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The small molecule drug CBL0137 interferes with DNA damage repair and enhances the sensitivity of NK/T-Cell lymphoma to cisplatin

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ABSTRACT

This study aimed to investigate the in vitro and in vivo antitumor effects and mechanisms of the small molecule anticancer drug CBL0137 in NK/T-cell lymphoma (NKTCL), as well as its efficacy when combined with chemotherapy or immunotherapy. Cell viability assays were performed to evaluate the inhibitory effect of CBL0137 on NKTCL cell proliferation in vitro. Flow cytometry was used to assess the effects of the drug on apoptosis and cell cycle progression. RNA sequencing (RNA-seq) was employed to explore the mechanism of action of CBL0137 in NKTCL, and Western blotting (WB) was used to validate the expression of related proteins. An in vivo xenograft model was used to confirm the antitumor activity of CBL0137. Additionally, immunohistochemistry analysis was conducted to further study tumor tissue. CBL0137 effectively inhibited the proliferation of NKTCL cells in vitro, induced apoptosis, and significantly blocked cell cycle progression. RNA-seq analysis revealed that CBL0137 exerts its antitumor effect primarily by interfering with DNA damage repair. In vivo experiments using xenografted mice confirmed the antitumor activity of CBL0137. CBL0137, when combined with PD-1 antibody, exhibits synergistic antitumor effects in mice, and its combination with cisplatin significantly enhances the sensitivity of NKTCL to cisplatin. CBL0137 inhibits DNA damage repair in NK/T-cell lymphoma and enhances its sensitivity to cisplatin.

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CBL0137; NK/T-cell lymphoma; DNA damage repair; cisplatin; PD-1 blockade; cancer therapy; mouse studies

1. Introduction

NK/T-cell lymphoma (NKTCL) is an aggressive subtype of non-Hodgkin's lymphoma.[1,2] NKTCL originates from natural killer (NK) cells or T cells and is closely associated with Epstein-Barr virus (EBV) infection.[3] The disease exhibits significant geographic variation, with higher incidence rates particularly observed in Asia and Latin America, and a notably higher prevalence in males compared to females.[4,5] Clinically, early-stage NKTCL patients show a favorable response to sole radiotherapy treatment,[6] whereas advanced-stage patients typically require a combination of radiotherapy and chemotherapy to achieve better therapeutic outcomes.[7] Due to the high expression of P-glycoprotein in NKTCL cells, they exhibit resistance to anthracycline-based therapies, such as the CHOP(Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone) regimen.[8] While L-asparaginase-based therapies have improved survival outcomes for NKTCL patients, most individuals still respond poorly to standard treatments.[9] In recent years, novel therapeutic strategies, such as targeted therapies and immunotherapy, have brought new hope for NKTCL patients.[10] However, the prognosis for relapsed or refractory patients remains poor.[11,12] Given the limited effectiveness of current therapeutic options, there is an urgent need for novel and more effective treatments for patients with relapsed or refractory NKTCL.

CBL0137, a second-generation member of the curaxin family, is a small-molecule anticancer agent.[13,14] CBL0137 exerts its anti-tumor effects by targeting the FACT complex, inhibiting the NF-κB signaling pathway, and activating the P53 signaling pathway.[13,15] In preclinical studies, CBL0137 has demonstrated significant anti-tumor activity across a range of malignancies, including lung cancer, ovarian cancer, and leukemia.[16–18] In addition to its efficacy as a monotherapy, CBL0137 has been shown to significantly enhance the therapeutic effects when combined with chemotherapy, radiotherapy, targeted therapy, and immunotherapy.[16,19–21] Results from phase I clinical trials also indicate that CBL0137 has a favorable safety profile.[22]

To date, CBL0137 has shown potent anti-tumor activity in various hematologic malignancies, including acute lymphoblastic leukemia, multiple myeloma, acute myeloid leukemia and B-cell non-Hodgkin lymphoma.[20,23–27] However, its effects on NK/T-cell lymphoma remain underexplored and warrant further investigation. In this study, we investigated the in vitro and in vivo effects of CBL0137 on NKTCL and explored its underlying mechanisms. We examined its impact on cell proliferation, apoptosis, and cell cycle arrest, as well as its potential synergistic effects when combined with chemotherapy and immunotherapy. These findings provide a foundation for the development of novel therapeutic strategies for NKTCL.

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2. Results

2.1. Effects of CBL0137 on NKTCL cell proliferation and cell cycle in vitro

In vitro, NKTCL cell lines (RMA, SNT16, and NKYS) were treated with different concentrations of CBL0137. The cell viability significantly decreased in a dose-dependent manner across various treatment durations (Figure 1(a)). After 24 hours of treatment, the median inhibitory concentrations (IC50) of CBL0137 for RMA, SNT16, and NKYS cells were 0.71 μM, 0.49 μM, and 0.50 μM, respectively. Cell cycle analysis showed that CBL0137 administration

