Electron Microscopy of the Lemmocyte in Peripheral Nerve Tumors (Neurolemmomas)*

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Rio-Hortega's impregnation techniques11,14 applied to peripheral nerve tumors (neurofibromas or peripheral neurolemmomas) clearly demonstrate the typical configuration of the principal cell, called the lemmocyte. This term was proposed by Rio-Hortega14 because he found these cells displayed the morphological features of Schwann cells, and bore a similar relationship to nerve fibers. Since Schwann cells are considered neuroglial elements derived from the embryonal lemmoblast or the neural crest6 it was reasonable for the Spanish author to conclude that the principal cells represented a neoplastic form of lemmocytes. This numerically predominant element is found associated with other less numerous cellular components which were considered of secondary importance for the development of these tumors.10,14 The present study deals with the fine structure of the lemmocyte, as studied in human peripheral nerve tumors.

Materials and Method

Small biopsies of human peripheral nerve tumors ("neurofibromas" or peripheral neurolemmomas) were immediately placed in 1 per cent osmium tetroxide solution in phosphate buffer, for 1 to 2 hours. After dehydration, the tissue was embedded in Araldite, according to the method of Luft.6 Unsupported sections were stained with lead citrate, uranyl acetate or phosphotungstic acid solutions. Photographs were taken with a RCA 3E Electron Microscope.

Observations

Light Microscopy. Observed with the light microscope, the general structure and the staining properties of the stroma of peripheral nerve tumors are similar to those of normal mesenchymal tissue stroma. Whorls and fasciculi in the growth often clearly follow patterns determined by inclusion of nerve bundles within it.11 Willis18 describes these tumors as expansion of the stroma with resultant separation of its nerve fiber component. Essentially peripheral neurolemmomas consist of a proliferation of a population of cells, in which Schwann cells of the involved nerves can often be recognized. (The term "neurolemmoma" is preferable to "neurofibroma" for naming tumors originating in peripheral nerves.12) However, it is often impossible to decide by routine staining methods whether a particular cell has the characteristics of a Schwann cell or a fibroblast.16 Many workers have concluded that these cells are predominantly of Schwannian appearance,16 but others believe that the bulk of the neoplastic tissue is formed by endoneurial or perineurial and fibroblastic cells.1

Electron Microscopy. The cells of these tumors, as observed with the aid of the light microscope, display elongated nuclei (Fig. 1) which are readily identified when the tissue is examined in the electron microscope. In silver carbonate preparations (Fig. 2) the cytoplasmic processes are drawn out into extremely attenuated extensions which correspond to the neuritides of Rio-Hortega.11,14

General Appearance. The principal cells or lemmocytes of these tumors are enmeshed haphazardly within the supporting tissue. Their commonly elongated forms (Fig. 3) are characteristic of these cells, and not due to distortion of their form due to surrounding tissue elements (Fig. 4). This opinion is supported by the presence of numerous other cell varieties such as mast cells23 and fibroblasts which display oval or round configurations.

Cell Body. The cell body or largest region of these spindle-shaped cells is largely occu-
When, in dilatations, the reticulum is not observed in the distal 2/3; nor is it commonly observed in shorter lengths of fine (and presumably rather distal) segments (Figs. 8 and 9). Free ribosomes are the only organelles observed in the most distal regions of the processes. Many large mitochondria are found in the proximal portion (Fig. 3), and a few smaller sized mitochondria may be observed more distally accompanying the endoplasmic reticulum (Fig. 9). Bundles of fine filaments observed in the perinuclear region can be followed for variable distances out into the proximal regions of the processes (Fig. 3).

**Principal Cells and Nerve Fibers.** Rio-Hortega observed that the processes of the principal cells of peripheral nerve tumors present a striking similarity to unmyelinated nerve fibers. With his silver impregnation techniques both lemmocyte processes and nerve fibers appear as black threads. These structures are intermingled in the tumor, and therefore light microscopic distinction between the two must be based on the connection of the lemmocyte process with a cell body, since the cell bodies of the axons are not present in the tumor preparation. However, the axons are always in apposition to the principal cells of the tumor or with normal Schwann cells. In areas where bundles of normal nerve fibers are surrounded by the

Fig. 1. Peripheral nerve tumor showing the typical arrangement of the tumor cell nuclei. H. & E. X900.

length of process is visualized, the reticulum is observed in the distal 2/3; nor is it commonly observed in shorter lengths of fine (and presumably rather distal) segments (Figs. 8 and 9). Free ribosomes are the only organelles observed in the most distal regions of the processes. Many large mitochondria are found in the proximal portion (Fig. 3), and a few smaller sized mitochondria may be observed more distally accompanying the endoplasmic reticulum (Fig. 9). Bundles of fine filaments observed in the perinuclear region can be followed for variable distances out into the proximal regions of the processes (Fig. 3).

