Ultrastructural Comparison between the Parenchymal Cells of Tumors Derived from Parent and Hybrid Lines of C1300 Mouse Neuroblastoma and C6 Rat Glioma

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SUMMARY

Hybrid cell line 108CC5, obtained by fusion of N18TG2 mouse neuroblastoma and C6BU1 rat glioma lines, was injected intracranially or s.c. into nude mice. The tissues of the resultant intracranial and s.c. tumors were processed for light, phase, and electron microscopy. For comparison, the tumors induced by inoculation of the parent lines in the respective animal hosts were also studied. Histologically, the hybrid tumor resembled a very cellular, anaplastic neoplasm bearing a greater resemblance to the neuroblastoma than to the glioma type of growth. Under the electron microscope hybrid tumor cells also showed a greater resemblance to neuroblastoma than to glioma tumor cells. Hybrid tumor cells were large (even huge). The cytoplasm contained all the typical organelles. Dense core vesicles and intracisternal type A particles were a regular feature of these cells. Annulate lamellae were also seen frequently. Some of the large cell processes contained numerous microtubules; others were instead packed with filaments. Dense core vesicles and clear vesicles were clustered along some of these processes and at their tips. Unequivocal synapses were not seen, but profiles suggestive of these structures were observed occasionally. Type C virus particles, both budding at the cell surface and lying extracellularly, were commonly noted in the specimens of the hybrid tumor.

In conclusion, hybrid tumor cells bore a greater morphological resemblance to neuroblastoma than to glioma tumor cells and showed the "differentiated" morphology of neuroblastoma cells in vitro under a variety of experimental conditions. It would seem, therefore, that parent and hybrid cells from quickly growing, anaplastic-looking tumors, or at least a contingent of cells from these tumors, can achieve morphological "differentiation" in vitro just as effectively as their counterparts do in vivo under a variety of experimental conditions.

INTRODUCTION

Cultured cells of rat glioma (7, 35, 38), mouse neuroblastoma (17, 34, 36), and hybrids derived from neuroblastoma × glioma cell lines (10) have already been studied at the ultrastructural level. In addition, some little-known electron microscopic studies of cell and cell-free extract-transplanted C1300 mouse neuroblastoma have also been reported (28, 33, 39). However, a previous parallel study of cell-transplanted C6 rat glioma has not yet been published.

In this paper we will report our morphological observations of a tumor induced in nude mice inoculated with a hybrid line obtained by fusion of C1300 mouse neuroblastoma and C6 rat glioma parent cell lines. For comparison, a brief account will be given of the findings of a companion study of the tumors grown from the corresponding parent cell lines. Our observations will be discussed and compared with the pertinent data in the literature.

The results of the studies to be reported here have been published in abstract form (3) and will be detailed elsewhere with some additional findings.

MATERIALS AND METHODS

Cells. C6 rat glioma sublines originated from an experimental brain tumor of an adult Wistar rat that had been given repeated i.v. injections of methylnitrosourea (5, 6). The neoplastic tissue recovered from the original host was established in culture and maintained in vitro. The C6BU1 5-bromodeoxyuridine (Sigma Chemical Co., St. Louis, Mo.)-resistant mutant line (27) was isolated from clone N18 (37) of a transplanted specimen of the tumor, which had been propagated in vitro from the original tumor.

C1300 mouse neuroblastoma sublines originated from a spontaneous tumor of a 4-month-old male A/J mouse that had developed a growth in the spinal region, which projected into the abdominal cavity. This tumor had been passage in vivo for almost 30 years before it was adapted to tissue culture (4, 23, 36). The N18TG2 6-thioguanine (Sigma)-resistant mutant line (27) was isolated from clone N18 (37) of a transplanted specimen of the tumor, which was about 1000 passages removed from the original neoplasm.

Hybrid cell line 108CC5 was obtained from N18TG2 and C6BU1 parent cell lines. Growth characteristics and morphological, electrophysiological, biochemical, and karyological properties of the hybrid cells, as well as details on the fusion procedure of the parent cells, have been reported (2, 10, 18-20).