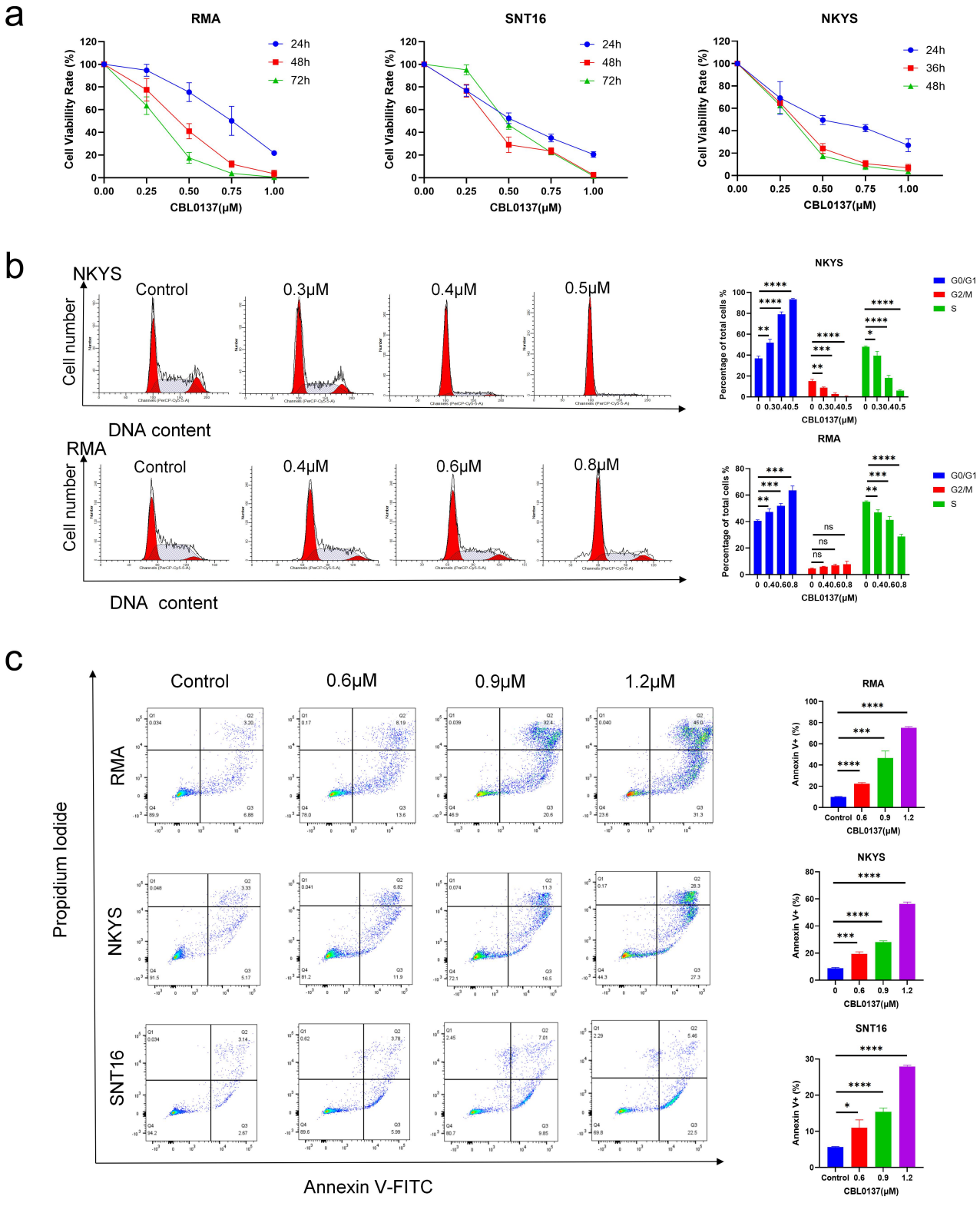

Figure 1. In vitro effects of CBL0137 on NK/T-cell lymphoma cells. (a)The CCK-8 test was used to assess the vitality of NKTCL cells. (b) Following 48 hours of CBL0137 administration, the distribution of cell cycles was examined by flow cytometry ($n = 3$). *$p < .05$, **$p < .01$, ***$p < .001$, ****$p < .0001$. (c) RMA, SNT16, and NKYS cells were treated with different concentrations of CBL0137 for 24 hours, respectively. Following treatment, cells were stained with the annexin V-FITC apoptosis detection kit, and flow cytometry was used to measure the rates of apoptosis ($n = 3$). *$p < .05$, **$p < .01$, ***$p < .001$, ****$p < .0001$, N.S., not significant.

led to a decrease in the S phase population and a dose-dependent rise in the percentage of cells in the G0/G1 phase (Figure 1(b)). From the experimental results, CBL0137 was found to significantly inhibit NKTCL cell proliferation in vitro and induced cell cycle arrest.

2.2. CBL0137 induces apoptosis in NKTCL cells

Next, we investigated whether CBL0137 inhibits NKTCL growth through additional mechanisms. NKTCL cells were stained with FITC-Annexin V/PI to assess apoptosis, and the proportion of apoptotic cells was then measured by flow cytometry analysis. After 24 hours of treatment, both early and late apoptosis increased in a concentration-dependent manner (Figure 1(c)).

