Transfer RNA Species in Tumors of Different Growth Rates

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SUMMARY

Tyrosyl-, histidyl-, lysyl-, and phenylalanyl-tRNA's from 3 tumors (DBAH, DBAH2, and DBA:i), differing in growth rates and from host mammary glands and liver, were compared by means of methylated albumin kieselguhr (MAK) column and by reverse-phase-5 chromatography. The elution profiles of lysyl-tRNA's from DBAH and DBA:i, phenylalanyl-tRNA's from DBAH and DBA:i, and histidyl-tRNA's from DBA:i tumors exhibited extra isoaccepting species, compared with host liver and mammary glands. The distribution of acylatable tyrosyl-tRNA's in DBA:i, and DBAH, phenylalanyl-tRNA's in DBAH and DBA:i, and histidyl-tRNA's in DBA:i is higher than that in liver, whereas no appreciable differences were observed in the lysyl-tRNA contents of the tumors and liver. The chromatographic alterations appeared to be a property of the tumor tRNA's and not due to differences in aminoacyl-tRNA synthetases or due to the aggregation of tRNA's. The structural and functional significance of these findings are discussed.

INTRODUCTION

Alterations of chromatographic elution profiles in the tRNA's of systems undergoing or having undergone changes in metabolic control processes have been reported. The possibility that the differences in isoaccepting tRNA's may be related to the regulatory functions in cell differentiation has recently been reviewed. The frequent finding of chromatographic profile variations of certain aminoacyl-tRNA's, namely, tyrosyl (2, 13, 18, 30, 38); aspartyl (7, 38, 39); phenylalanyl (14, 15, 18, 30, 35, 39); histidyl (4, 28, 35); seryl (4, 30, 35, 40); asparaginyl (4, 13–15, 28, 30, 35, 39, 40), and lysyl (34, 35) from neoplastic tissues suggests that these tRNA species may be involved in neoplastic transformation processes and in growth control. A number of neoplasms, namely, Ehrlich ascites tumors (30, 31), Novikoff (4) and Morris hepatomas (28, 35), and polyoma- and SV40-transformed mouse embryo cells (6, 11, 30), show differences in tRNA species, compared with their normal counterparts. For a number of years, we have been attempting to elucidate the biological and structural characteristics of neoplasms as related to their growth rate. Accordingly, to gain further insight as to whether specific tRNA's might play a role in cell growth, differentiation, and carcinogenesis, we have selected for this study 2 types of mouse mammary tumors, DBAH and DBAH2, and a lymphoblastic-type lymphoma, DBA:i. All 3 tumors are propagated in isogenic hosts, and they differ in growth rate. We have previously observed that the aspartyl-tRNA elution profile from each of the 3 tumors exhibited a 3rd elution peak as compared to the normal host liver (23). In this study, we have examined the tRNA's for phenylalanine, tyrosine, histidine, and lysine of the 3 neoplasms and compared them with the corresponding tRNA's from normal host mammary glands and liver.

MATERIALS AND METHODS

Tumors. The DBAH tumor arose in a female mouse of the DBA inbred strain and has been carried by serial transplants in isologous hosts for the past 20 years. The latent period (time elapsing from implantation of a small tumor graft, 2 x 2 mm, by the trocar technique s.c., to the appearance of a nodule of measurable size) is 8.3 days ± 1.1; doubling time is 2.5 days ± 1.1; DNA synthesis (T5) is 7 hr. The tumor tissue consists of nests of closely adjacent epithelial cells; narrow layers of fibrous connective tissue struma separate the cell nests (Fig. 1).

DBAH2 mammary tumor also arose in a female of the DBA/2J inbred strain; it is carried by serial transplants for about 6 years and has a latent period of 6.3 days ± 3.5; doubling time is 4.5 days ± 1.5; DNA synthesis (T5) is 7.5 hr. The tumor tissue consists of nests of closely packed cells separated by rather wide layers of fibrous stroma (Fig. 2).

The DBA:i tumor is a lymphoblastic-type lymphoma that arose spontaneously in a DBA/2J female mouse and consists of sheets of lymphoblastic cells. It is carried by serial transplants for about 5 years; its latent period is 3 days ± 1.2; doubling time is 2.0 days ± 1.2; DNA synthesis (T5) is approximately 8 hr. [The DNA synthesis time (T5) was determined by the use of [3H]thymidine and the autoradiographic technique (Fig. 3).]

