SATELLITE CELLS IN VARIOUS MOTOR DISODERS

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Modern views on the role of satellite cells in regeneration are based on experimental data obtained after injury to normal skeletal muscle [3, 5, 7]. Regeneration of pathologically changed skeletal muscles, especially in man, has so far been studied extremely inadequately [6, 7]. Yet the genesis of myosatellite cells in muscles under experimental and clinical pathological conditions may follow a different course [1, 2].

The study of satellite cells after denervation and during regeneration in man may be useful for an understanding of their function.

This paper gives the results of a study of material obtained during diagnostic biopsies from patients with various forms of myashthenia, the Lambert–Eaton myasthenic syndrome, amyotrophia spinalis, and various myopathies.

EXPERIMENTAL METHOD

Clinical and electromyographic studies of the patients and biopsies were undertaken by the staff of the Department of Human Neuromuscular Pathology with the All-Union Myasthenic Center (Director, Professor B. M. Gekht), Research Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR.

Pieces of skeletal muscle taken during biopsy were fixed consecutively in a cold solution of formal-sucrose and buffered 1% OsO_4 solution, and embedded in Araldite. Sections were stained with uranyl acetate and lead citrate by Reynold's method and studied in the JEM-7A electron microscope.

EXPERIMENTAL RESULTS

Ultrastructural analysis of muscle biopsy material revealed considerable changes in the muscle fibers. Thinning of the myofibrils was not frequently observed, and it sometimes extended to whole sarcomeres. Vacuoles and myelin-like formations appeared in the affected muscle fibers. Large spaces within the muscle fibers were filled with breakdown products of the myofibrils. The mitochondrial apparatus, sarcotubular system, sarcolemma, and also the nuclei all showed changes. In many muscle fibers the nuclei were situated centrally, a characteristic feature of denervation. Sequestration of the nuclei and an increase in the number of cells corresponding in their morphological criteria to satellite cells were noted.

The wide distribution of satellite cells in the muscle fibers in the pathological forms studied revealed all their diversity and enabled their formation and differentiation to be observed. The diversity of the ultrastructure of satellite cells evidently reflects the morphological and functional state of muscle fibers. Dark cells, stretched along the axis of the muscle fiber, and consisting of a large heterochromatic nucleus and a very narrow band of electron-dense cytoplasm, in which the single ribosomes, small dense mitochondria, and vesicles are difficult to distinguish (Fig. 1a), are the most widespread forms. In some satellite cells centrioles can be seen (Fig. 1c), evidence of their ability to divide. Micropinocytotic vesicles (Fig. 1d) were formed on the outer membrane in many cells. Satellite cells were located beneath the basement membrane of the muscle fiber (Fig. 1b) and separated from it either by a narrow slit or by a more or less wide space. Membranous filaments and

