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Pathogenesis of myasthenia gravis

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Abstract Various studies over the last 25 years in Man and animal models have revealed many steps in the pathogenesis of myasthenia gravis (MG) which is now considered the classical organ specific, autoantibody mediated and T cell dependent human autoimmune disease. Though not a disease entity, MG is associated with pathological alterations of the thymus in about 80% of cases. These are described here with reference to distinct models of autoimmunization against the acetylcholine receptor (AChR). In MG with thymitis, intrathymic production of AChR-specific autoantibodies is the result of a classical antigen-driven immune reaction that occurs completely inside the thymus and probably involves AChR on myoid cells as the triggering (myasthenogenic) antigen. Genetic factors contribute essentially to the pathogenesis of this form of MG. In thymoma-associated MG genetic factors are probably of marginal significance. Neither intratumour autoantibody production nor T cell activation seem to occur and the AChR is not the myasthenogenic antigen. Instead, abnormal neurofilaments that share epitopes with the AChR and other autoantigen targets in paraneoplastic MG are expressed in thymomas and may trigger autoantigen-specific, non-tolerogenic T cell selection by molecular mimicry. These data support the hypothesis that initial steps in the pathogenesis of most MG cases take place within abnormal thymic microenvironments, be they inflammatory or neoplastic. Where these initial steps occur in MG cases without thymic pathology is not known. Likewise, the factors involved in the initial triggering of MG remain enigmatic in all MG subtypes.

Key words Autoimmunity · Thymus · Thymoma · Acetylcholine receptor · Aetiology

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Myasthenia gravis as a prototypic model autoimmune disease

The triggering of a autoimmune disease is incompletely understood. In experimental models molecular alterations of autoantigens in an otherwise intact immune system may elicit autoimmunity [27], however, defects of the immune system facing an intact antigen repertoire may also lead to autoimmunity [75]. In addition, microenvironmental factors such as abnormal interleukin levels may change the interaction between a normal T cell repertoire and normal autoantigens [including the acetylcholine receptor (AChR)] as shown in mice [30, 77]. In mice, the loss of an established tolerance [65, 92, 93] or the recruitment of ignorant T cells [32, 76] have been described as mechanisms in the induction of autoimmunity but whether or not these mechanisms are involved in human autoimmune diseases has not been resolved.

In fact, myasthenia gravis (MG) may be an ideal model to investigate the role of T cell tolerance in humans. The target autoantigens in MG (the AChR and striational autoantigens) are well characterized [52] as are the autoreactive T cells that play a pivotal role in MG by providing B cell help [36, 61, 62, 82, 111]. Since the late steps in the pathogenesis are well defined, MG should be an ideal disease in which to investigate those early steps in pathogenesis that are unresolved in almost all autoimmune diseases; the triggering events and the antigens involved in the triggering processes. In practice, this may define the aetiology. Furthermore, MG can be regarded as a model with respect to the contribution of gender and genetic factors for autoimmune pathogenesis [3, 4, 28] (Table 1). The D-penicillamine (DP)-induced MG variant is one of the few autoimmune diseases with a known aetiology and has an HLA-association that is similar to that of DP-independent MG [16, 95, 118]. In this review only MG but not other autoimmune myasthenic syndromes like the Lambert-Eaton syndrome or acquired neuromyotonia [114] will be discussed. Likewise, the non-autoimmune congenital myasthenic syndromes [20] will not be dealt with. Clinical findings and

Table 1 Myasthenia gravis (MG) subtypes according to thymus pathology: correlation with clinical and epidemiological findings [a] *WDTC*, well differentiated thymic carcinoma , *AChR* acetylcholine receptor

Thymus pathology	Hyperplasia	Thymoma/ WDTC[b]	Atrophy
Onset of symptoms age (years)	10–20	15–80	>40
Sex (male:female)	1: 3	1: 1	2: 1
HLA-association	B8; DR3	(DR2)	B7; DR2
Autoantibodies against			
AChR	30–80%	>90%	90%
Striated muscle	10–20%	>90%	30–60%
Titin	<5%	>90%	30–40%

[a] See [1,16,19,24,43,83,120]
[b] See [44]

novel therapeutic approaches have recently been reviewed [19, 84].

