ISSN 2618-1584 Vol. 8, Issue 3: 41-47, DOI: 10.25236/FMSR.2026.080306

Research on Acetylation Modifications in the Occurrence, Development, and Treatment of Cholangiocarcinoma

Lei Peng[1,2,a], Lu Yueyue[1,b,*]

[1]*The First Affiliated Hospital of Yangtze University, Jingzhou, Hubei, 434000, China*
[2]*School of Clinical Medicine, Yangtze University, Jingzhou, Hubei, 434000, China*
[a]*2315949969@qq.com,* [b] *453369050@qq.com*
[*]*Corresponding author*

Abstract: *Cholangiocarcinoma (CCA) is one of the most aggressive malignant tumors of the hepatobiliary system, characterized by a complex pathogenesis and limited treatment options, leading to generally poor patient prognosis. In recent years, the role of metabolic reprogramming in tumor development has become a research hotspot, with increasing attention on the regulatory mechanisms of acetylation modifications mediated by acetyl-CoA in cholangiocarcinoma. This article systematically reviews the molecular mechanisms of acetylation modifications in cholangiocarcinoma, including the metabolic pathways of acetyl-CoA and its interactions with other metabolic networks, as well as its regulatory effects on malignant phenotypes such as tumor cell proliferation, invasion, and metastasis. Additionally, the critical role of acetylation modifications in reshaping the tumor immune microenvironment and the formation of treatment resistance is emphasized. Furthermore, this article summarizes the clinical application value of acetylation-based biomarkers in the diagnosis and prognosis assessment of cholangiocarcinoma, along with the latest research progress on targeted acetylation treatment strategies, providing new insights and potential intervention targets for the precise diagnosis and treatment of cholangiocarcinoma.*

Keywords: *Cholangiocarcinoma; Acetylation; Acetyl-CoA; Metabolic Reprogramming; Targeted Therapy*

1. Introduction

Cholangiocarcinoma (CCA) is a highly invasive malignant tumor of the biliary system, which, despite accounting for only 3% of gastrointestinal tumors, has shown a significant increase in global incidence and poor prognosis, with a five-year survival rate of only 7-20%[1]. Between 1995 and 2022, the incidence and mortality rates of cholangiocarcinoma have risen from 3.93 per 100,000 person-years in 1995 to 6.79 per 100,000 person-years in 2022, with intrahepatic cholangiocarcinoma being the primary driving factor[2]. Gad et al. conducted a comprehensive analysis based on the SEER database in the United States (2000-2015), revealing a significant increase in the incidence of CCA during this period, confirming that intrahepatic CCA (iCCA) is the main driving factor[3]. The rising incidence of CCA may be associated with metabolic diseases (such as diabetes and obesity)[4,5], specific environmental or occupational exposures[6], and a high prevalence of liver fluke infections in certain regions. Tumor cells support proliferation and survival by altering energy metabolism pathways, which is one of the ten hallmarks of cancer. Tumor cells modify their metabolic pathways to meet the bioenergetic and biosynthetic precursor demands of rapid proliferation. In this process, acetyl-CoA serves as a central node in cellular metabolism, intersecting metabolic and epigenetic regulation[7]. Acetyl-CoA is not only a key substrate for energy metabolism and biosynthesis but also acts as a substrate for protein acetylation, influencing gene expression by modifying transcription factors[8]. Acetylation modifications are widely present and reversible post-translational modifications of proteins, dynamically regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs)[9]. As a key metabolic node and major energy producer, acetyl-CoA plays a significant role in cancer invasion and metastasis. For instance, inhibiting acetyl-CoA synthetase 2 (ACSS2) can suppress the progression of multiple myeloma and breast cancer. Other therapeutic targets, such as inhibitors of fatty acid synthase (FASN) and pyruvate dehydrogenase kinase (PDK) (e.g., sorafenib and TVB-2640), can also inhibit tumor growth by regulating acetyl-CoA metabolism. In terms of epigenetic regulation, HDACs

ISSN 2618-1584 Vol. 8, Issue 3: 41-47, DOI: 10.25236/FMSR.2026.080306

and HATs control the upregulation of genes associated with poor prognosis in gliomas, lung cancers, and other malignancies[10].

