Myasthenia gravis is an autoimmune disease caused, in most cases, by antibodies attaching to the acetylcholine receptor. Some myasthenia gravis patients have antibodies that bind in a cross-striational pattern to skeletal and heart muscle tissue sections (striational antibodies). These antibodies react with epitopes on the muscle proteins titin and ryanodine receptor, are found mainly in sera of patients with thymoma and late-onset myasthenia gravis, and may correlate with myasthenia gravis severity. Their presence may predict an unsatisfactory outcome after thymectomy. The detection of titin and ryanodine receptor antibodies provides more specific clinical information than the immunofluorescent demonstration of striational antibodies.

**TITIN**

Titin is a giant protein (3000 kDa) and is the third most abundant protein in the skeletal and cardiac sarcomere (Figure 2A). The molecule is about 1 µm long, extending from the Z disk to the M line. Ninety percent of the titin mass is contained in a repetitive structure comprising 244 to 297 copies of 2 different 100-residue repeats; the 112 to 165 immunoglobulin superfamily domains, and 132 fibronectin-like domains. The rest of the titin mass consists of unique sequences with specialized functions. Titin molecules are arranged in a way that allow augmentation of mechanical stability and tension in the sarcomere. The titin-based tension is calcium responsive because titin is a calcium-dependent molecular spring that adapts to the physiological state of the cell.

The main immunogenic region of titin is called myasthenia gravis titin-30 (MGT-30) and is situated near the A/I-band junction (Figure 2A). Another im-

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munogenic region is located between the N1 and N2 lines. This consists of homologous immunoglobulin domains.6 These are differentially expressed; 15 modules are expressed in cardiac muscle, while there may be up to 68 such modules in skeletal muscle.6 Antibodies to the I-band epitope are present only in sera containing MGT-30 antibodies. When I-band epitope antibodies are present, a double-band immunofluorescence technique staining is obtained (Figure 2B). Patients who have antibodies attaching to I-band epitopes also have antibodies attaching to the main immunogenic region.6 The presence of antibodies attaching to the I-band epitopes may indicate titin epitope spreading.10

THE RyR

The RyR is a calcium release channel located in the sarcoplasmic reticulum. The name refers to the alkaloid ryanodine that binds selectively to the RyR. There are 2 forms of RyR, skeletal (RyR1) and cardiac (RyR2). The RyR antibodies from MG patients react with both. The RyR is a protein containing 5035 amino acids with a molecular weight of 565 kDa. It is composed of 4 homologous subunits that can build a tetramer with a central channel (Figure 3).11 The RyR is expressed mainly in striated muscle tissue, but it is also found in epithelium and neurons. The longitudinally spreading depolarization along the sarcolemma continues transversally through the T tubules to the terminal cisternae of the sarcoplasmic reticulum, inducing a conformational change in the RyR leading to calcium release which opens the RyR, allowing calcium flow into the sarcoplasm.11,12 The RyR epitopes are located on the handle domains of the RyR cytoplasmic assembly, near its junction with the transmembrane assembly.13 The main immunogenic region is the peptide chain 2 and RyR type 1 fusion protein located close to the N terminus, and for some sera a more centrally located region called peptide chain 25.14 Both regions are located near each other in the 3-dimensional conformation of the RyR. The antibody response to the central region may represent epitope spreading. The RyR antibodies cause allosteric inhibition of RyR function in vitro, inhibiting Ca²⁺ release from sarcoplasmic reticulum.14,15

OTHER STRIATIONAL ANTIGENS AND ANTIBODIES

Antibodies to human myosin were described in 1969.16 Cultured, dissociated, thymic lymphocytes from patients with MG secrete monoclonal striational antibodies that bind to skeletal muscle myosin, α-actinin, and actin.17 Patients with MG and thymoma have higher titers of anti-myosin and anti-actomyosin antibodies than patients with MG but without thymoma.17,18 Antibodies against rapsyn (a 43-kDa postsynaptic protein essential for anchoring and clustering AChR) have been identified in MG but are also found in serum samples from patients with lupus and chronic procainamide associated myopathy.19
STRIATIONAL ANTIBODIES IN SUBGROUPS OF MG

Myasthenia gravis can be classified into several subtypes based on the immunological profile. Nearly all patients with MG and thymoma and half of the late-onset MG subgroup (onset of MG at ≥50 years of age) demonstrate an antibody profile with a broad striational antibody response. In contrast, AChR antibody-positive patients with early-onset MG (onset of MG at <50 years of age) and AChR antibody-positive MG with purely ocular symptoms have a selective high antibody response against AChR. Striational autoantibodies are rarely found in AChR antibody-negative MG.

