

ISN Symposium Report on the

ISN Symposium on “ROLE OF GLIAL CELLS IN RARE DISEASES”

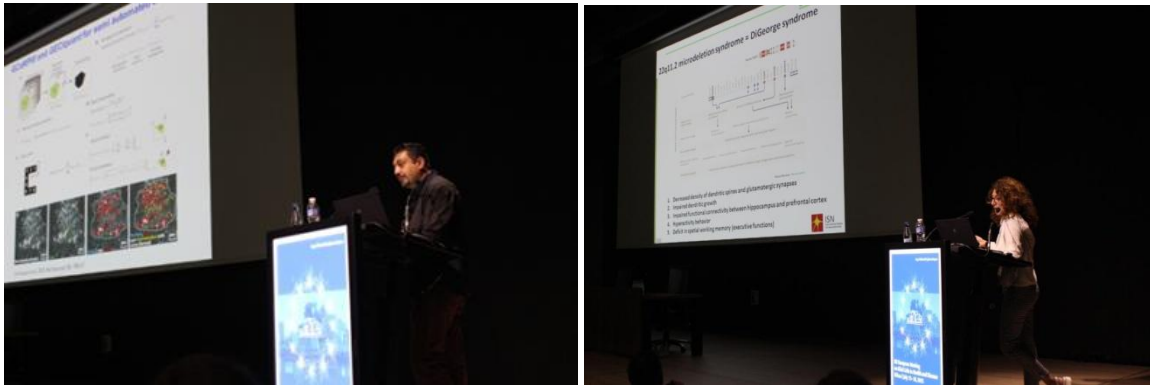
Which was held on Thursday, July 16, 2015, as part of the XII European Meeting on Glial Cells in Health and Disease, Bilbao (Spain), submitted by Prof Daniela Rossi (Pavia, Italy) and Prof Paola Bezzi (Lausanne, Switzerland).

The “XII European Meeting on Glial Cells in Health and Disease” (or Euroglia 2015) has invited participation from neuroglia researchers from all over the world to Bilbao (Spain). The Glial Meeting series has become a tradition since the first gathering in 1994 at the University of Heidelberg where more than 600 participants got together. Subsequent Glial Meetings have been held throughout Europe every second year. After the outstanding success of the Glia Meeting 2013 in Berlin, the conference returned to Spain and it was hosted in Bilbao. This year Euroglia 2015 was one of our more successful meetings with 1105 attendees, 669 posters and 148 talks. The attendees were composed of 386 students/postdocs, 17 exhibitors and 702 faculty/speakers. The distribution of attendees by continent was 13% North America, 4% South America, 75% Europe, 7% Asia, 1% Oceania.

Our ISN symposium was organized and chaired by Daniela Rossi (Maugeri Hospital, Pavia, Italy) and Paola Bezzi (UNIL, Lausanne, Switzerland). The Symposium began with a short introduction by Paola Bezzi, who emphasized the ISN support, the importance of studying glial cells in rare diseases and the contribution by the speakers of this field of research. The first speaker was **Baljit Khakh** (Los Angeles, USA, title: “Astrocyte dysfunctions in Huntington’s disease model mice”) who spoke about the spatio-temporal properties of astrocytic Ca^{2+} signalling in the physiology of mature neuronal circuits and their importance in the pathophysiology of Huntington’s disease. The second speaker was **Paola Bezzi** (Lausanne, Switzerland, title: “Astrocytes may be behind the pathogenesis of 22q11.DS”) who showed some of the peculiar features of cortical astrocytes during postnatal development in terms of metabolism and pointed out how dysfunctions in these properties may be crucial in the pathophysiology of cognitive deficits associated to 22q11 deletion syndrome. The third speaker of the session was **Brian Kaspar** (Columbus, USA, title: “Glial cell toxicity towards motor neurons in ALS”) who showed how microglia and astrocytes derived from human fibroblasts patients with amyotrophic lateral sclerosis (ALS) impair the viability of motor neurons by secreting neurotoxic mediators, therefore confirming the involvement of non –cell-autonomous mechanism in the ALS-driven neurodegenerative process. Our last speaker was **Daniela Rossi** (Pavia, Italy, title: “Functional deficits of the astrocytes in Amyotrophic Lateral Sclerosis”), who focused her talk on various aspects of functional deficits in astrocytes during the progression of the ALS. The session was well attended, with approximately 150 people. Each talk was followed by a vivid discussion involving the speaker and audience.

