Published in final edited form as:

J Neuroimmunol. 2008 March ; 195(1-2): 135–139. doi:10.1016/j.jneuroim.2008.01.016.

Membrane bound IL-15 is increased on CD14 monocytes in early stages of MS

Adi Vaknin-Dembinsky, Steven Brass, Roopali Gandhi, and Howard L. Weiner*

Center for Neurological Diseases, Brigham and Women's Hospital, Harvard Medical, School, Boston Massachusetts, 02115, United States

Abstract

IL-15 is a pro-inflammatory cytokine whose three-dimensional structure is similar to that of IL-2. IL-2 and IL-15 have similar as well as distinct biological functions. An active form of IL-15 that is membrane bound has also been described. Furthermore, IL-15 is known to play a role in autoimmune diseases. We thus investigated the expression of membrane bound IL-15 on monocytes (CD14+ cells) and studied its effect on T cell activation in MS patients. We found that unstimulated CD14+ cells from relapsing remitting MS patients had increased membrane bound IL-15. Those with high surface levels of IL-15 on monocytes were in the early stages of the disease. In addition, we found that T cells of MS patients had enhanced responsiveness to IL-15 and there was increased expression of IL-15 receptor on CD4+ T cells. Thus, IL-15 may be an important cytokine that drives Th1 responses early in the course of the disease and could serve as a target for immunotherapy and as an early marker in the immunologic staging of MS.

Keywords

Multiple sclerosis; IL-15; Monocytes

1. Introduction

IL-15 is a 14-kDa pro-inflammatory cytokine whose three-dimensional structure is similar to that of IL-2 and some biological functions of these cytokines are similar as well. For binding and signaling, IL-15 uses the γ and β subunits of the IL-2R as well as the specific IL-15R α chain (Giri et al., 1994; Giri et al., 1995; Grabstein et al., 1994). IL-15 mRNA has been detected in a variety of tissues and cells but its protein is produced mainly by peripheral blood monocytes, macrophages, dendritic cells, activated astrocytes and microglia (Waldmann and Tagaya, 1999). Like IL-15, IL-15 receptor (IL-15R) has a wide cellular distribution. It is expressed on T cells, B cells, macrophages, thymic cells, skeletal, lung and liver cells (Giri et al., 1995) which may indicate additional nonimmune functions as compared to IL-2 which is only expressed on immune cells (Tagaya et al., 1996).

Like IL-2, IL-15 induces T-cell proliferation and interferon-gamma (IFN- γ) production. In addition, IL-15 induces cytokine production by monocytes and polymorphonuclear cells (Carson et al., 1995). The main difference between IL-2 and IL-15 occurs in vivo. Whereas IL-2 signaling results in termination of lymphocyte responses, IL-15 is an anti-apoptotic cytokine (Bulfone-Paus et al., 1997). Despite the widespread expression of IL-15 intracellularly

as measured both at the protein and mRNA level, there are only low levels of IL-15 secretion both in vivo and in vitro. It has also been reported that under physiological conditions human monocytes constitutively express membrane-bound, biologically active, and IFN- γ inducible IL-15 (Musso et al., 1999).

IL-15 has been found to play a role in the pathogenesis of a variety of immune mediated diseases including rheumatoid arthritis, allograft rejection, sarcoidosis, and inflammatory bowel disease (Liu et al., 2000). IL-15 has chemoattractant properties in the synovial fluid of patients with active RA (Li et al., 1998; McInnes et al., 1996) and in collagen-induced arthritis in animals, administration of soluble IL-15R α prevented the disease (Ruchatz et al., 1998).

MS is an inflammatory demyelinating disease of the central nervous system felt to be T cell mediated autoimmune disease (Weiner, 2004). Pro-inflammatory cytokines such as IFN- γ , IL-12, IL-23 and IL-17 are believed to have an important role in the pathogenesis of MS. Although IL-15 appears to have an important role in the pathogenesis of a variety of inflammatory/autoimmune conditions, there are few studies on the production of IL-15 and its effect in patients with MS. It has been reported that MS patients have an increased number of peripheral blood mononuclear cells (PBMC) expressing IL-15 mRNA in the secondary progressive phase of the disease (Kivisakk et al., 1998) and augmented expression of IL-15 mRNA has been found in MS active plaques (Baranzini et al., 2000).

