p53-R273H gains new function in induction of drug resistance through down-regulation of procaspase-3

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Abstract

Development of drug resistance is one of the major obstacles in cancer chemotherapy. The molecular mechanism leading to drug resistance is still not fully understood. A10A cells, a doxorubicin-resistant subline of human squamous cell carcinoma A431 cells, showed cross-resistance to methotrexate and also resistance to the drug-induced apoptosis. The cells also showed overexpression of a mutated form of p53, p53-R273H (Arg to His at codon 273), and down-regulation of procaspase-3. Knockdown of p53-R273H by p53 small interfering RNA in A431 cells increased procaspase-3 level and sensitized the cells to drug-induced apoptosis. On the other hand, transfection of p53-R273H into p53 null human osteosarcoma Saos-2 cells down-regulated procaspase-3 level and induced resistance to the drug toxicity and drug-induced apoptosis. The results support the idea that p53-R273H may gain new functions in induction of drug resistance and impairment in drug-induced apoptosis through down-regulation of procaspase-3 level. The study sheds new light on the understanding of the gain of function and drug resistance mechanisms associated with mutant p53. [Mol Cancer Ther 2007;6(3):1054–61]

Introduction

The tumor-suppressor gene p53 is mutated in 50% of all tumors (1, 2). The majority of point mutation occurs at the central DNA-binding domain of the molecule—at “hotspot” codons 143, 175, 248, 273, etc. (3). The mutation in the p53 gene is manifested with increased malignancy and tumorigenicity primarily from the loss of the transcription function of wild-type p53 (4, 5). Although the loss of wild-type p53 function could be sufficient to promote tumor progression, evidence has shown that mutant p53 may gain new function in conferring the increases in cell survival, cell growth, and decrease in apoptosis in cells (6–8). On the other hand, mutant p53 may also gain new function in induction of drug resistance in cells. Mutant p53 is associated with the increased expression of multidrug resistance gene 1 (MDR1) in cells (9, 10). p53-V143A is reported to increase the resistance of human ovarian carcinoma A2780 cells to radiation, cisplatin, doxorubicin, and cytarabine (11). p53-R175H suppressed etoposide-induced apoptosis (12), induced the resistance to 5-fluorouracil through activation of dUTPase in p53-null human lung cancer H1299 cells (13), protected human osteosarcoma Saos-2 cells to doxorubicin-induced apoptosis through down-regulation of procaspase-3 (14), and also protected human prostate carcinoma PC3 cells from CD95-dependent cell death by suppression of Fas/CD95/Apo1 (15). Overexpression of p53-R273H induced resistance to cisplatin in H1299 cells (12), whereas knockdown of the mutant decreased the resistance of human colon cancer HT29 cells to doxorubicin, cisplatin, and etoposide (16). Overall, the mutant effect on drug resistance is mutant specific and the underlying mechanism is mostly not known.

In the present study, overexpression of p53-R273H and down-regulation of procaspase-3 were observed in A10A cells, a subline of human squamous cell carcinoma A431 cells that showed resistance to doxorubicin, cross-resistance to methotrexate, and also resistance to apoptosis induced by both drugs. It is postulated and subsequently confirmed by transfection of p53-R273H into p53 null human osteosarcoma Saos-2 cells that the mutant gains new function in induction of resistance to drug-induced apoptosis probably through down-regulation of procaspase-3 and impairment of drug-induced caspase activation.