2. Molecular Mechanisms of Acetylation in Cholangiocarcinoma

2.1 Production and Metabolic Pathways of Acetylation

Coenzyme A is synthesized from L-cysteine, ATP, and vitamin B5, forming acetyl-CoA, propionyl-CoA, and other derivatives through thioester bonds, participating in the tricarboxylic acid cycle (TCA), fatty acid (FA) synthesis, and histone acetylation. Acetyl-CoA exhibits compartmentalized distribution and functionality within cells, with distinct synthesis pathways in mitochondria, cytoplasm, and the nucleus. In the nucleus, it is locally generated through ACSS2 (which utilizes acetate released from histone deacetylation) or the nuclear-localized pyruvate dehydrogenase complex (PDC), regulating histone acetylation and activating the transcription of oncogenes (such as MYC and cyclin D1). In the cytoplasm, ATP-citrate lyase (ACLY) converts citrate exported from mitochondria into cytoplasmic acetyl-CoA, driving de novo fatty acid synthesis, promoting tumor cell membrane formation, and energy storage[11,12]. In cholangiocarcinoma, ACC1 serves as the first rate-limiting enzyme in de novo lipid synthesis, and the upregulation of acetyl-CoA carboxylase 1 (ACC1) expression is closely associated with poor prognosis in CCA patients. Inhibiting ACC1 not only disrupts lipid synthesis but also leads to excessive acetylation of intracellular proteins, subsequently inhibiting the growth and migration of CCA cells[13]. This indicates that, although the primary function of ACC1 is to consume acetyl-CoA for lipid synthesis, changes in its activity can indirectly regulate global acetylation levels by affecting the metabolic flow of acetyl-CoA. On the other hand, the expression of acyl-CoA thioesterase 12 (ACOT12) is significantly downregulated in intrahepatic cholangiocarcinoma (ICC) tissues and is associated with poor prognosis[14]. The function of ACOT12 is to hydrolyze acetyl-CoA into acetate and coenzyme A; its downregulation implies reduced degradation of acetyl-CoA within cells, potentially leading to the accumulation of acetyl-CoA, thus providing more ample substrates for the acetylation of histones and non-histones, promoting tumor progression. Studies have also found that histone deacetylase inhibitors (HDACi) such as Romidepsin can induce depletion of intracellular acetyl-CoA, leading to the activation of the RAS pathway and triggering lethal metabolism in cells. This reveals that the metabolic homeostasis of acetyl-CoA is crucial for maintaining tumor cell survival, and its depletion could serve as an effective anticancer strategy.

2.2 Interaction of Acetylation with Other Metabolic Pathways

Acetyl-CoA is a central node in the cellular metabolic network, with extensive interactions with pathways of glucose metabolism, lipid metabolism, and redox homeostasis, collectively driving the malignant phenotype of cholangiocarcinoma. Saisomboon found that inhibitors of acetyl-CoA carboxylase 1 (ACC1) or ACC1 gene knockout lead to the accumulation of acetyl-CoA, significantly increasing the total protein acetylation levels in CCA cells, thereby inhibiting CCA colony formation and migratory capacity. This confirms that protein acetylation, in conjunction with AKT, regulates the AKT/GSK3β/Snail pathway to exert tumor-suppressive effects[13]. Acetyl-CoA carboxylase 1 (ACC1), as a key enzyme linking acetyl-CoA metabolism to lipid synthesis, directly influences the progression of CCA. Inhibition of ACC1 reduces its catalytic product, malonyl-CoA, thereby disrupting de novo lipid synthesis and promoting autophagy, while also inhibiting the migration of CCA cells through the activation of the AMPK-NF-κB-Snail axis (catalyzing the generation of AMP and activating AMPK)[15]. Additionally, Pan et al. discovered that Withaferin A serves as a potent dual inhibitor of lipid deposition and cholangiocarcinoma, effectively inhibiting CCA proliferation and lipid accumulation. The mechanism was confirmed as WA directly binds with high affinity to the Lys1338 site of ACC1, reducing ACC1 own malonylation (Lys1338-dependent), thereby releasing its shielding effect on the binding of SQSTM1/p62, activating selective autophagy degradation, and also inhibiting the enzyme to lower ACC1 catalytic product, malonyl-CoA, while increasing the substrate acetyl-CoA[16]. At the level of metabolic enzyme regulation, acetylation modifications can finely tune metabolic flux. Although research directly targeting acetylation of CCA metabolic enzymes is limited, previous findings indicate that histone acetyltransferase 1 (HAT1) can promote the succinylation of key glycolytic enzymes (such as PGAM1, ENO1, PKM) through succinyl-CoA binding at the critical site T188, accelerating glycolytic flux. The phenomenon of global protein hyperacetylation due to ACC1 inhibition and its impact on cell growth suggest that the acetylation state of metabolic enzymes

