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Evaluation of the Inhibitory Effect of 2,5-Dimethyl-Celecoxib on Tamoxifen-Sensitive and -Resistant Human Breast Cancer Cells (MCF-7)

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KEYWORDS

Tamoxifen Resistance;
DMC;
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ABSTRACT

Acquired endocrine-resistance has become a big clinical challenge in breast cancer endocrine therapy.We previously reported that simvastatin inhibited TamR cell growth by reducing the expression of minichromosome maintenance protein 7 (MCM7) and retinoblastoma protein (Rb), which caused a significant up-regulation of γH2AX expression and subsequently induces DNA damage.Our previous studies have demonstrated that 2,5-dimethyl-celecoxib (DMC) can significantly reduce MCM7 and Rb protein expression in both MCF-7 and MCF-7/TamR cell lines. Aimed to investigate the effect of DMC on the proliferation of TAM-sensitive and -resistant breast cancer cell lines as well as to evaluate the possible underlying inhibitory mechanism, MTT and apoptosis analysis were performed to detect cell proliferation and apoptosis.Western blotting assays were performed to analyse the protein expression levels of cell cycle and apoptosis regulators. Furthermore, immunofluorescence and comet assays were carried out to explore the mechanism of DNA damage.Finally, *in vivo* experiments are performed to verify the results of *in vitro* experiments. The results demonstrated that DMC inhibited the proliferation and increased the apoptosis of both TAM-sensitive and -resistant breast cancer cells *in vitro*. In addition, DMC was observed to down-regulate Rb/MCM7 and induce DNA damage, particularly when used in combination with TAM. Notably,DMC also proved to have the same effect *in vivo* model. In summary , the growth inhibition generated by DMC may be achieved by inhibiting the protein expression of Rb/MCM7 and subsequently inducing DNA damage. This study provides a novel strategy for the treatment of TamR breast cancer patients in the clinical setting.

Introduction

Breast cancer is the most commonly diagnosed malignancy and a main cause of mortality among women worldwide(1). Endocrine therapy is the main choice for postoperative adjuvant treatment and has emerged as an advanced palliative treatment for ER-positive breast cancer(2, 3).Tamoxifen (TAM) is one of the most widely prescribed selective ER modulators and a gold standard endocrine treatment for all stages of breast cancer(4, 5). However, after 5 years of endocrine therapy with TAM, one-third of patients have been reported to develop drug resistance during or after chemo-

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therapy(6, 7). Acquired endocrine-resistance has become a big clinical challenge in breast cancer endocrine therapy and no effective solution has been reported. Therefore, understanding the underlying mechanism responsible for resistance during the course of endocrine therapy is critical and has important clinical value.

2,5-Dimethyl-celecoxib (DMC) is a methylated derivative of celecoxib(8). Despite the lack of selective cyclooxygenase-2 inhibition, DMC exhibits a tumor inhibition activity that is 20–50% higher than that of celecoxib, and it is devoid of cardiovascular toxicity(9). Many studies have showed that DMC has significant antitumor effects in several cancers, such as colorectal cancer, gastric cancer, lung cancer, human leukemia, glioblastoma, multiple myeloma, Burkitt's lymphoma, and breast cancer(10-19). However, whether DMC inhibits the proliferation of TAM-resistant (TamR) breast cancer cells has not been reported yet. We previously reported that simvastatin inhibits TamR cell growth by reducing the expression of MCM7/Rb, which causes a significant upregulation of γH2AX expression and subsequently induces DNA damage(20). In addition, our previous studies have demonstrated that DMC can significantly reduce MCM7 and Rb protein expression in MCF-7 and TamR cell lines.

In our research, we aimed to determine the effects of DMC on the proliferation and apoptosis of TAM-sensitive and -resistant breast cancer cell lines, as well as to evaluate the possible mechanism to provide a theoretical basis for the clinical application of DMC in the treatment of TamR breast cancer. In this research, as a model of human breast cancer, the cell line MCF-7 and the TamR cell line (MCF-7/TamR) were cultured *in vitro* and treated with various concentrations of DMC for different incubation periods. The effects of DMC on cell proliferation and apoptosis were investigated. The western blotting assays were performed to analyse the protein expression levels of cell cycle and apoptosis regulators.Furthermore, immunofluorescence and comet assays were carried out to explore the mechanism of DNA damage.Finally, *in vivo* animal experiments further validate *in vitro* results.

Materials and Methods

Cells and Reagents

MCF-7 cells were purchased from Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences.MCF-7/TamR was derived from MCF-7 as previously described(20). Dimethyl sulfoxide (DMSO), TAM, and DMC were obtained from Sigma-Aldrich (USA). Fetal bovine serum (FBS) and charcoal-dextran-stripped FBS were obtained from Gibco (USA). High-glucose Dulbecco's modified Eagle's medium (DMEM) and phenol-free DMEM were purchased from Hyclone (USA).