2.3. CBL0137 exerts its antitumor effects by inhibiting DNA damage repair

To investigate mechanisms, RNA sequencing (RNA-seq) was conducted on NKYS cells treated with CBL0137, identifying differentially expressed genes (DEGs). A total of 27,959 genes were analyzed, among which 5,624 were identified as DEGs, accounting for approximately 20.1% of the total. 3,253 genes were found to be upregulated and 2,371 genes to be downregulated out of 5,624 DEGs (Figure 2(a)). We conducted functional enrichment analysis of the differentially expressed genes (DEGs) using Gene Ontology (GO) and Reactome databases. GO enrichment analysis revealed significant alterations in gene sets associated with structural constituent of chromatin, single-stranded DNA helicase activity, single-stranded DNA binding, nucleosome, chromosome centromeric region, nuclear chromosome, chromosome telomeric region, heterochromatin, nucleosome assembly, and DNA replication-dependent chromatin assembly (Figure 2(b)). Furthermore, Reactome enrichment analysis demonstrated that DEGs were significantly downregulated in pathways related to DNA repair processes (Figure 2(c)). Western blotting analysis revealed that treatment with CBL0137 led to the downregulation of p-CHK1, a key regulator of the DNA damage response pathway, and the upregulation of γH2AX, a marker of DNA double-strand breaks, in NKYS cells (Figure 2(d)). These findings suggest that CBL0137 exerts its antitumor effects by disrupting DNA repair mechanisms, further enhancing its potential as a therapeutic agent for NKTCL.

2.4. Antitumor activity of CBL0137 in vivo

The antitumor activity of CBL0137 was further validated in vivo using an RMA tumor-bearing mouse model. C57BL6/J mice received subcutaneous injections of RMA cells, and once the tumors were palpable, medication intervention was started (Figure 3(a)). As shown, CBL0137 significantly inhibited tumor growth in the treated mice (Figure 3(b–d)). To investigate the antitumor mechanism in vivo, tumor tissues were analyzed by hematoxylin and eosin (HE) staining and immunohistochemistry (IHC). The results indicate that, compared to the control group, the CBL0137-treated group showed an increase in necrotic tissue, a significant reduction in the proportion of Ki-

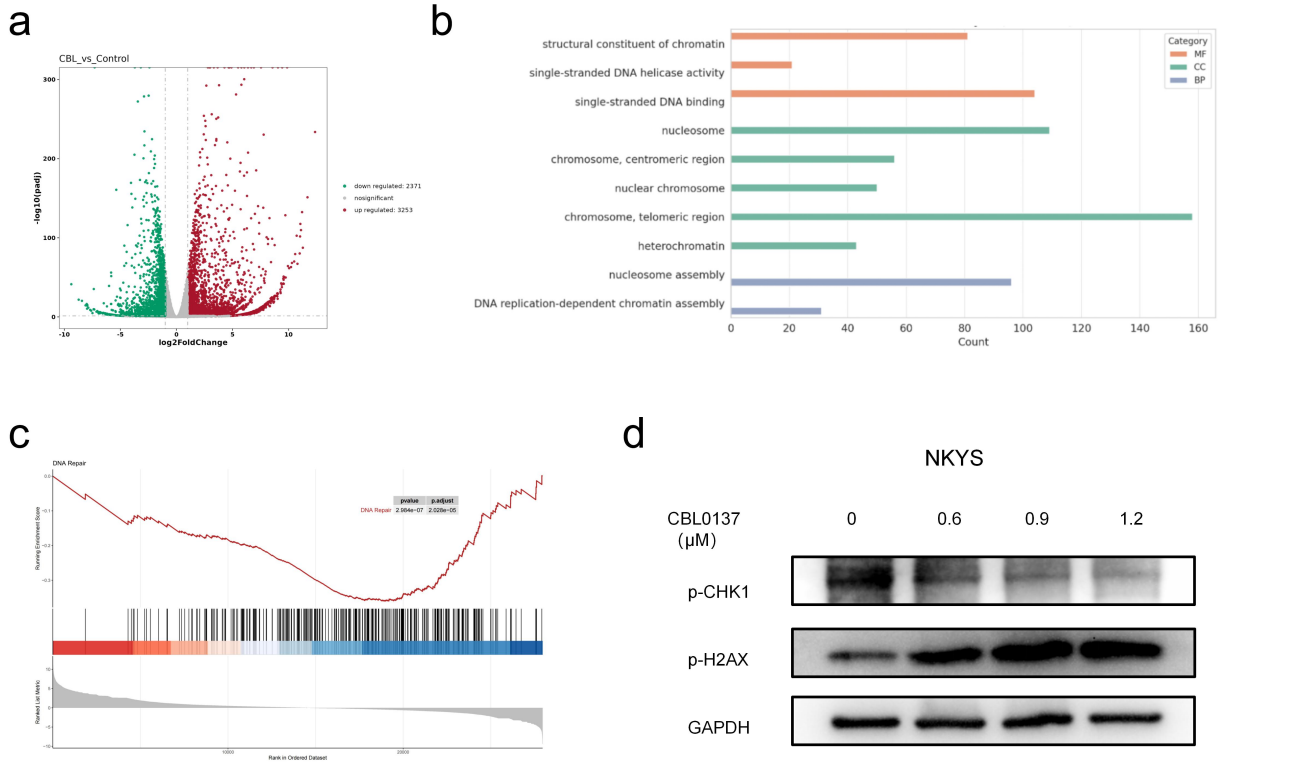

Figure 2. CBL0137 disrupts DNA damage repair in NKTCL. (a) A comparison of the CBL0137-treated and control groups revealed 5,624 differentially expressed genes (DEGs), of which 2,371 were downregulated and 3,253 were upregulated. (b) GO enrichment analysis of NKYS cell line. The y-axis represents the enriched GO functional categories, while the x-axis shows the number of different molecules in each functional category. BP, CC, and MF represent the three different functional components. (c) Results of DNA repair gene set from Reactome analysis. (d) Expression of DNA damage and repair-related proteins after 24 h CBL0137 treatment of NKYS cells in vitro.