ISSN 2618-1584 Vol. 8, Issue 3: 41-47, DOI: 10.25236/FMSR.2026.080306

themselves may serve as an important regulatory switch in CCA metabolic reprogramming[13,17]. Furthermore, specific acetylation events exist in CCA, where NAD(+)-dependent deacetylase inhibitors significantly upregulated K50ac. The K50 acetylation of 14-3-3ε protein inhibits its binding to phosphorylated YAP1, leading to YAP1 activation and promoting CCA growth[18]. ACOT12 (acetyl-CoA hydrolase) lowers histone acetylation by hydrolyzing acetyl-CoA, thereby inhibiting the expression of key EMT factors, ultimately obstructing the migration and metastasis of ICC cells. YAP1, as a transcriptional co-activator, is the primary effector molecule downstream of the Hippo signaling pathway. [14]When YAP1 is activated and enters the nucleus, it binds with transcription factors such as TEAD, initiating a series of gene expressions that promote cell proliferation, inhibit apoptosis, and drive tumorigenesis and metastasis. Research shows that the K50 site of 14-3-3εprotein can undergo acetylation, inhibiting its interaction with phosphorylated YAP1, leading to YAP1 activation and nuclear entry, thus promoting CCA growth[19].

2.3 The Role of Acetylation in Tumor Cell Proliferation and Invasion

Acetylation modifications profoundly influence the proliferation, invasion, and metastatic capabilities of cholangiocarcinoma cells by regulating histones, non-histone proteins, and metabolic enzymes at multiple levels. At the epigenetic level, histone acetylation is a key mechanism regulating gene transcription. Histone deacetylase 3 (HDAC3) is significantly overexpressed in CCA tissues and is closely associated with reduced patient survival. The class I HDAC selective inhibitor, romidepsin, promotes the acetylation of the transcription factor FOXO1 by inhibiting HDAC3 expression, thereby activating the autophagy pathway and inducing autophagy and apoptosis in CCA cells, ultimately inhibiting tumor growth[20]. Deng et al. similarly found that Lenvatinib upregulates AZGP1 expression by increasing the acetylation level of H3K27Ac in the AZGP1 promoter region while inhibiting histone deacetylases, but does not directly bind to the AZGP1 protein. This study revealed that Lenvatinib specifically downregulates TGF-β1 and phosphorylated Smad3 (p-Smad3) through the AZGP1/TGF-β1/Smad3 axis, inhibiting epithelial-mesenchymal transition (EMT) markers (N-cadherin, Vimentin) and upregulating E-cadherin, thus suppressing the EMT of ICC[21]. These findings indicate that targeting the balance of histone acetylation/deacetylation is an effective means to regulate the expression of oncogenes or tumor suppressor genes in CCA. Kim et al. first revealed that the acetylation of glucose-regulated protein 78 (GRP78) hinders its translocation to the cell membrane, resulting in GRP78 retention in the cytoplasm. The reduction of cytosolic GRP78 leads to decreased AKT phosphorylation, subsequently lowering the phosphorylation of Bad protein and promoting apoptosis in CCA[22]. At the level of metabolic enzyme regulation, acetylation modifications can finely tune metabolism. Although direct studies targeting acetylation of CCA metabolic enzymes are limited, the aforementioned succinylation of PGAM1 at the K99 site by HAT1 enhances its enzymatic activity, promoting glycolysis in cancer cells. The phenomenon of global protein hyperacetylation due to ACC1 knockout[23], accompanied by specific acetylation of HSP90β, PEX1, and POTEE[13], further suggests that the acetylation state of metabolic enzymes may serve as a critical regulatory switch in CCA metabolic reprogramming.

