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Cytological Studies of Tumors, XIX.
A Chromosome Survey of the MTK-sarcoma II and III
after Several Years of Serial Transfers

By

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(With 15 Text-figures)

Investigations in the recent several years on the chromosomes of ascites tumors in rats and mice have established with indisputable clearness the existence of the stemline cells as primary contributors to the neoplastic growth (Makino 1951a, 1952a, b, Levan & Hauschka 1952, 1953, Makino & Kanô 1953, 1955, Sachs & Gallily 1955, Tjio & Levan 1954, 1956, Levan 1956, Watanabe & Tonomura 1956, Yosida 1954, etc.). The evidence now available indicates that the stem-cells are generally characterized by a very pronounced constancy, allowing them to keep their characteristics through prolonged serial transfers. Even drastic application of chemicals, transformation into subcutaneous solid form, and heteroplastic transplantation usually fail to induce any permanent changes of the genetic constitution and/or chromosome individuality of the stem-cells (Makino 1951b, 1956, Makino & Tanaka 1953a, b, Makino & Tonomura 1955, Nakahara 1952, Sasaki 1956, Tanaka *et al.* 1955, Tonomura 1953, etc.).

Makino (1956)¹⁾ has expressed the view with some available evidence that the stability of the stem-cells, however, while very pronounced is not always permanent. Under certain conditions, changes will occur in the properties of the tumors, and such changes will sometimes be recognizable as morphological changes of the chromosomes. With the above point in mind, present writers attempted a reinvestigation on the chromosomes of the MTK-sarcoma II and III, in a hope to learn whether the constancy of the stemline characteristics are maintained or not during prolonged serial transfers.

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1) Lecture given before the International Genetics Symposia, held in Tokyo in September 1956. (Proc. Intern. Symp., Cytologia Suppl., 1957).

Jour. Fac. Sci. Hokkaido Univ. Ser. VI, Zool. 13, 1957 (Prof. T. Uchida Jubilee Volume).

Material and methods

The MTK-sarcoma II and III are the rat ascites tumors which were established by prolonged application of azo dyes by Tanaka and Kanô. General characteristics of these tumors were described by Tanaka & Kanô (1951) and Umetani (1953). The data on the chromosome analyses for the present paper were secured in October 1956 and January 1957. For observation of the chromosomes a pre-water treatment method was adopted: to droplets of ascites suspension was added a nearly equal volume of tap or distilled water on slide, left for 5 to 10 minutes and stained through the acetic dahlia squash technique.

Results

1. MTK-sarcoma II

In early transfer generations, as shown by Makino and Kanô (1953) and Tonomura (1954), the stem-cells of this tumor were provided with subdiploid chromosomes, 40 or thereabouts in number, comprising a single characteristic V-shaped element of remarkably large size, by the presence of which the tumor cells were clearly distinguishable from the somatic cells. The preparations from recent samplings revealed, however, that the stem-cells of this tumor were characterized by the existence of two remarkable large V-shaped elements, slightly unequal in size (Figs. 1~6, 12, 14). The modal ploidy in the recent material was also found at near-diploid; over 90 per cent of metaphasic cells were nearly diploid. As shown in Table 1, the diploid number of this tumor fluctuated within a range

Table 1. Chromosome number distribution around the $2n$ mode of the MTK-sarcoma II and III.