MG: definition and epidemiology

A disease characterized by progressively severe but transitory muscle weakness following muscle contractions was first described in 1672 but the term "myasthenia gravis pseudoparalytica" was coined by Jolly only in 1895 (see review by Pascuzzi [80]). Although MG symptoms are mediated by anti-AChR autoantibodies, MG is not defined by their presence but by clinical, electrophysiological and pharmacological findings, since autoantibodies – probably for technical reasons – are undetectable in about 60% of purely ocular MG and in about 10% of patients with otherwise typical generalized symptoms [39]. ("seronegative MG"). MG is thus defined by progressive muscle weakness and the transitory improvement of symptoms by acetylcholine esterase inhibitors. Electrophysiologically a "decrement" of muscle action potentials or a "jitter" by single fibre electromyography are characteristic [19]. Spontaneous remissions of these symptoms are rare, except in MG with a prepubertal onset [4]. While these criteria clearly define MG, the disease is not a clinical entity. Apart from purely ocular MG (in which there is generally no thymic pathology and no apparent HLA association) and "seronegative" MG [107], there is also heterogeneity with respect to clinical, histopathological and epidemiological findings, and the pathogeneses in the group of patients with autoantibody-positive, typical generalized MG [67]. Because of the obvious therapeutic implications and because of the correlation with epidemiological findings, it has become common practice to subdivide MG according to the MG-associated pathological thymic alterations (Table 1). It has been stressed that this subdivision of patients and their distribution in each category may not apply to non-Caucasians [13, 107]. In the Chinese and Japanese purely ocular MG and cases with prepubertal onset may be more frequent and HLA associations and the proportion of "seronegative" patients are different [37, 107]. In spite of improved diagnostic techniques, the incidence of MG has remained stable with an incidence of about 1:20,000 population [19].

Autoantigens in MG

The pentameric AChR at the neuromuscular junction (NMJ) is clearly the disease-relevant and most specific autoantigen in MG [14, 52]. At the NMJ of non-ocular muscles the AChR occurs in its adult form composed of two alpha chains and one beta, one delta and one epsilon chain. In the embryonic form of the AChR the epsilon subunit is replaced by a gamma subunit (reviewed in [52]). This type of AChR is expressed after birth constitutively only in thymic myoid cells (25,89) and in the multiply-innervated adult ocular muscle fibres [38]. Other autoantigens, so called striational autoantigens, are actin, myosin, actinin and titin [1, 24, 120] which have diagnostic significance mainly in paraneoplastic MG. Other skeletal muscle autoantigens are the beta-2-adrenergic receptor [123] and the ryanodine receptor [69, 70]. Finally, non-muscle autoantigens particularly in thymoma patients have been found in normal and neoplastic neuronal cells (reviewed in [55]). How non-AChR autoantigens might be involved in the pathogenesis of MG by molecular mimicry will be discussed below.

Autoantibodies in MG: clues to a heterogeneous pathogenesis of MG

Autoantibodies in MG are polyclonal, heterogeneous with respect to their idiotypes and recognize different epitopes on the AChR [3, 4, 8, 12, 17, 23, 108–110] and striational antigens [99, 120]. With few exceptions, differences in antigen specificity result from somatic hypermutation [11, 29, 105]. The majority of autoantibodies against the alpha subunit of the AChR recognize the epitope alpha 67–76, that has been termed the "main immunogenic region (MIR)" [52]. Whether this reflects an immunodominance of the MIR is controversial [118]. In non-thymoma patients with MG the gamma subunit can be the dominant autoantigen [25, 115]. In contrast, sera in pure ocular MG were found to exhibit a greater reactivity with AChR extracted from innervated muscle compared with that from partially denervated muscle [108], suggesting a role of the epsilon subunit as an autoantibody target. In addition, the preferred reactivity of autoantibodies from ocular MG patients with extraocular muscle [108] and (ocular) multiple-innervated endplates [74] suggests the occurrence of autoantibodies with specificity for so far uncharacterized antigenic determinants on ocular muscle AChR [74, 107]. Most autoantibodies against the AChR and striational antigens are IgGs with high affinities. Symptoms in "seronegative MG" seem to be caused, however, by low-affinity IgM autoantibodies [112, 121]. At least part of the autoanti-

body heterogeneity outlined here is thought to result from different pathogenetic mechanisms underlying tolerance breakdown in the various forms of MG [107].