Animals. A colony of nu/nu mice with a BALB/c genetic background was used. To whom requests for reprints should be addressed, at Max-Planck-Institut für Psychiatrie, Krefelinstrasse 2, D-8000 München 40, Federal Republic of Germany.

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2 To whom requests for reprints should be addressed, at Max-Planck-Institut für Psychiatrie, Krefelinstrasse 2, D-8000 München 40, Federal Republic of Germany.

3 A. P. Anzil, manuscript in preparation.

2236 CANCER RESEARCH VOL. 37

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Tumors Grown from Neuroblastoma and Glioma Cells

The cells spread out in sheets with focal areas of necrosis. The neuroblastoma x glioma tumor specimens also showed a very cellular type of tissue characterized by bulky cells with a voluminous nucleus of variable configuration (Fig. 3). Mitotic figures and multinucleated giant cells were a regular finding. Single necrotic cells and extensive areas of necrosis were frequent. Despite the large size and distinct pleomorphism of its cells, the hybrid tumor was more reminiscent of the neuroblastoma than of the glioma type of growth.

Phase Microscopy. The phase microscope study of semithin sections of the hybrid tumor confirmed the high cellularity of the neoplastic tissue. The cell processes occupied part of the intercellular space, often adhering to, and even indenting, the outline of the cell bodies. In addition, rounded areas stood out as enclaves of optically differentiated cytoplasm inside the cell bodies of isolated tumor cells (Fig. 23).

Electron Microscopy. Under the electron microscope hybrid tumor cells also showed a greater resemblance to neuroblastoma than to glioma tumor cells. Nonetheless, it was easy to assign correctly any given specimen to 1 of the following oncotypes, without previous information on the origin of that particular sample.

Glioma tumor cells (Figs. 4 and 5) corresponded closely to glioma cultured cells, as reported in the literature (7, 35, 38). The nuclei contained scattered masses of heterochromatin, which was generally condensed along the nuclear membrane. The perikarya showed the usual organelles embedded in a feltwork of about 100-Å filaments. Isolated microtubules were also seen. Dense bodies were numerous in an occasional cell. Most of them probably belonged to the lysosomal system; others, most likely, were examples of the osmiophilic particles known to occur in astrocytes of normal and pathological brain material of various species (12). Medium-sized to stout processes intervened between some of the cell bodies; many were packed with parallel running filaments interspersed with infrequent microtubules (Fig. 5).

Neuroblastoma tumor cells (Figs. 6 to 10) corresponded to neuroblastoma cultured cells (9, 14, 17, 34, 36) and to cell- and cell-free extract-transplanted neuroblastoma tumor cells (28, 39) except for the following features. Type C particles (28) were regularly observed in our material. Annu late lamellae were numerous in all of our specimens of neuroblastoma (Figs. 6 and 8). Cilia were rare. Occasionally, a transversely cut cilium revealed a 9 + 0 pattern (Fig. 10). Large collections of clear vesicles (9, 34) were not demonstrated in our N18TG2 neuroblastoma tumor cells. Profiles of a peculiar form of cell-to-cell interaction (14) were rarely encountered in our neuroblastoma specimens.

The following is a summary of the ultrastructural features of the tumor cells as they emerged after examination of many blocks of 5 different specimens of the hybrid tumor. The cells were large and had a rounded or grossly polygonal outline (Fig. 24) when no major process was given off in the plane of section. The nuclei also reached considerable dimensions and were often multiple and irregularly shaped (Fig. 13). Intranuclear inclusions were common (Figs. 13 and 14). An accumulation of cytoplasmic structures, particularly microtubules and smooth endoplasmic reticulum, oc-

RESULTS

A 100% hybrid tumor incidence was observed with the 1 × 10^6 inoculum of neuroblastoma x glioma cells. Neoplasms (i.c.) killed their hosts approximately 2 weeks after inoculation. Neoplasms (s.c.) developed just as quickly as i.e. killed their hosts approximately 2 weeks after inoculation.

