Graduate Training Centre of Neuroscience

Lecture **GENETIC AND MOLECULAR BASIS OF NEURAL DISEASE I**

Winter Term 2018/2019

Mondays, 9:00–10:30 am / DZNE seminar room

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Exam period: Feb 11 – Mar 22
Brain Aging and Longevity (Overview) (Mathias Jucker)

Brain aging is the strongest risk factor for many neurodegenerative diseases such as Alzheimer’s disease or Parkinson’s disease. I shall give an overview about the age-related changes in the brain and the myth of neuron loss with normal aging. Rather than neuron loss, neural dysfunction and increased neuronal vulnerability are the cause of age-related cognitive dysfunction. Mechanisms of longevity are commonly investigated in model organisms such as yeast, C. elegans, flies and mice and implicate pathways that regulate growth, energy metabolism, and reproduction as key regulator of life span.

Literature:

Cerebral Proteopathies (Overview) (Mathias Jucker)

The misfolding and aggregation of specific proteins underlie most of the age-related neurodegenerative diseases. I shall summarize studies of structure and nucleation of amyloids and relate the findings to observations on amyloid polymorphism, amyloid strains, amyloid toxicity, and transmissibility of amyloids. A deeper understanding of the general principles of protein misfolding and aggregation may identify common therapeutic targets to alleviate the clinical manifestations of cerebral proteopathies.

Literature:

Genetics of Neurodegenerative Diseases (Overview) (Peter Heutink)

Genetic mutations are at the starting point of the biological processes that lead to disease and are therefore attractive leads for researchers studying neurodegenerative diseases. Over the past few decades the field of genetics has been very successful in identifying genes for familial forms of disease. In more recent years the focus has shifted to the more complex and multifactorial forms of disease. The lecture will discuss the main methods and successes of the past years and the exiting new developments that are quickly changing the way we do genetics.

Literature:
International Parkinson’s Disease Genomics Consortium (iPDGC); Wellcome Trust Case Control Consortium 2 (WTCCC2) (2011) A two-stage meta-analysis identifies several new loci for Parkinson’s disease. PLoS Genet 6:e1002142
Prion Diseases
(Mathias Jucker)

Prion diseases are remarkable neurodegenerative diseases because they can be not only of genetic or sporadic origin but are also naturally transmitted. The protein-only hypothesis posits that the pathogenic agent consists of protein and lacks any informational nucleic acids. Its main component is PrPSc, a conformational isoform of a normal cellular protein termed PrPC. Despite all great research efforts, both the physiological function of PrPC and the molecular pathways leading to neurodegeneration in prion disease remain only partially understood. I will give an overview on what has been identified as key steps in prion diseases and highlight some of the efforts made to elucidate the still unknowns of the prion protein.

Literature:

Alzheimer’s Disease
(Mathias Jucker)

Alzheimer’s disease is the best known ‘proteopathy’ with extracellular deposition of the β-amyloid protein (amyloid plaques) and intracellular accumulation of the tau protein [neurofibrillary tangles]. Mutations causing Alzheimer’s disease have been identified in the amyloid precursor protein gene (APP) and in the presenilins (PSEN1, PSEN2) and all such mutations promote the aggregation of the β-amyloid protein. I shall summarize the genetic, molecular and cellular basis of Alzheimer’s disease, outline the mechanistic similarities to the prionoses, and give examples of current experimental strategies to develop causal therapies.

Literature:

Hereditary Spastic Paraplegia (HSP)
(Ludger Schöls)

Motorneurons exhibit an extreme anatomy with axons up to 1 metre in length containing more than 99% of the cytoplasm. This makes motorneurons especially dependent on frictionless axonal transport, perfect structure of microtubuli and optimal membrane shaping. Hereditary spastic paraplegias are a group of degenerative diseases preferentially affecting motorneurons in the spinal cord. Over the past few years more than 50 genes causing HSP have been identified. This lecture will give insight into their function and pathophysiological mechanisms underlying HSP.

Literature:

Motor Neuron Diseases and Frontotemporal Dementia
(Manuela Neumann)
Abnormal intracellular protein aggregates comprise a key characteristic in most neurodegenerative diseases, including the most common form of motor neuron disease, amyotrophic lateral sclerosis (ALS), as well as frontotemporal dementia (FTD). Over the last years major progress was made in the molecular dissection of the pathogenesis of FTD and ALS, with identification of novel disease proteins and genes like TDP-43, FUS and C9ORF72 playing key roles in both diseases. These data provide molecular evidence that both conditions are related. Moreover, the striking functional and structural similarities of TDP-43 and FUS, which are both DNA/RNA binding proteins, imply that abnormal RNA metabolism is a pivotal event in disease pathogenesis. I will review the neuropathology and molecular basis of FTD and ALS.

Literature:

Parkinson’s Disease
(Thomas Gasser)

For many years, Parkinson’s disease (PD) has been considered to be a single disorder with characteristic clinical and pathologic features. Today we know that PD actually comprises a spectrum of etiologically heterogeneous disorders. A number of different molecular pathways have been implicated in the etiology of PD. Aggregation of abnormally folded α-synuclein appears to be a common if not indispensable feature of PD. Other presumably implicated pathways include a deficiency of the proteasomal protein degradation, oxidative stress, mitochondrial dysfunction and excitotoxicity. While in some rare monogenic forms of PD one of these pathways may be responsible in isolation, the vast majority of sporadic cases is likely to be caused by a complex interaction of genetic susceptibilities and environmental factors involving multiple pathways.

Literature:
Gasser T, Hardy J, Mizuno Y (2011) Milestones in PD genetics. Mov Disord. 26:1042-8
Lewy Body Dementia, Atypical Parkinsonian Syndromes and Other Neurodegenerative Movement Disorders
(Thomas Gasser)

Many of the symptoms of Lewy Body dementia (LBD) bear a striking resemblance to Alzheimer's or Parkinson's disease. However, the presence of aggregated α-synuclein containing Lewy bodies in both the mid-brain and cortex is the notable distinguishing lesion characteristics. Patients with Lewy Body dementia often also have the amyloid plaque characteristic of Alzheimer's disease, while people with Alzheimer's Disease may also have cortical Lewy bodies. This overlap leads to frequent misdiagnosis. Other atypical Parkinson syndromes include progressive supranuclear palsy (PSP) or multiple systems atrophy (MSA), which also have overlapping characteristics with other neurodegenerative disorders including trinucleotide repeat disorders, but molecular pathogenesis is distinct.

Literature: