Oxidative Stress and Immune System Dysfunction in Autism Spectrum Disorders

Autism Spectrum Disorders (ASD) represent a group of neurodevelopmental disorders associated with social and behavioral impairments. Although dysfunctions in several signaling pathways have been associated with ASD, very few molecules have been identified as potentially effective drug targets in the clinics. Classically, research in the ASD field has focused on the characterization of pathways involved in neural development and synaptic plasticity, which support the pathogenesis of this group of diseases. More recently, immune system dysfunctions have been observed in ASD. In addition, high levels of reactive oxygen species (ROS), which cause oxidative stress, are present in ASD patients. In this review we will describe the major alterations in the expression of genes coding for enzymes involved in the ROS scavenging system, in both ASD patients and ASD mouse models. In addition, we will discuss, in the context of the most recent literature, the possibility that oxidative stress, inflammation and immune system dysfunction may be connected to, and altogether support, the pathogenesis and/or severity of ASD. Finally, we will discuss about the possibility of novel treatments, aiming at counteracting the interplay ROS/inflammation in people with ASD.

Animal research has rapidly advanced in recent years, and numerous models displaying many of the features characteristic of autism have been suggested (https://gene.sfari.org/). According to the AutDB database (http://autism.mindspec.org/autdb/Welcome.do, updated January 2020), 3145 animal models of ASD, including inbred, induced and genetic mouse models, are currently available. Genetic studies demonstrated that mutations in several genes coding for synaptic proteins, such as SHANK3 [2], NLGN3, NLGN4X [3], CNTNAP2 [4] and GABRB3 [3], are associated with ASD. Furthermore, ASD is syndromic with other neuropsychiatric conditions with single gene mutations including Fragile X syndrome (FMR1) [5], tuberous sclerosis (either TSC1 or TSC2) [2], Cowden syndrome (PTEN) [8] and Angelman syndrome (UBE3A) [9]. Interestingly, several genes associated with ASD, such as PTEN, TSC1 and TSC2, all involved in the phosphoinositide-3-kinase (PI3K) pathway, display immunoregulatory functions.

In this review, we first summarize recent literature discussing the contribution of oxidative stress to ASD. Taking advantage of a meta-analysis performed using the database dbMDEGA, we describe how genes involved in the ROS scavenging system are expressed in both ASD patients and mouse models of ASD.
addition, we will discuss about how oxidative stress may be linked to neuroinflammation, therefore contributing to an ASD-like phenotype. Finally, we will summarize the results of some studies, in which interventions using antioxidants as supplements or included in foods led to improvements in ASD symptoms.

It is becoming clearer how immune system dysfunctions may be associated with ASD. Indeed, impairments in both the innate and adaptive immune system support the onset of pro-inflammatory conditions, which may then lead to oxidative stress. In parallel, it is possible that the metabolism of several cell types (particularly brain cells) may be altered in ASD. In this way, oxidative stress may be promoted, which can then directly induce chronic inflammatory conditions. Thus, a strong connection between the immune system, inflammation and oxidative stress must be expected in ASD individuals. This opens up the possibility for novel treatments aiming at attenuating ASD-like behaviors in the patients. Many studies are currently investigating whether selected antioxidants present in plants, fruits and other foods may lead to improvements in the patients. In addition, dietary interventions are currently being planned in people with ASD. As oxidative stress and inflammation are strongly inter-connected, supplementation with anti-inflammatory drugs may additionally help in reducing the levels of oxygen radicals in the patients. As a proof of concept, the use of anti-inflammatory drugs has shown benefits in individuals with ASD [10]. Novel natural antioxidant and anti-inflammatory compounds must be tested in the clinic, in order to provide new weapons to fight against ROS/inflammation and immune system dysfunction in ASD in the best way. In addition, new strategies that may consider oxidative stress as a biomarker for the diagnosis and prognosis of ASD must be implemented.

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Keywords

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