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Research Article

Increased IL-17 and IL-21 Receptor Levels in Children with Autism

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Abstract

Interleukin-17 is a cytokine which is associated with inflammation. It interacts with the IL-17 membrane receptor (IL-17R). Interleukin-21 (IL-21) is a cytokine released by by CD4+ helper T cells. The receptor for IL-21 (IL-21R) is embedded in the membrane of T, B and NK cells. In this study, we established the levels of 5 interleukin receptors (IL-1 RI, IL-2 Rg, IL-10 RB, IL-17R and IL-21R) in autistic individuals and controls using immune-array technology. We found that IL-17R and IL-21R were significantly higher in the autistic group. Since these receptors and their ligands are associated with inflammatory mechanisms, this is further evidence suggesting a role of inflammation in the etiology of autism. We also suggest that the presence of high levels of these receptors might serve as a diagnostic marker for some populations of autistic individuals.

Keywords: *Increased IL-17; IL-21 Receptor; Children with Autism*

Introduction

Interleukin-17 is a cytokine which is associated with inflammation [1]. It interacts with the IL-17 membrane receptor (IL-17R) [2]. IL-17 causes many other cytokines to be produced, including TNF alpha, prostaglandins such as PGE and chemokines including IL-8. Cells that produce IL-17 include epithelial cells and macrophages [2], and the receptor, IL-17R, is expressed on endothelial cells, peripheral B and T cells, fibroblasts, lung cells, myelomonocytic cells, and bone marrow stromal cells [6].

The Interleukin-21 cytokine is secreted primarily by CD4+ helper T cells. It signals natural killer (NK) and cytotoxic T cells to neutralize cancer and virally infected cells. It also stimulates cell division. The IL-21 receptor (IL-21R) is embedded in the membrane of NK, T and B cells [3,4].

Serum IL-17A levels are elevated in autism and correlate with the severity of disease [5]. After maternal inflammation, cognitive and behavioral deficits related to ASD may emerge, and may be associated with IL-17. This inflammation effect cell division through intracellular enzymatic cascades. These effects can have significant consequences during cortical development associated with neural function [7].

Studies have shown individuals with autism also have increased IL-21 and IL-22, as well as decreased CTLA-4 expression on $CD4^+$ T cells [8,9].

In this study, we used immune-array technology to measure five interleukin receptors and found that IL-17 and IL-21 receptor levels were significantly elevated in individuals with autism. These findings confirm a strong role of inflammation in autism and may serve to be markers for diagnosis of certain populations of autism.

Methods

Subjects

Plasma tumor necrosis factor receptor superfamily members were measured in 27 (20 male mean age 10.6 years) autistic children and 22 age similar normal controls (17 male mean age 13.2 years). Plasma samples were obtained from the Autism Genetic Resource Exchange (AGRE)[1].

This study was approved by the IRB of the Health Research Institute[2].

Plasma

Plasma was obtained frozen and placed immediately at -7^{0}C before assayed.

Immuno-array assays

Immuno-array assays, were performed as previously described [12], by RayBiotech, Inc, Peachtree Corners, GA. 30092.

Statistics

T-tests with 95% confidence levels were used for statistical analysis.

Results

In this study, we established the concentration of 5 interleukin receptors (IL-1 RI, IL-2 Rg, IL-10 RB, IL-17R and IL-21R) in 27 individuals with autism, and 22 non-autistic, neurotypical controls using immune-array technology, We found that 2 of the receptors, IL-17R and IL-21R were significantly higher in the autistic group, whereas the other three were not different than the receptor concentrations of the controls (Figure 1 and 2).

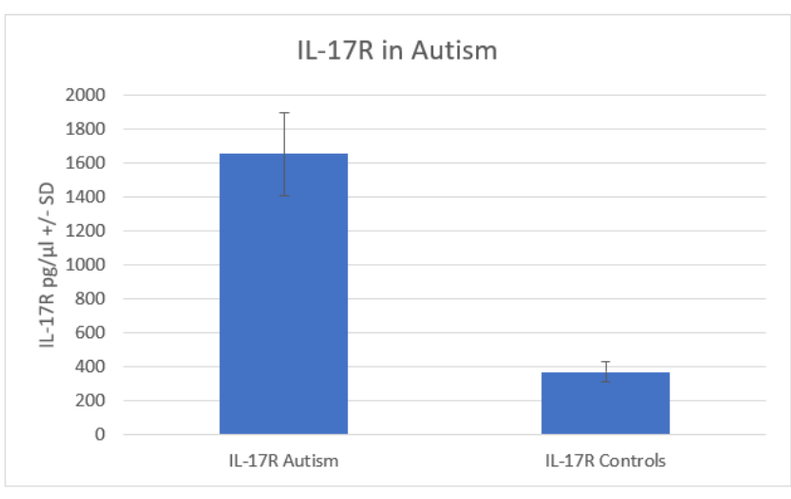

Figure 1: *IL-17 receptor concentration is significantly higher in the autistic group (1651.5 pg/µl +/- 246.4) compared to neurotypical controls (369.7 pg/µl +/- 60.9) (p = 0.03).*