MTT Assay

The cells(5 x 103 cells/well) were cultured in 96-well plates. After 24h, the cells were incubated with a series of concentrations of DMC and TAM. The treatment was performed either alone or in combination for different time periods (24, 48, 72 h). A 10-μl aliquot of MTT solution (5 mg/ml) was added and incubated at 37 °C for 4 h. After removing the medium, 100 μl of DMSO was added and shaken. Absorbance values were measured by using the microplate reader at 490 nm.

Flow Cytometric Analysis

Apoptosis was determined by using PE Annexin V apoptosis detection kit according to the manufacturer's guidelines. In brief, the cultured cells at a concentration of 5 × 104 cells/well in 6-well plates were washed twice with PBS and then resuspended in 100 μl of Annexin V binding buffer (1 × 106 cells/ml). Next, 5 μl each of PE Annexin V and 7-aminoactinomycin were added to the cells, the cells were incubated (30 min, in the dark), and staining and flow cytometric analysis were performed.

Western Blotting

Western blotting assays were carried out according to reported protocols, with slight modifications(21). Antibodies against p-Rb, γ-H2AX, p-ATM, p-CHK-2, Bcl-2, survivin, cleaved caspase 3, and PARP were diluted at 1:1000 (Cell Signaling Technology, USA) . Antibodies against Rb, MCM7, and PCNA were diluted at 1:500 (Santa Cruz, USA).

Immunofluorescence Assays

After treatment with drugs for 24h, the cells were each treated with 4% paraformaldehyde and 0.2% Triton X-100 for 10 min, and 5% BSA was blocked for 1 hour, then incubated with the primary antibody γH2AX at 4 °C overnight. Next day, incubated with an Alexa Fluor 488 anti-mouse secondary antibody for 1 h. Finally, the cells were stained with DAPI (5 μg/mL) and images were taken by a confocal fluorescence microscope (Leica SP5II).

Neutral Comet Assays

Neutral comet assays were carried out by using Trevigen's Comet Assay Reagent Kit according to the manufacturer's guidelines.Briefly, cells (106) were cultured in 6-well culture plates. An aliquot of 10 μl of cells at a concentration of 1 × 105 cells/ml was suspended in PBS solution, and the resulting suspension was mixed with 100 μl of molten LMAgarose at 37 °C in a 1:10 (v/v) ratio, followed by immediate loading of sample (50 μl) onto a CometSlide, which was kept at 4 °C for 30 min before subsequent experimentation. DNA staining was performed with SYBR® Gold, and visualization was carried out using epifluorescence microscopy (Leica DMi8, Germany). Finally, 50 cells per group were analyzed and quantified using CASP1.2.3 beta1 software.

