TabBO: A Model Reflecting Common Molecular Features of Androgen-independent Prostate Cancer

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ABSTRACT

We established two human prostate cancer cell lines, MDA PCa 2a and MDA PCa 2b, the TabBO model system, that reflect common features of human androgen-independent prostate cancer that are not present in other model systems: bone origin, prostate-specific antigen production, androgen receptor expression, and androgen sensitivity. We therefore hypothesized that molecular pathways in our model system reflect common alterations responsible for the progression of a subset of human prostate cancer. Progression to androgen independence has been hypothesized to be largely associated with impairment of the regulation of cell growth or apoptosis of prostate cancer cells. Therefore, in this study, we examined molecular markers known or suspected to be important in prostate cancer progression and key regulators of cell growth and apoptosis: p53, p21WAF1/CIP1, Bel-2, Bax, retinoblastoma (Rb), and p16INK4a/MTS1. We analyzed the expression of these markers in the cell lines, their tumor of origin, and tumors derived from the cell lines by s.c. inoculation into nude mice. DNA sequencing of the entire open reading frames of the p53 and p21 genes revealed no mutations. Additionally, accumulation of the p53 protein was not found by Western blot analysis, nor was overexpression of the Bel-2 oncoprotein detected. Bax expression was detected in MDA PCa 2a cells, whereas it was absent in MDA PCa 2b. Rb and p16 protein expression was normal as measured by both Western blot and immunochemical analyses. Immunohistochemical studies of p53, p21, Bel-2, and Rb in both samples from the original human cancer from which the lines were derived and mouse xenografts derived from the lines revealed similar levels of protein. These results are consistent with reports indicating that 40–50% of bone metastases of prostate cancer have wild-type p53, 50–70% do not overexpress the Bel-2 protein, and mutations in the p21 gene are rare. Therefore, we conclude that MDA PCa 2a and MDA PCa 2b reflect molecular pathways in a common subset of human androgen-independent prostate cancer and that important molecular players in apoptosis (namely, p53 and Bcl-2) seem to be intact in this subset of androgen-independent prostate cancer. Understanding the signal-transduction pathways operating in these cell lines may help to identify therapeutic targets for prostate cancer.

INTRODUCTION

We recently established a new model of prostate cancer that consists of two new human prostate cancer cell lines, MDA PCa 2a and MDA PCa 2b (1), which were derived from a bone metastasis of a patient with prostate cancer who relapsed 2 years after surgical castration. MDA PCa 2a and MDA PCa 2b are thought to represent two different clones of the same tumor (1). Initial characterization showed that the cells are sensitive to androgens both in vivo and in vitro, although the cells were derived from a tumor that was clinically described as androgen independent (1). We named the new cell lines the TabBO model of prostate cancer [taken from MDA PCa 2 (Two) a and MDA PCa 2 b bone metastases model].

The value of a model system is related to its reproducibility and capacity to reflect common features of the system under study. Our new model system reflects critical features of clinical androgen-independent prostate cancer: bone origin, prostate-specific antigen expression, and androgen sensitivity. We hypothesized that this new model system also reflects common molecular pathways in clinical androgen-independent prostate cancer.

Androgen ablation therapy is the most effective therapy for patients with metastatic prostate cancer; however, most metastatic cancers eventually progress to androgen-independent disease. The androgen-independent phenotype of human prostate cancer is clinically defined as the ability of the prostate cancer cells to grow under castrate plasma levels of testosterone. The emergence of androgen-independent prostate cancer is related to either selection of preexisting androgen-independent clones or to adjustment of the cells to a new environment. Alterations in the p53 tumor suppressor gene and Bel-2 oncoprotein are clearly associated with androgen-independent prostate cancer (2–9). Several studies have reported a high incidence of p53 gene mutations in advanced prostate cancer (4–7). Moreover, in a
comprehensive study, we found an association between accumulation of p53 protein and androgen-independent growth of prostate cancer (5). These data suggested that p53 alterations may be important in the progression of prostate cancer and that wild-type p53 protein may play a role in some cellular responses to androgens. Expression of the Bcl-2 oncoprotein has also been implicated in prostate cancer progression (2, 3, 8–10). Previous studies have shown that overexpression of Bcl-2 oncoprotein provides protection from apoptotic stimuli (8–10), and therefore, it has been suggested that Bcl-2 overexpression contributes to the survival of androgen-independent prostate cancer cells (3, 8–10). Nevertheless, at least 35% of androgen-independent prostate cancers have neither p53 nor Bcl-2 alterations.