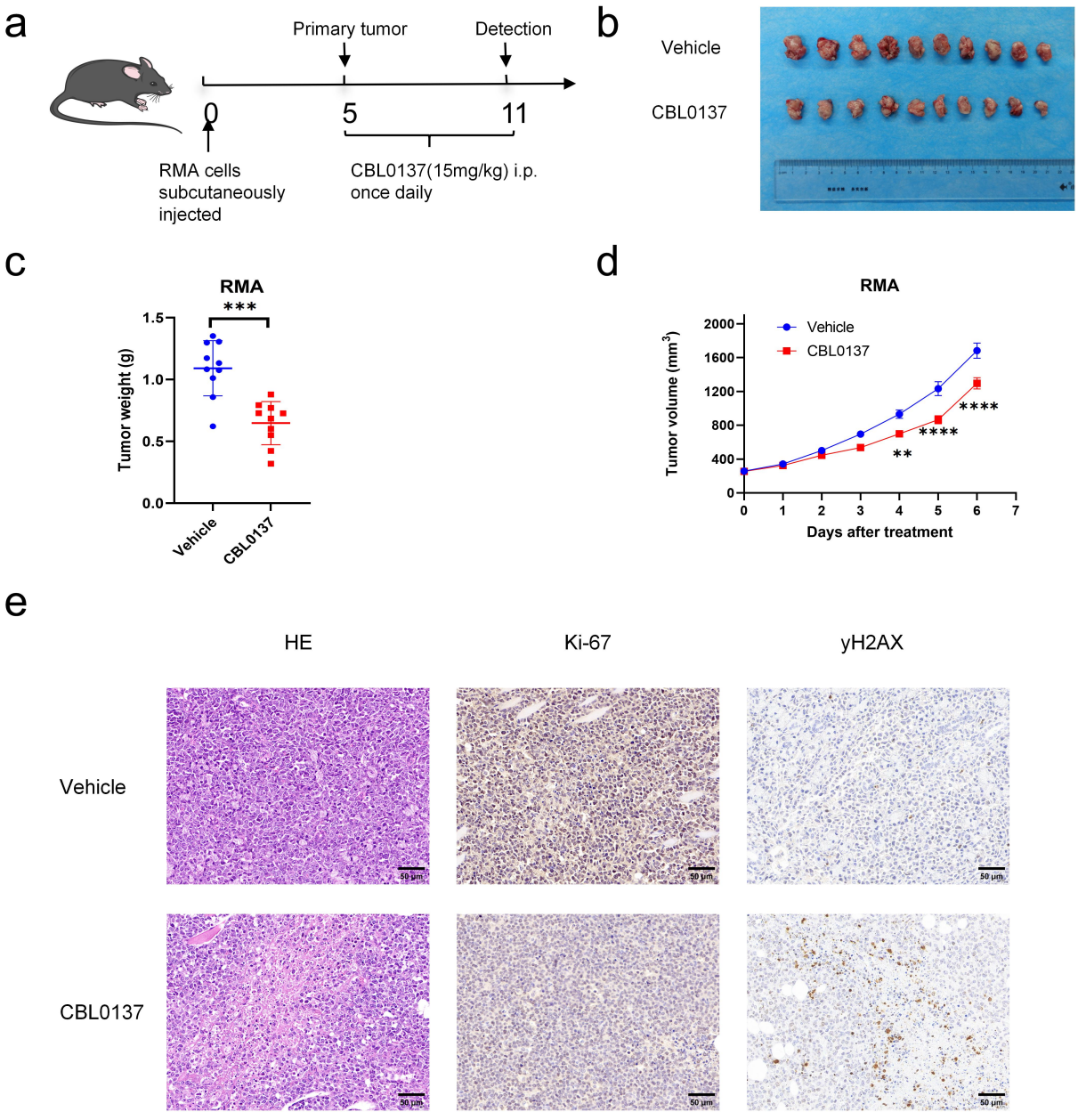

Figure 3. In vivo inhibition of NKTCL growth by CBL0137. (a) C57BL6/J mice were subcutaneously implanted with 1×10^6 RMA cells in the axillary area. At the time of tumors coursing touch, mice with successful hormonal tumors were randomly divided into 2 groups of equal number: an experimental group treated with CBL0137 drug and a control group treated with an equal amount of solvent($n = 10$). (b) Typical pictures of tumors from the control group and the group treated with CBL0137. (c–d) Quantitative analysis of tumor weight and volume. (e) Representative hematoxylin and eosin (HE) and immunohistochemical (IHC) staining of tumor tissue. Scale bar = 50 μm.

67 positive cells, and an elevation in the expression of the DNA double-strand break marker γH2AX (Figure 3(e)).