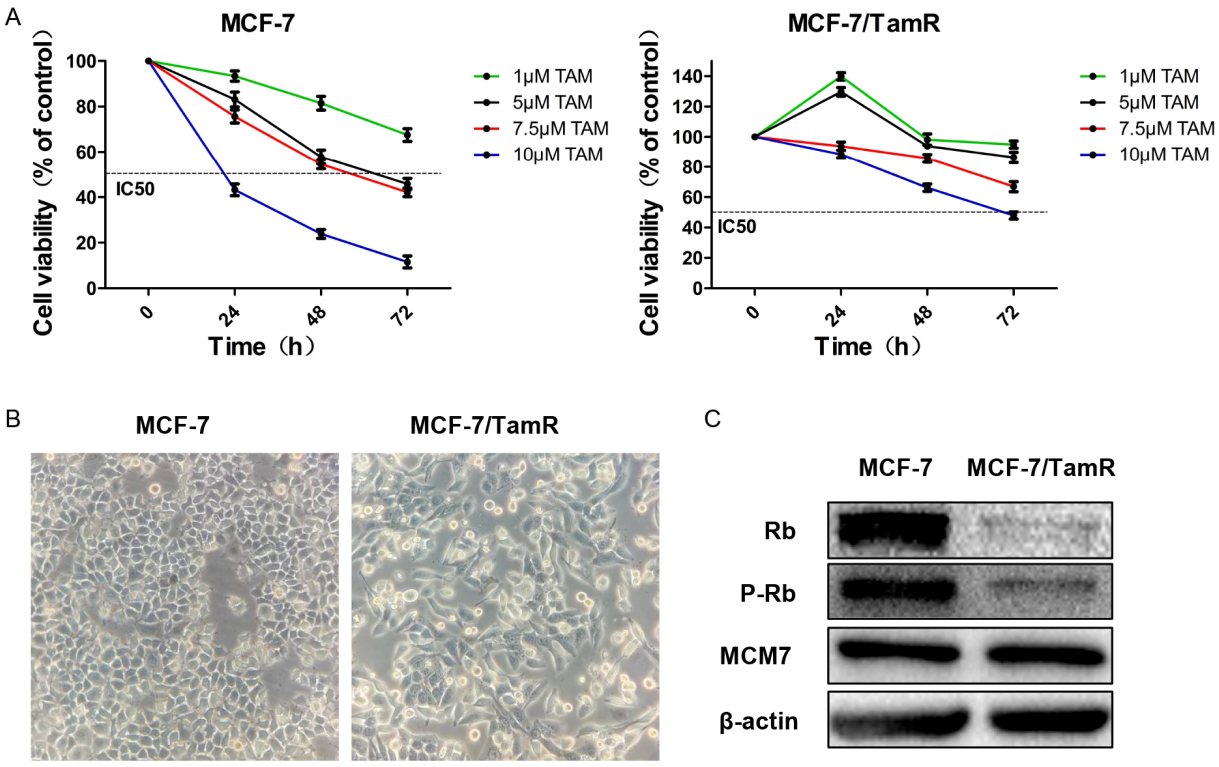

Figure 1 | Characteristics of MCF-7 and MCF-7/TamR cell lines

In Vivo Tumor Experiment

All animal experiments were done by protocols approved by the Institutional Animal Care and Use Committee of the First Affiliated Hospital of Xi'an Jiaotong University and four-week-old SCID-Beige female mice were from the Experimental Animal Center of the Medical College of Xi'an Jiaotong University. In this experiment, 5×106 MCF-7 and MCF-7/TamR cells were suspended in 100ml of PBS and injected into SCID female mice fat pad. At one weeks after injection,Tamoxifen (5 mg/kg in corn oil) and DMC (10 mg/kg in corn oil) was treated for 10 days by gavage .After 7 days , tumors were removed and photographed. The tumor were surgically fixed by using 4% paraformaldehyde for immunohistochemistry.

Immunohistochemistry

4μm sections of tissue wax block were attached to a glass slide, dewaxed by xylene, dehydrated by gradient alcohol, and blocked endogenous peroxidase activity, and then subjected to high temperature antigen retrieval in sodium citrate buffer.After cooling to room temperature, added 1:50 dilutions of primary antibody (MCM7, Rb) were incubated overnight at 4 °C in a refrigerator.The second day, horseradish peroxidase (HRP)-labeled secondary antibody was added, DAB staining,, hematoxylin counterstained and mounted.

Statistical Analysis

The data were expressed as the means ± standard deviation using GraphPad Prism software, version 5.00 (GraphPad Software, La Jolla, CA, USA, www.graphpad). The unpaired Student's t-test was carried out to compare two groups, and two-way analysis of variance and Dunnett's multiple comparison tests were used for multiple comparisons. $P < 0.05$ was considered statistically significant.

Results

Characteristics of MCF-7 and MCF-7/TamR Cell Lines

Initially, we evaluated the characteristics of the TamR cells using the MTT assay and western blotting analysis. The results of the MTT assay indicated that the half maximal inhibitory concentration (IC50) values of TAM in the MCF7 and MCF-7/TamR cell lines were 4.392 μM and 9.800 μM, respectively. Furthermore, the TAM resistance factor (RF) of MCF-7/TamR cell line was 2.231 (**Figure 1A**). Meanwhile, the morphology of the MCF-7 and MCF-7/TamR cell lines indicated that epithelial-mesenchymal transition-like changes were observed in the TamR cells (**Figure 1B**).Furthermore, western blotting assays revealed that the protein expression levels of p-Rb and Rb in the MCF-7/TamR cells were lower than those in the parental cells (**Figure 1C**). From above re-