Mammary glands from 4 lactating mice of DBA/2J strain, isogenic to the mammary tumors, were excised from the inguinal and axillary regions, immediately placed in cold 0.25 M sucrose solution, rinsed twice to remove the adherent milk from the cell surfaces, and processed for tRNA's by the same procedure described for the tumors and normal liver (Fig. 4).

Isotopes 3H- and 14C-labeled amino acids were obtained from Schwarz/Mann, Orangeburg, N. Y. UpUpU and ApApA were obtained from Sigma Chemical Co., St. Louis, Mo., and polyuridylic adenylic acid and polycytidylic adenylic acid were obtained from Miles Laboratories, Eckhart, Ind.

Received March 17, 1975; accepted June 9, 1976.

1 Supported in part by Grant CA-12076 from the National Cancer Institute, NIH.
**Aminoacyl-tRNA Synthetases and tRNA.** Aminoacyl-tRNA synthetases were prepared from normal liver and tumors according to the method of Nishimura and Weinstein (25). Crude tRNA was prepared by phenol extraction, essentially as described by Delilas and Staehelin (9). The tRNA was stripped of endogenous amino acids by incubation with 0.5 M Tris-HCl buffer (pH 8.4) for 30 min at 37°. The tRNA was further purified by fractionation with isopropyl alcohol (36). The final isopropyl alcohol precipitate was dissolved in 0.005 M sodium acetate buffer (pH 5.0) and stored at —20°.

**Aminoacylation of tRNA.** Charging of tRNA with labeled amino acids was accomplished in a 1-ml reaction mixture containing 0.1 M Tris-HCl (pH 7.4), 0.005 M MgCl2, 0.01 M ATP (neutralized), 0.0025 M CTP, 0.03 mM 14C-labeled amino acid (5 μCi), or 0.03 mM 3H-labeled amino acid (25 μCi), a mixture of 19 other nonradioactive amino acids (0.04 mM each, neutralized with Tris), 5 mM dithiothreitol, 1 mg tRNA, and sufficient enzyme to achieve maximum charging in 15 min at 37° as determined by prior assay. After incubation at 37° for 15 min, 0.25 volume of 0.05 M sodium acetate (pH 5.0) was added, and the mixture was deproteminized with phenol previously equilibrated with 0.05 M sodium acetate (pH 5.0). Two volumes of 95% ethanol were added to the aqueous layer. After standing at —20° overnight, the precipitate was collected by centrifugation and washed with 80% ethanol. The labeled aminoacyl-tRNA was dissolved in 0.5 ml of the starting buffer of the column (0.2 M NaCl-0.05 M sodium phosphate, pH 6.7).

**Column Chromatography.** A MAK column was prepared by the procedure described by Mandell and Hershey (21), and the column (3 x 3.5 cm) was prepared by a previously described method (3). The samples (0.5 ml of 3H-labeled and 0.5 ml 14C-labeled aminoacyl-tRNA's, 30,000 to 50,000 cpm each) were applied to the column. The column was first washed with 10 ml of the starting buffer (0.2 M NaCl-0.05 M sodium phosphate buffer, pH 6.7) and then with 250 ml of a linear gradient of 0.2 to 1.1 M NaCl (in 0.05 M sodium phosphate buffer, pH 6.7) at a flow rate of 1.25 ml/min. Fractions (2.5 ml) were precipitated by the addition of 2.5 ml of cold 10% trichloroacetic acid and 200 μg of carrier DNA and were collected on cellulose nitrate filters (Millipore, 25 mm in diameter), and washed with 4 5-ml portions of cold buffer, and the radioactivity was determined in a Nuclear-Chicago liquid scintillation counter.

