Pathogenesis of a Rhabdomyosarcoma (Undifferentiated Type) in Rats Induced by a Murine Sarcoma Virus (Moloney)

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SUMMARY

Murine sarcoma virus (Moloney) of mouse origin induced progressively growing local sarcomas in newborn Osborne-Mendel rats. Cell-free extracts prepared from the rat sarcomas were oncogenic in newborn mice and in newborn, 2-week-old, and 4-week-old Osborne-Mendel rats. The sarcomas were readily transplantable in Osborne-Mendel rats of the same age groups. Tumors in the early transplant generations tended to regress. However, tumors transplanted for 8 or more generations grew progressively.

The primary or transplanted rat sarcomas, in contrast to the induced mouse sarcomas, consistently metastasized to the draining lymph nodes and lungs. Whole cell transplants or cell-free extracts of the pulmonary tumor nodules also induced tumors in newborn rats.

Histologically the neoplasms were extremely cellular and composed of undifferentiated cells, some of which resembled rhabdomyoblasts both morphologically and in staining properties. Electron microscopy of these tumor cells revealed an abundance of cytoplasmic fibrils. Occasionally, typical Z bands were evident. The tumor at the site of inoculation and in the metastatic areas showed virus formation and virus particles which were indistinguishable from those found in the mouse sarcoma and in the virus-induced leukemias.

INTRODUCTION

The viral induction and pathogenesis of rhabdomyosarcomas in mice have been previously described (16, 18-20). Preliminary observations indicated that this virus was not effective in untreated newborn rats. However, with continued passage of the virus in mice, a preparation was ultimately obtained which was oncogenic in intact rats. The studies described here are concerned with the induction, histogenesis, ultrastructure, transplantability, and virus activity of tumors induced by the agent in rats.

MATERIALS AND METHODS

Source of Material. The virus used for initial tumor induction in the rat was obtained from primary viral induced rhabdomyosarcomas in BALB/c mice. The cell-free extracts used in this study were prepared by differential ultracentrifugation (15).

Whole cell inoculum used for transplantation studies were prepared as previously described (20).

The transplant generation and the cell-free passage employed in each experiment is listed in the text or tables. The inoculations were performed in the left inguinal area of the animals (subcutaneous and intramuscular).

Animals. Osborne-Mendel rats and BALB/c mice of both sexes were used throughout these studies. The number and sacrifice schedule of the test animals in the different experiments are noted in the text or in the respective tables.

Autopsy Procedure. The rats were sacrificed with ethyl ether immediately preceding autopsy. The total body weight, spleen weight, and tumor size were noted, and blood samples were taken. Sections of tumor, spleen, thymus, lymph nodes, liver, lung, heart, kidney, and pancreas were taken for histologic study. The excised tissues were fixed in Zenker-formol and routinely stained with hematoxylin and eosin. Other stains were employed as required, i.e., phosphotungstic acid-hematoxylin, Mallory Azan, van Gieson, Giemsa, iron hematoxylin, periodic-acid-Schiff (PAS), Wilder, and Masson's trichrome stain.

Electron Microscopy. Representative samples of the local tumors and pulmonary metastatic nodules of eight rats were fixed in chrome-osmium. Liver and spleen samples from the same eight tumor-bearing rats were also taken for microscopy. All tissues were dehydrated in ethyl alcohol and embedded in a mixture of Epon 812 and Araldite (17). Sections were cut out on an LKB ultramicrotome and double-stained with uranyl acetate and lead citrate (8, 23). Electron micrographs were taken with an RCA-ENU-3G microscope.

Hematology. White blood counts were performed on representative samples, and blood smears were examined after treatment with Wright's stain.