Autoantibodies impair AChR function by one of the following mechanisms [19, 47]. There may be a complement dependent destruction of the post synaptic membrane, resulting in a decreased number and flattening of synaptic folds and widening of the synaptic cleft. Increased AChR internalization after autoantibody-mediated receptor cross-linking, may occur a process referred to as antigenic modulation. There may also be blockade of the ACh binding site or an allosteric or direct blockade of the cation channel. Whether or not autoantibodies against non-AChR autoantigens play a role in the pathogenesis of MG is unknown.

Cellular immunity in MG

The production of the disease-related autoantibodies in MG is dependent on MHC class II restricted T cells [34–36, 82, 111]. In particular Th1 lymphocytes have been identified by proliferation assays [118] but Th2 cells which are thought to be involved in B cell help for antibody production have also been identified [50, 51, 122]. Using small AChR peptides, almost every epitope expressed on one of the AChR subunits has been shown to act as a stimulus in T cell proliferation tests [82]. The relevance of such investigations, however, has been questioned [111, 118], since it is generally assumed that processed native AChR stimulates the T cells involved in directing autoantibody synthesis in vivo [107]. The current data are insufficient to prove the existence of an immunodominant T cell epitope in humans. Whether autoaggressive T cell repertoires in the various MG subtypes are different is controversial [61, 62, 100]. Most importantly, AChR reactive T cells occur both in the majority of non-myasthenic controls [61, 100, 101] and a wide range of animal species (reviewed in [40]). These T cells, belonging to the normal T cell repertoire, are not anergized but naive (“ignorant”) [118]. These findings suggest that MG does not result from a lack of AChR specific T cell tolerance. However, future studies have to exclude the existence of “MG-specific” autoaggressive T cells (that is, of T cells absent from the normal repertoire) in terms of antigen specificity, cytokine profile or ability to provide B cell help. Although experimental autoimmune MG (EAMG) can clearly be elicited in the absence of a CD8/MHC class I interaction [5, 40, 96, 125, 126], the role of CD8+ T cells needs further study considering the strong association of non-thymoma related MG with MHC class I molecules B8 and B7 (Table 1). In fact, preliminary data suggest an immunosuppressive role of CD8+ T cells in MG with thymitis/hyperplasia [82, 124] but not in thymoma-associated MG (personal observations).

Genetic contributions to the pathogenesis of MG

Genetic factors must play an important role in the susceptibility to MG given the 40% concordance rate in pairs of monozygotic twins and the increased risk of developing MG and of having anti-AChR autoantibodies in relatives of MG patients (reviewed in [81, 107]). As with other autoimmune diseases, the genetic predisposition to MG most probably involves multiple genes [22, 73]. Of these genes, the contribution of the MHC loci is most obvious in non-thymoma patients (Table 1) but weaker associations of class II genes with MG have also been reported in patients with thymoma [10, 106]. Surprisingly for a disease assumed to depend on MHC class II restricted T cell help the strongest association is with the class I molecule B8 [107]. This may hint to an immunoregulatory role of CD8+ T cells, as described above. Other genes close to the class I locus such as genes for tumour necrosis factor, heat shock proteins or transporter associated with antigen processing (TAP) transporters have also been discussed with regard to the pathogenesis of MG [17, 107, 118]. Of the non-MHC related genes a polymorphic marker on the switch region of the immunoglobulin heavy chain gene has been reported to be associated with late-onset MG in patients with thymic atrophy [17], suggesting that a particular humoral immune response is crucial for the pathogenesis of this MG type. Significantly associated polymorphisms of immunoglobulin light chains with MG have also been reported [18]. How the polymorphism of other non-MHC related genes such as the AChR alpha subunit gene [22] may contribute to MG susceptibility is currently unknown.

