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Research Article

Increased Tumor Necrosis Factor Receptor Levels in Children with Autism

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Abstract

The TNF receptor superfamily help control many biological functions. In this study, we used immune-array technology to measure the concentration of 40 different receptors, including four as tumor necrosis factor receptor superfamily members in a group of individuals with autism and a group of neurotypical controls.

This data demonstrates that all four of the TNF receptors are significantly higher in this group of autistic individuals. Since abnormal concentration of TNF and/or its receptors are associated with immune dysfunction this data supports the hypothesis that immune system abnormalities are associated with the etiology of autism.

Keywords: *Tumor Necrosis Factor Receptor; Children; Autism*

Introduction

The TNF receptor superfamily., consisting of 19 ligands and 29 receptors help control many biological functions, including cell death, immune system homeostasis and cancer cell regulation [1].

Tumor-necrosis factor receptor (TNFR) superfamily member 4-1BB (CD137, ILA, TNFRSF9), originally was found to be a stimulatory molecule for the activation of T cells [2]. It promotes $CD8^+$ T cell survival and regulates the cell cycle, possibly by enhancing both glucose metabolism and fatty acid oxidation [3].

BCMA (TNFRSF17) is a cell surface receptor of the TNF receptor superfamily which recognizes B-cell activating factor (BAFF) [4]. This receptor is found on mature B lymphocytes and is associated with B cell development and autoimmunity [5]. BAFF, one of the ligands for BCMA, initiates inflammation and thereby unhealthy adipose cell formation. This may lead to enhanced insulin resistance. Therefore, BAFF may be a target for diabetes therapy [6].

DR6 (Death receptor 6), or tumor necrosis factor receptor superfamily member 21 (TNFRSF21), activates the NF-κB and JNK pathways [7] and may be involved in brain neurodegeneration of Alzheimer's disease. It may also be associated with signal transduction in cell

survival [8]. IRE1 (inositol requiring enzyme-1), a major enzyme associated with endoplasmic reticulum stress, when inhibited, modifies the effect of glucose deprivation on TNFRSF21 also suggesting a role for DR6 in glucose metabolism [9].

OPG (Osteoprotegerin), or osteoclastogenesis inhibitory factor (OCIF) or tumour necrosis factor receptor superfamily member 11B (TNFRSF11B), is encoded by the *TNFRSF11B* gene [10] has been associated with abnormal insulin levels in patients with type 2 diabetes [11].

In this study, we used immune-array technology to measure the concentration of 40 different receptors, including four as tumor necrosis factor receptor superfamily members in a group of individuals with autism and a group of neurotypical controls.

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 and neurotypical controls (17 male mean age 13.2 years). Subject plasmas were obtained from the Autism Genetic Resource Exchange (AGRE)[1].

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

Plasma

All plasma was received frozen and immediately placed at -70°C before Immunoassay analysis.

Immuno-array assays

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

Statistics

Statistical analysis was done using T-tests with 95% confidence and Pearson Moment for correlations.

Results

In this study, we measured the concentration of 40 different receptors in 27 individuals with autism, and 22 non-autistic neurotypical controls using immune-array technology. We found that all 4 of the above TNF receptors were significantly higher in the autistic group.

[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 clinical center and research institute, specializing neuro-behavioral disorders, including autism.

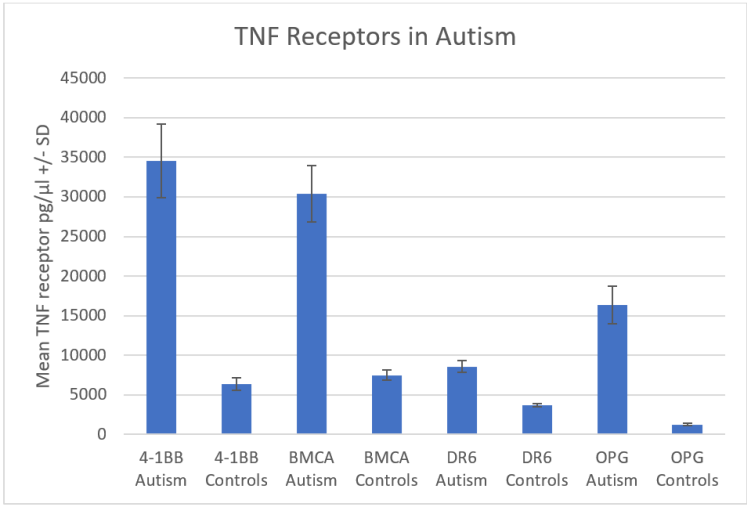

Figure 1: *Mean 4-1BB concentration was significantly higher (34550 +/- 4687 pg/µl) compared to neurotypical controls (6375 +/- 828 pg/µl) (p=0.0048). Mean BCMA concentration was significantly higher (30382 +/- 3558 pg/µl) compared to neurotypical controls (7492 +/- 624 pg/µl) (p = 0.0028). Mean DR6 concentration was significantly higher (8589 +/- 766 pg/µl) compared to neurotypical controls (3698 +/- 154 pg/µl) (p = 0.003). Mean OPG concentration was significantly higher (16359 +/- 2403 pg/µl) compared to neurotypical controls (1244 +/- 145 pg/µl) (p = 0.003).*

Discussion

Since the TNF family of receptors have been implicated in inflammatory responses, these data support the role of inflammation and the immune response in autism. This data (Figure 1) supports the finding of others who have found that levels of TNFα and its receptors are higher in individuals with autism [13,14]. Studies have also shown that impairments in autistic are strongly correlated with altered immune profiles [15]. This data shows that four different TNF receptors are significantly increased in individuals with autism.

TNFRs differ in their structural domains and therefore have unique intracellular signals. Reports demonstrate that T cell signaling is altered in children with ASD [16], suggesting that changes in pathways such as the mTOR pathway signaling may lead to altered immune activation. This supports our earlier findings that mTOR levels are also increased in individuals with autism [17] and may therefore be involved in altered immune response.

Abnormal proinflammatory and immunoinflammatory factors have been found in individuals with autism. Although the reasons are not completely understood, the pathophysiology of autism may be associated with elevated inflammatory factors such as TNF alpha [18,19].

Improved autistic symptoms have been shown to be associated with reduced levels of TNF [20].

Anti-TNF alpha therapies has been successful in reducing inflammation in diseases such as Inflammatory Bowel Disorder and Ulcerative colitis. If reducing inflammation is associated with reduced symptoms in individuals with autism, it is conceivable that anti-TNF alpha and/or anti-TNF alpha receptor may improve autistic behaviors.

Conclusion

In these experiments we found that the concentration of all four of the TNF receptors were significantly higher in the autistic group. Since abnormal concentration of TNF and/or its receptors are associated with immune dysfunction this data supports the hypothesis that immune system abnormalities are associated with the etiology of autism.

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