Experimental Procedures. Adult nude mice were inoculated with cells of hybrid line 10BC5 or neuroblastoma line N18TG2. NMRI mice were given injections of N18TG2 neuroblastoma cells, and Wistar rats received injections of C6BU1 glioma cells. The cells were suspended in 0.02 or 0.2 ml medium and were inoculated either i.c. or s.c., with the number of cells in the inoculum varying between 5 × 10^5 and 1 × 10^6 in the different experiments.

Tissue Studies. The experimental animals were slightly anesthetized, and the tumors were exposed. Fragments of the neoplasms with or without parts of the neighboring tissues were fixed in 3% glutaraldehyde or in 10% formalin. Histological sections were prepared from the formalin-fixed and paraffin-embedded specimens and were stained with hematoxylin and eosin. Glutaraldehyde-fixed specimens were postfixed in OsO4, dehydrated in graded alcohols, and embedded in Epon 812 (Carl Roth, Karlsruhe-West, Federal Republic of Germany). Semithin sections were prepared from selected blocks of hybrid tumor, stained with p-phenylenediamine (Merck-Schuchardt, Munich, Federal Republic of Germany), and examined with a phase microscope. Ultrathin sections were prepared with diamond knives from blocks of all 3 types of tumors, stained with uranyl acetate and lead citrate, and viewed with a Zeiss EM 9A or 10A electron microscope.

Light Microscopy. All specimens could be easily identified and assigned to 1 of the following oncotypes.

The samples of glioma showed a cellular tumor with medium-sized cells set in a small amount of lightly stained intercellular matrix (Fig. 1). The cells were ovoid or spindle shaped and possessed a moderate amount of cytoplasm tapering off at the opposite sides of the nucleus. Mitoses were rare. The cells were laid out in interwoven bundles.

The specimens of neuroblastoma were also quite cellular (Fig. 2). The neuroblastoma tumor cells had a greater diameter, a more rounded configuration, and a larger nucleus than the glioma tumor cells. Mitoses were not rare, nor were giant cells uncommon. Nuclear and cytoplasmic variability, however, was not a conspicuous feature of the tumor cells.

The abbreviation used is: i.c., intracranial.
tumor cell soma. Microfilaments often formed a narrow net singly or in small groups in many cells (Figs. 11 to 15). Most, work extending beneath the cytoplasmic aspect of theoplasm and on the inner side of the nuclear membrane occurred in some intranuclear inclusions (Fig. 14). The nu
of them. The preferential location of these particles was the plasma membrane (Fig. 17). Dense core vesicles occurred
lamellae cut in different planes of section were common. Clear chromatin was thinly distributed throughout the nu
A. P. Anzil et al.
endoplasmic reticulum. Only isolated cells had tall stacks of
lumen of the granular endoplasmic reticulum, including the perinuclear cisterna. Ribosomes were fairly abundant. They formed scattered rosettes throughout the cytoplasm and decorated the abluminal surface of sparse cisternae of endoplasmic reticulum. Only isolated cells had tall stacks of long, parallel cisternae of granular reticulum (Fig. 12). The multilaminar endoplasmic reticulum described by 1 of the authors (13) in the cells of a cerebellar astrocytoma and reported generally in neoplastic cells (29) was also found in the hybrid tumor cells (Fig. 15). The tumor cells gave off many processes of variable size and composition (Figs. 11, 16, 18, 19, 25, and 26). Collections of clear vesicles about 550 Å in diameter were encountered along the processes (Figs. 19 and 28) and, more often, at their expanded tips (Fig. 18). The tumor cells were generally dissociated. In the extracellular space, type C virus particles, either singly or in groups of up to 12 virions, were present in all specimens of the tumor (Figs. 20 and 21). The extracellular virions appeared in various stages of maturation ranging from forms with a toroidal nucleoid to those with a centrally placed, dense nucleoid (Fig. 22, d to i). Virus particles budding from the cell membranes were also observed regularly, but they were less common than extracellular virions (Fig. 22, a to d). An intercellular space of about 200 Å separated the cell membranes of the closely packed tumor cells. Focal areas of thickening on the cytoplasmic side of either cell membranes were common (Figs. 19 and 28). Some examples of cell-surface specialization approximated a typical-looking synaptic junction (Figs. 29 and 30). Occasionally, a large cell process (Figs. 25, 26, and 28) or a segment of a tumor cell body (Fig. 27) appeared as a cytoplasmic enclaves inside the soma of another tumor cell; an extension of the extracellular space was recognizable between the profile of the cytoplasmic inclusion and that of the investing perikaryon.

