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The microstructure of peripheral nerves

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This is an illustrated review of the basic essentials of the microstructure of peripheral nerves, with an emphasis on those aspects that can be considered relevant in clinical practice. The discussion includes basic definitions about nerves and their importance as well as a review of the exciting areas of normal and injured nerves.

Peripheral nerves

By definition, a nerve is the reunion of multiple bundles of axons gathered together as a discrete "organ" of the peripheral nervous system. A nerve can be considered an organ because, in addition to nervous tissue (neuronal axons and Schwann cells), it contains a connective tissue stroma and a nutritive blood supply. Functionally, the nerves, in company with the endocrine and immune systems, convey the control of many other tissues, organs, and systems.

Neurocytology

The axons of a nerve are extended processes (up to 5 feet long) of neurons whose cell bodies are located either in the dorsal root ganglia (DRG) for general somatosensory function or in the ventral horn for general somatic motor function. In addition, most nerves carry autonomic nervous system components that include mostly postganglionic sympathetic axons (nonmyelinated), some preganglionic axons (sympathetic and parasympathetic), and some autonomic ganglia (both parasympathetic and sympathetic). However, in most parts of a nerve, there are no neuron cell bodies. There are synaptic connections between neurons in the central nervous system and in the autonomic ganglia, but not in the DRG. These neural components are diagrammatically shown in Figure 1.

The axons contain a limited array of cytoplasmic organelles.[1] Neurofibrils include neurofilaments for structural support and neurotubules for axoplasmic transport. Because the latter is energy-dependent, mitochondria are abundant in the axoplasm. Vesicles may also be seen as they are transported up and down the axon, but their presence is more extensive at the axon tip. This tip might be within an intramuscular nerve at a normal neuromuscular junction (Figure 2) or at the growth cone in a regenerating front following injury (Figure 3). With a vibrating probe, currents can be detected at the growth cone front and at the injury site at 7 days following crush injury with an intervening space of 12 to 14 mm in a rat sciatic nerve experiment.[2] This study indicated that, following a 2-day delay, the regeneration rate is 2 to 4 mm/day. This has been supported by other studies using various types of nerve grafts.[3,4]

Connective tissues

The supportive tissues of a nerve extend beyond the Schwann cell. Immediately surrounding the axon is the endoneurial connective tissue, consisting of fibroblasts and their products: the collagen fibers and extracellular matrix (Figure 3). The smallest bundle of axons is called a nerve fascicle and is bound by the perineurium (Figures 4 and 5).

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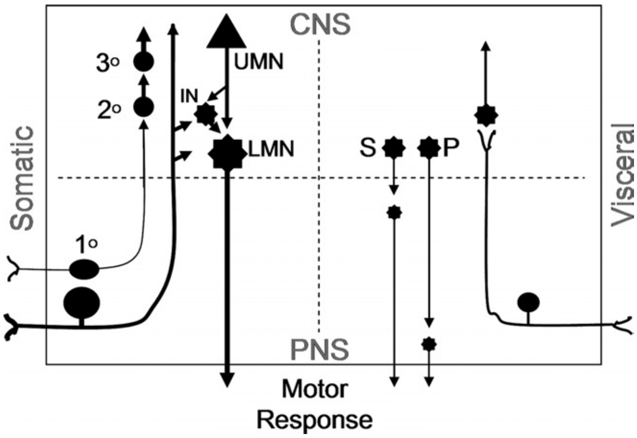

Figure 1 The basic scheme of the nervous system is to process a sensory stimulus to produce a motor response. Neurons may overlap the divisions of CNS (brain and spinal cord) and PNS (nerves and ganglia). The somatic side is musculoskeletal with three orders of neurons ascending in pathways to the cortex for perception, whereas upper motor neurons (UMN) descend to the lower motor neurons (LMN) sometimes through an interneuron (IN). The visceral side is autonomic to smooth muscle, cardiac muscle, and glands. Both the sympathetic (S) and parasympathetic (P) divisions have a two-neuron chain involving an autonomic ganglion before reaching the target. The other cell bodies in the PNS are sensory in function.

Most nerves have more than one fascicle (Figure 4). This perineurium is very cellular and consists of multiple layers of epithelial-like perineurial cells (Figure 5), joined by gap junctions and interspersed by basal laminae. The perineurium is one site for the blood–nerve barrier, which prevents the passage of large molecular weight molecules into the endoneurium, where the exposed axons reside. The outermost connective tissue layer is called the epineurium and surrounds each fascicle. The epineurium has a more loose arrangement of collagen fibers and includes adipose tissue (Figure 4B).

