Future perspectives in myasthenia gravis (Review)

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Abstract. Myasthenia gravis (MG) is a rare, highly polygenic autoimmune disease mainly caused by target-specific pathogenic antibodies, and its fluctuating course through the patient's life, often entails hospitalizations and difficulties in everyday life. The pathophysiology of MG is complex with a number of contributing factors, involving genetic, epigenetic and environmental factors are responsible for a limited immune tolerance. This heterogenic disease appears to have a common genetic background with other diseases and a number of single nucleotide polymorphisms (SNPs) have been found to be associated with different forms of MG through genome-wide association studies; i.e, the cholinergic receptor nicotinic alpha 1 subunit (*CHRNA1*) that encodes for subunit α of the acetylcholine receptor includes a SNP allele associated with MG. Additionally, specific genes or even genomic regions can be differentiated by a set of epigenetic factors, including methylations, non-coding RNAs and histone modifications. The role of epigenetics in MG has been reported in monozygotic twin studies, where the combination of specific methylations and numerous small changes in gene expression have been shown to contribute to the development of the disease, demonstrating a stronger genetic predisposition for MG. Establishing the genetic and epigenetic background of MG in the realm of autoimmune diseases can further promote basic research and the development of novel therapeutic approaches that can be used to overcome the limitations of current clinical practices.

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Contents

1. Introduction

Autoimmunity occurs when the disruption of differentiation between self-antigens and pathogens occurs in the adaptive system, leading to wrong immune responses with possible tissue damage and, thus, generating an autoimmune disease. Myasthenia gravis (MG) is a rare highly polygenic autoimmune disease mainly caused by target-specific pathogenic antibodies. A characteristic of the disease is its fluctuating course through the patient's life, which often entails hospitalizations and difficulties in everyday life. The pathophysiology of MG is complex with a number of contributing factors, involving genetic, epigenetic and environmental factors responsible for the limited immune tolerance. This heterogenic disease is mainly caused by a failure in the neuromuscular transmission as a result of autoantibodies targeting neuromuscular junction proteins (1). In the majority of cases (80-85%) the autoantibodies target the muscle nicotinic acetylcholine receptor (nAChR), and in a smaller percentage of patients, antibodies against the muscle-specific kinase are detected (2). There is also however, a small percentage of seronegative patients, and over the past years, new or improved assays have made possible the detection of other autoantigens, such as the low-density lipoprotein receptor-related protein 4 (3). As an autoantigen-mediated disease, MG is suitable for antigen-specific immunotherapies.

2. Myasthenia gravis therapies: The present

MG currently is mainly treated with specific drugs that exert a non-specific modulation or suppression of the patient's immune system. The main drug used for the majority of patients is an acetylcholinesterase inhibitor, named pyridostigmine bromide, which is a symptomatic treatment (4). Current

immunotherapies are subdivided into two categories: Conventional therapies that are non-specific symptomatic treatments with corticosteroids and immunosuppressants, and immunomodulating therapies that are non-antigen specific (5).

The first category includes drugs that have been used for a number of years and have succeeded in reducing the mortality rate and to provide patients with an improved quality of life. These include corticosteroids, such as oral prednisone and prednisolone, and immunosuppressants, usually antimetabolites such as azathioprine, mycophenolate, mofetil and calcineurin inhibitors, such as cyclosporine (6). Recently, the immunosuppressive drugs, methotrexate (antimetabolite) and tacrolimus (inhibitor), are concurrently used in an attempt to lower the high doses of prednisone (7).

The second category of non-antigen specific-immunomodulating therapies is used for short-term therapies to offer a beneficial suppression of symptoms. These therapies are often applied to patients that do not respond to conventional immunosuppression and have acute MG symptoms; these include plasma exchange (PLEX) and intravenous immunoglobulin (IVIG) (8). PLEX removes complement, antibodies, cytokines and other molecules from the blood circulation, while IVIG inhibits complement deposition, blocks the activation of Fc receptors, and neutralizes antibodies and cytokines (9). Both therapies have been found to be effective for the treatment of myasthenic crises with respiratory muscles involved, for disease exacerbations and for the prevention or minimalization of MG deterioration prior to surgeries (10-12). Both therapies can be used periodically for the treatment of patients with intolerance to immunosuppression (12).

3. The future of immunotherapies for myasthenia gravis

Novel therapies should aim to target the specific autoimmune components of the immune system of each patient. A method similar to PLEX is immunoadsorption, where the pathogenic autoantibodies are selectively removed through a suitable matrix. Other plasma components remain unaltered; however, circulating IgG antibodies are removed by binding to specially designed antigens, such as sepharose-immobilized autoantigens (13,14). Subcutaneous immunoglobulin has been reported in an open-label trial to have a good response in disease exacerbations (15) and in the chronic management of severe MG cases (16).

