SL1

Understanding Alzheimer pathophysiology: implications for clinical trials

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Alzheimer pathology is multi-faceted, including accumulation of Abeta as plaques and cerebral amyloid angiopathy, tau within neurons, microglial and astrocyte activation and loss of neurons and synapses. From a neuropathological perspective, usually at a single time point and often at the end stage of the disease, it is challenging to understand the cause and effect relationships between these components. There are at least four ways of trying to unravel these relationships. Firstly, studies at early time points show pathology begins years or decades before onset of dementia, and confusingly, seem to suggest different anatomical locations for initiation of Abeta and tau accumulation. Secondly, genetic studies demonstrate mutations that influence Abeta production, but not tau, can initiate AD; whereas genetic variants influencing risk for AD are mainly related to innate immunity and lipid metabolism. Thirdly, cause and effect studies in animal models are biased by models not fully replicating AD pathology. Fourthly, clinical trials of putative therapeutic agents may alter AD giving insights into cause and effect relationships. Most trials have targeted Abeta in established AD, mainly without evidence of functional benefit; the results of preventive trials are awaited. In this context, a sequence of Abeta accumulation followed by an inflammatory reaction which promotes tau accumulation and neurodegeneration explains much of the evidence. It is proposed that different therapeutic targets are required for different stages of the disease process: Abeta for primary prevention, inflammation for secondary prevention and tau for established disease.

SL2

Neuropathologic heterogeneity in autosomal dominant and late-onset Alzheimer disease

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Introduction: In the design of clinical trials, it has been proposed that autosomal dominant AD (ADAD) may be a useful model of the more frequent late-onset AD (LOAD). ADAD has a predictable age at onset, clinical course, and biomarker and neuroimaging trajectories, yet the neuropathology of these clinically well-characterized cohorts has not been systematically studied.

Methods: The Neuropathology Laboratory of the Knight Alzheimer Disease Research Center served as the single central laboratory for both DIAN and ADNI which enabled standardized neuropathologic assessments of all ADNI participants (n=63) who came to autopsy and participants (n=19) and family members (n=18) at DIAN sites. Histology included hematoxylin and eosin and immunohistochemistry was performed to detect four frequent molecular pathologies: Amyloid-beta (10D5; Eli Lilly), phospho-tau (PHF1; gift of P. Davies), phospho-alpha-synuclein (Cell Applications, Inc.), and phospho-TDP-43 (Cosmo Bio USA).

Results: Of 63 ADNI participants with AD dementia at expiration, 96% cases had AD neuropathologic change (ADNC); two cases had argyrophilic grain disease (AGD) and primary age-related tauopathy (PART). All 37 DIAN cases had florid ADNC at expiration. Twenty-two of 37 (59%) DIAN cases had diffuse Lewy body disease or amygdala-predominant Lewy body disease. In the ADNI cohort, 49% had Lewy body disease. Other comorbidities in LOAD included TDP-43 proteinopathy (30%), argyrophilic grain disease (19%), hippocampal sclerosis (8%), infarcts (5%), and aging-related tau astrogliopathy (14%). These comorbidities were absent in ADAD.

Conclusion: Both ADAD and LOAD have significant synucleinopathy (Lewy bodies) comorbidity in up to one half of cases. LOAD cases are distinguished from ADAD by the presence of age-related pathology. The presence of additional age-related pathologies in LOAD may indicate that a more complex therapeutic approach is required in this group in comparison with ADAD.

SL3

Methylation Profiling for Precision Diagnosis of Human Brain Tumors

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The WHO 2016 diagnostic approach to human brain tumors relies on morphological evaluation, immunohistochemistry and molecular tests focally targeting tumor specific alterations. Testing is mostly based on variations of FISH and DNA sequencing approaches. In a joint effort, teams in Heidelberg have explored the feasibility of different omics platforms for the classification of human brain tumors. Most stable throughout tumor progression proved methylome data, while genome and transcriptome data experience considerable change within an individual tumor. Therefore, we have established a classification system for brain tumors based on genome wide promoter methylation status.

2801 human tumor tissues forming a comprehensive reference group have been subjected to methylome analysis using 450K/850K-EPIC chips from Illumina. Unsupervised clustering or t-SNE analyses have been employed to identify methylation clusters. A tool named “the classifier” employing random decision forests has been developed and is updated on a regular schedule. The brain tumor classifier in its current version recognizes more than 80 different methylation groups. Approximately 5% of the tumors analyzed do not match to these groups and are expected to eventually be recognized as independent tumor entities pheno-copying established entities. In fact, several novel brain tumor entities have recently been identified mainly on grounds of their characteristic and unique methylation profile. The classifier is accessible to researchers at www.molecularneuropathology.com.

Within four years of testing the classifier has evolved an indispensable tool for the analysis of brain tumors in the Heidelberg research and diagnostic environment. Currently many diagnostic institutions are implementing the classifier because methylome based classification of human brain tumors adds decisively to the precision of diagnosis.

SL4

Molecular Mechanisms of Glioma Progression and Therapy Resistance

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Malignant gliomas are the most common primary intrinsic brain tumors. Despite aggressive multimodal therapy, including neurosurgical tumor resection, radiotherapy and chemotherapy with DNA-alkylating drugs such as temozolomide, malignant gliomas invariably progress and recur after first-line therapy. The present lecture will provide an overview of molecular mechanisms driving malignant progression, development of therapy resistance and tumor recurrence of malignant gliomas, in particular the most common type of IDH-wildtype glioblastoms. A particular focus will be placed on investigations of the genetic evolution of glioblastomas prior to and following treatment by large-scale molecular profiling of pairs of primary and recurrent tumors from individual patients using next generation sequencing of tumor genomes and transcriptomes. In addition, our ongoing studies on the role of non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), in glioma progression and therapy resistance will be presented. These studies cover molecular profiling of primary glioma tissue samples as well as functional analyses of selected lncRNA candidates using transient and stable knock-down glioma models, which are being characterized by cell biological assays, RNA sequencing and proteomics, In addition, the roles of candidate lncRNAs on glioma sensitivity to radiotherapy and temozolomide chemotherapy were determined in vitro and in orthotopic mouse models. These approaches identified and functionally characterized novel genetic and lncRNA-mediated pathomechanism that may contribute to clonal evolution and resistance to cytotoxic therapy of malignant gliomas.