To investigate the potential role of IL-15 in MS, we measured membrane-bound IL-15 on monocytes in relapsing–remitting MS (RRMS) patients, the expression of IL-15R on T cells, and the effect of IL-15 on T cell proliferation and IFN γ production. We found an increase in both membrane bound IL-15 on monocytes and IL-15R on T cells, which contributed to raised IFN- γ release by IL-15 in MS.

2. Materials and methods

2.1. Subjects

Peripheral venous blood was obtained after informed consent from healthy subjects and MS patients. All patients were seen at the Partners MS Center at Brigham and Women's Hospital. We studied the following groups (1) Untreated relapsing–remitting MS patients (RRMS), $n = 35$, 30F/5M, average age 47.7 ± 11 years (means $\pm$ S.D.). None of the patients had received steroid treatment for 2 months prior to blood drawing or beta interferon 10 months prior to blood drawing. None were previously treated with glatiramer acetate. (2) Interferon-beta 1a treated RRMS patient's $n = 15$, 10F: 5 M, average age 44.7 ± 11.8 years (means $\pm$ S.D.). (3) 8 untreated secondary progressive patients (4F: 4 M, average age 48 ± 5.2 years, means $\pm$ S.D.). The control group consisted of healthy subjects, $n = 22$, 14F: 8 M, average age = 39 ± 11 years.

2.2. Cell separation and culture

PBMC were isolated from heparinized venous blood by Ficoll–Hypaque density gradient centrifugation (Pharmacia LKB Biotechnology, Piscataway, NJ). Separation of T cells from PBMC was performed by using negative depletion of non-T cells with a human T cell enrichment column (R & D Systems) according to manufacturer's instructions. The isolated T cells were re-suspended (10^6 cells/ml) in complete culture media consisting of RPMI 1640 (Whittaker Bioproducts, Walkersville, MD) supplemented with 10% fetal bovine serum, 4 mM-glutamine, 25 mM HEPES buffer, 100 u/ml penicillin and streptomycin (all from Whittaker Bioproducts) and incubated in a 96-well plates, 200 ul/well (Costar, Corning, NY). The effect of IL-15 stimulation on cell proliferation and IFN- γ production was studied by adding recombinant human IL-15 at different concentrations (0, 1, 10, 100 ng/ml). A fraction of culture medium was harvested 48 h after adding rhIL-15, to measure the production of IFN-

γ by ELISA. 1 μ Ci of [3H] thymidine (NEN, Boston, MA) was added to each well during the last 10 h of the culture to measure [3H] thymidine incorporation using a liquid scintillation counter.

2.3. Cytokine ELISA

Production of IFN- γ was measured in 72 h cell culture supernatants by ELISA. The protocols for IFN- γ ELISA are as described (Balashov et al., 1997). The sensitivity of IFN- γ ELISA was 31.25 pg/ml.

2.4. Flow cytometry

Membrane-bound IL-15 on CD14 cells and IL-15R on CD4 cells were measured by flow cytometry. PBMC were stained in U bottom 96 well plates (Costar, New York, NY) by APC conjugated mouse mAb directed against human CD14 and by FITC conjugated mouse mAb directed against human IL-15. IL-15R was measured by two-step staining using biotin labeled mouse anti-human IL-15R and biotin labeled mouse IgG. The second step used streptavidin conjugated to Phycoerythrin and FITC conjugated CD4 (PharMingen San Diego, CA). All incubations were carried out at 4 °C for 20 min in staining buffer and cells were washed twice between and after incubations.

Flow cytometric analysis of 10^4 cells from each sample was performed on a FACSort flow cytometer (Becton Dickinson) according to standard procedures.

2.5. Statistical analysis

Results are expressed as mean $\pm$ S.E.M. for each group. Statistical significance was calculated using Student's or Welch's *t*-tests. Correlation analysis was made using Pearson's correlation test.