2.5. CBL0137 enhances immunotherapy in NKTCL

In recent years, CBL0137 has increasingly been recognized for its significant potential in cancer immunotherapy.[28] Several studies have demonstrated that treatment with CBL0137 significantly enhances the sensitivity of tumor cells to immunotherapy.[21,29] To further examine the anti-tumor efficacy of CBL0137, its combination with anti-PD-1 therapy was tested. Tumor-bearing mice were treated at designated time points with either vehicle, CBL0137, anti-PD-1, or a combination of CBL0137 and anti-PD-1 (Figure 4(a)). Compared to vehicle, CBL0137 significantly inhibited tumor growth, and the combination with anti-PD -1 produced a more substantial suppression of tumor growth than either treatment alone (Figure 4(b–d)). HE staining of major organs (heart, liver, spleen, lungs, and kidneys) showed no significant toxicity associated with the combination therapy (Figure 4(e)).

2.6. Antitumor activity of CBL0137 in combination with cisplatin

Cisplatin, a widely used chemotherapeutic agent, primarily exerts its anti-cancer effects through the induction of DNA damage, with resistance mechanisms often involving enhanced

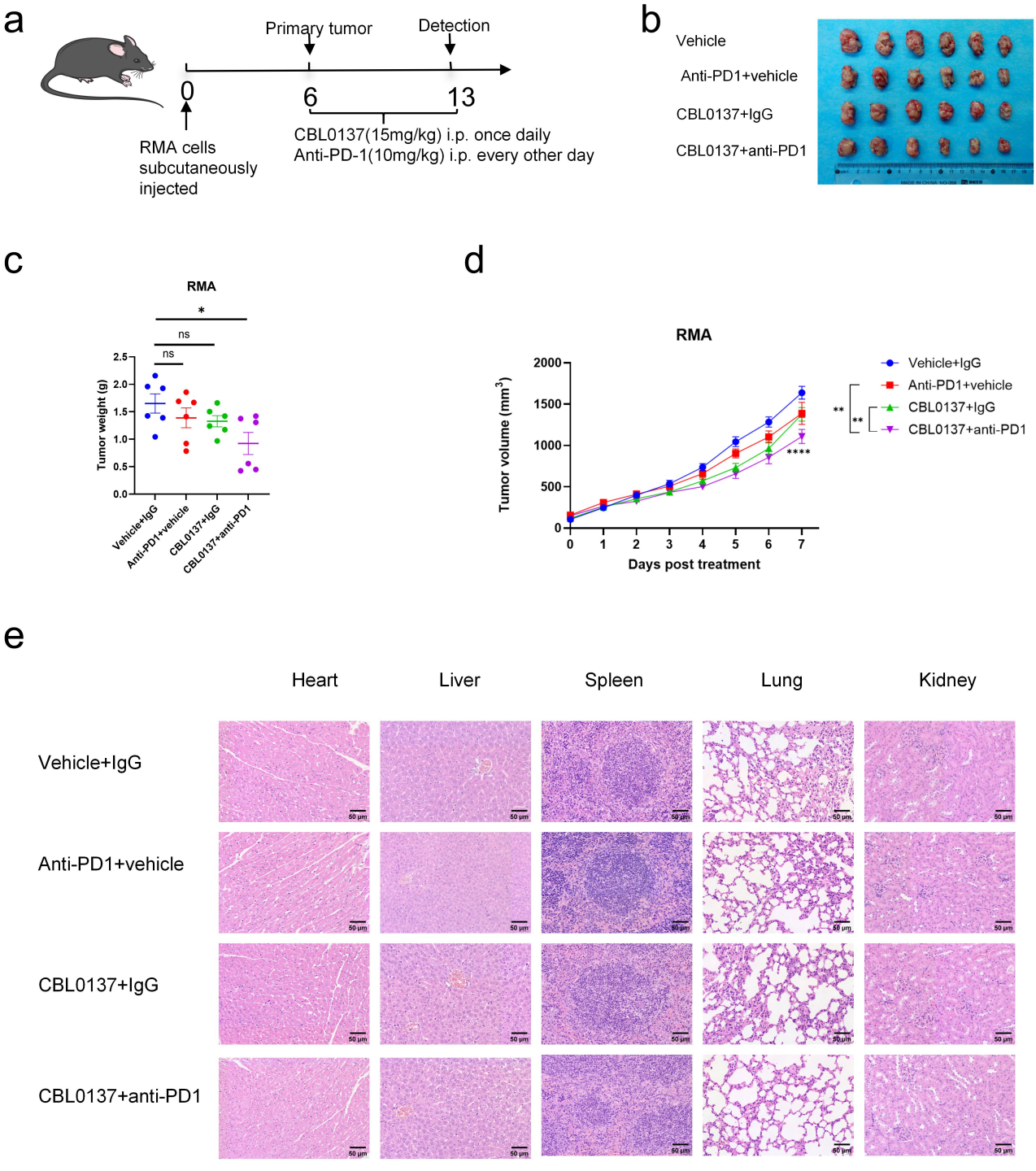

Figure 4. Synergistic inhibition of NKTCL by CBL0137 and PD-1 antibody. (a) To create a subcutaneous xenograft model, RMA cells were inserted into C57BL6/J mice. The mice were split into four groups at random once the tumors reached a palpable size. PD-1 antibody (10 mg/kg every 3 days), vehicle and anti-PD1 isotype antibody CBL0137 (15 mg/kg daily), or a combination of CBL0137 and PD-1 antibody ($n = 5$) were administered to the mice. (b) At the final stage of the experiment, tumors were removed. (c–d) Quantitative analysis of tumor weight and volume. (e) HE staining analysis of tissue samples from all four groups. Scale bar = 50 μm.

