Communication

Prospect on Damage Control in Current ASD Intervention

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Prospect on Damage Control in Current ASD Intervention

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Abstract: After decades of studies, the pathogenesis of Autism Spectrum Disorder (ASD) remains unclear and there still lacks effective treatment strategies for core symptoms. Our recent work [1,2], combined with others' research in a diversity of models and clinical trials [3], suggested a concise, but potentially rational theory that can illustrate the key of the pathogenesis and treatment of ASD from the aspect of damage control.

Keywords: autism; immune stress; brain damage; damage control

1. Viewpoint: Brain Damage Is Crucial for ASD Development, Consequently Damage Control Is Important for ASD Intervention

During the process of internal or external risk factors causing autism core symptoms, immunological, oxidative and nitrosative stress in brain were excessively activated and induce molecular and cellular abnormalities, which we termed as brain damage.

The development of ASD is intricately linked to the progressive accumulation of brain damage, which accumulates and deteriorates gradually. It start at the molecular level, progress to the cellular level, and eventually damage brain function, leading to autistic core behaviors. At molecular level, the damage manifested as an overabundance of stress-related molecules, including IL6, TNFα or NO. At cellular level, it presented as aberrant autophagy, apoptosis and necrosis.

The damage is mainly non-specific and stochastic. Majority of etiologic factors, including variations in low-risk and intermediate-risk genes, and various environmental factors like intestinal flora disorders and maternal immunity exposure, are most likely to affect ASD function related core neurons indirectly and non-specifically. The indirect routes begin by directly disturbing target neurons to activate excessive stresses, including immunological, oxidative and nitrosative stress, etc. in the surrounding environment. Changes in the local micro-environment trigger cascading effects and exacerbate the damage, thereby progressively and non-specifically impacting a broader spectrum of neurons, including ASD function related core neurons, which are directly implicated in the behavioral characteristic of ASD, specifically social avoidance and stereotyped repetitions.

Consequently, Damage Control, which impedes the accumulation and amplification of brain damage induced by developmental stresses, is crucial for preventing the progression of ASD.

2. Evidence: This Viewpoint Is in Line with a Lot of Clinical Observations

Thousands of risk factors could induce ASD-related neural abnormalities and subsequently triggering core behavioral characteristics, we think it is logical that they may share common pathogenesis routes. Current research implicate various stresses is the most likely common denominators, which presented as follows.

Many studies have demonstrated that ASD patients manifest chronic, sustained, and long-lasting stress reactions. Abnormalities in biochemical markers including high expression of

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inflammatory cytokins TNFα, IL-1β, IL-6, and IL-17A, chemokines MCP-1, CXCL1 and eotaxin, oxidative stress marker reactive oxygen species (ROS) and nitrosative stress marker NO [4], as well as abnormally elevated inflammatory activation of microglia in many brain regions, with high NF-κB expression [4].

Furthermore, interventions with small molecules such as minocycline, luteolin, pioglitazone [5], and others, can mitigate distinctive behavioral phenotypes, to some extent. Despite operating in distinct ways, these small molecule pharmaceuticals share a common capability of impeding stress responses.

3. Foresight: How this Viewpoint Inspire Fundamental Scientific Research and Clinical Intervention

From a fundamental scientific research perspective, it is essential to investigate the mechanism of ASD by individually analyzing each risk factors. From a medical point of view, considering the multitude and highly intricate nature of these risk factors, concentrate on identifying shared disease pathways and investigating effective interventions for the brain damage will be more advantageous to the patients.

Under the blueprint of this Viewpoint, ASD intervention involves two aspects: monitoring dynamic Damage Level and executing Damage Control.

In order to assess the dynamic damage level precisely, it is necessary to utilize a variety of biochemical markers, such as TNFα, IL-6, IL-1β, NO, and others. These markers provide insight into the stress status of various cells throughout the overall brain microenvironment, they also serve as an assessment of the effectiveness of Damage Control.

For Damage Control, prospective medication candidate includes minocyclin, luteolin and metformin, etc., which have potential mechanisms to inhibit excessive stress, regulate the homeostasis of brain cells, and consequently restrain the damage in local area. Utilization of a single type of medication or the cocktail of several medications necessitates a thorough study to determine which strategy yields more efficacious outcomes. Damage Control is complementary with currently main stream intensive behavior interventions, therefore the combination of both will optimize the effectiveness of the intervention.

Damage Control, unconsciously neglected by current ASD therapies, is crucial for ASD intervention as it will impede the accumulation of brain damage. There is a wide range of compounds that might be considered as potential candidates and are most likely to be safe. Consequently, implement of Damage Control will be of Low Risk and High Benefit to ASD patients.

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