BLOOD VESSEL CELLS AS THE SOURCE OF DEVELOPMENT OF DESMOID FIBROMA

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UDC 616-006.327-018.15-092:616.13/14-018.1

KEY WORDS: connective tissue; autoradiography; neoplasms.

We still have no sufficiently accurate information about the origin of cells forming tumors of fibrous connective tissue, because workers who have described these neoplasms have usually restricted themselves to a general statement that they develop from mesenchymal cells [8, 15-17]. Some workers postulate a histogenetic link between tumor cells and small blood vessels [12, 13]. A fundamentally important aspect of this problem is the accurate identification of the cells whose proliferative activity is the source of tumor growth. Much help with the solution of this problem can be obtained from the method of electron-microscopic autoradiography. The first results which we obtained from a study of certain tumors and tumor-like processes in connective tissue (keloid scars, lipomas) by means of this method showed that cells synthesizing DNA, i.e., possessing proliferative activity, are not uniformly distributed throughout the tumor but localized selectively in the walls of blood vessels and in their immediate vicinity [2, 9, 11].

It was decided to continue the investigation in this direction and to ascertain whether the data mentioned above reflect only a particular phenomenon or whether they are a manifestation of a certain general rule of histogenesis of connective-tissue neoplasms. For this purpose, in the investigation described below, electron-microscopic autoradiography was used to study a desmoid fibroma.

EXPERIMENTAL METHOD

Desmoid fibromas removed within the bounds of healthy tissue from three men and one woman were fixed in 10% neutral formalin and embedded in paraffin wax and celloidin. Sections were stained with hematoxylin and eosin and with picrofuchsine by Van Gieson's method. Pieces of tissue from the central regions of the tumors, measuring 0.5 × 1.0 × 1.0 mm, taken for autoradiographic study, were immersed immediately after excision in warm nutrient medium 199 containing 10% bovine serum. The fragments were incubated in this medium for 90 min at 37°C with the DNA precursor [^{3}H]thymidine in a dose of 10 μCi/ml, or with the RNA precursor [^{3}H]uridine in a dose of 100 μCi/ml. After incubation the fragments were washed with cold nutrient medium and with phosphate buffer, pH 7.4, then fixed with 2.5% glutaraldehyde solution and 1% OsO_4 solution. The material was embedded in Epon. Autoradiographs on semithin sections were first prepared from each block, after which electron-microscopic autoradiographs were prepared by the method in [6, 7].

EXPERIMENTAL RESULTS

The tumors in all specimens had a fibrous structure. The ratio between areas occupied by cells, on the one hand, and by bundles of collagen fibers and ground substance, on the other hand, varied in different patients and within the same tumor; on the whole, however, collagen and ground substance occupied the greater part of the section. The commonest cells found in the tumor were fibroblasts, less commonly cells of the vessel wall (endotheliocytes, pericytes), macrophages, adipocytes, and mast cells. Data on [^{3}H]uridine incorporation and

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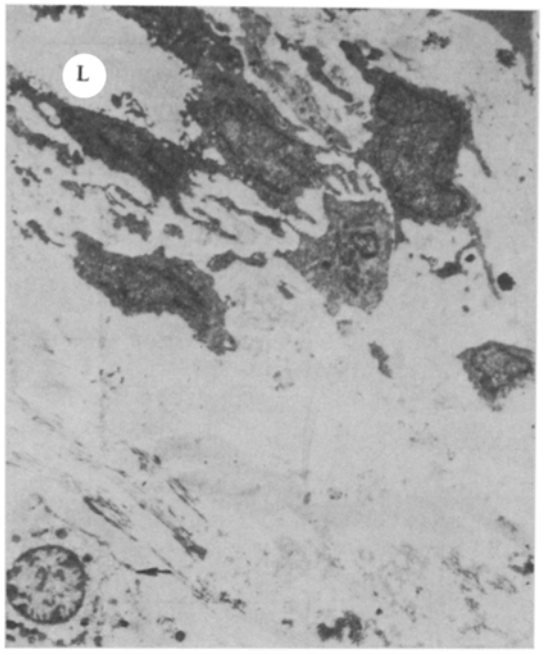
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 12, pp. 100-101, December, 1983. Original article submitted June 10, 1983.

