ISN Symposium Report on the

ISN Symposium on “microRNAs in the nervous system”

which was held on Thursday, April 4th, 2015, as part of the 17th International Neuroscience Winter Conference in Sölden, Austria, submitted by Prof. Dr. Michaela Kress (Austria). A total of $7,000 was approved.

Meeting details: Approximately 150 scientists including PhD Students, postdocs and senior scientists attended this high profile meeting which covered hot topics of the entire neuroscience field through key note lectures, workshops, symposia and poster presentations ranging from brain epigenetics up to ion channel biophysics which was addressed in a plenary lecture by nobel laureate Erwin Neher.

Symposium description: The symposium began with a short introduction by M. Kress, who emphasized the ISN support and then the four lectures as detailed below. Each talk was followed by a vivid discussion involving the speaker and audience. Several dozens of participants attended the workshop and people continually entered during the session, so that the audience at the end of our session was almost complete. Lecture subjects spanned different aspects of microRNAs, with a predicted focus on function and expression patterns in the brain and links were made towards neuropsychiatric disorders. Speakers and abstract talks were as follows:

Hermona Soreq (Israel) From mice to men: Fine tuning of cholinergic signaling by non-coding RNAs

Gerhard Schratt (Germany) miRNA function in synapse development and plasticity

Claudia Verderio (Italy) Glia-to-neuron shuttling of miR-146a via extracellular microvesicles modulates synaptotagmin I translation in neurons

Michaela Kress (Austria) microRNAs in nerve injury and neuropathic pain
Abstracts of the four presentations:

**From mice to men: Fine tuning of cholinergic signaling by non-coding RNAs**

Herna Sorog

The Institute of Life Sciences and the Edmond and Lily Safra Center of Brain Sciences, The Hebrew University of Jerusalem, Israel

Continuous communication between the nervous and the immune system is essential both for maintaining homeostasis and for ensuring rapid and efficient response to stressful and infection insults. Non-coding and microRNA (miRNA) regulators provide exciting and challenging models for studying this communication in anxiety and inflammation. Global genomic analyses show that miRNAs co-evolved with their target transcripts (Baradossi et al. Ivoi Bior Evol 2014) to efficiently control neuronal signaling pathways and enable contribution to the development of higher brain functions while avoiding damaging evolutionary impact. Specifically, microRNA controllers of acetylcholine signaling (Cholinomirs (Nadpor & Soreq Front Mol Neurosci 2014)) modulate both anxiety and inflammation reactions to external insults through physiologically relevant bidirectional competition on interaction with their targets. We found rapid increases of the evolutionarily conserved neuro-modulator acetylcholineserase (AChE)-targeted CholinomIR-132 in acute stress (Ghanial et al. Brain Struct Funct 2013), Insomnia inflammation (Makrushi et al. Inflamm Bowel Dis 2013) and post-schismic stroke, in its drastic reduction in the Alzheimer’s disease brain (Luu et al. EBio Med 2013). Furthermore, single-nucleotide polymorphisms interfering with the ACHEl-silencing capacities of the primate-specific CholinomirR-132 associate with elevated trait anxiety, inflammation and diverse anxiety-related diseases in humans volunteers (Khan et al. Hum Mol Genet 2014), whereas long non-coding RNAs compliment to such miRNAs are modulated in Parkinson’s disease and by deep brain stimulation (Soreq et al. PLoS Comput Biol 2014). Deeper understanding of the evolution and complexity of neuronal non-coding RNAs may highlight their role in the emergence of human brain functions while enabling the interventional treatment of diverse pathologies involving cholinergic signaling impairments.

**Glia-to-neuron shuttling of miR-146a via extracellular microvesicles modulates synaptogamin I translation in neurons**

1. Pradhan, D. E., Tumna, D., Copol, F., Pezzutto, C., Wardwell, J.
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Astrocytes and microglia release extracellular vesicles (EVs) upon activation, which participate to glia-to-neuron signaling. Using miRNA-tie real-time PCR panels we identified a set of miRNAs differentially expressed in EVs induced by pro-inflammatory compared to pre-regenerative microglia. Among them there was miR-146a, a sparsely expressed miRNA, which is abundant in brain edemas and targeted neuron specific genes. We showed that glia-derived EVs transfer their miR-146a cargo to cultured neurons, as proved by a Renilla luciferase/basically specific sensor, and increase immuneactivity of a co-cultured miR-146a target, i.e. the synaptic vesicle protein synaptogamin I. Additionally, by visualizing single EV-neuron contacts driven by optical manipulation we revealed highly dynamic interaction between EVs and neurons, with EVs moving along neuronal processes. More static contacts occurred between EVs and the cell bodies, where EVs stayed attached to the neuronal surface up to 2h after adhesion, ruling out the possibility that EVs undergo rapid internalization or full fusion with cell membrane. Further research is ongoing to identify surface proteins mediating EVs-neuron interaction and to clarify whether EVs can transport their cargo to promote neuronal gene expression. Our study sheds light on an unexpected regulated trafficking outside neurons of miRNA-storing EVs, and on capability of glia-derived EVs to modulate neuronal gene expression.

