Neuronal Development and Degeneration

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Pathogenic Protein Spreading and Neurodegeneration

The aim of our research is to reveal the role and mechanism of cell-to-cell spreading of potential toxic proteins in neurodegenerative disorders.
In neurodegenerative diseases the nervous system gets progressively altered. Impaired structure and function, due to degeneration of neural cells, results in severe behavioural disabilities and often death of the patient.
Understanding pathogenic mechanisms underlying the severe clinical progression of neurodegenerative disorders (NDs), like Alzheimer's (AD), Parkinson's (PD), and Huntington's disease (HD) is critical for developing novel therapeutic strategies. Patients display a progressive accumulation of pathological changes ranging from epigenetic and transcriptional abnormalities to degeneration of neural circuits. These lesions arise in a typical spatiotemporal pattern in the brain. This might be explained by a potential novel disease pathway, which is termed: misfolded protein spreading. A process in which disease-linked, misfolded proteins propagate from cell to cell and function as seeds which convert healthy, like-proteins into toxic species by a procedure called templated misfolding. This phenomenon was first identified in Prion disorders in which it underlies the progressive spatiotemporal spreading of neuronal lesions through the brain. A series of exciting new studies have provided strong experimental evidence that a 'prion-like' self-propagating mechanism is applicable to a variety of proteins related to dissimilar neurodegenerative protein misfolding diseases (PMDs). These include Aβ and tau in AD, α-synuclein in PD, SOD1 in amyotrophic lateral sclerosis (ALS), TDP-43 in ALS and frontotemporal lobar dementia (FTLD), and mutant huntingtin (mHTT) in HD. Recent work suggests that pathogenic protein spreading matches the spatiotemporal progression pattern of neuronal lesions through the brain and that it propagates along neural networks in a pattern that matches the architecture of functional synaptic connectivity in the healthy human brain. The spreading of misfolded proteins might therefore be an important contributor to neuronal damage in PMDs.

We use HD as a model disease to address the following questions:

- Is mHTT cell-to-cell spreading causally linked to neurodegeneration?
- Does mHTT transneuronal spreading depend on functional synaptic connectivity?
- Does mHTT spreading from spinal motor neurons to skeletal muscles contribute to muscle pathology?

These questions we address with a multidisciplinary experimental approach, including a wide array of tools, spanning from morphological and molecular cell biology to systemic physiology and behavioural analyses, applied to both HD mouse- and human induced pluripotent cell models.
With this approach we aim to disclose novel mechanisms of mHTT trans-neuronal spreading and consequences thereof for HD progression. The results likely are of high relevance to other neurodegenerative PMDs.

Selected Publications

Hörnberg H, Perez-Garci E, Schreiner D, Hattstatt-Burkle L, Magara F, Baudouin S, Matter A, Nacro K, Pecho-Vrieseling E and Scheiffele P (2020). Restoration of oxytocin receptor signaling and social recognition in a mouse model of autism. Nature 584(7820):252–6.

Jansen AH, Batenburg KL, Pecho-Vrieseling E and Reits EA (2016). Visualization of prion-like transfer in Huntington's disease models. Biochim. Biophys. Acta. 1863(3):793–800.

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* Equal contribution