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Pathophysiology and immunological profile of myasthenia gravis and its subgroups

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Myasthenia gravis (MG) is an autoimmune antibody-mediated disease characterized by muscle weakness and fatigability. It is believed that the initial steps triggering humoral immunity in MG take place inside thymic tissue and thymoma. The immune response against one or several epitopes expressed on thymic tissue cells spills over to neuromuscular junction components sharing the same epitope causing humoral autoimmunity and antibody production. The main cause of MG is acetylcholine receptor antibodies. However, many other neuromuscular junction membrane protein targets, intracellular and extracellular proteins are suggested to participate in MG pathophysiology. MG should be divided into subgroups based on clinical presentation and immunology. This includes onset age, clinical characteristics, thymic pathology and antibody profile. The immunological profile of these subgroups is determined by the antibodies present.

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Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune antibody-mediated disease characterized by muscle weakness and fatigability. It usually affects ocular, bulbar, and proximal extremity muscles, but in severe cases also involves respiratory muscles and can be life-threatening [1,2]. MG may inflict muscle weakness in patients at any age and has a prevalence of 150–300 in 1 000 000 and an annual incidence of 10 in 1 000 000 [3•,4]. In most cases, the disease is successfully treated with symptomatic agents combined with immunomodulatory drug treatment, intravenous immunoglobulin treatment, and thymectomy [5]. MG is divided into subgroups depending on onset age and immunological profile, and the preferred therapy varies among these subgroups [2].

Thymus and thymoma in MG autoimmunity

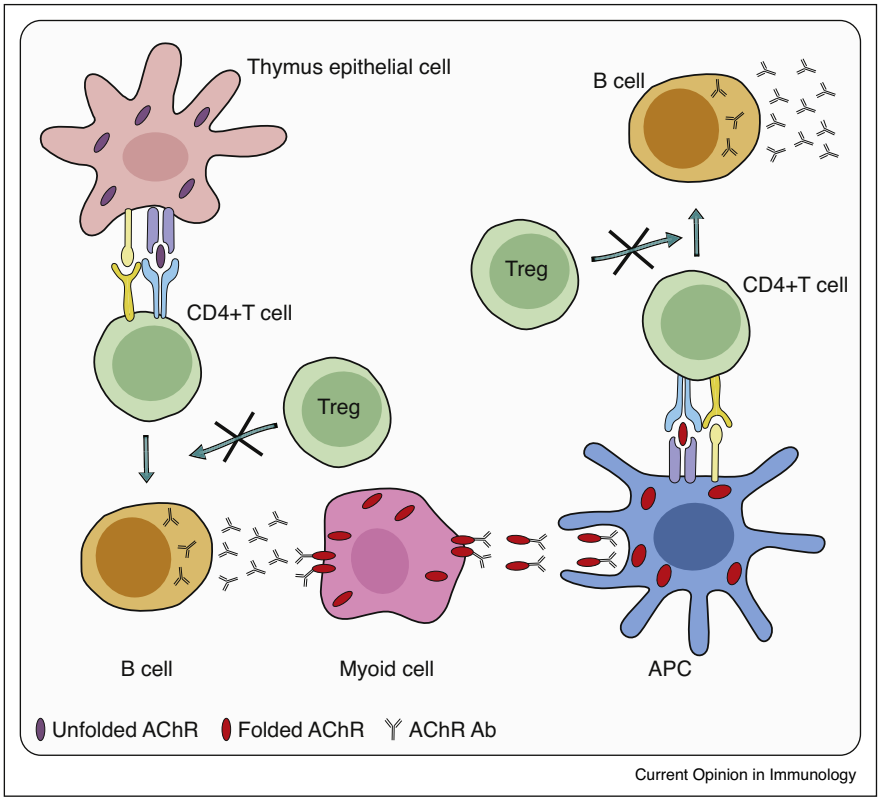
It is believed that the initial steps triggering humoral immunity in MG take place inside the thymic tissue and thymoma [6,7,8••]. In 10–15% of MG patients a thymoma is present, and up to 50% of thymoma patients develop MG [9–11]. Cortical thymomas have morphological similarities with thymic cortex, sharing the capacity to propagate maturation of naive CD4 T-cells and exporting mature T-cells into the periphery. Thymomas lacking this ability do not induce MG [8••]. Non-MG inducing thymomas also share defective epithelial expression of the autoimmune regulator (AIRE) gene and/or of major histocompatibility complex class II molecules, absence of myoid cells, failure to generate FOXP3(+) regulatory T cells, and genetic polymorphisms restricting T-cell signaling [8••].