Materials and Methods

Cell Lines, Antibodies, and Reagents

The doxorubicin-resistant A10A subline was derived from human squamous cell carcinoma A431 cells that survived after acute high dosage of 5 µg/mL followed by 10 µg/mL doxorubicin (17). The human osteosarcoma Saos-2 cells transfected with pcDNA-Bam-Neo vector alone (control) or vector carrying mutant p53-R273H (arginine to glycine) was a gift from Professor A.L. Levine (Cancer Institute of New Jersey, University of Medicine and Dentistry of New Jersey, New Brunswick, NJ; ref. 6). All cells were maintained in DMEM (Invitrogen, Inc., Carlsbad, CA) with 10% fetal bovine serum, 2 mmol/L L-glutamine, and, for Saos-2 cells only, 200 µg/mL of G418 (Merck...
Biosciences, Darmstadt, Germany) in 37°C humidified 10% CO₂ incubator. Antibody against p53 was purchased from Merck Biosciences; antibody against caspase-3 was from Santa Cruz Biotechnology (Santa Cruz, CA); and antibody against caspase-8 and caspase-9 were from Stressgen (San Diego, CA). Methotrexate and doxorubicin were purchased from Sigma Chemical Co. (St. Louis, MO); caspase-3 specific inhibitor (Z-DQMD-FMK) and caspase-9 inhibitor (Z-LEHD-FMK) were from Merck Biosciences.

**Drug Sensitivity Assay—3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide Assay**

Cells were seeded in each well of a 96-well plate for 2 days. After incubation with different concentrations of drugs for 5 days, the cells were incubated with 50 µL of 0.1 mg/mL 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma Chemical) in PBS for 3 h. The purple formazan formed was then solubilized by DMSO and absorbance at 570 nm was read by a microplate reader.

**DNA Fragmentation Assay**

After drug treatment, the cells were collected by trypsinization and lysed in lysis buffer (5 mmol/L Tris-HCl, 100 mmol/L EDTA, 1% SDS, and proteinase K) at 45°C. Genomic DNA was extracted by phenol/chloroform/isoamyl alcohol (25:24:1) and precipitated in 70% ethanol at -20°C. RNA was removed by incubation with RNase A. Thereafter, the same amount of DNA was loaded and visualized on a 1.5% agarose gel.

**Western Blot Analysis**

Cells were lysed in Laemmli lysis buffer (2.1 µg/mL aprotinin, 0.5 µg/mL leupeptin, 4.9 mmol/L MgCl₂, 1 mmol/L orthovanadate, 1% Triton X, and 1 mmol/L phenylmethylsulfonyl fluoride). Proteins were resolved in denaturing SDS-PAGE minigel and transferred to nitrocellulose membrane. After blocking with 5% nonfat dry milk, the membranes were washed by PBS containing 0.1% Tween 20 and incubated with primary antibodies followed by respective horseradish peroxidase–conjugated secondary antibodies. Signals were visualized with enhanced chemiluminescence (Amersham Life Sciences, Inc., Buckinghamshire, United Kingdom). Intensity of the bands was quantitated by Kodak Digital Science one-dimensional software. After normalization with the band intensity of β-actin, relative RNA expression of individual molecule was calculated by dividing the intensity of individual band by that of the control, of which the expression is designated as 1.0.

**p53 Small Interfering RNA Construction and Transfection**

The p53 small interfering RNA (siRNA) sequence targeting the coding region of p53 mRNA (nucleotides 160–179) was used. The sense and antisense oligonucleotide templates were 5'-UGGUUCACUGAGACCCAGUUAU-3' and 5'-UUACCAAGACUUCCUGGGUC-3', respectively. The oligonucleotides encoding the hairpin sequences of p53 siRNA were ligated into pSilencer 2.1-U6 Neovector as described by the manufacturer (Ambion, Inc., Austin, TX). The p53 siRNA plasmid was allowed to form complex with LipofectAMINE 2000 (Invitrogen) for 20 min at room temperature, and transfection was carried out at 37°C for 24 h.

**Results**

**A10A Cells Showed Resistance to Drug Toxicity and Drug-Induced Apoptosis**

By MTT assay, A10A cells were shown to be more resistant to both doxorubicin and methotrexate compared with A431 parent (AP) cells (Fig. 1A). The resistance is unlikely to be related to P-glycoprotein as its level was similar between the AP and A10A cells (results not shown). By DNA fragmentation assay, methotrexate and doxorubicin induced a dose-dependent DNA fragmentation in AP and A10A cells, whereas the induction was less obvious in A10A cells (Fig. 1B). The resistance to methotrexate- and doxorubicin-induced apoptosis in A10A cells was also shown by Annexin V binding assay. The percentages of apoptotic cells (early and late) for AP and A10A cells after 48 h of 0.05 µmol/L doxorubicin treatment were 38 and 25 (the percentages for the control cells were 16 and 15), respectively, whereas the percentages for AP and A10A cells with 25 nmol/L methotrexate treatment were 29 and 17 (9 and 11 for the controls), respectively (results not shown). The results from both assays imply that the drug resistance shown in A10A cells may be related to impaired drug-induced apoptosis.

