Myelinic nanochannels in neurodegenerative diseases

Berichterstattung

Projektinformationen

MyeliNANO

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Zusammenfassung vom Kontext und den Gesamtzielen des Projekts

The overarching goal of the ERC Advanced Grant MyeliNANO was a better understanding of the role of oligodendrocytes and central nervous system myelin in the adult brain and in age-dependent major neurodegenerative diseases that involve myelinated cortical and subcortical fiber tracts. To this end

we have successfully combined advanced mouse genetics, biochemistry and cell biology, novel metabolic imaging techniques, advanced electron microscopy with 3D rendering, and behavioural/clinical readouts to study the role of myelination in normal adulthood and in models of neuropsychiatric diseases. We have placed a specific emphasis on the function of nanometer-wide cytosolic channels within the myelin sheath (hence the acronym "MyeliNANO") and the role of oligodendroglial/myelin-derived metabolic support for maintaining functional axonal integrity. In the following I am listing the major experimental results that were achieved and disseminated by publications and preprints. The order of subprojects listed below is following the proposed experimental outline (B2) in the original MyeliNANO grant application.

Arbeit, die ab Beginn des Projekts bis zum Ende des durch den Bericht erfassten Berichtszeitraums geleistet wurde, und die wichtigsten bis dahin erzielten Ergebnisse

Part I: Studying higher brain functions and plasticity in myelin mutant mice

(1) Forebrain-specific targeting of myelin protein genes:

Isolated catatonia-executive dysfunction in aged mice with forebrain-specific loss of myelin integrity. In this paper we report the first mouse mutant, in which the genetic defect of oligodendrocytes is restricted to the forebrain and thus will not interfere with basic motor-sensory functions and behavioral testings. We have applied it to study aging-associated defects of myelin. A key feature of advanced brain aging includes structural defects of intracortical myelin that is associated with secondary neuroinflammation. A similar pathology is seen in specific myelin mutant mice that model 'advanced brain aging' and exhibit a range of behavioral abnormalities. However, the cognitive assessment of these mutants was problematic because myelin-dependent motor-sensory functions are required for most quantitative behavioral readouts. To dissect the role of cortical myelin integrity upon aging for higher brain functions, we generated mice lacking Plp1, encoding the major integral myelin membrane protein PLP, selectively from ventricular zone stem cells of the mouse forebrain. In contrast to conventional Plp1 null mutants, the (subtle) myelin defects were restricted to the cortex and underlying callosal tracts. As expected, forebrain-specific Plp1 mutants exhibited no defect of basic motor-sensory performance at any age tested. Surprisingly, several behavioral alterations that had been reported by another group for conventional Plp1 null mice were absent and even social interactions appeared normal. However, with novel behavioral paradigms, we determined catatonia-like symptoms and isolated executive function defects in both genders at an older age. This finding suggests that loss of myelin integrity has an impact on cortical connectivity and underlies specific defects of executive function, emerging only with increasing age. These observations are relevant for both human brain aging and neuropsychiatric conditions.
Arinrad et al., (2022) Elife, in revision

(2) Inducible arrest of adult myelination:

White matter integrity requires continuous myelin synthesis at the inner tongue. Myelin, the electrically

insulating sheath on axons, is composed of lipids and proteins with exceptionally long lifetimes. This raised the question how such a stable structure is renewed in adult life. We studied the integrity of myelinated tracts after experimentally preventing the formation of new myelin in the CNS, using an inducible Mbp null allele. MBP is known to be required for myelin growth in development. After myelination, oligodendrocytes survived Cre recombination and continued transcribing myelin genes, but in the absence of MBP expression failed to maintain compacted myelin sheaths. Using 3D electron microscopy and mass spectrometry imaging we visualized myelin-like membranes that failed to incorporate adaxonally, most prominently at juxta-paranodes. Myelinoid body formation indicated degradation of existing myelin at the abaxonal side and the inner tongue of the sheath. Thinning of compact myelin and shortening of internodes led, within about 20 weeks, to loss of ~50 % of myelin and to axonal pathology and neurological disease. This demonstrates that functional axon-myelin units require the continuous incorporation of new myelin membranes.
Meschkat et al. (2022) Nat. Comm., in press
https://www.biorxiv.org/content/10.1101/2020.09.02.279612v1

Part II: Myelinic nanochannels: a determining factor of brain aging and neurodegenerative diseases?

