MYASTHENIA GRAVIS PHYSIOPATHOLOGY: RELEVANCE TO CLINICAL PRACTICE

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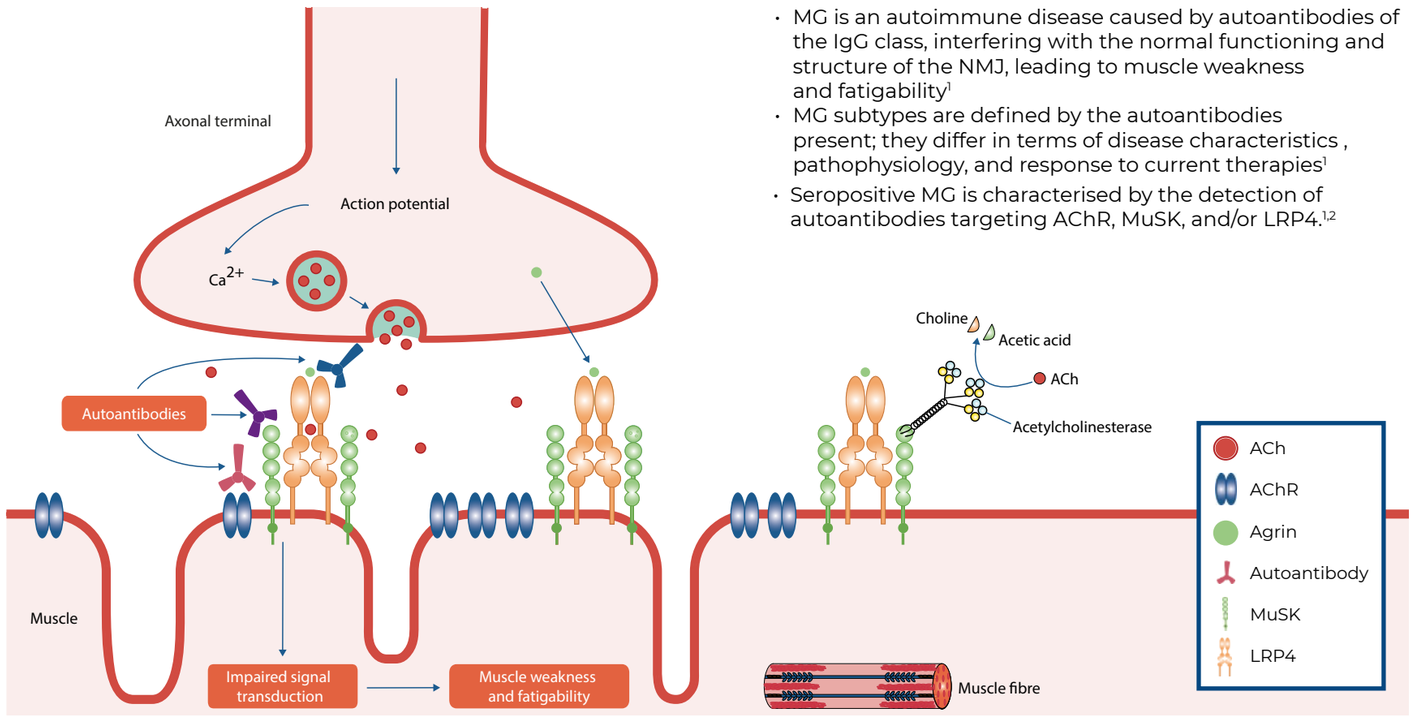
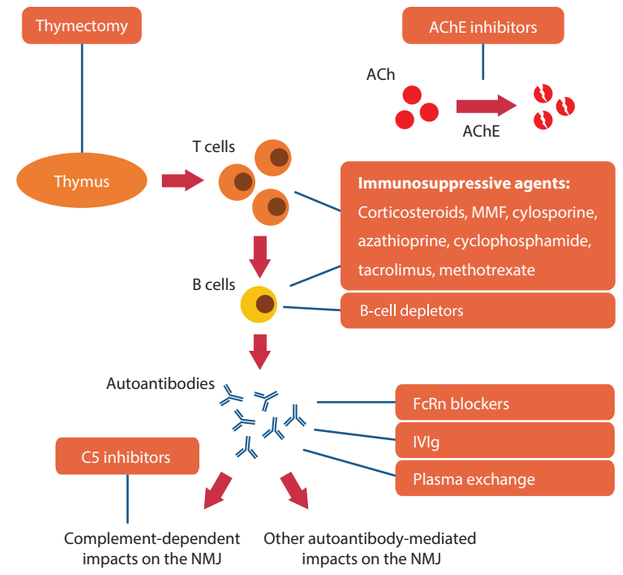
An Overview of MG