The thymus and MG

Thymic alterations are so frequent in MG (90%) that a role for the thymus in the pathogenesis of MG is almost certain [35]. This is supported by the association between pathological changes of the thymus and clinical and epidemiological findings as given in Table 1.

Thymitis with lympho-follicular hyperplasia in MG

This diagnosis is made in 70% of MG patients [68]. Histologically, perivascular spaces (PVS) are expanded by B cells forming follicles and germinal centers. The basal membrane and the continuous epithelial layer separating the PVS from the thymic medulla become interrupted which results in fusion of both compartments [42, 68]. Fibres in the PVS and medulla are increased as demonstrated by reticulin stains. In the medulla the numbers of CD11c- , HLA-DR- and CD1-positive interdigitating reticulin cells are also increased [41]. In contrast, myoid cells occur in normal numbers exclusively in the medulla as in the normal thymus and only outside germinal centres [9, 19]. The only abnormality of these myoid cells is their close apposition to KiM1-positive interdigitating

Table 2 Frequency of MG and expression of the AChR epitope alpha 373–380 in thymic epithelial tumours (*TET*) investigated between 1970 and 1994 in the Department of Pathology, University of Würzburg

Tumour	Cases investigated[a]	Frequency of MG	Tumors with alpha 373–380[b]	Tumors without alpha 373–380[b]
Organotypic TET				
Medullary thymoma	10	30%	0	3
Mixed thymoma	33	40%	1	14
Predominantly cortical thymoma	15	40%	6	5
Cortical thymoma	81	69%	14	1
Well differentiated thymic carcinoma	33	79%	11	0
Non-organotypic TET	24	0%	2	1
Tumours with MG			30	8
Tumours without MG			4	16

[a] All cases available (frozen and paraffin)
[b] Cases with available frozen material (allowing reactivity with mAB 155 against the AChR alpha 373–380 epitope)

reticulum cells [42]. Such contacts are very scarce in normal thymuses. As in the normal thymus, myoid cells in thymitis are MHC class II negative and express AChR [25, 42, 89]. The thymic cortex in lympho-follicular thymitis shows the normal age dependent morphology.

Thymitis with diffuse B cell proliferation

By definition this thymic cell proliferation lacks germinal centres on routine stains, however, foci of follicular dendritic cells may be detectable by immunohistochemistry [41]. This type of thymitis exhibits similar epidemiological findings to thymitis with lympho-follicular hyperplasia (Table 1) and is thought to result from a similar immunological process [41]. It is usually interpreted as an early stage of thymitis in MG. It is also a typical finding after azathioprine treatment [88]. Morphologically, thymitis with diffuse B cell proliferation resembles lympho-follicular thymitis except for the occurrence of germinal centres in the latter. The disruption of the basal membrane between perivascular spaces and the medulla helps to distinguish this type of thymitis from normal thymus [68].

Thymitis in seronegative MG

While lympho-follicular thymitis and thymitis with diffuse B cell proliferation are thought to be part of the same spectrum, thymitis in seronegative MG has been reported to be a separate entity [119]. In this type of thymitis germinal centres are rare and the number of B cells is almost normal. If results from an increase of mature T cells in expanded PVS [119] but whether it is accompanied by a breakdown of the barriers between the PVS and medulla has not been reported.

Thymic atrophy in MG

Thymic atrophy is encountered in 10%–20% of MG patients [68]. Because of distinct epidemiological and genetic findings (Table 1) and a short course of disease, thymic atrophy is not considered to be an end stage of thymitis. Morphologically, except from a slight increase in medullary B cells and interdigitating reticulum cells [41], the thymuses in these patients are equivalent to age-matched controls. In particular, the number of myoid cells per thymic tissue area (measured morphometrically) follows the same age-related decline [42].

