

A

bstracts - Whitaker

The John Whitaker Track



BI-DIRECTIONAL REGULATION OF NK CELLS AND DENDRITIC CELLS NECESSARY FOR GENESIS OF AUTOIMMUNITY

Autoimmune diseases are often characterized by inflammation associated with immune destruction of the target organs. Initiation of autoimmunity in the context of inflammation may involve the interplay of lymphocytes from both innate and adaptive immune systems. Here we show that during the initiation of autoimmune encephalomyelitis, a demyelinating disease of the central nervous system, reciprocal activation of natural killer (NK) cells and dendritic cells (DCs) is necessary for priming the myelin-reactive T cells. Targeted disruption of innate cytokines or Toll-like receptors leads to disturbance in these communications between NK cells and DCs. Consequently, DCs can not convey the NK cell-derived helper signals to instruct the differentiation of autoreactive Th1 cells, thereby preventing the genesis of autoimmune responses to myelin antigens. These findings indicate that NK cell-DC interaction is central for initiation of autoimmune disease.

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DYNAMICS OF INTERFERON- β BIOMARKERS IN MS PATIENTS WITH ANTI- INTERFERON- β NEUTRALIZING ANTIBODIES

Objectives: To evaluate multiple interferon- β (IFN β) specific markers in multiple sclerosis (MS) patients with anti-IFN β neutralizing antibodies (NAB) using a pharmacodynamic study design.

Methods: Fifteen patients who participated in an earlier open label trial of IFN β -1a immunogenicity during which NAB titers were obtained every 3-month for 5-year trial duration and 15 additional IFN β treated patients from our current practice were enrolled. A pharmacodynamic study design was used. Blood samples were obtained at pre-treatment, 4, 8-hour time points following the intramuscular dose of IFN β -1a. Total RNA was obtained from peripheral blood cells, processed to cDNA and analyzed using quantitative real-time polymerase chain reaction. The total RNA samples were analyzed for messenger RNAs of 6 genes: b actin, myxovirus resistance protein 1 (Mx1), myxovirus resistance protein 2 (Mx2), signal transducer and activator of transcription 1 (STAT1), b₂ microglobulin and TNF related apoptosis inducing ligand (TRAIL).

Results: At time of the study enrollment, 11 patients were NAB negative (mean age= 48.3 yrs, disease duration = 17.5 yrs, mean EDSS = 3.3); 8 patients were positive (titers > 50) for binding antibodies (mean age= 48.0 yrs, disease duration = 18.7 yrs, mean EDSS = 3.3, mean binding antibody titer = 181); 6 patients were positive (titers \geq 20) for NAB (mean age= 48.0 yrs, disease duration = 16.7 yrs, mean EDSS = 3.7, mean NAB titer = 165) and 5 patients previously positive for NAB during the immunogenicity trial (mean age= 49.0 yrs, disease duration = 18.1 yrs, mean EDSS = 3.7) that became negative at the time of enrollment.

Early assessment (at 4 hours after IFN β injection) of specific mRNA biomarkers STAT1, Mx1 and TRAIL was more sensitive than the later measurements. Furthermore, the NAB positive group had significantly lower gene expression responses than the NAB negative. Five patients who were previously NAB positive and converted to negative had average responses lower than the persistent NAB negative patients on several genes, notably STAT1 and TRAIL but Mx1 responses were similar.

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FLOW CYTOMETRY IN MULTIPLE SCLEROSIS PATIENTS ON COMBINED THERAPY

Background

Besides of CD4⁺ T cells, CD8⁺ T cells, B cells and natural killer (NK) cells are participating in the immunopathologic process of multiple sclerosis (MS). High-dose intravenous methylprednisolone induces apoptosis in peripheral blood CD4⁺ T cells without significant reduction in the absolute number of CD8⁺ T cells or B cells. Upregulated expression of TRAIL marker in peripheral blood monocytes in interferon β (INF β) responders has been reported.

Objectives:

To determine the effect of continuous combined immunomodulatory-immunosuppressive (CCIMIS) therapy on peripheral blood mononuclear cells (PBMC).