**RESULTS**

MAK column elution profiles of tyrosyl-tRNA's are presented in Chart 1. The tRNA's extracted from normal host liver and slow-growing mammary tumor DBAH2 have similar patterns with respect to 2 major peaks. However, an additional minor peak appears in the tRNA profile from DBAH2. Tyrosyl-tRNA's from the fast-growing lymphoblastic-type lymphoma, DBA13, and of intermediate-growth-rate DBAH mammary tumor show significant differences from those of host liver and DBAH2 in having 1 major component. Tyrosyl-tRNA1BAH has a broad irregular profile, whereas an additional minor component appears in tyrosyl-tRNA of DBAH13. As shown in Chart 2, A and B, elution patterns of lysine tRNA's from all the tumors, as well as normal liver, appear to be different. Lysyl-tRNA's from both DBA13 and DBAH2 have 4 isoaccepting species, whereas those from normal liver and DBAH2 have 3 isoaccepting species of each. Further, the major peaks of lysyl-tRNA1BAH and lysyl-tRNA1BAH, are eluted at a lower salt concentration, and minor peaks appear later as compared to lysyl-tRNA1BAH, and lysyl-tRNA1BAH, where a major peak of each is eluted at a lower salt concentration, and the major peaks appear later.

Since the differences in isoaccepting species of lysyl- and tyrosyl-tRNA's from normal liver and different tumors were not pronounced, these tRNA's were also resolved by RP-5. The results are shown in Charts 3 and 4. The RP-5 chromatographic profiles of tyrosyl- and lysyl-tRNA's from nor-
Chart 1. A, elution profiles of \[^{14}C\]-labeled tyrosyl-tRNA from DBAH\(_2\) tumor and \[^{3}H\]-labeled tyrosyl-tRNA from normal liver, cochromatographed on MAK column; B, elution profiles of \[^{14}C\]-labeled tyrosyl-tRNA from DBAH\(_2\) tumor and \[^{3}H\]-labeled tyrosyl-tRNA from DBAH\(_2\) tumor, cochromatographed on MAK column. Aminoacyl-tRNA synthetase from normal liver was used to charge the tRNAs.

Chart 2. A, elution profiles of lysine tRNA-\[^{14}C\] from DBAH\(_2\) tumor and \[^{3}H\]-labeled lysyl-tRNA from DBAH\(_2\) tumor, cochromatographed on MAK column; B, elution profiles of \[^{3}H\]-labeled lysyl-tRNA from normal liver and \[^{14}C\]-labeled lysyl-tRNA from DBA\(_3\) tumor, cochromatographed on a MAK column. Aminoacyl-tRNA synthetase from normal liver was used to charge the tRNAs.

Chart 3. A, elution profiles of \[^{14}C\]-labeled tyrosyl-tRNA from DBAH\(_2\) tumor and \[^{3}H\]-labeled tyrosyl-tRNA from DBAH\(_2\) tumor, cochromatographed on RP-5; B, elution profiles of \[^{14}C\]-labeled tyrosyl-tRNA from normal liver and \[^{3}H\]-labeled tyrosyl-tRNA from DBAH\(_2\) tumor, cochromatographed on a MAK column. Aminoacyl-tRNA synthetase from normal liver was used to charge the tRNAs.

Chart 4. A, elution profiles of \[^{14}C\]-labeled lysyl-tRNA from DBAH tumor and \[^{3}H\]-labeled lysyl-tRNA from DBA\(_3\) tumor cochromatographed on RP-5; B, elution profiles of \[^{14}C\]-labeled lysyl-tRNA from DBAH\(_2\) tumor and \[^{3}H\]-labeled lysyl-tRNA from liver, cochromatographed on RP-5. Aminoacyl-tRNA synthetase from normal liver was used to charge the tRNAs.

Chart 5. Elution profiles of histidyl-tRNA's from normal liver and different tumors revealed some qualitative differences as compared to the corresponding MAK column profiles. As in MAK column chromatography, 4 isoaccepting species of lysyl-tRNA from each of the DBAH and DBA\(_3\) tumors and 3 isoaccepting species of lysyl-tRNA's from each normal liver and DBAH\(_2\) tumor appeared in RP-5 chromatographic profiles. However, the number of isoaccepting species of tyrosyl-tRNA's from normal liver increased by 1 and that of DBAH\(_2\) decreased by 1 in RP-5 chromatography as compared to MAK column chromatography. RP-5 chromatography of histidyl-tRNA's from normal liver and DBAH\(_2\) tumor was repeated 3 times.

