

Chapter

Muscle-Nerve-Immune Crosschats: Troika Theorization

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Abstract

The muscle-nerve-immune “troika” – a dynamic, interdependent network critical for skeletal muscle health, disease, and repair. Moving beyond traditional siloed views, troika theory postulates that muscle fibers, neurons, and immunocytes, along with the molecular milieu resulting from their cross-talk, enable homeostasis, attune responses to injury, and facilitate tissue regeneration. Key mechanisms of cross-talk among the muscular, nervous, and immune systems are responsible for health, and the perturbation of troika homeostasis induces diseases. The troika model encompasses major biomolecules and signaling pathways governing tri-systemic interaction. Exemplary multisystem pathologies driven by troika dysregulation, including muscular dystrophies, autoimmune neuropathies, and age-related neurodegenerative conditions, are discussed. The translational and clinical potential of the troika rubric lies in interactional signatures that can serve as early risk prediction biomarkers, diagnostic tools, and novel therapeutic targets. The integration of multiomics, machine learning, and high-throughput analytical modalities accentuates the promise of precision medicine in disorders with troika involvement.

Keywords: myoneural, neuroimmune, neuromuscular, multisystem diseases, interorgan communication, multiomics integration

1. Introduction

1.1 Overview of skeletal muscle physiology

Skeletal muscle is a fundamental tissue of the human body, accounting for approximately 30–40% of total body mass and playing a pivotal role in voluntary movement, locomotion, posture, and overall metabolic homeostasis [1]. Skeletal muscle fibers are highly specialized, multinucleated cells characterized by a complex arrangement of contractile proteins organized into sarcomeres, which underpin their ability to generate force and movement through excitation-contraction coupling. Beyond its mechanical functions, skeletal muscle serves as a metabolic organ involved in glucose uptake, fatty acid oxidation, and secretion of myokines (signaling molecules released by muscle that influence systemic physiology). The cellular architecture of skeletal muscle features satellite cells, a population of muscle stem

cells (MuSC) that are indispensable for muscle growth, repair, and regeneration following injury or stress. The excitation-contraction process depends on neuromuscular signaling, calcium dynamics within the sarcoplasmic reticulum, and meticulous coordination of molecular events to convert chemical energy into mechanical force.

Skeletal muscle physiology reflects a dynamic balance between anabolic and catabolic processes, adapting to various physiological demands such as exercise, aging, and pathological insults. Its performance and integrity hinge on the interplay between cellular metabolism, structural organization, and intricate signaling pathways that regulate protein turnover, mitochondrial function, and cellular communication. Consequently, disruptions in any of these components may lead to muscle weakness, wasting, and impaired function, underscoring the necessity of an integrative understanding of muscle biology.

1.2 Traditional views on muscle, nerve, and immune systems

Stereotypically, skeletal muscle, nervous system, and immune system research have been conducted within distinct disciplinary silos, focusing on isolated organ functions and cellular roles. Muscle biology has primarily centered on contractile mechanics, fiber-type composition, and metabolic capacity. Neurobiology has detailed the roles of motor and sensory neurons in controlling muscle activity and conveying proprioceptive information essential for coordinated movement. Immunology has examined immune surveillance and responses primarily within the context of infection and inflammation, often detached from muscular and neuronal considerations.

Although these domains have developed robust knowledge individually, this stereotypical siloed approach has limited comprehension of the systemic interdependencies critical for maintaining musculoskeletal health [2–4]. For instance, the nervous system not only initiates muscle contraction but also modulates trophic support via neurotrophic factors. Similarly, immune cells, long regarded merely as responders to injury or infection, are now recognized as active regulators of muscle remodeling and neural plasticity. Emerging cross-disciplinary research reveals that interactions among muscle, nerve, and immune cells occur continuously during physiological states and are vital for tissue adaptation, repair, and stress response.

