Recurrent Deletions of Specific Chromosomal Sites in 1p, 3p, 6q, and 9p in Human Malignant Mesothelioma

Takahiro Taguchi, Suresh C. Jhanwar, Jill M. Siegfried, Steven M. Keller, and Joseph R. Testa

ABSTRACT

Detailed cytogenetic analyses were carried out on primary tumor specimens and cell lines from 23 patients with pleural malignant mesothelioma (MM). Clonal abnormalities were identified in 20 of 23 MM. In 3 cases, karyotypic data were compiled from harvests of both short-term cultures (1-3 days), and primary cultures grown on murine feeder layers for several weeks. The karyotypes obtained with these 2 different culture methods were very similar, although polyploid versions of abnormal clones were found only in the long-term cultures. In addition, while short-term cultures from 9 tumor biopsies usually exhibited near-diploid clones, cell lines derived from 11 tumors tended to have higher ploidies. Each of the cytogenetically abnormal MM displayed multiple clonal alterations. The 2 most frequent changes were chromosomal losses of specific regions in 1p (17 cases) and 9p (16 cases). The shortest regions of overlap of these losses were at 1p21-p22 and 9p21-p22, respectively. Other common abnormalities included losses of 3p21 (13 cases) and 6q15-q21 (9 cases), and numerical losses of chromosomes 14, 16, 18, and 22 (each observed in 10-13 tumors). In many of the MM examined, most or all of these recurrent changes occurred in combination, suggesting the involvement of a pathogenetic cascade in this cancer. The pattern of recurrent chromosomal losses suggests that these regions represent the locations of tumor suppressor genes whose loss/inactivation may have a pivotal role in MM tumorigenesis.

INTRODUCTION

MM is a relatively rare, mesodermally derived neoplasm. Exposure to asbestos has been implicated as a major contributory factor in the development of these tumors (1). Because of the uncommon nature of this cancer and the difficulties inherent in obtaining adequate karyotypes from solid tumor tissues, the cytogenetic data base for MM is relatively sparse, especially with regard to findings in primary tumor biopsies. Complete karyotypic findings are available on approximately 100 previously reported MM biopsy specimens, effusions, and cell lines (2-12). Among these, clonal chromosomal alterations have been identified in 80 cases. These investigations have revealed complex and heterogeneous chromosomal abnormalities in tumor cells from most MM patients, complicating efforts to identify consistent, potentially critical sites of chromosomal change.

Here we present detailed cytogenetic analyses of 12 tumor biopsies and 11 new cell lines from 23 patients with primary MM. Twenty cases displayed clonal chromosomal alterations. This study reveals recurrent losses of multiple chromosomes, particularly 1p and 9p, in MM. We delineate specific regions in 1p, 3p, 6q, and 9p that may play a pivotal role in the pathogenesis of this neoplasm.

MATERIALS AND METHODS

Tumor Specimens. Karyotypic analysis was performed on 12 fresh primary tumor specimens and 11 tumor cell lines obtained from 4 female and 19 male MM patients; ages ranged from 43 to 81 years. Informed consent was obtained from each subject. Karyotypes of 5 of these tumors, 4 of which showed clonal abnormalities, have been described in a previous report (8).

Conventional Harvests. Tumor biopsies were disaggregated mechanically by mincing the tissue with scalpsels, and enzymatically by shaking gently in collagenase A (2 mg/ml; Boehringer Mannheim, Indianapolis, IN) for 2-16 h at 37°C. Cell suspensions were cultured in RPMI 1640 (Gibco, Gaithersburg, MD) containing 15% FBS plus antibiotics. In most cases, an insulin (5 μg/ml)/transferrin (5 μg/ml)/sodium selenite (5 ng/ml) supplement (Sigma, St. Louis, MO) and sodium pyruvate (1 mm; Gibco) were added to the medium. Cells were cultured at 37°C in 5% CO2.

Feeder Cell Cultures. Three tumor biopsies (cases 5, 6, and 8) were also grown on feeder layers of Swiss 3T3 murine fibroblasts inactivated by treatment with mitomycin C. Tumor resections were minced with scalpsels, and fragments of tissue were then triturated in a 10-mm pipet and plated directly onto inactivated feeder layer cells in 50% Ham's F-12 medium (Gibco) containing 1% FBS/50% basal Eagle's medium (Gibco) containing 1% FBS, which was conditioned for 48 h by the lung carcinoma cell line A549-1 (13).

