Cytogenetic Alterations Associated with P-Glycoprotein- and Non-P-Glycoprotein-mediated Multidrug Resistance in SW-1573 Human Lung Tumor Cell Lines

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ABSTRACT

Multidrug resistance can be induced in mammalian cells by selection with a single cytotoxic agent. Overproduction of the energy-dependent drug efflux pump P-glycoprotein, encoded by the mdr1 gene, has been identified as the cause of one form of multidrug resistance. The molecular basis of other forms of multidrug resistance is unknown. Doxorubicin selection of the human squamous lung cancer cell line SW-1573 resulted in multidrug-resistant sublines in which a non-P-glycoprotein-mediated form of multidrug resistance precedes mdr1 expression. Here we present a cytogenetic analysis of both non-P-glycoprotein-mediated multidrug-resistant and P-glycoprotein-mediated multidrug-resistant sublines derived from SW-1573. Three independently derived non-P-glycoprotein-mediated multidrug-resistant sublines showed a heterozygous deletion of the short arm of chromosome 2 (p23-pter), whereas alterations of chromosome 7 were present in the P-glycoprotein-mediated multidrug-resistant cell lines. In one series of clonally derived P-glycoprotein-mediated multidrug-resistant sublines, mdr1 overexpression was accompanied by various markers of chromosome 7 with breakpoints at q22, the mdr1 gene being known to be located at q21.1. Our data suggest that in SW-1573 cells acquisition of non-P-glycoprotein-mediated multidrug resistance is accompanied by a specific deletion or a translocation involving the short arm of chromosome 2, whereas in the emergence of P-glycoprotein-mediated multidrug resistance a rearrangement of the long arm of chromosome 7 is a critical event.

INTRODUCTION

Resistance to anticancer drugs offers a serious impediment to cancer chemotherapy, especially inasmuch as acquired resistance to anticancer agents such as doxorubicin can be accompanied by the development of cross-resistance to a variety of structurally unrelated drugs, a phenomenon called MDR. One form of MDR is mediated by overproduction of the product from the mdr1 gene, which encodes a membrane glycoprotein, termed P-glycoprotein. This protein is thought to act as an energy-dependent drug efflux pump preventing accumulation of the drug in the cell (1-3). P-glycoprotein overproduction may be associated with gene amplification, often seen in rodent cell lines, where MDR is typically associated with HSRs and DMs accompanying MDR development have been made in rodent cells, where MDR is associated with gene amplification, often seen in rodent cell lines, where MDR is typically associated with HSRs and DMs. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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4 The abbreviations used are: MDR, multidrug resistance or multidrug-resistant; DM, double minute; FITC, fluorescein isothiocyanate; HSR, homogeneously staining region; SSC, standard sodium-citrate (150 mm sodium chloride, 15 mm sodium citrate, pH 7.0); cDNA, complementary DNA.

Thus far, most investigations into the cytogenetic alterations accompanying MDR development have been made in rodent cells, where MDR is typically associated with HSRs and DMs harboring amplified P-glycoprotein genes (7-9). Less information is currently available on the cytogenetic characteristics of human MDR cells. In a cytogenetic study of two human MDR tumor cell lines, one fibrosarcoma and one colon carcinoma line, development of MDR was accompanied by aberrations of chromosome 7 (10).

Recently mechanisms of MDR have been described that appear to be independent of overproduction of P-glycoprotein (11-16). In various sublines of the human lung tumor cell line SW-1573 non-P-glycoprotein-mediated MDR has been shown to precede P-glycoprotein-mediated MDR (16). Here we report a karyotypic analysis of the SW-1573 cell line and several non-P-glycoprotein-mediated as well as P-glycoprotein-mediated MDR derivatives, in an attempt to correlate these distinct MDR phenotypes with specific cytogenetic features.