3. The Role of Acetylation in Immune Regulation and Drug Resistance in Cholangiocarcinoma

3.1 The Impact of Acetylation on the Tumor Immune Microenvironment

Acetylation modifications play a crucial role in shaping the immunosuppressive tumor microenvironment in cholangiocarcinoma (CCA). The formation of this immunosuppressive environment is closely related to the complex interactions between tumor cells and infiltrating immune cells. The innate immune system significantly contributes to the immune microenvironment, where M2-type tumor-associated macrophages promote CCA progression through the IL-6/STAT3 pathway. Although natural killer (NK) cells possess antitumor potential, they are inhibited by TGF-β and PD-L1. Mature CD83+ dendritic cells in cholangiocarcinoma typically indicate a favorable prognosis; however, TGF-β in the CCA microenvironment suppresses their function. In the adaptive immune system, CD8+ T cells primarily infiltrate the fibrous septa rather than the tumor body. High infiltration of CD8+ T cells suggests better survival, but intratumoral upregulation of PD-L1 leads to immune evasion. Regulatory T cells (Tregs) inhibit immune responses through FoxP3 and IL-10, which are associated with lymphatic metastasis and reduced survival rates. Acetylation-related enzymes also affect the tumor microenvironment; for instance, ACSS2 promotes the formation of the transcription factor complex (CBP/HIF-2α) through HIF-2α acetylation, enhancing the expression of hypoxia-related genes (such as

ISSN 2618-1584 Vol. 8, Issue 3: 41-47, DOI: 10.25236/FMSR.2026.080306

erythropoietin, EPO) that support tumor cell survival[24]. Consequently, CCA has a low response rate to immune checkpoint inhibitors, attributed to its immunosuppressive microenvironment and "cold tumor" characteristics[25]. Ricci et al. systematically elucidated the impact of non-cellular components on the tumor immune microenvironment in intrahepatic cholangiocarcinoma, such as the extracellular matrix protein osteopontin, which promotes CCA progression via the Wnt/β-catenin pathway and chemokines activating the PI3K-AKT pathway through the CXCL12/CXCR4 axis[26]. The functional status of tumor-associated macrophages directly influences immune responses. Studies have shown that co-culturing tumor-associated macrophages with cholangiocarcinoma patient-derived organoids can promote organoid growth and induce resistance to chemotherapy[27]. Although the specific mechanisms require further exploration, existing evidence suggests that targeting immunosuppressive components in the tumor microenvironment and developing multimodal, multi-drug immunotherapy strategies are crucial directions for overcoming the immunosuppressive microenvironment of cholangiocarcinoma and improving therapeutic efficacy.

3.2 Acetylation Mediating Drug Resistance in Cholangiocarcinoma

Acetylation modifications mediate drug resistance in cholangiocarcinoma to chemotherapy and targeted therapies through various mechanisms, posing significant challenges in clinical treatment. In terms of chemotherapy resistance, gemcitabine and cisplatin are first-line standard treatment regimens for advanced cholangiocarcinoma; however, primary and acquired resistance are common[28]. The epithelial-mesenchymal transition (EMT) phenotype associated with acetylation modifications is linked to enhanced resistance. For example, in gemcitabine and 5-fluorouracil-resistant cholangiocarcinoma cells, proteomic analyses revealed upregulation of genes closely related to the EMT pathway (such as MET, LAMB1, ITGA3, NOTCH2, CDH2, NDRG1). Silencing these six genes with siRNA can reverse the resistant phenotype, inhibit CCA invasion, and enhance chemotherapy sensitivity[25]. High mobility group box 1 (HMGB1) is highly expressed in cholangiocarcinoma tissues, and acetylation of HMGB1 can promote its translocation from the intracellular to the extracellular space, subsequently inhibiting cell growth, migration, and invasion, while also enhancing sensitivity to gemcitabine and cisplatin[29]. In targeted therapy resistance, inhibitors targeting fibroblast growth factor receptor (FGFR) fusions have been approved for advanced cholangiocarcinoma treatment, but response rates are limited, and resistance develops rapidly. Inhibiting FGFR can feedback activate EGFR signaling, reinitiating the MEK/ERK and mTOR signaling pathways, diminishing the efficacy of FGFR inhibitors, and driving adaptive resistance. Combining EGFR inhibitors with FGFR inhibitors can persistently suppress downstream signaling and significantly induce apoptosis in ICC, and such combination regimens are also effective for certain FGFR2 mutations[30]. In terms of metabolic adaptive resistance, cholangiocarcinoma cells can remodel their metabolism to maintain survival under targeted therapy. Similarly, constructing a CCA cell line with ACC1 knockout revealed that inhibiting acetyl-CoA carboxylase 1 reduces intracellular lipid synthesis. ACC1 deficiency weakens the migration ability of cholangiocarcinoma cells via the AMPK-NF-κB-Snail axis, suggesting that combining ACC1 inhibitors with AMPK regulators may have clinical translational potential[15].