**miRNA function in synapse development and plasticity**


Institute for Physiological Chemistry, Philips-University Marburg, Germany

Our research group is interested in the role of microRNAs (miRNAs), a large class of small non-coding RNAs, in synapse development and plasticity in mammalian neurons, as well as the potential impact of miRNA regulation on higher cognitive functions and neurological disease. During the last years we have identified key neuronal miRNAs and their targets that are involved in dendrite and spine morphogenesis in rat hippocampal neurons. One of these miRNAs is part of a large imprinted, mammalian-specific miRNA cluster. Induced expression of the miRNA cluster by neuronal activity is required for dendritic arborization and the downregulation of excitatory synapses, a form of homeostatic plasticity that is frequently disturbed in neurodevelopmental and psychiatric disorders. Accordingly, validated target genes of this miRNA cluster are frequently deregulated in neurological disorders. Mechanistically, cluster miRNAs are regulated at the level of transcription, dendritic transport and by a novel competing endogenous RNA encoded by a gene frequently mutated in autism-spectrum disorders (ASD). Our results point to a significant role of miRNAs in the control of spine homeostasis and raise the possibility that impaired miRNA function could contribute to synaptic dysfunction in neurological disorders.

This work is supported by grants from the DFG (SFB133) and the EU (ERC GID “NeuroNet”).

**MicroRNAs in nerve injury and neuropathic pain**

Philipp Malisch, Rüka Zanger, Natasa Miele, Silvia Quarita, David Greenberg, Herna Sorog and Michaela Kress

1. Department of Physiology and Medical Physics, Division of Physiology, Institute for Medical, University, Aachen, Germany
2. Department of Biophysical Chemistry, The Life Sciences Institute and The Edmund and Lily Safra Center of Brain Sciences, The Hebrew University of Jerusalem, Israel, 91120

Nerve injury to a peripheral nerve initiates regenerative processes of neuronal axons but frequently is complicated by a pathological neurop- immune response leading to developing neuropathic pain. The communication between axons and macrophages regulating inflammation, regeneration and pain is still incompletely understood. Here, we report that the interleukin-6 signal transducer gp130 involved in inflammation and neuron regeneration (1-3) mediates biphasic body pain messages through microRNA (miRNA) regulators of neuroinflammation and neuroregeneration. Next generation non-invasive sequencing of mouse miRNAs from dorsal root ganglia (DRG), spinal cord, hippocampus and parahippocampal cortex (PFC) highlighted tissue-specific differences in miRNA changes induced by spared nerve injury compared to spinal nerve ligation injured over control mice (259 PFC miRNAS 30% over- or under-regulated compared to 124 hippocampal miRNAs). Furthermore, mice with absent gp130 in sensory neurons (gp130(-/-)) show a delay in sensory dysfunction and a protection from maintained nerve injury induced pain, presented generally limited induced miRNA differences in the pain pathway. These differences were smaller than the effect of sham operation, indicating intrinsic involvement of miRNA changes not only in neuroregeneration but also in neuropathic pain reactions. Specifically, we localized gp130 targeted miR-21(-/-) in neuronal cell bodies within the DRG and found miR-21 significantly up-regulated on day 7 and day 28 after nerve lesion in wt mice. Introduction of gp130 into viable vitro into gp130 deficient neurons in vitro recovered expression of nooopistop specific transduced miR-21 and the deficit in neurite outgrowth but not the reduced miR-21 levels associated with gp130 deletion. Our findings demonstrate that miRNAs participate in communicating body-brain messages associated with nerve injury and call for testing the potential of micro-RNAs as therapeutic targets for treating chronic pain and nerve injury.

References:
Financial report:

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**total** | **EURO** | **6.153,34**

**ISN grant** | **EURO** | **5.874,05** | **(USD 7,000,-)**

Difference was paid from other source

On behalf of all speakers and attendance, I would like to take this opportunity to thank the ISN for their generous support of this exciting symposium.

Sincerely,

Univ.-Prof. Dr. Michaela Kress