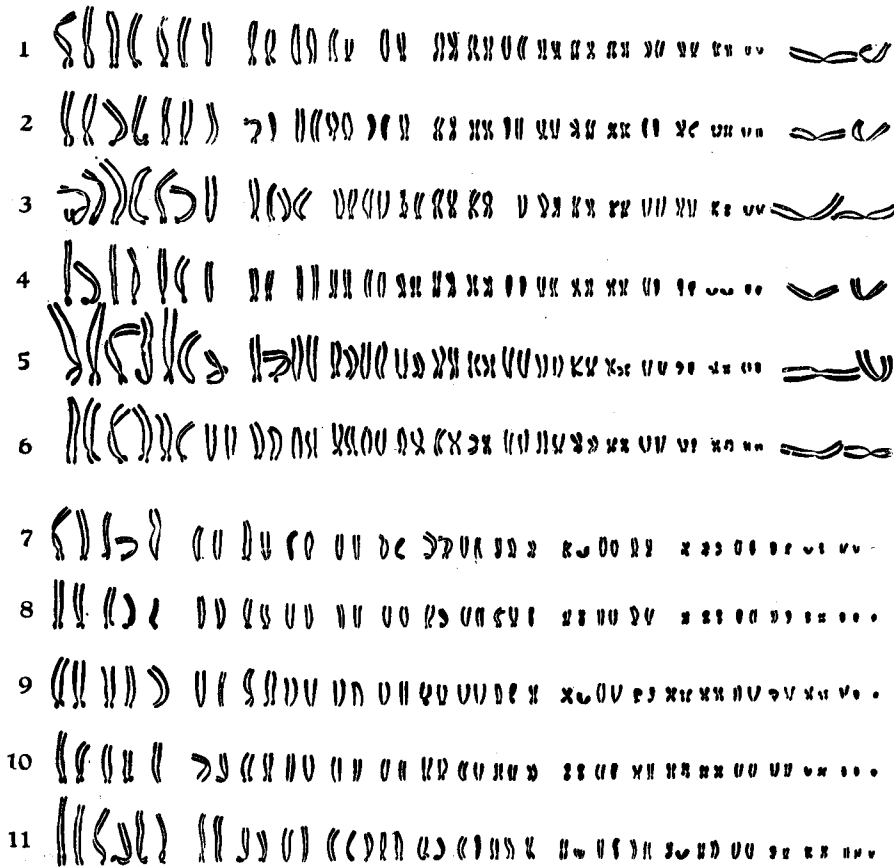
Tumor	Chromosome number											Total no. of cells observed
	34	35	36	37	38	39	40	41	42	43	44	
MTK-II	1 (1.6%)	—	1 (1.6%)	5 (7.9%)	7 (11.1%)	37 (58.7%)	11 (17.5%)	1 (1.6%)	—	—	—	63 (100%)
MTK-III	—	—	—	—	—	—	7 (14.9%)	34 (72.4%)	4 (8.5%)	1 (2.1%)	1 (2.1%)	47 (100%)

from 34 to 41, with the most common number (the modal number) at 39 (58.7%). It is highly probable that in the course of successive transfers the stem-cells may undergo a chromosome change, and that the resultant 2V-type cells having sufficient competitive ability are better conditioned in functional activity than 1V-type cells to survive. A comparative study of the relative length of individual chromosomes indicates that each arm of the two V-shaped chromosomes seems

to correspond to certain larger medium-sized elements in approximate order of size, so far as the superficial size order of chromosomes is concerned. A possible suggestion is made then that the two V-shaped elements probably originate from a centric fusion between certain four elements, though it is impossible to state which chromosomes take part in that centric fusion, although such an attempt has been made by Yosida (1955).

