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Progress in cyclin-dependent kinase 1 (CDK 1) in the treatment of liver cancer

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ABSTRACT
Primary liver cancer is the most widespread and most dangerous cancer in the world. However, in the last decade, the survival rate of patients with liver cancer has not increased. Most directions of liver cancer treatment contain the mechanism of CDK 1, and Cyclin-dependent kinase 1 (CDK 1) is a key enzyme in the regulation of cell cycle progression, especially plays a central role in the initiation and regulation of mitosis (M phase). It binds to cyclin (cyclins) and controls key stages of the cell cycle, including the G2 / M phase. One of the hallmarks of cancer cells is the deregulation of the cell cycle, leading to excessive cell proliferation. At home and abroad for CDK 1 in cancer treatment has made great progress, if the use of CDK 1 in the cell cycle of design drugs to stop the abnormal proliferation of cancer cells, can achieve true treatment in cancer treatment, this paper mainly set the domestic and foreign for CDK 1 in the latest research progress of various cancer treatment, detailed elaboration and summary.

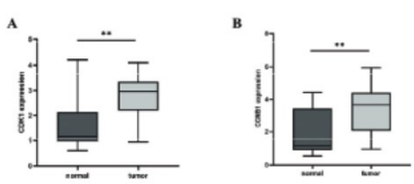
KEYWORDS
CDK 1; Liver Cancer; Cancer; Cycling-dependent Kinase; Cell Cycle

1 Introduction

The treatment of liver cancer has been a key goal of cancer research nationwide and worldwide. The main effective treatment is surgical [1]. However, the early symptoms of liver cancer are not obvious. When obvious physiological manifestations appear in the middle and late stage, it cannot be cured only with the help of surgical treatment. Therefore, targeted therapy is the top priority in the research on the treatment of liver cancer. At this point, it is difficult to achieve a radical cure simply relying on surgery, and may even lose the opportunity of surgical treatment. Therefore, how to effectively prolong the survival of patients and improve the quality of life has become a key issue in clinical research. In recent years, with the progress of medical technology, targeted therapy has become the focus in the field of Hcancer therapy. And CDK 1, as an important regulatory enzyme in the cell cycle, has become one of the main research objects.

2 Mechanism of CDK 1 involved in hepatocarcinogenesis

CDK 1 drives cells into the mitotic phase mainly by binding to cyclin B1 (Cyclin B1). Its hyperactivation may lead to cell cycle disorders, allowing cells to evade normal proliferation regulation, and subsequently promoting tumor formation of [3]. The results of the study showed that CDK 1 expression in HCC patients showed high levels compared with normal tissues and showed positive correlation with pathological stage (r = 0. 828, P <0. 01), indicating that CDK 1 has high clinical value in HCC [4].



A.正常组织和 HCC 组织中 CDK1 的表达水平; B.正常组织和 HCC 组织中 CCNB1 的表达水平; ** $P<0.01$。

图 1 CDK1 和 CCNB1 在 HCC 中高表达

Figure 1 CDK1 and CCNB1 are highly expressed in HCC

The data of the database show that the expression of CKD 1 gene rises in liver cancer tissues, obviously involved in liver cancer, and many related genes are highly expressed at the same time. Further studies found that they are mainly involved in DNA replication, substance metabolism, cell cycle and other pathways [5]. During the cell cycle, there are related genes PSMD12 regulating the switch in the G2 / M phase. Some experimental results showed that when changing the PSMD12 gene expression, CDK 1 also made the corresponding changes, confirming the direct interaction between the two. CDK 1 protein is highly expressed by the influence of PSMD12, promoting the malignant behavior of HCC cells and affecting the migration ability of cancer cells [6].

Not only that, but with the continuous development of technology in recent years, many pathways controlling or

linking to the expression of CDK 1 have been discovered. In liver cancer, the p53 pathway is an important pathway for CDK 1, and induced cancer stem cell production by inhibiting enzymes, interfering with transcription and disrupting checkpoint effects in G2 / M phase.

In conclusion, CDK 1 expression is affected by multiple pathways, resulting in the deregulation of CKD 1 activity, which will lead to the cell cycle disorder and the malignant proliferation of liver cancer cells.