Thymic epithelial tumours in MG

There are case reports of neuroblastoma, of oesophageal, thyroid and breast carcinomas, small cell lung cancers, amature ovarian teratoma, chordoma, phaeochromocytoma, lymphoma and Hodgkin's disease all associated with MG [2]. Nevertheless, paraneoplastic MG is essentially a characteristic feature of organotypic thymic epithelial tumours (1) [44] as shown in Table 2. The histomorphology of these tumours and their clinico-pathological correlations were recently published in detail [44, 46, 66, 67, 68, 83]. The features of these tumours in relation to the pathogenesis of MG are discussed in detail below. Interestingly, purely non-organotypic TET [68, 85, 97] like squamous cell carcinomas of the thymus, resemble their extrathymic counterparts and are never associated with MG (Table 2).

Pathogenetic models in MG

Because of a lack of experimental data, pathogenetic models have not been suggested for MG in patients with thymic atrophy or seronegative MG, in which the usefullness of thymectomy awaits further statistical support [3, 4, 119]. Therefore, the focus here will be on the pathogenesis of MG in lympho-follicular thymitis and TET.

Pathogenesis of MG in lympho-folicular thymitis

Some authors consider lympho-follicular thymitis a secondary phenomenon following the sensitization of T cells in the periphery, recirculation to the thymus and re-

stimulation there [118]. However, we and others favour a primary intrathymic pathogenesis of MG as suggested by Wekerle almost 20 years ago [116]. According to this hypothesis AChR on thymic myoid cells are primarily involved in the triggering of MG in lympho-follicular thymitis. Three findings support this notion; firstly a substantial percentage of autoantibodies in thymitis-associated MG specifically recognize the fetal type of AChR [115], secondly fetal type AChR (AChR with a gamma instead of an epsilon subunit) are expressed on thymic myoid cells but not on extrathymic muscle [25] except, probably, for multiply-innervated ocular muscles [38] and finally extrathymic immunization with the AChR can induce EAMG in animals but does not elicit lympho-follicular thymitis [60]. In support of this concept, Kirchner et al. [42] reported abnormal clusters of myoid cells and antigen presenting dendritic cells in thymitis. Since myoid cells remain negative for MHC class II in MG and therefore are unable to present antigen to T cells [42, 89], it is thought that the abnormal clustering enables dendritic cells to take up AChR released from myoid cells more efficiently. Processing of engulfed AChR in dendritic cells might result in a quantitatively improved presentation of AChR peptides to potentially AChR specific T cells; these have been found in increased numbers in thymuses with thymitis [62, 101]. Finally, the thymus with lympho-follicular thymitis is known to be the single most important organ where anti-AChR autoantibodies are produced both in absolute terms and on a per plasma cell basis [87]. Once produced, the autoantibodies may not only react with peripheral muscle AChR but also with AChR on thymic myoid cells. Whether such an antibody-mediated or a cytotoxic mechanism is the basis of the increased apoptosis of thymic myoid cells in MG [9] has yet to be investigated. As elegantly shown by the transplantation of thymitis specimens into mice with severe combined immunodeficiency (resulting in the prolonged production of human anti-AChR autoantibodies in these immunodeficient mice), such thymuses contain all the necessary constituents of a complete and self-sustaining autoimmune reaction [90, 91, 104]. The “intrathymic pathogenesis model” is shown schematically in Fig. 1.