 0007-4888/83/9612-1778$07.50 © 1984 Plenum Publishing Corporation



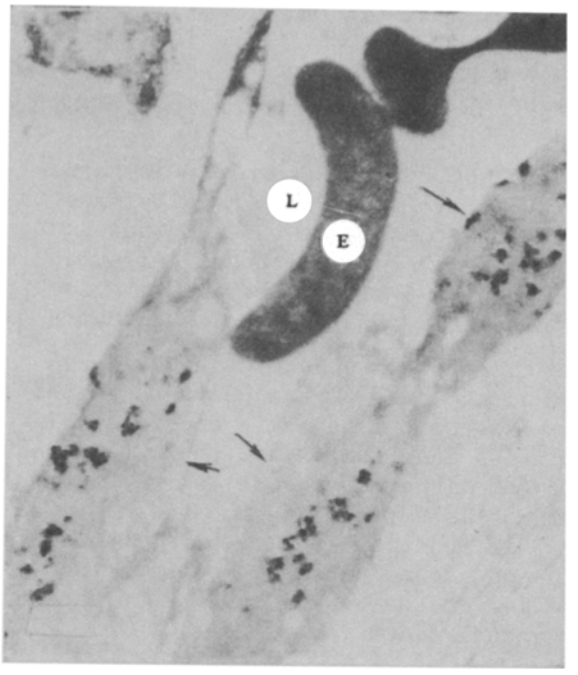


Fig. 1 Fig. 2

Fig. 1. Desmoid fibroma: cells localized mainly in perivascular zone; cell in a state of marked degeneration (arrow) can be seen at a distance from it. Here and in Figs. 2 and 3: L) Lumen of vessel. 3000 ×.

Fig. 2. Incorporation of [^{3}H]uridine (black grains of silver) into endotheliocytes (arrows). E) Erythrocyte. 9000 ×.

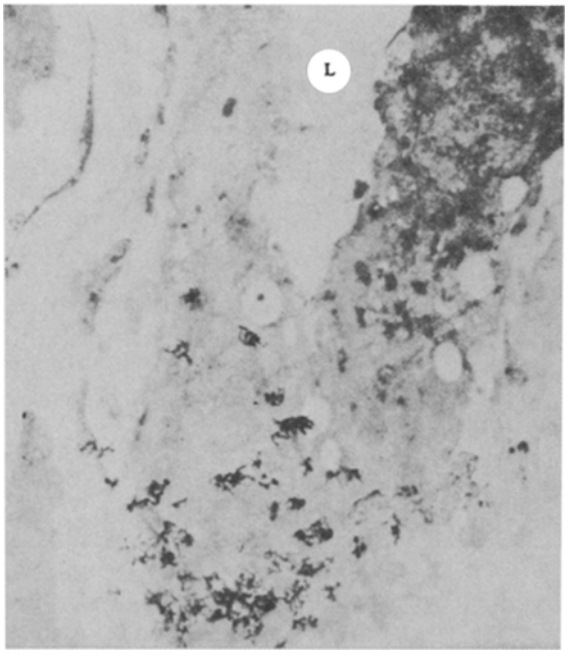


Fig. 3. DNA synthesis (black grains of silver) in cell of vessel wall. 12,000 ×.

the results of the electron-microscopic study suggest that most tumor cells are in a state of destruction. No [^{3}H]uridine is incorporated into such cells and their cytoplasm is distinguished by increased transparency and low density of its structures (Fig. 1). Individual normally functioning cells and clusters of them can be clearly distinguished from incorporation of [^{3}H]uridine. As a rule a vessel of precapillary, capillary, or venule type lies in

the center of these clusters of cells. The walls of these vessels were composed of endotheliocytes and pericytes labeled intensely with [^{3}H]uridine (Fig. 2). Sometimes the intensity of RNA synthesis in the cells could be seen to diminish with increasing distance from the lumen of the vessels.

Cells labeled with [^{3}H]thymidine were rarely seen (1-3 in 50 sections). Sections for electron-microscopic study were usually made in a region comparatively rich in cells, but nevertheless even these as a rule did not number more than 10-15 per section. It is very important to note that in all cases cells labeled with [^{3}H]thymidine were situated in a vessel wall (Fig. 3). These vessels were not found in every section, and when they were, their wall consisted of a few endotheliocytes and pericytes.

The description given above is evidence that a blood vessel with the group of cells surrounding it is what appears to be the elementary structural and functional unit of the tumor. This unit is dynamic and zonal, in the sense that during maturation the cells migrate from its inner zone into the outer zone. Proliferation of cells constituting the vessel wall (the inner-most zone) serves to replenish all the cells of the group. RNA synthesis in cells surrounding the vessel (middle zone) reflects differentiation and specific function. This function in fibroblasts leads to the accumulation of ever-increasing masses of collagen and ground substance between the vessel wall and plasma membrane, when they isolate the cell from the vessel and, besides exhaustion of the time program of the cell bring about its gradual death (outer zone).

The role of the vessel wall in the origin of desmoid fibroma cells was thus revealed as a result of one of the advantages of electron-microscopic autoradiography, namely its much greater sensitivity than the method based on discovery of mitoses; this is a matter of fundamental importance when working with desmoid fibromas in which, according to data in the literature, mitoses are rarely [14, 18] or never [19] observed.

The hypothesis put forward by several workers that vessels and their immediate cellular environment constitute a cambial zone, cells of which can proliferate and differentiate in different directions [1, 3-5, 10], is thus accurately confirmed by electron-autoradiographic studies.

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