MATERIALS AND METHODS

Drugs and Culture Methods. Doxorubicin (Adriblastina, produced by Farmitalia, Carlo Erba, Milan, Italy) was a gift from Bergel Nederland B.V., Heerhugowaard, the Netherlands. It was dissolved and stored in a stock solution of 5 μM in 0.9% NaCl and kept at −20°C in the dark. Monolayers of SW-1573 cells and the doxorubicin-resistant sublines derived from them were cultured as described previously (17). Cells were grown in 25-cm² tissue culture flasks (Nunc, Roskilde, Denmark) containing 5 ml Ham’s F-10 medium, supplemented with 10% fetal calf serum (Flow Laboratories, Ltd., Irvine, Scotland) and 2 mm glutamine (Flow). Cultures were maintained at 37°C under air/3% CO₂ and were subcultured twice a week. All cell lines were tested for Mycoplasma infection by cocultivation with an indicator strain (CV-1) as described previously (17), and found to be Mycoplasma-free.

Cells. The drug-sensitive parental cell line SW-1573 was originally obtained from Dr. A. Leibovitz (Scott and White Clinic, Temple, TX), who had characterized it as a squamous cell carcinoma of the lung. The cell line had been cultured for 2 years in the laboratory of Dr. J. van Rijn (Department of Radiotherapy, Free University Hospital), before the selection for doxorubicin-resistant cells was started. Possible mechanisms underlying MDR in doxorubicin-resistant SW-1573 sublines have been the subject of three earlier studies (16-18).

Selection for Doxorubicin Resistance. Selection for doxorubicin-resistant cells was carried out by increasing doxorubicin concentrations in the culture medium in a stepwise fashion, starting from 10 nM. Once the cells were fully adapted to the doxorubicin concentration used, the concentration was increased, usually 2- to 3-fold. In this way 3 independent series of sublines were selected, starting from 2 different passage levels of the drug-sensitive parental cell line S1 and S2 (see Table 1).

Since the cells of the sensitive parent used for the first selection procedure were considered passage 1. The drug-resistant subline resulting from this first procedure was called IR50. From line IR50 sublines with higher doxorubicin resistance were selected, which resulted in sublines IR500, IR1000, and IR10000. The numbers following R in the names of these sublines, as well as of the sublines discussed below, denote
the doxorubicin concentration in nm at which the cells were able to stably proliferate before they were harvested. The subline 1R500-0 was analyzed after culturing 1R500 in the absence of doxorubicin for 9 months.

The second series was started from passage 75 of the sensitive parent line by an identical stepwise increase in doxorubicin concentration starting from 10 nm, and this resulted in the 2R50 subline, which in one step produced a variant 2R80 (not karyotyped). From this 2R80 2 descendants arose simultaneously, 2R120 and 2R160 (18). Of these, only results on 2R160 are presented, since the results from 2RI20 do not alter the conclusions of this study.

The third selection procedure also started from passage 75 not by a stepwise increase of doxorubicin in the culture medium but by culturing the cells in medium containing 80 nm doxorubicin from the very start. After 1 month of growth the cells were allowed to recuperate during a drug-free period of 2 weeks, after which they were cultured in medium containing 80 nm doxorubicin from the very start.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Passage</th>
<th>Doxorubicin-resistance factor (fold)</th>
<th>mdr1 expression</th>
<th>Chromosome no.</th>
<th>% of polyploid cells</th>
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<td>Modal</td>
<td>Range</td>
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<tr>
<td>S1</td>
<td>1</td>
<td>1</td>
<td>±</td>
<td>68</td>
<td>60–73</td>
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<tr>
<td>S2</td>
<td>75</td>
<td>1</td>
<td>±</td>
<td>68</td>
<td>60–71</td>
</tr>
<tr>
<td>S3</td>
<td>150</td>
<td>1</td>
<td>±</td>
<td>67</td>
<td>61–71</td>
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<tr>
<td>1R50</td>
<td>44</td>
<td>7</td>
<td>–</td>
<td>57/62</td>
<td>52–67</td>
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<tr>
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<td>50</td>
<td>1</td>
<td>+</td>
<td>60</td>
<td>53–62</td>
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<tr>
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<td>1</td>
<td>n.d.</td>
<td>60</td>
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<td>85</td>
<td>2000</td>
<td>++</td>
<td>60</td>
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<td>110</td>
<td>40</td>
<td>+</td>
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<td>50</td>
<td>50</td>
<td>+</td>
<td>58</td>
<td>57–61</td>
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<tr>
<td>3R80</td>
<td>60</td>
<td>10</td>
<td>–</td>
<td>53</td>
<td>53–61</td>
</tr>
</tbody>
</table>

