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Practical anatomy of the neuromuscular junction in health and disease

Hiroshi Nishimune, Ph.D. and

Associate Professor, Department of Anatomy and Cell Biology, University of Kansas School of Medicine, Kansas City, KS, USA

Kazuhiro Shigemoto, M.D., Ph.D.

Team Leader, Research Team for Geriatric Medicine, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

SYNOPSIS

Neuromuscular junctions (NMJs) form between nerve terminals of spinal cord motor neurons and skeletal muscles, and perisynaptic Schwann cells and kranocytes cap NMJs. One muscle fiber has one NMJ, which is innervated by one motor nerve terminal. NMJs are excitatory synapses that use P/Q-type voltage-gated calcium channels to release the neurotransmitter acetylcholine. Acetylcholine receptors accumulate at the postsynaptic specialization called the end plate on the muscle fiber membrane, the sarcolemma. Proteins essential for the organization of end plates include agrin secreted from nerve terminals, Lrp4 and MuSK receptors for agrin, and Dok-7 and rapsyn cytosolic proteins in the muscle.

Keywords

Neuromuscular junction; motor neuron; muscle; active zone; acetylcholine receptors; MuSK; voltage-gated calcium channels

Neuromuscular junctions and motor nerves

Neuromuscular junctions (NMJs) are excitatory chemical synapses formed between nerve terminals of spinal cord motor neurons and skeletal muscle fibers that use acetylcholine as the neurotransmitter. Muscle fibers in the skeletal muscles receive monosynaptic input directly from the lower motor neurons in the spinal cord (Figure 1A). Therefore, motor neuron axons originating from the spinal cord travel a long distance to innervate muscle

CORRESPONDING AUTHOR: Hiroshi Nishimune, Mailing address: 3901 Rainbow Blvd., MS 3051, Hemenway Rm. 2073, Kansas City, KS 66160, USA, hnishimune@kumc.edu.
Kazuhiro Shigemoto, Mailing address: Tokyo Metropolitan Institute of Gerontology, Research Team for Geriatric Medicine, Sakae-cho 35-2, Itabashi-ku, Tokyo 173-0015 Japan, kazshige@tmig.or.jp

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fibers. In the majority of skeletal muscles, one muscle fiber has one NMJ. A mature NMJ is innervated by one motor nerve terminal (Figure 2 Normal); therefore, there is a one-to-one relationship between a given muscle fiber and motor neuron. However, one motor neuron innervates multiple muscle fibers by branching its axon within the innervation target muscle. This group of muscle fibers innervated by one motor neuron is called a motor unit. A nerve terminal innervates one NMJ and does not extend beyond the NMJ to innervate another muscle fiber (Figure 2 Normal). This type of innervation differs from synapses of the central nervous system where axons can make *en passant* synapses or boutons *en passant* to form multiple synapses by one branch on an axon.

In the human diaphragm, two phrenic nerve bundles reach the center area of the right and left hemi-diaphragm. Each nerve bundle trifurcates and further splits in a radial fashion in the hemi-diaphragm, forming a net of nerve branches covering the muscle [1]. NMJs are often located in the center area of the muscle fibers and are arranged in a line among the nearby muscle fibers. The postsynaptic specialization of NMJs is often called the “end plate” also know as motor point, and the narrow distribution pattern of NMJs in a muscle is referred to as the “end plate band” (Figure 1A).

End plates and acetylcholine receptors

NMJs form in an indented area or a trough on the muscle cell membrane known as the synaptic gutter (primary gutter). These synaptic gutters are shown as a trough in scanning electron micrographs and an NMJ profile in transmission electron micrographs (Figure 3A, B - Control). The postsynaptic muscle plasma membrane further invaginates to form the junctional folds (Figure 3B arrowhead). These junctional folds extend from the postsynaptic membrane perpendicularly into the muscle cytosol. These junctional folds contribute to (a) the increase in the muscle surface area to hold more acetylcholine receptors at the top of the junctional folds and part way down on the sides [2] and (b) the concentration of voltage-gated sodium channels at the trough of the junctional folds for generating action potentials in muscle fibers [3]. The synaptic gutter and junctional folds compose the end plates.