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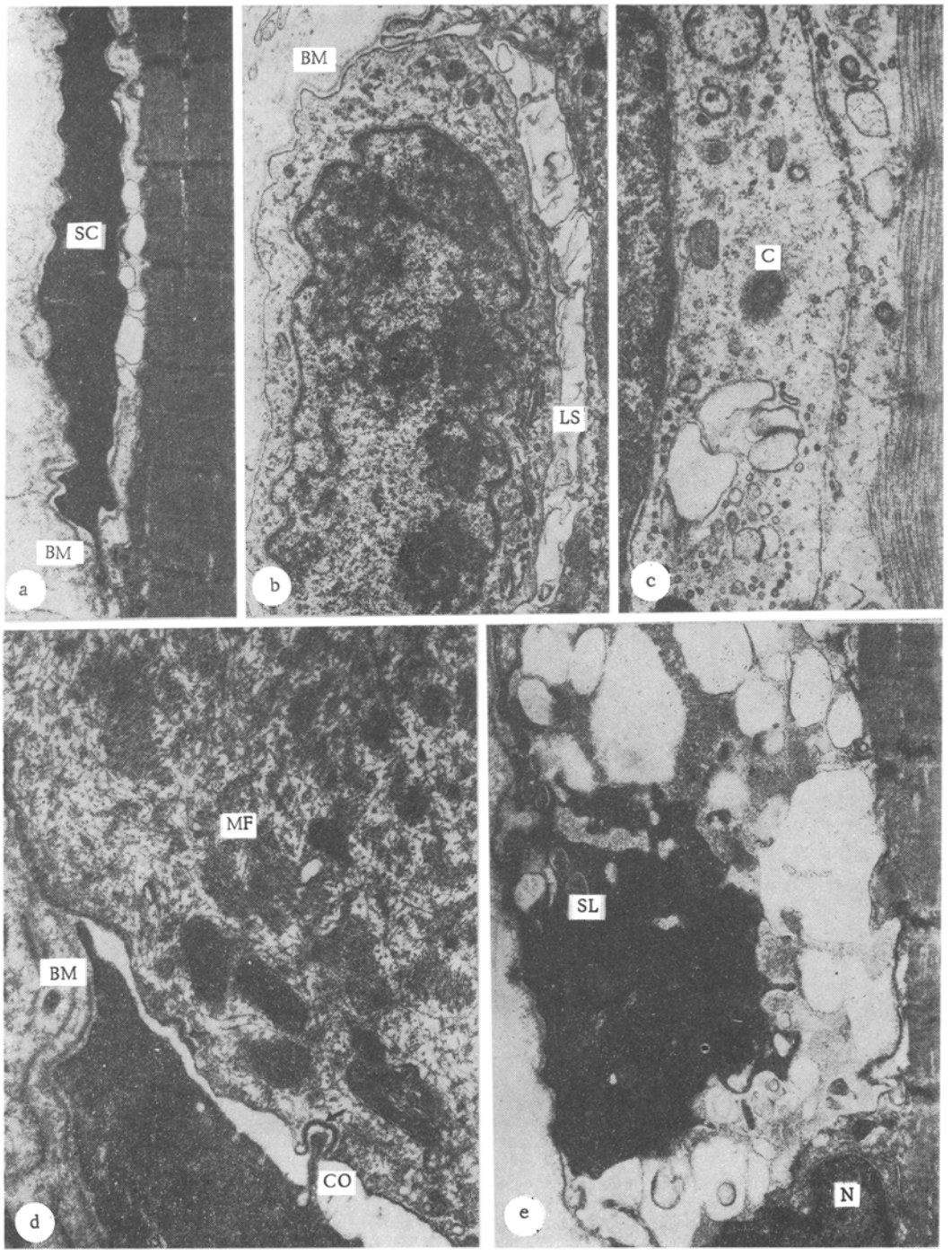

Fig. 1. Different forms of satellite cells (SC) in human skeletal muscle and their relations to muscle fibers. a) Most widespread type of satellite cell. Basement membrane (BM) split into two sheets: one formed around the separating satellite cell, the other around the muscle fiber. 16,000 ×; b) pale satellite cell located beneath basement membrane of muscle fiber. Numerous organelles (ribosomes, mitochondria, endoplasmic reticulum) clearly visible in cytoplasm. 23,400 ×; c) centriole (C) in satellite cell. 32,000 ×; d) structural reflection of connection between satellite cell and muscle fiber: cytoplasmic outgrowth (CO) of satellite cell terminates in recess of sarcolemma, which at this point has the appearance of a "bordered" membrane (arrow). 46,000×; e) satellite cell undergoing degeneration. 24,000 ×. LS) Lamellar structure, PV) pinocytotic vesicles, MF) myofilaments, SL) secondary lysosomes, N) nucleus, SC) satellite cell.

