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Review

The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes ☆,☆☆

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ABSTRACT

The thymus plays distinct roles in the pathogenesis of the different Myasthenia gravis (MG) subtypes. Inflammatory, neoplastic and age-related alterations of the thymus are of pivotal relevance for the initiation of anti-acetylcholine receptor (AChR) autoimmunity in early onset MG, thymoma-associated MG and, likely, late onset MG, respectively. By contrast, the thymus is presumably not related to MG that is due to autoantibodies to the muscle specific kinase, MuSK. Finally, the role of the thymus is still obscure in MG defined by antibodies against the agrin receptor LRP4 and in MG without all of the above autoantibdies (triple sero-negative MG) since these MG subtypes have been described only recently and thymectomy has not been their standard treatment. This review aims to give an update on intrathymic mechanisms of tolerance breakdown in MG, including abnormal T cell selection and activation, the role of thymic myoid cells, the autoimmune regulator (AIRE) and regulatory T cells.
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1. Introduction

Myasthenia gravis (MG) is an autoimmune disease characterized by autoantibodies against different components of the neuromuscular junction (NMJ), thereby eliciting muscle fatigability and weakness [1,2]. MG is a heterogeneous disease in terms of clinical presentation, autoantigens at the NMJ, and pathogenic mechanisms including genetic risk factors and associated thymic pathologies [3]. According to the targets of the pathogenic autoantibodies, MG is classified into: i) the most prevalent MG subtype ("AChR MG") due to autoantibodies against the muscle-type acetylcholine receptor, AChR [4]; ii) MG due to antibodies against the muscle specific kinase, MuSK ("MuSK MG")[5]; iii) MG due to autoantibodies against the agrin-receptor low-density lipoprotein receptor-related protein 4, LRP4 ("LRP4 MG") [6–8]; and iv) MG without known target autoantigen(s) ("triple sero-negative MG") [9]. The complexity of MG is augmented by the heterogeneity within the AChR MG subgroup: based on age of disease onset, gender and genetic biases, antibody specificities and associated thymus pathologies, early onset MG (EOMG), late onset MG (LOMG), and thymoma associated MG (TAMG) are distinguished. The etiologies and triggers of the different MG subtypes are only partially understood. Genome wide association studies (GWAS) hold promise to unravel new disease mechanisms [10]. In addition, clinical observations like the beneficial effect of anti-CD20 treatment in MuSK MG as compared to AChR MG give valuable clues to distinct pathogenic mechanisms that are differentially operative in the various MG subtypes.

2. MG due to antibodies against the acetylcholine receptor, AChR (AChR MG)

2.1. General principles

2.1.1. Clinical features, epidemiology

Clinical and pathogenic heterogeneity in this subgroup is greatest since it comprises patients with EOMG, LOMG, TAMG and patients with autoantibodies exclusively against clustered AChR (reviewed in [1]). The heterogeneity in relation to age of disease onset and thymic pathology is paralleled by typical gender biases in each subgroup, different genetic risk factors and associated additional autoimmune reactions against non-AChR targets (Table 1).

AChR MG shows a wide spectrum of clinical findings from pure ocular to generalized MG symptoms. Details can be found in excellent reviews [11–13]. Metaanalysis of epidemiological studies and a nationwide Norwegian analysis revealed a real increase of MG with anti-AChR antibodies, particularly among the elderly, and this is likely not only due to better disease recognition [14,15]. Environmental triggers underlying this increase (e.g. drugs or altered nutrition/microbiota) are enigmatic. Current incidence of AChR MG in Norway is 7 per million with a prevalence of 126 per million population [15].

2.1.2. The autoantigen

The AChR is a pentameric channel that exists in two forms with well defined stoichiometry of the homologous alpha (α), beta (β), gamma (γ), delta (δ) and epsilon (ε) subunits: the fetal AChR shows an $\alpha_2\beta\delta\gamma$, and the adult AChR shows an $\alpha_2\beta\delta\varepsilon$ composition. The α-subunit is distinguished by two features: first, an extracellular cystein loop that mediates ligand (acetylcholine, ACh) binding [16]; second, an extracellular sequence to which most anti-AChR autoantibodies are directed that is termed the main immunogenic region (MIR) [17,18].

During development and following innervation the γ-subunit of the fetal AChR is replaced by the ε-subunit yielding adult AChRs that have higher conductance, shorter activation episodes, a longer half-life and higher density when clustered at the neuromuscular junction [19]. Normally, functional AChR is only expressed by skeletal muscle cells and thymic myoid cells [20]. In the normal thymus, both adult and fetal AChR are expressed by non-innervated thymic myoid cells that likely play a role in the induction of immunological tolerance towards muscle proteins [21]. Under physiological postnatal conditions, the fetal AChR is only expressed on thymic myoid cells [20] and (for poorly understood reasons) on single extra-ocular muscle fibers [22].

In addition, *unfolded* AChR subunits (but not whole functional channels [23]) are expressed by medullary thymic epithelial cells [24], partly under the control of the autoimmune regulator (AIRE) [25]. Peptides derived thereof are presented by MHC molecules to developing T cells and normally support immunological tolerance towards the AChR — but likely become immunogenic in the context of thymitis in EOMG [26].

2.1.3. Autoantibodies against solubilised or clustered AChRs

Autoantibodies against solubilised AChRs or exclusively against clustered AChRs are present in 80% and ~5% of patients with generalized MG, respectively [27,28]. More details about the biochemistry, specificity and function of these autoantibodies and the pathophysiology that they elicit at the neuromuscular junction are given in paper 7 of this volume [29].

2.1.4. Determinant spreading

The initial focus of the immune response to single AChR sequences (a likely situation during the initiation of MG) can be lost: vaccination

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