Acetylcholine receptors are ligand-gated cation channels. Their density is more than 1000-fold higher at the postsynaptic specialization than in extrasynaptic area of the muscle fiber cell membrane [2,4]. Acetylcholine receptor subunits assemble a functional pentamer as $\alpha_2\beta\gamma\delta$ and insert into the cell membrane [2,5]. Acetylcholine binds to the extracellular domain of the α subunits on opposite sides of the channel pore [6]. The half-life of acetylcholine receptors is approximately 14 days at NMJs of living adult mice [7]. In myasthenia gravis patients, IgG1 auto-antibodies against the acetylcholine receptor α1-subunit cause progressive degeneration of the junctional folds and widening of the synaptic cleft [8].

Synaptic cleft

Motor nerve terminals fill the synaptic gutter to form NMJs. However, motor nerve terminals and muscle fibers do not make direct contact or form a cell adhesion complex, which is one the differences between NMJs and synapses of the central nervous system. Cell membranes of motor nerve terminals and muscle fibers are separated by a space called the

synaptic cleft, which is approximately 30 – 50 nm. In the synaptic cleft, acetylcholinesterase is concentrated to hydrolyze the neurotransmitter acetylcholine to terminate each synaptic transmission. The synaptic cleft is filled with extracellular matrix forming the basal lamina [9,10]. The extrasynaptic area of the sarcolemma, the cell membrane of muscle fibers, is surrounded by the internal basal lamina layer and external reticular lamina layer that form the connective tissue layer also called the basement membrane [9,10]. The basal lamina consists of collagens, fibronectins, laminins, nidogens, and perlecan [9–11]. These extracellular matrix proteins form an interwoven matrix in the synaptic cleft. Furthermore, NMJ-specific extracellular matrix proteins have been identified, including collagen IV α2, α3, and α6 chains; collagen XIII; and laminin α4, α5, and β2 chains [12]. These synaptic cleft-specific extracellular matrix proteins have functional roles for the organization and maintenance of the pre- and post-synaptic specialization of NMJs [12–15].

Presynaptic terminals

Mature NMJs show a branched and complex morphology (Figure 2, Normal). A motor nerve terminal faithfully traces the distribution pattern of an acetylcholine receptor cluster. A nerve terminal of a normal/healthy NMJ occupies most of the region of an acetylcholine receptor cluster with a near complete overlap (Figure 2, Normal, Merge). At the ultrastructural level, using transmission electron microscopy analysis, three main structures can be identified: active zones, mitochondria, and synaptic vesicles 30 – 50 nm in diameter (Figure 3B Control). Synaptic vesicles of NMJs contain the neurotransmitter acetylcholine and are localized near the presynaptic membrane. Specifically, synaptic vesicles accumulate at active zones of the presynaptic membrane.

The active zones are synaptic vesicle release sites where synaptic vesicles accumulate and fuse with the presynaptic membrane for exocytotic release of the neurotransmitter acetylcholine [16,17]. These active zones appear as electron-dense material protruding into the cytosolic side from the presynaptic membrane (motor neuron cell membrane) in electron micrographs (Figure 3B Control). These active zones are often found at the presynaptic membrane area facing the mouth of postsynaptic junctional folds, indicating an alignment of pre- and post-synaptic specialization. The active zones are composed of P/Q-type voltage-gated calcium channels and the cytoskeletal matrix at the active zone (CAZ), which includes Bassoon, ELKS/CAST2/Erc1, Munc13, Piccolo, and Rab3-interacting proteins 1 and 2 (RIM1/2). Calcium channels trigger synaptic transmissions, and CAZ proteins play roles in synaptic vesicle accumulation and functional modification of the calcium channels [18,19]. These P/Q-type voltage-gated calcium channels at NMJs are one of the targets for Lambert-Eaton myasthenia syndrome (LEMS) autoantibodies. The passive transfer mouse model of LEMS exhibits fewer active zones [20]. A similar decrease in active zone number was observed when the interaction between P/Q-type voltage-gated calcium channels and their extracellular ligand was perturbed, suggesting a role of active zones in the etiology of LEMS in addition to the decreased function of P/Q-type voltage-gated calcium channels [21].