DISCUSSION

Our studies confirmed in vivo an observation previously made in vitro, namely, that hybrid cells bear a greater resemblance to neuroblastoma than to glioma cells (10). In addition, we have shown that both hybrid and neuroblastoma tumor cells have essentially the morphology of so-called differentiated neuroblastoma cells in vitro. Therefore, growth conditions and factors promoting nerve cell differentiation in vitro seem to be equally present and effective in vivo, and perhaps more in vivo than under a variety of in vitro experimental conditions (15). However, “nerve cell differentiation,” as observed in neuroblastoma cells in vitro, entails loss of tumorigenicity (31) and blockade of the cells in the G1 phase of their cycle (32), besides acquisition and/or enhanced expression of certain morphological characteristics. Therefore, this concept of nerve cell differentiation developed from in vitro observations finds only limited support in our observations on neuroblastoma parent and hybrid cells of differentiated morphology entering in the composition of rapidly growing tumors.

Apart from the presence of type C virus particles and annulate lamellae and the absence of large clusters of clear vesicles, the morphology of our neuroblastoma cells in vivo corresponds essentially to that of neuroblastoma cells in vitro, as reported in the literature (17, 34, 36). At any rate, annulate lamellae are a regular feature of many tumor cells and have been repeatedly demonstrated in cultured neuroblastoma cells of human origin (16, 26). As for the clear vesicles, isolated profiles of this type and minute collections of them were not entirely absent in our neuroblastoma tumor cells.

The morphology of the hybrid cells in vivo also corresponded to that reported in a study of these cells in vitro (10), except for the occurrence of annulate lamellae, type C virus particles, and profiles of cells invaginating into other cells. On the whole, hybrid cells in vivo looked very much like “superneuroblastoma” cells. In other words, hybrid cells in vivo differed from neuroblastoma cells in vivo not because they had some characteristic feature but because they had all the usual features of neuroblastoma cells to an even higher degree. This was evident, for instance, in the case of the type C particles, which were numerous in hybrid tumor material but few and thinly scattered in neuroblastoma material (21).

The issue of whether a type C virus occurs in neuroblastoma tumor cells and in neuroblastoma cells either cultured or obtained by crossing a mouse neuroblastoma line with another line is fraught with contradictory data. For instance, morphological evidence for the occurrence of such a virus in neuroblastoma tumor cells in vivo was reported (28) prior to our own observation (21). However, there is as yet no morphological evidence for the same finding in neuroblastoma parent or hybrid cells in vitro. Likewise, levels of reverse transcriptase activity measured in supernatant fluid of neuroblastoma cells of the Neuro-2a line were indicative of a B-tropic murine type C virus (24). The same test performed by the same authors working with susceptible cells cocultivated with neuroblastoma cells grown from explants of the corresponding solid tumor gave no evidence for a type C virus (25). Finally, tumorigenicity tests with cell-free tumor extracts gave positive results in the hands of some investigators (33), but negative results in the hands of others (28). Considering our simple observation against the background of the available data, any positive statements about the origin, host range class, or general biological significance of the type C virus we found in our neuroblastoma parent and hybrid cells in vivo are unwarranted. The fact remains that inoculation of mice with neuroblastoma and neuroblastoma × glioma cultured cells probably free of
morphologically detectable virus resulted in solid tumors, the cells and cell interstices of which were seeded with type C particles.