Cell Lines. The mesothelial cell lines were established from surgically explanted primary MM. The methods for establishing these cell lines have been described (14).

Chromosome Banding and Cytogenetic Analysis. Actively growing cells were harvested for cytogenetics according to our usual procedures (8, 13). Fixation and G-banding of chromosomes were performed by standard methods (15). In most cases, chromosome counts were obtained from at least 20 metaphase spreads. For each tumor, at least 5 karyotypes per culture method. Chromosome identification and karyotypic designations were in accordance with the International System for Human Cytogenetic Nomenclature (16).

RESULTS

Clonal karyotypic abnormalities were detected in 20 cases. One of the 3 remaining patients had received extensive prior cytotoxic therapy, and karyotypic analysis revealed several nonclonal chromosomal abnormalities. Only normal metaphase spreads were found in cultures from 2 patients; these normal karyotypes presumably are not from tumor cells but, instead, may be representative of reactive mesothelial cells, fibroblasts, macrophages, and other inflammatory cells (10).

Clinical findings in the 23 MM are summarized in Table 1, and cytogenetic data are presented in Table 2. Nineteen of 20 karyotypically abnormal cases displayed more than 10 clonal chromosomal alterations. One case had a relatively simple karyotype with 3 chromosomal abnormalities: del(1)(p13p22 or p21), del(3)(p21p22), and -22. Among the entire 20 cytogenetically abnormal cases, the total number of different structural and numerical changes ranged from 3 to 57/tumor (median number of changes, 27). Karyotypic heterogeneity within individual MM was a common occurrence. The modal chromosome number was near-diploid in 13 cases, near-triploid in 4 cases, near-tetraploid in 2 cases, and near-hexaploid in one case. The incidence of near-diploid karyotypes in short-term cultures of cytogenetically abnormal tumor biopsy specimens (8 of 9 cases) differed from

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3The abbreviations used are: MM, malignant mesothelioma; FBS, fetal bovine serum; SRO, shortest region of overlap; NF2, neurofibromatosis 2.
that observed in cell lines (5 of 11) (P = 0.07, using a 2-tailed Fisher’s exact test). Six cell lines had higher ploidy levels (near-triploidy to near-hexaploidy). In addition, the total number of different structural and numerical alterations was somewhat higher in cell lines than in short-term cultures (median, 32 in cell lines versus 26 in short-term cultures).

In our 3 specimens for which cytogenetic analysis was performed on both conventional short-term cultures and tumor cells grown on murine feeder layers, the karyotypes obtained with the 2 different culture methods were generally very similar (Table 2). Minor numerical and structural differences were observed in each case. In cases 5 and 6, a polyploid (near-tetraploid) version of the abnormal clone (i.e., idemx2) was found in some tumor cells grown on feeder layers but in none of the karyotypes from the respective short-term culture.

All chromosomes contributed to numerical changes (Fig. 1). Numerical losses were more common than gains. Loss of chromosome 22 was the most common numerical abnormality (13 cases). Losses of chromosomes 14, 16, and 18 also were common, each occurring in 10–12 tumors. The chromosomes most frequently involved in numerical gains were numbers 6, 7, 11, 12, 17, and 21, each identified in 4–6 cases.

All chromosomes except the Y participated in structural changes. Chromosomes frequently involved in structural alterations included numbers 1 (19 cases), 3 (18 cases), and 9 (15 cases); and these frequently coexisted within the same tumor (Figs. 2 and 3). Rearrangements of chromosomes 5, 6, and 7 also were common (each present in 10 of 20 abnormal cases). Breakpoints involved in clonal rearrangements are indicated in Fig. 4. The breakpoints clustered at proximal 1p (16 cases), 3p (14 cases, including one case with an isochromosome of the long arm), proximal 3q (10 cases), and 9p (12 cases). The most frequent sites of breakage were at bands 1p13, 1p22, 3p13, and 9p13 (each in 6–10 cases).