RESULTS

Tumor Induction in Rats by Mouse-derived Virus. Virus preparations derived from tumors passaged in weanling BALB/c mice for 96, 101, and 109 generations were individually tested for oncogenicity in newborn Osborne-Mendel rats. Each rat was inoculated in the inguinal area with 0.1 ml of a 1-gm equivalent per 1 ml concentrate of the respective preparation. A 1-gm equivalent per 1 ml concentrate is equal to 1 ml of final material for each gram of tumor tissue processed. The results reveal that each of the three virus pools induced tumors at
K. Perk, D. A. Shachat, and J. B. Moloney

Table 1

<table>
<thead>
<tr>
<th>Consecutive passage numbers</th>
<th>Age of host inoculated (days)</th>
<th>Number of rats developing tumors/number inoculated*</th>
<th>Number of rats dead with tumorb</th>
<th>LPc</th>
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<td>1</td>
<td>2</td>
<td>17/17</td>
<td>10/10</td>
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Sarcoma virus passage in Osborne-Mendel rats.

a Each animal received an inoculation of 0.1 ml of a standard two gram equivalent per milliliter rat virus concentrate, subcutaneously and intramuscular.

b Adjusted for number of animals remaining after sacrifice for passage.

c LP latent period; mean time, in days, to death with tumor.

four to eight days postinoculation in all recipient hosts (12/12; 10/10; 15/15). The sarcomas grew progressively until the death of the hosts at two to four weeks postinoculation.

Rat-derived Virus Passage in Rats. Sarcomas induced in newborn rats by the mouse-derived virus were homogenized and fractionated by differential ultracentrifugation (15). Table 1 shows that the cell-free extracts of the induced rat sarcomas, representing eight consecutive virus passages in rats, were oncogenic in 100% of the newborn animals of the same species.

In addition, cell-free extracts of the rat sarcomas of the fourth transplant generation were tumorigenic. This material, 0.2 ml of a two-gram equivalent per ml concentrate, when inoculated in the inguinal area into two- and four-week-old Osborne-Mendel rats, induced tumors in all recipients (10/10 and 10/10). The ultimate fate of these rats and the tumorigenic effect of this virus at different concentrations in adult rats are under study.

Transplantation Studies. As can be seen from the data in Table 2, the primary rat tumor induced by the mouse-derived virus is consistently transplantable in normal newborn Osborne-Mendel rats through at least 20 whole-cell transplant generations. In early passages a high rate of tumor regression occurred; however, from the eighth passage, no regressions occurred. By the 18th transplant generation, a tumor cell suspension was obtained which induced a nonregressing tumor in all 2-week-old and 4-week-old recipients, 12/12 and 9/9 respectively.

Pulmonary tumor nodules from tumor-bearing rats of the 16th transplant generation were harvested, washed three times in buffered saline, minced, weighed, and a cell suspension prepared by the same procedure employed for the local tumor transplants. Each newborn rat received 0.1 ml of the cell suspension in the inguinal area. All eleven inoculated rats developed tumors at the site of inoculation, the sarcomas grew progressively until the death of the hosts. The time from whole cell inoculation to death ranged from 2 to 4 weeks.

Virus Recovery. Cell-free extracts were prepared from primary virus-induced tumors of newborn Osborne-Mendel rats, whole-cell passaged tumors of newborn Osborne-Mendel rats (16th passage generation), and metastatic lung nodules of the same tumor-bearing rats. The tumorigenic activity of the preparations was determined by inoculating graded doses (10⁻¹ through 10⁻⁴) of virus into newborn BALB/c mice or newborn Osborne-Mendel rats.

Virus preparations, from the primary rat tumors, when assayed in newborn BALB/c mice had an ED₅₀/ml (log dilution of one gram equivalent concentrate at which 50% of the animals developed tumors) of 3.18. Similar extracts of whole-cell passaged tumors had an ED₅₀/ml of 3.20. Viral preparations from the metastatic lung nodules induced progressing tumors in newborn BALB/c mice only when inoculated undiluted. Virus preparations from the primary induced tumors, whole-cell passaged tumors, and metastatic lung nodules induced progressing tumors in newborn Osborne-Mendel rats when administered undiluted.

