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ARTICLE

Research Advance on the Relationship between Wee1 and Tumor Genesis and Progression

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ABSTRACT

In the process of biological genetic information transmission, complete and correct genetic information can make cell mitosis proceed normally. In the development of most tumor cells, G2/M cell cycle checkpoint becomes the key checkpoint in the process of mitosis due to the lack of G1/S cell cycle checkpoint, which mainly depends on the abnormal DNA information blocked by Wee1 protein kinase in G2 phase to enter M phase and prolong the time of G2 phase to complete DNA sequencing So that the normal genetic information can be passed on. Wee1 protein kinase expression is significantly increased in most tumor cells, making it a potential target for tumor therapy.

1. Introduction

Wee1 protein kinase family includes Wee1A, Wee1B and Myt1 members [1]. The human Wee1 gene is located in the P15 region of chromosome 15 [2] (11p15.3-11p15.1), encoding 647 amino acids. Wee1 protein kinase consists of three domains: N-terminal domain, central kinase domain and C-terminal regulatory domain [3]. The N-terminal domain is the activation domain of Wee1 protein kinase, which plays a key role in guiding its destruction, and may inhibit the activity of Wee1 protein kinase [4]. However, the N-terminal domain is also a potential site for inhibiting CyCB/CDK1 dephosphorylation, thus causing cell cycle arrest. The central kinase domain is helpful for Wee1 localization in the nucleus at G2 phase; The C-terminal regulatory domain is the Wee1 protein kinase catalytic domain [5]. Studies have shown that Wee1 is mainly expressed in the nucleus of tumor cells [6]. In recent years, the research of Wee1 protein kinase in DNA repair of cell cycle damage and malignant tumors has become a hot spot. In normal cells, due to the existence of P53, cells can complete the damage repair in G1/S phase when DNA is damaged. However, the mutation of P53 occurs in most malignant tumors, resulting in that the damaged DNA can not be repaired in G1/S phase, and can only be repaired in G2/M phase [7], so that the correct and complete DNA can enter into M phase for mitosis. In this paper, the research progress of the relationship between Wee1 and tumor genesis and development is summarized as follows.

2. Role of Wee1 Protein Kinase in Cell Cycle

Cell cycle is a concept proposed by Howard et al in 1951. It refers to the whole process of a cell from the

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completion of one division to the end of the next division, which is divided into two stages: interphase and division phase. The interphase is divided into G1, S and G2 phases, and the division phase is M phase. In the process of cell proliferation, cell mitosis will encounter a variety of damage factors causing DNA damage and chromosome variation, so someone put forward the concept of cell cycle checkpoint, namely a kind of negative feedback regulation mechanism, which is mainly affected by DNA replication and damage. There are two key checkpoints: G1/S and G2/M phases,which block the heredity of genes with replication errors. In normal cells, DNA damage mainly depends on two pathways mediated by P53(tumor suppressor gene): ATM(Capillary ataxia mutant gene)/ATR-P53-CDK4/CyclinD or ATM/ATR-P53-CDK2/CyclinE inhibit Rb phosphorylation, and make the cell arrest in the G1 phase to complete DNA damage repair. However, studies have shown that most tumor cells lack two pathways in the G1/S phase checkpoint, which makes the DNA damage repair of tumor cells mainly depend on the G2/M phase. Studies have shown that [7] Wee1 and CDC25 play an important role in this checkpoint. ATM/ATR is activated when DNA damage [8], through the phosphorylation of downstream CHK1/2(effect kinase) make its activation [9]. On the one hand, activated CHK1 / 2 can phosphorylate downstream CDC25B/C to inactivate it, inhibit its dephosphorylation of downstream CDK1/CycB, and arrest cell cycle in G2 phase. On the other hand, CHK1/2 can directly activate Wee1 protein kinase. The activated Wee1 protein kinase phosphorylates the thy15 site of CDK1 [10] and inactivates it, which is the key factor for mitosis. The cell cycle is arrested in G2 phase until DNA damage repair is completed. The cell has the opportunity to enter M phase for mitosis. Wee1 protein kinase, as a potential molecular target of tumor cells, has become a focus of current research.