Abnormalities of chromosome 1 were identified in all 20 cytogenetically abnormal MM. In one case, the only alteration of chromosome 1 was a numerical loss. Structural rearrangements of chromosome 1 were identified in 19 MM, some of which also exhibited numerical changes of this chromosome. The rearrangements involved 1p in 17 cases and 1q in 9 cases. Interstitial or terminal deletions of 1p were found in 10 MM, 5 of which also had one or more other rearrangements of chromosome 1. The SRO of deletions of 1p is located at 1p21-p22 (Fig. 5). Seven other MM had derivative chromosomes that appeared to result in partial losses of 1p, 6 of which involved the region 1p21-p22. The exception was case 15, in which the missing segment was confined to 1p34-3pter.

Abnormalities of chromosome 3 were identified in 19 specimens. Among 18 cases with structural changes of this chromosome, 6 had alterations of 3p, 4 had rearrangements of 3q, and 8 had rearrangements of both 3p and 3q. Interstitial or terminal deletions of 3p were found in 6 cases; the SRO of deletions of 3p is located at 3p21 (Fig. 5). Seven other MM had derivative chromosomes or, in one case, an i(3)(q10), which appeared to result in losses of 3p, including band 3p21. Nine cases had alterations that may have resulted in partial losses of 3q. One of these tumors had an interstitial deletion of 3q13.2-q21; the other 8 cases had derivative chromosomes, 6 of which showed a common loss of 3q13-q21, and 2 of which had losses of 3q25-qter.

Losses involving chromosome 6 also were common in this series (10 cases). One case appeared to be missing both copies of chromosome 6. Nine cases had structural changes that resulted in partial losses of 6q. Eight of the latter displayed a common region of chromosomal loss involving 6q15-q21; the remaining case had a derivative chromosome with a breakpoint at 6q25. Five of the 8 cases with structural losses of 6q15-q21 had an interstitial or terminal deletion (Fig. 5). 2 had unbalanced derivative chromosomes resulting in partial loss of 6q, and one had both a 6q deletion and 2 copies of a der(6).

Various types of loss involving chromosome 9 were found in 16 MM. Two cases displayed numerical losses of chromosome 9, and 14 others had structural changes that resulted in partial losses of 9p (6 of the latter cases also had numerical losses of chromosome 9). Four cases had interstitial or terminal deletions of 9p, 8 had unbalanced derivative chromosomes resulting in partial loss of 9p, and 2 had both a 9p deletion and a der(9) showing partial loss of 9p. A near-diploid case had a dic(9;22)(p13;p17) as well as 2 apparently normal copies of chromosome 9. Thus, in this case there was a net gain of 9p13-qter. The SRO of deletions is located at 9p21-p22 (Fig. 5). Each of the der(9) had breakpoints at 9p11-p13 and, thus, also appeared to have losses of 9p21-p22.

