Dementia, Brain Disorders and Molecular Mechanisms

Late-onset brain disorders, including dementia, have multiple causes. While some neurodegenerative diseases are inherited and caused by mutation in specific genes, others are sporadic and are associated with diverse risk factors. A common challenge in neurodegenerative diseases is the current lack of curative treatments, which underlines the urgent need for development of treatment therapies for our aging society. A detailed knowledge of the molecular mechanisms underlying the onset and progression of such diseases is of utmost importance to develop novel treatment strategies. Traditionally, protein aggregation of disease-causing proteins has been a central focus of research. To date, numerous studies addressed cellular pathogenic processes underlying dementia, revealing diverse cellular and molecular mechanisms contributing to neurodegeneration and disease development, besides protein aggregation and its consequences. One example of such emerging mechanisms is RNA-mediated toxicity of mutated, disease-causing transcripts in affected cell types. Another important aspect of neurodegeneration is the specific cellular pathologies of brain cells besides neurons, such as astrocytes and microglia. It becomes more and more evident that these, previously only considered supporting cells of neurons, develop cell type-specific phenotypes, which might precede the observed phenotypes in neurons.

The affected cellular and molecular aspects within the different neurodegenerative diseases are highly diverse and cannot be captured in a single special issue. Thus, the focus of this special issue is on specific aspects of neurodegeneration including RNA-mediated toxicity, metal toxicity, dysregulation of cellular metabolism and the role and therapeutic potential of microglia in neurodegenerative diseases.

RNA-mediated toxicity can be mediated by several mechanisms. These include aberrant RNA–protein interactions of disease-causing transcripts with RNA-binding proteins, deregulation of the siRNA machinery, deregulation of splicing, and deregulation of protein translation affecting protein homeostasis.

Schilling *et al*. [1] are describing how RNA-binding proteins become trapped by mutant huntingtin repeat RNA. One characteristic feature of these diseases is the folding of the mutant RNA in a hairpin structure that traps RNA-binding proteins. Examples of such RNA-binding proteins captured by mutant trinucleotide expansion RNAs described in this special issue include splicing factors. Aberrant bindings to mutant repeat RNA functionally result in deregulated splicing, and thus, mis-splicing represents one RNA-mediated mechanism of toxicity.

Qawasmi *et al*. [2] are corroborating the notion that the RNAi machinery is central to the toxicity of expanded repeat RNA, using *Drosophila melanogaster* as a disease model.

The contributions of Krauss and Evert [3] and Ramakrishna and Muddashetty [4] are both focusing on the roles of microRNAs. Small non-coding RNAs regulate expression of diverse genes, including genes that are causally involved in pathogenesis of neurodegenerative diseases. Thus, another RNA-dependent mechanism of neurodegeneration addressed in this special issue is on microRNAs and their regulation of proteins and cellular processes affected in brain diseases.

Another group of RNAs important for disease development is the group of RNAs involved in protein translation, including ribosomal RNA (rRNA) and transfer RNA (tRNA). Tuorto and Parlato [5] are presenting that defects in both rRNAs and tRNAs have been described in neurodegeneration and are linking aberrant rRNA and tRNA regulation to translation deficits and neuropathogenesis. Neueder [6] summarized the current knowledge on merging RNA-based disease mechanisms like interference with regular splicing, the anomalous appearance of RNA–protein complexes and uncommon RNA species, as well as non-canonical translation.

Microglia have recently garner attention in the field of neurodegeneration, based on the fact that neuroinflammatory aspects are underlying all neurodegenerative diseases. Ferro *et al*. [7] are focusing on the role of microglia in ataxia and how microglia in the cerebellum have a specific hyper-vigilant immune phenotype compared to microglia from distinct brain regions. These specific microglia responses could be responsible for the specific cerebral vulnerability in ataxia. McQuade and Blurton-Jones [8] have summarized the current knowledge on how specific single-nucleotide polymorphisms can confer a higher risk of aberrant microglia responses in Alzheimer's disease. Haukedal and Freude [9] have provided a comprehensive overview of the disease contributions of microglia in frontotemporal dementia and amyotrophic lateral sclerosis, with a focus on current knowledge of impaired autophagy in these diseases.

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Another important aspects touched upon in this special issue are metabolic changes in neurons and astrocytes in the brain contributing to neurodegeneration. Aldana [10] is providing an overview of the current knowledge regarding disturbed brain metabolism including glucose hypometabolism and mitochondrial function. Moreover, she is discussing the metabolic demands of activated microglia, characteristic in neuroinflammatory responses, which could provide novel therapeutic intervention points. Vohra *et al*. [11] are providing intriguing evidence that retinal ganglion cells, which are specialized neurons within the eye and signaling through the optic nerve terminating in the occipital lobe of the brain, favor lactate over glucose as energy substrate. Moreover, they demonstrate that lactate is crucial of retinal ganglion cell survival during energetic crisis, providing evidence that interference into the metabolic aspects of lactate might be a suitable target for drug development for neurodegenerative diseases of the eye, such as glaucoma.

Environmental risk factors such as metallic elements can contribute and might even trigger the onset of neurodegenerative diseases. Huat *et al*. [12] are reviewing how essential metals such as iron, copper, zinc and manganese as well as toxic metals such as lead, aluminum and cadmium affect brain physiology and immunity. A specific focus is placed on the disruption of immune-related pathways, which is discussed to be the toxic event in the development of Alzheimer's disease.

The collection of articles provides an insight into some parts of the highly complex pathology of neurodegeneration caused by altered protein, RNA and cell type-specific functions. In addition, environmental factors are considered triggers and exaggerators of the disease pathology. It remains to be seen how these diverse cellular pathologies, genetic predispositions and environmental factors cause disease onset and progression. Nevertheless, all these puzzle pieces can potentially contribute to novel angles for treatment development, desperately needed in a field where the main focus is still on toxic protein aggregation and drugs trying to alleviate accumulated proteins.

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Kristine Freude
Institute of Clinical Veterinary and Animal Sciences, Faculty of Health Sciences, University of Copenhagen, Grønnegårdsvej 7, Frederiksberg 1870C, Denmark
Corresponding author.
E-mail address: kkf@sund.ku.dk.

Sybille Krauss
Milteny Biotech GmbH, Friedrich-Ebert-Str.68, 51429 Bergisch Gladbach, Germany
E-mail address: krauss.sybille@gmx.de.