Gross Pathologic Anatomy. The tumor arose at or near the site of inoculation of virus preparation or tumor cell implant in the left inguinal area. The rapidly growing sarcoma progressed caudally, replacing the leg muscles, and cranially along the dorsal musculature (Fig. 1). The consistency of the tumor mass was solid; however, small necrotic areas were noted in extensive tumors. Metastasis occurred regularly in the lungs (Fig. 1) and draining lymph nodes. Most of the tumor-bearing rats had slightly enlarged spleens and mottled livers (Fig. 1), and their blood was lipemic (the changes in serum constituents will be reported elsewhere).

To follow the sequence of the pathologic changes of this disease, 50 newborn Osborne-Mendel rats which received 0.1 ml of a 1:1 tumor cell suspension (from 11th passage) and 50 intact newborn rats which served as controls were studied. Four rats of each group were autopsied at two-day intervals commencing 3 days postinoculation.

All of the animals in the test group developed extensive tumors within one week of cell implantation. Death started one week after cell transplantation. All animals autopsied at 11 days later showed gross lung metastases. Histologically, lung metastases were also found in some of the rats autopsied at 9 days after transplantation.

The spleen weight changes were significant, however, because the spleens of the controls did not significantly increase in weight, the percentage increase was much higher in the test group. The lungs of the test animals were more extensively involved than those of the controls. The effects on the kidneys were not significant, while the liver weights were increased in both groups, the test group having a higher percent.
Pathogenesis of Viral Rhabdomyosarcoma

Histology. The predominant cells in the tumor were large (approximately 15 μ, or more in diameter), undifferentiated, spindle, round or polygonal (Figs. 2–4). The tumor was extremely cellular with numerous mitotic figures. Few reticular fibers were present and only in well-developed tumors, confined to the sparse connective tissue stroma (Fig. 5). The cells were closely packed together, sometimes arranged in sheets or whorls.

The cytoplasm, varying in amount, was clear, smooth or granular, and eosinophilic. In some cells stained with Masson’s trichrome stain, poorly developed longitudinal and cross striations could be observed. In addition, this stain and the Mallory azan stain imparted a red color to the cytoplasm of the tumor cells. PAS-positive granules, removable by diastase in tumor cells, were infrequently observed in tumor sections. The cells usually possessed one large oval or elongated, indented, centrally placed (but sometimes eccentrically placed) nucleus. The nuclei contained clumps of chromat, a delicate linear network, and extremely large, prominent, acidophilic, ovoid nucleoli. Some cells had two or more nuclei arranged in tandem. Stellated cells arranged in a loose syncytium were also observed. Extensive tumors frequently contained foci of necrosis. Histologic sections from rats autopsied in the early stages of tumor formation revealed a local reaction of edema and leukocyte infiltration with marked degeneration of muscle fibers (Fig. 6). However, small clusters of tumor cells, which at this stage were ovoid, were evident and randomly distributed in the area (Fig. 7).

One week after tumor implantation, metastatic nodules in the lungs were observed in almost all animals bearing extensive tumors. These nodules ranged in size from 2–3 cells to large clusters of cells (Fig. 8). They were randomly distributed throughout the lungs, and by light microscopy procedures the tumor cells were indistinguishable from the primary tumor cells (Fig. 9). In addition, metastatic involvement of draining lymph nodes occurred regularly (Figs. 10, 11). In a few cases, tumor nodules were present in the pancreas.

Random autopsies of rats which had received cell-free extracts of the mouse or rat sarcomas revealed the same histopathologic patterns as found in rats which were inoculated with the whole-cell preparations.

Additional Findings. Histologically, the enlarged spleens showed generalized hyperplasia of all cell types with no evidence of metastasis or leukemia. The liver cells showed fatty degeneration (Fig. 12), and there were also areas of hepatic necrosis. Some of the animals had hyalinization of the glomeruli with obliteration of capillaries in the kidney.

WBC were performed on 20 tumor-bearing rats and on 20 control rats. Although wide variations in total WBC were found in the tumor-bearing rats, they showed higher values, 12,990 (3,200–38,500), when compared to the respective controls, 4,860 (2,880–6,120). However, abnormal cells in the blood smears of the tumor-bearing animals were not found.

