly suppressed tumor development. All of these findings suggest that the IL-4R α -lytic hybrid peptide is a powerful medication that may provide patients with BTC with a new kind of treatment[20].

INTERLEUKIN-6

Interleukin-6 (IL-6) is a type I transmembrane receptor that is activated by the binding of the IL-6 Ligand to the coreceptor gp130 and the IL-6 receptor. Furthermore, soluble forms of the IL-6 receptor can attach to IL-6, allowing it to continue binding and activating the coreceptor gp130[21].

This process is known as transient IL-6 signaling. Autophosphorylation and Janus kinase (JAK) activation are started when the ligand binds to the receptor. Activated JAKs subsequently phosphorylate and trigger transcription factors known as STAT3 (signal transducer and activator of transcription 3). The active STAT3 factors then go to the nucleus, dimerize, and bind to DNA to control transcription. Most IL-6-dependent effects are ascribed to changes in gene expression regulated by STAT3's transcriptional regulatory function [21].

⁶ Biliary tract cancer is a highly malignant tumor that starts from bile duct epithelium. The production of inflammatory cytokines as a result of persistent infection created an inflammatory milieu that affects BTC carcinogenesis. A key player in BTC carcinogenesis, angiogenesis, proliferation, and metastasis is IL-6 which is a multifunctional cytokine that is released ⁶ by kupffer cells, tumor-associated macrophages, cancer-associated fibroblasts (CAFs), and cancer cells[22].

Furthermore, BTC is monitored, diagnosed, and prognosed for using IL-6 as a clinical biomarker. Furthermore, preclinical data suggests that IL-6 antibodies may increase the susceptibility of tumor immune checkpoint inhibitors (ICIs) by modulating the number of immune cells that infiltrate the tumor and controlling the expression of immunological checkpoints in the tumor microenvironment. It has recently been demonstrated that IL-6 induces the expression of programmed death ligand 1 in iCCA via means of the mTOR pathway. Nevertheless, there is not enough data to conclude that IL-6 antibodies might strengthen immune responses and possibly overcome BTC's resistance to ICIs[22].

In the biliary system, where ongoing inflammation significantly predisposes to cholangiocarcinoma, the relationship between chronic inflammation and the onset and spread of cancer is well illustrated. Through altered gene expression through autocrine processes, inflammatory cytokines such as IL-6 promote tumor development in cholangiocarcinomas[23].

Additionally, abnormal DNA methylation can contribute to carcinogenesis. IL-6 can influence the activity of DNA methyltransferases. Thus, it observed how long-term exposure to IL-6 affected methylation-dependent gene expression and altered cell development in cholangiocarcinoma in humans. Malignant cholangiocytes that had been stably transfected to overexpress IL-6 were used to evaluate the connection between autocrine IL-6 pathways, DNA methylation, and altered cell proliferation[23].

The methylcytosine concentration, growth in soft agar, and cell proliferation of malignant cholangiocytes were all reduced when the DNA methylation inhibitor 5-aza-2'-deoxycytidine was applied. On the other hand, IL-6-overexpressing cells did not exhibit this impact. The overexpression of IL-6 Led to modifications in the expression and promoter methylation of many genes, one of which being the epidermal growth factor receptor (EGFR). IL-6 enhanced gene and protein expression while decreasing EGFR promoter methylation[23].

Because IL-6 modifies the promoter methylation and gene expression of growth-regulatory pathways, including EGFR, it can thus contribute to the evolution of tumors

through epigenetic control of gene expression. Additionally, increased IL-6 expression could make tumor cells less sensitive to methylation inhibitor-based therapeutic interventions. ¹ These observations have important implications for cancer treatment and provide a mechanism, by which persistent cytokine stimulation can promote tumor growth[23].

Elevated levels of serum IL-6 have been associated with the start and progression of CCA, a common cancer generated by inflammation. ³ By employing multiplex immunofluorescence, it was possible to identify the expressions of IL-6, IL-6R, glycoprotein (gp130), C-reactive protein (CRP), Janus kinase 2 (JAK2), and signal transducer and activator of transcription 3 (STAT3) in CCA tissue microarray. It showed that in tumor tissues compared to normal tissues, STAT3 expression was greater and IL-6 expression was lower[24].