4. Clinical Research Progress: Acetyl-related Markers and Targeted Therapy

4.1 The Role of Acetylation-Related Biomarkers in Diagnosis and Prognosis

In vitro functional experiments confirmed that the deletion of acetyl-CoA acyltransferase 2 (ACAA2) activates the NF-κB signaling pathway, upregulating CXCL1 expression to recruit myeloid-derived suppressor cells (MDSCs) and Tregs, inhibiting antitumor immunity, and promoting HCC cell proliferation, migration, and invasion[31]. In recent years, multiple studies have indicated that the abnormal expression of acetylation-related metabolic enzymes and modifying enzymes is closely associated with the malignant progression of cholangiocarcinoma. Among them, the elevated expression levels of metabolic enzymes such as acetyl-CoA synthetase 2 (ACSS2) and pyruvate dehydrogenase kinase 1 (PDK1) can promote the generation of acetyl-CoA in tumor cells, thereby affecting the acetylation modifications of histones and non-histones and influencing gene transcription[32]. Dysregulation of histone acetyltransferases (such as p300, KAT2B) and deacetylases (such as HDAC1, HDAC6) has also been shown to be significantly associated with adverse pathological features of cholangiocarcinoma, such as TNM staging, lymph node metastasis, and vascular invasion[33]. In constructed antitumor models, KAT2B is frequently downregulated in CCA tissues, and its low expression is significantly correlated with poorer overall survival (OS) and

ISSN 2618-1584 Vol. 8, Issue 3: 41-47, DOI: 10.25236/FMSR.2026.080306

disease-free survival (DFS) in patients, indicating that KAT2B expression may serve as a potential prognostic biomarker for CCA[34]. Advances in mass spectrometry technology have provided new insights for non-invasive diagnosis of cholangiocarcinoma. Studies have found that changes in the levels of acetylated histone H3K27 and acetylated STAT3 in serum or tissue exosomes can reflect the biological characteristics of tumors[35]. The development of metabolite imaging technology offers a new dimension for clinical evaluation of cholangiocarcinoma. Positron emission tomography (PET) imaging using [11C] acetate or [18F] fluorinated acetate (FACE) can non-invasively assess the acetyl metabolic activity of tumors. Ding et al. discussed how histone acetyltransferases and deacetylases regulate immune responses in the tumor microenvironment by modifying immune-related molecules (such as PD-L1, CTLA-4), and proposed strategies for combining HDAC inhibitors (HDACi) with other immunotherapies[36].

4.2 Therapeutic Strategies Targeting Acetylation and Clinical Progress

HDAC inhibitors (HDACi) represent the most extensively studied drugs targeting acetylation at present. Pan-HDAC inhibitors such as vorinostat and panobinostat reverse the aberrant epigenetic status of tumor cells by inhibiting multiple HDAC isoforms, thereby inducing cell cycle arrest and apoptosis. Using a replicative senescence model, it has been verified that acetyl-CoA deficiency leads to reduced acetylation of key proteins and accelerates endothelial senescence by impairing mitochondrial function and cell cycle progression[37]. Cholangiocarcinoma (CCA) cells exhibit extensive metabolic reprogramming, including enhanced glycolysis and lipid synthesis[22].

Selective HDAC inhibitors, exemplified by the HDAC6-targeting ricolinostat, display more favorable safety profiles. Preclinical models have confirmed that ricolinostat sensitizes cholangiocarcinoma cells to chemotherapeutic agents including gemcitabine[38]. Notably, the combination of an HDAC inhibitor and a proteasome inhibitor has been approved for the treatment of relapsed multiple myeloma, representing a successful paradigm for overcoming NF-κB-mediated drug resistance. Several HDACi have entered Phase I/II clinical trials for cholangiocarcinoma, where they are evaluated in combination with standard chemotherapy regimens to assess synergistic efficacy[39].

