

EXPRESSION OF IL-16 CORRELATES WITH SEVERE RELAPSING-REMITTING EAE IN H-2^{b/s} MICE

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Experimental autoimmune encephalomyelitis (EAE) can be induced in genetically susceptible strains of mice by immunization with myelin proteins. It serves as a model for human demyelinating disease Multiple sclerosis (MS). While immune mechanisms governing the initiation of an autoimmune response to MOG₃₅₋₅₅ have been extensively studied, immune mechanisms underlying progression and relapsing-remitting course remain unclear. One of the major obstacles in addressing this question is H-2^b restriction of the response to MOG₃₅₋₅₅.

In order to overcome this obstacle, we developed an EAE model in (B6 x SJL) F1, H-2^{b/s} mice. Following the same immunization procedure with MOG₃₅₋₅₅, relapsing EAE develops in 97% of H-2^{b/s} mice compared to 20% of H-2^b mice. H-2^{b/s} mice develop 2-3 relapsing episodes over two months, with severity score two times higher than in H-2^b mice. Relapsing H-2^b mice develop only one relapse and completely recover, while H-2^{b/s} mice do not recover. Infiltrating lesions in relapsing H-2^{b/s} mice are scattered in the white matter and accompanied with extensive demyelination. Inflammatory lesions in relapsing H-2^b mice are mostly in the meninges and along large blood vessels. Quantitative analysis of cellular phenotypes revealed approximately four-fold higher infiltration of CD4⁺ T cells in H-2^{b/s} than in H-2^b relapsing lesion. Infiltration of B220⁺ B cells was also significantly higher in H-2^{b/s} mice. We further analyzed regulation of IL-16 in relapsing H-2^b and H-2^{b/s} mice. IL-16 has a role in chemoattraction, and activation of CD4⁺ cells by regulation of CD25 expression. It is constitutively expressed by T lymphocytes as pro-IL-16 and needs catalytic activity of Caspase-3 for cleavage into an active IL-16. Co-localization analysis revealed expression of IL-16 by CD3⁺ CD4⁺ T cells, B220⁺ B cells and some in CD8⁺ T cells in relapsing H-2^{b/s} mice. In H-2^b mice, IL-16 was observed mostly in CD8⁺ T cells. Expression of IL-16 was not detected in infiltrating Mac3⁺ macrophages or in Mac1⁺ microglia in either strain of mice. Expression of IL-16 by infiltrating inflammatory cells was accompanied by the co-expression of activated Caspase-3, suggesting that these cells produce active form of IL-16. Western blot analysis confirmed higher expression of 17-kd mature IL-16 in spinal cord of H-2^{b/s} relapsing mice. We also found higher CD25 expression by CD4⁺ T cells in relapsing lesions of H-2^{b/s} mice compared to H-2^b.

Taken together, data show correlation between high CD3⁺CD4⁺ T cell infiltration, and expression of IL-16, Caspase-3 and CD25, in the CNS of H-2^{b/s} mice with severe relapsing-remitting EAE. Our data suggests a role of IL-16 in more severe, progressive disease through chemoattraction and activation of CD4⁺ T cells.