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CONSTRUCTION OF RADIATION-REDUCED HYBRIDS AND THEIR USE IN MAPPING OF MICROCLONES FROM CHROMOSOME 10p11.2-q11.2

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Summary Radiation-reduced hybrids for mapping of DNA markers in the pericentromeric region of chromosome 10 were developed. A Chinese hamster/human somatic cell hybrid (762-8A) carrying chromosomes 10 and Y as the only human material were exposed to 40,000 rads of irradiation and then rescued by fusion with non-irradiated recipient Chinese hamster cells (GM459). Southern hybridization analyses revealed that 10 of 128 HAT-resistant clones contained human chromosomal fragments corresponding to at least one marker locus between *FNRB* (10p-11.2) and *RBP3* (10q11.2). These hybrids were then used to map microdissection clones previously isolated and roughly mapped to this chromosomal region by fluorescence *in situ* hybridization (FISH). Two of the six microclones studied could be mapped to the proximity of the D10-S102 locus. These radiation hybrids are useful for the construction of refined genetic maps of the pericentromeric region of chromosome 10.

Key Words radiation-reduced hybrid, microdissection clone, gene mapping, multiple endocrine neoplasia type 2 (MEN 2)

INTRODUCTION

Somatic cell hybrids generated by means of irradiation and fusion techniques have been successfully used for high-resolution genetic mapping and as resources for isolating DNA fragments from defined chromosomal regions. In this tech-

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nique, lethally irradiated cells are rescued by fusion with non-irradiated recipient cells, resulting in the generation of hybrid cells containing chromosomal fragments derived from the specific region of interest. The radiation hybrid mapping was first introduced by Goss and Harris (1975) and applied by Cox *et al.* (1990) to the construction of a high-resolution map of the proximal 20 Mb of the long arm of human chromosome 21. Combined with meiotic mapping and pulsed-field gel electrophoresis (PFGE) analysis, this mapping procedure constitutes a powerful method for the construction of refined genetic maps of human genomes (Bishop and Crockford, 1992). In addition, the obtained hybrids containing chromosomal fragments from selected regions of human genomes can be used as a DNA source for the construction of a region specific genomic library.

Multiple endocrine neoplasia type 2A (MEN 2A) is a familial cancer syndrome, involving medullary thyroid carcinoma (MTC), adrenal gland pheochromocytoma, and parathyroid hyperplastic lesions, which is inherited as an autosomal dominant trait. Linkage studies have placed the gene responsible for MEN 2A at the pericentromeric region of chromosome 10 (Mathew *et al.*, 1987; Simpson *et al.*, 1987). Genes for two related disorders, multiple endocrine neoplasia type 2B (MEN 2B) and familial medullary thyroid carcinoma (MTC1), have also been mapped to the pericentromeric region of the chromosome (Norum *et al.*, 1990; Lairmore *et al.*, 1991). Extensive studies have been carried out to identify genetic alterations related to these hereditary syndromes. These studies include fine scale linkage and physical mapping (Bowden *et al.*, 1989; Lichter *et al.*, 1992; Mathew *et al.*, 1987; Miller *et al.*, 1992; Nakamura *et al.*, 1989; Simpson *et al.*, 1987; Wu *et al.*, 1990; McDonald *et al.*, 1992), isolation of YAC clones (Lairmore *et al.*, 1992, 1993), and identification of several expressed genes (Brooks *et al.*, 1992a; Rousseau *et al.*, 1992).

Recently we isolated microclones from the pericentromeric region of chromosome 10 by microdissection of 10q11.1-q21.1 (Karakawa *et al.*, 1993). Some of the microclones were expanded into cosmid-sized inserts and mapped to the pericentromeric region of the chromosome by fluorescence *in situ* hybridization (FISH). In order to map these microclones more finely and to obtain DNA resources for construction of a region-specific genomic library, we have constructed radiation-reduced hybrids and successfully mapped two microclones to the proximity of the D10S102 locus.

MATERIALS AND METHODS

Cell lines. Two cell lines, 762-8A and GM459, were used. Cell line 762-8A, which was kindly donated by Dr. Carol Jones, contains chromosome 10 and Y as its only human component in a Chinese hamster genomic background (Fisher *et al.*, 1987). GM459 is a near-diploid Chinese hamster cell line deficient in hypoxanthine-guanine phosphoribosyl-transferase (HPRT) activity obtained from the NIGMS Human Cell Repository (Camden, NJ). The 762-8A cells were kept in

Ham's F-12 medium and GM459 cells in Dulbecco's modified Eagle's medium (DMEM), both supplemented with 10% fetal bovine serum, 100 U/ml penicillin, and 100 μg/ml streptomycin.