The expression of genes involved in the IL-6 pathway was usually downregulated, particularly in the tumor microenvironment. It's significant to note that gp130 and JAK2 showed a substantial correlation in tumor tissues but just a modest correlation in normal tissue. ³ IL-6, IL-6R, CRP, gp130, and JAK2 were inversely connected with vascular invasion, which is a risk factor for a poor prognosis in patients with CCA, even though ³ none of the gene expressions were directly linked to overall survival or disease-free survival. IL-6 signaling pathway can be useful in predicting the prognosis of CCA [24].

A malignant tumor of the biliary system, BTC includes CCA and gallbladder carcinoma (GBC). Because of delayed diagnosis and fast disease development, the 5-year survival rate for BTC is between 5 and 18%. One major risk factor for CCA and GBC specifically, is chronic inflammation. When IL-6 is released from the body, it can do so through soluble forms (sIL-6R, or "IL-6 trans-signaling") or by a membrane-bound receptor alpha-chain (mIL-6R, or "IL-6 classic signaling"). Still, not much is understood about how IL-6 trans-signaling affects BTC's cellular responses. It included searching The Cancer Genome Atlas database and analyzing original tumors as entire sections and tissue microarrays[25].

The overall survival of the patients was linked with the downregulation of IL-6R α in GBC as compared to non-inflammatory, non-neoplastic gallbladder tissue. Moreover, several CCA cell lines and substances for IL-6 traditional signaling and trans-signaling activation (IL-6 and Hyper-IL-6) or inhibition (Tocilizumab and sgp130Fc) were employed to ascertain their impacts on cellular processes between the two IL-6 signaling modalities. When sgp130Fc inhibited IL-6 trans-signaling, CCA cell line survival and apoptosis decreased while migration and proliferation increased. For GBC, IL-6R α expression is a favorable prognostic indicator. Additionally, tumor promotion can be achieved by activating IL-6 traditional signaling and suppressing IL-6 trans-signaling. These results support excluding individuals receiving IL-6R inhibitor medication if they have GBC or other cancers linked to bile metabolism [25].

Hepatobiliary carcinoma patients had higher levels of IL-6 than healthy controls. Increased pain ratings, a worse prognosis, and subpar performance status in patients were all linked to higher levels of IL-6. It discovered a correlation between high IL-6 Levels and portal vein thrombosis (PVT) around the time of cancer diagnosis[26].

Cholangiocarcinoma cells exhibit abnormal persistent phosphorylation (activation) of STAT-3, a signal transducer and activator of transcription 3 that leads to increased myeloid cell leukaemia 1 (Mcl-1) expression and resistance to apoptosis. This activation is mediated by IL-6. Another study investigated SOCS-3 regulation in human cholangiocarcinoma because the suppressor of cytokine signaling 3 (SOCS) regulates the IL-6/STAT-3 signaling pathway through a traditional feedback loops. The Mz-ChA-1 and CCLP1 human cholangiocarcinoma cell lines, as well as human cholangiocarcinoma tissue, were used to measure SOCS-3 expression. In cholangiocarcinoma, there was an inverse relationship found between the expression of SOCS-3 protein and phospho-STAT-3[27].

The SOCS-3 promoter showed significant methylation in the tumor but not in the corresponding no-tumor tissue in those tumors that did not express SOCS-3. Similarly, it was shown that two cholangiocarcinoma cell lines had methylation of the socs-3 promoter. Treatment with 5-aza-2'-deoxycytidine (DAC), a demethylating agent, ended

the phospho-STAT-3 response, decreased the amount of Mcl-1 in cells, and restored the induction of SOCS-3 by IL-6. The induction of Mcl-1 and phospho-STAT-3 by IL-6 was likewise inhibited by enforced SOCS-3 expression. The cells were rendered more susceptible to TRAIL-mediated apoptosis by either DAC treatment or induced SOCS-3 expression. Extended IL-6/STAT-3 signaling and elevated Mcl-1 expressions in cholangiocarcinoma are caused by SOCS-3 epigenetic silencing[27].

