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T Cell–Transfer Experimental Autoimmune Encephalomyelitis: Pillar of Multiple Sclerosis and Autoimmunity

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Experimental autoimmune encephalomyelitis (EAE) is known as the animal model of multiple sclerosis, the most common disabling neurologic disorder of young adults (reviewed in Refs. 1–3). Beyond its role as a specific disease model, EAE has served as a key paradigm for investigating fundamental problems of autoimmunity and immune tolerance. Classically, EAE is induced by active immunization with myelin autoantigens, such as myelin basic protein (MBP), myelin oligodendrocyte glycoprotein, or proteolipid protein, in adjuvant. This month’s *Pillars of Immunology* article features “T-transfer EAE,” a variant of EAE first described in 1981 by Ben-Nun et al. (4). In this article (cited >800 times), the investigators demonstrated that EAE can be adoptively transferred by injecting highly purified MBP-specific T line cells into syngeneic naive recipient animals. This effectively pinpointed myelin-autoreactive CD4⁺ T lymphocytes as the crucial effector cells of EAE, an observation that had far-reaching implications for autoimmunity research, in general, and for multiple sclerosis, in particular. The article resulted from a fruitful Israeli–German collaboration in which each side contributed an essential methodological component. Irun R. Cohen and Avraham Ben-Nun of the Weizmann Institute of Rehovot, Israel had experience with classical EAE and were skilled at propagating T cell lines, which was still a relatively new technique at the time. The German collaboration partner, Hartmut Wekerle, contributed his expertise in the selection and purification of autoreactive T cells. With a stipend from the Volkswagenstiftung, Ben-Nun visited Wekerle’s laboratory at the Max-Planck Institute of Immunobiology in Freiburg to learn how to isolate Ag-specific T cells from primed animals (5). Lymph node cells from immunized Lewis rats were cultured in the presence of myelin autoantigen (MBP) or control Ags (OVA or purified protein derivative of tuberculin). After 3 d of incubation, the cells were collected, and proliferating low-density lymphoblasts were separated from quiescent small cells by centrifugation on discontinuous Ficoll density gradients. The lymphoblasts were propagated and maintained in vitro in culture medium supplemented with supernatant from ConA-stimulated spleen cells. At regular intervals, the cultures were restimulated with the relevant Ag in the presence of irradiated syngeneic thymocytes as feeder cells. After Ben-Nun had returned to Israel, the experiment culminated in the first successful transfer of EAE, which was achieved by injecting freshly activated MBP-specific T line cells into naive recipient rats. About 1 million MBP-specific, but not purified protein derivative of tuberculin–specific, lymphoblasts were sufficient to induce EAE in the majority of recipients. One of the authors of this commentary (R.H.), who was a postdoctoral fellow in Wekerle’s laboratory at that time, will never forget when Irun Cohen’s telegram arrived from Rehovot with just the message “Heureka.”

The article reporting these findings (4) merits selection as a *Pillars of Immunology* publication for at least four reasons. First, it illustrates how the technique of culturing T cell lines and clones with T cell growth factor opened completely new avenues for autoimmunity research. Earlier studies on adoptive transfer of lymphoid cells in EAE had taken a different approach. One experiment showed that repeated transfer of myelin-sensitized lymphocytes suppressed actively induced paralysis (6). A second experiment showed that T cells sensitized to myelin could induce EAE, but only after the recipients were irradiated (7). The featured *Pillars of Immunology* article used, for the first time, purified autoreactive T cell lines for adoptively transferring EAE (4), thereby overcoming the need to irradiate the host. As highlighted in another recent *Pillars of Immunology* commentary (8), the discovery and initial characterization of T cell growth factor (9–11), which works across different species (e.g., mouse, rat, and human), was a major breakthrough in cellular immunology. It allowed the expansion of T cells with specificity for, theoretically, any Ag, including, as first shown by Ben-Nun et al. (4), a defined autoantigen of the nervous system. Subsequently, similar approaches were used for the isolation and propagation of autoantigen-specific T cell lines from human patients with autoimmune diseases, such as myasthenia gravis (12) and multiple sclerosis (13–17).