In this study, a molecular characterization of the new cell lines MDA PCa 2a and MDA PCa 2b (1) was performed. The cultured cells were screened for expression of and mutations in molecules that have been associated with the progression of prostate cancer to the androgen-independent phenotype. An added value of our model is that we have access to the human tumor of origin, which allowed testing of the fidelity with which the cells reflect their human tissue of origin. We also tested tumors derived from the cell lines by s.c. inoculation in nude mice. This new model system will be a paradigm of androgen-independent prostate cancers that have wild-type p53, no Bcl-2 overexpression, and no Rb,3 p16 INK4A/MTS1 (p16), or p21WAF1/CIP1 (p21) mutation. We therefore believe that the TabBO model reflects common molecular pathways of androgen-independent prostate cancer that will be relevant for understanding the progression of these cancers. Segregation of tumors on the basis of these molecular markers could facilitate the search for new treatment strategies for this subgroup of prostate cancers.

MATERIALS AND METHODS

Cell Culture and Cell Lines. MDA PCa 2a and MDA PCa 2b cells (1) were propagated in BRFF HPC1 (Biological Research Faculty and Facility, Inc., Jamesville, MD) with 15% fetal bovine serum and gentamicin (50 \( \mu \text{g/mL} \)). LNCaP, PC3, DU145, WI38, U-251 MG, and T24 cells, which were used as controls, were originally obtained from the American Type Culture Collection (Manassas, VA).

Tumorigenicity of MDA PCa 2 Cells in a Nude Mouse Assay. Six- to 8-week-old male athymic (nude) mice (BALB/c strain, Charles River Laboratory, Wilmington, MA) were used for the tumorigenicity assay of MDA PCa 2 cells. The animals were housed aseptically in the athymic animal facility of M. D. Anderson Cancer Center and manipulated under surgical aseptic conditions in a laminar flow hood. The cells to be injected were trypsinized, washed, counted, resuspended at 4–5 \( \times 10^6 \) cells/100 \( \mu \text{l} \) of growth medium, and injected s.c. at a concentration of 3 \( \times 10^6 \) cells per site.

Tissue Samples. MDA PCa 2a and MDA PCa 2b were derived from tissue samples of two different areas of a bone metastasis from prostate carcinoma (1). Mirror-image, formalin-fixed, paraffin-embedded tissue samples from the human prostate cancer bone metastasis from which MDA PCa 2a and MDA PCa 2b were established were obtained from the files of the Department of Pathology at the M. D. Anderson Cancer Center. Formalin-fixed, paraffin-embedded tissue samples from the mouse tumors were obtained from the M. D. Anderson Department of Veterinary Medicine. Serial 3-\( \mu \)m-thick sections were obtained from each sample; one section was stained with H&E, and adjacent sections were used for immunostaining.

Antibodies. Immunocytochemical, immunohistochemical, and immunoblot analyses were performed with the following antibodies: monoclonal human anti-p53 antibody DO-1, monoclonal anti-p53 PAb240, monoclonal anti-p21 (Ab 1) and anti-Bcl-2 (Ab-1) antibodies (Oncogene Research Products, Cambridge, MA), polyclonal anti-Rb antibody WL-1 (11), polyclonal anti-Bax antibody N-20 (Santa Cruz Biotechnology Inc., Santa Cruz, CA), monoclonal anti-\( \beta \)-actin antibody (Amershams Pharmacia Biotech, Arlington Heights, IL), and monoclonal anti-p16 antibody NCL-p16, clone DES-50 (Vector Laboratories, Burlingame, CA).

Immunocytochemical Analysis of p53. p53 expression was determined by immunocytochemical analysis of cells using antibody DO-1 (Oncogene Research Products), which reacts with both wild-type and mutant p53 proteins, and antibody P Ab240 (Oncogene Research Products), which only recognizes mutant p53 (12). The immunocytochemical staining was performed by following the procedure described below in cells fixed in ethanol.