A feature of interest in our hybrid tumor cells was the occurrence of cell profiles invaginating into other such profiles. We could not ascertain whether this finding documented some special form or a particular stage of tumor cell-tumor cell emperipolises or whether it had anything to do with the neural origin of the tumor cells per se. All we can say at present is that profiles of this kind are known to occur in mixed cultures of neuroblastoma and cardiac muscle cells (14) and in normal cells in vivo (11) and in vitro (22) of the particular tissue from which the original tumor of the A/J mouse was probably derived. Keeping this in mind, one can regard the C1300 mouse neuroblastoma as a tumor of neural crest origin composed of neuroblasts in various stages of maturation. In accordance with this view, the designation “sympathetic neuroblastoma” is more apt than the term “neuroblastoma,” by which the tumor is currently known.

Finally, despite an extensive search documented in a number of morphological studies, synaptic junctions between neuroblastoma parent and hybrid cells or between them and the appropriate target cell have not been demonstrated either in vivo or in vitro. Actually, the cell surface specializations we have seen in a few of our hybrid tumor cells are the closest yet to bona fide synaptic specializations. One can only conclude that synapses between these cells must be very rare, and to visualize them under the electron microscope may require a truly exhaustive search. The use of special staining procedures (1, 8, 30) could possibly facilitate the search and increase its chance of success.

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REFERENCES


Fig. 1. Photomicrograph of a histological section from the C6BU1 tumor grown in a Wistar rat inoculated with cell line C6BU1 of C6 rat glioma cells. The slightly elongated cells in a scanty intercellular matrix are compatible with a diagnosis of astrocytoma. H & E, × 384.

Fig. 2. Photomicrograph of a histological section from the N18TG2 tumor grown in a NMRI mouse inoculated with cell line N18TG2 of C1300 mouse neuroblastoma cells. The sheet-like pattern of growth is not inconsistent with that of a neuroblastoma; the moderately abundant cytoplasm of the tumor cells and the medium-sized nuclei with a small nucleolus and stippled chromatin are suggestive of a tumor composed of cells in a stage of maturation past that of the neuroblasts. H & E, × 384.

Fig. 3. Photomicrograph of a histological section from the 108CC5 tumor grown in a nude mouse inoculated with hybrid cell line 108CC5 obtained by crossing cell lines C6BU1 and N18TG2. The nuclear and cytoplasmic polymorphism of the tumor cells defies a precise oncotypic identification of the neoplasm; nonetheless, the hybrid growth resembles the N18TG2 more closely than the C6BU1 transplant tumor. H & E, × 384.

Fig. 4. Electron micrograph of a sample of the C6BU1 transplant neoplasm. This tumor cell has a relatively large, indented nucleus and a cytoplasm of medium density containing collections of randomly oriented filaments (arrows), × 18,000.

Fig. 5. Electron micrograph of a C6BU1 transplant tumor specimen. This tumor cell process contains a bundle of parallel filaments, about 100 Å thick, interspersed with infrequent microtubules. × 48,500.

Fig. 6. Electron micrograph of a sample of N18TG2 transplant tumor. This low-power view of the tumor cells allows recognition of an area teeming with intracisternal type A particles (long arrows), an array of annulate lamellae (short arrows), and a point of attachment between 2 cells (arrowheads), × 5,800.

Fig. 7. Electron micrograph of a specimen of N18TG2 transplant tumor. Collection of intracisternal type A particles in the cytoplasm of a tumor cell occupying one-half of the picture. The long, medium-sized cell process running across the other half of the picture has a core of longitudinally oriented microtubules (arrows), × 38,000.

Fig. 8. Electron micrograph of a N18TG2 transplant tumor specimen. A stack of annulate lamellae in a tumor cell. × 35,000.

Fig. 9. Electron micrograph of a specimen of N18TG2 transplant tumor. The attachment plaques found along a segment of plasmalemma join 2 adjacent tumor cells. × 54,000.

Fig. 10. Electron micrograph of a sample of N18TG2 transplant tumor. Transversely cut cilium with a 9 + 0 pattern in a tumor cell. × 43,600.

Fig. 11. Electron micrograph of a 108CC5 transplant tumor sample. Section of a tumor cell giving off a large, neurite-like process. × 9,000.

Fig. 12. Electron micrograph of a 108CC5 transplant tumor specimen. An orderly array of rough endoplasmic reticulum in the cytoplasm of a tumor cell. × 35,000.