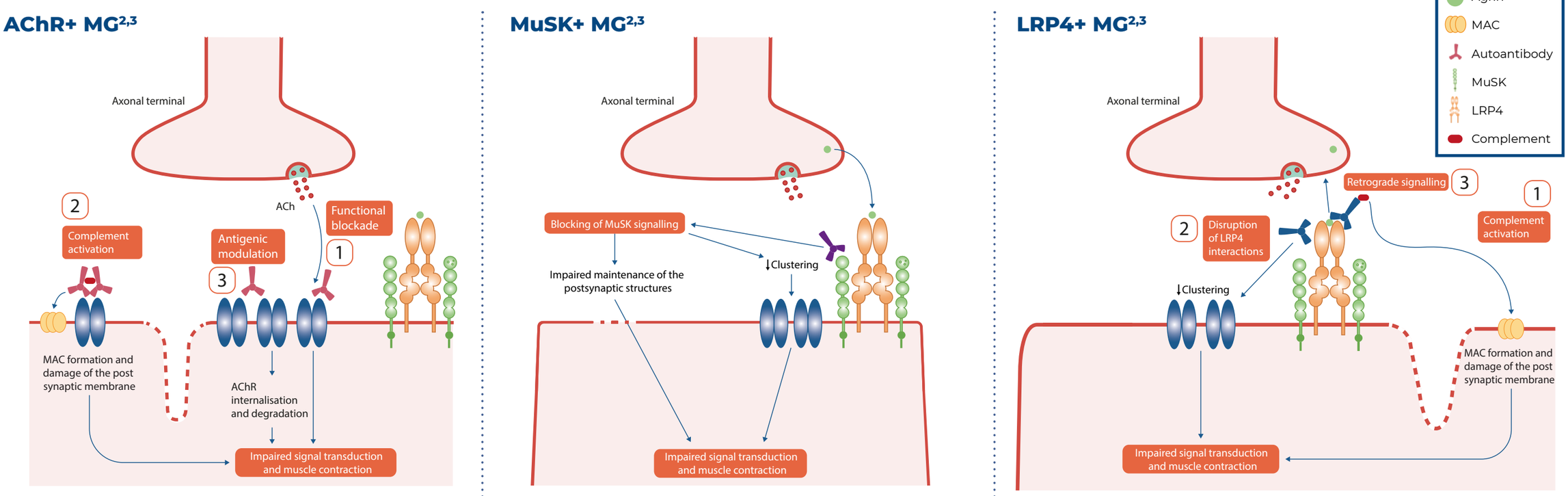
- MG is an autoimmune disease caused by autoantibodies of the IgG class, interfering with the normal functioning and structure of the NMJ, leading to muscle weakness and fatigability[1]
- MG subtypes are defined by the autoantibodies present; they differ in terms of disease characteristics , pathophysiology, and response to current therapies[1]
- Seropositive MG is characterised by the detection of autoantibodies targeting AChR, MuSK, and/or LRP4.[1,2]

Treatment Strategies for MG

Current MG treatment approaches (as detailed in the boxes directly below) are largely non-specific, and thus may be accompanied by a variety of side effects, particularly since lifelong immunosuppressive treatment is often required[1,2]

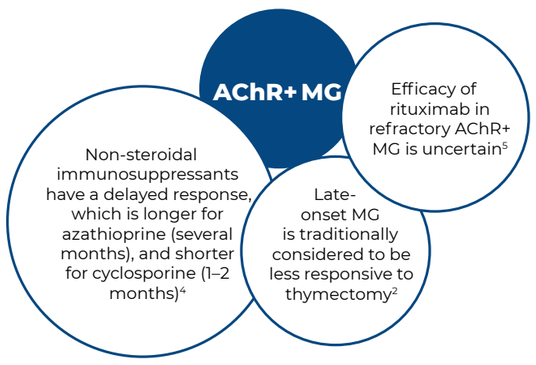


MG Autoantibodies Alter the NMJ Through Different Pathological Pathways



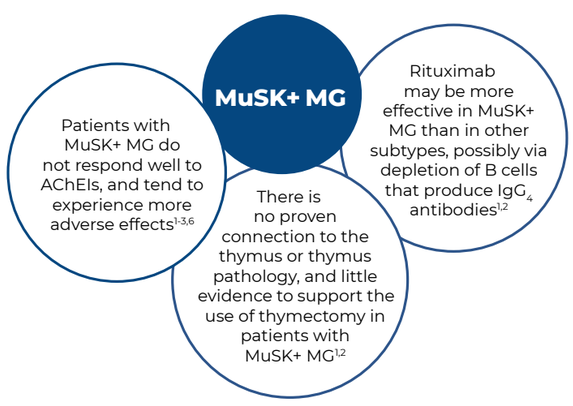
AChR+ MG[2,3]