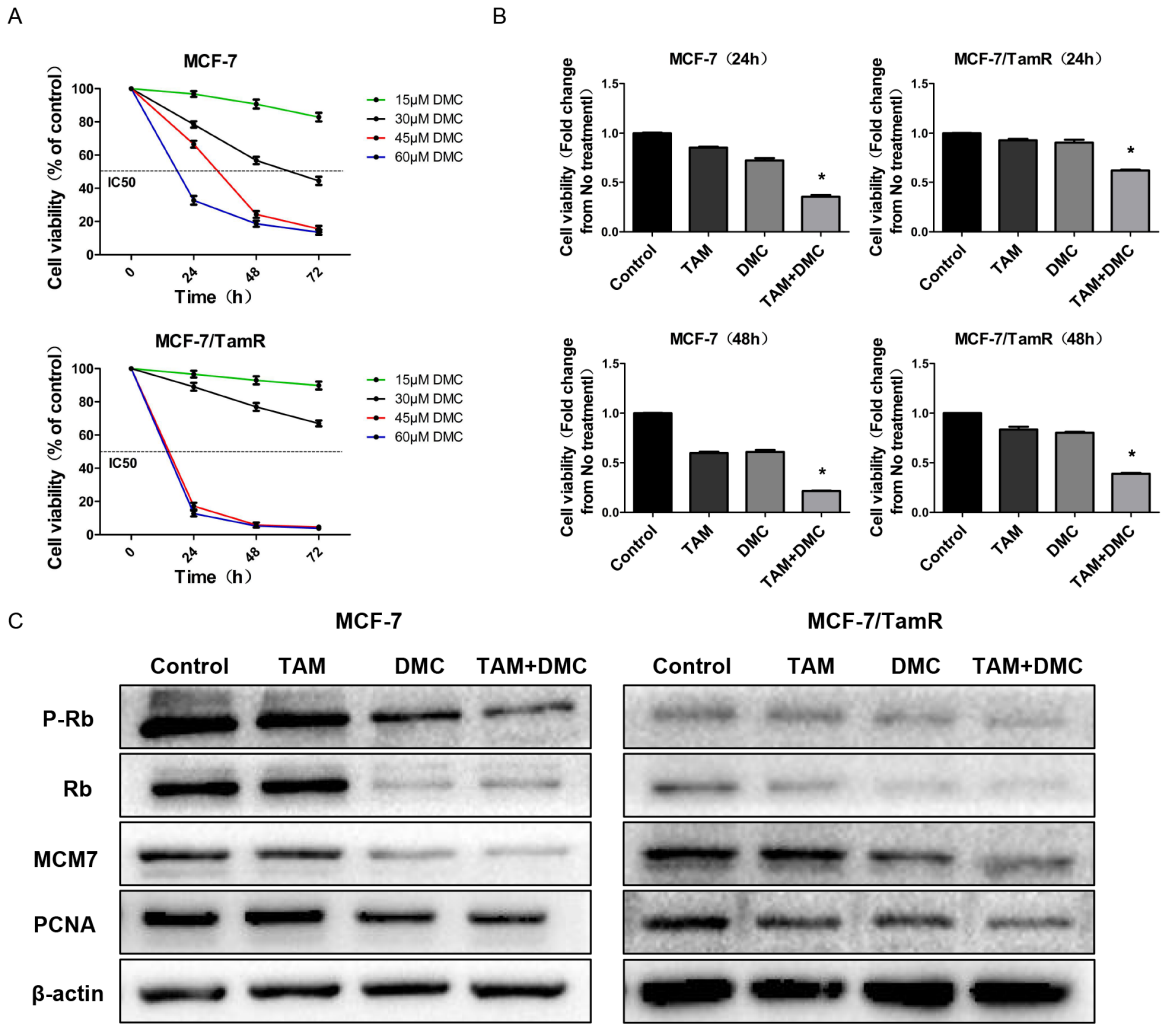

Figure 2 | DMC combined with TAM inhibits the growth of MCF-7 and MCF-7/TamR cell lines

*(A) MCF-7 and MCF-7/TamR cell lines were incubated with a series concentrations of DMC, and the MTT analysis were used to detect the proliferation inhibition effect of DMC on the cells. The concentration of DMC was 30 μM for the subsequent experiments. (B) DMC (30 μM) alone or combination with TAM (5 μM) was added to MCF-7 cells, and DMC (30 μM) alone or combination with TAM (7.5 μM) was applied to MCF-7/TamR cells; the cell proliferation was detected by the MTT analysis after 24 and 48 h. n = 3, *P < 0.05.(C) The expression of the cell cycle-related proteins Rb, p-Rb, MCM7, and PCNA were detected by Western blotting analysis.*

sults, our MCF-7/TamR cells has the characteristics of TAM-resistant cells.

DMC Combined With TAM Inhibits the Growth of MCF-7 and MCF-7/TamR Cell Lines

MCF-7 and MCF-7/TamR cell lines were treated with various concentrations of DMC (15, 30, 45, and 60 μM) for different incubation periods (24, 48, 72 h).As seen, the results showed that with an increase of DMC dose and incubation time, the proliferation rate was significantly inhibited in a time- and dose-dependent manner. Interestingly, when the DMC concentrations increased to a certain level(45 μM), the viability of MCF-7/TamR cells was significantly reduced, possibly due to the significant down-regulation of MCMs complex under the condition that the cell cycle progression was out of control due to Rb deficiency, resulting in lethal DNA damage further induced apoptosis(**Figure 2A**). Next, MCF-7 and MCF-7/TamR cell lines were incubated with a series of TAM and DMC concentrations either alone or in combination. The results of the MTT assay indicated that the cell viability of MCF-7 cells was inhibited significantly when they were treated with DMC (30 μM) and TAM (5 μM) for 48 h or 72 h; similarly, the cell viability of MCF-7/TamR cells was inhibited significantly when they were treated with DMC (30 μM) and TAM (7.5 μM) (**Figure 2B**). These two drug combinations were used in subsequent experiments. Furthermore, the protein expression levels of p-Rb, Rb, MCM7, and PCNA in MCF-7 and MCF-7/TamR cell lines were down regulated after treatment with DMC combined