When action potentials reach presynaptic terminals, voltage-gated calcium channels open and induce calcium influx at the active zones. The rise in the calcium concentration induces a conformational change of SNARE proteins (synaptobrevin/VAMP, SNAP-25, syntaxin 1)

and the fusion of docked synaptic vesicles with the presynaptic membrane. Acetylcholine is then released by exocytosis, spreads by diffusion across the synaptic cleft, binds to acetylcholine receptors concentrated at the postsynaptic membrane, and causes depolarization of the muscle fibers for contraction. Synaptic vesicle-related proteins involved in this process accumulate at presynaptic terminals, including the calcium sensor synaptotagmin and synaptophysin, synapsin I, and SV2.

Cells capping NMJs

NMJs are covered by glia cells called perisynaptic Schwann cells (also known as terminal Schwann cells, Figure 3B, Control) [22–24]. These perisynaptic Schwann cells contribute to the maintenance of the NMJ structure, synaptic transmission efficiency, and the regeneration of NMJs [22,25–27]. Ablation of perisynaptic Schwann cells causes the degeneration of NMJs in experimental animal models [25,26]. In addition, a fourth cell type has been identified at the NMJs and has been named ‘kranocytes’ [28]. The kranocytes cap NMJs above the perisynaptic Schwann cells and play roles in nerve regeneration and sprouting [23,28].

Molecular mechanism of NMJ organization

The molecular mechanisms of NMJ differentiation/organization have been studied actively, and the knowledge has contributed to the better understanding of myasthenia gravis. In short, proteoglycan agrin is secreted from nerve terminals and binds to postsynaptic receptors composed of low density lipoprotein receptor-related protein 4 (LRP4) and MuSK (muscle-specific kinase) [29–33]. This signaling induces cytosolic proteins Dok-7 and rapsyn to accumulate acetylcholine receptors and postsynaptic specialization [34–37]. In myasthenia gravis, transmembrane proteins, acetylcholine receptors and MuSK become targets of autoantibodies. The roles of MuSK are described in detail in the next sections.

MuSK is indispensable for the development of NMJs

MuSK is a receptor-tyrosine kinase that is concentrated at the tips of synaptic folds in the NMJs along with acetylcholine receptors (AChRs) [38]. MuSK is activated through an association with LRP4 and agrin, a nerve-derived heparan sulfate proteoglycan [29,39–41]. MuSK is also activated by its interaction with Dok-7, a cytoplasmic adaptor-like protein, without binding to agrin and Lrp4 [37,42]. These dual activation mechanisms of MuSK are required for the formation of NMJs during the developing stages of an embryo [29,37,39]. MuSK knock-out mice display devastating defects in both pre- and postsynaptic differentiation and die at birth because of apnea. In the mutant mice, branches of the main intramuscular nerve grow excessively and fail to establish normal contacts between specialized nerve terminals and the muscle, where AChR clusters are present on myotubes opposing ingrowing nerve terminals in the normal mouse (Figure 1) [29]. Furthermore, the nerve fibers cannot stop and wander aimlessly across the muscle width [29]. MuSK activates the signaling cascades required for all aspects of NMJ formation, including postsynaptic organization as well as postsynaptic differentiation by regulating the elaboration of retrograde signals. The same structural defects have been demonstrated in Dok-7 knock-out mice [37].

The roles of MuSK in mature NMJs

Is MuSK required for the maintenance of NMJs as well as during development? If so, what roles does MuSK play in mature NMJs? Important clues for the functions of MuSK in mature NMJs have been obtained by the study of pathogenic mechanisms of MuSK myasthenia gravis (MG). MuSK-MG patients often have severe bulbar dysfunction and respiratory insufficiency, and anti-MuSK antibodies in the patients predominantly belong to the IgG4 subclass, which does not activate the classical complement pathway [43–52]. The absence of destruction mechanisms against NMJs by the auto-antibodies in MuSK-MG patients provided the evidence to understand the roles of MuSK in the maintenance of the function and structure of NMJs. As observed in the patients, severe generalized MG was caused by passive transfer of the human IgG4 subclass derived from MuSK-MG patients into mice or by active immunization of the recombinant MuSK protein into rabbits [53,54]. The pathological changes in the NMJs of these animal models included a significant loss of AChR expression and a reduction in junctional folds at postsynaptic membranes (Figure 2 and 3) [55]. These striking alterations indicated that MuSK is indispensable for the maintenance of postsynaptic structures at mature NMJs.