3 Domestic research progress of CDK 1 in Hcancer treatment

3.1 Biological role and mechanism study of CDK 1

Chinese research team deeply studied the mechanism of CDK 1 in the cell cycle, there have been studies identified known separate CDK 1 is not active, all eukaryotic cells mitotic initiation is regulated by Cyclin / CDK 1 complex, can catalyze a variety of protein phosphorylation, which cause the structural and functional status of these proteins, and lead to the change of intracellular metabolic activity. However, the acetylation modification of CDK 1 may also be involved in the kinase activity of the complex, which ultimately affects the progression of the cell cycle [8]. Acetylation modification of CDK 1 remains the key to its mechanism of action. However, few studies on acetylation modification of CDK 1 have been reported. Through gene editing (knockdown of CRISPR / Cas 9) and CDK 1, the researchers revealed the function of CDK 1 in cancer cell proliferation, DNA damage repair and apoptosis. The study concluded that SFN could downregulate the expression level of CCNB 1 in HepG2 cells and CCNB 1 protein, and then inhibit its complex formation and activation, making human HepG 2 cells arrest [9] in the G 2 / M phase.

3.2 Screening and development of CDK 1 inhibitors

The development of small molecule inhibitors for CDK 1 has gradually become an important direction of drug research in China. Chinese researchers have screened and designed a series of CDK 1 inhibitors through various methods, such as high-throughput screening and computer-assisted drug design, and verified their antitumor activity in cellular and animal models. New small-molecule inhibitors are selected through virtual screening and structure optimization. However, these inhibitors showed strong antitumor activity in in vitro and in vivo experiments. Experimental studies show that the Eg 5 small molecule inhibitor SB-743921 blocks malignant proliferation and migration of CRPC cells through c-Myc / SP 1 / CDK 1 signaling, induce apoptosis and arrest the cell cycle in the G2 / M phase [10]. For classical inhibitors, some existing CDK inhibitors, such as RO-3306, showed inhibitory effects on CDK 1 in experiments. Researchers also continuously optimize the structure of these molecules to improve their selectivity and activity. Some experimental results show that the use of dogine or paclitaxel combined with CDK 1 inhibitor RO3306, under specific appropriate concentration conditions, can produce synergistic effect, enhance the effect of the inhibitor [11]. Unfortunately, no relevant research is reported in China, and the molecular mechanism is always not clear about [12].

3.3 Preclinical studies and clinical trials

Some Chinese biopharmaceutical companies and scientific research institutions have advanced CDK 1 inhibitors to the preclinical research phase, and some inhibitors have entered clinical trials. In this process, the pharmacokinetic properties, safety, and efficacy of the inhibitors were systematically evaluated.

4 Domestic progress of CDK 1 in Hcancer treatment

Cyclin-dependent kinase 1 (CDK 1) plays a key role in cell cycle regulation, and its importance in cancer therapy research is increasingly attracting international academic attention. Recent studies targeting CDK 1 have made significant progress, especially in the development of CDK 1 inhibitors and in exploring their use in cancer therapy. The international research team paid special attention to the specific molecular mechanism of CDK 1 regulation in the cell cycle and the interaction between CDK 1 and other cell cycle proteins ins and regulatory factors. The stent conclusions were obtained regarding the mechanistic principle aspects of CDK 1, both domestic and abroad. It also shows that the current theoretical results are universal and worthy of use and further study.

4.1 Development and improvement of CDK 1 inhibitors

International development of inhibitors for CDK 1 has made great progress in the fields of medicinal chemistry and biology. Various regulatory targets and physiological processes of CDK 1 have been thoroughly studied early on. [13]. In

terms of clinical studies, inhibitors targeting CDK 1 are being evaluated. For example, Milciclib, an inhibitor targeting CDK 1, CDK 2, CDK 4, and CDK 7, is currently in phase II clinical trials for hepatocellular carcinoma. Furthermore, Dinaciclib, an inhibitor targeting CDK 1, CDK 2, CDK 5, and CDK 9, has been approved for the treatment of chronic lymphocytic leukemia [14][15].