Production of radiation hybrids. 762-8A cells (10 ml, approximately 2×10^7 cells) were exposed to 40,000 rads of irradiation with a Rigaku RF-350 X-ray unit (180 keV, 15 mA) at a rate of 510 rads/min. Following irradiation, 5 ml of irradiated 762-8A cells (approximately 10^7 cells) was immediately added to 5 ml of unirradiated GM459 cells (approximately 10^7 cells), mixed, and centrifuged at 1,000 rpm for 4 min. These two kinds of cells were fused with the aid of polyethylene glycol or Hemagglutinating virus of Japan (HVJ). During cell fusion with polyethylene glycol, 0.5 ml of 50% polyethylene glycol 1000 (w/v) was added to the cell pellet with gentle mixing. The cells were then incubated in a 37°C water bath for 60 min. During fusion with HVJ, the cell pellet was suspended in 0.5 ml BSS (balanced salt solution; 140 mM NaCl, 5.4 mM KCl, 10 mM Tris-HCl, pH 7.6) containing 1 mM $CaCl_2$. The cell suspension was mixed with 0.5 ml of HVJ (1,000 HAU/0.5 ml), kept at 4°C for 5 min and then incubated in a 37°C water bath for 30 min while being shaken. Both of the fusion mixtures were centrifuged and re-suspended in 20 ml of DMEM containing 10% FBS. The cell suspension was then added to 100 mm plastic tissue culture dishes (20 in total), kept in DMEM for 24 h. The supernatant was replaced with the HAT medium (DMEM plus 100 mM hypoxanthine, 12 mM thymidine, and 1 mM aminopterin), which was subsequently changed every three days. HAT resistant colonies appeared in two to three weeks and were cloned into 100 mm dishes. Under HAT selection, a single colony was picked, replated, and grown for isolation of DNA.

Southern blot analysis. High molecular weight DNAs (10 μg) extracted from each of the hybrids, their parental cell lines and a human lymphoblastoid cell line with normal karyotype were completely digested with *Eco*RI, electrophoresed through 0.8% agarose gel, and then blotted onto nylon membranes (Pall BioSupport). The membranes were hybridized with DNA probes labeled with [α-^{32}P]-dCTP by means of the random hexanucleotide-priming method (Feinberg and Vogelstein, 1984). Hybridization was performed overnight at 65°C in a solution containing 10% SDS, 7% polyethylene glycol 8000, and 200 μg/ml of human placental DNA.

Hybridizing probes. DNA markers used for characterization of the hybrid cells are listed in Table 1. For the D10S34 locus, a 4.0 kb *Eco*RI-subfragment of cTBQ14.34 was used as a hybridization probe. A cosmid clone, c710, corresponding to the D10S94 locus, was obtained by screening of a genomic cosmid library probed with the PCR product containing the *Msp*I polymorphic site (Brooks *et al.*, 1992b). The order of the 7 loci has been determined by meiotic and YAC physical mapping (Miller *et al.*, 1992; Lairmore *et al.*, 1993; Mole *et al.*, 1993).

Mapping of microclones. Recently we obtained six microclones by microdissection of human chromosome 10q11.1-q21.1, which were mapped to the peri-

Table 1. DNA probes used for characterization of radiation hybrids.

Locus	Clone	Localization	Reference
FNRB	pGEM-32	10p11.2	Wu *et al.*, 1989
D10S34	cTBQ14.34[a]	10p13-cen	Nakamura *et al.*, 1988
D10Z1	pA10RP8	10cen	Devilee *et al.*, 1988
RET	pN6SB	10q11.2	Ishizaka *et al.*, 1989
D10S94	c710[b]	10cen-q11.2	Goodfellow *et al.*, 1990b
D10S102	cMEN203W1T1	10q11.2	Mathew *et al.*, 1991
RBP3	pH.4IRBP	10q11.2	Liou *et al.*, 1987

[a] A 4.0 kb *Eco*RI subfragment of D10S34 was used. [b] A 3.0 kb *Eco*RI subfragment of D10S94 was used.

centromeric region of the chromosome by FISH (Karakawa *et al.*, 1993). These six microclones were individually hybridized to the 10 radiation hybrids under the same stringent conditions as described above.

Pulsed-field gel electrophoresis (PFGE). Agarose blocks containing high molecular weight DNA were prepared according to the method described by Chu *et al.* (1986). DNAs in agarose blocks were completely digested with six rare-cutting enzymes (*Bss*HII, *Ksp*I, *Mlu*I, *Not*I, *Sal*I, and *Sfi*I). Pulsed-field gel electrophoresis was performed on a transverse alternating field electrophoresis (TAFE) system (Beckman, Gene Line II).

