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Early Diagnosis of Neurodegenerative Diseases – The Long Awaited Holy Grail and Bottleneck of Modern Brain Research – 19th HUPO BPP Workshop:

May 22–24, 2013, Dortmund, Germany

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Abstract

The HUPO Brain Proteome Project (HUPO BPP) held its 19th workshop in Dortmund, Germany, from May 22 to 24, 2013. The focus of the spring workshop was on strategies and developments concerning early diagnosis of neurodegenerative diseases

Keywords

Alzheimer; Brain; Brain Proteome Project; HUPO; Neurodegeneration; Parkinson

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The 19th HBPP workshop of the HUPO Brain Proteome Project Initiative (HUPO BPP) took place at the ISAS institute in Dortmund, Germany. More than 50 participants gathered

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at the magnificent lecture hall to discuss their latest developments in proteomics and pathology of neurodegenerative diseases. The initiative is the result of a global scientific community commitment to drive the analysis of the brain proteome forward.

After a warm welcome by Helmut E. Meyer, the psychiatrist Jens Wiltfang opened the workshop with a presentation about “Molecular biomarkers in Alzheimer’s disease”. Alzheimer’s disease (AD) is the most common cause of dementia. Current clinical approaches allow only a diagnosis at a late disease stage and currently available treatment is purely symptomatic. Therefore, biomarkers are essential for the development of early diagnostic tools, which could allow an early and sustainable therapy, preferably decades before the disease breaks out. Amyloid-beta (1–42), Amyloid-beta (2–42), total-Tau and phospho-Tau are the classical AD biomarkers in cerebrospinal fluid (CSF) analyses. Nevertheless, there is an urgent need for multiplex blood assays for early (predictive) diagnosis of AD. Jens Wiltfang also discussed the serious limitations faced by Alzheimer mouse models. It is a fact that Alzheimer mouse models do not recapitulate the complexity of AD genesis. Therefore, it is important for the world wide scientific community to use a suitable mouse model for the development of early diagnostic tools. A proper multigenetic Alzheimer mouse model is needed profoundly and should be developed as soon as possible. Further clinical aspects concerning biomarkers were discussed by Marcel Olde Rikkert while Lea T. Grinberg remarked on the role of acetylation of tau protein as an important step in AD and other tauopathy pathogeneses. There is strong evidence linking tau acetylation with tau inhibition and aggregation [1]. In addition to the established research on Tau and Amyloid-beta alternative hypotheses in AD pathogenesis become more and more popular and acceptance by the scientific community is growing constantly. Andreas Schrötter spoke about the underestimated autoimmune character of AD. Engelhardt and collaborators demonstrated that the injection of human IgGs from AD patients into the basal forebrain of living rats results in a loss of cholinergic neurons [2]. Giving special tribute to this work Schrötter and colleagues postulate that AD is a disorder with an autoimmune character which starts in the early phases of the lifespan. Furthermore Braak et al. [3] observed that neuronal damage of the different regions of the human hippocampus (CA1, CA2, CA3, fascia dentata) occurs in a time dependent matter, a process which might be also forced by an autoimmune reaction. The CA1 region is affected early, while the damage of the CA2, CA3 region and the fascia dentata is observed in a later state [3]). Taken all this together Schrötter and colleagues decided to analyse the content of these hippocampal regions of interest with a broad spectrum of classical biochemical methods and modern technologies like laser microdissection. They isolated the hippocampal brain regions of interest from human post mortem samples which were prepared by Helmut Heinsen and obtained valid data concerning the difference between these regions by performing a differential proteomic study with a label free LC-MS/MS approach combined with a couple of functional analyses. Thorsten Müller presented the potential Amyloid-Precursor-Protein intracellular domain (AICD) mediated pathways. There are convincing reasons that the AICD adapter protein FE65 plays a pivotal role in cell proliferation by modulating and interacting to nuclear proteins involved in DNA replication [4]. Elevated nuclear FE65 levels might increase cell proliferation potentially causing cell cycle re-entry and subsequently cell death in neurons. Thus, the delocalization of FE65 with increased nuclear enrichment might be causative for

neurodegeneration in AD. Gerd Schmitz discussed the role of platelets in AD, while Harald Prüβ deliberated on the general role of the NMDA receptor in neurodegeneration. Later in the course of the meeting, Young Mok Park showed the possibilities of quantitative proteomic in the analyses of murine hippocampi.

