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Roles of the PI3K/AKT Signalling Pathway in Cholangiocarcinoma: A Mini Review

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Abstract: Cholangiocarcinoma (CCA) is a diverse group of malignant tumors originating from the bile duct and other sites in the biliary tree. Effective treatment methods for CCA are currently lacking. Therefore, understanding the genetic mechanisms and therapeutic targets is crucial for improving treatment outcomes and survival rates. This review focuses on the key roles of the phosphatidylinositol 3-kinase (PI3K) signaling pathway in CCA tumor initiation and progression. Potential therapeutic approaches based on this pathway were also discussed. Results showed increased activation of the PI3K/AKT pathway in CCA tissues and proteins like p85α, mTOR, and GSK-3β were upregulated with tumor metastasis. However, PTEN expression, a tumor suppressor protein, was suppressed via loss or phosphorylation. The emergence of certain drugs aimed at the dysfunctional PI3K/AKT pathway shows potential for enhancing Cholangiocarcinoma treatment. For example. dual inhibitors such as NVP-BEZ235 can effectively inhibit CCA cell growth and phosphorylation of AKT and mTOR. This suggests that the use of inhibitors to alter this pathway could potentially enhance survival rates and further the progress of Cholangiocarcinoma drug development.

Keywords: Cholangiocarcinoma, Molecular Pathogenesis, PI3K/AKT Pathway, CCA Therapy

1. Introduction

Cholangiocarcinoma (CCA) is a highly aggressive malignancy that originates from the epithelial cells of the biliary tract. Based on the location of tumor occurrence, CCA is categorized into intrahepatic (iCCA) and extrahepatic (eCCA), with the latter further divided into perihilar (pCCA) and distal CCA (dCCA) (Figure 1) [1]. In particular, iCCA develops within the liver parenchyma, pCCA originates between the second-order bile ducts and the insertion point of the cystic duct, while dCCA develops from the area between the cystic duct's insertion point and up to, but excluding, the ampulla of Vater [2]. Despite these subtypes showcasing significant desmoplasia and indicators of cholangiocyte differentiation, each one possesses its own unique cancer biology and specific treatment alternatives. For instance, potentially curative surgery is a treatment option for all three subtypes, but only in cases of early-stage disease [3]. However, due to CCA's aggressive progression, the typical survival period post-diagnosis is less than 24 months [4].

The global incidence of CCA continues to escalate due to its unsatisfactory prognosis and the limited available treatment options [5]. This rising trend is a significant concern for healthcare professionals and researchers worldwide. At present, CCA has ranked as the second most prevalent primary liver cancer, just following hepatocellular carcinoma (HCC). It constitutes a substantial 10% to 20% of all liver cancer cases, further emphasizing its prevalent role in global cancer demographics [6]. CCA's challenging nature arises from its ability to evade early detection and its propensity for rapid progression. This often results in patients being identified at advanced stages, limiting the potential for effective treatment options. Additionally, CCA's heterogeneity, including its varied anatomical origin within the biliary tract, contributes to

the complexities of managing this disease [7]. In light of these challenges, there is a critical need to further our understanding of CCA's molecular pathogenesis and invest in research that can help develop new, targeted therapies. Efforts are also required to identify effective screening strategies to enable early detection and thereby improve patient outcomes.

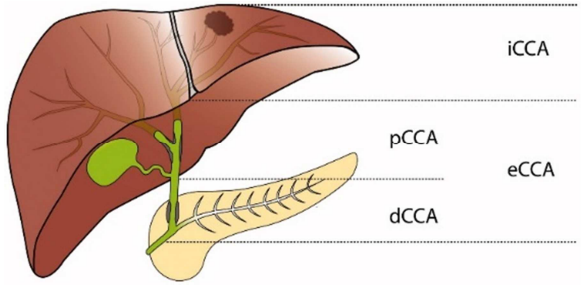

Figure 1. *Categorization of Cholangiocarcinoma according to the location of tumor occurrence [1]..*