As shown in Figure 1:

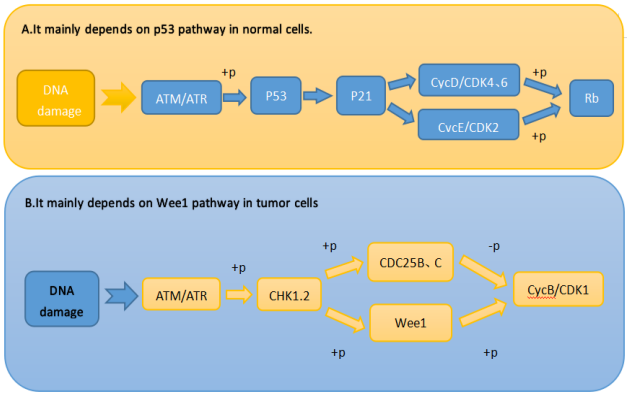

Figure 1. damage and repair process of G2 phase cells

3. Relationship between Wee1 Protein Kinase and Tumor

3.1 Wee1 and Gastric Cancer

Gastric cancer is one of the most common malignant tumors in China. Many chemotherapy drugs can cause DNA damage in gastric cancer tumor cells. Tumor cells lack G1/S phase and most of them rely on G2 phase arrest. Wee1 is a key factor of G2/M checkpoint. Kim et al. [11] first proposed that Wee1 protein kinase might be expressed in gastric cancer. After a series of experiments, it was found that Wee1 was positive in gastric cancer cells, and the positive rate was higher in tumor cells with lymph node metastasis, and the proliferation and invasion ability of tumor cells with Wee1 overexpression was stronger. Zhang et al. [12] also verified that the expression of Wee1 was increased in gastric cancer cells, and further demonstrated that ROP inhibited the proliferation and metastasis of gastric cancer cells by regulating the Wee1 pathway.

3.2 Wee1 and Melanoma

In malignant melanoma, regardless of the status of P53, the high expression of Wee1 can reduce the DNA damage of tumor cells, and is positively correlated with the proliferation, metastasis and poor prognosis of malignant melanoma [13]. Studies have shown that [14], different from most tumors, P53 expression is positive in malignant melanoma. Wee1 is a key signal molecule downstream of BRAF in MAPK signal transduction pathway. Wee1 can inhibit the P53-P21-CDK2/CycE-Rb-E2F pathway in the cell cycle, so that the cell cycle is blocked in the S phase, therefore, the expression of Wee1 protein kinase is still positive in melanoma. Wee1, as the most suitable target, its inhibitor and AKT3 protein kinase inhibitor combined to treat melanoma, so that the treatment effect of AKT3 inhibitor is more effective. In animal experiments, high expression of Wee1 and deletion of MicroRNA-155 (MiR-155) contribute to metastasis of malignant melanoma [15]. However, Bhattacharya et al. [16] showed that compared with primary melanoma, the expression of Wee1 in distant skin metastatic melanoma was down regulated, and the proliferation, migration and invasion ability of Wee1 positive primary tumor cells were decreased.

3.3 Wee1 and Colorectal Cancer

Wee1 can be expressed in both colon cancer tissues and paracancerous normal tissues, but it is highly expressed in colorectal cancer [17]. Experiments showed

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that the expression of Wee1 is mainly positive in the nucleus, but also slightly expressed in the cytoplasm, and the high expression of Wee1 is closely related to distant metastasis of colon cancer, lymph node metastasis and malignant degree of tumor [18]. Yin et al. [19] verified that Wee1 inhibition can reduce the proliferation ability of tumor cells in P53 mutated colorectal cancer, and Wee1 may become a potential target for the treatment of colorectal cancer. Webster et al. [20] also found that the positive expression rate of Wee1 was up-regulated in endothelial cells with liver metastasis from colorectal cancer, and Wee1 may be related to the formation of some branches of blood vessels in liver metastasis from colorectal cancer, which provides a theoretical basis for the research and development of Wee1 protein kinase inhibitors as tumor drugs.