STRIATIONAL ANTIBODIES AND THE DIAGNOSIS OF THYMOMA

Striational autoantibodies and computed tomographic scan of the anterior mediastinum show a similar sensitivity for thymoma MG. In our studies, computed tomographic scan failed to predict a thymoma in 27% of the cases. The positive predictive value for thymoma is significantly higher for RyR antibodies. The presence of titin/RyR antibodies in a young patient with MG strongly suggests the presence of a thymoma (testing for titin antibodies, but not RyR antibodies, is commercially available). The absence of these antibodies strongly excludes thymoma (Table). The AChR antibody serum concentration does not correlate with MG severity, mainly because of individual variations in AChR epitope specificity.

Myasthenia gravis tends to be more severe in patients with thymoma than in the early-onset MG subgroup. The presence of striational autoantibodies is associated with a more severe disease in all MG subgroups, and citric acid antigen, titin, and RyR antibodies occur significantly more often among patients with severe MG than among patients with less severe disease. These antibodies can therefore be used as prognostic determinants in MG patients.

STRIATIONAL ANTIBODIES AND THYMECTOMY IN MG

Patients with early-onset MG may benefit from thymectomy. The AChR antibody concentration does not predict the outcome of thymectomy. Titin and RyR antibodies are not found in early-onset MG. Patients with late-onset MG benefit far less from thymectomy. An improvement appears less likely in cases with titin and/or RyR antibodies. Myasthenia gravis severity and outcome over time seem to be equal in thymoma and non-thymoma MG. but the presence of RyR antibodies in thymoma MG and titin/RyR antibodies in nonthymoma MG indicates a less favorable prognosis. The RyR antibodies are often found in patients with an invasive or malignant thymoma.

STRIATIONAL ANTIBODIES AND HLA LINKAGE IN MG

The correlation between MG and specific HLA antigens has long been recognized. Patients with MG and titin antibodies often express the HLA-DR7 haplotype, while those with thymus hyperplasia and no titin antibodies express HLA-DR3. Extended haplotypes including tumor necrosis factor α or β polymorphisms confirm the

Table. Titin, RyR Antibodies, and CT Scan of the Anterior Mediastinum in Relation to the Occurrence of Thymoma in Our Myasthenia Gravis Population

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %*</th>
<th>Specificity, %†</th>
<th>Positive Predictive Value, %‡</th>
<th>Negative Predictive Value, %§</th>
<th>Test Accuracy, %¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titin</td>
<td>95</td>
<td>76</td>
<td>39</td>
<td>99</td>
<td>79</td>
</tr>
<tr>
<td>RyR</td>
<td>70</td>
<td>95</td>
<td>70</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>CT scan</td>
<td>73</td>
<td>90</td>
<td>47</td>
<td>65</td>
<td>85</td>
</tr>
</tbody>
</table>

Abbreviations: CT scan, computed tomography scan; RyR, ryanodine receptor.

* Sensitivity indicates number of true positive/number with thymoma.
† Specificity indicates number of true negative/number without thymoma.
‡ Positive predictive value indicates number with thymoma/number of positive test results.
§ Negative predictive value indicates number without thymoma/number of negative test results.
¶ Test accuracy indicates number of correct test results/number of tested patients with myasthenia gravis.

Figure 3. Drawing of the ryanodine receptor showing the localization of the 2 epitopes, pc2 (main immunogenic region) and pc25, which are recognized by antibodies in the serum samples of patients with myasthenia gravis.
linkage to specific major histocompatibility complex haplotypes. This supports that patients with and without striational antibodies belong to pathogenetically different subsets of MG.

DO STRIATIONAL ANTIBODIES HAVE A ROLE IN THE PATHOGENESIS OF MG?

The complement concentration in the serum of MG patients varies with disease severity, increasing during remission and decreasing during exacerbation. This can be explained by activated complement components attacking the AChR at the end plate. However, titin and RyR antibodies also activate complement in vitro through the IgG 1-mediated pathway. Complement activation caused by striational antibodies is therefore a potential mechanism for additional immune damage. The presence of T-cell antibodies in patients with MG correlates with their electromyographic evidence of myopathy. This does not prove any pathogenic role for titin and RyR antibodies in MG.

The initial steps in the triggering of humoral immunity in MG presumably take place inside the thymus. Fifty percent of patients with cortical-type thymoma have MG, and the presence of muscle-like epitopes within thymomas has been demonstrated. MG-associated thymomas are enriched in AChR-like epitopes and AChR-specific T-cells. Titin and RyR epitopes have also been identified on neoplastic thymoma cells. In MG associated thymoma, there is an overexpression of thymic musclelike epitopes and costimulatory molecules indicating that the T-cell autoimmunization is promoted by the pathogenic microenvironment inside the thymoma. Titin and RyR epitopes are coexpressed along with LFA3 and B7 (BB1), which are costimulatory molecules expressed on thymoma antigen-presenting cells in cortical thymoma. The steps in the autosensitization that lead to the development of humoral autoimmunity against muscle antigen are incompletely known, but involve both Th1 and Th2 lymphocyte responses.

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