Autism - Open Access
ISSN: 2165-7890

Woods et al., Autism 2013, 3:2
DOI: 10.4172/2165-7890.1000112

Research Article Open Access

Proteomics and Cholesterol in Autism

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Abstract

Autism Spectrum Disorder (ASD) diagnosis is increasing worldwide. ASDs are characterized by impaired social function, stereotyped behaviors/interests and communication deficits. ASD causes are poorly understood and treatments are largely limited to behavioral interventions once problems have developed and been detected. Here we discuss the potential use of mass spectrometry and proteomics in early diagnosis of ASD. The potential link between at least some subtypes of ASD, the cholesterol system and proteins that interact with cholesterol is also discussed.

Autism Spectrum Disorder (ASD)

ASD diagnosis is increasing worldwide. The estimated 2006 US prevalence was about 1 in 85 to 88 children; up 100% from 2002 [1], with similar prevalence in other world regions [2,3]. A recent survey has indicated that as many as 1/50 children have an ASD [4]. ASDs are characterized by impaired social function, stereotyped behaviors/interests and communication deficits [1]. ASDs are highly heritable [5] with numerous susceptibility genes identified [6]. Implicated genes include those associated with nervous system development and neurotransmitter systems [5,7,8]. Despite numerous genetic studies, ASD causes are poorly understood and treatments are primarily limited to behavioral interventions once problems have developed and been detected [1,9]. Early detection is key to prevent or reduce ASD symptom severity [9]. Genomic work provides critical clues, but full understanding of ASDs requires analysis of functional macromolecules. Such analysis can be accomplished using proteomics [10-33]. Therefore, proteomic profiling of human biomaterials from individuals with ASD and matched controls may ultimately aid in ASD treatment and diagnosis.

Proteomic Analysis of ASD

Proteomics is the study of the proteins using biochemical fractionation and mass spectrometry (MS) [13-15,19,20,24,34-40]. MS analyses are usually performed using Matrix Assisted Laser Desorption Ionization Mass Spectrometry (MALDI-MS) and/or nanoliquid chromatography-mass spectrometry (nanoLC-MS/MS) and the end result is the identification of a protein or a set of proteins [25,26,28,29,41,42]. In addition to qualitative information, MS may also provide quantitative information about a particular protein. Furthermore, characterization of post-translational modifications of proteins may also provide additional information, sometimes even more important than the protein characterization or quantification. For example, we have investigated N-linked glycosylation sites on the NXS/T sites in recombinant glycoproteins [26], disulfide linkages between cysteine residues in proteins [25,27] as well as alkylation of cysteine-less peptides using MS and proteomics [32]. Other investigators have identified dysregulations in protein phosphorylation [43] and acetylation [44] in ASD and fragile X syndrome, respectively. These post-translational modifications can potentially influence protein structure and function. In addition, such changes can be utilized as protein biomarkers and therefore present additional options beyond simply measuring protein presences, absence or levels.

Proteomic biomarker profiling has been applied to many diseases and disorders, but not as much to childhood developmental disorders, although there is clear potential for using these techniques to study ASD [45]. Unbiased examination of blood serum or other bodily fluids is one approach that can be used to identify putative candidates [45]. Protein analysis in ASD has already revealed altered levels of immune system-associated cytokines [46-49], growth factor changes [50-54] and neurotransmitter abnormalities [55,56]. Using MS, one group has found that complement proteins are dysregulated in children with ASD relative to non-ASD controls [17,18]. Recently, Taurines et al. [57,58] found differences in the protein content of sera taken from 16 children with ASD versus 16 age-matched normal controls using MALDI-MS but were not able to specify which proteins were altered. The researchers speculated that one of the proteins identified may be an apolipoprotein (APO), a cholesterol-carrying protein.

ASD and the Cholesterol System

Cholesterol is needed for brain development and is an important part of cell plasma membranes [59-61]. It regulates cell membrane permeability and is critical to the formation of synpases [59,62]. It is abundant in the brain, with 25% of all bodily cholesterol found there. Of brain cholesterol, about 70% is found in myelin, with the rest residing in neuron and astrocyte cell membranes [63]. Brain cholesterol is locally synthesized, which makes the function of APOs particularly important for recycling brain cholesterol and for maintaining brain homeostasis [63]. Proteomic analysis can help monitor these proteins, which seem to be dysregulated in ASD, potentially providing critical biomarkers for this disorder.