Mak column elution profiles of histidyl-tRNA's are presented in Chart 5. In the elution profiles of histidyl-tRNA\(_\text{Liver}\) and histidyl-tRNA\(_\text{DBAH}_2\), each tRNA exhibits 2 major species and a minor species. However, the elution profile of histidyl-tRNA's from DBAH exhibit 1 major species and 2 minor species, and histidyl-tRNA\(_\text{DBAH}_2\) also exhibits 1 major but 3 minor species. The presence of 1 major and 2 minor species of histidyl-tRNA in DBAH and 1 major and 3 minor species of histidyl-tRNA in DBA\(_3\) has also been revealed by RP-5 chromatography, as shown in Chart 6.

Mak column elution profiles of phenylalanyl-tRNA's are presented in Chart 7. The elution patterns of phenylalanyl-tRNA's from host liver and the fast-growing tumor DBA\(_3\) are very similar, each exhibiting only 1 major species. However, it can be seen that phenylalanyl-tRNA's from DBAH and DBAH\(_2\) exhibit 2 isoaccepting species which are present in roughly the same amounts. RP-5 chromatography also...
tRNA Species in Tumors

Chart 5. A, elution profiles of \(^{14}C\)-labeled histidyl-tRNA from DBAH tumor and \(^{3}H\)-labeled histidyl-tRNA from DBAH tumor, cochromatographed on MAK column; B, elution profiles of \(^{14}C\)-labeled histidyl-tRNA from DBA\(_3\) tumor and \(^{3}H\)-labeled histidyl-tRNA from normal liver, cochromatographed on MAK column. Aminoacyl-tRNA synthetase from normal liver was used to charge the tRNA's.

Chart 6. A, elution profiles of \(^{14}C\)-labeled histidyl-tRNA from DBAH tumor and \(^{3}H\)-labeled histidyl-tRNA from normal liver, cochromatographed on RP-5; B, elution profiles of \(^{3}H\)-labeled histidyl-tRNA from DBA\(_3\) tumor and \(^{14}C\)-labeled histidyl-tRNA from normal liver, cochromatographed on RP-5. Aminoacyl-tRNA synthetase from normal liver was used to charge the tRNA's.

Chart 7. A, elution profiles of \(^{3}H\)-labeled phenylalanyl-tRNA from DBA\(_3\) tumor and \(^{14}C\)-labeled phenylalanyl-tRNA from normal liver, cochromatographed on MAK column; B, elution profiles of \(^{3}H\)-labeled phenylalanyl-tRNA from DBA\(_3\) tumor and \(^{14}C\)-labeled phenylalanyl-tRNA from normal liver, cochromatographed on MAK column. Aminoacyl-tRNA synthetase from normal liver was used to charge the tRNA's.

Chart 8. A, elution profiles of \(^{14}C\)-labeled phenylalanyl-tRNA from normal liver and \(^{3}H\)-labeled phenylalanyl-tRNA from DBAH tumor, cochromatographed on RP-5; B, elution profiles of \(^{14}C\)-labeled phenylalanyl-tRNA from DBA\(_3\) tumor and \(^{3}H\)-labeled phenylalanyl-tRNA from normal liver, cochromatographed on RP-5. Aminoacyl-tRNA synthetase from normal liver was used to charge the tRNA's.

The specific tRNA profiles from the tumor with those from the tissue of origin. Two tumors, DBAH and DBAH\(_2\), were derived from the mouse mammary glands of inbred DBA/2J mice. We have compared the lysyl- and phenylalanyl-tRNA profiles from DBAH with those from the isogenic mammary glands. The results are shown in Chart 9. It was observed that lysyl- and phenylalanyl-tRNA profiles from the mammary glands were similar to those from host liver. The additional isoaccepting species of lysyl- and phenylalanyl-tRNA's that appeared in DBAH tumor are absent in mammary glands as in the liver.

It is evident from our results that different new isoaccepting tRNA species have appeared in 3 isologous tumors of different growth rates. A new histidyl-tRNA isoaccepting species, found in the faster-growing DBA\(_3\) tumor, is absent in the relatively slower-growing tumors, DBAH and DBAH\(_2\). Furthermore, the additional phenylalanyl-tRNA isoaccepting species observed in DBAH and DBAH\(_2\) are absent in DBA\(_3\).

Table 1 shows the number of isoaccepting species of each tRNA observed in different tumors and host liver.