The phosphoinositide 3-kinase (PI3K)/AKT signaling pathway is recognized as a central regulator of vital cellular functions, such as proliferation, survival, and metabolism, and is implicated in the pathogenesis of a wide variety of cancers [8-9]. The dysfunction of this pathway is a common occurrence in numerous cancer types, where it has been linked with tumor growth, metastasis, and therapy resistance [10-11]. The activation of the PI3K/AKT pathway can occur through diverse mechanisms, including genetic alterations, epigenetic changes, and growth factor signaling [10]. In the context of Cholangiocarcinoma (CCA), this pathway's activation has been correlated with the initiation, advancement, and chemotherapy resistance of tumors [12]. Notably, several upstream regulators of PI3K/AKT, such as EGFR and HER2, have been identified within CCA [13]. Additionally, frequent mutations have been found in PIK3CA, the gene that encodes the catalytic subunit of PI3K, thus underscoring the crucial role this pathway plays in disease pathogenesis [14-15]. Given the above, gaining a deep understanding of the molecular mechanisms of both CCA and the PI3K/AKT pathway is a critical step toward developing effective targeted therapies. In this study, we present an encompassing overview of our current knowledge about the molecular mechanisms underlying CCA, placing particular emphasis on the role of the PI3K/AKT signaling pathway in the development of the disease. We explore the upstream regulators, downstream effectors, and potential therapeutic targets of the PI3K/AKT pathway in the context of CCA. The objective of this article is to provide an exhaustive comprehension of the molecular mechanisms implicated in CCA and to pinpoint potential therapeutic targets for treating this lethal disease.

2. Cholangiocarcinoma

2.1. Symptoms of Cholangiocarcinoma

The CCA is a devastating disease presenting a wide array of symptoms and complications. The manifestation of symptoms in CCA largely depends on the tumor's location and size [16]. These may encompass abdominal discomfort, jaundice (a condition marked by yellowing of the skin and eyes), itching, weight loss, fatigue, and fever [17]. In certain instances, CCA may exhibit no symptoms and may be discovered accidentally during imaging tests. Beyond the physical symptoms, the diagnosis of CCA brings about significant psychological distress for patients and their families. The announcement of a CCA diagnosis is often a shocking revelation, given its frequent late-stage detection and the limited treatment options associated with acceptable survival rates [18]. Hence, patients with CCA often grapple with feelings of anxiety, depression, and hopelessness. They may also face practical challenges in managing their healthcare and securing suitable treatment. Moreover, the treatment for CCA often leads to significant side effects and complications [19], which further impact patients' quality of life. For instance, surgical removal of CCA tumors could lead to long-term complications such as bile duct strictures, liver failure, and infections [20]. Similarly, chemotherapy and radiation therapy can lead to a variety of side effects, including nausea, vomiting, fatigue, and hair loss [21-22]. In sum, both the disease itself and its treatment greatly affect the life quality of CCA patients.

2.2. Etiology of Cholangiocarcinoma

The etiology of CCA is intricate and remains to be fully unraveled, although numerous risk factors contributing to the disease's development have been identified, such as parasitic infections and primary sclerosing cholangitis [23]. Clinical trials have substantiated that sustained biliary tract inflammation, caused by infections, biliary stones, or autoimmune diseases, serves as a principal risk factor for elevated CCA incidence [5]. Furthermore, certain bile duct abnormalities, like choledochal cysts, have been linked with the onset and progression of CCA tumors [24-25]. Exposure to environmental toxins, such as dioxins and polychlorinated biphenyls (PCBs) in polluted environments, has been reported to correlate strongly with a higher risk of CCA [26]. Moreover, hereditary genetic mutations in genes like BRCA2, ATM, and PALB2 have been identified as contributing to an increased susceptibility to CCA [27]. It is crucial to highlight that CCA's development is likely a result of an amalgamation of several risk factors rather than a single cause. Enhancing our understanding of CCA's etiology is vital for devising more effective prevention and treatment strategies for this disease. By understanding the complex interactions among various risk factors, we can aim to lessen their impact and improve patient outcomes.