**Resistance to Drug-Induced Apoptosis and Elevated Proapoptase-3 Level in A10A Cells**

One of the key steps in drug-induced apoptosis is activation of proapoptases; therefore, the expression of the enzymes will likely determine the extent of induced apoptosis. To elucidate the molecular mechanism for resistance to drug-induced apoptosis in A10A cells, the protein levels of proapoptase-3, proapoptase-8, and proapoptase-9 were

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analyzed. Caspase-8 and caspase-9 are initiator caspases involved, respectively, in the extrinsic or death receptor apoptotic pathway and intrinsic or mitochondrial apoptotic pathways in which they trigger apoptosis both through activation of an effector caspase, caspase-3 (18, 19). As shown in Fig. 2A, the level of procaspase-3 was found to be down-regulated by 0.59-fold in A10A cells, whereas procaspase-8 and procaspase-9 were up-regulated by 2.18- and 1.28-fold, respectively, compared with AP cells (Fig. 2A). In the search for the molecular mediator that leads to down-regulation of procaspase-3 in A10A cells, p53 was found to be up-regulated by 1.7-fold in A10A cells when compared with AP cells (Fig. 2A). A431 cells carry a hotspot p53 mutant, with an arginine to histidine mutation at codon 273 (20). Another type of p53 mutant, p53-R175H, was previously reported to induce doxorubicin resistance through procaspase-3 down-regulation in cells (14). It is therefore hypothesized that mutant p53-R273H may also induce resistance to drug-induced apoptosis through down-regulation of procaspase-3 in A431 cells. To examine this hypothesis, the p53-R273H level in A431 cells was knocked down with p53 siRNA vector. The transfection with siRNA up-regulated the procaspase-3 level (Fig. 2B), and the A431 cells were then more sensitive to drug-induced DNA fragmentation (Fig. 2C). Furthermore, the increase in apoptosis was abrogated by the caspase-3–specific inhibitor Z-DQMD-FMK (results not shown). Transfection with scramble siRNA vector had no effect on p53 level, procaspase-3 level, and drug-induced apoptosis in cells (Fig. 2B and C).

Drug-Induced Caspase Activation and Resistance to Apoptosis in A10A Cells

In addition to the expression level, drug-induced apoptosis may also be affected by the level of drug-induced procaspase activation. By Western blot analysis, both methotrexate and doxorubicin induced caspase-3 activation in both A431 cells as indicated by the increase of the active caspase-3 level. The activation of caspase-3 by methotrexate and doxorubicin was more significant in AP cells than in A10A cells (Fig. 3). Similar results were observed for the effect of both drugs on caspase-9 activation. On the other hand, both drugs seemed to have minimal effect on the activation of procaspase-8 (Fig. 3). The data suggested that the apoptosis process induced by both methotrexate and doxorubicin were through the intrinsic pathways, whereas impairment of drug-induced caspase activation was shown in A10A cells.

p53-R273H Induced Resistance to Drug-Induced Apoptosis in Saos-2 Cells

Results from A431 cells suggest that p53-R273H may gain new function in down-regulation of procaspase-3, impairment of caspase activation, and induction of resistance to
drug-induced apoptosis in cells. To validate this notion, the p53 null human osteosarcoma Saos-2 cells were transfected with p53-R273H. Saos-2 p53-R273H transfectants were more resistant to methotrexate and doxorubicin (Fig. 4A) and also show reduced level of drug-induced DNA fragmentation when compared with the control transfectants (Fig. 4B). The reduction in drug-induced apoptosis in Saos-2 p53-R273H transfectants was confirmed by using

![Image](https://example.com/image1.png)