Second, the Ben-Nun et al. (4) study touched upon a fundamental issue of autoimmunity. According to Burnet’s
clonal selection theory (18), the lymphocyte repertoire needs to be purged of autoreactive lymphocytes early in development to avoid autoimmunity; in other words, self-recognizing clones are “forbidden.” This would imply that the autoaggressive T cells isolated by Ben-Nun et al. have arisen by somatic mutation. However, using essentially the same method, Schluesener and Wekerle (19) were able to isolate MBP-specific encephalitogenic T cells from lymph nodes of healthy Lewis rats. The special trick in this case was to eliminate spontaneously proliferating T cells via a round of negative selection and then to isolate MBP-reactive T cells in a second, positive-selection round (19). Using this approach, the investigators isolated a highly encephalitogenic T cell line with which they could transfer disease to naive recipient animals by injecting as few as \( 1 \times 10^4 \) T cells. Considering that there is no postthymic somatic hypermutation of TCRs, these observations prove the presence of potentially autoaggressive T cells in the healthy immune repertoire, raising the question of how these cells are normally held in check. Interestingly, the findings (19) were reported at a time when suppressor T cells had fallen into complete disregard and only later regained reputation (20). Based on the observation that autoimmune T cells are physiological components of the immune system, Irun Cohen proposed that physiological autoimmunity is essential for homeostasis and maintenance, an idea he elaborated with his concept of the “immunological homunculus,” the immune system’s “self-image” (21, 22).

Third, the T cell–transfer model opened a whole new field: in vivo imaging of encephalitogenic T cells by multiphoton live microscopy (reviewed in Ref. 23). Using in vitro retroviral transduction, MBP-specific rat T cells can be labeled with GFP so that their migratory paths can be visualized and followed in real time in vivo from the periphery into the CNS, including their transmigration across the blood–brain barrier (24, 25). More recently, it has become possible to observe local reactivation of the transferred T cells by in vivo calcium imaging (26, 27). These studies revealed a fundamental principle of T cell–mediated neuroinflammation: initial breach of the intact blood–brain barrier does not depend on the Ag specificity of the T cells but rather on their activation status. In contrast, mass invasion of the CNS by large numbers of T cells requires recognition of cognate Ag on strategically placed APCs located on the parenchymal side of the barrier (25).

Fourth, the T cell–transfer model has shaped our current T cell–centric model of the pathogenesis of multiple sclerosis, thereby inspiring major progress in the therapy of this disabling autoimmune disorder. T cell–targeting therapies range from Ag-selective T cell vaccination (28) and altered peptide ligand approaches (reviewed in Refs. 29–32) to more conventional immunomodulatory and immunosuppressive treatments (33). In addition to providing the conceptual basis for the therapeutic targeting of T cells, the T cell–transfer model has directly contributed to the development of new therapies for multiple sclerosis, as can be illustrated by the monoclonal anti–VLA-4 Ab natalizumab, whose in vivo impact was originally demonstrated using the T cell–transfer EAE model (34, 35). As a side note, recent clinical trials indicated that, perhaps unexpectedly, B cell depletion with anti-CD20 mAbs can be very effective in multiple sclerosis (36). However, this by no means contradicts the T cell–centric paradigm, because the effect of B cell–depleting therapy does not depend on the depletion of Abs but rather on the elimination of B cells as Ag-presenting and cytokine-secreting cells (37).

Like all models, the T cell–transfer model has its limitations. Despite its tremendous usefulness for studying T cell–mediated effector mechanisms, the model is obviously not suitable for investigating the initial triggering events of CNS inflammation. In this regard, genetically engineered spontaneous animal models are more appropriate (38). Finally, it should be kept in mind that the demonstration that myelin-autoreactive CD4+ T cells mediate EAE in rodent models does not necessarily imply that these T cells are the culprits in human multiple sclerosis, for which a unifying target (auto-) antigen has not been identified (reviewed in Refs. 32, 39).

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Disclosures
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References