Antigen-specific treatments may involve different approaches; a number of biological agents that are currently examined or used for other autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus, could potentially offer targeted therapy to the pathogenesis of MG. These immunotherapies are monoclonal antibodies (mAbs) or therapeutic fusion proteins. mAbs are humanized, when the whole IgG molecule is human, apart from the murine hypervariable region or chimeric, where only the Fc portion of the antibody is human (17). In therapeutic fusion proteins, the Fc region of IgG1 is fused to the extracellular domain of the molecules of interest, and in this manner, re-engineering the pathogenic autoantibodies (18). This approach may prove to be very effective in MG, as the engineered antibodies could potentially stop pathogenic autoantibodies from binding to the receptors and causing symptoms.

New biological agents may be directed selectively against B-cells and B-cell trophic factors, against molecules involved in T-cell activation or against the complement. Direct B-cell inhibitors, such as rituximab (RTX) have exhibited an increased use in the treatment of MG over the last decade (19). RTX (or Mabthera) is a chimeric monoclonal antibody targeting the CD20 molecule on B-cells (19). The humanized version of RTX is ocrelizumab and appears very promising in multiple sclerosis and could, potentially, be used for the treatment of MG (20). Both mAbs cause the depletion of circulating B-cells without affecting their population in the lymph nodes or bone marrow (17). The cytokine soluble B-cell activating factor (*BAFF*), which exhibits elevated levels in the serum of patients with MG and *APRIL* are two trophic B-cell factors, members of the TNF superfamily, that appear as potential therapeutic targets in MG (21).

Biological agents against T-cell signaling targets include Janus kinase (JAK) inhibitors that could be beneficial for patients with MG, such as tofacitinib, an oral JAK inhibitor (22,23). The blockade of these kinases results in the suppression of both T- and B-cells, while maintaining regulatory T-cell function and tofacitinib has been used successfully in the treatment of rheumatoid arthritis and ulcerative colitis (22,23). Another humanized monoclonal antibody, daclizumab, inhibits T-cell proliferation by binding to the IL-2 receptor antagonist, CD-25. It has been approved for the treatment of a form of leukemia and has been used in patients with multiple sclerosis, demonstrating positive results in a phase 2 study (24).

The inhibition of complement activation is achieved through IVIG, mentioned above, and a monoclonal antibody, eculizumab, a direct anti-complement agent against complement C5. It is the first drug approved for MG after the encouraging results of a phase 2 and a phase 3 REGAIN study (25,26). Another monoclonal antibody that has the same action mechanism is ravulizumab, and has been currently approved in the US and Europe for other diseases, and there have been positive results for patients with generalized MG in a phase 3 trial (27). Cost effectiveness is an important issue with eculizumab, and along with issues of long-term efficacy and tolerability, other complement targeted agents need to be explored towards the treatment of all forms of MG.

Furthermore, biological agents applicable for MG could be directed against pro-inflammatory cytokines, such as IL-6 and IL-17A, or against Fc receptors of the immunoglobulins. Anti-cytokine agents that target pathways involved in the pathogenesis of MG, such as IL-6 have yielded promising results in other diseases and may prove effective in MG. Tocilizumab is an anti-IL6 monoclonal antibody with promising results in systemic lupus erythematosus (28) relevant to MG, as cytokine IL6 inhibits T-regulatory cells and promotes pathogenic Th1 cells at the neuromuscular junction. On the same basis, other monoclonal antibodies that specifically target IL-17A (brodalumab and inekizumab) (29,30), have been approved for psoriasis and may be beneficial in treating MG. Effectiveness in psoriatic arthritis has been shown and observational studies have also demonstrated the use of ustekinumab, a human monoclonal antibody against IL-12 and IL-23, for the management of Crohn's disease (31,32); these may thus also be considered as future therapeutic options for MG.

Fc receptors are significant, as they participate in complement activation and determine antibody-mediated effector functions (33) and neonatal receptor (FcRn) is involved in IgG homeostasis, transport and catabolism; thus, they may be a future target in the treatment of MG. Engineering an appropriate IgG1 Fc fragment and generating a recombinant may improve the efficacy of current IVIG therapies (34). Based on this, an IgG1-derived Fc fragment, efgartigimod (ARGX-113), has been developed that binds to neonatal Fc receptor, increasing IgG clearance and leading to the rapid depletion of pathogenic autoantibodies, potentially beneficial for MG treatment, as shown in the results of a phase II trial (35).

4. The future of myasthenia gravis from a genetic aspect

MG is a complex genetic disorder that appears to have a common genetic background with other diseases. A number of single nucleotide polymorphisms (SNPs) have been found to be associated with different forms of the disease through genome-wide association studies and other studies (36). The role of the HLA-complex in determining adaptive responses has been demonstrated (37). An individual's response to antigens is influenced by the specific molecules expressed in the individual, thus implicating a susceptibility to disease and autoimmunity. The cholinergic receptor nicotinic alpha 1 subunit (*CHRNA1*) encodes the α subunit of the AChR and a SNP allele has been found to be associated with MG; this gene could provide evidence specific to the pathogenesis of MG (37,38).

Genes that express pro-inflammatory cytokines, such as IL17A and IL17F have been shown to be associated with MG (39) and have been shown to stimulate the expression of other cytokines and to possibly be connected with the pathogenesis of rheumatoid arthritis, systemic lupus erythematosus and possibly other autoimmune disorders (40,41). Another gene that has shown to be associated with MG and other autoimmune diseases is cytotoxic T-lymphocyte associated protein 4 (*CTLA4*), a member of the immunoglobulin superfamily that encodes a protein transmitting an inhibitory signal to T-cells (42).

