Comparison of Subacute Sclerosing Panencephalitis and Measles Viruses: an Electron Microscope Study

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The ultrastructure of CV-1 cells infected with subacute sclerosing panencephalitis (SSPE) viruses was compared with that of CV-1 cells infected with the wild or Edmonston strain of measles virus. Both SSPE viruses and the measles viruses produced two types of nucleocapsid structures: smooth filaments, 15 to 17 nm in diameter, and granular filaments, 22 to 25 nm. The smooth and granular filaments produced by SSPE and measles virus did not differ in appearance. In CV-1 cells infected with SSPE viruses, smooth filaments formed large intranuclear inclusions and granular filaments occupied a large area of the cytoplasm, but always spared the area under the cell membrane. Particles budding from the surface of these cells contained no nucleocapsids. In CV-1 cells infected with measles virus, only small aggregates of smooth filaments were seen in the nuclei. Granular filaments in the cytoplasm predominantly occupied the area under the cell membrane, and were aligned beneath the cell membrane in a parallel fashion and assembled into budding particles. These differences between SSPE and measles virus may be regarded as quantitative, but they do distinguish SSPE viruses from measles virus. Moreover, the formation of large nuclear inclusions filled with smooth filaments appears to be a characteristic process of SSPE, but not of measles, since this type of inclusion is invariably seen in SSPE brain tissues, brain cultures derived from them, and CV-1 cells infected with SSPE viruses.

Subacute sclerosing panencephalitis (SSPE), a slowly progressive inflammatory disease of the central nervous system in children, is characterized by the presence of eosinophilic nuclear inclusions in neurons and oligodendroglial cells (5, 6) and has been considered a slow virus disease. Recently, infectious viruses closely related to, or identical with, measles virus have been isolated from a number of patients with SSPE (1, 9, 10, 21). The techniques required for successful isolation of these viruses were indirect and depended on establishment of cell cultures from brain tissue obtained at biopsy.

In our laboratory, such viruses were isolated from two patients after fusion of their brain cell cultures with susceptible indicator cells in the presence of inactivated Sendai virus (1, 14, 15, 17, 20). These viruses share many antigenic determinants with measles virus. In tissue culture they produce a cytopathic effect characterized by syncytia, giant cells, nuclear inclusions, and

nucleocapsids (1). However, a more precise characterization of these viruses is required before their relation to measles and SSPE can be firmly established. The mechanisms of the pathogenesis of this disease remain obscure.

The present paper compares the ultrastructure of cells infected with two viruses isolated in SSPE (hereafter referred to as "SSPE viruses") with that of cells infected with two strains of measles virus.

MATERIALS AND METHODS

Cell line. CV-1 cells, a continuous line derived from African green monkey kidney cells and maintained in the laboratory in Eagle's basal medium supplemented with 10% heat-inactivated fetal calf serum, were used.

Viruses. The JAC and LEC viruses were derived from brain cell cultures of patients with SSPE by the method of cell fusion, previously described (1). The Edmonston (EDM) strain of measles virus was kindly supplied by Maurice Hilleman of Merck, Sharpe and Dohme, West Point, Pa., and a wild measles virus strain, Woodfolk, isolated from the throat of a patient with acute measles, by Edwin C. Lennette of the California State Public Health Laboratory, Berkeley, Calif. Stocks of all of these viruses were

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prepared in CV-1 cells. JAC virus was used in the fifth passage and LEC virus in the eighth passage.

Infection of cells. Cells were infected in suspension by exposure to the viruses at an input multiplicity of 0.01. The mixture was incubated for 1 hr at 37 C in a water bath. The cells were then centrifuged for 8 min at 1,000 rev/min at 4 C; the supernatant was discarded and the cell pellet was suspended in fresh medium and seeded into plastic flasks.

Electron microscopy. The infected monolayer cultures grown in plastic flasks were fixed in situ with phosphate-buffered 2% glutaraldehyde for 30 min and 1% osmium tetroxide for 1 hr, and were embedded in epoxy resin in situ. After polymerization of the epoxy resin, the plastic surface was removed by immersion in acetone. Since the thin layer of epoxy resin did not reduce the transparency of the cell layers, this procedure made it possible for the whole cell layer to be examined under a conventional light microscope or phase-contrast microscope. Small pieces of areas containing giant cells were then cut out and glued to previously polymerized epon blocks so that thin sections could be cut parallel to the plane of the cell surface.

Serial thin sections were prepared on a Porter-Blum MT-1 microtome, stained with uranyl acetate and lead citrate, and examined under a Siemens Elmiskop 1 electron microscope.

Fluorescence microscopy. Infected cells were seeded on cover slips and harvested after the cytopathic effect became prominent. They were then washed twice in phosphate-buffered saline solution, air-dried, and fixed in acetone for 10 min at room temperature. They were exposed to serum from an SSPE patient and subsequently stained with fluorescein isothiocyanate-conjugated anti-human IgG rabbit serum obtained commercially from Behring Werke.