The development for CDK 1 have focused on ATP competitive small molecule inhibitors and selective CDK 1 inhibitors. For example, some broad-spectrum CDK inhibitors, such as Roscovitine and Flavopiridol, have entered clinical trials, but are often accompanied by strong toxic side effects [16] due to the lack of selectivity. Recently, several novel small molecule inhibitors, such as BAY 1251152 and RO-3306, have shown better CDK 1 selectivity and demonstrated anticancer activity [17] in preclinical studies.

In addition to a single inhibitor targeting CDK 1, the investigators also explored combined targeting strategies. A study published in Nature found that the inhibition of both CDC7 and CDK 1 may be more effective in preventing cancer cell proliferation. This combined inhibition strategy is expected to overcome the resistance of cancer cells to single agents and improve the therapeutic efficacy.4.2 Clinical study evaluation.

Currently, some CDK 1 inhibitors are currently in clinical trials. For example, BAY 1251152 demonstrated good antitumor activity in multiple cancer models and initially verified its safety and efficacy in phase I clinical trials [17]. However, most of the CDK 1 inhibitors are still in the preclinical research stage, and their efficacy and safety still need further evaluation. Unfortunately, although many inhibitor drugs are already in clinical trials, no drugs are approved for [18].

5 Research evaluation and future development opportunities

5.1 Feasibility analysis

As an important regulator of cell cycle progression, the dysregulation of its activity can lead to cell cycle disorder and promote excessive proliferation of cancer cells [19]. This regulatory role has brought much interest to the potential significance of CDK 1 in cancer treatment. Moreover, CDK 1 also interacts with DNA damage repair pathways to influence the sensitivity of tumor cells to radiotherapy and chemotherapy [20].

Inhibitors targeting CDK 1 have emerged as potential cancer therapeutic strategies. By inhibiting the activity of CDK 1, cancer cells fail to complete the cell cycle smoothly, leading to cell arrest or apoptosis. The methods and techniques to studying CDK 1 in cancer therapy cover multiple pathways including small molecule inhibitors, RNAi, gene editing, and synthetic lethal strategies. A large body of research literature indicates that CDK 1 is very effective [21][22] for inhibiting the abnormal proliferation of cancer cells, so CDK 1 has extensive research and clinical applications as an innovative target for cancer treatment. In addition, due to the different cell cycle regulation mechanisms of different cancers, targeting CDK 1 can be used in combination with targets related to gene mutations to achieve more accurate cancer treatment and reduce the damage to normal cells. In the future, with the development of precision medicine, screening sensitive populations based on biomarkers, combined with personalized treatment strategies, is expected to improve the clinical application value of CDK 1 targeted therapy [17].

5.2 Research challenges

Although CDK 1 as a cancer treatment target shows good prospects, but still face some challenges, CDK 1 and other CDK of the CDK family members (such as CDK 2, CDK 4) has high sequence homology, technically difficult to study only for with CDK 1 inhibition structure, easy to inhibition of other CDK family genes, so the development of highly selective CDK 1 inhibitor is still difficult [3]. At the same time, tumor cells may evade drug action by activating alternative signaling pathways or upregulating CDK 1 expression levels, so combination treatment strategies may be the main direction in the future [23].

6 Conclusion

CDK 1 plays a key role in cancer development and progression, and its inhibitors have important potential in cancer therapy. As a new therapeutic target, CDK 1 is different from traditional anticancer targets. As a key regulator of the cell cycle, CDK 1 inhibition can directly block the proliferation cycle of cancer cells and intervene in tumor development from the source. Although there are still challenges such as selectivity, drug resistance and toxic side effects, the application prospect of CDK 1 as an anticancer target through optimizing targeted strategies, combination therapy and precision medicine is worth expecting. In the environment where many cancer patients develop resistance to chemotherapeutic drugs, CDK 1 inhibitors, as a new mechanism of action, are expected to show effects in drug-resistant cancer patients and expand the therapeutic indications for treatment. By examining the expression level of CDK 1 and its role in tumors, it can

identify patient populations sensitive to CDK 1-targeted therapy and promote personalized precision therapy.

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