Failure to appreciate these interactive networks contributes to incomplete models of disease, where musculoskeletal conditions are often accompanied by neuroimmune alterations. Conditions such as autoimmune myopathies, neuropathies, and degenerative muscle diseases manifest clinical features that reflect the integrated dysfunction among these systems rather than isolated pathology. Thus, there has been a paradigm shift toward viewing muscle, nerve, and immune functions as a triadic system whose cross-talk underlies both health and disease processes.

1.3 Rationale for the troika rubric

The troika rubric is proposed as a conceptual model to encapsulate the dynamic and reciprocal interactions among skeletal muscle fibers, peripheral nerve components, and immune cell populations, forming an interdependent and

regulatory triad. This model transcends reductionist approaches by emphasizing the systemic nature of muscle health and pathophysiology. It provides a scaffold to integrate molecular, cellular, and physiological information from traditionally separate fields into a coherent narrative explaining how homeostasis is achieved and disrupted.

Central to the troika rubric is the recognition that each node in the triad continuously communicates through direct cell-cell contact, paracrine signaling, and systemic mediators such as cytokines, chemokines, neurotransmitters, and growth factors. This communication modulates cellular behaviors, including survival, differentiation, inflammation, and regeneration, which collectively determine tissue outcomes. Importantly, signals originating from muscle fibers influence neural and immune responses; reciprocally, neuronal input modulates immune activity and muscle function, while immune cells regulate neurogenic and myogenic processes.

This integrative perspective also rationalizes the occurrence of complex multisystem disorders, where perturbations in one domain propagate deleterious effects across the network. The troika rubric offers a strategic approach to identify novel biomarkers, elucidate disease mechanisms, and develop multifaceted therapies targeting this coordinated system rather than isolated components. It serves as a foundation for future research aimed at uncovering the multidimensional interactions crucial for musculoskeletal health, with implications spanning from basic biology to clinical translation. A visual rendition of the troika theory is provided in **Figure 1**.

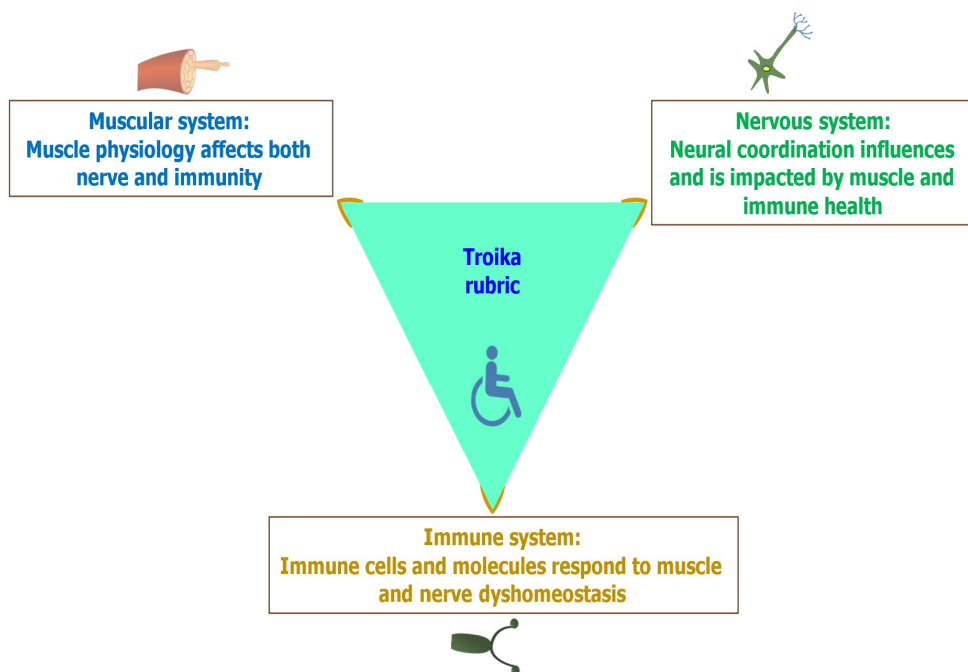


Figure 1. Foundations of “troika” theory: schematic representation of the muscle-nerve-immune “troika” rubric. The diagram illustrates that the muscle-nerve-immune “troika” is a complex, dynamic, and interdependent network essential for skeletal muscle health, disease progression, and tissue repair. The central triangle evinces integrated three-way cross-talks essential for homeostasis and disease response.