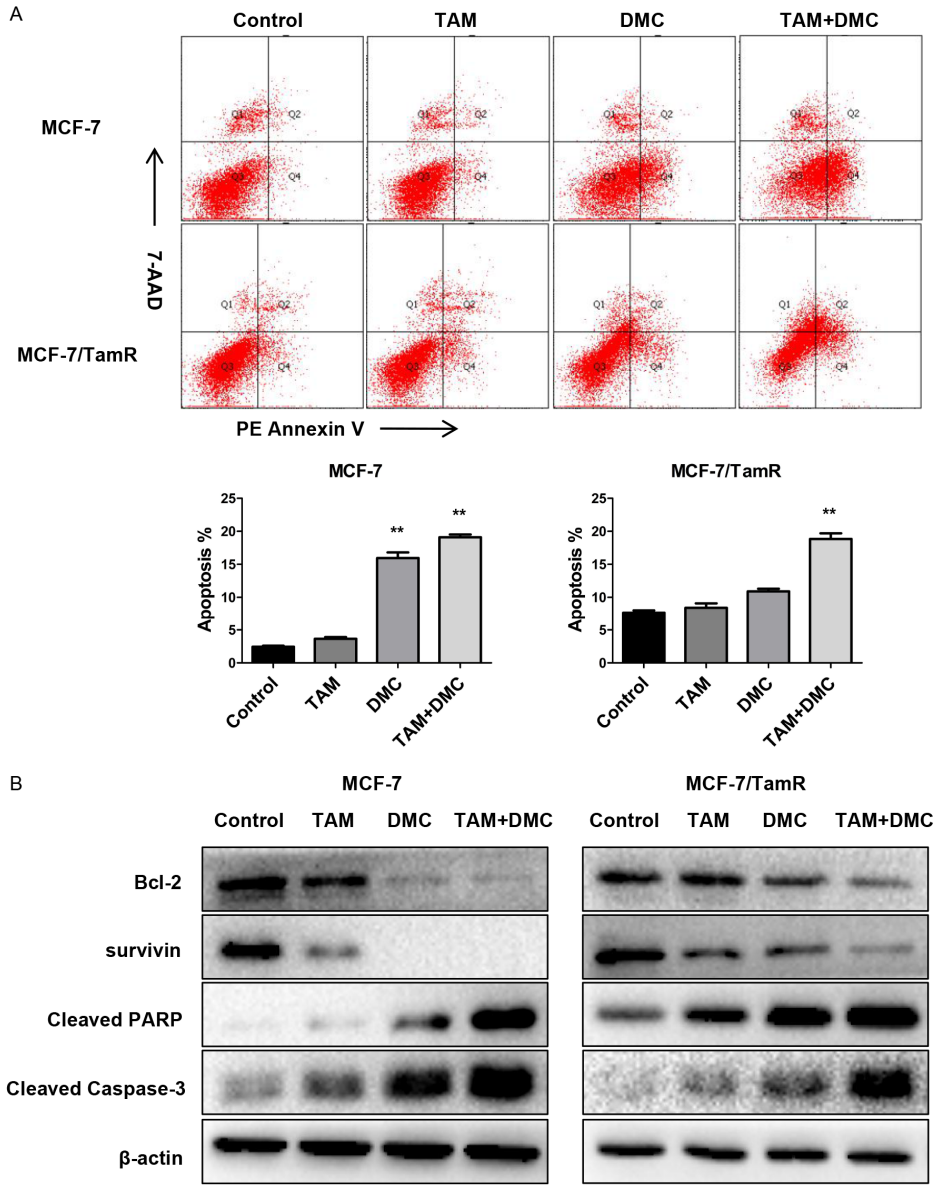

Figure 3 | DMC combined with TAM induces apoptosis in MCF-7 and MCF-7/TamR cell lines

*(A) Flow cytometry was performed to analyze the apoptosis of both cell lines after DMC treatment alone or in combination with TAM. n = 3, **P < 0.01. (B) The protein expression levels of cleaved caspase 3, Bcl2, cleaved PARP, and survivin were measured by western blotting analysis.*

with TAM for 48 h (**Figure 2C**). It is well known that the lost of Rb is related with increase cellular proliferation, but the simultaneous decreased in Rb and MCM7 inhibited cell proliferation(22). This is consistent with our experimental results. These results suggest that DMC combined with TAM inhibits the growth of MCF-7 and MCF-7/TamR cell lines.

DMC Combined With TAM Induces Apoptosis in MCF-7 and MCF-7/TamR Cell Lines

The flow cytometry assay showed that incubated with DMC combined with TAM for 48h caused the number of apoptotic cells for both MCF7 and MCF7/TamR cell lines to be increased (**Figure 3A**).Furthermore, the protein expression levels of cleaved caspase 3 and cleaved PARP were up-regulated, whereas Bcl2 and survivin were down-regulated obviously in the two cell lines after treatment (**Figure 3B**). In summary, DMC combined with TAM induces apoptosis in both MCF7 and TamR cell lines.