DNA repair.[30,31] Recent studies have shown that CBL0137 can significantly enhance the antitumor efficacy of traditional chemotherapeutic agents through multiple mechanisms, particularly demonstrating unique advantages in the treatment of highly invasive tumors and drug-resistant tumor cells.[32,33] In the subsequent experiments, we further investigated the antitumor effects of CBL0137 in combination with cisplatin in vivo. Tumor-bearing RMA mice were treated with vehicle, CBL0137, cisplatin, or a combination of CBL0137 and cisplatin (Figure 5(a)). Tumor volumes were monitored and recorded over one week. Both CBL0137 and cisplatin alone significantly inhibited tumor growth in vivo, with the combined treatment demonstrating an even more pronounced suppression of tumor progression (Figure 5(b–d)). Analysis of HE staining and immunohistochemistry results from the four tumor groups revealed that the combination of CBL0137 and

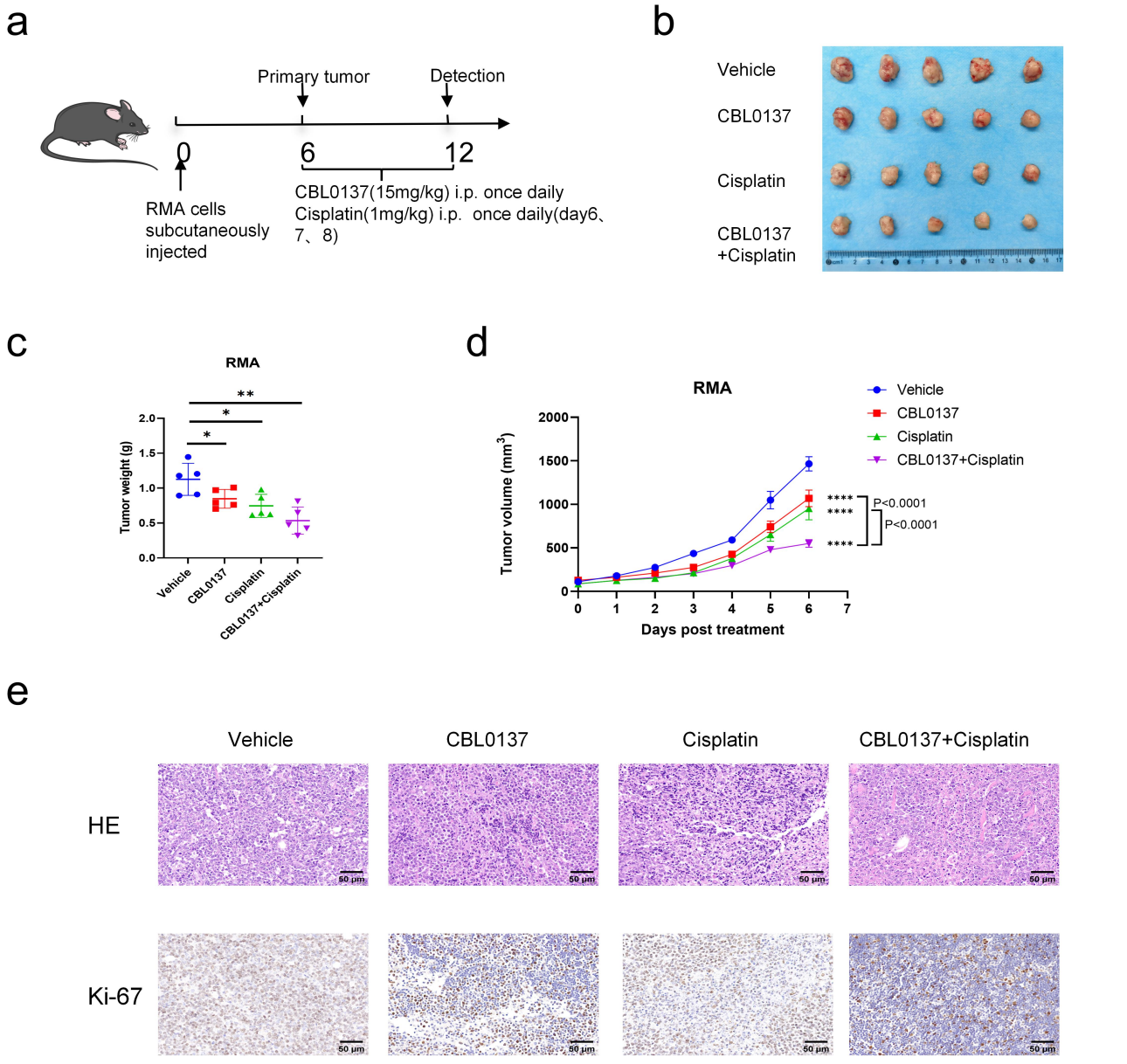

Figure 5. CBL0137 and cisplatin synergistically inhibited NKTCL. (a) RMA cells were implanted into C57BL6/J mice to establish a subcutaneous xenograft model. Once tumors developed, mice were randomly assigned to four groups. Mice received either vehicle, CBL0137 (15 mg/kg daily), cisplatin (1 mg/kg for three consecutive days), or a combination of cisplatin and CBL0137 ($n = 5$). (b) At the final stage of the experiment, tumors were removed. (c–d) Quantitative analysis of tumor weight and volume. (e) Representative HE and IHC staining of tumor tissues. Scale bar = 50 μm.

cisplatin produced the highest proportion of necrotic tissue and the lowest percentage of Ki-67-positive cells (Figure 5(d)).