Histone acetyltransferase (HAT) inhibitors constitute another promising class of targeted agents. p300 is highly expressed in cholangiocarcinoma tissues and serves as an independent risk factor for poor patient prognosis. In vitro experiments demonstrate that small-molecule inhibitors (e.g., C646, A-485) or siRNA-mediated knockdown of p300/CBP effectively inhibit proliferation and invasion, and induce cell cycle arrest and apoptosis in cholangiocarcinoma cell lines (e.g., HuCCT1, RBE, TFK-1). In mouse xenograft models, HAT inhibitors markedly suppress tumor growth and metastasis[34]. Emerging evidence also suggests that combined administration of HAT inhibitors with HDAC inhibitors (e.g., panobinostat) or DNA methyltransferase inhibitors may exert synergistic antitumor effects, offering an epigenetic "double-hit" strategy. Nevertheless, issues of selectivity and toxicity remain major obstacles to clinical translation, requiring further structural optimization to improve the therapeutic window.

Metabolic enzyme inhibitors regulate acetylation modification at the source. For instance, the ATP-citrate lyase (ACLY) inhibitor SB-204990 blocks acetyl-CoA production, concurrently targeting two pro-tumorigenic pathways: protein acetylation and lipid synthesis[40].

5. Conclusion and Outlook

Research on acetylation modifications in cholangiocarcinoma has gradually transitioned from basic mechanistic exploration to clinical translation. As a core regulatory node in metabolic reprogramming and malignant phenotypes, acetylation provides a new perspective for precise intervention in cholangiocarcinoma. The abnormalities in acetyl metabolic pathways, changes in the acetylation status of key proteins, and the dysregulation of HATs/HDACs collectively constitute the "acetylation switch" that drives malignant behaviors in tumors. This network not only regulates epigenetic reprogramming but also influences energy metabolism, DNA repair, and the immune microenvironment, promoting tumor proliferation, metastasis, and drug resistance. HDAC inhibitors have demonstrated clear efficacy in preclinical models by restoring the expression of tumor suppressor genes, inducing apoptosis, and enhancing chemotherapy sensitivity; early clinical trials have also validated their safety. However, the lack of selectivity of existing HDAC inhibitors may lead to toxic side effects, and the efficacy of monotherapy is limited, indicating the need to design more precise targeted strategies based on cholangiocarcinoma-specific acetylation profiles. Current research on the "double-edged sword" effect

ISSN 2618-1584 Vol. 8, Issue 3: 41-47, DOI: 10.25236/FMSR.2026.080306

of acetylation modifications remains controversial, as the inhibition of certain HDAC subtypes may simultaneously suppress tumor metastasis and weaken immune responses. To address this, it is necessary to distinguish pro-cancerous and anti-cancerous modification sites through multi-omics integrated analysis, and validate target specificity using organoid models and patient-derived xenografts (PDX). The study of acetylation modifications is driving the treatment of cholangiocarcinoma from a "one-size-fits-all" approach to a paradigm of "precise regulation." Despite the challenges that remain, the deep integration of basic and clinical research has the potential to make targeting the acetylation network a significant breakthrough in improving the prognosis of cholangiocarcinoma. Future efforts should focus on strengthening interdisciplinary collaboration to translate laboratory discoveries into quantifiable clinical benefits, ultimately achieving the goal of personalized treatment.

References

[1] Qurashi M, Vithayathil M, Khan S A. Epidemiology of cholangiocarcinoma[J]. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 2025, 51(2): 107064.

[2] Jensen M D, West J, Weber B, et al. Cholangiocarcinoma in denmark: Time-trends in incidence and mortality[J]. JHEP Reports, 2025, 7(9): 101493.

[3] Gad M M, Saad A M, Faisaluddin M, et al. Epidemiology of cholangiocarcinoma; united states incidence and mortality trends[J]. Clinics and Research in Hepatology and Gastroenterology, 2020, 44(6): 885-893.

[4] Da Fonseca L G, Hashizume P H, de Oliveira I S, et al. Association between metabolic disorders and cholangiocarcinoma: Impact of a postulated risk factor with rising incidence[J]. Cancers, 2022, 14(14): 3483.

