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# Treating muscle-specific kinase myasthenia gravis from the inside out

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Myasthenia gravis (MG) with antibodies to muscle-specific kinase (MuSK) is an autoimmune disease of the neuromuscular junction with some remarkable characteristics. Although MuSK is expressed in all skeletal muscles, patients with this disease present with particularly cranial, bulbar, and respiratory muscle weakness, leading to a relatively high frequency of respiratory crises.<sup>1</sup> Despite several available immunosuppressive or immunomodulatory treatments, patients with MuSK MG often retain residual muscle weakness and experience more often severe muscle atrophy than patients with the more frequent MG with acetylcholine receptor (AChR) antibodies.<sup>2</sup> Symptomatic treatment with acetylcholinesterase inhibitors is usually ineffective or even detrimental in MuSK MG,<sup>1</sup> although 3,4-diaminopyridine might be effective in some patients.<sup>3</sup> Therefore, treatment of MuSK MG today still mostly relies on immunosuppressive treatment.<sup>1</sup>

At the basis of the development of fatigable muscle weakness in patients with MuSK MG is the trophic signaling cascade that enables the motor nerve terminal to instruct the muscle membrane to differentiate into a mature postsynapse. MuSK is at the heart of this signaling cascade. Several groups have shown that perturbation of MuSK signaling by binding of patients' IgG4 MuSK antibodies leads to loss of this differentiation signal (MuSK phosphorylation), subsequent synaptic disintegration, failure in neuromuscular transmission, and ultimately fatigue.<sup>4,5</sup> The predominance of IgG4 subclass autoantibodies is particularly important, as the anti-inflammatory characteristics of this type of antibody imply that the disease mechanism, response to therapy, and possibly also the etiology are different from other forms of MG with IgG1 or IgG3 autoantibodies.

In this issue of *Neurology*<sup>®</sup>: *Neuroimmunology & Neuroinflammation*, Huda et al.<sup>6</sup> use the current knowledge on the pathophysiology of MuSK MG to test a new therapeutic strategy by targeting the muscle directly. Normal MuSK signaling/phosphorylation is normally halted by intracellular Rous sarcoma gene (SRC) homology 2 domain-containing phosphotyrosine phosphatase 2 (SHP2). Inhibition of this phosphatase results in spontaneous and agrin-independent MuSK phosphorylation and AChR clustering in vitro. Huda et al. tested whether an SHP2 inhibitor, NSC-87877, could overcome the inhibitory effect of MuSK autoantibodies in mouse myotube cultures. The study clearly shows improved MuSK activation levels, indicated by increased MuSK phosphorylation and restoration of AChR cluster formation in MuSK autoantibody-treated myofibers. AChR clusters in myotubes are generally considered immature, as they do not express the adult epsilon subunit nor contain the complex morphology required for natural neuromuscular junction transmission. In vivo, agrin (in combination with several other extracellular proteins) is considered critical for induction of maturation of the postsynaptic structure and AChR clusters. A next exciting step will be to extend these observations in vivo and confirm whether SHP2 inhibition can induce formation and maintenance of mature postsynaptic structures also after prolonged exposure to patients autoantibodies. Downstream of kinase 7 overexpression, another form of intracellular activation of MuSK phosphorylation, was shown successful in maintaining synapses in several neuromuscular disorders.<sup>7</sup> Huda et al. show that their SHP2 inhibitor also increased the number of AChR clusters in

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SHP2 inhibitor protects AChRs from effects of myasthenia gravis MuSK antibody

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downstream of kinase 7-overexpressing myotubes. A negative effect of chronic activation of MuSK through SHP2 inhibition *in vivo* is not expected, as chronic activation of MuSK phosphorylation with a monoclonal antibody in a mouse model for amyotrophic lateral sclerosis showed positive effects on innervation and did not show a deleterious effect.<sup>8</sup> Importantly, SHP2 is expressed in many cell types of the human body. The authors discuss the potential off-target effects, especially the risk of tumorigenesis, and suggest that based on current knowledge, the risk of tumorigenesis is not increased.

When these technical challenges are overcome, SHP2 inhibition has the potential to become a new symptomatic treatment for patients with MuSK MG. It is tempting to speculate which other disorders with neuromuscular junction impairment may benefit from strengthening synapses from “the inside out” using SHP2 inhibitors.<sup>9</sup>

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### Disclosure

LUMC, M.G. Huijbers, and J.J.G.M. Verschuuren have applied for patents in the field of MuSK myasthenia gravis. J.J.G.M. Verschuuren has been involved in consultancies for Argenx, Alexion, and Rappharma. All reimbursements were

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