Intriguingly, the morphological changes were not confined to the postsynaptic membrane where MuSK is selectively expressed. Reductions in the size of NMJs and a retraction of motor terminals from NMJs have been observed in both patients and MuSK-MG animals (Figure 3) [53–57]. In addition, electrophysiological studies have demonstrated functional defects in postsynaptic AChRs as well as presynaptic terminals. Acetylcholine sensitivity was reduced as a result of the loss of postsynaptic AChRs; however, a compensatory increase in acetylcholine release from presynaptic terminals was also lacking in both MuSK-MG patients and animal models [55,57]. 3,4-Diaminopyridine, a drug that increases the release of acetylcholine quanta, can alleviate the impairment in the compensatory responses in MuSK-MG patients and animals [58–60]. In contrast, compensatory acetylcholine release from presynaptic terminals is preserved as a homeostatic response in AChR-MG patients and animals [56,57]. Because MuSK is selectively expressed in skeletal muscle but not in motor neurons [38], MuSK probably acts via retrograde signals to maintain the pre-synaptic structures and functions. Despite the impairment of the retrograde signals caused by anti-MuSK autoantibodies, outgrowth and sprouting of axons can still be observed, suggesting a compensatory mechanism for the partial denervation in MuSK-MG patients and animal models (Figure 2 and 4) [53–57].

Summary

NMJs maintain a highly organized structure to achieve reliable synaptic transmission for neuromuscular functions. However, NMJs remain stable and maintain their structure for the lifetime of humans and animals. Therefore, autoimmune attack of NMJ proteins and congenital mutations of genes coding the NMJ components cause neuromuscular diseases and myasthenia syndromes.

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KEY POINTS

- Neuromuscular junctions are excitatory chemical synapses that use acetylcholine as the neurotransmitter.
- Neuromuscular junctions form between nerve terminals of spinal cord motor neurons and skeletal muscles and are covered by perisynaptic Schwann cells and kranocytes.
- MuSK is indispensable for the accumulation of acetylcholine receptors at end plates.

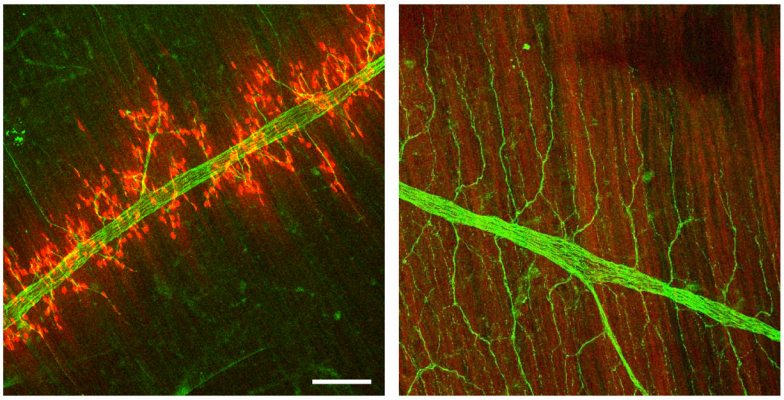

Figure 1.

Aberrant structures of pre- and postsynaptic differentiation in the diaphragm muscle from a MuSK−/− mutant mouse. A whole-mount diaphragm muscle from a wild-type (A) or a MuSK−/− mutant (B) was simultaneously stained with antibodies against neurofilament to label motor axons (green) and with rhodamine-labeled α-bungarotoxin to label AChRs (red) on the postsynaptic muscle membrane. NMJs are not formed in MuSK−/− mutant mouse. Scale bar, 200 μm. (From Shigemoto, K. Kubo, S. Mori. S. Yamada, S. Miyazaki, T. Akiyoshi, T and Maruyama, S. The Immunopathogenesis of Experimental Autoimmune Myasthenia Gravis Induced by Autoantibodies against Muscle–specific kinase. *In: Myasthenia gravis Diseas Mechanisms and Immune Intervention.* Editor: Premkumar Christadoss. Linus Publication, Inc. In Chapter 17, p304–323. 2009; with permission.)

