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NEWS AND VIEWS

A landmark systems analysis of prion disease of the brain

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In a recent article in *Molecular Systems Biology*, Leroy Hood's group at The Institute for Systems Biology in Seattle and George Carlson's group at the McLaughlin Research Institute in Great Falls, Montana, presented a comprehensively annotated analysis of the initiation and progression of prion disease in the mouse (Hwang *et al*, 2009). This paper is likely to become a landmark in systems biology, both for its design and specific methods and for its novel findings.

Since the emergence of 'omics technologies,' global analyses of gene expression (mRNA) and proteins have yielded increasingly long lists of disease-associated molecules. Distinguishing true-positive from false-positive signals and organizing the findings into pathways, networks, and modules related to histopathological and clinical phenotypes in temporal and spatial dimensions is an overwhelming set of challenges. The task is quadrupled by the complexity of the brain, the peculiarities (if not mysteries) of the transmissible protein agents of prion diseases, and the variability in both prion properties and genetic make-up of infected organisms.

Remarkably, these problems were turned into levers to enhance the studies by Hwang *et al*. With two prion strains, characterized by different incubation times, and mice from six different genetic backgrounds, including strains with altered prion protein (PrP) expression levels, they set up a subtractive analysis that drastically reduced biological and experimental noise and focused on sets of genes reflecting the disease process in common across the host genotypes and infectious agent strains. They defined the pathological/clinical end point as 'disease incubation time' from inoculation at age 5 weeks to advanced clinical impairment, ranging from 56 to 392 days. Genome-wide analysis of gene expression in whole brain homogenates was performed over 8–10 time points, with 1–4 week time intervals adjusted to the wide range of incubation times.

From the massive amount of data accumulated, the authors extracted a core of just 333 genes that were differentially expressed in all five of the combinations involving mice with normal levels of prion protein (compared with 7400 genes differentially expressed in at least one of those five backgrounds). These 333 genes are presented as central to prion disease; 161 were mapped onto functional pathways using protein–protein interaction, metabolic, and signaling pathway information from public databases. Visualization of changes in gene expression in critical biological modules functioning in cellular and subcellular compartments over the months of disease progression provides a dynamic scheme for the processes that characterize the molecular conversion of benign prion protein (PrP^{C}) to disease-causing PrP^{Sc} isoforms accumulating in lipid rafts, followed by the three stages of neuropathology: synaptic degeneration, activation of microglia and astrocytes, and neuronal cell death.

There are many implications of this study. The same principle of interaction of host and infectious agent variation can be applied to eco-genetic systems analysis of other infections (tuberculosis, malaria, HIV, influenza, *Escherichia coli*, and so on). In fact, the concept can be generalized even further by considering infectious agents as an example of environmental and behavioral variable that act on genetic variation to modify risk and manifestations of disease. From the methodological point of view, the subtractive design adopted by Hwang *et al* is a powerful strategy to reduce biological and experimental/technical noise in large-scale data sets. Finally, the kinds of neuropathological responses appear to be limited, so other degenerative disorders, including forms of Alzheimer's disease, may activate the same molecular and cellular processes and express similar molecular signatures. For example, there are clues from altered cholesterol, sphingolipid, and glycosaminoglycan homeostasis that might justify proposing statins and other drugs for the prevention of both prion and Alzheimer's disease.

The primary data (http://prion.systemsbiology.net) will be a goldmine for secondary analyses by other researchers. Notably, 178 genes not previously associated with prion disease were identified among the 333 differentially-expressed, highly associated genes, including sets encoding functional modules for androgen, iron, and arachidonate/prostaglandin metabolism.

There are also limitations. Functional validation of the roles of specific genes and of identified modules in the definable

stages of disease progression must proceed beyond selective RT–PCR. At the system level, it will be interesting to investigate the functional and pathophysiological consequences of the dynamical changes in network architecture observed by the authors. They recognize that this study examined only the transcriptome. Epigenomics and miRNA analysis will inform gene regulation, and proteomics and metabolomics will confirm and reveal new downstream effector pathways and molecular targets for therapeutic and preventive interventions. Relevant regions of the brain could be compared, especially the thalamus where prion replication seems to start. Validation of the mouse model also must overcome a large experience that animal models are often quite different from the human disease.

An area for future research is the creation of mathematical models to describe the process and predict the dynamical behavior of genes, mRNAs, miRNAs, proteins, and metabolites in the disease process. Both approximate and rigorous modeling could be helpful in generalizing and predicting results. Qualitative applied mathematical methods are generally limited to three nonlinear differential equations, which are insufficient to characterize these complex systems; global sensitivity analysis, switching from mathematical to numerical analysis, should be more effective (S Schnell, personal communication; e.g. Chen *et al*, 2009). Determination of the kinetic parameters governing each step in prion activation and progression of disease would promote modeling of temporal and spatial dynamics (Kholodenko, 2006), whereas biochemical pathways can be reconstructed using mass action time series data from perturbed systems (Srividhya *et al*, 2007). The resulting networks can be queried for alignment, integration, and evolution (Sharon and Ideker, 2006). In this regard, tools such as those hosted at The National Center for Integrative Biomedical Informatics (http://ncibi.org) will be quite useful. In sum, the Hwang *et al* data set provides a valuable resource to apply such approaches in mammalian systems.

Future prion disease research will generate molecular explanations at the level of 3D structures, chemical modifications, and patterns of misfolding for the distinct strains of infectious prions with differences in sites of infection in the brain, duration of incubation, and other properties governing interactions with the host. At the practical level, brain-specific plasma markers for the core processes discovered here could become assays for testing asymptomatic cattle and people for prion infections.

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