Immunohistochemical Analysis of p53, p21, Rb, and Bcl-2. Protein expression was examined by immunohistochemical analysis in tissue sections of tumors from which the cell lines MDA PCa 2a and MDA PCa 2b were derived and from tumors that these cell lines produced in mice. The sections were deparaffinized with xylene and incubated with the appropriate antibodies. The sections were stained by using the avidin-biotin-peroxidase complex technique with a kit from Vector Laboratories. The labeling was visualized with the chromogen 3,3'-diaminobenzidine.

Protein Extraction and Western Blot. Expression of the p53, p21, p16, Bax, Rb, and Bcl-2 proteins in the cell lines was studied by Western blot analysis. Protein extracts from cells growing in monolayers were obtained by using radioimmunoprecipitation assay buffer and following standard procedures (13). Cell lysates were centrifuged at 100,000 \( \times g \) for 45 min at 4°C. The supernatants were normalized for protein content, and 50–100 \( \mu \)g of protein per lane was fractionated on 7.5–12% SDS-polyacrylamide gels (the percentage depending on the molecular weight of the proteins to be detected). The proteins were blotted to a Hybond-ECL nitrocellulose membrane (Amershams Pharmacia Biotech) that was probe and washed according to the instructions for the enhanced chemiluminescence Western blotting detection system (Amershams Pharmacia Biotech).

As controls for p53 expression the following were used: the human cancer cell line U-251 MG, which was established from a glioblastoma multiforme, has a p53 mutation in codon 273 (14) and is known to accumulate nuclear p53 protein; the human prostate cancer cell line LNCaP, which is known to have a wild-type p53 gene (15, 16); and the human prostate cancer cell line PC3, which is known to have a single base deletion in the
p53 gene, resulting in a stop codon, and so does not produce p53 protein (16).

The LNCaP was also used as a positive control for p21, Bcl-2, and Bax expression (17–19), and PC 3 was used as a positive control for the expression of Bcl-2 and Bax (17–19) and as a negative control for p21 (17). The human prostate cancer cell line DU145 was used as a negative control for Bax expression (20). As controls for Rb and p16 expression, we used the normal human fibroblast cell line WI38 and the human bladder cancer cell line T24, which does not express p16 and has high Rb protein expression. The same cells used for Rb analysis were used for the p16 studies (11).

**DNA Sequencing of the p53 and p21 Genes.** DNA extraction of the two cell lines was performed following standard procedures (13). PCR products from exons 2–11 of the p53 gene and exons 2 and 3 of the p21 gene were generated using the primers detailed below. For these PCR amplifications, the conditions were as described previously (5). The thermocycler parameters used to analyze all exons consisted of an initial cycle at 95°C for 5 min followed by 30 cycles at 95°C for 1 min; the annealing temperature was between 57 and 62°C for each primer set for 1 min, 72°C for 1 min, and 72°C for a final extension for 7 min. Primers and dNTPs were then removed from amplified products by enzymatic digestion with shrimp alkaline phosphatase and exonuclease I (United States Biochemical Corp., Cleveland, OH). Direct sequencing of PCR products was performed in both (sense and antisense) directions for all exons using the ABI PRISM dye terminator cycle sequencing kit (Perkin-Elmer Corp., Foster City, CA) according to the manufacturer's specifications; PCR primers were used as sequencing primers. Purified sequencing reactions were run on an ABI 373 DNA sequencer (Applied Biosystems Division of Perkin-Elmer Corp.).