2. Structural basis of muscle-nerve-immune interaction

2.1 Anatomy of skeletal muscle and innervation

Skeletal muscle is composed of bundles of muscle fibers, each fiber being a multinucleated cell packed with contractile proteins organized into sarcomeres. Motor neurons innervate muscle fibers at specialized synapses to initiate contraction, while sensory neurons provide feedback on muscle status. Sympathetic nerves regulate blood flow and metabolism, contributing to muscle function. Effective neuromuscular communication is essential for movement and muscle health [5].

2.2 Cellular components of the immune system in muscle

Muscle hosts resident immune cells such as macrophages, dendritic cells, and T cells, distributed mainly in connective tissue layers. These cells respond to injury by clearing debris, modulating inflammation, and supporting muscle repair through growth factor secretion [6]. Immune cells closely interact with MuSCs, orchestrating regeneration and remodeling in a dynamic and context-dependent manner.

2.3 Neuromuscular junction: Interface of nerve and muscle

The neuromuscular junction (NMJ) is a highly specialized synapse where motor neurons transmit signals to muscle fibers by releasing acetylcholine, which binds to receptors on the muscle membrane to trigger contraction. Supported by Schwann cells, the NMJ is a critical site of neuromuscular communication and plasticity [7, 8]. Its integrity is vital for muscle function and is sensitive to neuroimmune modulation.

2.4 Connective tissue and vascular networks facilitating crosschats

The extracellular matrix and connective tissue layers (endomysium, perimysium, epimysium) provide structural scaffolding and support for force transmission. Embedded vascular networks facilitate the delivery of nutrients and the trafficking of immune cells. Pericytes and endothelial cells within vessels contribute signaling cues that integrate muscle, nerve, and immune functions, forming a microenvironment essential for tissue homeostasis and repair [9].

3. Molecular mediators of troika crosschats

3.1 Cytokines and chemokines in muscle-immune signaling

Cytokines and chemokines are key signaling proteins mediating communication between muscle and immune cells. Muscle fibers and infiltrating immune cells secrete proinflammatory cytokines like TNF- α and chemokines such as CCL2 which recruit immune cells to injury sites and regulate inflammation [10]. These molecules orchestrate immune cell activation and muscle regeneration by modulating satellite cell behavior, debris clearance, and extracellular matrix remodeling. IL-6 has both proinflammatory and antiinflammatory effects in muscle tissue, with its dual role

depending on the specific signaling pathway activated and the overall physiological context, such as exercise or chronic disease [11]. During exercise, muscle-derived IL-6 primarily acts as an antiinflammatory agent and energy allocator by enhancing glucose uptake and lipolysis [12]. In contrast, when secreted by other cells in response to chronic inflammation, IL-6 can exacerbate muscle wasting (atrophy), and hindering IL-6/JAK/STAT3 signaling helps repair it [13]. The above-cited evidence suggests that balanced cytokine signaling is essential; dysregulation can exacerbate chronic inflammation and muscle pathology.

3.2 Neurochemicals affecting muscle and immune cells

Neurotransmitters, including acetylcholine and norepinephrine, influence both muscle contraction and immune cell activity within the muscle microenvironment. Neurotrophic factors like brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) support neuronal survival and promote muscle regeneration via innervation [14, 15]. These molecules mediate neuroimmune cross-talks by modulating inflammation and facilitating repair processes, highlighting their integral role in maintaining troika homeostasis.