Due to inadequate diagnosis methods and limited clinical value, intrahepatic cholangiocarcinoma (iCCA) is a deadly bile system malignancy with a poor prognosis. Peripheral blood indices and cytokine levels were examined to diagnose iCCA. Both the lymphocyte-to-monocyte ratio (LMR) and IL6 can predict iCCA (AUC = 0.91 (0.85-0.97) and 0.81 (0.68-0.93); sensitivity and specificity are 0.70 and 0.91 and 0.85, respectively. Individuals are susceptible to developing iCCA if their LMR is less than 7.2 (OR = 58.08, $P < 0.001$) or if their IL6 concentration is more than 11.635 pg/mL (OR = 23.33, $P < 0.001$)[28].

The poor prognosis and lack of effective therapies associated with biliary tract cancers pose problems. Recent research has demonstrated the growth factor status of IL-6 in human bile duct epithelium and its association with tumor burden. After photodynamic treatment (PDT), it assessed the change in IL-6 blood levels in cholangiocarcinoma patients. Patients with BDC had higher blood levels of IL-6, as this prospective research shows. Furthermore, it indicated the function of IL-6 as a tumor marker following PDT[29].

Chronic inflammation may be a contributing factor in the development of cholangiocarcinomas, since inflammation may provide survival signals to the malignancy[30].

It demonstrated the autocrine contribution of the inflammatory cytokine-like IL-6 to survival signals and the significant role played by myeloid cell leukaemia-1 (Mcl-1), an antiapoptotic member of the B-cell leukemia-2 family, in the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) resistance in this neoplasm. This study assessed whether Mcl-1 over-expression in cholangiocarcinoma is caused in part by IL-6

signaling. Using immunohistochemistry, the expression of Mcl-1 and protein kinase B (Akt) in human tissue was evaluated. In cell lines, the connection between IL-6 signaling, Akt activity, and Mcl-1 expression was investigated[30].

The preneoplastic bile duct inflammatory illness primary sclerosing cholangitis and human cholangiocarcinoma tissues both have significant expressions of the serine/threonine kinases Akt and Mcl-1. Three human cholangiocarcinoma lines had constitutively phosphorylated Akt, as shown by immunoblotting. Subsequent investigation revealed that anti-IL-6-neutralizing antiserum therapy resulted in decreased Mcl-1 expression, lower Akt phosphorylation, and increased TRAIL sensitivity. Similarly, reduced Akt pathway activation, reduced Mcl-1 expression, and increased TRAIL-mediated apoptosis were seen with the Akt inhibitor A443654.3. These results demonstrate that Mcl-1 expression was elevated in cholangiocarcinoma due to an autocrine IL-6/Akt signaling pathway, and they also offer a potential method to overcome the apoptosis resistance[30].

Rat thioacetamide (TAA)-induced intrahepatic CCA shares histological and molecular similarities with human iCCA. In TAA-CCAs, activation of the EGFR and IL6 pathways, as well as important genes involved in cancer-related glucose metabolic reprogramming were confirmed. A further epigenetic pro-tumorigenic writer, G9a, was upregulated in TAA-CCAs. It demonstrated that both mutant KRAS^{G12D} and EGFR signaling may stimulate IL6 production in CCA cells. Moreover, there was an upregulation of phosphoglycerate dehydrogenase (PHGDH), the rate-limiting enzyme in the serine-glycine pathway, in human iCCA, which was associated with the expression of G9a[31].