3.4 Wee1 and Breast Cancer

Triple Negative Breast Cancers (TNBCs) are breast cancers that are negative for estrogen receptors, progesterone receptors and human epidermal growth factor receptors. Studies have found [21] that p53 mutations in the vast majority of TNBCs lead to deletion of G1/S stage checkpoints, making Triple Negative Breast Cancer dependent on G2/M stage checkpoints to repair DNA damage. Experimental results showed [22] that Wee1 inhibitor combined with ATR inhibitor can inhibit proliferation and metastasis of TNBCs and induce apoptosis of cancer cells. Ghiasi et al. [23] eliminated G2 phase arrest, accumulated P53, increased G1 phase arrest and significantly reduced the expression of pro-tumor vascular growth factor VEGF by inhibiting Wee1, thus weakening the proliferation ability of cancer cells, indicating the cancer-promoting effect of high expression of Wee1 in breast cancer cells.

3.5 Wee1 and Lung Cancer

Yoshida et al. [24] analyzed 79 patients by immunohistochemistry, including 16 recurrent cases, and found that there was almost no difference in the positive rate of Wee1 between tumor cells and normal cells. Moreover, the recurrence rate and mortality of patients with Non-Small Cell Carcinoma(NSCLC) with negative Wee1 expression were significantly higher than those with positive Wee1 expression.These results suggest that Wee1 expression may act as a protective mechanism against cancer in NSCLC. However, Ku et al. [25] proved that Wee1 protein kinase inhibitor was effective in the treatment of non-small cell lung cancer with KARs gene mutation in TP53 mutated cancer cells, which was similar to the effect of Wee1 inhibitor combined with mTOB inhibitor in the treatment of NSCLC with KARs gene mutation studied by Hai et al. [26]. Jhuraney et al. [27] found that Wee1 and PAXIP1 were commonly expressed in lung cancer,and had no relationship with the status of p53. When both were expressed at the same time, Wee1 inhibitor combined with Cisplatin was effective.Sen et al. [28] a used PCR method to study and found that Wee1 was significantly increased in small cell lung cancer cells compared with normal tissues and non-small cell lung cancer cell lines. Therefore, the mechanism and expression of Wee1 may be different in different types of lung cancer.

3.6 Wee1 and Lymphoma

Lymphoma is a malignant tumor originated from lymphohematopoietic system, which is a systemic disease. At present, the main treatment is chemotherapy, but lymphoma is heterogeneous, and the therapeutic effect is different greatly among different patients. Chemotherapy drugs such as cytarabine can cause DNA damage in B-cell lymphoma. The results showed that [29] in vivo and in vitro, Wee1 inhibitor combined with chemotherapy drugs was only effective in the treatment of B-cell lymphoma with G2 phase arrest. Diffuse large B-cell lymphoma (DLBCL) accounts for about 31% of all non Hodgkin's lymphoma. Although R-CHOP Regimen is more effective, there are still a lot of relapses or deaths.Studies have shown that Wee1 is more significantly expressed in DLBCL [30]. Wee1 inhibitors combined with CDK1 inhibitors may improve the prognosis of patients with DLBCL [31], and Wee1 may become a target for the treatment of Diffuse Large B-cell Lymphoma. De Jong et al. [31] first proposed and verified that Wee1 inhibitor can enhance the anti-apoptotic dependence of DLBCL, and the combination of Wee1 inhibitor and anti-apoptotic inhibitor has better efficacy. Chila et al. [33] demonstrated that CDK1 inhibitors and Wee1 inhibitors were more effective in Mantle Cell Lymphoma (MCL) than solid tumors and other lymphomas, but the high toxic side effects of dual-targeted agents remain to be addressed.