Table 1 Clinical data on 23 patients with malignant mesothelioma
Table 2  

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Culture duration (days or passage no.)</th>
<th>Clonal abnormal karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>32-45.5Y,del(1)(p13q22) or p21),del(3)(p12p21q75),-22[cp4]/46.XY[X2]</td>
</tr>
<tr>
<td>2</td>
<td>1.2,3</td>
<td>41-44.X,add(1p13q11),dup(2q)(q31q33),del(2q)(p21q),add(3p)(p13q17),add(7q)(q34),-9,del(9q)(p21q),idic(13p)(q17),add(17p)(p11),-18,-19,-20,-22,del(22q)(p11),-5,mar[p9]</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>35-46,Y,add(7q)(q34),del(1p12p13q11),+45del(1)(p13q17),idic(13p)(q17),add(17p)(p11),-18,-19,-20,-22,del(22q)(p11),-5,mar[p9]</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>44-46.X,47(Y),add(1p13q11),+5,mar[p3]/88,ider(21)(q14q21Y)</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>36-45,X,der(1p12p13q11),+5,mar[p3]/88,ider(21)(q14q21Y)</td>
</tr>
<tr>
<td>p. 1</td>
<td>[Feeder layer karyotype showed the differences of: absence of der(?)(7q3), add(13), and no loss of chromosome 15. Also, feeder layer culture had 84-88, ide(2)Y(19)]</td>
<td></td>
</tr>
<tr>
<td>1.2,3</td>
<td>46-47,Y,add(1p13q11),+5,mar[p3]/88,ider(21)(q14q21Y)</td>
<td></td>
</tr>
<tr>
<td>p. 1</td>
<td>(One karyotyped metaphase from feeding layer culture was nearly identical to that shown above. With 86-98, ide(2)Y(19)]</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>43-56,Y,67(X),+5,mar[p3]/88,ider(21)(q14q21Y)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>42-47,X,del(1p13q11),-12,add(12)(q21q23),+9,add(13)(p13q14q22),+12,del(13q)(p11q13),+14-15,add(14)(p12q13),-16,17,18,19,20,21,22</td>
</tr>
<tr>
<td>p. 60</td>
<td>[Feeder layer culture showed the following differences: loss of 3, no loss of chromosome 4, gains of 9 and mar4]</td>
<td></td>
</tr>
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<td>40</td>
<td>57-79,3n:XY,−X,−1,+5,der(7q)(p13q13),-8,-9,10,-11,+12,+12,der(12q)(p13q13),-13,der(13q)(p11q13),+14,add(14q1p11),-15,add(15q)(p15q15),-16,17,18,19,20,21,22</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>78-85,3n:XY,−X,−1,+5,der(7q)(p13q13),-8,-9,10,-11,+12,+12,der(12q)(p13q13),-13,der(13q)(p11q13),+14,add(14q1p11),-15,add(15q)(p15q15),-16,17,18,19,20,21,22</td>
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<td>73</td>
<td>68-80,3n:XY,−X,−1,+5,der(7q)(p13q13),-8,-9,10,-11,+12,+12,der(12q)(p13p13),+14,add(14q1p11),-15,add(15q)(p15q15),-16,17,18,19,20,21,22</td>
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<tr>
<td>40</td>
<td>66-58,3n:XY,−X,−1,+5,der(7q)(p13q13),-8,-9,10,-11,+12,+12,der(12q)(p13q13),+14,add(14q1p11),-15,add(15q)(p15q15),-16,17,18,19,20,21,22</td>
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<td>49</td>
<td>39-45,3n:XY,−X,−1,+5,der(7q)(p13q13),-8,-9,10,-11,+12,+12,der(12q)(p13q13),+14,add(14q1p11),-15,add(15q)(p15q15),-16,17,18,19,20,21,22</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>122-140,3n:XY,−X,−1,+5,der(7q)(p13q13),-8,-9,10,-11,+12,+12,der(12q)(p13q13),+14,add(14q1p11),-15,add(15q)(p15q15),-16,17,18,19,20,21,22</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>39-41,3n:XY,−X,−1,+5,der(7q)(p13q13),-8,-9,10,-11,+12,+12,der(12q)(p13q13),+14,add(14q1p11),-15,add(15q)(p15q15),-16,17,18,19,20,21,22</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>67-78,3n:XY,−X,−1,+5,der(7q)(p13q13),-8,-9,10,-11,+12,+12,der(12q)(p13q13),+14,add(14q1p11),-15,add(15q)(p15q15),-16,17,18,19,20,21,22</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>69-84,3n:XY,−X,−1,+5,der(7q)(p13q13),-8,-9,10,-11,+12,+12,der(12q)(p13q13),+14,add(14q1p11),-15,add(15q)(p15q15),-16,17,18,19,20,21,22</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>35-44,3n:XY,−X,−1,+5,der(7q)(p13q13),-8,-9,10,-11,+12,+12,der(12q)(p13q13),+14,add(14q1p11),-15,add(15q)(p15q15),-16,17,18,19,20,21,22</td>
<td></td>
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<tr>
<td>23</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>None</td>
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</table>
Fig. 1. Distribution of clonal numerical abnormalities in 20 cytogenetically abnormal MM from this series. Gains (gray bars) and losses (black bars) of whole chromosomes 1–22, X, and Y are indicated. Changes seen in feeder layer cultures but not in short-term conventional harvests are not included.