KRAS^{G12D} enhanced PHGDH expression, glucose flow towards serine synthesis, and CCA cell survival in a way that was reliant on G9a activity. Compared to controls, KRAS^{G12D} CAA cells were more susceptible to PHGDH and G9a inhibition. G9a pharmacological targeting decreased PHGDH expression in mouse iCCA. It discovered novel pro-tumorigenic pathways in CCA. The serine-glycine pathway is activated during glucose metabolism reprogramming in insulin-producing cancers (iCCA);

mutant KRAS drives PHGDH production in a G9a-dependent manner; PHGDH and G9a emerge as therapeutic targets in iCCA; EGFR signaling activation or KRAS mutation promotes IL6 expression in tumor cells [31].

INTERLEUKIN-8

Of the specialized cytokines produced and released by different normal and malignant human cell types, interleukin-8 (IL-8) is a member of the chemokine family. Its ability to cause leukocytes to migrate in a specific direction is what makes these cytokines unique. Their secretion usually occurs in reaction to pathophysiological circumstances, inflammatory cytokines, and growth factors[32-34].

As a chemotactic agent generated by activated monocytes and macrophages, IL-8 was one of the first chemokines to be discovered. It promoted the directed migration of neutrophils, basophils, and T lymphocytes. Subsequently, it was revealed that IL-8 plays a significant part in autoimmune, inflammatory, and infectious diseases. Due to its strong pro-inflammatory characteristics, tight regulation is in place, resulting in low or undetectable expression in normal tissues[35-39].

The 5-year survival rate for **intrahepatic cholangiocarcinoma (ICC)** which **is a rare but extremely aggressive malignant tumor** that arises **within the liver**, is about 20-40% following surgery. It is still unclear how IL-8 contributes to the development of ICC. The prometastatic gene CD97 and important epithelial-mesenchymal transition components vimentin and E-cadherin were first shown to be significantly upregulated using a transcriptome technique based on IL-8 stimulation. They are both independent predictors of the ICC prognosis, according to multivariable Cox regression. In QBE and QBC-939 cells, IL-8 administration mechanistically produced CD97 expression at 50 and 100 ng/mL, respectively[40].

Furthermore, EMT-associated gene expression was significantly suppressed, and CD97 RNA interference reduced the IL-8-induced stimulation of cell migration and invasion. When siCXCR2 was used, it was demonstrated to dramatically reduce the carcinogenic effects of IL-8 by preventing the phosphorylation of PI3K/AKT, therefore

indicating whether CXCR1 or CXCR2 are downstream effectors of IL-8. Ultimately, the PI3K pathway's stimulation of CD97 expression was confirmed by the administration of the inhibitor LY294002[40].

When CD97 was silenced in nude mice, the substantial effects of IL-8 injection on lung metastasis and tumor development were significantly reduced in vivo. The work as a whole provides a unique mechanism of the IL-8-CXCR2-PI3K/AKT axis in controlling CD97 expression, which mostly results in EMT-mediated ICC metastasis. Targeting the tumor microenvironment in metastatic ICC may have different options[40].

The biological processes, particularly the growth of cancer, have been linked to IL-8, matrix metalloproteinase-9 (MMP-9) and neovascularization. Nevertheless, not much research has been done on the function of IL-8 in human hilar cholangiocarcinoma. To assess the clinicopathological importance and prognostic usefulness of IL-8, MMP-9, and microvessel density (MVD) in hilar cholangiocarcinoma was investigated. It examined the relationship between IL-8 and MMP-9 expression, MVD, clinicopathological characteristics, and patient survival time[41].

A significant correlation was found between the expression of IL-8 in 56.5% of tumors and the advanced TNM stage as well as tumor recurrence. MVD and MMP-9 expression showed a promising connection with IL-8. Additionally, patients' overall survival was considerably lower in those with high IL-8 expression compared to those with low expression. IL-8 was validated as an independent prognostic factor by multivariate analysis. In summary, MVD and IL-8 expression showed a substantial correlation, and IL-8 was a useful predictor of human hilar cholangiocarcinoma[41].