* S1, S2, and S3, drug-sensitive parental SW-1573 strain at 3 passage levels. 1R50, 1R500, 1R1000, 1R10000 are sequentially S1-derived drug-resistant sublines resistant to 50, 500, 1000, and 10000 nm doxorubicin, respectively, which were analyzed after the indicated number of passages in the continuous presence of these drug concentrations; 1R500-0 are 1R500 cells cultured for 60 passages in the absence of doxorubicin. The 2R series of sublines were derived from parent S2; 2R160 was selected from 2R50. 3R80 cells were derived from S2 in a single selection step.

RESULTS

In Table 1 some characteristics of the SW-1573 sublines studied are summarized, i.e., the lineages of the different sublines, number of passages undergone in the continuous presence of doxorubicin (drug concentrations in nm are included in the name of the subline), resistance factors (17), mdr1 expression (16), and chromosome numbers.

Parental Cell Line. The modal number of chromosomes of the parental cell line was 67/68, and it remained in the hypotriploid range during 2 years of in vitro cultivation (Table 1). While no 2 cells were identical in the early passages of this cell line, a stemline had developed at passage 75: 68,XX, the karyotype of which was found in 30% of the cells at passage 150. In Fig. 1 a representative karyogram of the cell line at passage 75 is shown.

Non-P-Glycoprotein-mediated MDR Sublines 1R50, 2R50, and 3R80. The early steps in the acquisition of doxorubicin resistance were invariably accompanied by a random loss of 7 to 10 chromosomes/cell. In all 3 sublines of low resistance tetraploidy started to appear in approximately 10% of the cells. This percentage increased with time and increasing resistance. No stemlines developed in any of the resistant sublines.

Figs. 2–4 show representative karyograms of the sublines.

In the 1R50 (Fig. 2), which was 7 times more resistant to doxorubicin than the parent cell line, structural aberrations were observed, especially of chromosome 1.

The 2R series yielded a subline (2R50; Fig. 3) which was 5 times more resistant to doxorubicin than the parental cell line. Chromosomes 2 and 3 were affected at least twice. The 3R80 (Fig. 4) was a 10-fold resistant subline, in which chromosome 1 was involved in new translocations twice.

Chromosomes 1, 2, and 12 were affected in all three non-P-glycoprotein-mediated MDR sublines, but the only specific
Fig. 2. Representative karyogram of subline 1R50. Typical numerical changes in this subline: -1, -2, -3, -4, -5, -6, -7, -8, -10, -11, -13, -18; +22; +M2, +M[4-7], +M10, +M12 (for description of these markers see legend to Fig. 1); +, identified clonal markers: M1a t(1;7)(p11—p34:?), M3a t(1;7)(q14—q21:?), M3b t(1;7)(p13—ql1:?), M13 del(2)(p23), M14 del(2)(p25—ql1:?), M15 t(4;7)(4qter—4q11:?), M16 t(5;7)(5qter—5q13:?), M17 del(6)(q23-q27), M18 del(7)(q22) (2 copies in >50% of the cells). Unidentified markers: clonal, 3-5/cell; sporadic, 0-2/cell. In this particular cell M3b is not present. Msp, sporadic marker, found only in this cell.