DISCUSSION

While occasional MM may display a few (7, 8) or even a single cytogenetic change (11, 12), the vast majority of such tumors have complex karyotypes with multiple numerical and structural abnormalities (2–10). No single specific cytogenetic alteration is common to all of our 20 cytogenetically abnormal MM. However, several recurrent changes were found, particularly losses or structural rearrangements of 1p, 3p, 9p, and 22. A comparison of the findings in our series with those in previous reports reveals some similarities and some differences in the profile of karyotypic changes in MM. For example, one report described nonrandom losses of 3p, 6q, 9p, and 22 in a series of MM (10). Structural alterations of 1p and 1q were frequently observed in that study; however, since both homologues were often rearranged and sometimes were present in 2 or more copies, no clear picture emerged regarding partial loss or gain of chromosome 1 material (10). In addition, loss of chromosome 4 was a nonrandom change in that series of MM, but this abnormality was observed in only 4 of our 20 cases. Another investigation of MM revealed recurrent losses (total or partial) of 1p, 3p, 9p, 14, and 22, in agreement with our data, as well as nonrandom loss of chromosome 4 and nonrandom gains of chromosomes 7 and 11 (7), which were less prominent in our series. In addition to possible differences in the interpretation of karyotypes and in data analysis, the discrepancies among reports could reflect dissimilarities in the type and level of exposure to asbestos fibers (7) or genetic differences in the study populations. For example, it has been suggested that chromosomal

Fig. 2. Karyotype of a Giemsa-banded metaphase spread from a near-diploid MM cell line (case 10) showing interstitial deletions of 1p and 3p, 2 different unbalanced rearrangements of 9p, monosomy 22, and several other numerical and structural alterations. Arrows, rearranged chromosomes.
fragile sites could be individually and geographically different and may be responsible for some of the cytogenetic differences reported in MM (10).

Losses of 1p21-p22 due to numerical loss, deletions, or other unbalanced rearrangements were found in 17 of our 20 (85%) cytogenetically abnormal tumors. In a previous report, we noted that loss of this region is a recurrent change in MM (8). Such losses were identified in each of 4 cytogenetically abnormal cases examined in that small series. Other investigators have also observed frequent alterations of chromosome 1, particularly of 1p, in MM (3, 5, 7, 10, 17, 18). Deletions and translocations at 1p13-p22 have also been observed in malignant melanoma, malignant lymphoma, adenocarcinoma of the breast, and leiomyosarcoma of the intestine (19). As in MM, however, such alterations of 1p are found in combination with other abnormalities in these cancers. An early report suggested that abnormalities of chromosome 1 were generally dissimilar in MM and proposed that such rearrangements may be nonspecific, secondary changes associated with karyotypic evolution of malignant cells (3). However, the high incidence of loss of 1p seen in our series suggests that this change represents an important event in the progression of MM. Moreover, the SRO of 1p deletions is at 1p21-p22, and several of our tumors displayed relatively small interstitial deletions overlapping this region, including 5 cases with a del(1)(p13p22) (Table 2; Fig. 5). This evidence suggests that the segment 1p21-p22 is the site of a putative tumor suppressor gene important in mesothelial cell tumorigenesis.

Deletions and other rearrangements of 3p have often been reported in MM tumor specimens and cell lines (3-8, 10, 17, 18). In our series, the SRO of chromosomal loss in 3p appears to reside at 3p21 (Fig. 5). Similarly, the SRO of chromosomal loss in our previous investigations on non-small cell lung cancer was at 3p21 (20), and frequent allelic loss at this same band has been reported in all major types of lung cancer (21, 22). Deletion of 3p14-p23 was first reported as a consis-

Fig. 3. Karyotype of a Giemsa-banded metaphase spread from a fresh MM tumor biopsy specimen (case K) displaying several alterations of chromosome 1 (see Table 2), including a der(1)del(1)(p21p31)(1;21q21q21), and a der(9)-t(3;9)(p11p13). There are also several other structural and numerical changes, including losses of chromosomes 14, 16, and 22, each of which was frequently observed in this series. Arrows, rearranged chromosomes.

Fig. 4. Idiogram depicting breakpoints (•) of clonal chromosomal rearrangements seen in 20 MM. Changes seen in feeder layer cultures but not in short-term cultures are not included. Whenever a single case had 2 or more rearrangements with breaks at identical bands, only one of these breakpoints is depicted.
tent chromosomal aberration in small cell lung cancer (23). More recently, recurrent deletions of 3p have been observed in a number of other cancers, including renal cell carcinoma, breast cancer, ovarian cancer, and malignant lymphoma (19). Consequently, it has been suggested that loss of 3p may represent an important generalized tumorigenic event common to various neoplasms, including MM (5).