The thymic epithelial cells are capable of expressing epitopes cross-reactive with skeletal muscle proteins, such as acetylcholine receptor (AChR), titin, and ryanodine receptor (RyR) [12]. The muscle-like epitopes are presented to T-cells together with co-stimulatory molecules [8••]. Autoreactive T-cells specific for AChR and titin are found both in thymomas and in peripheral blood from thymoma MG patients' sera [13]. Thymoma epithelial cells present AChR peptides to T-cell lines in thymoma MG patients, facilitating intrathymic immunization [14] (Figure 1).

When MG occurs together with a thymoma, MG constitutes a paraneoplastic disease caused by the presence of the thymoma. Thymoma MG accounts for around 10–15% of all MG cases [6,7].

The immune response against an epitope expressed on thymoma cells spills over to neuromuscular junction components sharing the same epitope [8••,15]. In thymoma MG, epitopes are shared between the thymoma and muscle proteins. Furthermore, there is evidence of large-scale abnormalities in both naive and memory B cell repertoires in MG. Some abnormalities are unique to either AChR-MG or MuSK-MG indicating that the repertoires reflect the distinct properties of MG subgroups, pointing toward a deformed B cell repertoire as a fundamental component of MG pathogenesis [16•]. There is also evidence of upregulation of inflammatory proteins that could play a role in MG autoimmunity, especially

Figure 1



The typical thymic change of early-onset MG with AChR antibodies is thymic follicular hyperplasia, with the occurrence of intrathymic lymphoid follicles and germinal centers. The pathogenesis of MG involves a two-step model [45,46]: helper T cells respond to unfolded AChR subunits expressed by thymic epithelial cells and stimulate the production of early AChR antibodies. Thymic myoid cells that express intact AChRs are then attacked by these antibodies, and release AChR-immune complexes, these in turn activate antigen presenting cells and diversify the autoantibody response to recognize intact AChRs [12,46].

matrix metalloproteinase (MMP)-10, transforming growth factor alpha, and an extracellular newly identified receptor for advanced glycation end-products binding protein [17].

Neuromuscular membrane-associated protein antibody targets in MG pathophysiology

MG is mainly caused by antibodies targeting AChR at the postsynaptic neuromuscular junction membrane, leading to impaired signal transduction, muscle weakness, and fatigability. AChR antibodies are found in 80% of all MG patients [2]. They are usually detected by routine laboratory assays but in some cases can only be detected with more sensitive, cell-based assays [18], especially in patients with antibodies only to clustered AChRs [19•]. In a recent study using novel highly sensitive radioimmuneassay, such antibodies were identified in 25% of MG sera previously found negative in routine assays (Hong Y, Zisimopoulou P, Trakas N, Karagiorgou K, *et al.*: **Multiple antibody detection in "seronegative" myasthenia gravis patients**. *Eur J Neurol* 2017, submitted for publication). AChR antibodies are predominantly IgG1 and IgG3, capable of activating complement and therefore causing postsynaptic membrane damage and blocking the signaling pathway [20].

Antibodies against AChR alfa subunit are more pathogenic than those against other subunits. AChR epitope pattern influences disease severity [21].

Muscle specific kinase (MuSK) is an AChR related membrane protein critical for the neuromuscular junction formation [22•]. MuSK antibodies occur in 1–10% of patients with MG and are more prevalent in the Mediterranean area than Northern Europe. Genetic and environmental factors play a role in this diversity [2,20,23•]. IgG4 is the prevalent subclass of MuSK antibodies. Although IgG4 is not a potent complement activator, MuSK antibodies bind to the extracellular N-terminal Ig-like domains of the AChR, retaining direct pathogenic capability by reducing postsynaptic AChR density, impairing the alignment between motor nerve terminal and postsynaptic membrane [24].