In the initial experiments, we used host liver as standard test tissue for comparison to tumor tissue. However, it is more appropriate, from the genetic standpoint, to compare

revealed only 1 major species of phenylalanyl-tRNA in both normal liver and the fast-growing DBA\(_3\) tumor, as shown in Chart 8. Two isoaccepting species of phenylalanyl-tRNA from DBAH were also observed in RP-5 chromatography. However, the relative amounts of the 2 isoaccepting species differ, as compared to MAK column chromatography. The difference in the relative amounts of the peaks might be due to the difference in the recovery of the peaks in different columns. The 1st peak, however, was reproducible in 3 experiments.

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Since elution profiles of the charged aminoacyl-tRNA's studied here from different tumors were found to be altered, it was of interest to determine whether the ability of these tRNA's to recognize the specific codons was also altered. The results are shown in Table 3. No significant differences in codon recognition capacity of the tRNA's from different tumors and normal host liver were found. However, further studies are necessary to determine the codon recognition capacity of individual isoaccepting species of each different tRNA, and a larger number of codons must be tested.

DISCUSSION

The data presented in this paper indicate that multiple isoaccepting species of specific tRNA's exist in different tumors and normal host mouse livers and mammary glands. We have found 3 peaks for histidyl- and lysyl-tRNA, 2 peaks for tyrosyl-tRNA, and 1 peak for phenylalanyl-tRNA from mouse livers. Using reverse-phase chromatography, Volkers and Taylor (35) also obtained 3 peaks for histidyl- and lysyl-tRNA, 1 peak for phenylalanyl-tRNA, and 3 peaks of tyrosyl-tRNA instead of 2 (as observed in our studies) from both Buffalo and AC1 rat livers. Taylor et al. (30) suggested that tRNA's of corresponding tissues from different mammals are very similar.

However, it is evident from our results that MAK column and RP-5 chromatographic elution profiles of tyrosyl-, histidyl-, lysyl-, and phenylalanyl-tRNA's from the 3 neoplasms and the relative amounts of these specific tRNA's present in the neoplasms (Table 2) appear to be different from those obtained from normal host livers and mammary glands. We have found a new lysyl-tRNA species from DBAH and 2 new histidyl-tRNA species from DBAH1, and a new phenylalanyl-tRNA species from both DBAH and DBAH2. However, tyrosyl-tRNA species of all 3 neoplasms and liver appear to be the same as revealed in RP-5 chromatography. The relative amounts of isoaccepting species of tyrosyl-tRNA in...
normal liver and tumors differ, however. The appearance of new lysyl-tRNA in DBAH and phenylalanyl-tRNA species in both DBAH and DBAH₂ tumors, and the absence of these tRNA species in isogenic mammary glands which are physiologically and metabolically active, may be considered to be of interest.

We have observed quantitative differences in various isoaccepting species of different tRNA's present in the tumors, in liver, and in mammary glands. The significance of such quantitative differences in various isoaccepting species of a specific tRNA is not clear at present. Further experiments should be done to shed light on this observation.

The presence of additional isoaccepting tRNA species in tumors may account for the greater amounts of acylatable tRNA's in tumors, compared with normal liver (Table 2). These findings are in agreement with those of Ouellette and Taylor (26), who have found that the distribution of acylatable histidyl-, lysyl-, phenylalanyl-, seryl-, tyrosyl-, arginyl-, and methionyl-tRNA's is significantly higher in hepatoma 5123D than that in normal rat liver, and in no instance was the distribution of acylatable tRNA's in hepatoma lower than that in liver.

The appearance of these new species of tRNA in tumors is not due to an artifact introduced in the preparation of the tRNA, since they are repeatable with different batches of tRNA prepared in the same way. Similarly, different batches of enzymes from liver and tumors give the same results. Furthermore, charging of tumor tRNA's with liver synthetase gives a similar profile. The extra peaks of tumor tRNA's are not caused by aggregation of the tRNA's, since heating the tRNA to 80° for 1 min before aminoacylation (1) caused no alteration in the MAK column elution pattern. Further, aminoacylation of another specific tRNA with the radioactive amino acid has been eliminated by the addition of 19 other cold amino acids to the reaction mixture.

The results suggest that the difference between the aminoacyl-tRNA's of tumors and normal liver and mammary glands used in these studies may be due to the neoplastic nature of these tumor cells.