(3) Injury to myelinic nanochannels in MS-relevant models of neuroinflammation

Myelin as a risk factor in autoimmune mediated axonal injury. In Multiple Sclerosis (MS), secondary axonal degeneration determines the clinical outcome of disease, which is widely thought to result from denuded axons exposed to immune-mediated damage mechanisms. We have challenged this view after finding that myelin itself can increase the risk of axons to degenerate under inflammatory conditions. Mice with MOG-EAE, a model of inflammatory demyelination and MS, were compared (1) on a genetic wildtype (c57Bl6) level and (2) on a new Mbp mutant mouse, in which myelin was thinner and 10-20% axons were unmyelinated. Surprisingly, axonal pathology was less severe when myelin was thin and the phenotype of the mutant mouse with EAE was ameliorated. The inflammation was unchanged and an adoptive transfer EAE protocol confirmed that this partial rescue is not caused by reduced autoimmunity. We thus propose a revised model for demyelinating diseases in which axons, when shielded from the extracellular milieu, remain fatally dependent on structural myelin integrity to receive oligodendroglial support.
Schaeffner et al., (2022) Nat Neurosci, in review
https://europepmc.org/article/ppr/ppr419913

Microglia facilitate repair of demyelinated lesions via post-squalene sterol synthesis. The repair of inflamed, demyelinated lesions in multiple sclerosis (MS) necessitates the clearance of cholesterol-rich myelin debris by microglia/macrophages and the switch from a pro-inflammatory to an anti-inflammatory lesion environment. Subsequently, oligodendrocytes increase cholesterol levels as a prerequisite for synthesizing new myelin membranes. We hypothesized that lesion resolution is regulated by the fate of cholesterol from damaged myelin and by oligodendroglial sterol synthesis. By integrating gene expression profiling, genetics and comprehensive phenotyping, we found that, paradoxically, sterol synthesis in myelin-phagocytosing microglia/macrophages determines the repair of acutely demyelinated lesions. However, rather than producing cholesterol, microglia/macrophages synthesized desmosterol, the immediate cholesterol precursor. Desmosterol activates liver X receptor

(LXR) signaling to resolve inflammation, creating a permissive environment for oligodendrocyte differentiation. Moreover, LXR target gene products facilitated the efflux of lipid and cholesterol from lipid-laden microglia/macrophages to support remyelination by oligodendrocytes. Consequently, pharmacological stimulation of sterol synthesis boosted the repair of demyelinated lesions, suggesting even novel therapeutic strategies for myelin repair in MS.
Berghoff et al. (2021) Nat Neuroscience 24:47-60
https://www.biorxiv.org/content/10.1101/2021.08.13.456070v1

Myelin lipids are nervous system energy reserves. Neuronal functions and impulse propagation depend on the continuous supply of glucose. Surprisingly, the mammalian brain has no obvious energy stores, except for astroglial glycogen granules. Oligodendrocytes make myelin for rapid axonal impulse conduction and also support axons metabolically with lactate. We found that myelin itself, a lipid-rich membrane compartment, becomes a local energy reserve when glucose is lacking. In the mouse optic nerve, a model white matter tract, oligodendrocytes survive glucose deprivation far better than astrocytes, by utilizing myelin lipids which requires oxygen and fatty acid beta-oxidation. Importantly, fatty acid oxidation also contributes to axonal ATP and basic conductivity. This metabolic support by fatty acids is an oligodendrocyte function, involving mitochondria and myelin-associated peroxisomes, as shown with mice lacking Mfp2. To study a reduced glucose availability in vivo without physically starving mice, we deleted the Slc2a1 gene from mature oligodendrocytes. This led to a decline of the glucose transporter GLUT1 from the myelin compartment and caused myelin sheath thinning. We can propose a novel working model of myelin metabolism that can explain the gradual loss of myelin that is seen in a range of neurodegenerative diseases with underlying hypometabolism.
Asadollahi et al. (2021) Nature, in revision

(4) Protein deposits within myelinic nanochannels in mouse models of neurodegenerative disease

Antagonistic Functions of MBP and CNP Establish Cytosolic Channels in CNS Myelin. The myelin sheath is a multilamellar plasma membrane extension of highly specialized glial cells laid down in regularly spaced segments along axons. Recent studies indicate that myelin is metabolically active and capable of communicating with the underlying axon. To be functionally connected to the neuron, oligodendrocytes maintain non-compacted myelin as cytoplasmic nanochannels. Here, we used high-pressure freezing for electron microscopy to study these cytoplasmic regions within myelin close to their native state. We identified 2,030-cyclicn nucleotide 30-phosphodiesterase (CNP), an oligodendrocyte-specific protein previously implicated in the maintenance of axonal integrity, as an essential factor in generating and maintaining cytoplasm within the myelin compartment. We provide evidence that CNP directly associates with and organizes the actin cytoskeleton, thereby providing an intracellular strut that counteracts membrane compaction by myelin basic protein (MBP). Our study provides amolecular and structural framework for understanding how myelin maintains its cytoplasm to function as an active axon-glial unit.
Snaidero et al., Cell Rep 18, 314-323.