4. Wee1 Protein Kinase Inhibitors

Among tumor therapy drugs, targeted therapy drugs have been widely used in clinic. In recent years, Wee1 protein kinase has attracted more and more attention in tumor cells with G1/S checkpoint deletion, and Wee1 protein kinase plays a key role in G2/M phase, making Wee1 protein kinase become a potential target for clinical treatment of tumors. Wee1 protein kinase inhibitor

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AZD1775, also known as MK1775, is an effective selective inhibitor of Wee1. AZD1775 can inhibit the activity of CDK1 by phosphorylating the Try15 residue of Wee1 protein kinase, so that DNA damage repair can not be carried out smoothly, and cells can not produce substances entering M phase in G2 phase, which leads to apoptosis. Studies have proved that AZD1775 alone is effective in the treatment of tumors. Currently, the treatment methods for patients with ovarian cancer are not perfect. Zhang et al. [34] verified through animal experiments that Wee1 inhibitor MK1775 as a single preparation has an inhibitory effect on tumor cells of ovarian cancer, and Wee1 may become a potential target of ovarian cancer. Bi et al. [35] determined that the expression of Wee1 was increased in esophageal squamous cell carcinoma cells, and thus verified that AZD1775 alone could inhibit the proliferation and metastasis of cancer cells and induce their apoptosis. Jin et al. [36] found that Wee1 inhibitor AZD1775 can block mitosis in S phase in pancreatic cancer, and make the cells in this phase be inhibited and apoptosis, so as to achieve the effect of treating pancreatic cancer.

In recent years, Acute Lymphoblastic Leukemia (ALL) treatment drugs have made patients get very effective treatment effect, but tumor recurrence has become a problem perplexing patients and doctors. It has been proved that [37] AZD1775 combined with CHK1/CHK2 inhibitor can act in S phase to make DNA damage and achieve therapeutic effect on patients with ALL. Junchenghu et al. [38] found that T-ALL was more dependent on G2/M phase in DNA damage due to the lack of G1/S phase, making Wee1 a key therapeutic target. The experimental results showed that Wee1 was closely related to the glycolysis of cells, which verified that Wee1 inhibitor AZD1775 combined with GLS1 inhibitor CB-839 and BPTES had better efficacy in the treatment of T-ALL than using the two drugs alone. According to Cody W. Lewis et al. [39], the presence of Myt1 in the cell cycle can phosphorylate the Thy14 site of CDK1, and also block the mitosis of cells, which can enhance the drug resistance of some tumors such as breast cancer to AZD1775. Therefore, the combined application of Wee1 inhibitor and Myt1 inhibitor in the treatment of some tumors may reduce the resistance of tumor cells to Wee1 inhibitor.

Other studies have demonstrated that Wee1 inhibitors will appear drug toxicity and drug resistance when used alone or in combination with other drugs to treat tumors, while Wee1 inhibitors will have better efficacy and fewer side effects when used continuously with other anti-tumor drugs. Yongfang et al. [40] showed that nausea, weight loss and other symptoms could occur when Wee1 inhibitors were combined with PARP inhibitors, while continuous use of the two drugs alone could not only kill tumor cells, but also improve toxicity in normal cells. There have also been studies [41] showing that sequential therapy with gemcitabine followed by Wee1 inhibitor can increase the number of tumor cell apoptosis more than alternating sequential therapy with gemcitabine followed by Wee1 inhibitor or combination therapy of gemcitabine and Wee1 inhibitor.

5. Summary

In this review, the role of Wee1 protein kinase in the cell cycle and the relationship between Wee1 protein kinase and tumor were summarized, and the development of Wee1 protein kinase inhibitors in tumor therapy was summarized. Wee1 protein kinase inhibitors are potentially targeted tumor therapy drugs. Currently, there are many researches on Wee1 inhibitors, but how to use Wee1 inhibitors to minimize the toxic and side effects of the treatment regimen is still controversial: Some scholars believe that single use is more effective than combined use; some scholars believe that combined use can reduce the side effects caused by Wee1 inhibitors, and combined use can maximize the efficacy; while others believe that neither single use nor combined use can bring the maximum benefit to patients as sequential therapy. As Wee1 protein kinase inhibitors are still in phase II clinical trials [42], how to keep the efficacy of the drug itself, and at the same time control the balance between Wee1 protein kinase inhibitors and other drugs or treatments to bring the greatest benefits to patients is the current research direction.

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