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NEWS AND COMMENTARY

Huntington's Disease

A transcriptional report card from the peripheral blood: Can it measure disease progression in Huntington's disease?

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As the underlying molecular basis for genetically based neurodegenerative disorders such as Huntington's disease (HD) has been revealed, these diseases now present critical new challenges to workers in the field. While the development of effective interventions to limit or halt the inexorable progression of the disease process has become a central research focus, the ability to do accurate and efficient clinical trials has also emerged as a key rate-limiting step in the development of an effective clinical intervention.

Current functionally based measures of disease status and progression have limited sensitivity. A more directly biologically based measure of disease status and progression might significantly increase the power and reduce the time required for clinical trials for neurodegenerative disease. In a recent study, Borovecki *et al*[1] took a novel approach to this problem, by focusing their attention far from the primary site of pathology in HD, the brain, and instead looked to the peripheral blood, using DNA microarrays to identify a set of mRNAs that appeared useful as biomarkers to reflect disease status and progression for HD.

The rationale for their approach was that the Huntingtin protein is expressed in all tissues, including peripheral blood, and that one of the impacts of pathological Huntingtin is through alterations in the transcriptional apparatus. Perhaps pathological effects on peripheral blood transcription patterns are correlated with those found in the brain. If this was the case, then peripheral blood transcription patterns could serve as an easily measured surrogate for pathological effects in the brain.

Indeed, a study by Sawa *et al*[2] has suggested that lymphocytes from HD patients showed increased stress-induced apoptotic death. However, Borovecki *et al*[1] went further in their approach to the problem, suggesting that peripheral blood cells could serve as reporters of the clinical status of the patient's disease. Based on this reasoning, they isolated RNA from peripheral blood of HD patients at various stages of disease progression, presymptomatic HD patients, and normal controls, and did their analysis on two independent microarray platforms (Affymetrix and Amersham).

Hierarchical clustering algorithms reduced the complexity of the genome wide expression data set from more than 40 000 transcripts to 322, which revealed a striking pattern that clearly distinguished symptomatic HD patients from unaffected individuals. Importantly, presymptomatic individuals had patterns that were intermediate between the two extremes.

It would appear that microarray analysis of peripheral blood might provide a useful readout of clinical status. However, microarrays are not a practical tool for repeated measurements in a clinical setting. Perhaps with this concern in mind, Borovecki *et al*[1] turned their attention to further reducing the microarray data to a manageable subset of a dozen transcripts that could be quantified by QRT–PCR and still differentiate HD patients from controls, and the different stages of HD progression.

These transcripts now became the focus of the two most intriguing studies reported in the paper. First, they attempted to correlate the transcriptional profiling changes in peripheral blood with those in the brain. Indeed, upregulation was observed for seven of the 12 genes in pathological HD brain specimens compared with control brains. Could this mean that peripheral blood cell transcription patterns indeed reflect the pathology of transcription in the brain?

This may well be the underlying basis for the results, but this need not be the case. Peripheral blood cells may bring a transcriptional report of disease activity in the brain that is not mechanistically related to brain pathology in a direct manner. Could the transcriptional profile differences observed, for example, represent a component of a specific immune response to CNS pathology. Further work on this question will clearly be of interest.

Regardless of the mechanism which underlies the alterations in transcript profile, it is the second study reported by Borovecki *et al*,[1] which may be a harbinger of the future for clinical studies in HD. They superimposed a transcriptional analysis on a 4-week dose-finding study for the HDAC inhibitor phenylbutyrate. They found a small but significant decrease in the expression levels of the 12 marker set by QRT–PCR after 4 weeks of treatment with phenylbutyrate.

These results hold the promise for a direct, rapid and easily quantifiable readout for drug efficacy. However, much more needs to be performed before this promise could even be partially realized. The challenge here is to integrate measurements of mRNA level with more detailed longitudinal studies of HD progression as well as longer term studies of drug efficacy, which hopefully will include at least one agent which gives significant clinical benefit in HD.

A successful validation of the expression measurements in peripheral blood as a surrogate for measurements of pathology in the brain could have great value beyond HD, particularly if they can be extended to other neurodegenerative diseases and mechanisms of pathology such as in Parkinson's disease, Alzheimer's disease and Amytrophic Lateral Sclerosis■

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