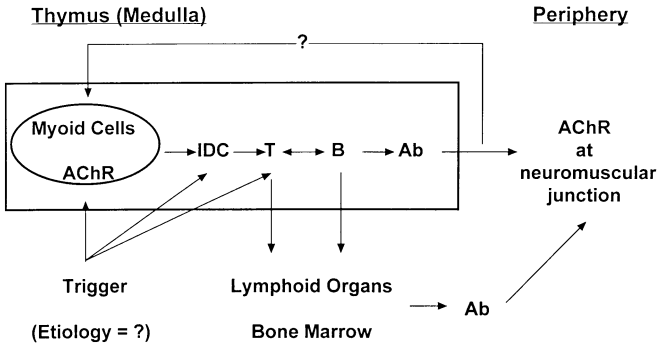

Fig. 1 Pathogenesis of myasthenia gravis (MG) in patients with lympho-follicular thymitis. The model suggests that an unknown trigger (aetiology) initiates the mechnism inside the thymus [60,116], eliciting a complete immune reaction, including the production of autoantibodies (*Ab*). Ab then encounter their target [the acetylcholine receptor (AChR)] at the neuromuscular junction and, perhaps, on myoid cells. In long-standing MG AChR-specific *T* and *B* cells can disseminate to lymphoid organs and the bone marrow where plasma cells add to AChR specific antibody production. After this dissemination the same self-sustaining “circulus vitiosus“ shown in Fig. 2 may maintain the autoimmune process in patients with thymitis

Pathogenesis of paraneoplastic MG

It is generally agreed that the pathogenesis of paraneoplastic MG differs from the pathogenesis of MG in lympho-follicular thymitis [68, 118]. The absence of tumour autoantibody production is the most striking difference [21]. Different clinical, epidemiological and genetic features strengthen this statement (Table 1). Furthermore, the pathogenesis of paraneoplastic MG may be heterogeneous considering the heterogeneous morphological and functional findings in the various thymoma subtypes [68]. Only about 20% of patients with paraneoplastic MG exhibit lympho-follicular thymitis in the residual thymus while 80% show thymic atrophy [14, 68]. Nevertheless, MG-associated thymic epithelial tumours share common features:

1. MG-associated TET are organotypic (Table 2). Squamous cell carcinomas, carcinoids, and other (non-organotypic) category II malignant TET [97] are never associated with MG. Moreover, it is a striking observation that rhabdomyosarcomas that express large numbers of adult and fetal type AChR are not associated with MG. It can be concluded that the organotypic property of MG-associated TET to provide homing and maturation of immature T cells is an indispensable prerequisit of autoimmunization [54]. In fact, we have shown that MG-associated TET provide T cell development from the most immature precursors to phenotypically mature thymocytes [72].

2. Potentially myasthenogenic antigens occur in TET. Concurrent autoimmunity against three apparently unrelated types of autoantigens is highly characteristic of paraneoplastic MG; these autoantigens are the AChR, the striated muscle antigen titin and certain neuronal antigens. Autoimmunity to the ryanodine receptor is also highly characteristic but less frequent [69, 70]. With respect to anti-AChR autoimmunity, the occurrence of mRNAs of muscular and neuronal AChR has been reported [23, 31, 45, 63]. However, the respective proteins have not been detected in TET [43, 54, 98] and a positive correlation between the expression of AChR mRNAs and the occurrence of MG has not been observed. Instead, Kirchner [43] clearly demonstrated the abnormal expression of the AChR epitope alpha 373–380 in cortical type TET and a highly significant correlation between the expression of this epitope and the presence of MG (Table 2). By analogy, neither ryanodine receptors nor titin are expressed in TET but epitopes of both autoantigens are [57, 70]. In contrast, anti-neuronal autoimmunity in

paraneoplastic MG [55] led to the detection of hypophosphorylated neurofilaments that are abnormally expressed in MG-associated TET [57]. Even more striking was the finding that the medium molecular weight neurofilament expressed in TET contains epitopes equivalent to the AChR epitope alpha 373–380 (manuscript in preparation) and epitopes of titin [57]. How the abnormal expression of a single molecule with crossreacting epitopes of the three most frequent autoantigens may evoke the simultaneous autoimmunity against the AChR, titin and neuronal antigens will be discussed below.

