A bird’s-eye view of T cells during natalizumab therapy

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Neurology® 2013;81:1372–1373

Natalizumab binds to α4 integrins expressed on lymphocytes and monocytes. It blocks the interaction of these integrins with their binding partners on vascular endothelial cells, and thereby prevents immune cells from entering inflamed tissues. Natalizumab is an effective treatment, but it carries the risk of progressive multifocal leukoencephalopathy (PML). Results reported in this issue of Neurology® are relevant to both the beneficial and adverse effects of natalizumab. The authors investigated how natalizumab affects the T-cell receptor (TCR) repertoire of patients with multiple sclerosis (MS). Their main observations are that 1) the TCR repertoire seems to “normalize” during natalizumab treatment, that is, revert to the state observed in healthy subjects, and 2) the onset of PML and immune reconstitution inflammatory syndrome (IRIS) is accompanied or preceded by the appearance of distinct clonal T-cell expansions in blood or CSF.

Regarding the first observation, normalization of the TCR repertoire, the authors used a method called complementarity-determining region-3 (CDR3) spectratyping to obtain a “high-altitude, bird’s-eye overview” of the global landscape of antigen-specific receptors expressed by circulating T cells. In essence, this method relies on the length distribution of the TCR’s antigen-recognizing CDR3 regions. In healthy subjects, this distribution is normal (Gaussian). Any deviation from the Gaussian distribution can be quantified with a “complexity score.” Low complexity scores indicate a “distorted” TCR repertoire, due to either disappearance or expansion of individual T-cell clones. In a cross-sectional comparison, the authors found that the TCR repertoire of natalizumab-treated patients resembled the TCR repertoire of healthy subjects, whereas the TCR repertoire of untreated patients with MS showed reduced complexity scores. This indicates that natalizumab may “normalize” the distorted TCR repertoire observed in untreated patients with MS.

If pathogenic T cells are expanded in the blood of untreated patients with MS, and if natalizumab mainly works by blocking the entry of T cells into the CNS, it is difficult to understand how natalizumab can normalize the peripheral TCR repertoire. It should be noted, however, that natalizumab exerts numerous additional effects on the immune system. For example, natalizumab blocks T-cell migration across parenchymal microvessels not only in the CNS but also in the gut; perturbs B-cell homing in secondary lymphoid organs and leads to a disproportionate increase of B cells in blood; affects the trafficking of CD34+ hematopoietic progenitor cells; and increases the number of new thymic emigrant T cells. Although the precise mechanisms are unknown, it is conceivable that a multitude of effects might contribute to the observed normalization of the peripheral TCR repertoire. It should be emphasized, however, that this was inferred from a cross-sectional comparison of treated and untreated patients with MS. Longitudinal analyses of individual patients will be needed to confirm this finding.

Regarding the second main observation, the appearance of new clonal expansions around the time of PML diagnosis, strong evidence comes from 2 patients who developed PML during the course of the study, and in whom the TCR repertoire could be followed longitudinally. Interestingly, whereas some clonal expansions were detectable in CSF or blood just prior to or at the time of PML diagnosis, additional expansions appeared just after plasma exchange, preceding IRIS. The most plausible interpretation is that the newly appearing T cells represent JC virus (JCV)-specific T cells. However, this remains speculative because neither the antigen specificity nor the CD4 or CD8 type of these cells is known. For example, the antigen specificity of the T cells could be investigated with tetrameric complexes of human leukocyte antigen–bound JCV peptides. Such tetramers bind directly to the corresponding antigen-specific T cells and therefore can be used for detection and labeling of JCV-reactive T cells.

The observed clonal changes may eventually help to design new biomarkers for early detection of PML and IRIS. Further, precise identification of the JCV epitopes recognized by the newly appearing T cells should inform vaccination strategies. Finally, the observation that some but not all PML-related clonal expansions occurred in both the blood and CSF compartment supports the view that the anti-JCV immune response has a systemic and sequestered component.
Apart from a better understanding of PML and IRIS, the methods applied in the current article might also be useful for tracking the migration of autoantigen-specific T cells thought to be responsible for the rebound of MS activity that is sometimes observed after stopping natalizumab therapy. Thus, we may be optimistic that future “bird’s-eye view” studies like the one described here, ideally in combination with phenotypic and functional characterization of the expanded T cells, will provide further insights into the complex relationship between leukocyte migration, PML, IRIS, and possibly rebound of MS activity after cessation of natalizumab treatment.

STUDY FUNDING
No targeted funding reported.

DISCLOSURE
R. Hohlfeld has served on scientific advisory boards for and received research grant support from Novartis, Biogen-Idec, Bayer, Merck Serono, Sanofi-Aventis, Teva, and Genzyme. O. Stüve has received research grant support from Teva Pharmaceuticals. Go to Neurology.org for full disclosures.

REFERENCES