RESULTS

A total of 128 hybrids fused with PEG 1000 or HVJ were obtained. The DNAs from these hybrids were hybridized with a series consisting of the seven markers previously mapped to the pericentromeric region of chromosome 10 to test for the presence or absence of the marker loci within the pericentromeric region of chromosome 10. As a result, 10 of the 128 hybrids proved to contain at least one marker locus. A representative autoradiogram of Southern hybridization is shown in Fig. 1 and characteristics of the 10 hybrids are schematically shown in Fig. 2A. During hybridization with pH.4IRBP (*RBP3*) and pGEM-32 (*FNRB*), cross-hybridizing signals were observed in the hamster DNAs, which could, however, be easily distinguished from the human specific signals by the difference in size.

Six microclones were individually hybridized to the 10 radiation-reduced hybrids. As shown in Fig. 2B, the hybridization patterns of m135 and m149-2 are identical to that of D10S102 locus, suggesting that these two microclones are located near the D10S102 locus. Moreover, m135 and m149-2 showed identical restriction patterns to those of cMEN203W1T1 in PFGE analysis (data not shown).

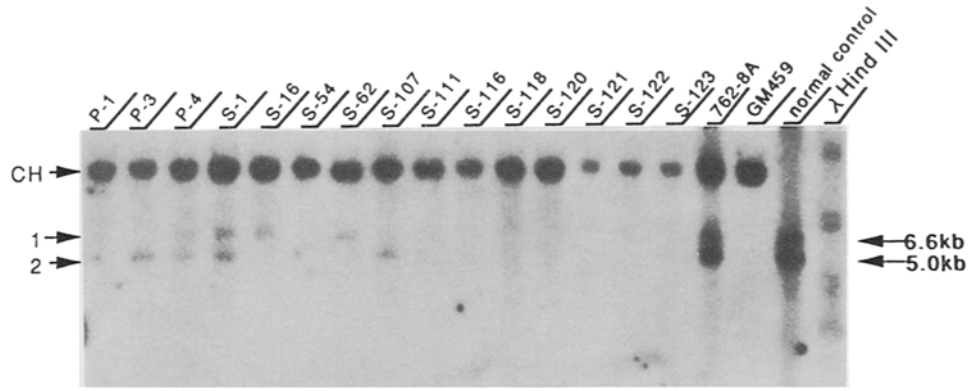

Fig. 1. Autoradiogram of Southern blot analysis of radiation hybrids. The DNA (10 μg) of each hybrid cell was digested with *Eco*RI. Arrows 1 and 2 on the left indicate signals corresponding to the *RBP3* and *RET* loci, respectively. Arrow CH indicates cross-hybridizing hamster bands detected by the pH.4IRBP probe (*RBP3*). Three hybrid cells (P1–P4) are hybrids fused with polyethylene glycol and the remaining 12 hybrids (S1–S123) with the Sendai virus (Hemagglutinating virus of Japan). The sizes of the *Eco*RI bands are indicated on the right.

DISCUSSION

Irradiation-reduced hybrids for gene mapping were first developed by Goss and Harris (1975) using selection for the HPRT gene on the distal part of Xq. This procedure has been employed with modifications to produce cell lines useful for mapping genes on various human chromosomes such as chromosome 3 (Siden *et al.*, 1992; Tamari *et al.*, 1992), 4 (Cox *et al.*, 1989; Doucette *et al.*, 1991; Altherr *et al.*, 1992), 5 (Warrington *et al.*, 1991), 6 (Ragoussis *et al.*, 1991; Zoghbi *et al.*, 1991), 9 (Jackson *et al.*, 1992), 10 (Goodfellow *et al.*, 1990a; Rothschild *et al.*, 1992), 11 (Glaser *et al.*, 1990; Richard *et al.*, 1991), 16 (Ceccherini *et al.*, 1992), 21 (Graw *et al.*, 1988; Burmeister *et al.*, 1991; Boehnke, 1992), 22 (Frazer *et al.*, 1992), and X (Benham *et al.*, 1989; Benham and Rowe, 1992). Linkage analyses have been performed so far mainly for the mapping of DNA markers flanking the loci of specific hereditary diseases (Bowden *et al.*, 1989; Lichter *et al.*, 1992; Mathew *et al.*, 1987; Miller *et al.*, 1992; Nakamura *et al.*, 1989; Simpson *et al.*, 1987; Wu *et al.*, 1990). When localization of the gene responsible for a certain hereditary disease is narrowed down to within a small region, fine mapping of flanking markers is required. In such instances, mapping by linkage analysis requires much time and effort to analyze a large number of meiosis in reference families. Moreover, ordering the flanking markers cannot be achieved when the recombination fraction (θ) is zero. Even in such instances, however, the resolution of closely linked markers could be enhanced by using radiation hybrids constructed with a high dose of irradiation. Another advantage of radiation hybrid mapping is that newly isolated

