Mitochondrial dysfunction in autism spectrum disorder

Autism spectrum disorder (ASD) affects ~2% of children in the United States. The etiology of autism spectrum disorder likely involves environmental factors triggering physiological abnormalities in genetically sensitive individuals. One of these major physiological abnormalities in children with autism spectrum disorder is abnormal mitochondrial function. This is very interesting since the mitochondria is very vulnerable to environmental factors, making it a key mediator of environmental-genetic interactions. We systematically reviewed the literature on human studies of mitochondrial dysfunction related to ASD to summarize the evidence for mitochondrial dysfunction in ASD.

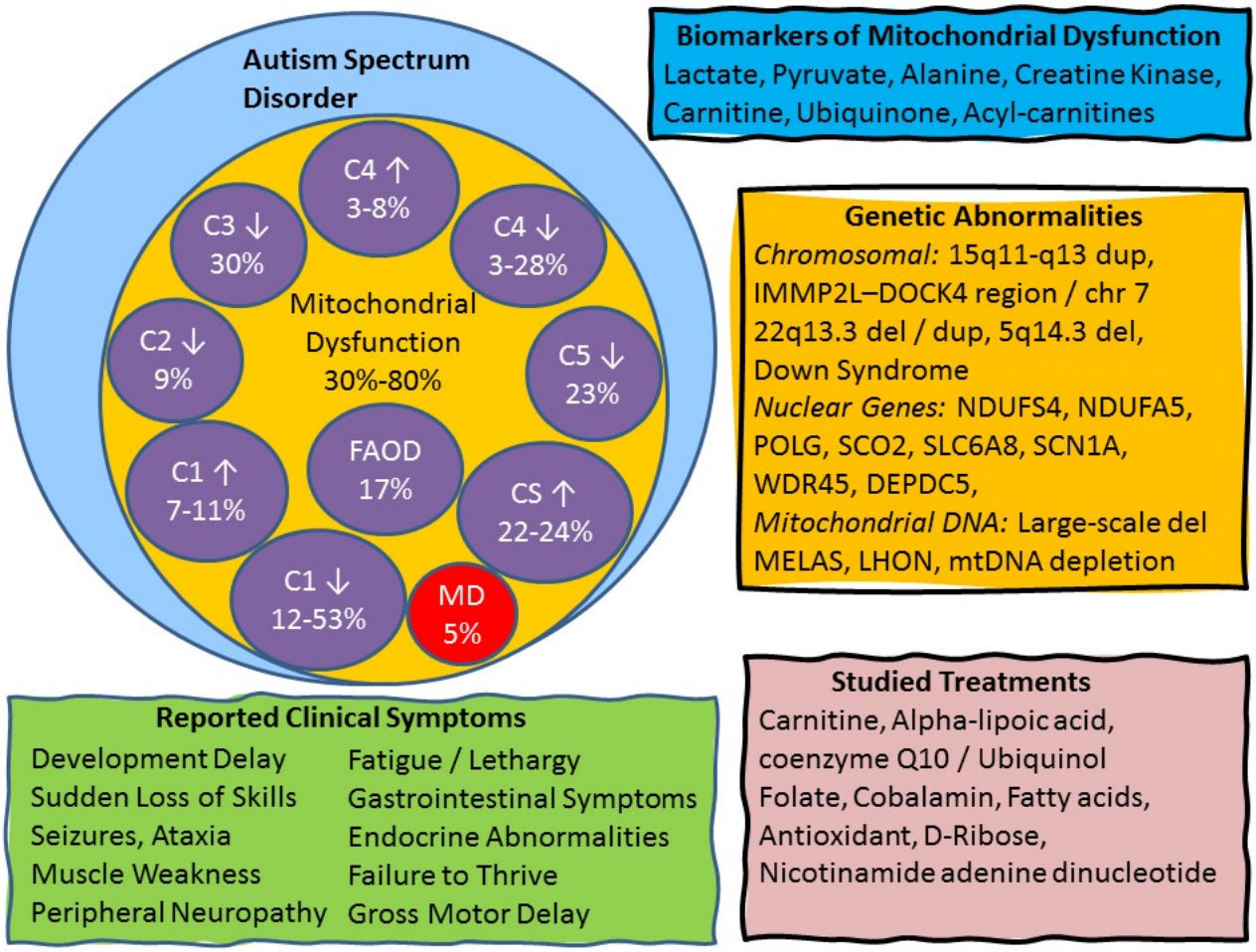

Fig. 1. Various aspects of mitochondrial dysfunction in autism spectrum disorder. From 30-80% of individuals with autism spectrum disorder have mitochondrial dysfunction. Several specific parts of the mitochondrial have been documented to be functioning abnormal in individuals with autism spectrum disorder; this includes frank mitochondrial disease (MD) both increase and decreased activity in electron transport chain (ETC) complex I (C1) and IV (C4), increased activity in citrate synthase (CS), decreased activity in ETC complex II (C2), III (C3) and V (C5) as well as fatty acid

oxidation defects (FAOD).

Figure 1 depicts some of the major findings of the review. In general, mitochondrial dysfunction effects from 30-80% of children with ASD with different types of mitochondrial dysfunction documented, including frank mitochondrial disease (MD), abnormal activity, both increased and decreased, of electron transport chain complexes 1-5 (C1-5) as well as fatty acid oxidation defects. Clinical aspects of mitochondrial dysfunction in ASD include gastrointestinal symptoms, seizures, motor delays, fatigue, lethargy and unusual