INTERLEUKIN-10

Together with TGF- β and IL-35, interleukin-10 (IL-10) is an essential anti-inflammatory cytokine. The primary producers of IL-10 are activated immune cells, namely monocytes/macrophages and T cell subsets like Treg, Th1, and Th1. Working via a transmembrane receptor complex made up of IL-10R1 and IL-10R2, IL-10 efficiently

controls the activities of different immune cells. In monocytes/macrophages, IL-10 promotes antigen absorption while inhibiting the generation of inflammatory mediators and impeding antigen presentation. Moreover, IL-10 is important for the biological functions of T and B cells [42].

It has been demonstrated that the development of certain malignancies, including ICC is correlated with M2-polarized tumor-associated macrophages (M2-TAMs). Nevertheless, it is unclear exactly how M2 macrophages and ICC interact with one another. Another study aimed to ascertain if M2 macrophages contribute to the ICC's malignancy and how. In both of the mouse models, it was discovered that the ICC tissues had a notably larger concentration of M2 macrophages than the normal bile ducts. Compared to intratumoral regions and normal liver, there was a significant increase in M2 macrophage infiltration in peritumoral areas[43].

The M2-TAM phenotype was produced by ICC cells in macrophages, and the *in vitro* proliferation, invasion, and epithelial-mesenchymal transition (EMT) of ICC cells were enhanced by coculturing with these M2 macrophages. Mechanistically, STAT3 signaling was used by IL-10 produced from M2-TAM to enhance the malignant characteristics of ICC cells. Additionally, M2 macrophage effects on ICC were somewhat mitigated by blocking IL-10/STAT3 signaling[43].

INTERLEUKIN-17

One important cytokine that connects T-cell activation to neutrophil mobilization and activation is interleukin-17 (IL-17; often referred to as IL-17A). Therefore, IL-17 may either have a role in the pathophysiology of inflammatory illnesses like psoriasis and rheumatoid arthritis or mediate beneficial innate immunity against pathogens. According to a growing body of research using both human and animal models, IL-17 signaling ultimately contributes to the development of illness. IL-17 has strong pro-osteoclastogenic effects in addition to stimulating neutrophilic inflammation, which may aid in the aetiology of rheumatoid arthritis, periodontitis, and other disorders involving bone immunopathology [44].

A chronic inflammatory illness of the biliary tract that increases the chance of developing CCA is called primary sclerosing cholangitis (PSC). It is believed that a chronic inflammatory milieu plays a crucial role in the pathogenesis of CCA associated with PSC, but this is not entirely understood. Another study investigated how the proliferation rate of cancer cells was affected by cytokines associated with inflammation in PSC. For this, Ki-67 immunohistochemistry was used to calculate the proliferation index in PSC-CCA and spontaneous CCA[45].

Compared to random CCA, PSC-CCA had a considerably greater percentage of Ki-67 positive cancer cells. Patient-derived CCA organoids (CCAOs) were exposed to five PSC-related cytokines (interleukin (IL)-1 β , IL-6, IL-17A, interferon-gamma, and tumor necrosis factor-alpha) to determine whether cytokines in the inflammatory milieu could induce cancer cell growth. In CCAOs, organoid size increased by 45.9% \pm 16.4% ($P < .01$) and proliferation rate by 38% \pm 16% ($P < .05$) in response to IL-17A being the only stimulant that showed a meaningful effect on cell proliferation. According to IL-17A immunohistochemistry, PSC-CCA may express higher IL-17A than random CCA[45].

Furthermore, IL-17A expression and proliferation were revealed to be significantly correlated in both PSC-CCA and random CCA by correlation analysis. In summary, compared to sporadic CCA cells, PSC-CCA cells exhibit higher tumor cell proliferation. In vitro, IL-17A promotes the proliferation of CCA cells, which might be a factor in the high rate of proliferation seen in PSC-CCA in situ. Thus, IL-17A is a novel target for possible therapy in (PSC-)CCA that will be investigated in upcoming studies[45].