Electron Microscopy. Virus particles were observed in thin sections of the rat tumors, these particles were indistinguishable from the murine leukemia viruses or from those found in virus-induced mouse rhabdomyosarcoma (4, 20). Formation of the virus by budding from the tumor cell plasma membranes was observed frequently. In most cases, “ramification” of virus budding was confined to relatively small areas of the tumor cell membrane (Fig. 13). However, buds forming at the surface of the cell, randomly distributed or from cell extensions, were also observed frequently (Fig. 14). Occasionally multivesicular bodies, which are known to play a role in autophagy (27), or small vacuoles containing virus particles were observed (Figs. 15, 16). Small numbers of virus particles were also observed between tumor cells. Particles clustered in large numbers between the cells, seen in the induced tumors of mice (20), were not observed in the rat sections.

It is of interest that the tumor cells found in the lung metastases showed the same virus formations (budding, etc.) as those found in the primary or local tumor cells. In the liver and spleen cells of the tumor-bearing rats, virus formation was not found.

Tumor Cells. In the tumors studied, there was a preponderance of large, elongated, oval, or fusiform cells, characterized by cytoplasmic fibrils in varying amounts (Figs. 17–24). These fibrils showed periodicity and were oriented in many different planes in the cytoplasmic matrix (Figs. 17, 19, 20). Some cells showed the cytoplasmic fibrils in groups (Figs. 18, 21–23). The Z-line, which transverses the fibril bands and is composed of amorphous material showing increased electron density, was only occasionally observed (Fig. 24). In the area of the Z-bands, the filaments appeared to be slightly thickened. Granular material was regularly found in close association with these filaments. Most of the cells possessed an abundance of small “free ribosomes” but a very poorly developed ribosome-studded endoplasmic reticulum (Fig. 20). However, the ergastoplasm of some cells was well developed, the cisternae of the endoplasmic reticulum tending to be elongated along the long axis of the cell. The cisternae contained a flocculent, moderately electron-dense precipitate (Figs. 18, 22). In cells with large numbers of fibrils, the amount of “free ribosome” was reduced and the mitochondria were located primarily in the cell periphery, along the long axis of the cell. The mitochondrial profiles were usually circular or oval. The Golgi complex was moderately well developed, possessing the usual three components, vacuoles, small vesicles, and flattened sacs (Fig. 17). The nucleus of the tumor cells was large, oval or elongated, usually undulated or deeply indented, and possessing one or more large, prominent nucleoli (2 μ) which contained clusters of dense particles. The location of the nucleus varied in the tumor cells but tended to be eccentric in cells that showed numerous fibrils. Some tumor cells showed lipid globules.

The metastatic tumor cells in the lung closely resembled the cells of the primary tumor; however, they were less differentiated and contained fewer fibrils. The collagenous stroma of this tumor, either at the site of the inoculation or in the lungs, was extremely scant.

DISCUSSION

Cell-free extracts of mouse rhabdomyosarcomas (16, 18) induced nonregressing, metastasizing sarcomas in newborn Os-
borne-Mendel rats. The virus preparations obtained from the rat tumors were oncogenic in all newborn, two-week-old and four-week-old Osborne-Mendel rats tested. Further, it has been reported (24, 25) that the intracerebral inoculation of newborn rats with this agent induced hemangioendotheliomas, meningiomas, and gliomas at the site of inoculation; a few rats also developed primary bone plasmaeytomas. These findings are in accordance with studies in the mouse system which indicated that immunologic competence may not be the critical factor in oncogenesis in this tumor-virus system (6).

In the present studies, the primary tumors induced by mouse-derived virus in the newborn rat were found to be freely transplantable in animals of the same strain. This tumor in early passages showed a high rate of regression. In later passages all tumors implanted grew progressively and killed the host. Similar findings of increased malignancy following serial transplantation have been reported and discussed for the same viral-induced tumor in mice (20) and for a spontaneous rhabdomyosarcoma in rats (14). Since newborn and adult rats are susceptible to primary tumor induction, and since the tumors contain oncogenic virus, it is difficult to determine under the present experimental conditions whether the tumors developing following whole cell transplantation are progeny of the original transplanted cells or whether they represent de novo oncogenesis by the virus released from the tumor cells. This may be resolved by studies analogous to those performed with this viral tumor in mice (7), i.e., transplantation or implantation of parental tumor cells into F1 recipients and determination of the isoantigenic characteristics of resultant tumors.