Unidentified markers:

UM1

clonal

1R1000 and 1R10000 could not be fully karyotyped because of the inferior quality of the metaphases found, but the presence of two of the markers of chromosome 7 was confirmed microscopically in 30 metaphases in 1R10000. The deleted chromosome 7 (M18) had disappeared from these lines, and M18a, t(7;?), had become a complex marker (M18b; Fig. 8) in 1R1000. Representative karyotypes of 1R500 and 2R160 are shown in Figs. 6 and 7, respectively. In the 1R500 the long arm of chromosome 7 was involved in two new translocations (M6a and M18a), which continued to be present in 1R500-0 (karyotype not shown, but essentially the same as that of 1R500).
Fig. 3. Representative karyogram of 2R50. Typical numerical changes in this subline: —1, —2, —3, —6, —8, —10, —13, —X; +9, +12, +20, +21; +M1, +M2, +M[4-8], +M9', +M10 (see legend to Fig. 1); +, identified clonal markers: M3d t(l;?) (q1ter—1q12::?), M13 del(2)(p23), M27 del(3)(q21q25), M28 del(3)(p23), M26 der-(6)t(2;6)(ql2;q25), M29 der(12)t(12;?) (p11;?), M30 der(18)t(18;?) (p11;?). Unidentified markers: clonal, 1-4/cell; sporadic, 2-4/cell.

Unidentified markers:

clonal
sporadic

1R10000. No HSRs or DMs were seen in this or any other of the variant lines.

In the P-glycoprotein-overproducing cell line 2R160 (see Fig. 7), developed from 2R50, a translocation involving 1 arm of the isochromosome i(7q), breakpoint 7q22, was seen, but only in 4 of the 30 metaphases that were checked for this marker. In addition, a reciprocal whole-arm translocation of chromosomes 2 and 7 (M33 and M34) was detected in all the cells karyotyped. For a summary of the above-mentioned rearranged chromosome 7 markers, see Fig. 8.

Fluorescent in Situ Hybridization. In situ hybridization confirmed the results obtained by karyotyping. The mdr1 gene was on chromosome 7 and all of its markers and, except for the highly resistant 1R10000 (see “Discussion”), it was not found on any of the unidentified marker chromosomes. The p7 probe confirmed the number of chromosomes 7 and markers of 7 as identified by GTG banding in all the variant sublines (results not shown). Fig. 9 illustrates the results of in situ hybridization with the digoxigenin-labeled cosmid probe c-HM6: the mdr1 genes on the marker chromosomes of 7 in the 1R500-0 cell line (Fig. 9A) and on M3b in 1R10000 (Fig. 9A, inset), and the centromeres of chromosome 7 in the markers M33 and M34 resulting from the reciprocal translocation t(2;7) of the 2R160 variant (Fig. 9C). In situ hybridization with the mdr1 cDNA probe labeled with biotin gave similar results (not shown).
Fig. 4. Representative karyogram of 3R80. Typical numerical changes in this subline: -1, -1, -8, -10, -13, -14, +9, +16, +18, +20, +20, +21; +M1, +M2, +M5, +M6, +M9, +M10 (see legend to Fig. 1); +, identified clonal markers: M3f t(l;7)(qter—q12::?), M13 del(2)(p23), M8a t(l;10;13)—(10qter—10p11::1p11—1p34;13q14—13qter), M7a t(8;10;12)(10qter—10q26::8q13—8q24::12q12—12qter). Unidentified markers: clonal, 2-4/cell; sporadic, 2-5/cell. Msp, sporadic marker.

DISCUSSION

General Cytogenetic Characteristics. The sensitive parent SW-1573 cell line S1 appeared to be heterogeneous, but quite stable; during the 2 years of in vitro cultivation only 2 new marker chromosomes developed (M11 and M12), one of which (M11) had disappeared again at passage 150. At passage 150 a stemline had developed: 30% of the cells were chromosomally identical. This tendency towards greater homogeneity was apparent only in the absence of a selective agent, for in none of the MDR variant sublines was there evidence for the development of a new stemline. Due to the clastogenic effect of doxorubicin, a number of new marker chromosomes arose in the sublines cultured in the presence of doxorubicin (10-12/4366