The second major topic of the workshop was the biogenesis and pathology of Parkinson's Disease (PD). Dirk Woitalla discussed problems with the interpretation of proteomic data and pinpointed out the significance of potential biomarkers and immunological processes in PD. In this line, Marcel Verbeek and Brit Mollenhauer presented there data regarding promising candidates for the development of clinical biomarker. Caroline May and Renata Leite are focused on the "spreading" aspects of the pathogenesis of PD. Therefore they have been analysing the proteomic profile of the different regions of interest and try to find specific targets for postulated antibodies which might induce a degradation of the substantia nigra. Konstanze Winklhofer presented her work regarding the neuroprotective role of Parkin. She discussed the stress-protective activity of Parkin dependent on NEMO (NF-κB essential modulator) and NF-κB. The E3-Ligase Parkin interacts with LUBAC (linear ubiquitin chain assembly complex) to increase linear ubiquitination of NEMO. As a result, NF-κB is activated, translocates into the nucleus and increases expression of OPA1 (mitochondrial guanosine triphosphatase) via NF-κB-responsive elements in the OPA1 promoter. OPA1 acts as a downstream mediator of Parkin that increases mitochondrial fusion and prevents apoptosis under cellular stress [5]. Zachary A. Miller shared his data regarding primary progressive aphasia (PPA). Each of the three variants of PAA results in different clinical symptoms and the underlying pathology is usually AD or an entity belonging to the FTLD (Frontotemporal Lobar Degeneration) spectrum. Semantic variant PPA seems to have unique associations with lateralization mechanisms in brain development and a high prevalence of related autoimmune disorders. Furthermore, the logopenic variant PPA has a unique association with developmental dyslexia. The shown results imply that neurodevelopmental factors may play a role in future neurodegenerative disease vulnerability, which could lead to new possibilities for prevention strategies. Daniel Martins-de-Souza presented new insight in FTLD proteomics [6]. He and his colleagues used shotgun mass spectrometry to characterize molecularly atypical cases of FTLD with fused in sarcoma inclusions (aFTLD-U) which have been recently described as part of the FTLD umbrella. aFTLD-U present early-onset (~35 years old) with uncertain prevalence and symptoms include disturbed social conduct and psychosis. The comparative analyses of three different brain regions – prefrontal cortex, cerebellum and occipital lobe – from aFTLD-U patients and controls yielded 107 differentially expressed proteins. Proteins associated to cellular transport were more prominently found in the prefrontal cortex, while energy metabolism proteins were found in the cerebellum and in the occipital lobe. Protein candidates were validated by selective reaction monitoring (SRM), an automated and sensitive multiplex proteomic platform. aFTLD-U proteomic findings presented similarities with AD findings, which may be related to neurodegenerative processes as well as to schizophrenia which may be related to psychotic states. Further studies of aFTLD-U and other FTLD subtypes are warranted, although this will require intensive biobanking efforts. The renowned anatomist Helmut Heinsen discussed the complexity of the human brain and shared his experience regarding the structure of this extraordinary organ. Predominantly he

pinpointed out that the different regions of the human brain are asymmetric and have to be analysed in a proper manner.

The final talks were given by Edson Amaro Jr. and Oliver Kraff. They showed modern applications of magnetic resonance imaging (MRI) and demonstrated the advantages and the disadvantages of a 7 Tesla MRI as a clinical diagnostic tool. The closing remarks were given by Helmut E. Meyer, Katrin Marcus, Young Mok Park and Lea T. Grinberg. They summarized the essence of the talks and gave a flashback about the past and an outlook of the coming meeting of the HUPO community. The next HBPP workshops will be during the 12th HUPO World Congress (14.–18.09.2013) in Yokohama, Japan and May 2014 in Honolulu, Hawaii, USA.

The following workshops are planned:

20^{th} HUPO BPP workshop in Yokohama, Japan, September 2013

21^{th} HUPO BPP workshop in Honolulu, Hawaii, USA May 2014

The HUPO BPP is an open project – thus, anyone interested in the project shall be welcomed cordially, and the latest information will always be publicly available at http://www.hbpp.org.

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References

1. Cohen TJ, Guo JL, Hurtado DE, Kwong LK, et al. The acetylation of tau inhibits its function and promotes pathological tau aggregation. Nat. Commun. 2011; 2:252. [PubMed: 21427723]
2. Engelhardt JI, Le WD, Siklós L, Obál I, et al. Stereotaxic injection of IgG from patients with Alzheimer disease initiates injury of cholinergic neurons of the basal forebrain. Arch. Neurol. 2000; 57:681–686. [PubMed: 10815134]
3. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991; 82:239–259. [PubMed: 1759558]
4. Schrötter A, Mastalski T, Nensa FM, Neumann M, et al. FE65 regulates and interacts with the Bloom syndrome protein in dynamic nuclear spheres – potential relevance to Alzheimer's disease. J. Cell. Sci. 2013
5. Müller-Rischart AK, Pilsl A, Beaudette P, Patra M, et al. The E3 ligase parkin maintains mitochondrial integrity by increasing linear ubiquitination of NEMO. Mol. Cell. 2013; 49:908–921. [PubMed: 23453807]
6. Martins-de-Souza D, Guest PC, Mann DM, Roeber S, et al. Proteomic analysis identifies dysfunction in cellular transport, energy, and protein metabolism in diffrent brain regions of atypical frontotemporal lobar degeneration. J. Proteome. Res. 2012; 11:2533–2543. [PubMed: 22360420]

Figure 1.
The participants at the 19th HUPO Brain Proteome Workshop in Dortmund, Germany.