RESULTS

Cells infected with viruses isolated in SSPE. Cells infected with one or the other SSPE virus did not differ ultrastructurally, but the LEC virus induced more pronounced changes than the JAC virus.

One prominent change was the presence of aggregates of filamentous structures in the nuclei of these cells (Fig. 1 and 3, SF). In most instances, the aggregates were large, occupying almost the entire nucleus, with occasional parallel array formations, sparing narrow areas under the nuclear membrane and around the nucleoli (Fig. 1). This type of aggregate will be referred to as "inclusion type." In other cases, the aggregates appeared as small foci of tangles or bundles, 2 to 3 nm in diameter, scattered in an otherwise normal-appearing karyoplasm. When examined in serial sections, they proved not to be apical portions of the inclusion-type aggregates. This type of aggregate will be referred to as "speckled type."

At a higher magnification, individual filaments

within both the inclusions and the "speckles" showed hollow structures with periodic striations on the outer surface; their outer diameter measured approximately 15 to 17 nm, and their inner diameter, 5 to 7 nm (Fig. 2). The length of the filaments varied owing to their random position in the thin sections, but most of them, in parallel arrays cut tangentially, measured approximately 300 nm. These filaments will be referred to as "smooth filaments."

The cytoplasm of these cells contained filamentous structures of different appearance (Fig. 3, GF, and Fig. 4). They were essentially tubular, but fine granular material was attached to their outer surface, making them somewhat ill-defined (Fig. 4). Occasionally they were associated with ribosomes (Fig. 4, arrows) and rough-surfaced endoplasmic reticulum, appearing as if they were derived from them.

Although morphologically they resembled the smooth filaments in the nuclei, their size, 22 to 25 nm in diameter, was larger than that of the smooth filaments and, unlike the smooth filaments, their width was not uniform. They were never found in the nucleus and were never arranged in bundles or arrays, as were the smooth filaments. They will be referred to as "granular filaments." In most cases, they occupied a vast area of the cytoplasm, dispersed diffusely or in an insular fashion; they were seen predominantly in the perinuclear zone, and the area immediately under the cell membrane was always spared. In no instance were they seen to be aligned beneath the cell membrane, as was the case in cells infected with measles virus.

Minute undulations were observed occasionally over long stretches of the membrane. There were also numerous round, pleomorphic particles, 150 to 250 nm in diameter, seen free on the surface of these undulations (Fig. 5) as if they were being formed by budding from the cytoplasm (Fig. 5, arrows). There were no surface spikes projecting to the outside either on the undulated cell membrane or on the envelope of these pleomorphic particles (Fig. 5, insert). The contents of the buds was the same as that of the cytoplasmic substance immediately under the undulated cell membrane. They were not constituted of nucleocapsids but rather of fibrillar substance. Complete measles-like particles were not seen. These particles were quite obviously different from the microvilli observed in uninfected CV-1 cells.

Cells infected with the Woodfolk (WOOD) strain of measles virus. In a few nuclei, aggregates of smooth filaments of the speckled type were seen (Fig. 6, SF), but those of the inclusion type were never seen. The appearance of the individual filaments was the same as in the SSPE virus-

FIG. 1. Multinucleated giant cell among CV-1 cells infected with LEC virus, containing the inclusion type of smooth filaments in the nuclei. Note their parallel array formations. SF, smooth filaments; NO, nucleolus. $\times 18,000$.

FIG. 2. High magnification of smooth filaments from a nucleus of a CV-1 cell infected with LEC virus. $\times 155,000$.

FIG. 3. CV-1 cell infected with JAC virus. Granular filaments (GF) are dispersed mainly in the perinuclear zone. Note their granular and ill-defined appearance in contrast to the smooth filaments (SF) in the nucleus. $\times 24,000$.

FIG. 4. CV-1 cells infected with LEC virus. High magnification of granular filaments in the cytoplasm. The filaments are associated with fine granular material, attached to their outer surface, and, occasionally, with ribosomes (arrows). $\times 63,000$.