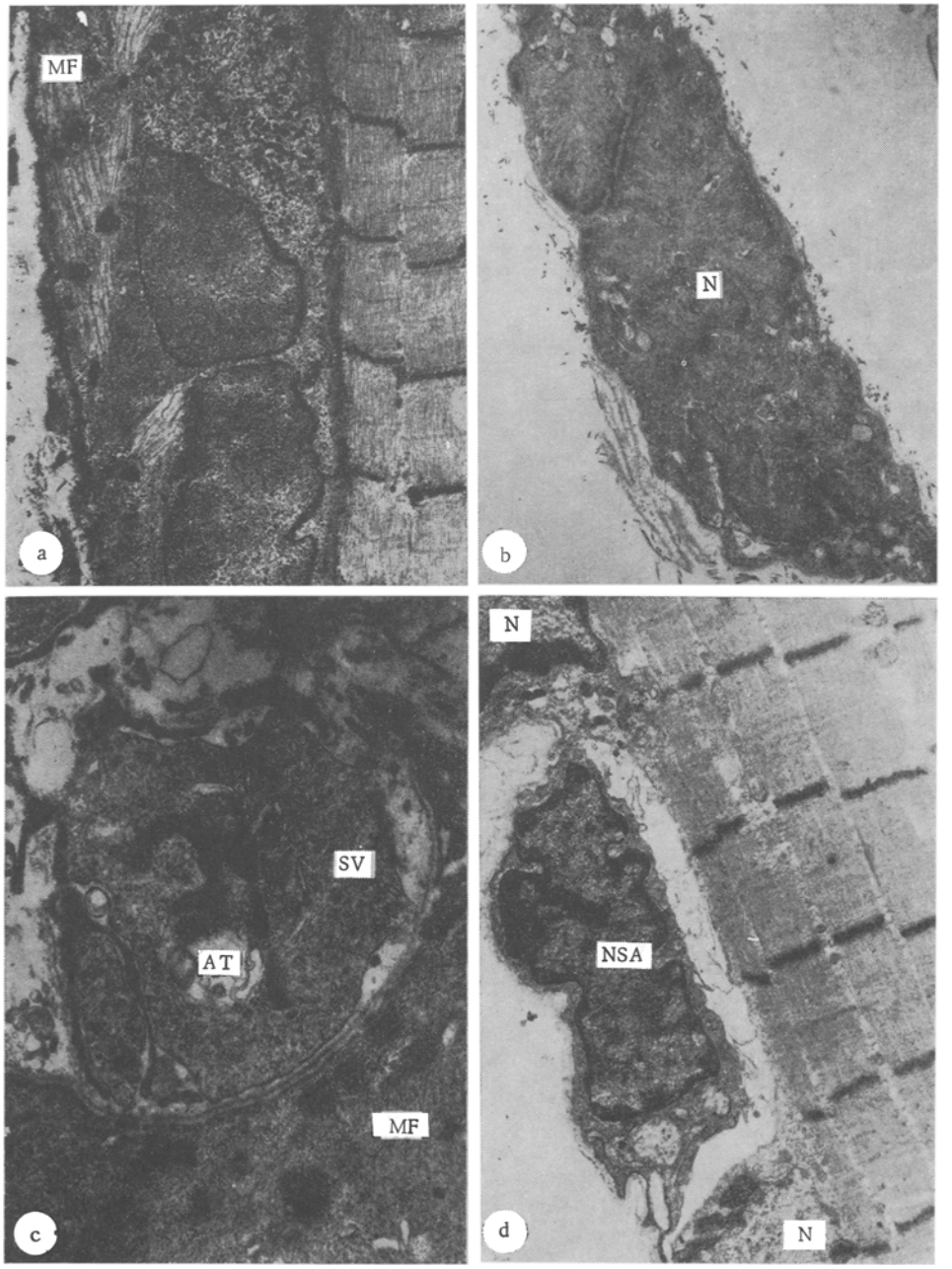

Fig. 2. Differentiation of satellite cells during regeneration in human skeletal muscles. a) Multinuclear cell (muscle tube?) lies next to a mature muscle fiber. 11,000 ×; b) muscle tube in intercellular space (chaotic arrangement of myofibrils). 7000 ×; c) formation of synaptic junction on muscle tube. Synaptic vesicles, mitochondria, slit-like vacuoles visible in axon terminal (AT). Postsynaptic membrane begins to form synaptic folds (arrow). 33,600 ×; d) splitting of nucleo-sarcoplasmic region from muscle fiber. 22,000 ×. SV) Synaptic vesicles, NSA) nucleo-sarcoplasmic area. Remainder of legend as to Fig. 1.

lamellar structures were often observed in this space. Sometimes the satellites had club-shaped cytoplasmic outgrowths, which terminated in a recess of the muscle fiber, formed by the electron-dense plasma membrane (Fig. 1d).

