# Putting the brakes on hyperreactive immune cells in neuromuscular pathologies

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The immune system is implicated in several neuropathologies. From the degradation of the myelin sheath facilitated by autoreactive lymphocytes in multiple sclerosis to the activation of microglia caused by the progression of Huntington's chorea, the immune system is a well-characterised mediator of both common and rare neurological conditions.

While neurological conditions at large often coincide with immune system dysregulation, neuromuscular diseases are a subset of disorders that are increasingly linked to hyperreactivity of immune cells. One area in which the role of the immune system significantly contributes to the onset and course of disease is the neuromuscular junction.

In a talk at the *European Academy of Neurology* conference in Oslo, three main types of neuroimmune interactions were identified. These were referred to as causal, co-operative and consequential activities which have numerous effects on neurophysiological architecture.

In a "causal" interaction, the immune system is either the sole or a major etiological factor of a neurological disease. An example of this is Guillain-Barré Syndrome (GBS), a disorder in which nervous system damage is caused by white blood cells damaging the myelin sheath in conjunction with complement activation. Other forms of GBS are mediated by antibodies which either target axonal membranes or gangliosides located in the peripheral nervous system.

A "co-operative" interaction constitutes a state where the immune system has protective effects on nervous system functionality, such as in the case of a muscle avulsion. Soon after an injury, the myelin sheath of the affected nerve fibres undergoes Wallerian degeneration. This process is mediated by macrophages which upon receipt of signals from Schwann cells and damaged axons, migrate into the central or peripheral nervous system and clear away the debris of degraded myelin. After the clearance has taken place, the expression and production of neurotrophic molecules is significantly increased by Schwann cells and fibroblasts. In this situation, the immune system prevents the injury from causing further damage to additional nervous system components.

The "consequential" type of neuroimmunological interaction, the immune system contributes significantly to the downstream pathophysiology of the disease, such as in the case of Charcot-Marie-Tooth (CMT) disease, a hereditary motor and sensory neuropathy. Characterised by symptoms such as muscle weakness, spasmodic contractions and skeletal deformations, the pathophysiological mechanisms of action include chronic repetition of demyelination and remyelination cycles, which has been linked to oxidative stress and persistent inflammation, activated by the disruption of calcium homeostasis.

The pharmaceutical pipeline for neuromuscular disorders is increasingly focusing on strategies to attenuate the hyperreactive immune response. An example of this includes sequestering or destroying autoantibodies produced against host proteins, a major pathophysiological driver of many cases of myasthenia gravis, a condition that causes muscle weakness. Other therapeutic immunosuppressive strategies include anti-apoptotic methods that work by inhibiting the formation of the membrane attack complex (MAC), a structure that is attached to a species targeted for programmed cell death. Formation of the MAC is a step in the complement pathway, a cascade of small haematological proteins that facilitate the clearance of damaged cell debris, elimination of pathogens and prevention of infection. In conjunction with findings from clinical research, drug developers are devising other immunosuppressive techniques including the inhibition of specific cytokines, B cells, and T cells. Simultaneously, strengthening the signalling capacity of damaged neuromuscular junction machinery will also relieve symptoms which significantly decrease patients' quality of life.

Fundamentally, preserving the functionality of the immune system is important not only to protect the body from infection and clear the remnants of damaged cells, but also to perform processes such as those involved in repairing soft tissue injuries and limiting oncogenesis.

It is equally as important however, to offer effective treatments to patients with neurological diseases that are exacerbated by the biological system that is supposed to protect them.