Río-Hortega's drawings revisited with fluorescent protein defines a cytoplasm filled channel system of CNS myelin. A century ago this year, Pío del Río-Hortega (1921) coined the term ‘oligodendroglia’ for

the ‘interfascicular glia’ with very few processes, launching an extensive discovery effort on his new cell type. One hundred years later, we review his original contributions to our understanding of the system of cytoplasmic channels within myelin in the context of what we observe today using light and electron microscopy of genetically-encoded fluorescent reporters and immunostaining. We use the term myelinic channel system to describe the cytoplasm-delimited spaces associated with myelin; being the paranodal loops, inner and outer tongues, cytoplasm filled spaces through compact myelin and further complex motifs associated to the sheath. Using a central nervous system (CNS) myelinating cell culture model that contains all major neural cell types and produces compact myelin, we find that td-tomato fluorescent protein delineates the myelinic channel system in a manner reminiscent of the drawings of adult white matter by Río-Hortega, despite that he questioned whether some cytoplasmic figures he observed represented fixation artefact. Further, we show that the myelinic channel system, whilst relatively stable, can undergo subtle dynamic shape changes over days. Importantly, we capture an underappreciated complexity of the myelinic channel system in mature myelin sheaths.
Edgar et al. (2021) J. Anat. 239:1241-1255.

SOD aggegates clogging myelinic nanochannels in a mouse model of ALS: Amyotrophic lateral sclerosis (ALS) is a highly debilitating and fatal disease characterized by the progressive loss of motor neurons. The mechanisms leading to disrupted oligodendroglial support of motor neurons in ALS are poorly understood. To investigate this, we first confirmed that selective removal of oligodendroglial mutant SOD1-G37R expression delays disease onset, prolongs survival, and improves neurological score. Next, we utilized immuno electron microscopy and found that mutant SOD1 is present within paranodal loops and the inner periaxonal tongue. This raises the intriguing possibility that SOD1 aggregates within the myelinic nanochannels could perturb the motor-driven transport of transporter proteins within oligodendrocytes and disrupt the free diffusion of nutrients from the oligodendrocyte to the motor neuron. To further investigate the role of perturbed myelinic nanochannel integrity as a potential mechanism of impaired oligodendroglial metabolic support of motor neurons in ALS, we crossed mutant SOD1-G93A mice with mice lacking expression of CNP, a protein that keeps myelinic nanochannels open by preventing excessive myelin membrane compaction. Double SOD1-G93A and CNP-deficient mutants show reduced survival and worsened neurological scores. Decreased frequency of myelinic nanochannels in CNP-deficient mice likely accelerates ALS disease progression by further limiting the transport of nutrients from the oligodendroglial compartment to the axonal compartment. These data provide novel insights into the mechanisms leading to impaired oligodendroglial support of motor neurons in ALS.
Mot, A. et al., manuscript in preparation

(5) Impact of reduced myelinic nanochannels on proteolytic processing of APP

Ageing-associated myelin dysfunction drives amyloid deposition in mouse models of Alzheimer’s disease. The prevalence of Alzheimer’s disease (AD), the leading cause of dementia, shows a strict age-dependency, but why aging constitutes the main risk factor for this disease is poorly understood. Brain aging affects oligodendrocytes and the structural integrity of myelin sheaths, the latter associated with secondary neuroinflammation. Since oligodendrocytes support axonal and neuronal health, we hypothesized that aging-associated loss of myelin integrity could be an upstream risk factor

and driver of Amyloid-ß (Aß) deposition, the neuropathological hallmark of early AD. Here we show in AD mouse models that different genetically-induced defects of myelin integrity or demyelinating injuries (Cuprizone, EAE) are potent drivers of amyloid deposition in vivo, quantified by whole brain light sheet microscopy. Conversely, the developmental lack of myelin from the forebrain provides protection against plaque deposition. Mechanistically, we find that myelin dysfunction drives the accumulation of the Aß producing machinery within axonal swellings and increases cortical APP cleavage. Surprisingly, AD mice with dysfunctional myelin lack plaque-corralling microglia. Bulk and single cell transcriptomics reveal that myelin damage causes microglia to adopt a disease-associated-microglia (DAM)-like phenotype. These activated microglia, however, are primarily engaged with myelin, preventing the protective reactions of microglia to Aß plaques. This suggest a new model in which myelin dysfunction in the aged brain is an upstream risk factor for amyloid deposition. Improving oligodendrocyte health and myelin integrity is a promising target delay AD.
Depp, Sun et al. (2021), Nature, in revision

Fortschritte, die über den aktuellen Stand der Technik hinausgehen und voraussichtliche potenzielle Auswirkungen (einschließlich der bis dato erzielten sozioökonomischen Auswirkungen und weiter gefassten gesellschaftlichen Auswirkungen des Projekts)

MyeliNANO comprises experimental and conceptual aspects that are completely 'beyond state of the art', as indicated in the summaries above. For example in part I of the project, this is the first demonstration that cortical myelin is required for information processing, in addition to its known function in speeding conduction This novel function involves the newly discovered axonal metabolic support by oligodendrocytes (Moore et al., Nat Comm, 2020). It will soon be complemented by the behavioural analysis of mice that selectively lack intracortical myelin in the forebrain.

In part II of the project, the hypothesis-driven discovery that myelin itself that can be mobilized upon glucose withdrawal has the potential to completely change our view on white matter as a previously overlooked giant energy reserve in the brain.

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