3. Discussion

NKTCL is a malignancy originating from NK/T cells. Although chemotherapy, particularly regimens involving asparaginase-based drugs, has significantly improved patient prognosis, the therapeutic outcomes for patients with relapsed or refractory NKTCL remain unsatisfactory.[2,3,12] Current research focuses on discovering new targeted therapies and improving existing treatment strategies in hopes of achieving better clinical outcomes.[10,34] Through a series of in vitro and in vivo experiments, we investigated the potential of CBL0137 in the treatment of NKTCL, with a particular focus on its synergistic antitumor effects in combination therapies. This study aims to provide new therapeutic strategies for patients with NKTCL.

To investigate the in vitro toxicity of CBL0137 on NKTCL cell lines, we first assessed its impact on NKTCL cell proliferation. The experimental results demonstrated that CBL0137 significantly inhibited NKTCL cell proliferation in a time- and dose-dependent manner. Notably, the IC50 values varied across different cell lines, suggesting that different NKTCL cell lines may exhibit varying sensitivities to CBL0137. Dysregulation of cell cycle control is one of the key factors driving the uncontrolled proliferation of tumor cells.[35] Flow cytometry analysis in this study revealed that CBL0137 treatment led to a significant accumulation of NKTCL cells in the G0/G1 phase, with a marked reduction in the proportion of cells in the S phase, and this effect was concentration-

dependent. Additionally, using FITC-Annexin V/PI staining and flow cytometry, we observed that both early and late apoptosis of NKTCL cells increased significantly with the concentration of CBL0137.

In this study, we performed enrichment analysis of differentially expressed genes (DEGs) in NKYS cells treated with CBL0137 using the GO and Reactome databases.

GO database enrichment results revealed that molecular functions related to chromatin structural components, single-stranded DNA helicase activity, and single-stranded DNA binding were significantly affected, suggesting that CBL0137 may disrupt chromatin stability and impact DNA replication and repair processes. CBL0137 is an inhibitor of Facilitates chromatin transcription (FACT), a complex composed of Suppressor of Ty homology −16 (SPT16) and Structure specific recognition protein 1 (SSRP1). FACT acts as a chromatin remodeling factor and regulates chromatin structure by disassembling and reassembling nucleosomes during DNA replication, transcription, and repair.[36,37] FACT is generally highly expressed in tumor cells and is closely associated with tumor cell proliferation and malignant phenotypes.[32,38] FACT was initially identified as a key factor promoting dynamic changes in chromatin structure during transcription elongation, and recent studies have highlighted its significant role in the DNA damage response (DDR) and DNA repair mechanisms.[19,39–41]

Furthermore, Reactome enrichment analysis further revealed that DEGs after CBL0137 treatment showed significant downregulation in pathways related to DNA repair. Western blot analysis indicated that CBL0137 treatment resulted in a downregulation of p-CHK1, a key regulatory protein in the DNA damage response pathway, and a significant upregulation of γH2AX, a marker of DNA double-strand breaks. These results suggest that CBL0137 exerts its effects by inhibiting DNA damage repair pathways, which enhances the accumulation of DNA damage and subsequently promotes tumor cell death.

CBL0137 also increases the immunogenicity of tumor cells,[28] suggesting that its antitumor activity may be linked to immune responses. While immune checkpoint blockade therapies have brought hope to many cancer patients, the proportion of patients who achieve sustained responses to immunotherapy remains small.[42] Ting Zhang et al. were the first to combine CBL0137 with anti-PD1 therapy in a mouse tumor model. CBL0137 was shown to bypass ADAR1-dependent immune silencing by triggering the formation of left-handed Z-DNA in cells, inducing ZBP1-dependent necroptosis, and reversing ICB resistance in melanoma mouse models.[21] We further explored whether the addition of CBL0137 could enhance the efficacy of PD-1 antibodies in treating NKTCL. The combination of CBL0137 and anti-PD1 showed a synergistic effect in the RMA tumor model, with no significant toxicity. Although the results showed statistical differences, the overall effect was not particularly satisfactory, likely due to the influence of other immune-related factors.

CBL0137 has also demonstrated synergistic therapeutic effects with cisplatin in tumor models of small cell lung cancer (SCLC).[16] We investigated the therapeutic efficacy of combining CBL0137 with cisplatin for the treatment of NKTCL. Encouragingly, the combination of CBL0137 and cisplatin exhibited the strongest antitumor activity, significantly inhibiting tumor progression in the RMA mouse model.

Both in vitro and in vivo experiments demonstrate that CBL0137 exhibits potent anticancer activity against NKTCL, primarily due to its interference with DNA damage repair. When combined with anti-PD-1 antibody or cisplatin, CBL0137 shows a synergistic effect. This preclinical study provides a solid foundation for the future clinical development of CBL0137 and its potential to be transformed into a therapeutic option. Furthermore, it offers additional treatment alternatives for NKTCL patients.