The primers used for PCR amplification and DNA sequencing of p53 were as follows. Exon 2: 2U,5 TGG AAG CGT CTC ATG CTG GA; 2 L,5 CAG AAC GTT GTC TTC AGG AA. Exon 3: 2U,5 TGG AAG CGT CTC ATG CTG GA; P3-30, AGA GGA CCA GGT CCT CAG CC. Exon 4: P4-51, GAC TGC TCT TTT CAC CCA TC; GE4R,5 CTA AGG GTG AAG GTA AGA GGA CCA GGT CCT CAG CC. Exon 5: p5-50,5 CTG ACT TTC AAC TCT GTC TC; P5-30,5 GCC CAG ACC TAA GAG CAA TCA GTG, Exon 6: p6-500,5 AGC AGC TGG GGC TGG AGA GA; p6-3,5 ACA GGG CTG GTC GCC CAG GTG; p6-50,5 ACA GGG CTG GCC CAG GTG; p6-30,5 TAC TGC TCA CCC GGA GGG CCA CT. Exon 7: p7-50,5 CTT GCC ACA GGT CTC CCC AA; p7-30,5 GTC AGA GGC AAG CAG AGG CT. Exon 8: p8-50,5 CTG CTT GCT TTC TTT TTC CTA; p8-3,5 AAG TGA ATC TGA GGC ATA AC. Exon 9: GE9F,4 GTA AGC AAG CAG GAC AAG AA; GE9R,4 ACG GCA TTT TGA GTG TTA GA. Exon 10: P10-50,5 CTT GAA CCA CTT TTT AAC TCA GGT A; P10-31,5 GCA GGG GAG TAG GCC CAGT AAG G. Exon 11: P11-50,5 GCA CAG ACC CTC TCA CTC ATG TGA T; P11-31,5 GGA GGG AGG CTG TCA GTG GGG AAC.

The primers used for PCR amplification and DNA sequencing of p21 were as follows. Exon 2: F2, TGT ATC TCT GCT GCA GGC GC; R2, TTC GTG GCA CAT GTC CGC AC. Exon 3: F3, TTC CTC AGT TGG GCA GCT CC; R3, GAC TAA GGC AGA AGA TGTT AGA GCG G.

**RESULTS**

**Histopathological Analysis and Immunohistochemical Analysis of p53, p21, Bcl-2, Rb, and p16.** Histopathological analysis revealed that the tumors grown in nude mice retained the morphology of the tumor of origin. To assess the extent to which gene expression in the MDA PCa 2a and MDA PCa 2b cell lines reflects that in the tumor of origin, we performed immunohistochemical analysis of p53, p21, Bcl-2, and Rb in tissue sections from the specimen from which the cell lines were derived and from the tumors that the cells lines produced in mice after s.c. injection. For both cell lines, the same pattern of protein expression in the paired specimens (tumor of origin and nude-mouse derived tumors) was observed (Figs. 1 and 2). p53 protein accumulation was found in 10–30% of the nuclei of MDA PCa 2a paired specimens and 30–40% of the nuclei of MDA PCa 2b paired specimens (Fig. 1, A and B). Immunohistochemical analysis revealed p53 staining in approximately 30% of the cells in culture using D01 antibody (Fig. 1C). Antibody PAb240, which detects only mutant p53, showed no staining (Fig. 1D), supporting the concept that the protein was wild type. p21 nuclear protein was present in a small percentage of cells (less than 5%), in both the original tumors and the tumors derived from the MDA PCa 2a cells. A greater proportion of MDA PCa 2b cells had p21 positive nuclei (10–20%; Fig. 2A). Bcl-2 expression was found in only a few tumor cells in MDA PCa 2a and MDA PCa 2b paired specimens (Fig. 2B). Fig. 2C shows the normal heterogeneous pattern of Rb expression in the human tumor from which MDA PCa 2a was derived. The tumor from MDA PCa 2a cells grown in the mouse had the same normal heterogeneous staining pattern (Fig. 2C2) as did the mouse MDA PCa 2b tumor (not shown). Lastly, staining of p16 showed a normal heterogeneous pattern similar to that found for WI38 cells and was negative for T24 cells (not shown).

**Western Blot Analysis of p53, p21, Bcl-2, Bax, Rb, and p16.** Western blot analysis of MDA PCa 2a and MDA PCa 2b cells was performed with monoclonal antibodies to human p53 (DO-1) and human p21 (Fig. 3). The expression levels of p53 and p21 protein in MDA PCa 2a and MDA PCa 2b cells were similar to the levels in LNCaP cells, the positive control. Immunoblot analysis of Bcl-2 revealed 4–5-fold more expression in PC3 and MDA PCa 2b cells than in MDA PCa 2a cells (Fig. 4). No Bcl-2 overexpression was detected in the tumors produced by MDA PCa 2b cells in nude mice. Expression of Bax was found in MDA PCa 2a but not MDA PCa 2b cells (Fig. 4).

Rb protein was present primarily in the hypophosphorylated form in MDA PCa 2 cells, as in the normal human...
fibroblast cell line WI38 (Fig. 5). The human bladder cancer cell line T24 showed a high Rb expression, particularly the hyperphosphorylated form of Rb. Finally, Western blot analysis of p16 showed a normal pattern similar to that of WI-38 cells, whereas no p16 protein expression was seen in the T24 cells (data not shown).

