POSSIBLE LOCATION OF THE GENE OF HUMAN CELL SENSITIVITY TO COXSACKIE B VIRUS IN THE SHORT ARM OF CHROMOSOME 21

A. M. Amchenkova, A. N. Narovlyanskii, N. E. Gulevich, and Ya. E. Khesin

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Antiviral resistance may ultimately depend on the expression of genes determining the sensitivity of human cells to a particular virus. Genes of human cell sensitivity to several viruses have now been mapped: genes of sensitivity to poliomyelitis [11], ECHO-11 [5], and type C baboon M7 viruses are located in chromosome 19, and genes of sensitivity to herpes simplex virus in chromosome 3 or 11 [8, 10]. It has been shown in the writers' laboratory, with a high degree of statistical significance, that the sensitivity of human cells to Coxsackie B virus is mainly linked with chromosome 21. Chromosome 21 is present in practically every cell of a sensitive culture and is absent in 74% of cells of the resistant subline [3]. Clones of the resistant subline preserving all their virological, morphological, and cytochemical properties characteristic of the original J-41 subline were subsequently obtained. Chromosome 21 was practically completely absent from the cells of these clones [1]. This was further evidence that the gene of human cell sensitivity to Coxsackie B virus is located in that same chromosome. A detailed cytogenetic study of human cell cultures sensitive and resistant to the homologous virus revealed material of chromosome 21, in the composition of M11 marker chromosomes, in the karyotype of the resistant subline [4].

The aim of the present investigation was to compare the morphological and functional state of chromosome 21 or of its material in human cell cultures sensitive and resistant to Coxsackie B viruses.

EXPERIMENTAL METHOD

A culture of reticular cells highly sensitive to Coxsackie B viruses (J-96) and a subline (J-41) obtained from it, with high and specific resistance to the homologous virus [2], were used. Preparations for karyologic analysis were obtained by the usual method. The chromosomes were stained by R-, C-, and Ag-methods [6, 9, 12]. Altogether more than 40 metaphase plates in each culture were studied by the methods listed above. The Fisher–Student method was used for statistical analysis of the data.

EXPERIMENTAL RESULTS

Comparative analysis of marker chromosomes of the sensitive and resistant cell lines revealed a chromosome which corresponded in size to chromosomes of human group E, and which was found only in cells of the resistant subline. This chromosome was called M11 (M the initial of the word metacentric, 11 the serial number within the group of metacentric marker chromosomes). Differential staining by the R-method showed that this chromosome was formed by Robertsonian translocation of group G chromosomes, specifically by translocation of chromosome 21 to chromosome 21 (marker chromosome M11-a) or of chromosome 21 to 22 (marker chromosome M11-b; Fig. 1). Comparison of the frequency of occurrence of M11 markers in cells of the sensitive and resistant cultures with the presence of chromosomes of the 21st and 22nd pairs in them (Table 1) showed that, first, these markers are completely absent in sensitive cells and, second, the process of marker formation is evidently not accidental, and that chromosome 21 is primarily involved in it.

Cells of the original sensitive culture may contain from one to three chromosomes of the 21st pair. In our opinion the process of formation of M11 markers can be represented as follows: If only one chromosome

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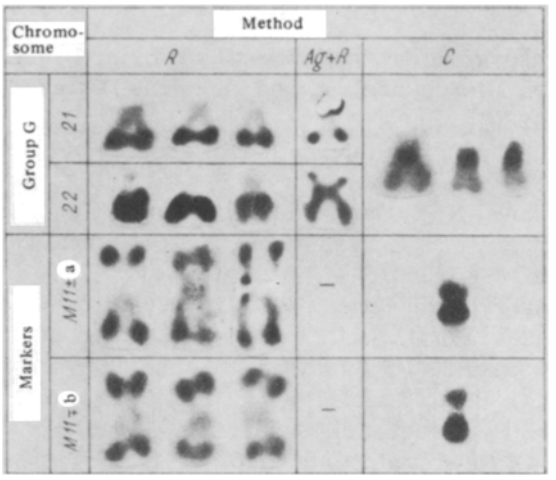

Fig. 1. Montage of chromosomes 21, 22, M11-a, and M11-b, stained by different methods. Magnification: objective 100, Optovar 1.25 ocular. Phase contrast.

TABLE 1. Comparison of Frequency of Occurrence of Chromosomes 21, 22, and M11 in Cultures of Human Cells Sensitive (J-96) and Resistant (J-41) to Coxsackie B Virus

Chromosome	Cell culture		P
	J-96	J-41	
21	1,57±0,10	0,26±0,09	<0,0001
22	1,36±0,17	1,14±0,13	>0,5
M11	—	0,76±0,09	<0,0001

21 is present in the original cell the marker is formed from chromosomes 21 and 22; if, however, the original cell contains two chromosomes 21, the marker is formed from two chromosomes 21; finally, if there are three chromsomes 21 in the original cell, two M11 markers are formed: the first (M11-a) from two chromosomes 21, and the second (M11-b) from chromosomes 21 and 22. The number of chromosomes of the 22nd pair evidently does not play a decisive role in this process. In none of the cells studied was the M11 marker formed by two chromosomes of the 22nd pair.

In the case when two chromosomes 21 took part in the formation of the marker (M11-a) the short arms of these chromosomes were absent; in the second variant (M11-b), when translocation of chromosome 22 to chromosome 21 took place, the first chromosome was completely preserved, but the short arm was absent in the chromosome 21. Data obtained by differential staining of chromosomes by the R-method were confirmed by the results obtained by the C-method. In fact, as Fig. 1 shows, in some cases heterochromatic regions in the M11-a marker were located in the immediate vicinity of one another, and short arms of chromosome 21 were absent, whereas in other cases (M11-b marker) an unstained region of the chromosome, the length of which corresponded to that of the short arm of chromosomes of the G group, could be distinguished between the centromere regions.

Investigation of the chromosomes of these cells by silver impregnation by the method of Bloom and Goodpasture [6] revealed no regions of the nucleolar organizer in M11 marker chromosomes.

The results of these experiments thus indicate that acquisition of specific antiviral resistance by cells, coupled with eliminations of intact chromosome 21 from the set, is accompanied not by the total loss of this chromosome, but only by modification of its structure. The short arm of chromosome 21 is absent in this case. It can be postulated on the basis of these findings that the gene of human cell sensitivity to Coxsackie B viruses is most probably located in the short arm of chromosome 21.

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