3. Results

3.1. Membrane-bound IL-15 is increased on CD14 cells of MS patients

Although it has been reported that there are increased levels of IL-15 mRNA and IL-15 protein in PBMCs of MS patients (Kivisakk et al., 1998), the only physiologically active form of IL-15 is either the secreted form or the membrane bound form. Because secreted levels of IL-15 are extremely low, and the membrane bound form on CD14 cells is biologically active, we stained for IL-15 on CD14+ cells from MS patients and healthy controls. As shown in Fig. 1, we found significantly increased staining of IL-15 on CD14 cells from untreated relapsing remitting MS patients compared to healthy controls (membrane bound IL-15, RR=38 $\pm$ 5.6 vs. 8.7 $\pm$ 2.1 in healthy controls $p<0.001$; SP=12.64 $\pm$ 5.02, $P=0.37$ vs. healthy controls). Relapsing remitting, interferon beta treated patients ($n=15$), also had elevated levels vs. controls 44.85 $\pm$ 7.6 $p<0.001$ vs. control. Secondary progressive patients had membrane bound IL-15 levels that were not different from the healthy control group. We then examined the relationship between membrane bound IL-15 on CD14 cells and disability as measured by the Expanded Disability Status Scale (EDSS). As shown in Fig. 2 we found an inverse correlation between EDSS and percentage of membrane bound IL-15 ($R=-0.558$, $P<0.001$).

3.2. IL-15 activates T cells of RRMS patients more than T cells of normal individuals

Investigation of synovial fluid T cells in rheumatoid arthritis (RA) patients and T cells from inflammatory bowel disease (IBD) have demonstrated that T cells in these diseases have enhanced responsiveness to IL-15. To test this in MS, negatively selected T cells from RRMS patients and controls were stimulated with 1 ng/ml IL-15.

As shown in Fig. 3, we found enhanced proliferation with 1 ng/ml of IL-15 (1253 ± 987 vs. $11,003.4 \pm 6320$ $p < 0.001$; HD vs. MS). When we stimulated T cells with plate bound anti-CD3, we found no significant difference between RRMS patients and controls. Proliferation was not different between the MS patient group and the healthy controls. ($37,563$ vs. $34,653$ CPM, respectively). Activation of human T cells with IL-15 results in the production of IFN- γ and IFN- γ has been reported to have a pathogenic role in MS (Panitch et al., 1987). Therefore we investigated the effect of IL-15 on IFN- γ production by stimulating negatively selected T cells from RRMS patients with IL-15. As shown in Fig. 3, untreated RRMS T cells, when stimulated with IL-15 demonstrated significantly higher IFN- γ in the culture supernatants than those from control (316 ± 69 vs. 3628 ± 1835 $p < 0.05$; HD vs. MS). No difference was found in the secretion of IL-13, a Th2 type cytokine (not shown).

3.3. Increased expression of IL-15 receptor on CD4 T cells of MS patients

Our findings of increased activation of T cells by IL-15 as measured by higher proliferation and IFN- γ secretion, suggested that there might be increased IL-15R expression on T cells in RRMS (Fig. 4). Therefore, we stained for IL-15 receptor expression on CD4 cells of MS patients and normal controls. We found increased levels of IL-15 receptor on CD4 cells of both SPMS and RRMS patients compared to normal individuals. CD4 cells of RRMS patients has IL-15R = 14.87 ± 2.8 vs. 2.6 ± 0.66 in normal individuals ($p = 0.0014$). For SPMS, IL-15 = 32.66 ± 10.55 ($P < 0.001$ vs. control).