4. Materials and methods

4.1. Cell lines and cell culture

The NKYS cell line was generously provided by Dr. Wing C. Chan at the City of Hope Medical Center, while the RMA cell line was obtained from WheLab, and the SNT16 cell line was supplied by Guangzhou Bairui Biomedical Technology Co., Ltd. (China). NKTCL cell lines were cultured in RPMI-1640 medium (Gibco) supplemented with 10% fetal bovine serum (Oricell), 100 units/mL penicillin, 100 μg/mL streptomycin (Gibco), and an anti-mycoplasma reagent (Hanbio). For the growth of NKYS cells, 100 IU/mL of IL-2 was also added to the medium. Every culture was incubated in a humidified environment with 5% CO at 37°C.

4.2. Reagents and antibodies

CBL0137 hCl, cisplatin, anti-mouse PD-1 (CD279)-InVivo, and its isotype control antibody (Rat IgG2a isotype control-InVivo) were all purchased from Selleckchem (origin:United States).

4.3. Cytotoxicity assay

Graded doses of CBL0137 were applied to NKTCL cells after they were seeded in 96-well plates at a density of 1×10^4 cells per well. After treatment, each well received 10 μL of the Cell Counting Kit-8 (CCK-8) reagent, which was then incubated for an hour at 37°C in an incubator with 5% CO_2. A microplate reader was then used to detect absorbance at 450 nm. Additionally, we established a negative control group and a blank control group to facilitate the calculation of cell survival rates.

4.4. Cell cycle assay

After 48 hours of treatment with various concentrations of CBL0137, NKTCL cells were collected and rinsed with PBS. After being fixed in 75% ethanol that had been cooled beforehand, the cells were incubated at 4°C for the whole night. Following more PBS washes, cells were stained with a cell cycle detection kit and allowed to sit at room temperature for 15 to 30 minutes in the dark. BD Pharmingen's flow cytometry was used to examine the cell cycle distribution, and ModFit LT 3.2 software was used for processing.

4.5. Apoptosis assay

For apoptosis analysis, the NKTCL cell suspension was adjusted to a concentration of 1×10^5 cells/mL. A 1 mL aliquot of the NKTCL cell suspension was added to each well of a 24-well plate. CBL0137 was then added to the cells at the required concentrations, and the cells were incubated for 24 hours. Following treatment, the cell suspension was collected, centrifuged, and the supernatant discarded. The cells were washed with PBS and resuspended in the apoptosis buffer provided in the detection kit. Subsequently, Annexin-V/PI apoptosis detection reagent was added, and the cells were stained in the dark at room temperature for 15 minutes. Flow cytometry (BD Pharmingen) was used to quantify apoptosis, and FlowJo software was used for analysis.

4.6. RNA-seq

Hangzhou KaiTai Biotechnology Co., Ltd. constructed and sequenced mRNA libraries after total RNA was isolated from NKYS cells using the Trizol reagent. For high-throughput sequencing, the Illumina Novaseq 6000 platform was utilized. FDR < 0.05 and $|\log_2 FC| > 1$ were set as the thresholds for the identification of differentially expressed genes.

4.7. Western blotting

Cells were lysed in RIPA lysis buffer with protease inhibitor mixture and phosphatase inhibitor mixture. Equal amounts of protein extracts were separated by SDS-PAGE electrophoresis and then transferred to PVDF membranes. After being closed with TBST punch containing 5% BSA for 2 h at room temperature, the membrane was incubated with primary antibody overnight at 4°C and secondary antibody for 1 h at room temperature. Band images were digitally captured with a ChemistryTM XRC + system (Bio-Rad Laboratories).

4.8. Mouse studies

All animal experiments were approved by the Henan Provincial Laboratory Animal Center (approval no. ZZU-LAC20240531[25]) and conducted in compliance with their established guidelines. Female C57BL6/J mice were purchased from GemPharmatech. At 4–6 weeks of age, the mice were inoculated with 1×10^6 RMA cells by subcutaneous injection into the right axilla. Once tumors became palpable, drug interventions were administered. While the control group was given an equivalent volume of solvent, the treatment groups were given an intraperitoneal injection of 15 mg/kg of CBL0137. The cisplatin treatment group was given 1 mg/kg cisplatin via intraperitoneal injection (total volume: 0.15 mL), with the corresponding control group receiving an equivalent solvent injection. Anti-mouse PD-1 (CD279)-InVivo and its isotype control antibody were administered via intraperitoneal injection at 10 mg/kg. Tumor volume and body weight were monitored using calipers and an electronic balance. The experiment was terminated when the tumor volume in mice approached 2000 mm^3. Euthanasia was performed using cervical dislocation, and the final tumor volume and weight were recorded. Statistical analyses of the experimental data were performed using GraphPad Prism 9.5 software.

4.9. Immunohistochemistry (IHC)

After euthanasia, tumor tissues were harvested from the mice, fixed in formalin for over 24 hours, paraffin-embedded, sectioned, and subjected to serum blocking. Sections were incubated with the primary antibody overnight, followed by thorough washing, and then incubated with the corresponding secondary antibody. The antigen-antibody reaction was observed by DAB staining. After drying the sections, they were counterstained with hematoxylin and prepared for microscopic examination.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Conception and design: Xudong Zhang, Mingzhi Zhang, Qingjiang Chen
Data analysis and interpretation: Siyu Qian, Yue Zhang, Hang Gu
Manuscript writing: Hang Gu
Final approval of manuscript: All authors

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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