Fig. 5. Chromosome 2 as found in the 3 non-P-glycoprotein-mediated MDR sublines. Left, normal 2; right, deleted 2 (M13).
subline, including unidentified markers) and no 2 cells had identical karyotypes. Chromosome 1 was by far the most heavily affected chromosome, both in the sensitive parent cell line and in the doxorubicin-resistant sublines, where it was involved in translocations 9 times. The frequent involvement of chromosome 1 in rearrangements in solid tumor cells has been observed by many others (24), and it has been proposed that the rearrangements might involve an oncogene such as N-ras (25). It is, of course, also the longest chromosome and the most characteristic as to banding pattern, which facilitates recognition of very small alterations, as is illustrated by subline 1R50 (Fig. 2). Polyploidization invariably accompanied the acquisition of doxorubicin resistance in our sublines. Remarkably, drug-resistant cells cultured in the absence of a selective agent showed no decrease in the number of polyploid cells as might have been expected, but a gradual increase up to 65% of the cells, a percentage still present at passage 150 (results not shown). Slovak et al. (10) have also noted polyploidization after in vitro culturing in the presence of doxorubicin in the HT1080 fibrosarcoma cell line and the almost total replacement by polyploid cells after a drug-free period, but in their lines this was also observed in the sensitive parent line. In our lines this phenomenon is seen only in the MDR variant lines, and especially after removal of the selective agent. Our data seem to indicate that cells may acquire a tendency toward polyploidization by exposure to low levels of doxorubicin, even though this characteristic does not seem to contribute to doxorubicin resistance.

Non-P-Glycoprotein-mediated MDR Sublines 1R50, 2R50 and 3R380. Apart from other chromosomal alterations all non-P-glycoprotein-mediated MDR sublines had aberrations of 1, 2,
and 12, but only in the case of chromosome 2 did the same chromosomal band appear to be involved: 2p23. In addition to this deleted chromosome, however, the variant lines contained one or two apparently normal copies of chromosome 2. We can only speculate about the possible role for this deletion in the acquisition of non-P-glycoprotein-mediated MDR. If emergence of non-P-glycoprotein-mediated MDR would require activation of a normally inactive or repressed "non-P-glycoprotein-mediated MDR gene," the present data could be interpreted in two ways. Either genes on the short arm of chromosome 2, from band p23 to pter, may have moved to another locus, causing cis-activation of the non-P-glycoprotein-mediated MDR gene, or the drug-sensitive parental SW-1573 cells are heterozygous for a locus at chromosome 2 (region
with a centromere 7-specific probe, whereas in a minority of the cells a translocation with breakpoint q7q22 was seen.

The appearance of abnormalities of chromosome 7 in 1R500 and 2R160 corroborates the findings by Slovak et al. (10) that acquisition of the MDR phenotype is accompanied by rearrangements involving chromosome 7. The rearrangements in the 2 doxorubicin-resistant (200–300-fold) tumor cell lines HT 1080 (fibrosarcoma) and LoVo (colon adenocarcinoma) included inversions (7p); a dicentric; rearrangements with chromosomes 1, 5, and 10; a duplication 7(q21q32); and a deletion 7(q21q32) (10).

We have shown previously that the mdrl gene is overexpressed only in the cell lines 1R500, 1R500-0, 1R10000, and 2R160 (16). In all these lines we found rearrangements involving chromosome 7q. The translocations with breakpoints 7q22 suggest transcriptional activation of the mdrl gene by a positional effect, inasmuch as the gene for P-glycoprotein has been assigned to 7q21.1 (27).

