Pathophysiology of myasthenia gravis

In myasthenia gravis (MG), pathogenic autoantibodies at the neuromuscular junction (NMJ) impair synaptic signaling, causing reduced muscle contraction[1-3]

In a healthy body, T-cell differentiation and the establishment of central tolerance occur in the thymus, a primary lymphoid organ[4,5]

Thymus

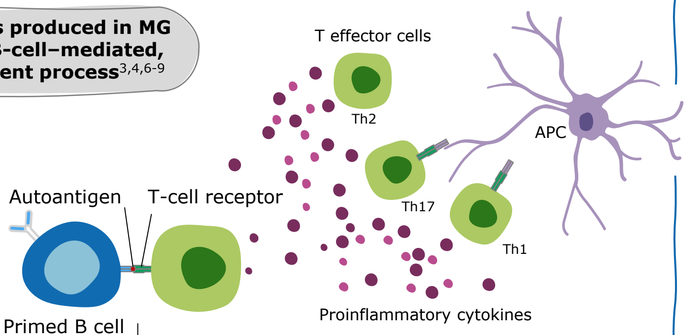
In MG, dysfunctional T-cell selection allows autoreactive T cells to escape central immune tolerance[4,5]

UPSTREAM

Initiation of autoimmune response and autoantibody production

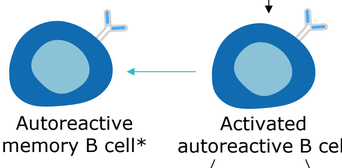
Autoantibodies produced in MG are part of a B-cell–mediated, T-cell–dependent process[3,4,6-9]

Therapeutic strategies can focus on either "upstream" or "downstream" targets

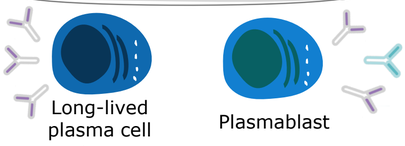


Autoreactive T cells interact with and activate B cells in germinal centers[4]

Autoimmune B-cell differentiation



Autoantibody-secreting cells



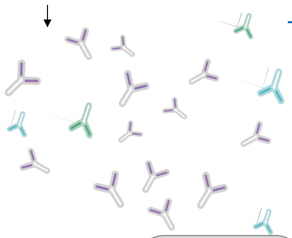
Autoantibodies

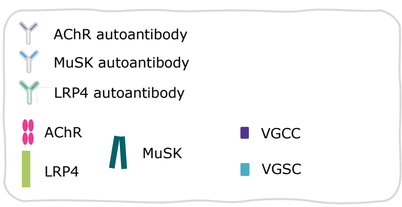
Examples include[1,9,10]:

AChR: IgG1 and IgG3

MuSK: IgG4

LRP4: IgG1



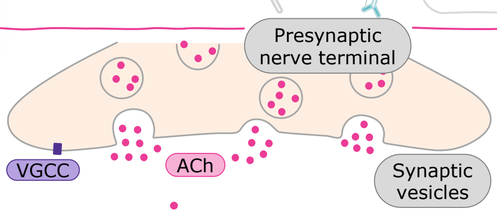


DOWNSTREAM

Autoantibody effects at the NMJ and signal transmission processes

NMJ[9,11,12,†]

In MG, neuromuscular transmission is impaired by[1,13]**:**



AChR autoantibodies

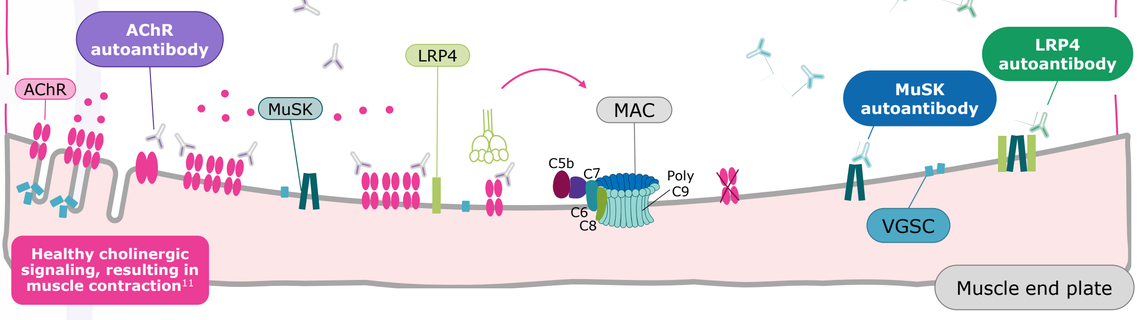
- *AChR signaling disruption or AChR internalization*[1]
- *Activation of complement cascade triggering complement-mediated membrane damage*[1]

MuSK autoantibodies

- *AChR clustering disrupted*[1]

LRP4 autoantibodies

- *Hypothesized to interfere with agrin– and LRP4–MuSK interactions and AChR clustering*[1,13]



By targeting components of the NMJ, the autoimmune process disrupts cholinergic signaling and impairs muscle contraction, causing the fatigue and weakness characteristic of MG[1,10,11,13,14]

*Upon reactivation, autoreactive memory B cells can produce plasma cells.[6,9,10]

†Adapted from Iorio R. Nat Rev Neurol. 2024;20(2):84–98, Howard Jr. JF. Ann N Y Acad Sci. 2018;1412(1):113–128, and San PP, Jacob S. Front Neurol. 2023;14:1277596.

ACh, acetylcholine; AChR, acetylcholine receptor; APC, antigen-presenting cell; C, complement; Ig, immunoglobulin; LRP4, low-density lipoprotein receptor-related protein 4; MAC, membrane attack complex; MG, myasthenia gravis; MuSK, muscle-specific kinase; NMJ, neuromuscular junction; Th, T helper cell; VGCC, voltage-gated calcium channel; VGSC, voltage-gated sodium channel.

1. Lazaridis K, Tzartos SJ. Front Neurol. 2020;11:596981. **2.** Gilhus NE. N Engl J Med. 2016;375(26):2570–2581. **3.** Koneczny I, Herbst R. Cells. 2019;8(7):671. **4.** Dresser L, et al. J Clin Med. 2021;10(11):2235. **5.** Berrih-Aknin S. Clin Exp Neuroimmunol. 2016;7:226–237. **6.** Akkaya M, et al. Nat Rev Immunol. 2020;20(4):229–238. **7.** Schneider-Gold C, Gilhus NE. Ther Adv Neurol Disord. 2021;14:17562864211065406. **8.** Dalakas MC, Meisel A. Expert Rev Neurother. 2022;22(4):313–318. **9.** Iorio R. Nat Rev Neurol. 2024;20(2):84–98. **10.** Fichtner ML, et al. Front Immunol. 2020;11:776. **11.** Howard JF Jr. Ann N Y Acad Sci. 2018;1412(1):113–128. **12.** San PP, Jacob S. Front Neurol. 2023;14:1277596. **13.** Yu Z, et al. Neurology. 2021;97(10):e975–e987. **14.** Uzawa A, et al. Clin Exp Immunol. 2021;203(3):366–374.

US-NONNI-02466 | GL-NONNI-02611 | June 2026

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