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Common sense paths follow brain injuries

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In this month's issue of the *Journal of Neuroimmune Pharmacology*, we are treated to a meta-analytical approach that attempts to identify common disease mechanisms and pathways for a number of complex, neurocognitive disorders. Borjabad and Volsky in, "Common Transcriptional Signatures from Patients with HIV-1 Associated Neurocognitive Disorder (HAND), Alzheimer's disease (AD) and Multiple Sclerosis (MS)", has used genome-wide microarray analysis of coordinated changes in CNS gene expression profiles from patients with HAND, AD, and MS (Borjabad and Volsky, 2012). This is a landmark study that examined published expression data from brain tissue from 32 studies that met relatively stringent criteria for inclusion in this analysis. Research in chronic, progressive neurologic disease is always hampered by the inherent challenges to study the disease organ (the CNS) and thus, much expression profile observations are on peripheral compartments such as blood or CSF that is much easier to obtain. However, the useful translation of these 'expression signatures' from blood or CSF (one form of biomarker discovery) to our understanding of CNS processes in these neurologic disorders is still unclear. Here, Borjabad and Volsky have used a more selected approach that focused exclusively on brain material from three clinically diverse disorders with distinct etiologies but perhaps sharing common neurodegenerative properties (Borjabad and Volsky, 2012). The goal was to determine if it would be possible through meta-analysis of large datasets to identify altered gene expression motifs that may suggest such common biological pathways shared among these disorders.

While all three diseases are complex, the findings from this approach has shown that there was significant overlap between HAND and AD transcriptomes and less so between HAND and MS. Overall, 35% of altered genes in the HAND brains were also dysregulated in the AD brain compared with only 13% in MS. This was further confirmed when analyzed as a functional categorization of gene families where HAND and AD had common dysregulations (again, more so than in MS) in a number of biological pathways responsible for defective neurocognitive functions. A more detailed pathway analysis reveals that 61% of the down-regulated pathways common to HAND and AD are associated with nervous system functions that include synaptic transmission, nervous system development, and neurocognitive processes. This was quite different when comparing HAND to MS where only 37% of the common pathways were reacted to nervous system function and 40% were related to basic cellular mechanisms. The authors suggest that collectively these results demonstrate that HAND and AD brains share a greater fraction of dysregulated genes and

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biological pathways (more associated with neuronal function) than do HAND and MS brains.

So what may be common among all three neurodegenerative conditions? While there were relatively few genes that were dysregulated in common with all three disorders (80 genes total), some of these down-regulated genes were linked to neuronal and especially synaptic functions and would be consistent with the shared neurocognitive impairment observed in HAND, AD, and MS. Genes that were upregulated were, surprisingly, mostly genes associated with immune response processes such as genes associated with response to external stimuli, inflammation, and innate immunity. Some of these genes include CD14, CD44, MHC genes class I and II, interferon response-related genes, and IL10RB. These are familiar players particularly for MS (Steinman and Zamvil, 2003) and HAND and more recently have been associated with other neurodegenerative disorders such as AD, Parkinson's disease and amyotrophic lateral sclerosis (ALS) (Letiembre et al., 2009). These observations nicely support the overarching goal of this study which is to identify genes associated with particular sets of dysregulated pathways that may play a role in a variety of neurodegenerative disorders, even beyond the three analyzed by Borjabad and Volsky (Borjabad and Volsky, 2012).

While it is tempting to interpret this study as a potential laundry list of known and novel sets of genes and pathways that may be shared (or unique) to any of the diseases in this report, the larger message here is to see the utility of this approach to use large data sets from multiple independent studies using genomic data and bioinformatic tools as a comparative approach to define commonalities that may be shared by neurodegenerative diseases. Similar meta-analytical approaches have been successfully used in genomic screens where, for example, a wide variety of autoimmune diseases including, MS, lupus, Crohns, familial psoriasis, type-I diabetes, clustering of autoimmune candidate loci from multiple autoimmune diseases and even murine model systems have identified common genes and pathways (Becker et al., 1998). Likewise, gene expression profiling (particularly challenging in the CNS) in a wide range of neurodegenerative conditions will certainly lead to a better understanding of common, shared, 'thematic' pathways, and mechanisms. Through analysis of common pathways the results presented in this article suggest that even though the three diseases in this study have different pathophysiology associated with a variety of etiological triggers, there may be commonalities in the shared neurodegenerative processes such as cognitive and behavioral impairments. This work strongly argues that there may be 'core' dysregulated pathways in the brains of patients with these diseases that could even be extended to other neurodegenerative disorders. As discussed by Borjabad and Volsky such information of putative shared processes of neuropathogenesis will enable the development of therapeutic interventional strategies for these neurodegenerative diseases that can benefit the large and ever increasing number of patients that suffer from these disorders (Borjabad and Volsky, 2012). Moreover, coupling this approach with complimentary genomic, epigenomic, and proteomic analysis (a more systems biology concept) (Noorbakhsh et al., 2009) will integrate large sets of data to better define mechanisms of disease pathogenesis, identify patients at risk for disease or progression, and perhaps allow for the optimization of disease modifying therapies tailored to the needs of the individual, the era of 'personalized medicine'.

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