COMMENTARY

Thymectomy and myasthenia gravis

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Myasthenia gravis (MG) is a disorder of the neuromuscular junction mediated by the actions of autoantibodies directed against one of several proteins expressed on the postjunction muscle membrane. For the large majority of MG patients the target for the autoantibodies is the acetylcholine receptor (AChR) (1) that interacts with acetylcholine, the transmitter released by the motor nerve, to trigger muscle contraction.

The Thymus in Myasthenia Gravis

There is a well-known association between abnormalities in the thymus, the central immune organ for development of T cell-mediated immune system and the site of central immune regulation during development (1–3), and the AChR form of MG. The most common abnormality consists of atypical follicular germinal centers in the thymic medulla, so-called thymic hyperplasia, occurring in ∼60 to 75% of patients. In 10 to 15% of patients, neoplastic changes (thymoma) occur, and the remainder of patients exhibit normal involution (1, 4). The etiologic connection between the thymic changes and MG is uncertain (5). For many years there have been series reporting improvement after thymectomy. Recently a prospective single-blinded controlled study demonstrated that thymectomy in patients already receiving corticosteroid therapy is superior to corticosteroids both at 3 y (6) and confirmed at 5 y (7). The improvement was not universal, and it could take several years to become evident, raising the question of why that might be. A study by Jiang et al. (8) in PNAS offers insights into these issues.

There has long been evidence of abnormalities of immune function in the hyperplastic thymus, with heightened B cell and plasma cell number and function, along with a reduction in regulatory functions (9–13). Thymic lymphocytes can synthesize AChR antibodies in vitro without additional in vitro stimulation, although antibodies to other antigens can also be detected (14–16). It has been hypothesized that the initial sensitization resulting in the development of AChR-producing B cells and plasma cells occurs in the inflammatory milieu of the thymus (reviewed in ref. 5). The etiology of this initial inflammation, which includes inflammatory cytokines, some of which are important for development of germinal follicles, is not known, but viral or other infectious agents have been hypothesized (12). AChR is expressed in the small subset of thymic myoid cells and histologic analysis demonstrates the presence of appropriate cells necessary to develop an immune response. It has also been shown that blood and bone marrow lymphocytes can also synthesize AChR antibodies in vitro. Unlike thymic lymphocytes, blood lymphocytes generally require additional in vitro stimulation by T cells to further activate the B cells to produce these antibodies (17).

Trafficking of Cells between Thymus and the Peripheral Immune Compartment in MG

Using a series of state-of-the-art molecular biologic techniques, Jiang et al. (8) demonstrate shared B cell receptor repertoires between B cell and plasmablast populations from areas enriched for germinal follicular regions in thymuses of patients undergoing thymectomy (eight patients from the thymectomy trial and one other individual) and the equivalent cell populations in the blood of these same individuals. Both the thymic and blood cells had the characteristics of being antigen-driven. Using these same techniques they are able to imply that the peripheral blood B cells and plasma cells were more likely to have originated in the thymus rather than the reverse, although there is evidence in the literature that supports the ability of antibody-producing cells that have been reactivated in vivo to migrate to the thymus (16).

The authors then went on to study blood B cells and plasmablasts from these individuals 12 mo after the thymectomy and were able to demonstrate

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persistence of these cells, among them presumably cells producing AChR antibodies. This keeps with the fact that while there is a decrease in serum AChR titers postthymectomy it is often modest and delayed. In addition, as the authors also point out, plasma cells are often long-lived and need not be influenced by T cells or driven by antigen. If they are correct, it supports the theory that thymectomy should be performed early in the course of the disease before a large number of AChR-producing and potential AChR antibody-producing cells have seeded the peripheral immune system. However, memory B cells once in the periphery could continue to produce more antibody-producing B cells as well as, ultimately, plasmablasts and long-lived plasma cells.

Mechanism of Action of Thymectomy in MG

Jiang et al. (8) attempted to see if there were quantitative changes in the presumed thymic origin of peripheral blood cell populations that correlated with clinical response to thymectomy in these same individuals. In the relatively small number of patients in this highly sophisticated immunologic study there was a trend toward correlation between reduced thymus-derived cells in blood sampled at 1 y postthymectomy and the time to clinical improvement, often at 2 y or longer, but it is hard to come to a firm conclusion. One could hypothesize that removing the thymus as the source of the major antibody response ultimately helps lower the levels of circulating AChR antibodies, or perhaps a subset of these antibodies. The persistence of these antibodies for some time, or perhaps indefinitely, relates to the persistence of the antibody-producing cells in the peripheral immune compartment. Even if some of these cells have some characteristics of being antigen-driven, there is certainly ample expression of AChR in skeletal muscle to provide any needed antigenic drive. Thus, we still do not have a definite answer to the question of how thymectomy works in patients with MG with AChR antibodies but likely have a potential explanation of the delay in clinical improvement and the limit in degree of improvement.

Future Directions

It would be of great interest if these same thymectomized individual patients could be studied again in the future to see if there are further changes in the persistence of these B cells and plasma cells, circulating lymphocytes that synthesize AChR antibodies in vitro, serum antibodies to AChR, and clinical status of these patients.

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