- Approximately **80%** of patients with MG present with autoantibodies against the muscle AChR[2]
- These autoantibodies mostly belong to the IgG_1 and IgG_3 subclasses, with three pathogenic mechanisms:[2]
  1. Functional blockade of the binding site on the AChR[2,3]
  2. Activation of the complement cascade, leading to damage of the postsynaptic membrane[2,3]
  3. Antigenic modulation: cross-linking, internalisation, and degradation of surface AChRs[2]



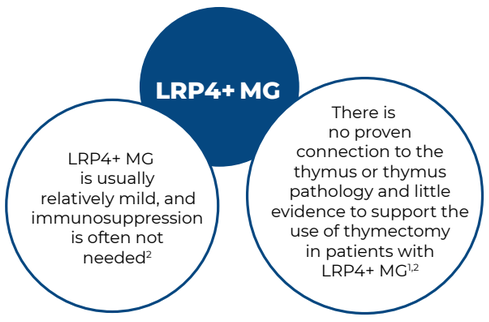
MuSK+ MG[2,3]

- MuSK autoantibodies are detected in **1–10%** of patients with MG, and are more common in patients from the Mediterranean area versus Northern Europe[2]
- MuSK is a transmembrane protein responsible for the clustering of AChR and the maintenance of the postsynaptic membrane[4]
- MuSK autoantibodies, which are mainly of the monovalent IgG_4 subclass, do not activate complement, and typically prevent the interaction of MuSK and LRP4, among other proteins, leading to reduced AChR clustering on the postsynaptic membrane[1]



LRP4+ MG[2,3]

- LRP4 autoantibodies are detected in **1–5%** of patients with MG, primarily in patients without AChR or MuSK autoantibodies[1,2]
- LRP4 is a receptor for neural agrin that relays the signal to MuSK to initiate AChR clustering. The pathogenicity of anti-LRP4 antibodies in MG remains to be established, but pathogenic mechanisms may include:[4]
  1. Activation of the complement cascade, leading to damage of the postsynaptic membrane[3]
  2. Disruption of the interaction between LRP4 and agrin, or LRP4 and MuSK[2,3]
  3. Disruption of retrograde signalling from LRP4 to the motor neuron[3]



Seronegative MG

- Patients with MG without detectable antibodies against AChR, MuSK, or LRP4 are referred to as seronegative[2]
- This subgroup constitutes approximately 10% of generalised patients with MG, depending on the sensitivity of antibody tests used[2]
- Seronegative patients are commonly excluded from clinical trials,[8] but some FcRn blockers have recently been studied in this population[8]

This heterogeneous subgroup may include patients with:

- Autoantibodies that may have affinities/concentrations too low to detect[2]
- Autoantibodies against unidentified antigens[2]
- Myasthenic symptoms that may not be antibody-mediated[2]

Summary

- **Disease pathogenesis and response to therapy varies between MG subtypes, according to autoantibody pattern[2]**
- **Therapy should be tailored to the individual patient, and guided by the MG subtype[2]**
- **Currently, it is challenging to optimise the use of available treatments for the individual patient with MG[2]**
- **Focusing on decreasing autoantibodies by targeting the FcRn pathway may be a valuable treatment approach for MG[9]**

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Abbreviations: ACh: acetylcholine; AChR: acetylcholine receptor; AChEI: acetylcholinesterase inhibitor; Ca^{2+}: calcium ions; FcR: fragment crystallisable receptor; FcRn: fragment crystallisable neonatal receptor; HCP: healthcare professional; IgG: immunoglobulin G; IVIg: intravenous Ig; LRP4: low-density lipoprotein receptor-related protein 4; MAC: membrane attack complex; MG: myasthenia gravis; MMF: mycophenolate mofetil; MuSK: muscle-specific tyrosine kinase; Na^{2+}: sodium ions; NMJ: neuromuscular junction.

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