[5] Kumar D, Bansal V, Raza S A, et al. Widening health disparities: Increasing cholangiocarcinoma incidence in an underserved population[J]. Gastro Hep Advances, 2022, 1(2): 180-185.

[6] Kumagai S. Mini-review: Occupational health topics series on the effects of chemicals. Occupational cholangiocarcinoma incident[J]. Journal of Occupational Health, 2025, 67(1): uiaf001.

[7] Guertin, D. A., & Wellen, K. E. (2023). Acetyl-CoA metabolism in cancer. Nature reviews. Cancer, 23(3), 156–172. https://doi.org/10.1038/s41568-022-00543-5

[8] Chen G, Bao B, Cheng Y, et al. Acetyl-CoA metabolism as a therapeutic target for cancer[J]. Biomedicine & Pharmacotherapy, 2023, 168: 115741.

[9] Shvedunova M, Akhtar A. Modulation of cellular processes by histone and non-histone protein acetylation[J]. Nature Reviews. Molecular Cell Biology, 2022, 23(5): 329-349.

[10] Hao Y, Yi Q, XiaoWu X, et al. Acetyl-CoA: An interplay between metabolism and epigenetics in cancer[J]. Frontiers in Molecular Medicine, 2022, 2: 1044585.

[11] Guertin D A, Wellen K E. Acetyl-CoA metabolism in cancer[J]. Nature reviews. Cancer, 2023, 23(3): 156-172.

[12] He W, Li Q, Li X. Acetyl-CoA regulates lipid metabolism and histone acetylation modification in cancer[J]. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 2023, 1878(1): 188837.

[13] Saisomboon S, Kariya R, Mahalapbutr P, et al. Augmented global protein acetylation diminishes cell growth and migration of cholangiocarcinoma cells[J]. International Journal of Molecular Sciences, 2024, 25(18): 10170.

[14] Zhou X, Zhou Y, Shao W, et al. ACOT12-mediated acetyl-CoA hydrolysis suppresses intrahepatic cholangiocarcinoma metastasis by inhibiting epithelial-mesenchymal transition[J]. Journal of Cancer, 2022, 13(6): 1734-1744.

[15] Saisomboon S, Kariya R, Boonnate P, et al. Diminishing acetyl-CoA carboxylase 1 attenuates CCA migration via AMPK-NF-κB-snail axis[J]. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 2023, 1869(5): 166694.

[16] Pan Y, Zhang N, Fu X, et al. Pharmacological induction of acetyl-CoA carboxylase 1 autophagic degradation attenuates lipid accumulation and cholangiocarcinoma progression[J]. Journal of Experimental & Clinical Cancer Research : CR, 2025, 44: 310.

[17] Yang G, Yuan Y, Yuan H, et al. Histone acetyltransferase 1 is a succinyltransferase for histones and non-histones and promotes tumorigenesis[J]. EMBO Reports, 2021, 22(2): e50967.

[18] Zhang Y, Yan M, Yu Y, et al. 14–3-3ε: A protein with complex physiology function but promising therapeutic potential in cancer[J]. Cell Communication and Signaling : CCS, 2024, 22: 72.

[19] Fan K, Zhu K, Wang J, et al. Inhibition of 14-3-3ε by K50 acetylation activates YAP1 to promote cholangiocarcinoma growth[J]. Experimental Cell Research, 2022, 421(2): 113404.

[20] Li Y, Zheng J, Huo Q, et al. Chidamide suppresses the growth of cholangiocarcinoma by inhibiting