DMC Combined With TAM Upregulates γH2AX and Induces DNA Damage in MCF-7 and MCF-7/TamR Cell Lines

Our previous research indicated that DNA damage induced by inhibiting the protein expression of Rb and MCM7

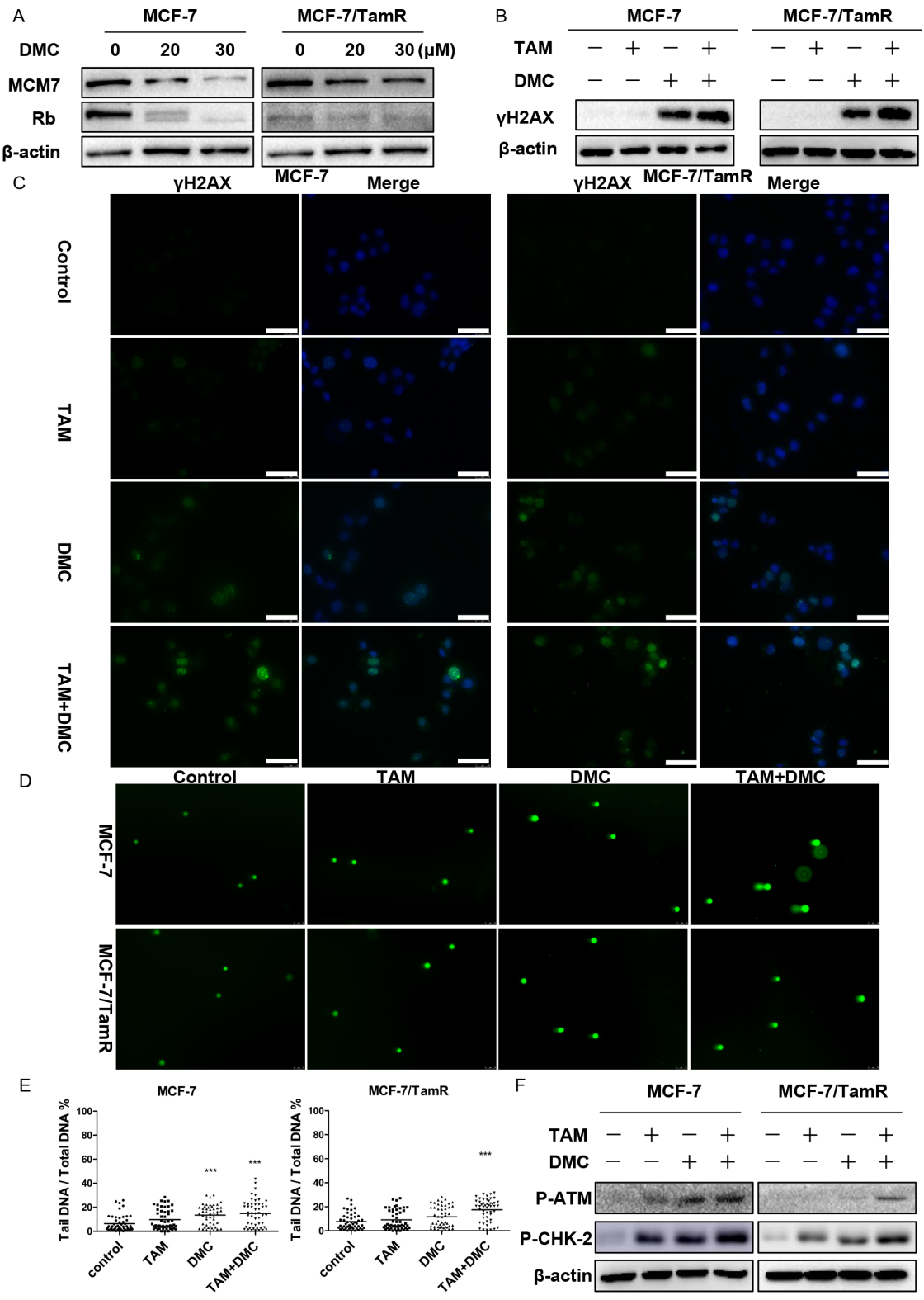

Figure 4 | DMC combined with TAM upregulates γH2AX and induces DNA damage in MCF-7 and MCF-7/TamR cell lines

*(A) MCF-7 and MCF-7/TamR cell lines were incubated with different doses (0, 20, and 30 μM) of DMC for 24 h, and the total cellular proteins of the cell extracts were analyzed by western blotting. (B) MCF-7 and MCF-7/TamR cell lines were incubated with control, TAM (5 μM)/(7.5 μM), DMC (30 μM), or TAM (5 μM) plus DMC (30 μM)/TAM (7.5 μM) plus DMC (30 μM) for 24 h, and the total cellular proteins were extracted for western blotting analysis. (C) MCF-7 and MCF-7/TamR cell lines were treated as described above and immunofluorescence assays were performed. The bar represents 100 μm. (D) The two cells were treated as described above and neutral comet assay was carried out. The bar, 100 μm. (E) Quantitative analysis of comet tail DNA content/total DNA content (%) in 50 cells per group.n = 3, ***P < 0.001. (F)Two cells were treated as described above, and the extracted total cellular proteins were analyzed by western blotting.*