3.3 Receptor systems and signal integration across cell types

Muscle, nerve, and immune cells express a variety of receptors – cytokine receptors, neurotransmitter receptors, and pattern recognition receptors, especially toll-like receptors (TLRs) – enabling them to detect and respond to cross-system signals [16, 17]. Signal integration through these receptors governs cellular behaviors such as proliferation, differentiation, and immune activation. The convergence of multiple signaling pathways facilitates coordinated responses essential for tissue homeostasis and effective repair.

3.4 Emerging molecular pathways and their functional roles

Evidence highlights crucial pathways involved in troika interactions, including NF- κ B signaling, JAK-STAT pathways, interaction with gangliosides, and inflammasome activation [18]. These pathways control gene expression programs that regulate inflammation, cell survival, and regeneration across muscle, neural, and immune cells. Understanding these emerging mechanisms offers insights into troika dysregulation in diseases and presents opportunities for targeted therapeutic interventions.

4. Physiology of muscle-nerve-immune homeostasis

4.1 Mechanisms maintaining troika equilibrium in health

Homeostasis in the muscle-nerve-immune troika is maintained through tightly regulated cellular and molecular interactions that balance proinflammatory and antiinflammatory signals, neuromodulation, and tissue integrity. Immune surveillance by resident cells works alongside neurogenic control to modulate inflammatory responses and ensure effective muscle function [19]. Key pathways

involve cytokine signaling, neuroimmune synapses, and metabolic regulation to sustain equilibrium and prevent pathological activation.

4.2 Adaptive responses to physiological stress and exercise

Exercise and physiological stress induce adaptive changes across the troika. Muscle contraction releases myokines that modulate immune responses and support neural plasticity [20]. Concurrently, sympathetic nervous system activation influences immune cell trafficking and cytokine production [21]. These coordinated adaptations enhance muscle endurance, promote antiinflammatory environments, and optimize repair mechanisms, highlighting the dynamic plasticity within the troika.

4.3 Repair and regeneration processes involving all three systems

Following injury, the troika collaborates to initiate repair through immune cell recruitment, satellite cell activation, and neuronal remodeling. Macrophages clear debris and secrete factors aiding satellite cell proliferation. Neural inputs modulate inflammation and support reinnervation, critical for muscle recovery [22]. Feedback between these systems governs the timely resolution of inflammation and restoration of tissue architecture.

4.4 Feedback loops and network controls

Complex feedback mechanisms and network controls involving cytokines, neurotransmitters, and growth factors regulate troika functions. Positive and negative feedback loops ensure precise modulation of immune activation, neuronal excitability, and muscle metabolism [23]. Dysregulated feedback can lead to chronic inflammation or degeneration, emphasizing the necessity of integrated control to maintain tissue health.

5. Pathophysiological consequences of troika dysregulation

5.1 Muscular dystrophies and secondary neuroimmune effects

Muscular dystrophies, such as Duchenne muscular dystrophy (DMD), result from genetic mutations disrupting structural proteins like dystrophin, causing muscle fiber fragility and progressive degeneration [24]. Muscle damage leads to chronic inflammation, with infiltration of macrophages and T cells amplifying muscle wasting. Neuroimmune interactions exacerbate the pathology by affecting motor neuron function and NMJ integrity [25], highlighting the contribution of immune dysregulation to disease severity.

5.2 Autoimmune neuropathies and neuromuscular disorders

Autoimmune neuropathies involve an immune-mediated attack on peripheral nerves, impairing neuronal signaling to muscles. Disorders like Guillain-Barré syndrome (GBS) and myasthenia gravis exemplify how aberrant immune responses

disrupt neuromuscular transmission, causing muscle weakness [26]. The inflammation-induced damage triggers secondary muscle pathology, underlining the intertwined pathogenesis of nerve and immune system dysfunction in neuromuscular diseases.

5.3 Age-related sarcopenia and neurodegeneration

Aging leads to sarcopenia, characterized by loss of muscle mass and strength, accompanied by a decline in motor neuron number and function [27]. Chronic low-grade inflammation, or “inflammaging,” activates immune pathways that impair muscle regeneration and neural plasticity. Neuroimmune imbalance contributes to progressive neuromuscular degeneration, emphasizing the importance of troika homeostasis in healthy aging.