3. Autoaggressive T cells occur in MG associated TET. Little data has been published on AChR-specific T cells in paraneoplastic MG [100]. Our own data on five mixed thymomas and five cortical thymomas and well differentiated thymic carcinomas confirm the occurrence of T cells reactive against the AChR alpha subunit. In contrast to Sommer et al. [100], we always find better AChR-specific T cell responses in the peripheral blood and residual thymus than in thymomas (unpublished data). The response of thymoma thymocytes is higher than the response of normal thymus-derived T cells (in preparation). In addition we find that the hyperexpression of neurofilaments is not associated with the complete deletion of NF-reactive T cells but results in the production of at least some of them. It is also noteworthy that T cells against intracytoplasmic epitopes of the AChR alpha subunit occur in MG-associated thymomas. However, T cells reactive with the AChR peptide alpha 373–380 [43] have not been detected although the intratumour expression of this epitope is associated with anti-AChR autoimmunity (Table 2). This apparent paradox is explained in connection with the pathogenetic model given below. Another controversial question is whether intratumour autoaggressive thymocytes are generated in situ or are preferably activated there. By three-colour flow cytometry, all MG-associated mixed or cortical-type TET investigated so far were devoid of CD4+ T cells with an activated phenotype (CD25+, CD54+) while a single medullary thymoma contained activated T cells [72]. In summary, TET subtypes highly associated with MG (mixed and cortical thymomas and well differentiated thymic carcinomas) seem to lack a substantial number of activated T cells.

A pathogenetic model of paraneoplastic MG

Despite the considerable progress outlined above there is no unequivocal hypothesis for the pathogenesis of MG [118]. In our opinion, the following findings need to be explained by an appropriate pathogenetic model. The first is that paraneoplastic MG occurs only in organotypic TET that contain CD1+ *immature* T cells [68]. Secondly, in cortical type TET and probably mixed thymomas (unpublished observations) the occurrence of neurofilaments with AChR and titin epitopes is associated with autoimmunity against AChR, titin and neuronal structures [43, 57]. Thirdly, AChR and neurofilament-reactive

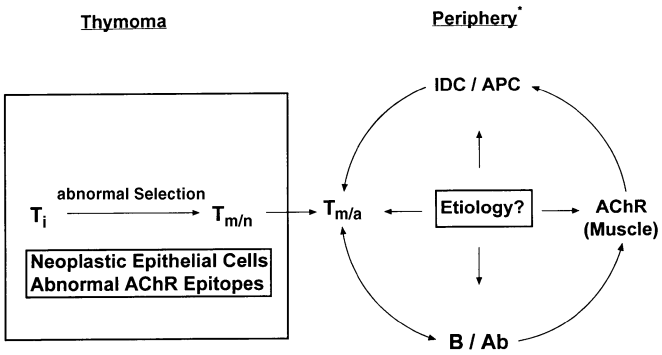

Fig. 2 Pathogenesis of paraneoplastic MG in thymoma patients. According to this model abnormally expressed AChR epitopes provide the molecular basis for an abnormal positive selection that turns immature T cells (T_i,) into mature and naive T cells ($T_{m/n}$). These AChR specific T cells are thought to leave the thymus and become actived T cells ($T_{m/a}$) outside the tumour. As in thymitis-associated MG it is not known what the triggering event (aetiology) in thymoma patients is and whether it initially activates cross-reacting T or B cells, interdigitating/antigen presenting cells (*IDC/APC*) or whether it primarily amplifies the natural shedding of autoantigen. Once initiated, the autoimmune reaction is postulated to be self-sustaining. This hypothesis explains why thymoma surgery is not helpful with respect to MG symptoms [102]

T cells occur in mixed and cortical thymomas and well differentiated thymic carcinomas [100, own findings]. Finally, activated mature T cells are absent in almost all MG-associated TET [72] and there is no intratumour antibody production [21]. Considering the experimental evidence from mice for the involvement of endogenous protein in the process of positive selection [6, 33, 78] we favour the hypothesis that the aberrant expression of neurofilaments with AChR and titin epitopes in neoplastic epithelial cells may cause false-positive selection of immature T cells. In particular we suggest that the intratumour peptide homologues of the MG-associated AChR epitope alpha 373–380 could function as selecting peptides for *immature* T cells with prospective AChR specificity [56]. Since selecting peptides in the thymus are either non-stimulatory or antagonistic for *mature* T cells [6, 33] this scenario would explain the apparent paradox that we and others [107] did not find T cell responses to alpha 373–380 in vitro. To become pathogenetically relevant, non-activated autoantigen-specific T cells have to be exported from thymoma to the “periphery” where they could provide help for autoantibody producing B cells after adequate activation [57, 68]. This model (summarized in Fig. 2) implies that there should be a particular population of AChR-specific, autoaggressive T cells in thymoma patients that is essentially absent from the normal T cell repertoire. This has to be further investigated. The “periphery” where T cell activation occurs can clearly be the residual thymus that we found enriched by autoreactive T cells in most cases of thymoma (unpublished observations). However, other lymphoid organs and probably the bone marrow have also to play a role in this process because complete surgical removal of a thymoma together with the residual thymus is not fol-