A major challenge for MG research is to identify the primary cause of the disease. The differences in the age of disease onset and evidence suggesting different genes associated with early-onset MG (EOMG) and late-onset MG (LOMG) (36), differences in abnormalities in the thymus gland that is associated with the disease, familial cases of MG (43) and other factors indicate that further research is warranted to fully determine the genetic causes of MG.

5. Role of epigenetics in myasthenia

Specific genes or even whole genomic regions can be differentiated by a set of epigenetic factors, including methylations, non-coding RNAs and modifications of histone proteins (4). The role of epigenetics is mentioned in twin studies, where epigenetic deregulation has been shown to contribute to the severity of autoimmune diseases and even to the manifestation of the disease (44). Twin studies constitute an important tool towards understanding the reasons for disease manifestation and susceptibility and, in cases of complex diseases such as MG, they allow for the discrimination between genetic and environmental factors, particularly in monozygotic (MZ) twins where a shared genetic background exists (45).

A high concordance rate between MZ twins is considered to be associated with a stronger genetic predisposition for a disease, contrary to low concordance rates that indicate environmental interference. The MZ twin study by Mamrut *et al* (46) suggested that methylation and numerous small changes in gene expression may, in combination, contribute to the development of MG. A high similarity in expression and in methylation profiles was observed in twins and the results revealed distinct DNA methylation profiles in patients with MG vs. healthy subjects (46).

Despite numerous advances being made in medicine as regards the treatment of MG, there are still gaps, and an innovative and efficient therapy is required. The missing link between genetic predisposition and the onset of autoimmune diseases, including MG, may be represented by epigenetics, and mechanisms contributing to the epigenome and characterizing specific diseases (47). Modifications of miRNA profiles and the resultant up- or downregulation of affected genes have been described in several autoimmune diseases, and their identification has altered the way scientists approach epigenetic predisposition to diseases. A contribution to the onset of disease may occur by variations in miRNA expression levels that may be specific to a disease and appear in the circulation or in certain tissues and cells. In MG, epigenetic investigations in thymic epithelial tumors show a clear distinction in epigenetic profiles in thymomas compared to thymic carcinomas and, moreover, thymic carcinomas often exhibit the loss of chromosome 16q and have an elevated mutation burden compared with thymomas (48).

6. Conclusions and future perspectives

The development of therapies that prevent or cure the disease is crucial. Current treatments are either symptomatic or cause non-specific immunosuppression, while a combination of weakening the autoimmune response by targeting specific molecules and strengthening the neuromuscular synapse may prove to be a more beneficial intervention strategy for MG.

The pathogenesis of MG is well-characterized with directly pathogenetic autoantibodies having been identified; however, current treatments do not target the specific antibodies and, as a result, full remission without the need for further therapy is not achieved in the majority of patients. Thoroughly understanding the mechanisms involved in any autoimmune disease, and MG in particular, appears to be crucial in order to introduce effective therapies. As aforementioned, large number of drugs have exhibited beneficial effects in other autoimmune diseases, such as rheumatoid arthritis; thus, these should perhaps also be evaluated for MG.

Apart from the introduction of immunological targeted therapies, other treatments should be examined, such as the transplantation of autologous hematopoietic stem cells for patients that do not respond to conventional treatment and the disease could prove life-threatening for them (49). Novel biomarkers, such as circulating miRNAs, have been hypothesized to play a possible role in designing personalized treatment schemes (50). One of the main difficulties is predicting the

clinical course of the disease in each patient, as there are many MG subgroups (EOMG vs. LOMG, the presence of a thymoma or not, antibody subtype) creating the need for reliable and objective biomarkers in order to predict the patient's response to treatment and to help as precise diagnostic tools.

Towards personalized treatment, identifying all relevant genes and polymorphisms associated with the disease may prove to be a beneficial tool. Utilizing modern bioinformatics tools and the available information could lead to the understanding of the genetic base of MG and of autoimmune disorders in general. Furthermore, epigenetic methods should be applied to the study of MG and other autoimmune diseases in order to better understand the disease mechanisms and to identify ideal targets for novel personalized treatments (47). Large studies that combine the genetic and epigenetic landscape are warranted in order to identify possible relevant epigenetic biomarkers that can be clinically utilized for predicting and treating MG.

In conclusion, overcoming the limitations of traditional therapeutic approaches, establishing new biological agents in the form of monoclonal antibodies and fusion proteins that target specific molecules, engineering antibodies to act as decoys, designing new diagnostic tools and improving the diagnostic tests available and utilizing bioinformatics in order to establish the disease's genetic background along with further genetic research in the disease may help to establish novel and more effective therapeutic options for patients with MG; these may also be applicable to other autoimmune diseases.

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Authors' contributions

All the authors (RG, EP and DV) contributed to the conceptualization, design, writing, drafting, revising, editing and reviewing of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

DV is an Editor of the journal. However, he had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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