It is uncertain if the proliferative cytokine IL-22 and the proinflammatory cytokine IL-17A are involved in the inflammatory and immunological mechanisms that cause CCA linked to liver fluke infection. In this instance, the quantities of Th cells that produced IL-22 and IL-17A as well as the levels of cytokines in 30 patients with chronic liver fluke infection and CCA, 40 patients with hepatic fluke infection but no CCA, and 16 healthy controls were compared. When liver fluke infection was present in CCA patients, immunohistochemical labeling revealed lower expression of IL-22 and IL-17A ($P < 0.01$). Patients with CCA had a considerably higher median percentage of IL-22-

producing T helper cells (2.2%) according to flow cytometry than did patients without it (0.69%) or controls (0.4%, $P < 0.001$)[46].

For T helper cells that produced IL-17A, similar outcomes were seen. It demonstrated that plasma concentrations of IL-22 were 4.6 times higher in controls and 1.3 times higher in patients with CCA than in those without it ($P < 0.001$). IL-17A plasma concentrations were 2.5 times higher in CCA patients than in non-patients and 21 times higher in controls[46].

Patients with CCA had considerably greater blood levels of IL-22 and IL-17A mRNAs than did the other two groups. Plasma concentrations of IL-22 were associated with those of IL-17A, as were the percentage of CD4+CD45RO+ T cells generating IL-22 and IL-17A. It is suggested that IL-17A and IL-22 have an impact on the development of CCA associated with hepatic fluke infection[46].

INTERLEUKIN-23

A cytokine with pro-inflammatory characteristics, interleukin-23 (IL-23) belongs to the IL-12 family. Its capacity to significantly boost T helper type 17 (Th17) cell proliferation suggests that it is the cause of several inflammatory autoimmune reactions. Recent research indicates that IL-23 plays a pivotal role in the central control of the inflammatory cell pathways. Through Th17 cells, IL-23 and IL-17 establish a novel axis that has developed in response to human illnesses such as bacterial or viral infections, chronic inflammation, and immunopathology. One possible treatment strategy for autoimmune illnesses, such as psoriasis, multiple sclerosis, inflammatory bowel disease, and rheumatoid arthritis, is to target IL-23, the IL-23 receptor, or the IL-23 axis [47].

Intrahepatic cholangiocarcinoma has an extremely bad prognosis while having a low incidence. Cancer incidence and development are correlated with the expression level of the interleukin 23 receptor (IL23R). The Gene Expression Omnibus (GEO) database provided the messenger RNA (mRNA), microRNA (iRNA), and circular RNA (circRNA) datasets. Functional enrichment analysis was performed using the Kyoto

Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO), and the results were confirmed using gene set enrichment analysis software[48].

Clinical data were sourced from The Cancer Genome Atlas (TCGA), and the DriverDBv3 database and Gene Expression Profiling Interactive Analysis website were utilized for survival analysis. The immune cell infiltration investigation of IL23R was obtained from the TIMER2.0 database. Verification of IL23R expression was done by real-time quantitative polymerase chain reaction or RT-qPCR. Differentially expressed (DE) mRNAs were shown to be more abundant in the immune-related tumor microenvironment, amino acid metabolism, and the phosphoinositide 3-kinase-serine/threonine kinase signaling pathway. Moreover, cells linked to immune infiltration were linked to the expression of IL23R[48].

Moreover, networks of circRNA-miRNA-IL23R and IL23R protein-protein interactions were created. The most significant finding was the decreased expression of IL23R, a prognostic gene, in intrahepatic cholangiocarcinoma. Further investigation into the potential prognostic and immune-related biomarkers of IL23R in intrahepatic cholangiocarcinoma is warranted, as evidenced by the identification of a circRNA-miRNA-IL23R network[48].

INTERLEUKIN-25

The cytokine family IL-17 includes interleukin 25 (IL-25), commonly referred to as IL-17E, which is a crucial modulator of the type 2 immune response. A growing body of research indicates that IL-25 has a complex role in many organ systems and interacts with a variety of immune and non-immune cells. The physiology and pathophysiology of the gut have been somewhat explored concerning IL-25. Since the gut is a major source of epithelial cells, IL-25 is involved in intestinal immune responses and is linked to the development of cancer tumors, autoimmune disorders, and incorrect allergy reactions [49].