**Figure 2.** p53-R273H down-regulation of procaspase-3 level in A431 cells. A, the basal expression levels of p53 and procaspase-3, procaspase-8, and procaspase-9 in A431 cells as measured by Western blot analysis. After lysing of subconfluent cells, proteins from different samples were resolved by SDS-PAGE and then probed with specific primary antibodies. The expression level of individual protein was quantitated as described in Materials and Methods. SD was obtained from more than three separate experiments. *, P < 0.05, the expression of p53 or caspase between AP and A10A cells is significantly different as assessed by Student’s t test. B, p53-R273H regulation of procaspase-3 level in A431 cells. Cells were transfected with scramble siRNA vector (S) or p53 siRNA vector (p53i) for 24 h and then harvested for total protein. C, control. Procaspe-3 level was analyzed by Western blot analysis. C, the role of p53-R273H in methotrexate- and doxorubicin-induced DNA fragmentation in A431 cells. Cells were transfected with p53 siRNA vector for 24 h and then incubated with 25 nmol/L methotrexate or 0.1 μmol/L doxorubicin for 72 h followed by DNA fragmentation assay.

![Image](https://example.com/image2.png)

**Figure 3.** Methotrexate- and doxorubicin-induced caspase activation in A431 cells. Cells were incubated with 25 nmol/L methotrexate for 72 h or 0.1 μmol/L doxorubicin for 48 h, and the protein was then harvested for Western blot analysis. Specific antibodies that recognize both pro and active forms of caspase-3, caspase-8, and caspase-9 were used. In each cell line, relative expression for individual enzyme in each sample was calculated as described in Materials and Methods. SD was obtained from more than three separate experiments. One representative experiment is shown. *, P < 0.05, the level of the specific enzyme in the drug-treated cells is significantly different from that of the respective control as analyzed by Student’s t test.

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<th>MTX (25mM)</th>
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<td>A10A</td>
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<td>Procaspe-3</td>
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<td>1.33±0.10*</td>
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<td>Active caspase-3</td>
<td>1.00</td>
<td>2.14±0.08*</td>
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<tr>
<td>Procaspe-9</td>
<td>1.00</td>
<td>1.56±0.03*</td>
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<td>Active caspase-9</td>
<td>1.00</td>
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<tr>
<td>Procaspe-8</td>
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<td>Active caspase-8</td>
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Annexin V binding assay. The percentages of apoptotic cells (early and late) for Saos-2 control cells and p53-R273H transfectants with no drug treatment were 12 and 15, respectively, whereas the percentages were 60 and 42, respectively, for 72 h of 0.1 μmol/L doxorubicin treatment and were 79 and 39, respectively, for 72 h of 50 nmol/L methotrexate treatment. To investigate the mutant effect on caspase expression and activation, the levels of procaspase-3, procaspase-8, and procaspase-9 were measured by Western blot analysis. Procaspase-3 was found to be down-regulated by 0.6-fold, whereas procaspase-8 and procaspase-9 were found to be up-regulated by 1.74- and 1.34-fold, respectively, in Saos-2 p53-R273H transfectants when compared with the control cells (Fig. 4C). This result was comparable with that observed in A431 cells. Moreover, the mRNA level of procaspase-3 was reduced by 0.68-fold and that of the procaspase-8 and procaspase-9 were increased by 1.7- and 1.1-fold in Saos-2 p53-R273H transfectants. The results therefore indicate that p53-R273H may regulate the caspase at the transcription level (Fig. 4C).

By Western blot analysis, both methotrexate and doxorubicin induced caspase-3 and caspase-9 cleavages in Saos-2 cells. The activation of both enzymes was more significant in Saos-2 control cells than in p53-R273H transfectants except for doxorubicin activation of caspase-9 of which the activation is similar between the two cell lines. On the other hand, both drugs seemed not to activate procaspase-8 in Saos-2 cells (Fig. 5). Therefore, results from Saos-2 cells further confirm the role of p53-R273H in down-regulation of procaspase-3, impairment of caspase activation, and induction of resistance to drug-induced apoptosis in cells.