Cells of the tumor types that exhibit differences in specific tRNA species include Ehrlich ascites tumor and virus-transformed hamster cells (30), virus-transformed mouse and rat embryo cell lines (11), certain plasma cell tumors (39), Morris hepatomas (28, 35), Novikoff hepatomas (4), and a human lymphocytic leukemia cell line (12).

The cause of chromatographic differences found in certain tRNA species from the tumors is, as yet, unclear. They may be due to a change in primary sequence not related to secondary modification or to changes in secondary structure, such as methylation, which may cause the particular tRNA species to elute differently. Our results in Table 3 indicate that, to the extent tested, the tumor tRNA's specific for lysine, histidine, tyrosine, and phenylalanine appear to have normal codon recognition; therefore, it is unlikely that they have an altered sequence in their anticodons. The new species of tRNA present in the tumors are probably altered in some other region. Srinivasan et al. (28) have also found that isoaccepting species of tyrosyl-tRNA's present in normal rat liver and Morris hepatoma have the same codon recognition. Taylor et al. (31) also observed that different isoaccepting species of phenylalanyl-tRNA's from rat kidney and Ehrlich ascites tumors have the same codon recognition.

There seems to be a reasonable possibility that the altered chromatographic profiles may be due to secondary modification, such as methylation and other modifications. The overmethylation of tumor tRNA's may be supported by the fact that the total tRNA of certain tumors appears to contain higher levels of methylated bases than the tRNA from the corresponding control tissues (5, 33). Furthermore, it has been reported (32, 37) that a variety of tumors have increased levels of tRNA-methylating enzymes. However, Randerath et al. (27) recently reported that the total base composition of the tRNA's from Morris hepatomas 7777 and 5123D did not reveal a general overmodification or overmethylation, but the total modified and methylated base content was found to be slightly lower than in tRNA from normal liver and host liver.

Another possibility is that the new species of some specific tRNA's in the tumors might be of viral origin. Recently, Gallagher et al. (11) observed that aspartyl-tRNA profiles obtained from SV40- or polyoma-transformed mouse embryo cells are characterized by the appearance of a 3rd aspartyl peak which is absent in corresponding control tissues. These investigators suggested that the new aspartyl-tRNA species is coded by the viral gene. We have found virus particles in 2 mammary tumors, DBAH and DBAH₂, whereas no virus could be detected electron microscopically in the lymphoblastic-type lymphoma, DBA. Recently, Gonano et al. (16) found that an additional isoaccepting species of phenylalanyl-tRNA is present in both Morris hepatoma 5123C and embryonic rat liver, as compared to normal rat liver, and suggested that the presence of embryonic tRNA's in the neoplastic cell may be an epiphenomenon of the malignant transformation. We have also found an additional isoaccepting species of phenylalanyl-tRNA in each of the 2 mammary tumors, DBAH and DBAH₂. Most recently, Grunberger et al. (17) showed that the minor phenylalanyl-tRNA species in Morris hepatoma 7777, eluted from RP-5 column at a lower salt concentration, is devoid of Y base. It follows that this phenylalanyl-tRNA species is structurally different from the major phenylalanyl-tRNA species in hepatoma 7777 and from the single phenylalanyl-tRNA species in normal rat liver, both of which contain the Y base.

Recently, Cortese et al. (8) pointed out that the appearance of an isoaccepting species of tRNA might result from the lack of pseudouridylation. These investigators have shown that his-T mutants of Salmonella typhimurium contain a histidyl-tRNA lacking 2-pseudouridine in the anticodon region of wild-type histidyl-tRNA. They have further demonstrated that his-T mutants lack the enzyme that catalyzes the formation of specific pseudouridine residues in the anticodon region of tRNA.

The functional significance of the alterations in certain tRNA's noted in the neoplasms is not yet clearly understood. Ames and Hartman (2) suggested that a tRNA recognizing a certain codon could play a part in the regulation of protein synthesis if it were present in rate-limiting amounts.
ACKNOWLEDGMENTS

During viral carcinogenesis. In connection with the comments of Gallagher et al. (11), it is of interest to point out that in our tumor system the DBAH and DBAH2 tumors are mammary adenocarcinomas and both carry the characteristic mammary tumor virus. In the DBA2 tumor (although it had developed in a male of the same inbred strain, DBA/2J), no virus particles could be detected electron microscopically.

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ACR 36

CANCER RESEARCH VOL. 36

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