The next step in Biomarker discovery. Linking genes to cells and disease processes involved in AD and DLB.

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Research question and background

The brain has many specialized functions, which require a large molecular and cellular heterogeneity. This complex organization of the nervous system is also reflected in neurodegenerative disorders, which often affect specific cell types or brain structures. In addition, the majority of these disorders exhibit multiple interacting pathological processes (e.g. neuro degeneration, inflammation), each with distinct cellular and molecular pathways. Neurodegenerative disorders like Alzheimer's disease and diffuse Lewy body disease (DLB), which shares pathogenic pathways with Parkinson's disease (PD), are affecting cortical and limbic brain structures causing progressive cognitive decline, loss of motor functions and have a huge impact on patients and their families. There is a great need for clinical tools to diagnose disease specific or common disease processes, monitor disease progression and treatment effects and ultimately therapies that intervene with disease specific or common disease processes.

Diagnostic and therapeutic biomarkers are biological molecules that can be used to identify disease processes, monitor disease progression and treatment effects or can be targets for (drug) treatment. The search for new biomarkers and therapeutic targets is dominated by high-throughput omics approaches. These approaches enable genome wide analysis of transcripts and proteins in healthy and disease-affected tissues. However, these quantitative techniques lack cellular resolution and do not provide information on the cellular (cell type) expression and subcellular (cellular compartments) distribution of proteins. The search for biomarkers in neurodegenerative disorders would greatly benefit from a large scale detailed mapping of the distributions of identified genes, linking target proteins to brain regions, cell types, molecular pathways and pathological processes. Furthermore, these long list of potentially interesting biomarkers lack filtering and contain many widely expressed genes unsuitable for any diagnostic or therapeutic strategy.

Methods and tissues used

We recently performed an RNAseq experiment comparing the transcriptome of the human cortex (frontal cortex) to 26 other organs and tissue types (manuscript under review). Based on this comparison we identified 24 genes which have a >50x higher expression in the cortex compared to any other tissue type (Highly-enriched), 316 genes with >5x higher expression in the cortex compared to any other tissue type (Enriched), 259 genes that are >5x higher expressed in the brain and 2-7 other tissue types (Group-enriched) compared to other tissue types and 510 genes that have >5x higher expression compared to the mean expression across 27 tissue types (Enhanced). These 1009 genes are non-housekeeping genes containing many genes involved in synaptic signaling and neurodevelopmental processes (gene ontology analysis). Matching this list of brain specific genes to results obtained from micro-array studies identifying altered gene expression in AD and cortical samples of PD resulted in a list of 185 brain enriched or enhanced genes with altered expression in the AD brain and 32 genes significantly up or down regulated in the cortex of PD patients. Interestingly 13 genes have altered expression in both disorders. The human protein atlas project (http://www.proteinatlas.org) has generated over 45,000 antibodies against more than 18,000 genes (>85% of the genome) with the goal to have at least 1 antibody against every human gene. This unique collection of antibodies against human targets opens new venues to investigate not only global changes in protein expression but also allows a much more detailed analysis of local cellular changes in protein expression and distribution associated with ongoing disease processes.

Results and conclusion

investigating the cellular and subcelluar distribution of previously identified biomarker candidates that that are highly expressed in the human cortex and identify changes in protein expression and distribution in the vicinity of ongoing disease process shared or specific for AD and DLB using an immunofluorescence and tissue micro array based approach. We are currently extending our panel of neurodegenerative disorders and will also include multiple

sclerosis, HIV-dementia, Parkinson’s disease, Huntington’s disease, stroke, traumatic brain injury and epilepsy.

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