2.3. Therapy Methods of Cholangiocarcinoma

CCA is recognized as a highly aggressive cancer. Despite diagnostic advancements in recent decades, treating CCA remains a formidable challenge. A variety of treatment modalities for CCA exist at present, but their efficacy hinges upon the cancer stage, tumor location, and the patient's overall health status. Here, we present some of the prevalent therapies for cholangiocarcinoma, with a discussion of their pros and

cons.

1. Surgery: Currently, surgery stands the most effective treatment method for CCA, yet it's only viable if the cancer is detected early and hasn't metastasized. A common surgical procedure for CCA is radical resection [28], involving removal of the afflicted liver region and the bile duct. The primary advantage of surgery is its potential for a complete cure, however, it carries risks of complications and requires the patient to be healthy enough to withstand major surgery.
2. Chemotherapy: Used for annihilating cancer cells not removable via surgery, chemotherapy can be delivered intravenously or directly into the bile duct. While it possesses the ability to shrink tumors and extend life, chemotherapy may lead to unpleasant side effects like hair loss, fatigue, and nausea [29].
3. Radiation Therapy: Radiation therapy, used alongside chemotherapy for treating CCA, harnesses high-energy radiation to eliminate cancer cells, shrink tumors, and slow disease progression. However, it does come with side effects such as fatigue, nausea, and skin irritation, resembling a severe sunburn condition called radiation dermatitis [30-33]. In some cases, long-term effects like scarring, damage to nearby tissues and organs, and increased risk of secondary cancers can occur. Despite these side effects, radiation therapy can effectively treat CCA when managed correctly. This involves continuous health monitoring, providing supportive care, adjusting treatment plans as needed, and ensuring patients are well-informed about their treatment journey.
4. Targeted Therapy: These are drugs that zero in on proteins overexpressed in cancer cells. For CCA, targeted therapies inhibiting the PI3K/AKT pathway are currently under clinical trial evaluation [34]. Targeted therapy boasts of its selective cancer cell targeting ability, but it can be costly and lead to side effects, including nausea and diarrhea.
5. Immunotherapy: This cancer treatment method assists the immune system in identifying and attacking cancer cells. Preliminary studies hint that immune checkpoint inhibitors may be effective against CCA. While immunotherapy can stimulate the immune system's ability to combat cancer, it can cause side effects such as fatigue and immune-related adverse events [35].

Overall, a multidisciplinary approach is required to treat CCA, with the optimal treatment plan contingent upon the individual patient's disease stage, location, and overall health. Each treatment has its own set of benefits and drawbacks, and the decision to utilize one or more of these treatments should be made after consulting with a medical professional.

3. Phosphoinositide 3-Kinase (PI3K)/AKT Signaling Pathway

As first revealed in the 1980s, the PI3K/AKT pathway is a key facilitator of insulin signaling, a concept noted by [36]. The PI3K enzyme family stimulates the phosphorylation of inositol lipids in cell membranes, resulting in the formation of the lipid secondary messenger, phosphatidylinositol-3, 4, 5-trisphosphate (PIP3) [37]. This PIP3 then activates AKT, a serine/threonine kinase also known as protein kinase B and mammalian target of rapamycin (mTOR) (Figure 2) [38]. Once turned on, AKT phosphorylates an array of downstream targets, such as crucial regulators of cell cycle progression, apoptosis, and metabolism. It has been observed that tyrosine kinases and other receptor molecules, including hormones and mitogenic factors, can trigger this pathway [39].