FIG. 5. Surface area of a giant cell infected with LEC virus. Numerous pleomorphic particles are seen on the undulated cell membrane. Some particles are being formed through the budding process (arrows). $\times 17,000$. Insert: High magnification of the particles. They do not contain the nucleocapsid. $\times 34,000$.

infected cells. In the cytoplasm, both smooth and granular filaments were observed (Fig. 7 and 8). Smooth filaments usually formed small aggregates, well demarcated from the rest of the cytoplasm, but they were rare (Fig. 7, SF, and Fig. 8, SF). A major change in these infected cells was the presence of a large number of the granular filaments which appeared the same as those seen in SSPE virus-infected cells (Fig. 6–8, GF, and Fig. 9). They were seen not only in the cells whose nuclei contained smooth filaments, but also in those whose nuclei appeared unchanged. They were usually distributed widely throughout the cytoplasm, but, in contrast to SSPE virus-infected cells, their predominant location was the area under the cell membrane; they were not seen in the perinuclear zone (Fig. 6). In some portions, they were aligned in a parallel fashion beneath the cell membrane (Fig. 6 and 9, arrows), which appeared thickened where they assumed tangential position to the direction of the sectioning (Fig. 9, arrows with dark heads). In addition on the surface of these altered portions of the cell membrane, there were minute spikes projecting outwards (Fig. 9) and virus particles, both in the process of budding from these changed

portions (Fig. 9) and free on the cell surface (Fig. 7 and 10). They were round, oval, or pleomorphic and ranged from 100 to 800 nm in diameter. The limiting membrane of these particles appeared the same as the altered cell membrane, with aligned granular filaments beneath and minute projections on the surface (Fig. 9 and 10). When sections of these particles were cut close to their outer surface, granular filaments appeared tangential and were seen to be coiled closely under the limiting membrane (Fig. 9).

Cells infected with Edmonston (EDM) strain of measles virus. Cytoplasmic changes in cells infected with the EDM strain were essentially the same as those in cells infected with the wild measles virus. However, the nuclei did not contain smooth filaments and appeared unchanged. Generally, changes in cells infected with EDM were less intense and virus particles were less numerous than those in cells infected with the wild measles virus.

These findings are summarized in Table 1.

Fluorescence microscopy. An examination of parallel cell samples by fluorescence microscopy demonstrated different staining patterns between SSPE- and measles-infected CV-1 cells (V. ter

FIG. 6. CV-1 cell infected with the wild strain of measles virus. Only small aggregates of smooth filaments (SF) of the speckled type are seen in an otherwise unchanged karyoplasm. Granular filaments (GF) occupy the area under the cell membrane but not the perinuclear zone. Note their parallel alignment under the plasma membrane (arrow). $\times 11,000$.

FIG. 7. CV-1 cell infected with the wild strain of measles virus. Note granular filaments (GF) dispersed diffusely in the cytoplasm and an aggregate of smooth filaments (SF) in the cytoplasm. $\times 10,000$.

FIG. 8. Higher magnification of the area enclosed by the rectangle in Fig. 7. Note differences between granular filaments (GF) and smooth filaments (SF) in appearance and size. $\times 40,000$.

FIG. 9. CV-1 cell infected with the wild strain of measles virus. Parallel alignment of granular filaments under the cell membrane and the envelope of a particle in the process of budding (arrows with light heads). Portions of the cell membrane where granular filaments assume the tangential position appear thickened

Meulen et al., *in preparation*). Sera from patients with SSPE produced two types of configurations of nuclear fluorescence, corresponding to those of the smooth filaments of the inclusion-type and speckled-type aggregates in SSPE-infected CV-1 cells (Fig. 11), but only fluorescent speckles appeared in CV-1 cells infected with the wild strain of measles virus. No nuclear fluorescence was observed in CV-1 cells infected with the Edmonston strain of measles virus. Diffuse cytoplasmic staining was seen in cells from all of the specimens, either of SSPE sera or of antimeasles serum (Fig. 12).

DISCUSSION

Electron microscopy of CV-1 cells infected with SSPE viruses or two strains of measles virus revealed two types of nucleocapsid structures: smooth and granular filaments. The smooth and granular filaments produced by the SSPE and measles viruses did not differ in appearance, although there were differences in the quantity of smooth filaments, in the distribution pattern of granular filaments, and in the production of virus particles.

One of the major differences observed was the formation of large nuclear inclusions filled with smooth filaments in CV-1 cells infected by SSPE viruses, and the absence of such inclusions in CV-1 cells infected with measles virus. Similar inclusions have been consistently observed in brain tissue biopsies obtained from patients with SSPE (2, 15, 22, 25) and in cell cultures derived from these biopsies (3, 15, 20), so that formation of this type of inclusion seems to be a process characteristic of SSPE. Although such inclusions have been described in green monkey kidney cells (18), HeLa cells (13), and Vero cells (16) infected with measles virus, they were unusual features of such infections.

Another point of difference of CV-1 cells infected with the SSPE viruses was the distribution pattern of granular filaments and the production of virus particles. In SSPE-infected cells, granular filaments usually spared the area under the cell membrane and consequently never exhibited parallel alignment beneath the cell membrane. This may be responsible for the absence of these filaments in the buds or particles on the cell surface. Thus, granular filaments do not become incorporated into budding particles. Although the particles do not contain nucleocapsids and spikes on the envelope, they resemble measles virions in

(arrows with dark heads). Minute spikes are projected to the outside from the changed membrane. Note association of granular filaments with the endoplasmic reticulum (ER). GR, granular filaments. $\times 40,000$.