4. Discussion

MS is a presumed Th1 type inflammatory disease of the central nervous system. Several lines of evidence suggest that Th1 type responses play major role in the pathogenesis of MS (Sospedra and Martin, 2005; Weiner, 2004). Our group has reported that the percentage of monocytes producing the Th1 type cytokine, IL-12 is increased in MS patients and correlates with disease activity on MRI (Makhlof et al., 2001). We also showed that the levels of IL-18 positive T cells are higher in MS patients, especially in secondary progressive MS patients and that myeloid dendritic cells are activated (Karni et al., 2006; Karni et al., 2002). Recently a newly described subset of CD4 $^{+}$ T cells was described and was found to play a role in autoimmunity (Bettelli et al., 2007). We found an increased production of IL-17 in CD4 $^{+}$ T cells isolated from MS patients as compared to healthy controls (Vaknin-Dembinsky et al., 2006). It has recently been reported that IL-15 exacerbates collagen-induced arthritis with an enhanced CD4 $^{+}$ T cell response that produce IL-17 (Yoshihara et al., 2007).

IL-15 is a pro-inflammatory Th1 type cytokine that has been implicated in diverse inflammatory disorders such as SLE, sarcoidosis, RA, IBD, and organ transplantation (Agostini et al., 1996; Baranda et al., 2005; Liu et al., 2000; Turkowet al., 1997). In addition, IL-15 has anti-apoptotic and chemotactic activity on T cells and induces their polarization (Nieto et al., 1996). Being an anti-apoptotic cytokine and having a pro-inflammatory role, IL-15 signals could be involved in maintaining the memory T cell repertoire. However, the possible role of IL-15 in MS has been extensively investigated.

Pashenkov et al. have shown that IL-15 positive PBMCs are elevated in MS patients compared to healthy controls (Pashenkov et al., 1999). The studies done regarding the role of IL-15 in MS patients have focused on the intracellular staining of IL-15 and serum levels of IL-15. However, IL-15 is expressed and functions on the membrane of monocytes both as a membrane-anchored and as part of an IL-15/IL-15R α ligand/receptor complex (Van Belle and Grooten, 2005).

In this study we found increased expression of membrane bound IL-15 on CD14 cells of MS patients. These data support the concept that there is increased synthesis of IL-15 in MS and

correlates with the known fact of increased serum levels of IL-15 in MS (Rentzos et al., 2006). Interestingly, we found an inverse correlation between the membrane bound IL-15 and EDSS. As shown in Fig. 2, the lower the EDSS the higher the level of membrane bound IL-15. No correlation was found between T cell IL-15R expression and EDSS or between paired membrane-bound IL-15 and T cell IL-15R expression. Increased membrane bound IL-15 was found in both the untreated and treated MS patients groups. Thus, we believe that the levels of membrane bound IL-15, correlate more with disease staging than therapy. The fact that membrane bound IL-15 is not suppressed in patients on IFN-beta therapy suggests that it might be related more to stage of disease than to inflammation. Further research is needed including longitudinal studies, temporal relationship to relapses and gadolinium enhancement on MRI in order to use IL-15 as marker for disease staging. We also found an increase in IL-15 receptor (IL-15R) expression and an increased response to IL-15 by T cells of MS patients as detected by T cell proliferation and IFN- γ production. The enhanced proliferation and IFN- γ production can be explained either by increased expression of IL-15R or by enhanced downstream pathways stimulated by IL-15. We did not find differences between MS patient and controls in T cell proliferation using anti-CD3 stimulation. This suggests that there is not a generalized increase in the activation state of T cells in MS patients but changes that appear restricted to the IL-15 pathway. It is likely that either the increased expression of IL-15R is the main cause of the enhanced response to IL-15 or that both increased IL-15R and activated downstream pathways of IL-15 in MS T cells are linked to the enhanced proliferation.

Recently, Gonzalez-Alvaro et al. (2006) have found that activation of monocytes with IFN- γ increased the expression of membrane bound IL-15. Given the fact that MS patients have increased IFN- γ compared with normal individuals (Link et al., 1994), this may explain our finding of increased membrane bound IL-15 on monocytes of MS patients.

In summary, we have found that MS patients show increased in vivo IL-15, and have an increased response to IL-15, most probably as a result of increased expression of IL-15 receptor. Furthermore, we observed an inverse correlation between membrane bound IL-15 on monocytes of MS patients and their disability, which suggests that IL-15 may be a marker for immunological staging of MS by being linked to early stages of MS whereas other immunologic changes such as increased IL-18 and IL-12 production and activated dendritic cells are linked to the later progressive stages of the disease (Balashov et al., 1997).