Tumor growth and carcinogenesis are influenced by a variety of cytokines. Certain tumor cells can manufacture cytokines on their own. APEX-1 was shown to be highly

expressed in CCA cell lines by secretome profiling. It was discovered through this secretome analysis that CCA cell lines overexpressed IL-25 and other associated cytokines. The current work determined that CCA cell lines have overexpressed IL-25 by performing detailed secretome analysis on cytokines and associated chemicals in CCA cell lines. ¹ The expression of IL-25 in the cancer tissues of 20 CCA patients in Northeastern Thailand was then examined utilizing immunohistochemistry techniques[50].

The clinical characteristics of the patients and the levels of IL-25 expression were correlated. The findings demonstrated that compared to normal bile ducts and surrounding tissues, malignant tissues had considerably greater levels of IL-25 expression. Western blot analysis was used to confirm that the IL-25 protein was overexpressed in CCA tissue. Furthermore, CCA patients with metastasis had considerably greater levels of IL-25 expression in malignant tissues compared to those without metastasis[50].

A higher expression of IL-25 was linked to a shorter survival period for CCA patients, according to survival analysis. It has been suggested that IL-25 may be a useful prognostic biomarker as aberrant expression of the protein in CCA tissue was linked to tumor spread and a poor prognosis. Future research on the biological functions of IL-25 in the origin and development of CCA is warranted[50].

INTERLEUKIN-33

³ As an alarmin cytokine, interleukin-33 (IL-33), a member of the IL-1 family, has critical roles in cancer, viral infection, allergic and non-allergic inflammation, tissue homeostasis and repair, and type 2 immunity. ¹³ The nuclei of tissue-derived cells, such as blood vessel endothelial cells, barrier tissue epithelial cells, and fibroblastic stromal cells from diverse tissues, are rich in IL-33. When cells express the ST2 (IL-1RL1) receptor, IL-33 is produced in response to cell damage or tissue injury, activating signaling pathways that are dependent on Myd88. Studies conducted in murine models and analysis of human samples confirm the critical role that IL-33/ST2 signaling plays in

allergic inflammation in a variety of tissues and illnesses. Among the most often repeated susceptibility loci for asthma are IL33 and IL1RL1/ST2. However, the IL-33/ST2 pathway also plays a significant role in non-allergic inflammation [51].

CCA develops more easily in a mouse model when IL-33 an alarmin generated upon tissue damage is present. The relationship between IL-33 and human CCA is not entirely understood, though. During hepatectomy for CCA, IL-33 is produced, which then promotes the growth of subclinical CCA and ultimately results in recurrent illness. It evaluated the expression of IL-33 in a range of human and mouse samples, including resected liver and matched plasma samples taken during and after hepatectomy, and found that it had an impact on recurrent disease and prognosis[52].

When homogenized human liver tissues with either high or low IL-33 expression were introduced to the human CCA cells' growth media, the alterations in migration and proliferation were assessed. To investigate the impact of blocking the hepatectomy-induced release of IL-33, murine CCA cells were syngraft transplanted into C57BL/6J mice, either with or without IL-33 blockage. There was a correlation between the baseline liver expression and the quantity of IL-33 released into the plasma following hepatectomy[52].

An independent risk factor for recurrence was the high expression of IL-33 in the liver. Tumor cell migration and proliferation were both accelerated by homogenized liver tissue that expressed IL-33 significantly. Hepatectomy-affected mice showed CCA development in the remaining liver, although tumor progression was prevented by blocking IL-33 during the procedure. Consequently, a curative hepatectomy for CCA promoted the release of IL-33, which in turn made CCA recurrence easier, and hepatectomy anti-IL-33 treatment may lower the chance of CCA recurrence[52].