FIG. 10. Virions from a CV-1 cell infected with the wild strain of measles virus. Granular filaments are aligned under the envelope of the virions (arrow). $\times 80,000$.

TABLE 1. Summary of findings in CV-1 cells infected with SSPE or measles viruses

Virus	Smooth filaments			Granular filaments in the cytoplasm	Alignment of granular filaments	Virions
	Nucleus		Cytoplasm			
	Inclusion type	Speckled type				
SSPE						
JAC.....	++	+	—	+++	—	—
LEC.....	+++	++	—	+++	—	—
Measles						
WOOD.....	—	++	+	+++	+++	+++
EDM.....	—	—	+	+++	++	++

regard to their size, pleomorphism, and manner of formation through budding. They are similar to the incomplete measles particles described by Nakai et al. (18). Complete measles-like particles could not be found in the SSPE-infected CV-1 cells that were examined, and this may be related to the relatively low infectivity titers of SSPE viruses (12).

In measles-infected CV-1 cells, on the other hand, granular filaments occupied mainly the area under the cell membrane and were characteristically aligned beneath the cell membrane,

probably preparatory to virus formation. That they were then assembled into virions through the budding process can be seen by the fact that the structure of the filaments aligned under the viral envelope was identical with that of the granular filaments. Smooth filaments were never noted in the virus particles. Although this process of virus maturation was not observed by Nakai et al. in BSC-1 cells infected with the Edmonston strain of measles virus (18), similar features of virus maturation were demonstrated in primary hamster cerebellum culture infected with the

FIG. 11. Multinucleated giant cell from a CV-1 culture infected with LEC virus, showing nuclear fluorescence of the inclusion type (arrows) in addition to the cytoplasmic fluorescence. $\times 500$.

FIG. 12. Multinucleated giant cell from CV-1 culture infected with Edmonston strain of measles virus, showing only cytoplasmic fluorescence. The antigen is aggregated in globules. Arrows point to nuclei free from fluorescence. $\times 500$.

Edmonston strain of measles virus (24), as well as in a number of paramyxoviruses (4, 7, 11, 23). In CV-1 cells infected with measles virus, the virus maturation was thought to follow a process similar to that in paramyxoviruses, so that it is likely that the granular filaments seen in the cytoplasm are the nucleocapsids of measles virus.

The structure of the granular filaments that appeared diffusely in the cytoplasm resembled that of the smooth filaments in regard to their tubular nature, but granular filaments: (i) were larger, (ii) were not uniform in width, (iii) had a fine granular material on their surface, (iv) were located only in the cytoplasm, (v) did not form arrays, and (vi) were assembled in the virus par-

ticles in cells infected with measles virus. It is quite probable that their origin is different from that of smooth filaments. An association of the granular filaments with rough-surfaced endoplasmic reticulum suggests that they may be derived from the endoplasmic reticulum and may contain ribonucleoprotein. On the other hand, the different appearance of the nucleocapsids in the nuclei and in the cytoplasm in measles (EDM)-infected cells was noted previously by Matsumoto in Vero cells (16) and recently by Raine et al. in primary hamster cerebellum culture (24). Two types of the nucleocapsid structures were recently demonstrated by us, as well, in SSPE brain tissues (S. Oyanagi et al., *in preparation*) and cell cultures derived from them (20). Moreover, in specimens from primary monkey kidney cells infected with the Edmonston strain of measles virus and studied by negative staining, Norrby and Magnusson (19) noted two kinds of the internal components, one with an outer diameter of 16 to 19 nm, and the other, of 26 to 28 nm. This evidence, taken together with our present observations, indicates that there are two kinds of nucleocapsid structures in cells infected with measles or SSPE viruses but that their distribution is characteristic for each of these viruses. However, Nakai et al. (18) failed to detect the larger nucleocapsid structures in measles-infected cells, and their findings are in contrast to those of Matsumoto and of Raine et al., and the ones we have now reported.

Regarding the nature of these two filaments, Raine et al. (24) suggested that they were essentially identical and that the nuclear ones lacked granular material because they were within the nuclear environment; however, this interpretation is untenable because in measles-infected CV-1 cells and in SSPE brain cultures (20) aggregates of smooth filaments were also seen in the cytoplasm.

Although the viruses isolated in SSPE exhibited a close relationship to measles virus, producing the same components (smooth and granular filaments) in CV-1 cells, and having differences which were quantitative rather than qualitative, the formation of large nuclear inclusions containing smooth filaments appears to be characteristic and invariable in SSPE in brain tissues (Oyanagi et al., *in preparation*), brain cell cultures (20), and cells infected with viruses isolated from SSPE. In this respect, the SSPE viruses differ from measles virus.

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