Symposium Chairs and Speakers:

Left to right: Baljit Khakh, Paola Bezzi



Abstract of the session:

S08-01 Astrocyte dysfunctions in Huntington's disease model mice

B. Khakh, R. Jiang

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Huntington's disease (HD) is characterized by striatal medium spiny neuron (MSN) dysfunction, but underlying mechanisms remain unclear. We recently explored roles for astrocytes (1), which display mutant huntingtin in HD patients and mouse models. We found that symptom onset in R6/2 and Q175 HD mouse models was not associated with classical astrogliosis, but was associated with decreased Kir4.1 K⁺ channel functional expression, leading to elevated in vivo levels of striatal extracellular K⁺, which increased MSN excitability in vitro. Viral delivery of Kir4.1 channels to striatal astrocytes restored Kir4.1 function, recovered aspects of MSN dysfunction, prolonged survival and attenuated some motor phenotypes in R6/2 mice. These findings indicated that components of altered MSN excitability in HD may be caused by heretofore unknown astrocyte disturbances. Astrocytes display dynamic intracellular Ca²⁺ fluctuations, which are considered important for a variety of physiological processes (2). In the present study, we used genetically encoded Ca²⁺ and glutamate indicators and mouse models of Huntington's disease to explore when astrocytes display Ca²⁺ signaling in the striatum. In healthy mice, striatal astrocytes displayed numerous spontaneous Ca²⁺ elevations, but failed to respond to stimulation of cortical inputs. In R6/2 mice, spontaneous Ca²⁺ elevations were significantly reduced, but astrocytes displayed robust Ca²⁺ elevations during stimulation of cortical inputs. These action-potential evoked Ca²⁺ responses were mediated by glutamate receptors, accompanied by prolonged glutamate levels in the extracellular space and reproduced in healthy mice by blocking Glt1 glutamate transporters. Moreover, dysfunctional astrocyte Ca²⁺ signaling in R6/2 mice was significantly rescued by astrocyte expression of Kir4.1 via a mechanism involving Glt1, whose expression was reduced in HD but rescued by Kir4.1 (1). Thus, astrocyte engagement in the striatal microcircuitry dramatically changes in HD and is regulated by its key homeostatic functions. Taken together, our data suggest that defects in neurodegenerative diseases may be remedied by targeting astrocyte-mediated homeostasis. Support: CHDI Foundation and NINDS 1. Tong, X., Ao, Y., Faas, G. C., Nwaobi, S. E., Xu, J., Hausteiner, M. D., Anderson, M. A., Mody, I., Olsen, M. L., Sofroniew, M. V., and Khakh, B. S. (2014) *Nat Neurosci* 17, 694-703 2. Khakh, B. S., and McCarthy, K. D. (2015) *Cold Spring Harb Perspect Biol* doi: 10.1101/cshperspect.a020404

S08-02 Astrocytes may be behind the pathogenesis of 22q11 J

J. Lopatar¹, T. Zehnder¹, L. Pucci¹, F. Petrelli¹, L. Magrassi², S. Lengacher³, P. Magistretti³, J. A. Gogos⁴, P. Bezzi¹

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The onset and etiology of schizophrenia has been associated with a wide range of genetic and epigenetic factors including perturbations in mitochondrial function and oxidative stress responses. The 22q11 deletion syndrome (DS) is one of the highest genetic risk factors for schizophrenia and includes the gene proline dehydrogenase (PRODH) coding for mitochondrial enzyme regulating Lproline (L-Pro). Aim of this work is to elucidate the role of PRODH in the pathophysiology of 22q11DS. The expression of PRODH is typically ascribed to proliferating tissues (Polyak et al., Nature, 1997) where it regulates cell proliferation and metabolism (Liu et al., PNAS, 2012). We and others have found that PRODH expression in the brain is limited to postnatal development, the temporal period commonly associated with gliogenesis. Interestingly, we have found the PRODH expression in the astrocytes seems to be limited to the prefrontal cortex (PFC). These astrocytes, similar to the proliferating cells, showed enhanced glycolytic rates which could render astrocytes more susceptible to mitochondrial perturbations. Indeed, in astrocytes of PRODH-deficient mice, respiration, ATP levels and mitochondrial transmembrane potential ($\Delta\Psi$) were impaired. These mice showed also cognitive impairments associated with PFC. We concluded that PRODH expression during postnatal development is necessary to maintain a proper mitochondrial function. Support contributed: NCCR Synapsy to P. Bezzi