neurodevelopmental regression, especially if triggered by an inflammatory event. Traditional biomarkers of mitochondrial dysfunction are most commonly documented to be abnormal in ASD but newer biomarkers are emerging. Chromosomal abnormalities, mutations in nuclear genes and both mutations and large-scale deletions in mitochondrial DNA have been reported in ASD. Interestingly, many of the chromosomal abnormalities and nuclear gene mutations seem to affect non-mitochondrial nuclear genes, suggesting that mitochondrial dysfunction in autism spectrum disorder may arise secondary to disturbances in cellular physiological processes not directly involving the mitochondria. In such cases, it is not clear whether the mitochondrial is simply being negatively affected by other dysfunction cellular processes or whether it has altered its activity to compensate for dysfunctional cellular processes. Promising studies have suggested that treatment targeting mitochondrial function may be helpful for individuals with ASD but most of these studies are small and preliminary and do not measure mitochondrial function directly.

Figure 2 shows some of the biochemical pathways and enzymatic machinery that has been found to be affected in the mitochondria of children with ASD. Environmental factors which have been associated with adverse effects on mitochondrial function in children with autism spectrum disorder including various toxicants, inflammation, microbiome metabolites and an oxidized microenvironment. The mitochondrial is important for may key physiological processes and is particularly important for supporting neuronal activity. As such, the consequences of mitochondrial dysfunction are both systemic and specific to particular organs or cellular processes. This is one of the reasons mitochondrial dysfunction can cause wide ranging symptoms and significantly affect multiple aspects of health.