[1]We gratefully acknowledge that all autism family serums were provided by the Autism Genetic Resource Exchange (AGRE) Consortium and the participating AGRE families. The Autism Genetic Resource Exchange is a program of Cure Autism Now and is supported, in part, by grant MH64547 from the National Institute of Mental Health to Daniel H. Geschwind (PI).

[2]The Health Research Institute is a treatment center, as well as a research institute, specializing neurological diseases such as autism.

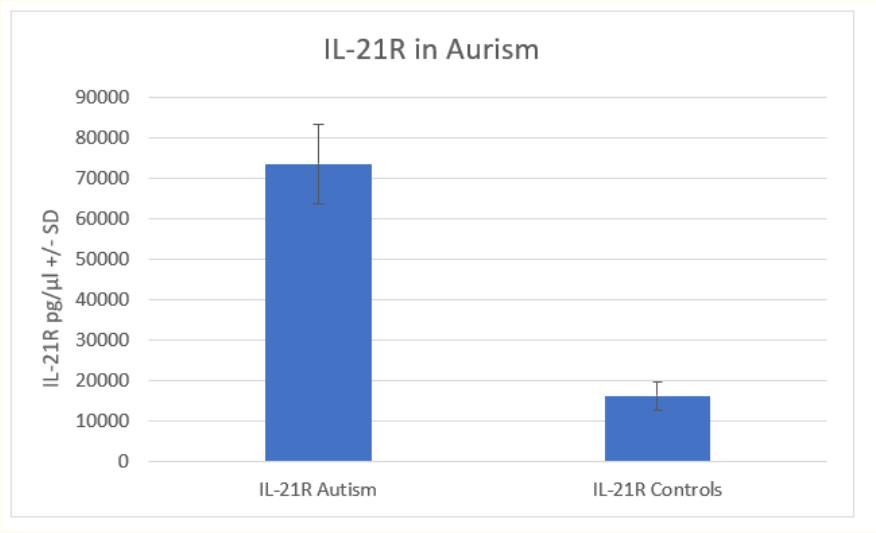

Figure 2: *IL-21 receptor concentration is significantly higher in the autistic group (73572 pg/µl +/- 9803.2) compared to neurotypical controls (16279.4 pg/µl +/- 3415.3) (p = 0.02).*

Discussion

The cytokine receptor Interleukin-17 (IL-17R) interacts with the proinflammatory ligand, IL-17A, a member of IL-17 cytokines which are produced by T helper 17 cells (Th17) [10].

High levels of IL-17R has been observed in hematopoietic, bone marrow, thymus, and spleen tissues. The receptor, IL-17R, is found on CD8+ T cells, and at low levels in the intestines and lung tissues. This receptor increases in the presence of the cytokines, IL-15 and IL-21. The receptor, IL-17R may move inside of cells after binding IL-17A [11].

Binding of IL-17R initiates the MAPK (mitogen-activated protein kinases) pathways [12], which results in the release of inflammatory cytokines such as TNFα, and chemokines, which drive infiltration of macrophages and antimicrobial products such as defensins and mucins [13].

Over activation of IL-17R by IL-17A contributes to the etiology of several autoimmune diseases, such as psoriasis or rheumatoid arthritis [14].

Interleukin 21 binds to IL-21R. This receptor transduces the growth promoting signal of IL21 and is important for the proliferation and differentiation of T cells, B cells, and natural killer (NK) cells [15].

The dysfunction of T helper 17 (T_H17) cells may be associated with the etiology of some inflammatory and autoimmune diseases [16]. It has also been suggested that these cells and their cytokine mediators may also play a role in the etiology of ASD. For example, elevated interleukin-17a (IL-17a) has been found in a subset of autistic children [17,18], and IL-17a may be required for induction of ASD-like phenotypes in offspring in a mouse model [19].

This study supports the hypothesis that IL-17 and IL-21 may be associated with the etiology of autism through elevated receptors (IL-17R and IL-21R) for these cytokines.

Conclusion

Our data shows that IL-17 and IL-21 Receptors are significantly higher in individuals with autism. Since these receptors and their ligands are associated with inflammatory mechanisms, this is further evidence suggesting a role of inflammation in the etiology of autism. We also suggest that the presence of high levels of these receptors might serve as a diagnostic marker for some populations of autistic individuals.

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