Design and Methods:

Flow cytometry in 69 MS patients (17 individuals on Avonex monotherapy-30 mcg injection i.m. q week; 36 individuals on Avonex and prednisone-average dose less than 0.12 mg/kg per day; and 16 individuals on Avonex, prednisone and azathioprine-2 to 3 mg/kg per day) and 17 controls was performed. Monoclonal antibodies to seven antigens, CD3, CD4, CD8, CD14, CD16, CD19 and TRAIL, were used.

Results:

The annualized relapse rate in the MS patients on CCIMIS therapy with Avonex and prednisone was < 0.20 and in individuals on Avonex, prednisone and azathioprine (AZA) 0.44. CCIMIS therapy was associated with significant decrease in the absolute number of peripheral blood CD19⁺ cells and with increase in CD14⁺ and CD14⁺ TRAIL⁺ cells as compared to Avonex monotherapy and controls. Added-on AZA decreased CD16⁺ T cells cell count.

Discussion:

Physiologic dose of prednisone probably compensates in MS patients subclinical hypofunction of the hypothalamic-pituitary-adrenal axis. It decreases absolute B cell count and modifies the proportion of peripheral blood CD14⁺ and CD16⁺ T cells regardless of clinical and MRI findings.

Conclusion:

CCIMIS therapy using Avonex with prednisone and if indicated added-on AZA results in MS patients in superior clinical results as compared to Avonex monotherapy. Cytofluorometric findings may be prospectively used by adequately trained clinicians to adjust CCIMIS therapy in individual MS patients.

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CONTRIBUTION OF IL-21 IN AUTOIMMUNITY AGAINST NEUROANTIGEN

The cytokine interleukin (IL)-21 is closely related to IL-2 and IL-15, a cytokine family that uses the common gamma chain for signaling. IL-21 is expressed by activated CD4+ T cells. We examined the role of IL-21 in the autoimmune disease, experimental autoimmune encephalomyelitis (EAE), an animal model for human multiple sclerosis. IL-21 administration prior to induction of EAE with a neuroantigen, myelin oligodendrocyte glycoprotein (MOG) peptide 35-55 and adjuvant enhanced the inflammatory influx into the central nervous system as well as the severity of EAE. Autoreactive T cells purified from IL-21 treated mice transferred more severe EAE than did the control encephalitogenic T cells. No such effects were observed when IL-21 was administered after EAE progressed. Further studies demonstrated that IL-21 given before the induction of EAE boosted natural killer (NK) cell function including secretion of interferon-gamma. Depletion of NK cells abrogated the effect of IL-21. Therefore, IL-21, by affecting NK cells, has differential effects during the initiation and progression of autoimmune responses against neuroantigens.

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IMPROVING LEARNING AND MEMORY FOR FUNCTIONAL ACTIVITIES IN MULTIPLE SCLEROSIS

Research has indicated that many individuals with Multiple Sclerosis (MS) experience learning and memory difficulties, largely due to difficulty in the initial acquisition of information. Initial learning has been shown to be at the root of these memory deficits and, because of this, treatment focusing on improving the acquisition of information may improve the recall and recognition performance. The purpose of this study was to apply two strategies from cognitive psychology known to enhance new learning to functional tasks in persons with MS. One strategy, the *generation effect*, suggests that items that are self-generated by individuals are remembered better than items simply read or provided otherwise. The second strategy, the *spacing effect*, has indicated that information is better learned when trials are distributed over time (spaced presentation) compared to consecutive learning trials (massed presentation). The present study consisted of two experiments examining the generation effect and the spacing effect in improving activities of daily living. Each study employed a within-subjects design and included 20 participants with MS. In the generation effect experiment, participants engaged in two tasks examining functional abilities (e.g., preparing food and managing finance) under a generated condition and a provided condition. In the spacing effect experiment, the participants again engaged in two tasks designed to test functional abilities (route learning with a map and paragraph recall from a newspaper) were learned in a spaced trials manner and compared to similar tasks learned in a massed trials manner. Results from separate experiments demonstrated that material learned under "generated" conditions and "spaced" learning trials were better recalled and performed than material learned under "provided" conditions or using "massed" learning trials, respectively. Thus, these data indicate that cognitive interventions that integrate techniques to improve new learning may enhance performance of activities of daily living for individuals with MS.

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