Acknowledgements

This work was supported by funding through the National Institutes of Health Grant NS23132, the Nancy Davis Foundation and the Gruss Lipper Foundation.

References

- Agostini C, Trentin L, Faccio M, Sancetta R, Cerutti A, Tassinari C, Cimarosto L, Adami F, Cipriani A, Zambello R, Semenzato G. Role of IL-15, IL-2, and their receptors in the development of T cell alveolitis in pulmonary sarcoidosis. *J. Immunol* 1996;157:910–918. [PubMed: 8752945]
- Balashov KE, Smith DR, Khoury SJ, Hafler DA, Weiner HL. Increased interleukin 12 production in progressive multiple sclerosis: induction by activated CD4+ T cells via CD40 ligand. *Proc. Natl. Acad. Sci. U. S. A* 1997;94:599–603. [PubMed: 9012830]
- Baranda L, de la Fuente H, Layseca-Espinosa E, Portales-Perez D, Nino-Moreno P, Valencia-Pacheco G, Abud-Mendoza C, Alcocer-Varela J, Gonzalez-Amaro R. IL-15 and IL-15R in leucocytes from patients with systemic lupus erythematosus. *Rheumatol. (Oxford)* 2005;44:1507–1513.
- Baranzini SE, Elfstrom C, Chang SY, Butunoi C, Murray R, Higuchi R, Oksenberg JR. Transcriptional analysis of multiple sclerosis brain lesions reveals a complex pattern of cytokine expression. *J. Immunol* 2000;165:6576–6582. [PubMed: 11086101]