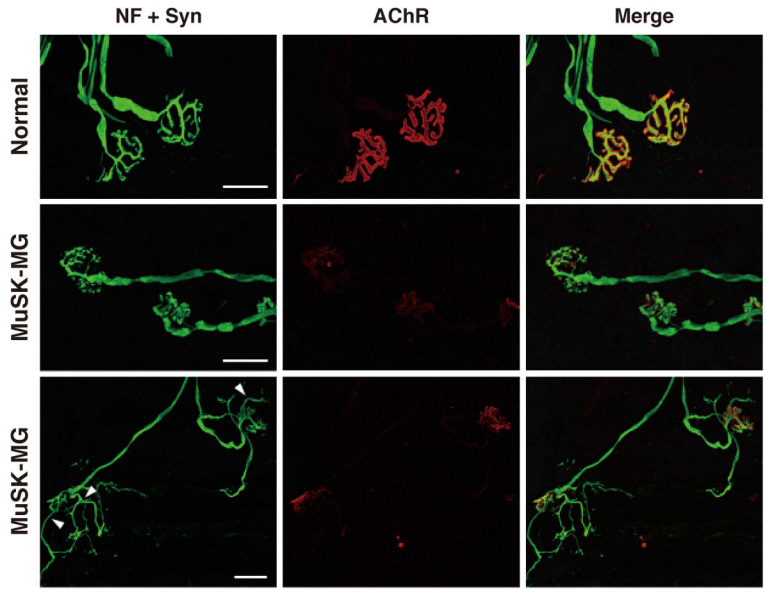

Figure 2.

Disorganization of both presynaptic and postsynaptic structures of NMJs in MuSK-MG mice. Axons and nerve terminals (green) were stained with anti-neurofilament and anti-synaptophysin antibodies (NF + Syn), and AChRs (red) were labeled with rhodamine-labeled α-bungarotoxin. Some NMJs with axon sprouts were observed in MuSK-MG mice (arrowheads). Scale bars: 30 μm. (Reprinted from Mori et al.[55] with permission from Elsevier Inc.)

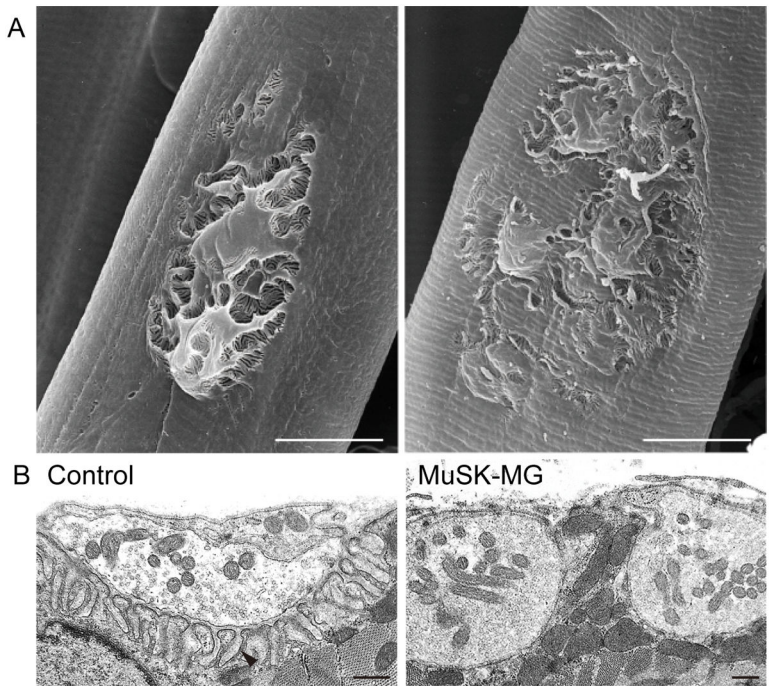

Figure 3.

Disruption of the NMJ ultrastructure in MuSK-MG mice. (A) Complex synaptic gutters containing numerous slit-like junctional folds (Control) were observed at NMJs of control tibialis anterior muscle by scanning electron microscopy. Synaptic gutter flattening and fewer slit-like junctional folds were observed in NMJs of MuSK-MG mice (MuSK-MG). Scale bars: 15 mm. (B) Evenly distributed junctional folds (arrowhead) of comparable depth were observed in controls via transmission electron microscopy. A loss of junctional folds was observed in MuSK-MG mice. Scale bars: 500 nm. (Reprinted from Mori et al.[55] with permission from Elsevier Inc.)