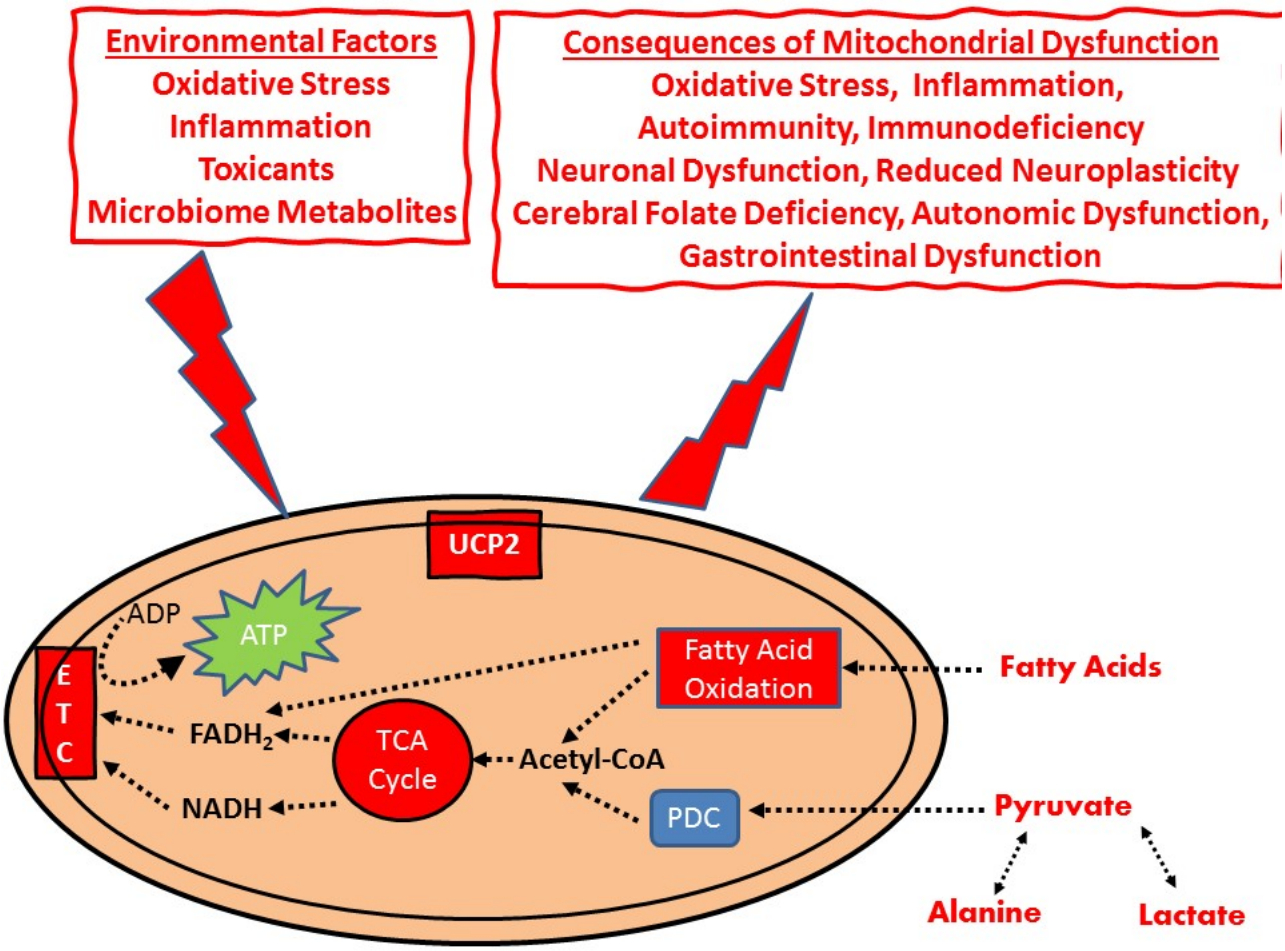

Fig. 2. Environmental factors can cause mitochondrial dysfunction and the consequences of mitochondrial dysfunction are significant. Metabolites and metabolic pathways that have been documented to be abnormal in individuals with ASD are highlighted in red. These include the Tricyclic Acid Cycle (TCA), the Electron Transport Chain (ETC) and the uncoupling protein (UCP2). PDC = Pyruvate Dehydrogenase Complex; ATP = Adenosine Triphosphate.

In most cases, the origin of why the mitochondria is dysfunctional is not clear since most cases are not associated with specific genetic abnormalities. Additionally, criteria for best defining mitochondrial dysfunction which does not rise to the level of mitochondrial disease has not been developed. Despite these limitations, it is very possible that the mitochondria could be a target for novel treatments and prevention strategies in individuals with ASD.

Richard E. Frye
Barrow Neurological Institute, Department of Neurology,
Division of Neurodevelopmental Disorders, Phoenix Children's Hospital, Phoenix, AZ, USA

Department of Child Health, University of Arizona College of Medicine – Phoenix, AZ, USA

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