Discussion

Mutant p53-R273H gains new function in induction of drug resistance and also resistance to drug-induced apoptosis in cells through down-regulation of procaspase-3 and impairment of drug-induced caspase activation. It is supported by the studies of p53-R273H endogenously expressed A431 cells and ectopically expressed Saos-2 cells. In addition to drug resistance, A10A cells also showed resistance to drug-induced apoptosis, overexpression of p53-R273H, and down-regulation of procaspase-3.
Up-regulation of procaspase-3 level and the eventual sensitization of methotrexate- and doxorubicin-induced apoptosis were shown in A431 cells upon knockdown of p53-R273H by p53 siRNA (Fig. 2). In Saos-2 cells that are devoid of endogenous p53, overexpression of p53-R273H down-regulated procaspase-3 level and increased resistance to methotrexate- and doxorubicin-induced apoptosis (Fig. 4). In addition to the enzyme level, impairment of caspase-3 activation may also likely contribute to p53-R273H effect on resistance to drug-induced apoptosis. Treatment with methotrexate and doxorubicin was shown to activate caspase-3 and caspase-9, but not caspase-8, in both A431 and Saos-2 cells (Fig. 3). However, only the specific enzyme activity of caspase-3, but not that of the caspase-9, showed correlation with p53-R273H effect on apoptosis in cells. The specific enzyme activity of caspase-3 upon treatment with either methotrexate or doxorubicin was less significant in both A431 cells and Saos-2 cells with elevated level of p53-R273H. Such kind of correlation, however, cannot be shown for caspase-9; the specific enzyme activity of caspase-9 in Saos-2 control cells and p53-R273H transfectants upon treatment with doxorubicin was similar (Fig. 6). The results suggested that if impairment of caspase activation is to be considered as the possible factor contributing to the effect of p53-R273H on resistance to apoptosis, the enzyme involved will likely be caspase-3 rather than caspase-9. How p53-R273H suppresses the drug-induced caspase-3 activation is not known. In any case, it will unlikely be due to caspase-8. Whether that will involve a caspase other than caspase-8 or caspase-9 (e.g., caspase-2; ref. 21), molecules in the intrinsic apoptotic pathway (e.g., Bcl-2 family protein), mitochondrial activity, or molecules in the other pathways (e.g., cathepsin L; ref. 22) will need detailed analysis.

p53-R273H effect on resistance to drug-induced apoptosis is similar to that shown for the other mutant, p53-R175H; however, the two mutants may act differently in regulation of their respective target genes. p53-R273H is considered as contact mutant, whereas p53-R175H is a structural mutant (7). Similar to p53-R273H, p53-R175H was reported to gain new function in impairing doxorubicin-induced apoptosis in Saos-2 cells through down-regulation and inactivation of procaspase-3 (14). On the other hand, p53-R273H also has effect on the expressions of procaspase-8 and procaspase-9, whereas there is no effect for p53-R175H. The differential between the effects of two mutants indicates that the regulation of p53 mutants on their target genes is likely to be mutant specific as that reported in other studies (7, 8, 13). The implication and the biological consequence for the up-regulation of caspase-8 and caspase-9 by p53-R273H thus far is not known and will need further investigation. However, the up-regulation seemed unlikely to be important for p53-R273H role in drug-induced apoptosis as the elevated level of procaspase may likely favor the process of drug-induced apoptosis instead. In fact, in the process of cancer development, impairment of apoptosis pathway may take place and the impairment may involve more than one molecule in the pathway. Similar to that shown by other studies, the findings from the present study suggest that induction of apoptosis by chemotherapeutic drugs in cancer cells may not solely depend on the overall changes in the apoptotic potential after the impairment as the individual molecule involved may play a more dominant role than the others in the induction regulation (23–25).