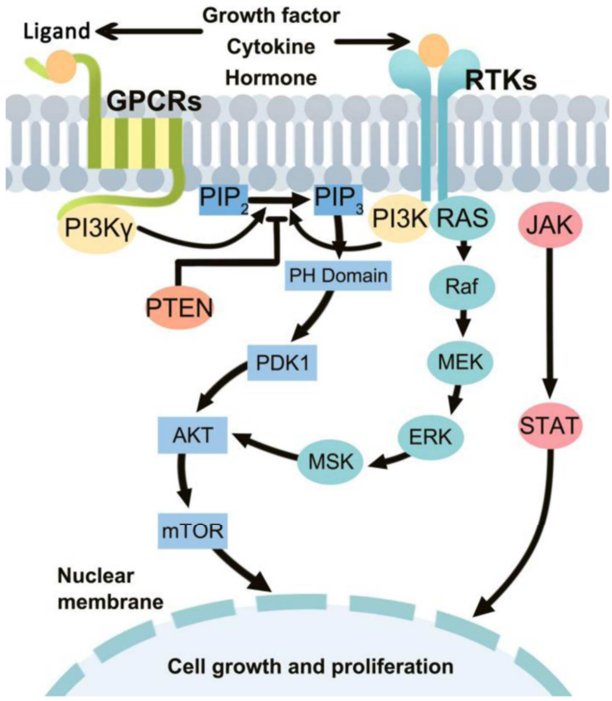

Figure 2. *The overview of PI3K/AKT/mTOR signaling pathway [40].*

The PI3K/AKT signaling pathway, presently acknowledged as controlling numerous cellular processes such as cell growth, survival, motility, metabolism, and proliferation, has been implicated in the abnormal survival and propagation of cancer cells when activated improperly [41]. This pathway's dysregulation has been linked to the development and advancement of various human cancers, leading to heightened cell growth and survival [42]. Gene mutations in the pathway's components are common in many cancers, including CCA, making the targeting of the PI3K/AKT pathway a pivotal approach in cancer therapy. Several therapeutic drugs have been developed that target PI3K/AKT pathway components and are either in clinical use or under development [43]. These comprise inhibitors of PI3K, AKT, and mTOR, in addition to dual inhibitors of both PI3K and mTOR, due to their significant role in cancer drug resistance and autophagy regulation, the latter being crucial in programmed cell death. Promising results have been reported from preclinical and clinical trials for these drugs, and they are currently under evaluation for the treatment of several cancers,

including CCA. At present, the standard practice for treating patients with advanced or metastatic disease involves systemic chemotherapy with gemcitabine and cisplatin.

4. PI3K/AKT Pathway-Based Protein Expressions

PI3K signaling plays a critical role in CCA, as well as anti-cancer drug resistance and autophagy, the type II program cell death regulation. One of the most common alterations in the PI3K/AKT pathway in cancer cells is the overexpression or activation of growth factor receptors, such as the epidermal growth factor receptor (EGFR), that activate PI3K. [44] reported that increased activation of PI3K/AKT signaling was reproducibly observed in the CCA tissues. The expression of p85α, mTOR, and GSK-3β was significantly correlated with metastasis. They studied 30 CCA cases and found no or very weak positive staining of all proteins investigated in normal bile duct epithelia, while the increased expression was observed in pre-cancerous and cancer cells. The expression of p85α, p110α, AKT, p-AKT (T308), mTOR, p-mTOR (S2448), GSK-3β, and p-GSK-3β (S9) in CCA tissues was detected out, but their concentrations varied significantly, with percent expression of is 27, 90, 50, 57, 67, 20, 40, and 27%, respectively. During them, the expression of p85α, mTOR, and GSK-3β was significantly correlated with metastasis. However, the PTEN expression is inhibited with an increased activation of PI3K/AKT pathway [45-46]. This indicates that the expression of these PI3K/AKT pathway related proteins are corrected with a more aggressive phenotype of CCA. For instance, p85α was found significantly associated with tumor metastasis [44]. This can lead to increased production of the lipid second messenger, PIP3, and increased activation of AKT, promoting cell growth and survival. In addition to alterations in growth factor receptors, mutations or alterations in other components of the PI3K/AKT pathway can also contribute to its dysregulation in cancer cells. For example, mutations in the gene encoding the catalytic subunit of PI3K, PIK3CA, are frequently observed in many cancer types and lead to increased PI3K activity and AKT activation. In contrast, normal cells tightly regulate the activity of the PI3K/AKT pathway through a variety of regulatory mechanisms. For example, phosphatases such as PTEN and INPP4B function to dephosphorylate PIP3, limiting the activity of the pathway. Additionally, negative regulators of the pathway, such as TSC1/2 and LKB1, function to inhibit the activity of downstream components, such as mTOR.