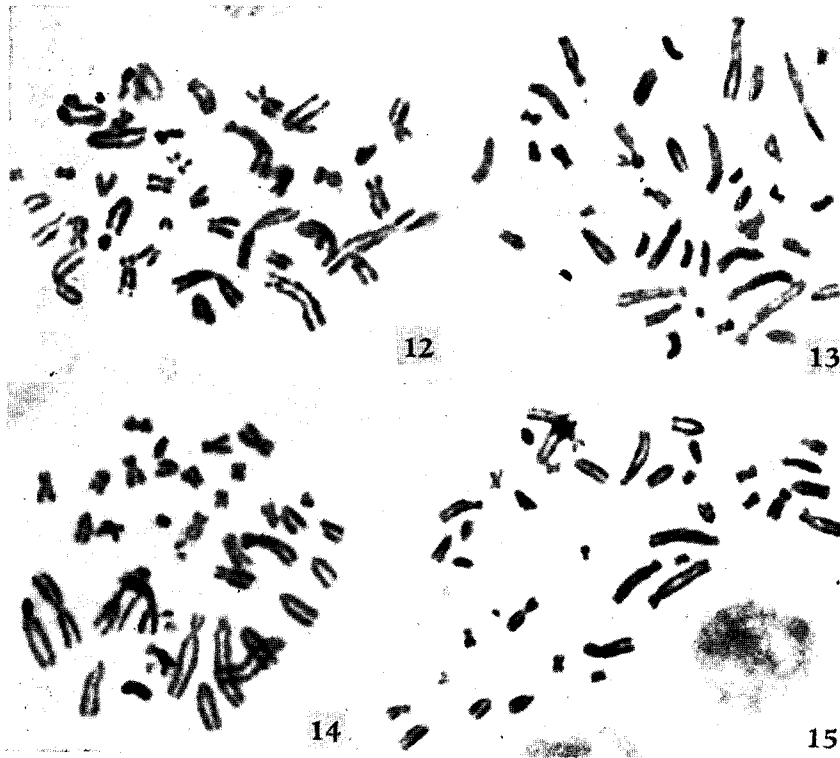
2. MTK-sarcoma III

This tumor is also a kind of diploid tumor; in the samples derived from recent transplant generations, over 95 per cent of metaphasic cells were nearly diploid.



Figs. 1-11. Ideogram analyses of the MTK-sarcoma II and III. Serial alignments were made in approximate order of size. The members do not indicate the actual homologous mates. Figs. 1-6, MTK-sarcoma II, Figs. 7-11, MTK-sarcoma III.

It has been found in early transfer generations that the stem-cells of this tumor were characterized by a hypodiploid modal number with the presence of two separate stem-line cells, one of which comprised a V-shaped chromosome of prominently large size while the other contained no such element at all (Umetani 1953). In the recent samplings, however, it was found that this tumor was similar to normal somatic cells in both morphology and number of the chromosomes (Figs. 13, 15), though the likeness may be merely superficial, since considerable



Figs. 12-15. Photomicrographs of chromosomes of the MTK-sarcoma II and III. $\times 1800$. Figs. 12, 14, MTK-sarcoma II. Figs. 13, 15, MTK-sarcoma III.

structural changes had been taken place in the tumor chromosomes. The gross differences are found in the fact that No. 3, No. 12, and No. 22 in an approximate order of size undergo changes in shape and size (Figs. 7~11). As shown in Table 1, the chromosome number distribution around the $2n$ mode shows a range from 40 to 44, among which 41 chromosome cells were most numerous (72.4%). The 1V-type cells occurring very often in the early transfer generations were rarely found in the recent generations. It is probable that shift has occurred in the

frequency of two lines of tumor cells during repeated transfer generations. Of the two stem lines one would tend to surpass the other in functional activity. This seems to indicate that the neoplastic population is labile. Similar condition has been reported by Makino and Kanô (1953, 1955) in the stem-lines of the Hirosaki sarcoma.

Discussion

The results of the present observations are suggestive of the fact that changes do occur in the stemline chromosomes of the MTK-sarcomas after often-repeated serial transfers. In the MTK-sarcoma II, it is probable that 2V-type cells are superior in viability to 1V-type cells and possess competitive ability sufficient to enable survival as a stemline population. In the MTK-sarcoma III, no V-type cell population seems to be superior in competitive ability to the other cell population provided with 1V-type cells. Yosida (1955) reported in the MTK-sarcoma III which have been kept in the National Institute of Genetics at Mishima, the occurrence of two large V-shaped elements, though there is a doubt in sampling of the material. These facts seem to indicate that different cell types forming separate stemlines are not always the same in their competitive survival ability. The frequency of several cell-types may vary with serial transfer generations, or may vary in different transfer lines. This relationship may be attributable to differences in metabolic activity on the one hand, and on the other hand to the genetic constitution of the host. Similar change in number and morphology of stemline chromosomes have been reported by several authors (Hauschka 1953, Ising 1955, Kaziwara 1954, Levan 1956, *etc.*). In the Yoshida sarcoma and in some others, the occurrence of several sublines which differ in both chromosomal constitution and type of disease from the stock tumor has been reported (Makino 1956).

It can be stated on the basis of the above evidence that the stemline cells in the tumor population are not necessarily stable, and under certain conditions changes will occur in the stemline chromosome complement with the shift in the properties of the tumors.

Summary

The present study deals with a reinvestigation on the chromosomes of the MTK-sarcoma II and III after several years' continuance of serial transfers. A comparison of the stemline ideograms between early and recent transfer generations has revealed that the stemline chromosome complements have undergone shifts in both the MTK-sarcoma II and III. It seems apparent that the stability of the stem-cells is not necessarily permanent, and under certain conditions changes occur in the stemline chromosome complement with the shift in the properties of the tumors.

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