lowed by a decline in autoantibody titres [102]. Which autoantigens maintain this prolonged autoantibody response has not been determined but the AChR itself is an obvious candidate. By analogy with the postulated release of AChR from thymic myoid cells (Fig. 1) the destruction of skeletal muscle endplates by autoantibodies or cytotoxic mechanisms could release AChR and striational antigens which may be processed and presented to autoreactive T cells by the intramuscular inflammatory infiltrate [58, 71] or by antigen presenting cells in regional lymph nodes (Fig. 2).

The aetiology of MG

While many steps in the pathogenesis of MG have been clarified (Figs. 1, 2), the aetiology, by which we mean the disease trigger, has remained enigmatic except in DP-induced MG [118]. Infections have long been thought to be triggers [7, 86, 94] but how they might break T cell tolerance is controversial. It has been suggested [103] that superantigens expressed by bacteria or viruses might stimulate the antigen presenting cells and unprimed AChR-specific T cells that occur in the normal human T cell repertoire non-specifically [62, 101]. Autoimmunity in this situation may be elicited only in the context of a suitable genetic background, as suggested for multiple sclerosis [127]. More popular has been the view that microbial antigens cross-reacting with self antigens may trigger autoreactivity [19, 94]. However, experimental evidence for such molecular mimicry is still lacking (see [19]). Cross-reactivity could happen both on the B and T cell level. Molecular mimicry on the B cell level concerning epitopes of the AChR or other autoantigens relevant in MG has been reported previously [15, 26, 64, 70, 79, 117] but whether these epitopes are important in vivo has not been elucidated [79, 107, 118]. In particular, it has not been shown that B cells can elicit antigen-specific autoreactive T cell activation by shared B plus T cell epitopes, although B cells in mice can contribute to the diversification of immune responses [53]. Rather, there is some experimental evidence that molecular mimicry on the T cell level could play a role in initiating autoreactivity even if only one T cell epitope is involved [34, 54]. This situation is now described as "determinant spreading" (reviewed in [48]). When mice are immunized with only one immunodominant peptide of an autoantigen, the initial T cell response against the peptide is followed by a secondary response towards a variety of epitopes expressed on the autoantigen. Since these other (cryptic) epitopes are not part of the immunizing peptide, the secondary response against many epitopes of the antigen is thought to result from the processing and presentation of endogenous antigen. In the context of the human disease (MG), endogenous AChR could be released from peripheral skeletal muscle or thymic myoid cells as a consequence of either an inflammatory response in the vicinity of MG endplates [58, 71] or an abnormal attack of interdigitating dendritic cells on myoid cells in thymitis [9, 42]. The mechanisms of autoantigen release and autopresentation, however, are unknown. The scenario of determinant spreading combined with a molecular mimicry mechanism is applicable to EAMG. When rabbits are immunized with an immunodominant human (!) AChR peptide, they finally develop a diverse T cell response that is stronger against various rabbit than against human AChR peptides [107, 113]. Determinant spreading on the T cell level is translated into a diverse B cell response that can be stronger against the host autoantigen (rat AChR) than against the source of the peptide used for immunization (human AChR) [49, 59]. By analogy, exogenous or (cryptic) endogenous peptides with cross-reacting AChR T cell epitopes might trigger an avalanche of T and B cell responses with a diverse spectrum of anti-AChR reactivities in MG. Once initiated, the process may be self-sustaining due to the constant release of endogenous autoantigen (Fig. 2). Detecting the (triggering) needles in the haystack of secondary events will obviously be the challenge of future experiments and epidemiological investigations addressing the aetiology of MG.

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