- Betelli E, Oukka M, Kuchroo VK. T(H)-17 cells in the circle of immunity and autoimmunity. *Nat. Immunol* 2007;8:345–350. [PubMed: 17375096]
- Bulfone-Paus S, Ungureanu D, Pohl T, Lindner G, Paus R, Ruckert R, Krause H, Kunzendorf U. Interleukin-15 protects from lethal apoptosis in vivo. *Nat. Med* 1997;3:1124–1128. [PubMed: 9334724]
- Carson WE, Ross ME, Baiocchi RA, Marien MJ, Boiani N, Grabstein K, Caligiuri MA. Endogenous production of interleukin 15 by activated human monocytes is critical for optimal production of interferon-gamma by natural killer cells in vitro. *J. Clin. Invest* 1995;96:2578–2582. [PubMed: 8675621]
- Giri JG, Ahdieh M, Eisenman J, Shanebeck K, Grabstein K, Kumaki S, Namen A, Park LS, Cosman D, Anderson D. Utilization of the beta and gamma chains of the IL-2 receptor by the novel cytokine IL-15. *Embo J* 1994;13:2822–2830. [PubMed: 8026467]
- Giri JG, Kumaki S, Ahdieh M, Friend DJ, Loomis A, Shanebeck K, DuBose R, Cosman D, Park LS, Anderson DM. Identification and cloning of a novel IL-15 binding protein that is structurally related to the alpha chain of the IL-2 receptor. *Embo J* 1995;14:3654–3663. [PubMed: 7641685]
- Gonzalez-Alvaro I, Dominguez-Jimenez C, Ortiz AM, Nunez-Gonzalez V, Roda-Navarro P, Fernandez-Ruiz E, Sancho D, Sanchez-Madrid F. Interleukin-15 and interferon-gamma participate in the cross-talk between natural killer and monocytic cells required for tumour necrosis factor production. *Arthritis Res. Ther* 2006;8:R88. [PubMed: 16684368]
- Grabstein KH, Eisenman J, Shanebeck K, Rauch C, Srinivasan S, Fung V, Beers C, Richardson J, Schoenborn MA, Ahdieh M, et al. Cloning of a T cell growth factor that interacts with the beta chain of the interleukin-2 receptor. *Science* 1994;264:965–968. [PubMed: 8178155]
- Karni A, Abraham M, Monsonego A, Cai G, Freeman GJ, Hafler D, Khoury SJ, Weiner HL. Innate immunity in multiple sclerosis: myeloid dendritic cells in secondary progressive multiple sclerosis are activated and drive a proinflammatory immune response. *J. Immunol* 2006;177:4196–4202. [PubMed: 16951385]
- Karni A, Koldzic DN, Bharanidharan P, Khoury SJ, Weiner HL. IL-18 is linked to raised IFN-gamma in multiple sclerosis and is induced by activated CD4(+) T cells via CD40-CD40 ligand interactions. *J. Neuroimmunol* 2002;125:134–140. [PubMed: 11960649]
- Kivisakk P, Matusevicius D, He B, Soderstrom M, Fredrikson S, Link H. IL-15 mRNA expression is up-regulated in blood and cerebrospinal fluid mononuclear cells in multiple sclerosis (MS). *Clin. Exp. Immunol* 1998;111:193–197. [PubMed: 9472681]
- Li XC, Roy-Chaudhury P, Hancock WW, Manfro R, Zand MS, Li Y, Zheng XX, Nickerson PW, Steiger J, Malek TR, Strom TB. IL-2 and IL-4 double knockout mice reject islet allografts: a role for novel T cell growth factors in allograft rejection. *J. Immunol* 1998;161:890–896. [PubMed: 9670967]
- Link J, Soderstrom M, Olsson T, Hojeberg B, Ljungdahl A, Link H. Increased transforming growth factor-beta, interleukin-4, and interferon-gamma in multiple sclerosis. *Ann. Neurol* 1994;36:379–386. [PubMed: 8080246]
- Liu Z, Geboes K, Colpaert S, D'Haens GR, Rutgeerts P, Ceuppens JL. IL-15 is highly expressed in inflammatory bowel disease and regulates local T cell-dependent cytokine production. *J. Immunol* 2000;164:3608–3615. [PubMed: 10725717]
- Makhlof K, Weiner HL, Khoury SJ. Increased percentage of IL-12+ monocytes in the blood correlates with the presence of active MRI lesions in MS. *J. Neuroimmunol* 2001;119:145–149. [PubMed: 11525812]
- McInnes IB, al-Mughales J, Field M, Leung BP, Huang FP, Dixon R, Sturrock RD, Wilkinson PC, Liew FY. The role of interleukin-15 in T-cell migration and activation in rheumatoid arthritis. *Nat. Med* 1996;2:175–182. [PubMed: 8574962]
- Musso T, Calosso L, Zucca M, Millesimo M, Ravarino D, Giovarelli M, Malavasi F, Ponzi AN, Paus R, Bulfone-Paus S. Human monocytes constitutively express membrane-bound, biologically active, and interferon-gamma-upregulated interleukin-15. *Blood* 1999;93:3531–3539. [PubMed: 10233906]
- Nieto M, del Pozo MA, Sanchez-Madrid F. Interleukin-15 induces adhesion receptor redistribution in T lymphocytes. *Eur. J. Immunol* 1996;26:1302–1307. [PubMed: 8647209]
- Panitch HS, Hirsch RL, Haley AS, Johnson KP. Exacerbations of multiple sclerosis in patients treated with gamma interferon. *Lancet* 1987;1:893–895. [PubMed: 2882294]