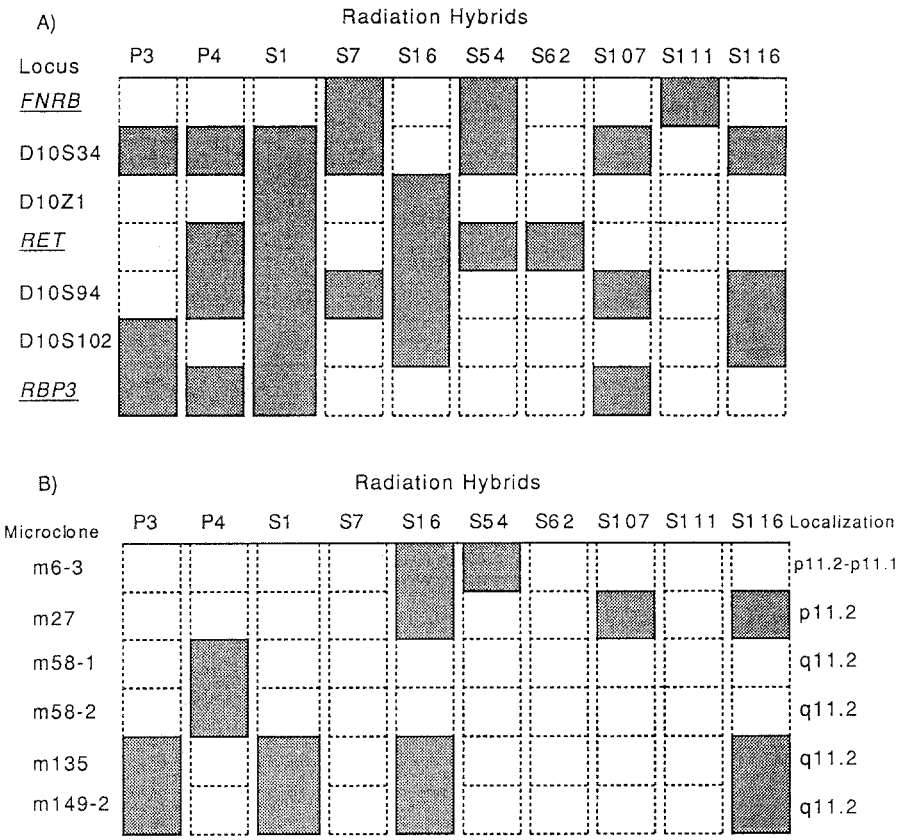

Fig. 2. Schematic representation of Southern blot analysis of radiation hybrids. Probes corresponding to the seven loci that had been previously localized in the pericentromeric region of chromosome 10 were used for characterization of the hybrids (A). Microclones mapped by FISH to the chromosomal region were used as probes (B). Presence (▒) or absence (□) of the corresponding signals is also shown.

genes or DNA fragments can be placed on the radiation hybrid panel without the need to develop polymorphisms.

For the high-resolution mapping of the pericentromeric region of chromosome 10, we adopted a relatively high dose of irradiation (40,000 rads). As a result, we obtained 10 radiation hybrids which contain chromosomal fragments corresponding to at least one marker locus within the chromosomal region. These radiation hybrids were then used for mapping of microclones of which the corresponding cosmids had been roughly localized by FISH to the chromosomal region. As a rule, microclones obtained by microdissection cannot be easily mapped by linkage analysis or FISH, for which corresponding larger genomic fragments are often required. However, once radiation hybrid mapping panels have been con-

structed, these microclones can be mapped more easily and rapidly. Two of the six microclones could be mapped near the D10S102 locus, but the remaining four microclones could not be localized with our mapping panel. One of the reasons may be that these microclones are located outside the chromosomal region between *FNRB* and *RBP3*. Alternatively, a certain proportion of the pericentromeric region of the chromosome might not be included in these 10 radiation hybrids.

In addition to their usefulness for high-resolution mapping, radiation hybrids are valuable for isolation of DNA fragments from specific chromosomal regions of interest. One of the hybrids obtained in this study, S16, which contains chromosomal fragment from between the D10Z1 and D10S102 loci, could be used to isolate DNA fragments from the proximal portion of the long arm of chromosome 10, in which gene(s) responsible for MEN 2A, MEN 2B, and MTC1 are thought to reside. Thus, the 10 radiation hybrids constructed by us and the two microclones regionally assigned to the proximity of the D10S201 will be useful for the construction of continuous physical maps of the pericentromeric region of chromosome 10.

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