**Sequence of the p53 and p21 Genes.** We directly sequenced PCR-generated fragments of exons 2–11 of the p53 gene and adjacent portions of the introns from both MDA PCa 2b cell lines. The entire coding sequence of the LNCaP cell line was also sequenced as a control. We found no mutations in the MDA PCa 2 p53 genes. In LNCaP, we detected a silent mutation previously reported to be present in codon 152 (15, 16). Also, a previous study reported that the human p53 gene has a polymorphism at codon 72 that changes amino acid residue 72 from arginine (CGC) to proline (CCC; Ref. 22). MDA PCa 2a

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**Fig. 1** Immunohistochemical staining of p53 protein in the human tumor from which MDA PCa 2b cells were obtained (A) and the tumors that MDA PCa 2b cells produced in nude mice after s.c. inoculation (B) revealed nuclei staining in 30% of the cells. Immunocytochemical staining of p53 protein was performed in MDA PCa 2b cells growing in cell culture chambers. We used D01 (C), which reacts with both wild type and mutant p53, and PAb240 (D), which only recognizes mutant protein. Note that MDA PCa 2b cells had positive immunostaining with D01 in 30–40% of cell nuclei and that there was no nuclear staining with PAb240.
Model of Androgen-independent Prostate Cancer
prostate cancer cells to grow despite castrate plasma concentrations of circulating androgens was shown to be effective in the treatment of human androgen-independent prostate cancer (Table 1). This approach is palliative, not curative, both in vivo and in vitro (1). Moreover, as determined by immunostaining, AR is expressed in the tumors of origin as well as in the tumors produced by the cell lines in nude mice (data not shown). Mutations in the AR gene are not uncommon in metastatic prostate cancer (24–28, 33), and some of these mutations increase the sensitivity of cells to hormones, including androgens (26, 28). Several studies have demonstrated that most metastatic androgen-independent prostate cancers express high levels of AR gene transcripts (24–28, 33). Therefore, it has been suggested that the androgen independence at the metastatic tumor site correlates with high expression of the AR (mutated or wild type), which may cause sensitivity to low levels of circulating androgens or low-affinity ligands (24, 28). This could account for the proliferative advantage in these cells.

The alterations most clearly associated with the androgen-independent growth of prostate cancer in the clinic has been AR overexpression, p53 mutation, and Bcl-2 overexpression. How-

DISCUSSION

We have provided evidence using the TabBO model system that the status of several putative molecular markers involving the cell cycle and apoptotic pathways reflects their status in the tumors of origin. Previous studies, including clinical samples, indicate that 40–50% of bone metastases of prostate cancer have wild-type p53 (3–7), 50–70% of bone metastasis do not overexpress the Bcl-2 protein (2, 3), mutations in the p21 gene are rare (17, 23), and the AR is expressed in a high proportion of metastatic prostate cancers (24–28). Therefore, the TabBO model also reflects molecular pathways of a common subset of androgen-independent prostate cancer (Table 1).

It has been more than 50 years since withdrawal of androgens was shown to be effective in the treatment of human prostate cancer. However, this approach is palliative, not curative (30). Although most patients initially respond to androgen ablation, it is believed that all eventually relapse with androgen-independent disease. The androgen-independent phenotype of human prostate cancer is defined in the clinic as the ability of prostate cancer cells to grow despite castrate plasma concentrations of testosterone (30, 31). No current standard therapy consistently confers a significant survival benefit to patients who develop androgen-independent prostate cancer (30, 31).

Clinical studies of apoptosis in the ventral prostate of the rat clearly establish that castration results in the involution of the prostate, primarily through the loss of prostatic epithelial cells of the secretory layer (9, 10, 32). As these cells require androgens for both proliferation and survival, the consequences of androgen withdrawal include the cessation of cell cycle progression and induction of apoptotic cell death (9, 10). Therefore, androgen-independent growth of human prostate cancer has been largely attributed to the impairment of cell growth regulation and apoptosis in response to androgen withdrawal.

