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

Hermona Soreq

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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 (Barbash et al. Mol Biol Evol 2014) to efficiently control neuronal signaling pathways and enable contribution to the development of higher brain functions while avoiding damaging evolutionary impact. Specifically, miRNA controllers of acetylcholine signaling (CholinomiRs (Nadorp & 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 acetylcholinesterase (AChE)-targeted CholinomiR-132 in acute stress (Shaltiel et al. Brain Struct Funct 2013), intestinal inflammation (Maharshak et al. Inflamm Bowel Dis 2013) and post-ischemic stroke, inversely to its drastic reduction in the Alzheimer's disease brain (Lau et al. EMBO Mol Med 2013). Furthermore, single nucleotide polymorphisms interfering with the AChE-silencing capacities of the primate-specific CholinomiR-608 associate with elevated trait anxiety, inflammation and diverse aging-related diseases in human volunteers (Hanin et al. Hum Mol Genet 2014), whereas long non-coding RNAs complementary to such miRNAs are modulated in Parkinson's disease and by deep brain stimulation (Soreq et al. PLoS Comput Biol 2014). Deepened understanding of the evolution and complexity of neuronal non-coding RNAs may highlight their role in the emergence of human brain functions while enhancing the ability to intervene with diseases involving cholinergic signaling impairments.

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

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Astrocytes and microglia release extracellular vesicles (EVs) upon activation, which participate to glia-to-neuron signalling. Using miRNA real-time PCR panels we identified a set of miRNAs differentially expressed in EVs produced by pro-inflammatory compared to pro-regenerative microglia. Among them there was miR-146a, a glial-enriched microRNA, which is altered in brain disorders and targets neuron specific genes. We showed that glia-derived EVs transfer their miR-146a cargo to cultured neurons, as proved by a *Renilla* luciferase-based specific sensor, and decrease immunoreactivity of a validated miR-146a target, i.e. the synaptic vesicle protein synaptotagmin I. Additionally, by visualizing single EV-neuron contacts driven by optical manipulation we revealed highly dynamic interaction between EVs and neurites, with EVs moving along neuronal processes. More stable 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 investigation is ongoing to identify surface proteins mediating EVs-neuron interaction and to clarify whether EVs can open a transient pore to transfer their cargo to neurons.
Our study sheds light on an unexpectedly 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

J. Valluy, S. Bicker, R. Fiore, M. Lackinger, M. Rajman, A. Aksoy-Aksel and **G. Schratt**

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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 downscaling 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 disease. 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 function of microRNAs in the control of synapse homeostasis and raise the possibility that impaired miRNA function could contribute to synaptic dysfunction in neurodevelopmental disorders, including ASD.

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MicroRNAs in nerve injury and neuropathic pain

Philipp Maisch[1], Rivka Zangen[2], Natalia Schiefermeier[1], Serena Quarta[1], David Greenberg[2], Hermona Soreq[2] and **Michaela Kress[1]**

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Nerve injury to a peripheral nerve initiates regenerative processes of neuronal axons but frequently is complicated by a pathological neuro- immune response leading to persisting neuropathic pain. The communication pathways linking between signals regulating inflammation, regeneration and pain are still incompletely understood. Here, we report that the interleukin-6 signal transducer gp130 involved in inflammation and neuron regeneration (1-3) may convey bidirectional body-brain pain messages through microRNA (miRNA) regulators of neuroinflammation and neuroregeneration. Next generation non-biased sequencing of mouse miRNAs from dorsal root ganglia (DRG), spinal cord, hippocampus and pre-frontal cortex (PFC) highlighted tissue-specific differences in miRNA changes induced by spared nerve injury (snI) compared to sham operation, with largest differences in the PFC of injured over control mice (295 PFC miRNAs 30% over- or under-regulated compared to 124 hippocampal miRNAs). Furthermore, mice with ablated gp130 in sensory neurons (SNS-gp130$^{-/-}$), which show a delay in peripheral nerve regeneration and a protection from maintained nerve injury-induced pain, presented generally limited snI-induced miRNA differences in the pain pathway. These differences were smaller than the effect of sham operation, suggesting causal involvement of miRNA changes not only in neuroregeneration but also in neuropathic pain reactions. Specifically, we localized ngf targeted miR-21 (4) 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. Reintroduction of gp130 with viral vectors into gp130 deficient neurons in vitro recovered expression of nociceptor specific transducer ion channel TRPA1 and the deficit in neurite outgrowth but not the reduced miR-21 levels associated with gp130 depletion. 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

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Financial report:

Hermona Soreq	EURO	1.189,34	travel (flight & transfers)
Hermona Soreq	EURO	680,00	accommodation
Hermona Soreq	EURO	396,00	registration fee
Gerhard Schratt	EURO	300,00	travel (car)
Gerhard Schratt	EURO	680,00	accommodation
Gerhard Schratt	EURO	396,00	registration fee
Claudia Verderio	EURO	300,00	travel(car)
Claudia Verderio	EURO	680,00	accommodation
Claudia Verderio	EURO	396, 00	registration fee
Michaela Kress	EURO	60,00	travel(car)
Michaela Kress	EURO	680,00	accommodation
Michaela Kress	EURO	396,00	registration fee
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