Consistent features in the pathogenesis of the tumor in the rat were the high incidence of pulmonary involvement and the draining lymph nodes. The tumor nodules found in the lungs are either from metastasis or primary virus-induced neoplasms at that site. The following observations support a metastatic origin for the pulmonary tumors. The tumors appeared and grew in the lungs only after extensive tumors developed at the site of inoculation. Further, intravenous inoculation of mice with this virus rarely produced tumors in the lungs, although tumors appeared extensively in various striated muscle tissue (19). It is also possible that the origin of the pulmonary lesions are both metastatic and primary virus induced. Pulmonary metastases, histologically similar to these reported in this paper, have been frequently observed in children with rhabdomyosarcomas (21; and D. Pinkel, personal communication 1967) as well as in rats carrying a spontaneous transplantable rhabdomyosarcoma (14).

In the mouse system, it was indicated that this neoplasm may be classified as a rhabdomyosarcoma (4, 18). The histologic appearance of the tumor in the rat showed less differentiation toward muscle cells and a higher incidence of mitoses than in the mouse tumor (19). The cells comprising the rat tumor were undifferentiated, spindle, and round or polygonal; only occasionally, cells showed poorly developed longitudinal and cross striations, while the staining properties of the cytoplasm resembled closely that found for the mouse tumor cells. The electron microscopic appearance of the rat tumor cells were characterized by cytoplasmic fibrils. The size of the cytoplasmic fibrils and the occasional appearance of the horizontal banding (Z-bands) resembles the basic pattern found in early stages of myoblast formation of the rat skeletal muscle (1) and in childhood rhabdomyosarcoma (11). Although numerous cytoplasmic fine filaments are frequently observed in a variety of different normal and tumor cells not of "muscle origin" (2, 5, 10, 12, 13), they are generally thinner and lack the horizontal banding noted in this study.

The electron microscopic findings and the histologic staining properties of this tumor in the rat suggest classification of this sarcoma as an undifferentiated rhabdomyosarcoma. It is noteworthy, however, that cross striations are helpful but not essential in establishing this diagnosis (22).

In the rat system, the tumor cells, both at the site of inoculation and in the metastatic nodules, showed active virus formation. They are indistinguishable from those found in mouse and rat leukemias and identical to the virus found in this neoplasm in mice. However, the smaller type particle (most probably the LDH agent) which was also found in some of the mouse tumors (4) or tumorous spleens (20), and felt not to be related etiologically to this sarcoma, were not observed in the rat system.

During routine passage of Moloney's leukemia virus in rats, Harvey (9) isolated from the plasma of a leukemic rat a virus that produces tumors in mice, rats, and hamsters. These neoplasms share some histopathologic similarities to the sarcoma presented herein. The tumors found by Harvey (3, 9) were grossly either solid or cystic and filled with blood. The cystic tumor had an angiomatous response consisting of multiple dilated sinuses filled with blood and lined with cuboidal cells. The cystic tumor was not observed in animals inoculated with the Moloney sarcoma isolate. The spleen response and the peripheral blood smear patterns differ in animals which receive the Moloney or Harvey isolates. The marked splenomegaly, the death from splenic rupture, the histology of the spleen, and the peripheral blood smear that resembles Friend and Rauscher disease were not observed in the rats inoculated with Moloney sarcoma. The splenomegaly associated with this sarcoma isolate is very moderate and is due to an increase in both the red and white pulp.

However, by employing a "focus purified" line of Harvey sarcoma virus, the massive splenomegaly and splenic rupture which was induced by the virus before purification did not occur in newborn C57/BL mice (26). Thus, it appears that a symptomatic characteristic of the Harvey sarcoma virus disease has been eliminated by cell culture passage. The exact relation between the reported agent and MSV-Harvey, both ostensibly derivatives of the Moloney leukemia, has still to be determined.