Previous research indicates that cholesterol and associated molecules (such as APOs) may indeed be altered in ASD [64]. For this reason, a large-scale clinical trial examining cholesterol supplementation on ASD symptoms has been initiated [65]. An investigation of ASD/non-ASD sibling pairs found dysregulated cholesterol metabolism-associated

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Received August 02, 2013; **Accepted** August 27, 2013; **Published** September 04, 2013

Citation: Woods AG, Wormwood KL, Wetie AGN, Ryan JP, Darie CC (2013) Proteomics and Cholesterol in Autism. Autism 3: 112. doi:10.4172/2165-7890.1000112

genes in those individuals with ASD [6]. Smith-Lemli-Opitz-Syndrome (SLOS) is characterized by a decline in cholesterol synthesis, and ASD symptoms are frequently found in individuals with SLOS, along with mental retardation, facial abnormalities, seizures and other problems [66,67]. SLOS symptoms improve slightly but incompletely with cholesterol supplements. In general, cholesterol supplementation is not an effective treatment for SLOS. Children who have ASD but not SLOS may additionally have relatively low total cholesterol [64]. Adults with ASD and intellectual disability appear to have significantly lower fasting blood glucose relative to controls, and according to one study also had significantly lower total cholesterol, although this difference was lost with statistical corrections [68]. Increased total cholesterol and low-density lipoprotein (LDL) cholesterol has been observed in Asperger syndrome, an ASD subtype identified in the prior DSM IV-TR but not the current DSM-5 (although retained in the ICD-10) [69]. Higher triglycerides (TG), lower high density lipoprotein cholesterol (HDL) and higher low density lipoprotein cholesterol (LDL)/HDL ratio was measured in boys with autism in comparison to boys who did not have autism [70]. The cholesterol carrying proteins, APO B-100 and APO A-IV, have been measured at higher levels in children with high versus low functioning autism [71]. APO A1, a critical component of cholesterol synthesis/metabolism, is present in neurons in the central nervous system [72,73] attesting to a possible role in cognition and mental processes. This APO may also be dysregulated in ASDs (our unpublished observations). Therefore, dysregulation of either cholesterol metabolism or of the levels of proteins involved in cholesterol metabolism may be responsible for the onset of ASD in children and/may serve as biomarkers for certain ASD subtypes. Further research into this area is warranted.

ASD and Cholesterol: Potential Link to Reelin

Numerous studies have supported the idea that alterations in the reelin gene and protein may contribute susceptibility to autism [74-78]. Reelin signaling is linked to cholesterol processing. APOE, cholesterol, reelin and APOE receptors control synaptic functions critical to cognitive processes, memory and behavior [79]. APOE acts in the Reelin signaling pathway, through competitive antagonism of reelin binding to APOE receptor 2 and to very-low-density lipoprotein receptors. Different APOE alleles may have different binding affinity, with the APOE2 protein variant displaying the lowest receptor binding affinity versus APOE3 and APOE4. According to one report, APOE2 alleles may be more commonly transmitted to autistic offspring over E3 and E4 alleles. The authors of this study speculated that the APOE2 allele may contribute to ASD vulnerability or may protect from the miscarriage and infertility that has been previously described for parents of children with ASDs [80]. The potential connection between reelin protein with cholesterol processing dysfunction in ASD supports the idea of combining studies on cholesterol homeostasis with studies on proteomics.

Conclusion

Proteomics could be successfully applied to analyze sera from children with ASD and matched controls that will hopefully identify new relevant serum biomarker candidates that can be used in early diagnosis of ASD and for directing children to an Early Intervention Program, or for identifying children, adolescents and adults and addressing their symptoms. Identification of a link between ASD and cholesterol metabolism, and brain regulatory proteins (such as reelin) may ultimately help treat individuals with ASD through dietary modifications or medications.

Acknowledgements

This work was in part supported by the David A. Walsh '67 Fellowship, awarded to KLW & CCD. This work was also supported in part by Mary Joyce, Robert Matloff, Ken Sandler and by the SciFund challenge contributors.

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