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Review

Myasthenia Gravis: Paradox versus paradigm in autoimmunity

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ABSTRACT

Myasthenia Gravis (MG) is a paradigm of organ-specific autoimmune disease (AID). It is mediated by antibodies that target the neuromuscular junction. The purpose of this review is to place MG in the general context of autoimmunity, to summarize the common mechanisms between MG and other AIDs, and to describe the specific mechanisms of MG. We have chosen the most common organ-specific AIDs to compare with MG: type 1 diabetes mellitus (T1DM), autoimmune thyroid diseases (AITD), multiple sclerosis (MS), some systemic AIDs (systemic lupus erythematous (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SS)), as well as inflammatory diseases of the gut and liver (celiac disease (CeD), Crohn's disease (CD), and primary biliary cirrhosis (PBC)).

Several features are similar between all AIDs, suggesting that common pathogenic mechanisms lead to their development. In this review, we address the predisposing factors (genetic, epigenetic, hormones, vitamin D, microbiota), the triggering components (infections, drugs) and their interactions with the immune system [1,2]. The dysregulation of the immune system is detailed and includes the role of B cells, Treg cells, Th17 and cytokines. We particularly focused on the role of TNF-α and interferon type I whose role in MG is very analogous to that in several other AIDS. The implication of AIRE, a key factor in central tolerance is also discussed.

Finally, if MG is a prototype of AIDS, it has a clear specificity compared to the other AIDS, by the fact that the target organ, the muscle, is not the site of immune infiltration and B cell expansion, but exclusively that of antibody-mediated pathogenic mechanisms. By contrast, the thymus in the early onset subtype frequently undergoes tissue remodeling, resulting in the development of ectopic germinal centers surrounded by high endothelial venules (HEV), as observed in the target organs of many other AIDs.

1. Introduction

Because many autoimmune diseases (AIDs) start at a relatively young age but are chronic, they have a major effect on public health. Although individual AIDs are relatively uncommon, in total they affect about 5–8% of the population. In addition, the prevalence of chronic autoimmune and inflammatory diseases is increasing in developed countries.

AIDs can be classified as organ-specific or non-organ-specific depending on whether the autoimmune response is directed against a particular specific tissue or against widespread antigens. Myasthenia Gravis (MG) is a paradigm of organ-specific AID mediated by antibodies that target the neuromuscular junction and could be classified in several subtypes (Table 1). Each AID is the result of an autoimmune reaction that targets an organ or a tissue via a humoral and/or cellular response against specific auto-antigens (Table 2). Several features are similar between all AIDs, suggesting that common pathogenic mechanisms lead to their development.

The hypothesis of immune origin of MG was first suggested by Simpson in 1960 [3]. In the 1970s, Fambrough observed a reduced number of acetylcholine receptors (AChRs) on the muscle endplates of MG patients [4] and evidence that the AChR is the target in MG was demonstrated by muscle weakness after the immunization of rabbits with the AChR purified from torpedo fish [5]. The central role of autoantibodies in MG development was demonstrated *in vivo* by the occurrence of MG-like symptoms in animals