Loss of 9p was the second most frequent change observed in this series. Sixteen of 20 cases (80%) displayed losses due to numerical or structural changes, and the SRO of deletions is at 9p21-p22 (Fig. 5). Two other reports have also described frequent loss of chromosome 9, particularly 9p, in MM (7, 10). Deletions of the interferon loci at 9p21-p22 have been reported in malignant melanomas (24), acute lymphoblastic leukemias (25), and glial tumors (26). The data presented here provide further evidence that this chromosomal region is involved in cancers of various origins, implicating a common pathogenetic mechanism, namely tumor suppression, by a gene(s) on 9p in the vicinity of the interferon loci. Recently, investigators have identified the SRO of 9p chromosomal losses in acute lymphoblastic leukemia and malignant melanoma (27, 28). This 2-3-megabase region at 9p21 is proximal to the interferon loci, indicating that the interferon genes are not directly involved. We and others are using molecular approaches to further delineate this critical deleted region and are attempting to isolate a putative tumor suppressor gene(s) involved in MM and other cancers.

Monosomy 22 was the single most consistent numerical change observed in this study (Fig. 1). In a previous review of other reports of cytogenetic changes in MM, loss of chromosome 22 was seen in 11 of 28 patients examined cytogenetically, and 22q has been proposed as a possible site of a tumor suppressor gene important in this neoplasm (8). Loss of chromosome 22 has also been reported as a recurrent abnormality in meningeoma and rhabdoid brain tumors (29). Furthermore, loss of heterozygosity studies have demonstrated allelic losses of 22q at the location of the NF2 locus in acoustic neuroma (30, 31), and a candidate gene for the NF2 tumor suppressor has been identified that was altered in 2 independent NF2 families and in meningiomas from 2 unrelated NF2 patients (32).

In addition to the frequent changes described above, losses of the region 6q15-q21 were found in 9 of our tumors. Other investigators have also reported abnormalities of chromosome 6, particularly 6q, in MM (3–6, 10). Furthermore, a derivative chromosome 6, leading to loss of the segment 6q15-q24, was the sole chromosomal anomaly observed in one MM specimen, suggesting that 6q- may be a primary cytogenetic change in some MM (12).

Ploidy differences were noted between those tumors for which short-term cultures were examined and those for which the analysis was performed on cell lines. Eight of 9 specimens examined by a short-term culture method had near-diploid karyotypes, compared to 5 of 11 cell lines. These data and the findings in the 3 specimens examined by both short-term conventional culture and long-term feeder layer culture methods indicate a tendency toward higher ploidy levels in MM cells grown in vitro for extended periods. A previous investigation of cell lines derived from 3 MM specimens revealed that the karyotype of each cell line was similar to that of the tumor cells obtained directly from each patient (17). However, one of the tumor biopsies had a near-triploid karyotype, whereas most of the effusion cells from this patient and all of the cells from a cell line derived from the biopsy had a near-hexaploid karyotype. Taken together, these data and our findings indicate that the chromosomal alterations found in short-term cultures generally are conserved in MM cell lines, regardless of the ploidy. Thus, such cell lines represent valuable models for molecular investigations of MM.

The high frequency of specific chromosomal losses in MM suggests a recessive mechanism for oncogenesis (33, 34) in this cancer. In many MM, most or all of the recurrent changes described above (i.e., losses of 1p, 3p, 6q, 9p, and 22) occur in combination (Figs. 2 and 3; Table 2). All 5 of these abnormalities were found in 5 of our MM. Losses of 1p, 3p, 9p, and 22 coexisted in another 3 cases, and various combinations of 3 of these 4 abnormalities were seen in 7 others. Thus, the accumulated losses of critical segments of 1p, 3p, 6q, 9p, and 22, carrying wild-type alleles of putative tumor suppressor gene(s), may be critical genetic changes in the initiation or progression of MM. Presumably, some of these changes represent secondary events associated with tumor progression, because losses of chromosomes 1, 3, 6, 9, and 22 each have been reported to be nonrandomly involved in several different cancers (29, 35). Other, less consistent alterations, such as losses of chromosomes 3q, 14, 16, and 18, may represent late changes. This pattern of recurrent losses of several chromosomal regions in MM could be consistent with a multistep pathogenetic process, which has been well-documented in colorectal cancer (36). A similar cascade scheme has been proposed to be involved in the genesis of MM (12). Although the available cytogenetic data strongly support the view that specific chromosomal losses play a pivotal role in the development and progression of MM, extensive research at the molecular level will be required to elucidate the genetic implications of these deletions.

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