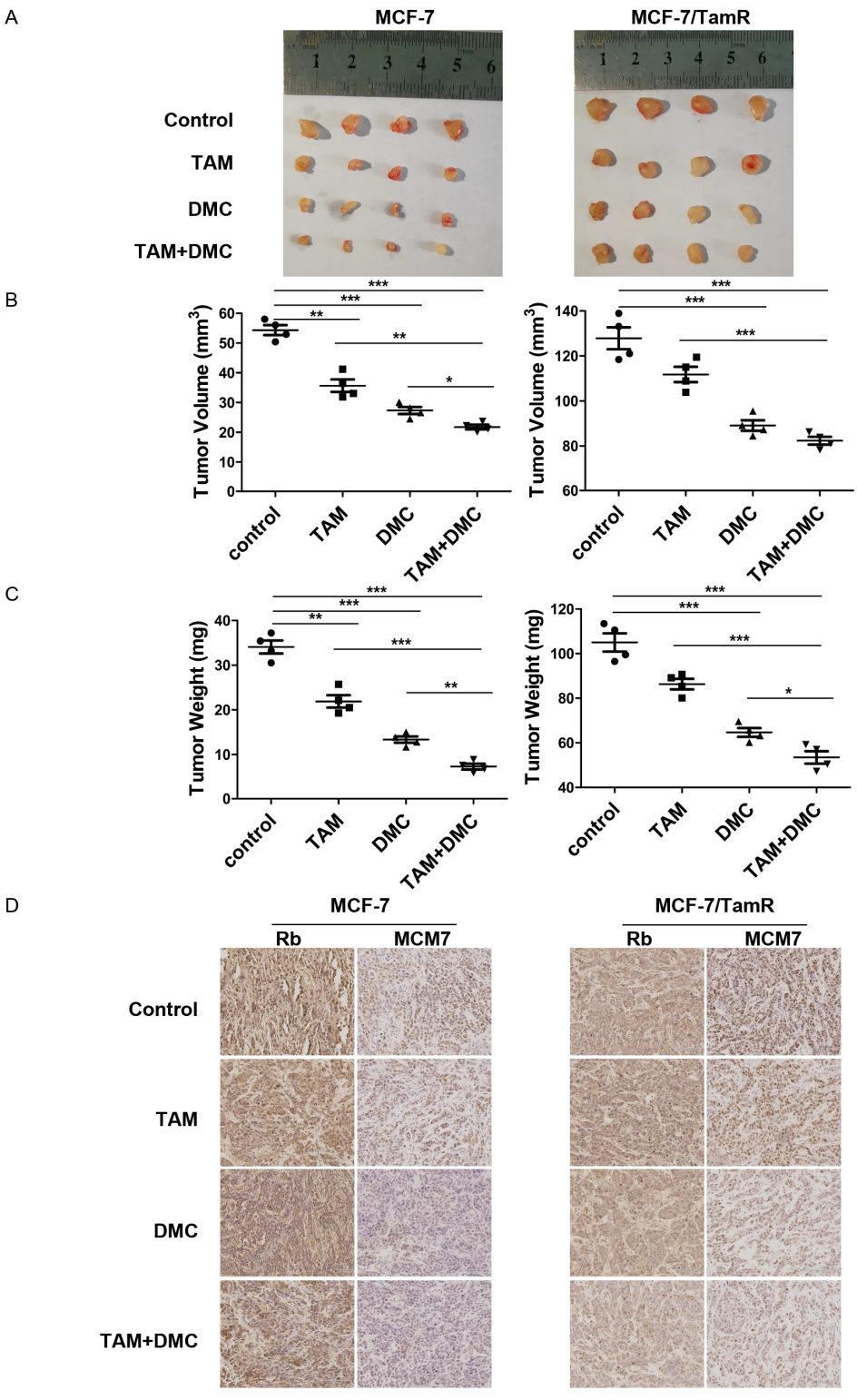

Figure 5 | DMC combined with TAM inhibits the growth of MCF-7 and MCF-7/TamR cells *in vivo*