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REFERENCES

Pathogenesis of Viral Rhabdomyosarcoma


Fig. 1. Gross photograph of a tumor-bearing rat 13 days after injection of tumor cell suspension. Note pulmonary metastases.

Fig. 2. Low-power view of a typical tumor. Mallory-azan, $\times$ 100.

Fig. 3. Enlargement of a section of Fig. 2. Note mitotic figures. H & E, $\times$ 400.

Fig. 4. Enlargement of a section of Fig. 2. Note distinct nucleoli. Masson's trichrome, $\times$ 650.

Fig. 5. Low-power view of an extensive tumor, showing the sparse connective tissue stroma. Wilder, $\times$ 100.

Figs. 6, 7. Histologic sections from rats autopsied in the early stages of tumor formation. Note the local reaction and clusters of tumor cells. H & E, $\times$ 250.

Fig. 8. Low-power view of a tumor node in the lung. Masson's trichrome, $\times$ 85.

Fig. 9. Enlargement of a section of Fig. 8. Masson's trichrome, $\times$ 650.

Fig. 10. Lymph node replaced by tumor cells. H & E, $\times$ 140.

Fig. 11. Enlargement of a section of Fig. 10. H & E, $\times$ 650.

Fig. 12. Liver of a tumor-bearing rat; see text. H & E, $\times$ 140.
K. Perk, D. A. Shachat, and J. B. Moloney
Pathogenesis of Viral Rhabdomyosarcoma

Fig. 13. Virus budding confined to relatively small areas of a tumor cell-plasma membrane. × 99,000.
Fig. 14. Four viral buds at the surface of a tumor cell obtained from a pulmonary tumor nodule. × 44,000.
Fig. 15. Small tumor cell vacuoles containing virus. × 99,000.
Fig. 16. An area of the cytoplasm of a tumor cell showing multivesicular bodies containing virus particles. × 44,000.
Figs. 17-19. These low-power electron micrographs show typical tumor cells obtained either from the primary tumor or from pulmonary metastases. The preparations were stained with uranyl acetate and lead citrate.
Fig. 17. Tumor cell obtained from the primary tumor, showing fibrils which occupy much of the cytoplasm and the poorly developed endoplasmic reticulum. Mitochondria, Golgi complex, and lipid droplets appear at the cortical site of the cell. × 8,600.
Fig. 18. Part of a tumor cell obtained from the primary tumor, illustrating bundles of fibrils intermingled with a granular substance along the borders of the cell. The ergastoplasm shows an orientation along the longitudinal axis of the cell. A flocculent granular precipitate in the cisternae of the endoplasmic reticulum can be seen. The mitochondria have mostly circular or oval profiles. × 12,000.
Fig. 19. Tumor cell, similar to Fig. 17 but obtained from a pulmonary metastasis. Note undulation and projections of the nucleus. Pinocytotic vesicles and virus particles are at the cell plasma membrane (bottom). × 8,600.
Fig. 20. Enlargement of a section of Fig. 15 showing an area of the cytoplasm of a tumor cell. Details of the fibrils and the poorly developed ribosome-studded endoplasmic reticulum can be seen. × 44,000.
Fig. 21. An area of the cytoplasm of a tumor cell obtained from a pulmonary metastasis, showing bundles of fibrils coursing through the cell. × 44,000.
Fig. 22. Enlargement of a section of Fig. 18 showing a bundle of fibrils at the border of the cell. × 44,000.
Fig. 23. Part of the cytoplasm of a tumor cell, obtained from the primary tumor, showing a bundle of fibrils coursing through the midportion of the cell. × 44,000.
Fig. 24. Part of the cytoplasm of a tumor cell, obtained from a pulmonary metastasis, showing bundles of fibrils. Electron-dense areas of the bundles give the suggestion of Z bands. Note granular material in close association with the fibrils. × 54,000.
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