ISSN 2618-1584 Vol. 8, Issue 3: 41-47, DOI: 10.25236/FMSR.2026.080306

HDAC3 and promoting FOXO1 acetylation[J]. Stem Cells International, 2022, 2022: 3632549.
[21] Deng L, Bao W, Zhang B, et al. AZGP1 activation by lenvatinib suppresses intrahepatic cholangiocarcinoma epithelial-mesenchymal transition through the TGF-β1/Smad3 pathway[J]. Cell Death & Disease, 2023, 14(9): 590.
[22] Kim C, Lee S, Kim D, et al. Blockade of GRP78 translocation to the cell surface by HDAC6 inhibition suppresses proliferation of cholangiocarcinoma cells[J]. Anticancer Research, 2022, 42(1): 471-482.
[23] Yang G, Yuan Y, Yuan H, et al. Histone acetyltransferase 1 is a succinyltransferase for histones and non-histones and promotes tumorigenesis[J]. EMBO Reports, 2021, 22(2): e50967.
[24] Ling R, Chen G, Tang X, et al. Acetyl-CoA synthetase 2(ACSS2): A review with a focus on metabolism and tumor development[J]. Discover. Oncology, 2022, 13: 58.
[25] Yu X, Zhu L, Wang T, et al. Immune microenvironment of cholangiocarcinoma: Biological concepts and treatment strategies[J]. Frontiers in Immunology, 2023, 14: 1037945.
[26] Ricci A D, Rizzo A, Schirizzi A, et al. Tumor immune microenvironment in intrahepatic cholangiocarcinoma: Regulatory mechanisms, functions, and therapeutic implications[J]. Cancers, 2024, 16(20): 3542.
[27] Guo Y, Li Q, Ye Q, et al. Construction and drug screening of co-culture system using extrahepatic cholangiocarcinoma organoids and tumor-associated macrophages[J]. Heliyon, 2024, 10(17): e36377.
[28] Zheng Q, Zhang B, Li C, et al. Overcome drug resistance in cholangiocarcinoma: New insight into mechanisms and refining the preclinical experiment models[J]. Frontiers in Oncology, 2022, 12: 850732.
[29] Alobuia W M, Pawlik T M. Recent advances in the management of intrahepatic cholangiocarcinoma: The role of actionable mutations and targeted therapies[J]. Expert Review of Anticancer Therapy, 2025, 25(12): 1391-1404.
[30] Wu Q, Zhen Y, Shi L, et al. EGFR inhibition potentiates FGFR inhibitor therapy and overcomes resistance in FGFR2 fusion-positive cholangiocarcinoma[J]. Cancer discovery, 2022, 12(5): 1378-1395.
[31] Wu D, Liao G, Yao Y, et al. Downregulated acetyl-CoA acyltransferase 2 promoted the progression of hepatocellular carcinoma and participated in the formation of immunosuppressive microenvironment[J]. Journal of Hepatocellular Carcinoma, 2023, 10: 1327-1339.
[32] He W, Li Q, Li X. Acetyl-CoA regulates lipid metabolism and histone acetylation modification in cancer[J]. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 2023, 1878(1): 188837.
[33] Carmona B, Marinho H S, Matos C L, et al. Tubulin post-translational modifications: The elusive roles of acetylation[J]. Biology, 2023, 12(4): 561.
[34] Ma W, Zhang J, Chen W, et al. The histone lysine acetyltransferase KAT2B inhibits cholangiocarcinoma growth: Evidence for interaction with SP1 to regulate NF2-YAP signaling[J]. Journal of Experimental & Clinical Cancer Research : CR, 2024, 43: 117.
[35] Zhang D, Tang Z, Huang H, et al. Metabolic regulation of gene expression by histone lactylation[J]. Nature, 2019, 574(7779): 575-580.
[36] Ding P, Ma Z, Liu D, et al. Lysine acetylation/deacetylation modification of immune-related molecules in cancer immunotherapy[J]. Frontiers in Immunology, 2022, 13: 865975.
[37] Lin T, Yang W qi, Luo W wei, et al. Disturbance of fatty acid metabolism promoted vascular endothelial cell senescence via acetyl-CoA-induced protein acetylation modification[J]. Oxidative Medicine and Cellular Longevity, 2022, 2022(1): 1198607.
[38] Zhao Z, Wu Y, Cheng F, et al. High levels of histone acetylation modifications promote the formation of PGCs[J]. Poultry Science, 2025, 104(2): 104763.
[39] Wang W, Sun Y, Liu X, et al. Dual-targeted therapy circumvents non-genetic drug resistance to targeted therapy[J]. Frontiers in Oncology, 2022, 12: 859455.
[40] Swindale L Y, Stevens A J, Whalley S J, et al. Predictive liver lipid biomarker signature of acetyl-coenzyme a carboxylase inhibitor related developmental toxicity in non-pregnant female han wistar rats – lipidomics biomarker discovery and validation[J]. Toxicology Letters, 2023, 380: 62-68.