Several studies on the mechanisms of the androgen-independent progression in prostate cancer have focused on alterations in the AR. Our new cell lines express AR and are androgen responsive, both in vivo and in vitro (1). Moreover, as determined by immunostaining, AR is expressed in the tumors of origin as well as in the tumors produced by the cell lines in nude mice (data not shown). Mutations in the AR gene are not uncommon in metastatic prostate cancer (24–28, 33), and some of these mutations increase the sensitivity of cells to hormones, including androgens (26, 28). Several studies have demonstrated that most metastatic androgen-independent prostate cancers express high levels of AR gene transcripts (24–28, 33). Therefore, it has been suggested that the androgen independence at the metastatic tumor site correlates with high expression of the AR (mutated or wild type), which may cause sensitivity to low levels of circulating androgens or low-affinity ligands (24, 28). This could account for the proliferative advantage in these cells.

The alterations most clearly associated with the androgen-independent growth of prostate cancer in the clinic has been AR overexpression, p53 mutation, and Bcl-2 overexpression. How-
ever, p53 and Bcl-2 were not altered in the TabBO model of prostate cancer. In a recent study of a large series of androgen-independent prostate cancer bone metastases, we reported that 65% of all tumors had p53 mutations, Bcl-2 overexpression, or both (3). It has been suggested that p53 and Bcl-2 may serve as effecter and repressor, respectively, of a common cell death pathway (3), and therefore alterations in downstream effectors or upstream regulators of p53 or Bcl-2 could also result in an androgen-independent phenotype.

Bax is a Bcl-2-related protein that promotes apoptosis in cultured cells. It has been proposed that Bax acts downstream of p53 in the induction of apoptosis and that Bcl-2 can interfere with Bax-induced apoptosis (34). Recent publications have also provided evidence for the role of Bax as a tumor suppressor gene involved in the p53-mediated apoptotic response (35). Moreover, frameshift mutations in the gene encoding Bax were found in colon cancer of the microsatellite mutator phenotype as well as in the human prostate cancer cell line DU145 (20). The authors suggested that heterozygous Bax mutations may also contribute to tumor progression by reducing the amount of wild-type Bax. In the study reported here, we found that Bax expression was lost in MDA PCa 2a and MDA PCa 2b cells. Cells with a wild-type p53 gene could acquire a growth advantage from alterations that block different apoptotic pathways, even if the pathways are not essential. For instance, although Bax is not essential for p53-mediated apoptosis, the ratio of Bax to Bcl-2 is thought to be critical for apoptosis. Prostate cancer cells with AR overexpression, increased Bcl-2 expression, and absence of Bax would have an altered apoptotic pathway and therefore obtain a survival advantage in an androgen-depleted environment and possibly drug resistance. Studies including other members of the Bcl-2 family may clarify the role of the p53-Bcl-2 pathway in these cell lines and prostate cancer progression.

Because of the high rate of p53 mutations in prostate cancer bone metastases, one might expect alterations in the p53 downstream pathway (e.g., in p21 or Bax) or in alternate pathways regulating cell growth in androgen-independent prostate cancer with wild-type p53. p53 mutation is the most prevalent alteration in human tumors, and the tumor suppression function of the p53 gene is illustrated by the high rate of malignancies in mice lacking functional p53 (36). It is well established that induction of the p53 protein in cells results in either cell cycle arrest or apoptosis (36–38). The downstream effector of p53, the p21 protein, has been shown to arrest cell cycle progression by inhibiting the activity of cyclin-dependent kinases and also by interacting with proliferating cell nuclear antigen and thereby directly preventing DNA synthesis (36). In this study, we also explored the p16-cyclin D1-cdk4-Rb pathway, which is also relevant to the regulation of the G1-to-S transition (36). Western blot and immunohistochemical analysis of Rb and p16 showed a normal protein pattern at the expected molecular weight and heterogeneous nuclear staining. Therefore the cell-growth regulators Rb and p16 were considered to be normal in our model system.

The above results define a subgroup of androgen-independent prostate cancers based on the expression of genes known to be important in the genesis of most tumors, namely p53, p21, Bcl-2, Rb, and p16, all of which appear to be normal. Future studies using this new model system may identify novel molecules involved in cell cycle regulation or apoptosis in prostate cancer progression and may therefore open new opportunities for therapeutic interventions.

**REFERENCES**


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