We have attempted to map the breakpoint more precisely by pulsed field gel electrophoresis of DNA from the SW-1573 lines S1, 1R500–0, and 1R10000. Using the restriction enzymes NotI, SfiI, SacII, and MluI, we could not detect any gross alterations around the mdrl gene. These enzymes cover a region extending at least 80 kilobases 5’ and 180 kilobases 3’ of the mdrl gene (28). The fact that the breakpoint is relatively far away from the mdrl gene does not rule out the possibility of activation due to a translocation. cis-activation over a distance as long as 300 kilobases has been reported (29) and it might even extend over a longer region. Thus far all experiments to test whether the mdrl gene(s) are activated in cis or in trans have been inconclusive. Transfection experiments using MDR promoter-reporter gene constructs in normal and multidrug-resistant cell lines have not provided evidence for trans-activation (30, 31). However, one cannot rule out the possibility that in the constructs used some cis-acting sequences necessary for promoter activity were missing. Within the resolution of our in situ hybridization and cytogenetic analysis the breakpoint could be as far as a few megabytes away from the mdrl locus, but the fact that the translocation is present in all P-glycoprotein-producing MDR cell lines and a subpopulation of the 2R160 strongly suggests a causative relation. The presence of the 7q22 translocation (M6c) in only a subpopulation of the 2R160 cells is in line with an immunohistochemical staining pattern and fluorescence-activated cell sorting analysis of 2R160 cells, which revealed heterogeneity in cellular P-glycoprotein levels.

We therefore favor the hypothesis that the 7q22 translocation is causally linked to a high level of P-glycoprotein expression. Subcloning experiments and cytogenetic analysis of the 2R160 subline are currently being carried out to test this hypothesis. In situ hybridization confirmed the localization of mdrl to 7q21 (27) and provided evidence that the mdrl genes were not translocated to different chromosomes or markers in our cell lines. Only in subline 1R10000 did we observe a signal on the long complex marker of chromosome 1 (M3b; see Fig. 9, inset) in addition to the mdrl signal on chromosome 7. This confirms the finding of other investigators (32) that copies of an amplified gene may become integrated in different chromosomes.

The 1R10000 is the only subline in which the mdrl gene was amplified [4 to 5 times (16)]. Because the manifestations

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**Fig. 8. Chromosome 7 as found in the parental cell line and the marker chromosomes involving chromosome 7 present in the P-glycoprotein-mediated MDR sublines 1R500, 1R10000, and 2R160. Ideogram shows breakpoints and location of mdrl gene at 7q21.1. Marker chromosomes: M6 i(7q), M6a t(4q;7q), M6c t(7q21—cen—7qter), M6b t(7q21—cen—7qter—7q22—?), M18 del(7)(7q21—cen—7qter), M18a t(4;7)–(4qter–4ql2::7q22—cen—7qter), M18b t(7;?)(q22–?), M33 del(7)(4qter–4ql2::7q22—cen—7qter), M34 del(7)(2p7::7q22—cen—7qter), and M34 del(7)(2p7::7q22—cen—7qter).**

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p23—pter) coding for a trans-acting element that keeps the non-P-glycoprotein-mediated MDR gene in the repressed state. However, since non-P-glycoprotein-mediated MDR is apparently dominant in cell hybrids (26) the possibility of cis-activation is favored.

P-Glycoprotein-mediated MDR Sublines 1R500 and 2R160. Attainment of a higher level of resistance concomitant with P-glycoprotein-mediated MDR in the 1R500 was accompanied by additional alterations of the chromosomes 1, 3, 4, 5, and 7, the most consistent being the translocations involving chromosome 7 at band q22. In 2R160 alterations of chromosome 7 were also seen. All cells carried a marker with the breakpoint at the centromere, which was confirmed by in situ hybridization

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6 H. J. Broxterman and C. M. Kuiper, unpublished data.
of gene amplification, HSRs and DMs, were not observed in this variant line, the presence of additional copies of the gene on a different chromosome is in line with the finding of mdr1 gene amplification. Independent cytogenetic data from other human tumor cell lines will have to be collected in order to establish critical involvement of specific alterations in chromosomes 2 and 7 in the development of drug resistance. Such studies should help to assess the mode of regulation of mdr1 expression in P-glycoprotein-mediated MDR and may help to identify the gene(s) involved in non-P-glycoprotein-mediated MDR.

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REFERENCES


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