

A NEW MOUSE MODEL FOR LATE ONSET AUTOIMMUNE MYASTHENIA GRAVIS

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Although myasthenia gravis (MG) can be generated in young rodents immunized with the acetylcholine receptor from *Torpedo californica* (T-AChR), older mice are resistant to disease induction. This was somewhat surprising since approximately one half of human MG patients first develop symptoms after the age of 40 (late onset MG). Thus, we examined the age-associated effects on development of an anti-AChR immune response in mice. As expected, the antibody response to T-AChR was decreased in older mice and, in some cases, there was a narrowing in the anti-AChR repertoire. On the other hand, the recall B-cell response was only slightly diminished in older mice. Clonotypic analysis of recall responses confirmed that memory B-cells are maintained during aging. Moreover, when certain memory B-cell responses were recalled in old age, MG was induced. Thus, recall immunity was exploited to generate the first animal model of late-onset MG. This suggests that late-onset MG in humans could be due to re-activation of a B-cell response initiated at a younger age but kept under control by tolerance mechanisms. To study the loss of age-sensitive tolerance mechanisms, a transgenic model was developed in which the T-AChR alpha chain is expressed in muscle tissue and AChR α -specific T-cells are tolerized. When immunized with the T-AChR alpha chain alone, the B cell response is also tolerized. Thus, future work will examine: 1) the roll of recall responses and tolerance loss in autoimmunity and 2) the possibility of exploiting recall responses to enhance vaccination protocols for the elderly.