What T-cell receptors can tell us about neurologic disease

Chronic demyelinating polyradiculoneuropathy (CIDP) is an acquired, potentially crippling sensory-motor polyneuropathy of variable course. It is likely autoimmune because sural nerve histopathology reveals infiltrating CD68+ macrophages, endoneurial and epineurial CD3+ T cells with immunoglobulin G, immunoglobulin M, and complement deposits on myelin sheaths. Macrophages penetrate the basal lamina of Schwann cells and split myelin lamellae, a process referred to as “macrophage-mediated demyelination.” Nerve injury ensues due to a combination of antibody-, complement-, and macrophage-dependent demyelination. The majority of patients therefore respond to corticosteroids, plasmapheresis, or IV immunoglobulin (IVIg). The Immune Globulin IV CIDP Efficacy (ICE) study, the largest therapeutic trial in CIDP, convincingly demonstrated short- and long-term benefits of IVIg treatment. Response to plasmapheresis or IVIg is consistent with humoral and Fc receptor–mediated cellular effector mechanisms.

In this issue of Neurology®, Schneider-Hohendorf et al. present evidence that CD8+ cytotoxic T cells contribute to the pathogenesis of CIDP: nerve-infiltrating CD8+ T cells are clonally expanded, with expanded T-cell clones also detectable in blood. In one especially informative patient, expanded T-cell receptor (TCR) β-chain variable (TCRVβ) 5.1+ T cells were enriched in sural nerve compared to blood. To interpret and understand these results, one needs to consider the methodology used in the study, CD8+ (cytotoxic) T cells typically recognize a short peptide composed of 8–10 amino acids bound to a human leukocyte antigen (HLA) class 1 molecule displayed on the surface of a target cell. The HLA-bound peptide is recognized by the hypervariable, complementarity determining region (CDR) of the antigen-specific TCR on the cytotoxic T cell. TCRs are clonally distributed: about 1015 different TCRs are theoretically possible, and about 3 x 107 to 109 distinct T-cell clones are present in the human immune system, each carrying one type of unique TCR. In contrast to B-cell receptors, which are also clonally distributed, TCRs do not undergo affinity maturation by somatic hypermutation, so that the post-thymic TCR repertoire is essentially fixed. Therefore, analysis of the clonal composition of tissue-infiltrating T cells and of their TCR repertoire indicates their distribution and antigen recognition properties, and therefore, their pathogenic relevance. This is the basis for the greatly popular “TCR repertoire studies” by clinical immunologists.

To prove T cells are pathogenic, there should be morphologic evidence of CD8+ T-cell–mediated tissue injury. The mere presence of CD8+ cells provides only tentative evidence, but direct contact between T cells and HLA class 1–expressing target cells is strong evidence for a CD8+ T-cell–mediated attack. For example, in muscle of patients with inclusion body myositis, non-necrotic, HLA class 1–expressing muscle fibers are surrounded and invaded by activated CD8+ T cells, which release their cytotoxic granules toward the attacked fiber. Such a “kiss of death” between a cytotoxic T cell and a target cell (neuron or astrocyte) also occurs in Rasmussen encephalitis. The morphologic evidence in the CIDP article is indirect, because only the presence of CD8+ T cells was demonstrated. A second line of evidence is clonal expansion or clonal dominance of the incriminated T cells, demonstrated by immunostaining with monoclonal antibodies directed against 24 human TCR variable β-chain (Vβ) families. In the CIDP study, this was achieved in one patient by using an anti-TCR Vβ5.1 monoclonal antibody. Furthermore, molecular evidence for clonal expansion may be obtained by “TCR-CDR3 spectratyping.” This method makes use of the “junctional diversity” generated when TCRs are created by somatic recombination of TCR-encoding gene segments. This occurs in the thymus and results in varieties of the CDR3 regions of the TCR Vβ chains. Using oligonucleotide primers for 24 human Vβ gene families, the CDR3 length distribution can be analyzed for each TCR Vβ family. A significant devi-
Evidence for a pathogenic role of CD8+ T lymphocytes in putative autoimmune diseases of muscle (PM and IBM), CNS (MS), and peripheral nerve (CIDP)