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Abbreviations

AChR	acetylcholine receptor
AIDs	autoimmune diseases
AIRE	autoimmune regulator
AITD	autoimmune thyroid disease
ALS	amyotrophic lateral sclerosis
CD	Crohn's disease
CeD	celiac disease
CIA	collagen-induced arthritis
CNS	central nervous system
CTRL	control
DC	dendritic cells
EAE	experimental autoimmune encephalomyelitis
EAMG	experimental autoimmune Myasthenia Gravis
EBV	Epstein–Barr virus
EDSS	expanded disability status scale
ER	estrogen receptor
GA	Graves' disease
GC	germinal center
GF	germ-fee
GWAS	genome-wide association study
HC	healthy controls
HD	Hashimoto's disease
HCV	Hepatitis C virus
IBD	inflammatory bowel disease
IFN	interferon
Ig	immunoglobulin
IL	interleukin
INS	insulin
IvIG	intravenous immunoglobulins
JIA	juvenile idiopathic arthritis
LPS	lipopolysaccharides
LRP4	Lipoprotein-related protein 4
mDCs	myeloid DCs (mDCs)
MG	Myasthenia Gravis
EO	Early-onset
LO	Late-onset
MHC	major histocompatibility complex
miRNA	microRNA
MS	multiple sclerosis
MuSK	muscle-specific kinase
PBMC	peripheral blood mononuclear cells
pDCs	plasmacytoid DCs
Poly(I:C)	polyinosinic–polycytidylic acid
RA	rheumatoid arthritis
RRMS	relapsing-remitting MS
SF	synovial fluid
SLE	systemic lupus eryhtematosus
SPF	specific-pathogen free
SPMS	secondary progressive MS
SS	Sjogren's syndrome
SSc	systemic sclerosis
Tconv	conventional T cells
TEC	thymic epithelial cell
TG	thyroglobulin
TLR	toll-like receptor
TNF	tumor necrosis factor
TNIP1	tumor necrosis factor a-induced protein 3-interacting protein 1
TPO	thyroid peroxidase
Treg	regulatory T cells
TSH	thyrotropin (thyroid-stimulating hormone)
VDR	vitamin D receptor
VNTR	variable number tandem repeat
WT	wild-type

transferred with purified immunoglobulins (IgG) from MG patients [6] and *in vitro* by the degradation of the AChRs on cultured muscle cells treated with IgGs from MG patients [6] or with monoclonal anti-AChR antibodies [7]. The titration of the antibodies in the myasthenic patient sera showed that almost 85% of the patients were positive for the anti-AChR antibodies [8,9]. The recent discovery of two novel neuromuscular targets (muscle-specific kinase (MuSK) and Lipoprotein-Related Protein 4 (LRP4)) has reduced the percentage of patients without known antibodies [10–12].

Similarly to other AIDs, MG is multifactorial and its manifestation results from the combination and interactions between multiple genetic and environmental risk factors [13–15]. The classification of MG takes into account the nature of the antibodies, the age of onset, and the involvement of the thymus (Table 1) [16]. MG is therefore a prototype autoimmune receptor disease with highly specific antibodies, and can be considered as a model of autoimmunity.

Table 1
Classification of MG subtypes. According to the nature of the antibodies, MG could be divided in several subtypes that differ by the age at onset, the gender predominance and the thymus pathology.

Antigen	Age at onset	Thymus	Gender predominance	Name in the review
AChR	<50 years	Hyperplasia	F > M	EOMG
AChR	>50 years	Thymoma/ involuted	F = M	LOMG
MuSK	<50 years	Involuted	F > M	MG-MuSK
LRP4	<50 years	?	F > M	MG-LRP4

One of the common features to all AIDs is the genetic predisposition, and several predisposing genes are common between the different AIDs. However, possessing the predisposing genes is not sufficient to develop an AID, as shown in the studies on monozygotic (MZ) discordant twins [17], except for few genetic diseases [17]. Indeed, direct links between genes and autoimmunity have been shown for some specific diseases in which genes are mutated, such as AIRE whose mutation leads to autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) [18,19], Foxp3 whose mutation leads to immunodysregulation, polyendocrinopathy, and enteropathy, X-linked [20] or the autoimmune lymphoproliferative syndrome associated with the FAS mutation [21,22].

For most AIDs, environmental factors are necessary to trigger the development of the disease. The list of environmental factors is becoming longer and longer and includes both predisposing factors, such as low vitamin D [23], and hormones [24,25], as well as triggering factors, such as infections and drugs. Another major common feature of AIDs is defects in the regulatory immune system, but it is not yet clear whether this defect is intrinsic or results from the triggering event. There is a surprising paucity of data on other environmental factors, including the role of chemicals in loss of tolerance [26,27]. Finally, we should note the increasing importance of epigenetics and the environment [1,2,20,28,29].

Many of the mechanisms described in AIDs are also involved in MG. In this review, we address the genetic and environmental factors, as well as their interactions with the immune system. The