INTERLEUKIN-35

Immunoregulatory cell populations and immunosuppressive cytokines sustain the equilibrium between inflammatory and anti-inflammatory immune responses. An inhibitory cytokine that is a member of the IL-12 family, interleukin-35 (IL-35) can cause

induced regulatory T cells (iT_h35) to produce IL-35 and effectively reduce T cell proliferation. This helps to control inflammatory reactions. A growing body of research conducted in the last ten years has shown that IL-35 is crucial in regulating immune-related conditions, such as cancer, infectious illnesses, and autoimmune diseases [53].

Though its precise effect on ICC is unknown, IL-35 is linked to carcinogenesis. Examining the precise impact of IL-35 on patient prognosis was the goal of the current investigation. Furthermore, following curative resection, it developed an efficient prognostic nomogram for ICC patients. To investigate IL-35 expression and IL-35 receptor (IL-35R) in 102 ICC patients, immunohistochemistry was used. IL-35 was substantially expressed in ICC tumor tissues, was correlated with lymph node metastasis (LNM), TNM stage, and vascular invasion, and served as a stand-alone predictor of patients' OS and RFS (recurrence-free survival)[54].

The ICC cancer tissues exhibited elevated expression of IL-35R (gp130 and IL-12R β 2). However, just gp130 exhibited independent prognostic significance for OS and RFS and was essential for the IL-35-mediated prognosis of ICC. When compared to the TNM stage for OS, the nomogram containing carcinoembryonic antigen, LNM, IL-35, and gp130 expression had a higher predictive accuracy. This finding validates the correlation between high IL-35 expression and aggressiveness in ICC, highlighting it as a useful biomarker for assessing the course and prognosis of ICC in clinical settings[54].

In the pathophysiology of cholangiocarcinoma, cytokines such as IL-1, IL-4, IL-6, IL-8, IL-10, IL-17, IL-23, IL-25, IL-33, and IL-35 play a crucial role by coordinating a complex interaction between inflammation, immune evasion, tumor microenvironment modification, and tumor growth. Through processes including angiogenesis, chronic inflammation, and the epithelial-mesenchymal transition (EMT), pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-17, IL-23, and IL-33 encourage the development and spread of tumors. Cytokines such as IL-4, IL-10, IL-25, and IL-35, on the other hand, help create an immunosuppressive milieu that promotes tumor immune escape and treatment resistance. New approaches to treatments become possible when the precise functions and interconnections of these cytokines are understood. Targeting cytokine

signaling pathways may provide new techniques to break the inflammatory environment that supports tumor growth and reestablish efficient anti-tumor immunity. Future studies should concentrate on creating cytokine-based biomarkers for early diagnosis and prognosis, creating selective cytokine inhibitors, and creating combination therapies that incorporate cytokine modulation with currently used treatments including immunotherapy, chemotherapy, and targeted medicines. To maximize the timing and specificity of therapies, it will also be crucial to clarify the temporal and spatial expression patterns of these cytokines during cholangiocarcinogenesis. Ultimately, a deeper molecular understanding of cytokine networks in CCA will pave the way toward more personalized and effective treatment strategies, improving patient outcomes in this aggressive malignancy.

CONCLUSION

CCA is a type of cancer that originates in the bile ducts, and its pathogenesis is influenced by various factors, including chronic inflammation. Interleukins, which are a group of cytokines, play a crucial role in mediating the immune response and inflammation. This article concluded that ⁵IL-1, IL-4, IL-6, IL-8, IL-10, IL-17, IL-23, IL-25, IL-33 and IL-35 play significant roles in the pathogenesis of CCA as explained in Figure 1 and Table 1. Further research is required to find the association of other ILs such as IL-3, IL-5, IL-7, IL-11 and more in the pathogenesis of CCA. ILs contribute to cholangiocarcinoma pathogenesis by promoting chronic inflammation, enhancing tumor cell survival, proliferation, and invasion, and shaping a tumor microenvironment that supports cancer growth and metastasis. Controlling the pathogenesis of ILs in cholangiocarcinoma requires a multifaceted approach, including targeted therapies, immunotherapies, and lifestyle modifications. By inhibiting the signaling pathways and reducing the inflammatory responses mediated by ILs, it is possible to slow or prevent the progression of cholangiocarcinoma.

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