<table>
<thead>
<tr>
<th>Morphologic evidence of CD8+ T-cell-mediated destruction of HLA class I-positive target cell</th>
<th>IBM/PM</th>
<th>MS</th>
<th>CIDP</th>
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<tr>
<td>Clonal expansion of CD8+ cells (e.g., by TCR CDR3 spectratyping)</td>
<td>+</td>
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<tr>
<td>Clonal pervasiveness</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Clonal persistence</td>
<td>+</td>
<td>+</td>
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<td>Silent nucleotide exchanges in TCR CDR3 region</td>
<td>+</td>
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Abbreviations: CIDP – chronic inflammatory demyelinating polyradiculoneuropathy; IBM – inclusion body myositis; MS – multiple sclerosis; PM – polymyositis; TCR – T-cell receptor.

formation from the usual distribution in the transcripts of any TCR Vβ family is evidence for clonal expansion of the corresponding T cells in the inflammatory infiltrate and is, therefore, evidence of pathogenic importance. In the CIDP study, CDR3 spectratyping revealed strong clonal expansions in sural nerve biopsy specimens. The same expansions could be observed in CD8+ T cells from patients’ peripheral blood. Clonal identity was confirmed by sequence comparison of the TCR CDR3 regions.

Apart from clonal expansion, TCR repertoire analysis may provide additional clues to pathogenic relevance. One such feature is “pervasiveness”: the pathogenic role of an expanded T-cell clone is corroborated if it is present at different sites in the affected tissue, or in other tissues (e.g., blood or CSF). Similarly, temporal persistence of expanded T-cell clones would argue for their pathogenic relevance. Finally, silent nucleotide exchanges in the TCR CDR3 regions point to pathogenic relevance. These additional features were detected, for example, in MS, but have not yet been demonstrated in CIDP (table).

The new study provides startling, yet preliminary evidence for a pathogenic role of CD8+ in CIDP. Even if future investigations showed that the nerve-infiltrating CD8+ T cells do not act directly as cytotoxic effector cells, they might still play a role by recognizing a target antigen involved in the immunopathogenesis of CIDP. This might be an autoantigen or, perhaps, viral antigen. How could one proceed to further analyze the nerve-infiltrating T cells? One approach would be to “resurrect” the T cells from nerve specimens, and to use the resurrected cells for identifying their target antigens. This task is far from trivial, but owing to a new method, it would be technically feasible.

**AUTHOR CONTRIBUTIONS**

Dr. Hohlfeld: drafting/revising the manuscript, study concept or design. Dr. Dormmair: drafting/revising the manuscript.

**DISCLOSURE**

Dr. Hohlfeld serves on scientific advisory boards for Novartis, Biogen Idec, Bayer Schering Pharma, Merck Serono, sanofi-aventis, Teva Pharmaceutical Industries Ltd., and CSL Behring; has received funding for travel from Novartis, Biogen Idec, Bayer Schering Pharma, Merck Serono, sanofi-aventis, and Teva Pharmaceutical Industries Ltd.; serves on the editorial boards of Neurology®, Brain, Deutsche Medizinische Wochenschrift, Expert Opinion on Biological Therapy, International MS Journal, Journal of Neuroimmunology, Multiple Sclerosis, Nervenarzt, Practical Neurology, Seminars in Immunopathology, and Therapeutic Advances in Neurological Disorders; has served as a consultant for Novartis, Biogen Idec, Bayer Schering Pharma, Merck Serono, sanofi-aventis, and Teva Pharmaceutical Industries Ltd.; and has received research support from Novartis, Biogen Idec, Bayer Schering Pharma, and Teva Pharmaceutical Industries Ltd. Dr. Dormmair reports no disclosures.

**REFERENCES**