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Mini Review

Combined Exploration of APE1 and Autophagy in non-small Cell Lung Cancer: A New Perspective of Platinum Resistance Research

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ABSTRACT

Concurrent mediastinal Germ Cell Tumors (mGCTs) and hematological malignancies in the same patient have been reported in 2-3% of extragonadal GCT cases. In most cases, the involved GCTs are non-seminomatous and mediastinal, while the Hematological Malignancies (HMs) are often acute megakaryoblastic leukemia. Isochromosome 12p has been frequently detected in both tumors. Recently, two cases of concurrent mGCT and acute myeloid leukemia harboring *TP53* and *PTEN* mutations were reported. We published our research article about the case of a 37-years old male patient with concurrent GCT and acute megakaryoblastic leukemia. Similar to previous studies, *TP53* and *PTEN* mutations were shared in both tumors, in addition to the other seven shared mutations. This suggests that the concurrent occurrence of GCTs and HMs are associated with a common founding clone with a characteristic coexistence of *TP53* and *PTEN* mutations.

Keywords: Acute myeloid leukemia; Germ cell tumor; *TP53*; *PTEN*

INTRODUCTION

The status of platinum drugs in Non-Small cell Lung Cancer (NSCLC)

Globally, there are approximately 2.1 million new cases and 1.8 million deaths of lung cancer each year, accounting for 11.6% and 18.4% of all cancer cases [1]. Pathologically, NSCLC accounts for 85% of the lung cancer cases, so the importance of exploring the diagnosis and treatment of NSCLC is self-evident [2]. At present, rapid progress has been achieved in the field of drug research and development, with more than 10 kinds of small molecule targeted drugs or immune agents for NSCLC being marketed during 2015-2020 alone. In general, the indications of traditional chemotherapy drugs have narrowed, the application scenarios of targeted therapy and immunotherapy have increased, and the combination therapy of different categories of drugs has become a new strategy for patients with NSCLC. Even so, platinum drugs are still the most widely used drugs in the treatment of NSCLC. According to statistics, about 50% of NSCLC patients would receive platinum-based chemotherapy during the whole treatment process [3]. Platinum drugs play an important role not only in advanced or metastatic NSCLC without driver gene sensitive mutations, but also in the neoadjuvant and adjuvant therapy of NSCLC [4]. In terms of combination therapy, the combination with radiotherapy, targeted therapy and immunotherapy may also involve the use of platinum drugs [4]. Thus, the development of research on platinum drugs may be related to the overall treatment of NSCLC.

PLATINUM RESISTANCE IN NSCLC

Platinum drugs have been applied in the treatment of NSCLC for more than 30 years and have been updated to the third generation, yet the survival benefit for NSCLC patients has not been significantly improved [5,6]. The underlying reason is the resistance of platinum drugs. Platinum drugs work by causing DNA damage in cells. The DNA Adducts formed by platinum drugs and DNA can cause single-strand DNA damage, thus activating cell cycle checkpoint molecules and promoting apoptosis [7-10]. Due to the different states of DNA damage repair system of cells, the degree and outcome of DNA damage caused by platinum drugs are different in different patients and in different status. The DNA damage repair system mainly includes five categories: Mismatch Repair (MMR), Nucleotide Excision Repair (NER), Direct Repair (DR), Double-strand Break (DSB) repair, and Base Excision Repair (BER). The single-strand damage caused by platinum can usually be repaired by NER and BER [10,11]. Tumor cells with DNA repair defects are more sensitive to platinum-based chemotherapy. Conversely, tumor cells with a complete DNA repair system are more likely to develop platinum resistance. In addition to the molecules related to the DNA repair system, cell cycle checkpoint molecules, apoptosis molecules and autophagy molecules also play an important role in the overall exploration of the mechanism of platinum drugs resistance? The molecular functions and molecular

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signaling pathways involved above can be explored to understand the resistance of platinum drugs more specifically and accurately.