Mutant p53-R273H suppresses caspase-3 but induces caspase-8 and caspase-9 in p53-R273H endogenously expressed A431 cells and ectopically expressed Saos-2 cells. The underlying mechanisms for the regulation of caspase-3, caspase-8, and caspase-9 by p53-R273H remain to be elucidated. It is possible that modulation of the activity of various molecules in the intrinsic apoptotic pathway (e.g., Bcl-2 family proteins), mitochondrial activity, and other pathways (e.g., cathepsin L; ref. 22) is responsible for the differential effects of these mutants on their respective target genes. As the current study did not address the underlying mechanisms of the regulation of caspase activity by p53-R273H, future investigation is necessary to resolve this issue.

**Figure 5.** Methotrexate- and doxorubicin-induced caspase activation in Saos-2 cells. Cells were incubated with 25 nM/L methotrexate for 72 h or 0.1 μM/L doxorubicin for 48 h, and the proteins were harvested for Western blot analysis. The membranes were probed with specific antibodies that recognize both pro and active forms of caspase-3, caspase-8, and caspase-9. In each cell line, relative expression for individual enzyme in each sample was calculated as described in Materials and Methods. SD was obtained from more than three separate experiments and one is shown as a representative. *, P < 0.05, the level of the specific enzyme in the drug-treated cells is significantly different from that of the respective control as analyzed by Student's t test.
caspase-8, and caspase-9 by p53-R273H and the differential in the regulation of these three enzymes by the mutant are not clear. Differential in regulation of its target genes has also been reported for other p53 mutants (7–9, 13, 15, 26, 27). Mutant p53 may regulate the expression of the target gene at the levels of transcription, posttranscription, etc. However, a lot of the current studies have emphasis on the transcription level. In many studies, the gain of function by p53 mutant in transcription regulation of the target genes may require intact COOH-terminal and possibly NH2-terminal domain of the protein. The mutant protein may interact directly with other proteins (e.g., MBP-1) and through such interaction regulates the transcription of the target genes. On the other hand, the mutant might also interact with the promoter region of the target genes. The mutant may interact directly with the promoter DNA sequence or tether indirectly with the help of other DNA-binding proteins (e.g., transcription factor SP1, NF-Y). For direct interaction of the mutant protein with the promoter sequence of the target gene, the consensus binding sequences for individual mutants are yet to be identified, and some will suggest that the interaction might be through recognition of specific DNA structure (e.g., MAR) by the mutant (7, 8, 28). It is also possible that the mutant protein might act through some still yet to be identified pathways to regulate the methylation status of the gene promoter in regulation of gene expression (e.g., caspase-8; ref. 29). The promoter sequences for human caspase-3 and caspase-9 are thus far not yet isolated, whereas the one for caspase-8 is reported. In any case, the promoter sequences for all three enzymes in rodents are known. The promoter sequences for all three rodent caspases contain “TATA-less” sequence and also multiple GC boxes. There are similarity and discrepancy for the consensus binding sequences among the three promoter sequences. For instance, the binding sequence for SP1 is detected in all three promoters, whereas HIF-1 is only seen in caspase-9 (30–33). The differential for p53-R273H in regulation of the expressions of caspase-3, caspase-8, and caspase-9 can be due to the difference in the promoter binding sequences.

Figure 6. Specific enzyme activity of caspase-3 and caspase-9 in A431 (A) and Saos-2 (B) cells. Specific enzyme activity was calculated by dividing the expression level of the active form of the specific caspase with the total expression level of both pro and active forms of each respective caspase. The specific enzyme activity for cells at 0 h of drug treatment was defined as 1.
sequence of the three enzymes or due to other factors that are yet to be identified. In any case, the work may only be confirmed when the promoter sequences for human caspase-3 and caspase-9 have been isolated.

Taken together, p53-R273H is confirmed to gain new function in regulation of drug resistance as supported by results from the mutant endogenously expressed A431 cells and ectopically expressed Saos-2 cells. The resistance is through the mutant effect on down-regulation of procaspase-3 and subsequent impairment of drug-induced apoptosis. Although detailed study is still needed to identify the mechanism involved, results from the study, however, can help to have a better understanding about the gain of function of p53 mutant and the drug resistance mechanism in, in particular, for those cells carrying mutant p53. Furthermore, it may also suggest that the mutant p53 itself may serve as a potential target for further drug development in overcoming drug resistance in cancer therapy.

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References
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