*The xenograft tumors model were established by injecting 5 x 106 MCF-7 and MCF-7 / TamR cells into the SCID / Beige mice fat pad. After seven days, mice were treated with TAM (5 mg/kg) / DMC (10 mg/kg) alone or combination for 10 days by gavage. Tumor size (A,B), tumor weight (C) and immunochemical staining with RB and MCM7 antibodies(D); The bar,100 μm. *p < 0.05, **p < 0.01 and ***p < 0.001.*

could strongly inhibit the proliferation of TamR cells(22). Consistently, the western blotting assay results indicated that the protein expression levels of Rb and MCM7 were down-regulated significantly after incubated with DMC for 24 h (**Figure 4A**). The γH2AX expression was increased significantly after incubated with DMC for 24 h and further increased upon treatment with a combination of DMC and TAM (**Figure 4B**). In addition, the immunofluorescence assay showed consistent experimental results with the western blot assay results (**Figure 4C**). Neutral comet assays were used to detect double-stranded breaks, and the results showed that severe DNA damage was caused in MCF-7 and MCF-7/TamR cell lines after treatment with DMC alone or in combination with TAM for 24 h (**Figure 4D,E**). Finally, western blotting assays demonstrated that the protein expression of the DNA damage checkpoint proteins p-ATM and p-Chk2 was up-regulated after a 24h treatment with DMC combined with TAM (**Figure 4F**). All of these results demonstrate that DMC combined with TAM up-regulates γH2AX and induces DNA damage in MCF-7 and MCF-7/TamR cell lines.

DMC Combined With TAM Inhibits the Growth of MCF-7 and MCF-7/TamR Cells *in Vivo*

To explore the *in vivo* effects of DMC, we established a xenograft tumor model in SCID / Beige mice using MCF7 and MCF7 / TamR cell lines.When tumors were touchable,mice were treated with TAM (5 mg/kg)/DMC (10 mg/kg) alone or combination for 10 days by gavage. The xenograft tumors were significantly inhibited after DMC alone or TAM combined with DMC treatment(**Figure 5A to C**).In addition ,the result of immunochemistry showed that Rb and MCM7 expression were reduced after DMC alone or combined with TAM treatment *in vivo*(**Figure 5D**).Therefore, our results revealed that DMC can be consistent with *in vitro* experiments by inhibiting Rb/MCM7 expression and inhibiting tumor growth *in vivo*.

Discussion

In recent years, the traditional nonsteroidal anti-inflammatory drug celecoxib has become a hot spot for anti-tumor research as it causes cell cycle arrest, inhibits human breast cancer cell proliferation, promotes apoptosis, and also inhibits migration and invasion. Additionally, it has been shown to be a beneficial therapeutic in patients with an increased sensitivity to radiotherapy and chemotherapy(23-26). However, its mechanism of action involves COX-2 inhibition, which may cause severe cardiovascular toxicity if used for a long period of time(27). DMC, a methylated derivative of celecoxib, has shown a tumor suppression activity that is 20–50% higher than that of celecoxib; in addition, it lacks COX-2 inhibitory activity and also is devoid of cardiovascular toxicity. It has been revealed that DMC plays a role in inhibiting cell cycle progression and inducing apoptosis in human leukemia cells(14). Moreover, it has demonstrated cytotoxic and antitumor effects both *in vitro* and *in vivo* by downregulating the expression of the antiapoptotic protein survivin and subsequently inducing apoptosis(28).

In our study, we also observed that DMC significantly inhibited proliferation and induced apoptosis in MCF-7 and MCF-7/TamR breast cancer cell lines. It has been revealed that DMC has drug-sensitizing effects when used in combination with ABT-737 to increase the sensitivity of gastric cancer cells as well as with imatinib to treat colorectal cancer(10, 12). Our study indicated that the combination of DMC with TAM had a further enhancement on proliferation inhibition and apoptosis induction. Additionally, DMC has shown antiangiogenic activity in the tumor vasculature both *in vivo* and *in vitro*; thus, it plays an antitumor effect(29). In breast cancer, DMC has demonstrated a killing effect on triple-negative and chemotherapy-resistant breast cancer cells by aggravating endoplasmic reticulum stress(19, 30), but its role in TAM resistance of breast cancer has not been reported. In our research, we examined the mechanism of action of DMC on MCF-7 and MCF-7/TamR cell lines , the results indicated that DMC down-regulated the protein expression of Rb and MCM7 but up-regulated γH2AX and also induced DNA damage in MCF-7 and MCF-7/TamR cell lines. Interestingly, in combination with TAM, these effects were further enhanced. Notably,DMC also proved to have the same effect *in vivo* model, our results revealed that DMC can be consistent with *in vitro* experiments by inhibiting Rb/MCM7 expression and inhibiting tumor growth *in vivo*. Unlike celecoxib, DMC has not been studied in humans, therefore, further assessment of the *in vitro* mechanism would be of great significance provided that *in vivo* experiments are also performed. In addition, appropriate preclinical testing should be performed to further verify the effects.

In conclusion, we observed that DMC inhibited proliferation and induced apoptosis of TAM-sensitive and -resistant human breast cancer cells (MCF-7) both *in vitro* and *in vivo*. Moreover, DMC significantly downregulated Rb and MCM7 expression and induced DNA damage in both cell lines. Our data suggest that growth inhibition generated by DMC may be achieved by inhibiting the protein expression of Rb and MCM7 and subsequently inducing DNA damage.This study provides a novel strategy for the treatment of TamR breast cancer patients in the clinical setting.

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Conflict of interest statement The authors declare no competing interests.

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