5.4 Inflammatory myopathies and chronic inflammation in muscle

Inflammatory myopathies, including polymyositis and dermatomyositis, are characterized by sustained immune cell infiltration and cytokine production within muscle [28]. Persistent inflammation damages muscle fibers, disrupts NMJs, and impairs repair processes. Dysregulated troika signaling drives chronic disease progression, causing profound muscle weakness and disability.

6. Translational and clinical implications

6.1 Biomarker discovery exploiting troika signatures

Biomarkers derived from integrated muscle-nerve-immune signaling profiles hold promise for the sensitive detection and monitoring of neuromuscular diseases. Proteomic, transcriptomic, and metabolomic studies reveal candidate molecules such as cytokines, muscle-specific proteins, and neurotrophic factors that reflect disease activity and progression. Multiomics and machine learning (ML) analyses enhance the identification of troika signatures that could enable precision diagnostics and prognostication.

6.2 Diagnostic platforms for early detection of neuromuscular diseases

Advances in high-throughput and minimally invasive technologies have facilitated the development of diagnostic platforms that leverage troika biomarkers for early detection. Blood-based assays, imaging modalities, and electrophysiological tools capture neuropathic, myopathic, and immune dysfunction markers. Integration of these modalities promises earlier diagnosis, patient stratification, and personalized treatment planning.

6.3 Therapeutic targets in muscle-nerve-immune interplay

Targeting key molecular mediators within the troika offers novel therapeutic avenues. Modulating inflammatory cytokines, enhancing neurotrophic support, and stabilizing NMJs are strategies under investigation. Therapies aiming at restoring

troika homeostasis have the potential to slow disease progression, improve muscle function, and mitigate secondary neuroimmune damage.

7. Future directions and research needs

7.1 Bridging clinical and experimental research

Advancing troika understanding requires integrative approaches that connect clinical observations with mechanistic experimental studies. Longitudinal patient cohorts, combined with animal models and cellular systems, can validate hypotheses and identify causative pathways [29–31]. Multidisciplinary collaborations between neurologists, immunologists, and muscle biologists are essential to translate findings into clinical practice.

7.2 Unresolved questions and hypotheses

Key gaps remain regarding the precise molecular mechanisms governing muscle-nerve-immune interactions, particularly in chronic and complex diseases. Questions include how the temporal dynamics of troika signaling influence disease onset, the role of novel cell types, and interactions with systemic factors like metabolism and microbiota. Addressing these unknowns will deepen the conceptual framework and therapeutic potential.

7.3 Technologies poised to advance troika research

Emerging technologies such as connectomics integration [32, 33] are poised to progress troika research. These tools enable high-resolution mapping of cellular interactions and pathways in health and disease, facilitating the identification of novel biomarkers and targets. Integration of multiscale data will provide holistic insights.

7.4 Potential for precision medicine and personalized therapies

Understanding patient-specific troika signatures opens avenues for precision medicine, enabling tailored interventions based on unique molecular, cellular, and systemic profiles. Personalized therapies targeting multiple troika nodes promise improved efficacy and reduced side effects. Future clinical trials incorporating troika-based biomarkers will refine patient stratification and treatment optimization.

Acronyms

BDNF	Brain-Derived Neurotrophic Factor
CCL2	Chemokine (C-C motif) Ligand 2
DMD	Duchenne Muscular Dystrophy
ECM	Extracellular Matrix
GBS	Guillain-Barré syndrome

IL-6	Interleukin-6
JAK	Janus Kinase
ML	Machine Learning
MuSC	Muscle Stem Cell
NF- κ B	Nuclear Factor kappa B
NMJ	Neuromuscular Junction
STAT	Signal Transducer and Activator of Transcription
TNF- α	Tumor Necrosis Factor-alpha
TLR	Toll-Like Receptor
GDNF	Glial Cell-Derived Neurotrophic Factor

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