**Cell Processes or Neurilides.** The processes can be followed electron-microscopically for as much as 100 μ. They can also be observed as processes of highly irregular shape that occasionally seem to branch (Fig. 7). The multiple polar processes described by Rio-Hortega have not been observed as yet with the electron microscope, but the use of thin sections probably precludes such observations.

The endoplasmic reticulum is commonly dilated into cisterns. It is regularly observed in the proximal portion of the processes. When, as occasionally happens, a great

Fig. 2. Silver carbonate preparation of the same tumor shown in Fig. 1. The processes of the tumor cells are characteristically impregnated. Rio-Hortega's method. X750.
Fig. 3. Electron micrograph of a principal cell or lemmocyte of the tumor shows a typically elongated nucleus and its attenuated cytoplasmic process (PR). The cytoplasm contains endoplasmic reticulum (Er) and mitochondria (Mi). The tumor stroma is occupied by abundant collagen (Co), embedded in a mucopolysaccharide matrix of low electron density. Uranyl acetate stain. ×12,600.
Fig. 4. Large bundles of collagen (Co) surround a few principal cells and processes (pr). The associated basal lamina of one of these processes is indicated (BL). Phosphotungstic acid stain. ×27,000.

Tumor growth, apparently normal Schwann cells are associated with axons (Fig. 10). Electron-microscopically, the axons usually exhibit a clearer cytoplasmic matrix containing long, fine filaments, and are surrounded by the protoplasmic extensions of the Schwann cell as is found in normal peripheral nerve (Figs. 5, 10, and 11). The principal cell processes characteristically contain many more free ribosomes than are found in axons.

**Principal Cell and Basal Lamina.** The basal lamina* is either a condensation of the ground substance¹ or produced by the epithelial cells.¹⁰ This lamina is considered by Pease¹⁰ to surround isolated epithelial cells or to underlie sheets of them. In peripheral nerve tumors the basal lamina is associated with the principal cells. If, as Pease suggests,

* Coggeshall and Fawcett⁴ suggest the term basal lamina in place of “basement membrane” when this pertains to the mucopolysaccharide extracellular layer of epithelia.
the basal lamina is an important characteristic of all epithelial cells including Schwann cells, it may be inferred that the principal cells of these tumors are of epithelial origin.

The basal lamina, however, is not always observed with every principal cell in these tumors. Fig. 6 (see right side of figure) displays this lamina on one side but not on the other. Fine processes with no distinct basal lamina also may be found (Fig. 8).

Discussion

The derivation of the principal cell of the peripheral nerve tumors has been the subject of long-standing controversy. The present ultrastructural description of these cells supports the original interpretation of Rio-Hortega which was based upon studies employing his special silver impregnation technique. We have confirmed his observations that many of the principal cells of peripheral nerve tumors are associated with nerve fibers; we found a number of tumor cells that surrounded nerve fibers in a manner resembling that of normal Schwann cells.

As the proliferation of principal cells in these tumors is not accompanied by proliferation of nerve fibers, not every tumor cell can contain nerve fibers, and the tumor cells cannot always be identified by their relationship with nerve fibers. The axon-principal cell relationship commonly observed in these tumors suggests a Schwann cell origin for these cells. Other characteristics of the Schwann cell are consistent with this interpretation.

In an electron microscopic study of material from normal peripheral nerves, Causey and Barton found that nuclei associated with cytoplasm containing either myelinated or unmyelinated fibers (and therefore Schwann nuclei), accounted for 85 per cent of

