5. Expression of the Acetylcholine Receptor \(\alpha\)-Subunit Gene is Associated with Paraneoplastic Myasthenia Gravis in Mixed Thymoma

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Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by autoantibodies against the acetylcholine receptor (AChR) at the neuromuscular junction [1]. The muscular AChR has been extensively characterized [2], but the etiology of MG is still obscure. Whether the muscular AChR or another (auto)antigen plays a role during the initiation of MG is unknown [3]. The muscular AChR is a pentameric ion channel composed of four different subunits. The \(\alpha\)-subunit contains the acetylcholine binding site and the main epitopes recognized by MG autoantibodies [2]. The human muscle AChR \(\alpha\)-subunit exists as two isoforms, P3A\(^-\) and P3A\(^+\) [4]. This is a result of alternative splicing of the P3A exon located between exons three and four. The P3A\(^+\) isoform does not bind \(\alpha\)-bungarotoxin or monoclonal antibodies against the AChR main immunogenic region and is not integrated into functional AChR [5]. The muscular AChR belongs to the family of nicotinic AChRs as do neuronal AChRs. Since muscular and neuronal AChRs share significant molecular homology [6], neuronal AChRs have been considered as candidate autoantigens able to elicit autoimmunity against the muscular AChR by molecular mimicry [7].

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Expression of AChR α-Subunit Gene

Material and Tissues

Thirty-five thymic epithelial tumors (TET), seven hyperplastic thymuses, three normal thymuses and two tumor biopsies of rhabdomyosarcoma patients were studied by RT-PCR using tissue snap-frozen within four hours after surgery. TETs were classified according to Müller-Hermelink and co-workers [15, 19]. Cortical thymoma (CT) and "well differentiated thymic carcinoma" (WDTC), though morphologically different, are so closely related in clinical, histogenetic and functional terms [13, 15] that they were considered as one tumor group here. CT and WDTC were compared with mixed thymomas (MXT), which are the second most frequent MG-associated tumors [15, 19]. In addition two medullary thymomas (MDT) were studied. Invasiveness of tumors was staged according to the proposal of Masaoka [20]. Normal thymuses were obtained from patients without immunological disorders undergoing thoracic surgery. Thymuses with thymitis (THY) and two different ex vivo rhabdomyosarcoma biopsies were tested. The tumor stage [20] ranged from I to II in MDT and MXT and from II to IVa in CT and WDTC. The clinical diagnosis of MG was routinely confirmed electromyographically and by the detection of anti-AChR autoantibodies by a radioimmunoassay using human muscle-derived, $^{125}$I-labeled AChR. All thymitis cases corresponded to the typical lymphofollicular thymitis as reported by Kirchner and co-workers [21].

For PCR-based detection of muscular AChR gene expression the embryonal