PLATINUM RESISTANCE RELATED MOLECULES AND SIGNALING PATHWAYS

DNA repair system: NER is a highly conserved and important way for the repairment of the platinum-induced DNA damage [12]. In NER signaling pathway, ERCC1 and ERCC2 are representative molecules. ERCC1 was come into view due to the significant correlation between its elevated expression and platinum resistance [13]. It has been found to perform DNA repair by forming an ERCC1-XPF heterodimer with XPF [14]. ERCC1 SNPs can cause changes in mRNA and protein expression, and some SNP sites have been found to be related to platinum treatment response, such as rs11615, rs3212986, etc [15-17]. However, ERCC1 is still only used as a potential biomarker to predict drug response and prognosis, and there is no relevant drug development. ERCC2 is a DNA helicase that also plays an important role in DNA repair. Its expression was significantly correlated with platinum drug resistance [18]. ERCC2 Asp312Asn and Lys751Gln polymorphisms are associated with platinum sensitivity, but their relationship with NSCLC prognosis remains controversial [19,20]. Of course, BER, DSB and MMR signaling pathways have also been found to be related to platinum resistance, with representative molecules such as XRCC1, XRCC3 and MSH2 [21-23]. The mechanism of their correlation with platinum drug resistance still needs to be further explored. Cell cycle checkpoint: If the cells in the cell cycle have not received repairment after the occurrence of platinum-induced DNA damage, the apoptosis process would be initiated. In this process, some cell cycle related molecules play a regulatory role. Such as P21, the regulator of cell fate, and the dynamic change of its expression is related to the occurrence of cell senescence in the process of G1 to G2 [24, 25]. Overexpression of p21 was found can reverse platinum resistance induced by HOTAIR [26]. WEE1 regulates G2/M phase checkpoint by phosphorylation of CDK1. Inhibiting WEE1 activation can reduce drug resistance to platinum drugs. WEE1 inhibitor AZD1775 has been proved to play a sensitization effect in combination with platinum-based chemotherapy [27,28]. Apoptosis: Apoptosis is an expected outcome after DNA damage induced by platinum drugs, but this occurrence is often affected by molecules of apoptosis pathway. The most representative molecule is p53, which can inhibit the expression of anti-apoptotic genes and promote the occurrence of apoptotic reaction when the damage cannot be repaired [29]. However, in vitro, it has been found that p53 mutant cell lines have pluripotency in the occurrence of apoptosis, and it usually promote apoptosis and increase platinum sensitivity only in cells with high degree of DNA damage and weak repair ability [30-32]. The typical anti-apoptotic molecules, such as XIAP family proteins and survivin, pro-apoptotic molecules, such as Bcl-2 family proteins, also play an important role in the occurrence of platinum drug resistance [33-35]. The researchers found that the expression level of Bcl-2 was significantly increased in cisplatin-resistant lung adenocarcinoma cells [34]. In NSCLC cells, sensitivity to cisplatin can be enhanced by downregulation of survivin expression [35]. Apoptosis-related MAPK, PI3K/Akt and Wnt signaling pathways are closely related to the occurrence of platinum resistance [36-38].

THE EFFECT OF APE1 AND AUTOPHAGY ON PLATINUM RESISTANCE

APE1 is located at 14q11.2, and the encoding protein is mainly distributed in the nucleus and cytoplasm. It is involved in DNA repair and acts as a transcription factor in redox regulation [39,40]. DNA repair is realized via positive regulation of BER pathway [41]. It was found that APE1 knockdown can enhance platinum sensitivity in A549 lung adenocarcinoma cells. Meanwhile, the expression of APE1 was increased in platinum-resistant NSCLC tissues, and the increased expression of APE1 indicated a poor prognosis of NSCLC [42]. In NSCLC patients, serum APE1 levels can also predict therapeutic efficacy and prognosis after platinum-containing chemotherapy [43,44]. What is the relationship between APE1 and the mechanism of platinum resistance? Initially, it is generally considered that APE1 might induce platinum resistance by reducing DNA lesions and promoting redox. Interestingly, Li et al. indicated that APE1 promoted platinum resistance in A549 cells by inducing Parkin-mediated mitochondrial-specific autophagy [45]. Autophagy, as a self-survival protective behavior of cells response to therapeutic stress, has been shown to play an important role in the development of drug resistance in cancer cells. It acts a dual role in two different scenarios. On the one hand, drug resistance is exerted by maintaining the survival of cells under the action of drugs; on the other hand, the occurrence of autophagic cell death caused by excessive consumption leads to the inhibition of cell proliferation induced by drugs [46-49]. However, most of the current studies focus on the role of the former in the occurrence of drug resistance and try to achieve the reversal of drug resistance by inhibiting autophagy. Recently, Ren et al. found BER and autophagy signal pathway were enriched, and APE1 expression was significantly increased via quantitative proteomic experiments of KRASG12S mutant A549 lung adenoma cell line treated with cisplatin. Paradoxically, contrary to previous studies, inhibition of APE1 could promote the occurrence of autophagy, explaining the reason why inhibition of APE1 or autophagy alone could not achieve the optimal resistance to platinum [50]. The special feature of this study is that, firstly, because of the phenotypic differences in specific RAS alleles mutant, the selection of RAS-specific mutant cell lines for screening target molecules is more consistent with the strategy of individualized therapy. Secondly, an interesting triple complex comprising APE1-p53-LC3 was found to be related to platinum resistance, and it was found that autophagy may be a drug resistance compensation mechanism of APE1 deficient cells. Dual inhibition of APE1 and autophagy can more effectively promote platinum-induced apoptosis. This is also consistent with the exploration route of combination therapy in clinical practice.

CONCLUSION

In the field of lung and ovarian cancer, platinum resistance has been studied for decades. However, the clinical application combined with platinum drugs for improving sensitivity did not bring a leap in cancer treatment. Discovery of new targets and new mechanisms are the obligatory step for platinum drugs to be used in a new way. Studies such as dual combined inhibition of APE1 and autophagy provided a new perspective for the research of platinum resistance. In the future, it may be a promising path to try to overcome platinum resistance through muti-target combination and multi-therapeutic combination.

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