Fig. 5. A low power view of a typical field in the peripheral nerve tumor. Unmyelinated nerve fibers, (NF), and occasionally even collagen (Co, lower right) may be observed to be surrounded by principal cells. These cells and their processes are in turn surrounded by basal laminae (BL). A large principal cell, and its cytoplasmic process (PR), contains bundles of fine intracytoplasmic filaments. Uranyl acetate stain. X9,000.
FIG. 6. This electron micrograph figure shows a cross-section of 2 typical principal cells. Their nuclei (nPC) display patchy chromatin distribution. The cytoplasm of the cell seen in the upper portion of the figure surround circular profiles identified as unmyelinated nerve fibers (NF). These cells are surrounded by a basal lamina (BL). Longitudinally sectioned cell processes (PR) are also encased by basal lamina. The process observed in the right of the figure (PR$^1$) has a basal lamina, but it is clearly observed in one side only. A thick process in the lower right corner of the figure (PR$^2$) is observed to contain numerous fine filaments in its cytoplasm, and also engulfs an unmyelinated nerve fiber. The collagen (Co) in the tumor stroma is prominent. Uranyl acetate stain. ×24,000.
the total nuclei counted. Ten per cent of the total were endothelial nuclei, and 5 per cent were "other nuclei." On the basis of these figures they suggested that neoplasms of peripheral nerve were more likely to be of Schwannian derivation. The mature Schwann cell retains the potential for proliferation, as was demonstrated by Thomas17 and Nathaniel and Pease9 in studies of peripheral nerve repair.

The presence of a basal lamina around many of the principal cells, further supports an epithelial derivation for these cells. The basal lamina, however, is not conspicuous on every tumor cell. There are 2 possible explanations for this seeming inconsistency. The absence of a basal lamina around some processes of principal cells may be due to disarrangement of the cells by their neoplastic activity; that is, it is possible that the basal lamina has not been formed normally or consistently in nerve tumors. When the

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**Fig. 7.** Processes (PR) of the principal cells are highly irregular in shape, and occasionally appear to branch. Collagen (Co) is abundant and occupies most of the intercellular space. The basal lamina (BL) is prominent in this field. Uranyl acetate stain. ×12,600.

**Fig. 8.** Embedded in the moderately electron dense and presumably mucopolysaccharide ground substance of the peripheral nerve tumor are numerous thin processes of the principal cells (pr), and bundles of collagen (Co). No definite basal lamina is observed around these processes. Uranyl acetate stain. ×16,800.
principal cells are near nerve fibers or are wrapped around them, the basal lamina is almost always present surrounding the cell body and processes. The fact that these more nearly "normal" Schwann cells retain the ability to elaborate a basal lamina suggests that its absence in other regions is related to a more severe disarrangement of the cell environment or metabolism. The process of fixation may provide the basis for an alternative explanation, however, since these tumors display a large amount of intercellular substance, mostly collagen. Possibly this substance has slowed down the penetration of the fixative, permitting a prefixation loss of basal lamina material. This explanation would account for the occasional appearance of diffuse continuity of the basal lamina material and the mucopolysaccharide matrix of the tissue stroma, and for the occurrence of

Fig. 9. A large process (PR) is surrounded by what is apparently a condensation of the tumor ground substance. Note the layered appearance of this material below the indicated process. A small process (pr) does not have a well-defined basal lamina. Numerous ribosomes are observed throughout the thicker process. Uranyl acetate stain. X16,800.

Fig. 10. A myelinated nerve fiber (MNF) is surrounded by the normal Schwann cell cytoplasm (SC). A large dark process (PR) and smaller light process (pr) both exhibit prominent basal laminae. Another process is containing unmyelinated nerve fibers (NF). Uranyl acetate stain. X27,000.
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Fig. 11. Unmyelinated nerve fibers (NF) in the tumor, are surrounded by principal cell cytoplasm. Small profiles of principal cell processes (PR) which do not contain nerve fibers are also present in the field. The basal laminae (BL) of these processes are clearly demonstrated. Uranyl acetate stain. X27,000.

the basal lamina on one side of a process while on the other side it is indistinct or absent (see Fig. 6).

Winkelmann and Johnson have recently provided additional support for an epithelial origin of principal cells in peripheral nerve tumors. Non-specific cholinesterase has been found in epithelial growths derived from neural tissue such as dermal nevus, and in Masson's neural nevus. Winkelmann and Johnson found a positive non-specific cholinesterase reaction in cutaneous "neurofibromas." No similar enzymatic activity was found in normal dermal connective tissue, dermatofibromas, or other forms of mesenchymal tumors.

Our study supports the suggestion advanced by Masson, Murray and Stout, and by Río-Hortega, that the principal cell of the peripheral nerve tumor is of epithelial origin.

Summary

We have described the ultrastructure of the lemmocyte or principal cell in peripheral nerve tumors examined by electron microscopic techniques. The relationship of these cells to unmyelinated nerve fibers and the presence of a basal lamina around many of the cells suggests their probably epithelial or Schwann cell derivation.

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References

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