5. PI3K/AKT Pathway-Based Inhibitors

These alterations in the regulators of the PI3K/AKT pathway in cancer cells compared to normal cells are important for the development and progression of cancer. Targeting these altered regulators of the pathway has become an important strategy for cancer therapy. Several drugs that target the regulators of the PI3K/AKT pathway are currently in clinical use or in development and have shown promising results in preclinical and clinical studies for the treatment of various cancers, including CCA.

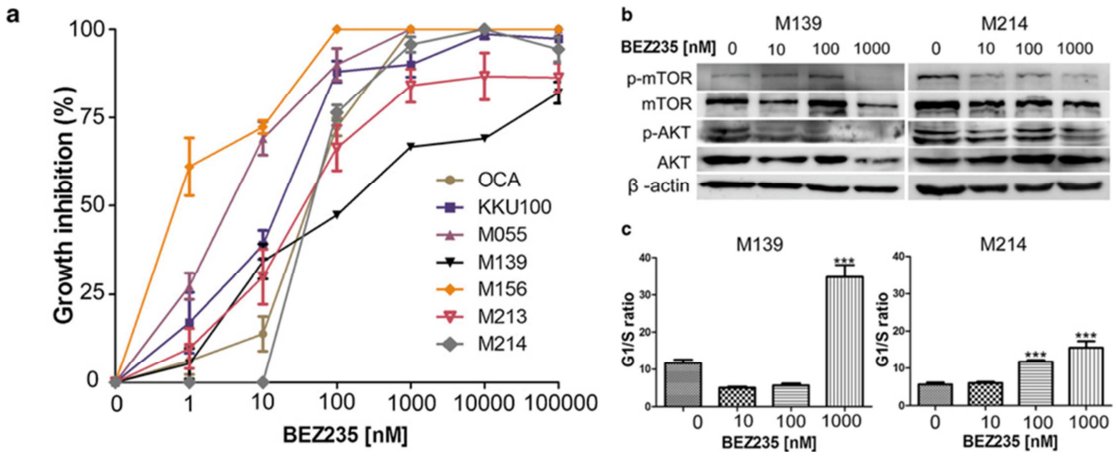

Figure 3. *NVP-BEZ235 inhibits the proliferation of CCA cells.*

Interestingly, PTEN suppression by loss of expression or inactivation by phosphorylation was observed in the majority of patients. Furthermore, NVP-BEZ235 effectively inhibited CCA cell growth and migration through reduced AKT and mTOR phosphorylation and significantly induced G1 arrest without apoptosis induction, although an increased autophagy response was observed (Figure 3). In conclusion, the constitutive activation of the PI3K/AKT pathway in CCA is mainly due to PTEN inactivation by either loss of expression or phosphorylation along with an increased expression in its pathway components heralding a poor prognosis for CCA patients. This work also indicates that inhibition of PI3K and mTOR activity by the inhibitor NVP-BEZ235 has anticancer activity against CCA cells which might be further tested for CCA treatment.