Myelin sheath

The myelin sheath surrounding an axon is formed by a Schwann cell. The cytoplasmic process wraps around the axon, extruding the cytoplasm and leaving compacted membranes with a certain periodicity.[1,5] As the axon diameter increases, so does the thickness of the myelin sheath (Figure 5). There is a leaflet of cytoplasm at the inner and outer layer; the latter is also contained within an outer basal lamina. In between myelin sheath segments is a space devoid of myelin called the node of Ranvier (Figures 6 and 7), where Schwann cell processes interdigitate just outside the exposed axon (Figure 7B). This is seen in a transverse view at the light and electron microscopic level in Figure 7. Here the axon membrane has a concentration of sodium channels responsible for membrane depolarization and rapid salutatory conduction down the axon. The nucleus of the Schwann cell is somewhere in the midportion of the internode segment of myelin (Figure 6A). Other interruptions in the myelin sheath are called clefts of Schmidt–Lantermann (Figures 6 and 7) and contain an angular spiral of cytoplasm from the inside outward, but they do not influence impulse conduction. The juxtaparanode region of the myelin sheath overlies a region of the axon that has a high concentration of potassium channels and is located adjacent to the nodal region. Axons are usually counted in transverse sections (Figure 7A). However, given the varying appearance and dimensions, the sizes should be measured only in the internode profiles (#1 in Figure 7A).

The axons in a typical nerve can be nonmyelinated but still ensheathed by a Schwann cell (Figure 5B); these could be sensory C-fibers (slow pain), or visceral motor (postganglionic sympathetic) to smooth muscle, cardiac muscle, or glands. When a growing axon exceeds 1 to 2 μm in diameter, it becomes myelinated by Schwann cells (like beads on a string). The largest axons could be 20 μm in diameter with parent cell bodies that are also very large (100 μm) and that conduct action potentials very fast ($6 \times 20 = 120$ m/s). It is not possible by anatomical methods to distinguish the sensory from motor fibers in a typical mixed nerve, although some cutaneous nerves might be considered primarily sensory (ie, sural nerve). It is likely that the myelinated axon in

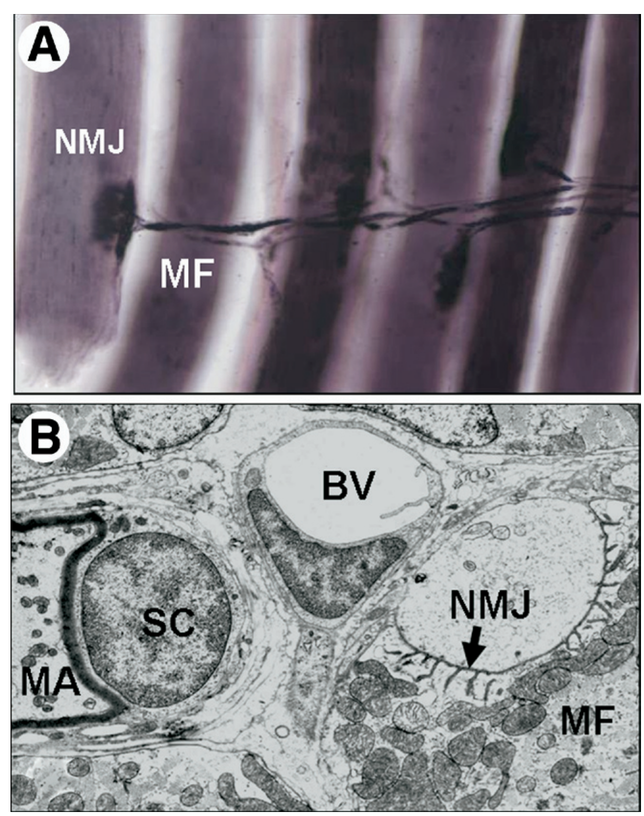

Figure 2 Neuromuscular junctions (NMJ) involve the endings of a LMN on skeletal muscle fibers (MF) as seen at both the light (A) and electron (B) microscopic levels. The Schwann cells (SC) follow the myelinated axon (MA) down to the terminals which lack a myelin sheath. Blood vessels (BV) are nearby.