S08-03 Glial cell toxicity towards motor neurons in ALS

B. Kaspar

Nationwide Children's Hospital/ The Ohio State University, Pediatrics/Gene Therapy, Columbus, United States

For the last century, research on neurological disorders has focused on the most prominent affected cell type - the neurons. However, with increasing knowledge of the diverse physiological functions of glial cells, their impact on neurological disorders has become more evident. Therefore, many conditions appear to have more complex origins than initially thought. Since neurological pathologies are often sporadic with unknown etiology, animal models are difficult to create and might only reflect a small portion of patients in which a mutation in a gene has been identified. Therefore, reliable in vitro systems to study these disorders are urgently needed. They might be a pre-requisite for improving our understanding of the disease mechanisms as well as for the development of potential new therapies. In this talk focused on the motor neuron disease Amyotrophic Lateral Sclerosis, a summary of the function of different glial cell types in the disease will be discussed. We will then describe different types of culture systems to model non-cell autonomous interactions in vitro and evaluate advantages and disadvantages.

S08-04 Functional deficits of the astrocytes in Amyotrophic Lateral Sclerosis

L. Brambilla¹, F. Martorana¹, G. Guidotti¹, C. F. Valori², P. Bezzi³, D. Rossi¹

¹ IRCCS Fondazione Salvatore Maugeri, Laboratory for Research on Neurodegenerative Disorders, Pavia, Italy ² German Centre for Neurodegenerative Diseases, Tübingen, Germany ³ University of Lausanne, Lausanne, Switzerland

Collective evidence indicates that motor neuron degeneration in Amyotrophic Lateral Sclerosis (ALS) is non-cell-autonomous and requires the interaction with the neighboring astrocytes. Astrocytes can hurt motor neurons by secreting neurotoxic factors, but they can play deleterious roles also by losing functions that are supportive for neurons. Recently, we reported that stimulation of inositol 1,4,5 triphosphate (IP₃)-generating group I metabotropic glutamate receptors in ALS astrocytes triggers abundant and persistent elevations of intracellular Ca²⁺ concentrations in the absence of spontaneous oscillations. This correlates with mitochondrial disarrangement and cell death in subsets of astrocytes. The interaction of IP₃ receptors with the anti-apoptotic protein Bcl-XL was previously described to prevent cell death by generating pro-survival Ca²⁺ oscillations. In ALS astrocytes, we found that the sole BH4 domain of Bcl-XL, fused to the protein transduction domain of the HIV-1 TAT protein (TAT-BH4), is sufficient to restore sustained Ca²⁺ oscillations and cell death resistance. Furthermore, chronic treatment of ALS mice with the TATBH4 peptide exerts a positive impact on the disease manifestations. Besides, we demonstrate that ALS astrocytes aberrantly respond to the neuroinflammatory microenvironment, exhibiting a functional impairment of their neurotrophic properties.

Financial report: A total of \$ 6.700 was approved to cover travel and accommodation expenses of speakers. ISN support will provide partial reimbursement for all three speakers. The breakdown of costs were as follows: Baljit Khakh 2,500 \$ (\$2,000 for transportation, \$500 for Hotel accommodation), Paola Bezzi 1,170 \$ (220 \$ for transportation, 950 \$ for Hotel accommodation) , Brian Kaspar 2,500 \$ (\$2,200 for transportation, 300\$ for Hotel accommodation), Daniela Rossi 700 \$ (300 \$ for transportation, 400 \$ for Hotel accommodation).

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

Sincerely,

A handwritten signature in black ink, appearing to read 'Paola Bezzi', with a horizontal line underneath it.

Paola Bezzi, PhD