A Selection of seven CCA cell lines were exposed to varying concentrations of NVP-BEZ235 for a period of 48 hours, followed by the implementation of a SRB assay to evaluate cell

proliferation. The data, indicative of one representative experiment, are presented as mean ± SEM. Each trial was conducted independently three times. b Effects of NVP-BEZ235 on reducing of AKT and mTOR phosphorylation in CCA cells. Following a 48-hour treatment with NVP-BEZ235 at designated concentrations, cell extracts underwent immunoblotting analysis for AKT, p-AKT (S473), mTOR, and p-mTOR (S2448), respectively. c A cell cycle arrest at the G1 phase was instigated by NVP-BEZ235. Post a 48-hour treatment with NVP-BEZ235, cells were subjected to propidium iodide staining analysis. The results, expressed as mean ± SD, were derived from three separate experiments. *$p < 0.05$ when compared with control cells [44]. Idelalisib (GS-1101, CAL-101, or Zydelig®) is an FDA-approved, orally administered PI3K inhibitor that targets the PI3Kδ isoform primarily found in hematopoietic cells. This drug disrupts the cellular signaling pathways necessary for B-cell viability, proving effective in various B-cell leukemias and lymphomas, particularly for relapsed or refractory CLL, FL, and SLL. This brief overview focuses on the clinical impact of idelalisib, especially in CLL studies [47]. Additional PI3K/AKT pathway associated inhibitors were listed in Table 1 for treating various cancer types. As to potential implications for CCA treatment, the PI3K pathway has been found to be frequently dysregulated in many cancers. The introduction of a PI3K inhibitor like idelalisib could theoretically obstruct this pathway, slowing tumor growth or possibly even inducing tumor cell death. However, the specific effect of idelalisib on CCA requires further investigation, given its primary design to target hematopoietic cells, and not specifically the cell types involved in CCA. It underscores the importance of ongoing research in this area to ascertain the full potential of PI3K pathway inhibitors for CCA treatment.

Table 1. *Inhibitors associated with the PI3K/AKT pathway and their roles in cancer therapy.*

Inhibitor	Roles	References
Idelalisib	A PI3K inhibitor of controlling p110δ expression.	[47]
Buparlisib	A PI3K inhibitor by regulating the p-pS6K/total pS6K and p-FOXO3/total FOXO3 levels.	[48]
Alpelisib	The PI3K inhibitor by regulating the p110α expression as an inhibitor of PI3K.	[49]
Pictilisib	The PI3K inhibitor by affecting the p110α, p110β, p110δ, and p110γ.	[50]
Ipatasertib	The ATP-competitive AKT inhibitor	[51]
Perifosine	An AKT inhibitor by enhance the cytotoxic effects of fluorouracil, likely primarily through the nuclear transcription factor-kappa B pathway.	[52]
Everolimus	An inhibitor of mTOR for metastatic renal cell carcinoma	[53-54]
Temsirolimus	An inhibitor of mTOR for regulating HER2 and PTEN expression.	[55]

6. Conclusion

In the era of personalized or precision medicine, understanding the molecular and genetic basis of cancer, along with the development of tumor-specific therapeutics, has become of paramount importance. In the context of CCA, a notoriously difficult-to-treat cancer, significant progress has been made in deciphering its complex mutation landscape. The PI3K/AKT signaling pathway, a crucial controller of cell growth and survival, is often found dysregulated in CCA and other malignancies. Unraveling the role and influence of the PI3K/AKT pathway, alongside other genetic drivers, in the progression of CCA, promises to shape the future of personalized therapy. The approach would then be based on each patient's specific tumor driver mutation, which includes mutations in the PI3K/AKT pathway. Even though targeted therapeutic strategies addressing these specific mutations are in their early stages, initial results have been encouraging. Tumor immunotherapy represents another exciting development in cancer treatment, with promising results seen in malignancies responsive to immune receptor inhibition, like the programmed cell death receptor. While CCA is known for its genetic heterogeneity, its stromal components present a more genetically uniform landscape. This observation has led to intriguing possibilities in cancer treatment. For instance, preclinical studies have indicated the potential effectiveness of targeting cancer-associated fibroblasts within the CCA tumor microenvironment, resulting in tumor regression and improved survival rates. Thus, the stroma, much like the PI3K/AKT pathway within the tumor cells, could serve as a valuable target in CCA treatment. There is a growing need for further research to design combination therapies that target not only the cancer cell, including the PI3K/AKT pathway but also the cancer stroma in CCA, thereby providing a more comprehensive and potentially effective treatment strategy.

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