- Pashenkov M, Mustafa M, Kivisakk P, Link H. Levels of interleukin-15-expressing blood mononuclear cells are elevated in multiple sclerosis. *Scand. J. Immunol* 1999;50:302–308. [PubMed: 10447940]
- Rentzos M, Cambouri C, Rombos A, Nikolaou C, Anagnostouli M, Tsoutsou A, Dimitrakopoulos A, Triantafyllou N, Vassilopoulos D. IL-15 is elevated in serum and cerebrospinal fluid of patients with multiple sclerosis. *J. Neurol. Sci* 2006;241:25–29. [PubMed: 16316662]
- Ruchatz H, Leung BP, Wei XQ, McInnes IB, Liew FY. Soluble IL-15 receptor alpha-chain administration prevents murine collagen-induced arthritis: a role for IL-15 in development of antigen-induced immunopathology. *J. Immunol* 1998;160:5654–5660. [PubMed: 9605172]
- Sospedra M, Martin R. Immunology of multiple sclerosis. *Annu. Rev. Immunol* 2005;23:683–747. [PubMed: 15771584]
- Tagaya Y, Bamford RN, DeFilippis AP, Waldmann TA. IL-15: a pleiotropic cytokine with diverse receptor/signaling pathways whose expression is controlled at multiple levels. *Immunity* 1996;4:329–336. [PubMed: 8612127]
- Thurkow EW, van der Heijden IM, Breedveld FC, Smeets TJ, Daha MR, Kluin PM, Meinders AE, Tak PP. Increased expression of IL-15 in the synovium of patients with rheumatoid arthritis compared with patients with Yersinia-induced arthritis and osteoarthritis. *J. Pathol* 1997;181:444–450. [PubMed: 9196444]
- Vaknin-Dembinsky A, Balashov K, Weiner HL. IL-23 is increased in dendritic cells in multiple sclerosis and down-regulation of IL-23 by antisense oligos increases dendritic cell IL-10 production. *J. Immunol* 2006;176:7768–7774. [PubMed: 16751425]
- Van Belle T, Grooten J. IL-15 and IL-15Ralpha in CD4+T cell immunity. *Arch. Immunol. Ther. Exp. (Warsz)* 2005;53:115–126. [PubMed: 15928580]
- Waldmann TA, Tagaya Y. The multifaceted regulation of interleukin-15 expression and the role of this cytokine in NK cell differentiation and host response to intracellular pathogens. *Annu. Rev. Immunol* 1999;17:19–49. [PubMed: 10358752]
- Weiner HL. Multiple sclerosis is an inflammatory T-cell-mediated autoimmune disease. *Arch. Neurol* 2004;61:1613–1615. [PubMed: 15477521]
- Yoshihara K, Yamada H, Hori A, Yajima T, Kubo C, Yoshikai Y. IL-15 exacerbates collagen-induced arthritis with an enhanced CD4+ T cell response to produce IL-17. *Eur. J. Immunol* 2007;37:2744–2752. [PubMed: 17823984]

Fig. 1.

Membrane-bound IL-15 is increased on CD14 cells of MS patients. Membrane bound IL-15 expression was measured by FACS analysis on CD14 cells of untreated relapsing remitting MS patients (RRMS), secondary progressive MS patients (SPMS), and healthy donors (HD). Each dot represents the percentage of membrane bound IL-15 of one individual. RRMS = 38 ± 5.6 , SPMS = 12.64 ± 5.02 and 8.7 ± 2.1 in HD $p < 0.001$ RRMS vs. HD.

Fig. 2.

Inverse correlation between EDSS and percentage of membrane bound IL-15. Examination of the relationship between membrane bound IL-15 on CD14 cells and disability as measured by the Expanded Disability Status Scale (EDSS) revealed an inverse correlation between EDSS and percentage of membrane bound IL-15 ($R=-0.558$, $P<0.001$).

Fig. 3.

IL-15 activates T cells of RRMS patients more than T cells of normal individuals. T cells from RRMS patients and controls were stimulated with and without IL-15. Enhanced proliferation and IFN-g production of T cells from RRMS patients compared to controls with 1 ng/ml of IL-15 (CPM; 1253 ± 987 vs. 11003.4 ± 6320 $p < 0.001$; IFN-g; 316 ± 69 vs. 3628 ± 1835 $p < 0.05$; HD vs. MS).

Fig. 4. Increased expression of IL-15 receptor on CD4 T cells of MS patients than normal control. Increased levels of IL-15 receptor on CD4 cells of RRMS patients compared to normal individuals. CD4 cells of RRMS patients has IL-15R = 14.87 ± 2.8 vs. 2.6 ± 0.66 in normal individuals ($p = 0.0014$).