In some satellite cells an asymmetrical position of the nucleus and also numerous outgrowths of cytoplasm were found. In the ground substance near many of the satellite cells parallel bands of material of the basement membranes were found (Fig. 1d). The impression was created that satellite cells can migrate along muscle fibers toward the site of injury

and, changing from the inactive into the active form, they subsequently undergo differentiation and in that way enable fragments of muscle tissue to be restored. This hypothesis is supported by the presence of large cells, in close apposition to the muscle fiber. These cells had one or more nuclei with a diffuse arrangement of their chromatin. Their cytoplasm was rich in organelles: ribosomes, polysomes, mitochondria, elements of a lamellar apparatus, and endoplasmic reticulum. Myofibril formation took place at the periphery of the cells: sarcomeres with characteristic transverse flattening, resembling Z lines, were formed (Fig. 2a). A large proportion of satellite cells split away from muscle fibers. Under these circumstances the individual stages of this process could be identified. To begin with, a chain of vesicles was formed on the boundary with the sarcolemma, and these merged together, dilated, and formed cavities separating the cells from the muscle fiber. When they were finally set free, the total layer of basement membrane split into two sheets, one of which was formed along the plasma membrane of the muscle fiber, whereas the other wound around and isolated the satellite cell (Fig. 1a).

The separating satellite cell enters upon the cycle of differentiation. Free cells with complicated structure, essentially muscle tubes, surrounded by a basement membrane, could be seen in the intercellular space. Cells of this kind contained one or more nuclei. The cytoplasm, of average density, was rich in different kinds of intracellular organelles. Myofilaments were grouped in these cells to form sarcomeres (Fig. 2b). Thus the satellite cell may be converted into a myoblast which, in turn, is transformed into a muscle tube. The formation of a synaptic junction could be observed on a newly formed muscle tube or on the regenerated part of a muscle fiber, which was necessary for them to complete their development (Fig. 2c).

Meanwhile in many satellite cells (Fig. 1e), myoblasts, and even muscle tubes, signs of degenerative changes were found, namely disturbance of the homogeneity of the cytoplasm, local translucency, the appearance of vacuoles, lipid drops, and secondary lysosomes. The development of irreversible changes of this kind causes death of the cell, and this is reflected in the normal process of muscle tissue regeneration.

In many muscle fibers, besides satellite cells, separation of muscle nuclei with areas of sarcoplasm could also be observed (Fig. 1d). As a rule, newly formed cells of this kind were located around one, or sometime two, muscle nuclei. The ways in which they formed an independent cell and its subsequent behavior were identical with those of satellite cells.

Thus investigation of biopsy material from patients with various neuromuscular and muscular diseases revealed the presence of regeneration as well as degeneration of muscle cells. A considerable increase in the number of satellite cells was found in the damaged muscle fibers. This can evidently take place not only through their division, but also through the formation of new cells as a result of segregation of nucleo-sarcoplasmic areas. Satellite cells, converting into the axis form, become a potential source of new myoblasts. Myoblasts can insinuate themselves into a muscle fiber, to replace damaged fragments or to form muscle tubes and also, perhaps, new muscle fibers. The reasons why regeneration may be incomplete or delayed are disturbances of innervation, occurring in neuromuscular pathology, and dystrophic changes in the muscle fibers, which spread also to satellite cells.

On the basis of the above account satellite cells can be regarded as elements of a dynamic system which is devoted to maintenance of the normal state of muscle tissue, and responds sensitively to changes in the conditions of its functioning or injury. It can be tentatively suggested that satellite cells are responsible not only for processes of regeneration, but also for a unique form of intercellular interaction.

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