Fig. 13. Electron micrograph of a 108CC5 transplant tumor sample. Multinucleated tumor cell with a peculiar distribution of the chromatin material in some of the nuclear profiles. × 8,000.

Fig. 14. Electron micrograph of a specimen of 108CC5 transplant tumor. A large pseudoinclusion in the nucleus of a tumor cell. The elements of the smooth endoplasmic reticulum are clearly concentrated within the confines of the inclusion. × 12,000.

Fig. 15. Electron micrograph of a sample of 108CC5 transplant tumor. Segment of a tumor cell with extensive formation of multilaminar endoplasmic reticulum between isolated stretches of annulate lamellae. × 18,000.

Fig. 16. Electron micrograph of a specimen of 108CC5 transplant tumor. A large pseudoinclusion in the nucleus of a tumor cell. The elements of the smooth endoplasmic reticulum are clearly concentrated within the confines of the inclusion. × 12,000.

Fig. 17. Electron micrograph of a sample of 108CC5 transplant tumor. A fuzzy network of interwoven microfilaments can be recognized beneath the plasmalemma of the tumor cell (long arrows); an isolated type A particle is budding into a cisterna of the tumor cell perikaryon (short arrow), × 54,000.

Fig. 18. Electron micrograph of a 108CC5 transplant tumor specimen. The tumor cell process in the middle of the picture displays numerous clear vesicles admixed with a number of dense core vesicles. × 18,000.

Fig. 19. Electron micrograph of a sample of 108CC5 transplant tumor. A tumor cell process containing many clear and dense core vesicles and showing an attachment point along its contour (long arrow) indenting the profile of a tumor cell; dense material undercoats the small cytoplasmic invagination along the plasmalemma of the tumor cell profile (short arrow), × 18,000.

Fig. 20. Electron micrograph of a specimen of 108CC5 transplant tumor. Type C virus particles in the extracellular space of the tumor; a budding particle is also included in this picture (arrow), × 45,200.

Fig. 21. Electron micrograph of a sample of 108CC5 transplant tumor. Many type C particles are lying extracellularly; transversely cut collagen fibers are seen in the vicinity. × 44,200.

Fig. 22. Electron micrograph of several specimens of 108CC5 transplant tumor. A composite picture of type C virus particles in various stages of cell surface budding (a to d) and extracellular maturation (d to i). b and c, × 90,000; others, × 125,000.

Fig. 23. Phase-contrast micrograph of a 108CC5 transplant tumor specimen. Tumor cells have a polygonal outline; a well-demarcated, small, round area stands out in the cytoplasm of a tumor cell. Epon embedded section, about 1 μm thick, stained with p-phenylenediamine. × 1,200.

Fig. 24. Electron micrograph of a specimen of 108CC5 transplant tumor. The attachment plaques found along a segment of plasmalemma join 2 adjacent tumor cells. × 54,000.

Fig. 25. Electron micrograph of 108CC5 transplant tumor sample; same ultrathin section as in the preceding figure. The invaginating cell profile is seen to be caught up in the perikaryon of another tumor cell. × 4,800.

Fig. 26. Electron micrograph of 108CC5 transplant tumor sample; same ultrathin section as in the preceding figure. The invaginating cell profile is seen to be caught up in the perikaryon of another tumor cell. × 4,800.

Fig. 27. Electron micrograph of a 108CC5 transplant tumor section. The attachment plaques found along a segment of plasmalemma join 2 adjacent tumor cells. × 18,000.

Fig. 28. Electron micrograph of a specimen of 108CC5 transplant tumor. Part of a tumor cell harboring a sunken cell process; dense core vesicles are numerous in the engulfed process, while 2 small, coated cytoplasmic invaginations (arrows) are seen along the plasmalemma of the cell investing the engulfed process. × 18,000.

Fig. 29. Electron micrograph of a specimen of 108CC5 transplant tumor. Part of a tumor cell harboring a sunken cell process; dense core vesicles are numerous in the engulfed process, while 2 small, coated cytoplasmic invaginations (arrows) are seen along the plasmalemma of the cell investing the engulfed process. × 18,000.
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