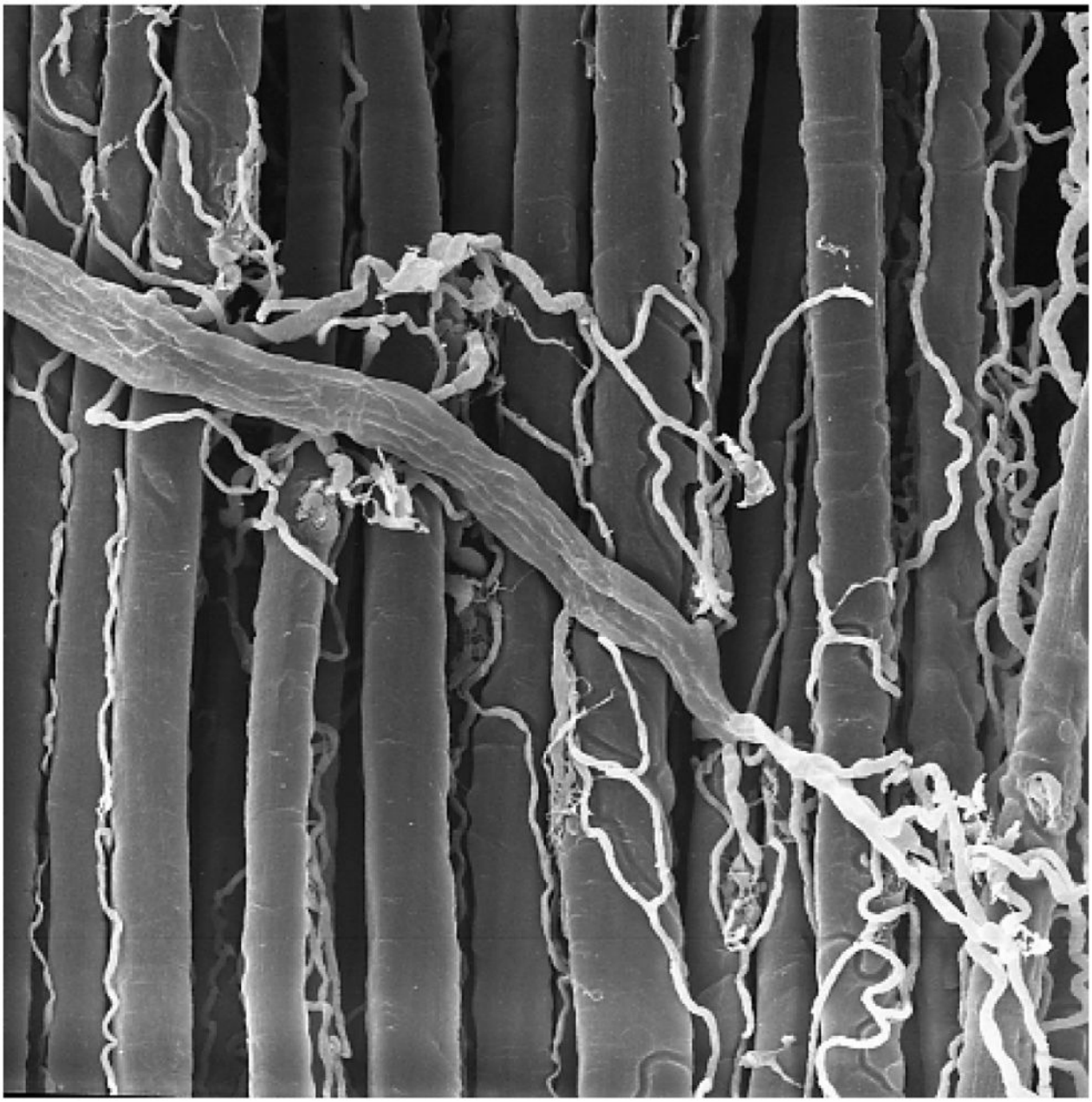

Figure 4.
Increased branching of intramuscular nerve fibers was observed in MuSK-MG mice by scanning electron microscopy.