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Editorial

Neuroscience & immunology: a fruitful alliance against persistent threats to the nervous system

25 years of the Institute of Neuroimmunology of Slovak Academy of Sciences

Rostislav Skrabana and Peter Filipcik

Institute of Neuroimmunology, Slovak Academy of Sciences, Bratislava, Slovakia
E-mail: rostislav.skrabana@savba.sk
peter.filipcik@savba.sk

In the ancient, pre-scientific western world, people debated where the human mind is located, whether in the head or heart. Galen of Pergamon, Greek physician (129 CE – to about 216 CE), one of the first experimental neurologists, suggests the brain as the prime candidate for this prominent location (Crivellato and Ribatti 2007; Baloyannis 2016). The foundation of modern neuroscience as a scientific discipline can be attributed primarily to Santiago Ramón y Cajal, many centuries later (Llinas 2003). On the other hand, immunology is a relatively modern branch of biology; its establishment has been attributed to Russian biologist Ilya Ilyich Mechnikov, German physician Paul Ehrlich and other biologists of 19th century (Kaufmann 2019), although first signs and examples of immunity as a phenomenon of organism defence were observed in the ancient world as well (Silverstein 1989).

The 1980s witnessed the birth of neuroimmunology – a distinct scientific discipline focusing initially on autoimmune neurological diseases (which still remain one of the major neuroimmunology focus points), but concurrently aiming at the explanation of the complexity of "brain – periphery" and "periphery – brain" interactions, which are important for proper functioning of both (Nutma et al. 2019). Neuroimmunology passed various stages of development. What once seemed as two realms with very small intersection in between (e.g., brain was conceived as a completely immune privileged organ (Medawar 1948)) is now more and more recognized as ingeniously collaborating systems (Harris et al. 2014; Louveau et al. 2015). For example, cytokines released during peripheral immune response to an inflammatory event can act as neuromodulators; they shape the neuronal connectivity and may influence behaviour (Salvador et al. 2021). On the other hand, the brain's capacity to collect the signals and build a prediction upon them can shape immune responses by immune conditioning (Schiller et al. 2021).

The central nervous system (CNS) and immune system are encircled by various barriers separating the bloodstream and the brain. Selective permeability and specific cell type composition of these barriers may confer an explanation of neuroimmune interactions, determine the neurological marker flux in the periphery, and allow for the entry of immunotherapeutics into the brain. These barriers also harbour a distinct capacity to participate in the immune response (Stolp et al. 2013). Brain parenchyma behind the barriers contains resident sentinel macrophages, microglia, which are activated by misfolded proteins during neurodegeneration and participate in neuroinflammation (Zilka et al. 2012; Papadopoulos et al. 2020). Although there are still many unknowns in the development and functioning of microglia, they are now generally considered to be critical players in the field of neuroimmunology (Li and Barres 2018). With respect to direct immunologic surveillance of the CNS, brain antigens can drain *via* meningeal lymphatics towards the periphery and elicit humoral immune response in lymph nodes (Papadopoulos et al. 2020), or they can be captured by antigen-presenting dendritic cells and macrophages dwelling in *dura mater* that subsequently activate the patrolling T-cells infiltrated from *dura sinuses* (Rustenhoven et al. 2021). These processes may lead to CNS autoimmunity but may also induce a beneficial immune response against pathogenic forms of brain proteins.

Neuroimmune interactions can be mediated *via* several peripheral endocrine modulators as well. For example, leptin – an adipokine hormone discovered in 1994 – regulates both

innate and adaptive immune responses and, at the same time, has protective function in neurological disorders (Naylor and Petri 2016; Fujita and Yamashita 2019). Regulation of microglia activation by various hormones including leptin represents one more way how the periphery may regulate the brain's immune machinery. Neuroimmune interactions are also important in inducing a beneficial response in the processes of spontaneous or pharmacologic healing of CNS injuries or degeneration. This may have important consequences for development of a cure for long-recognized brain maladies. One of the fascinating possibilities to cure neurodegenerative proteinopathies like Alzheimer's disease (AD) is to explore antibodies naturally occurring in the elderly. Following the hypothesis that the immune system of humans who resisted the development of neurodegeneration may produce antibodies eliminating toxic amyloids in the brain led to the discovery of several monoclonal antibody candidates for passive immunotherapy targeting amyloid beta or tau protein (Sevigny et al. 2016; Apetri et al. 2018).

This issue of the journal General Physiology and Biophysics is a collection of original and review articles reflecting current experimental neuroimmunology research in Slovakia. It is published on the occasion of the 25th anniversary of the Institute of Neuroimmunology of Slovak Academy of Sciences (INI SAS). The Institute was founded by Prof. Michal Novak, the co-author of the tau hypothesis of AD at the MRC Laboratory of Molecular Biology in Cambridge, England (Wischik et al. 1988). The INI SAS originated from a department of the Institute of Virology, Slovak Academy of Sciences and evolved into a fully-fledged independent academic institution. The main neuroimmune research theme of INI SAS from the beginning was the investigation of the tau protein pathogenic cascade in AD. Now, after two and a half decades of its existence the Institute pursues a large spectrum of neuroimmune themes.

Introductory article of this issue is dedicated to the lifework of Professor Michal Novak in the field of neuroimmunology (Novak and Zilka 2021). In the review of Mihaljevic et al. (2021) the role of the choroid plexus as a blood-cerebrospinal fluid barrier in different neurological conditions such as neurodevelopmental, autoimmune, and neurodegenerative diseases is described. The choroid plexus tumours are also briefly mentioned; moreover, the involvement of the choroid plexus in pathogen invasion of the CNS, including the current SARS-CoV-2 virus is reviewed as well.

Various aspects of neurodegenerative diseases of the brain are reflected in four papers of this issue. Tau pathology is central for development of neurodegenerative tauopathies including AD. A review by Palova et al. (2021) summarizes neuroprotective and neurotoxic activities of microglia in healthy and AD tauopathy brains. Microglia, as the only resident leucocyte of the brain, are key players in the pathogenesis of AD. Current data indicate that microglia can be induced by some tau protein-directed immunotherapies to phagocyte and eliminate pathological tau from the brain. Therefore, they can help to inhibit the spreading of tau pathology through the brain and stop the disease progression. The review article of Cehlar et al. (2021) provides an analysis of three-dimensional structures of tau local linear motifs as seen in high-resolution structures of tau complexes with various binding partners and tau-tau complexes. The properties of the partially stabilized conformations of tau linear motifs can be essential for the initiation of physiological and pathological neuroimmune processes. The spreading of pathology through the brain is a highly debated issue in neurodegeneration progression research. An experimental animal model of tauopathy allowed Csicsatkova et al. (2021) to investigate the molecular changes that govern the AD misfolded tau seed spreading and the induction of pathology. At the level of gene expression, they reported 15 genes involved in the inflammatory signalling pathways mediated by a network of cytokines and chemokines, along with toll-like receptor and JAK-STAT signalling. Finally, the paper of Cente et al. (2021) associates the neurodegenerative phenotype with changes in endocrine and metabolic profile in an animal model of tauopathy. The authors clearly show that tauopathy in animals leads to profound changes in the peripheral level of leptin despite having no effect on the brain regions responsible for central leptin regulation. The full explanation of this effect still remains elusive.

A comprehensive methodologic paper of Pichlerova and Hanes (2021), which can serve as an up-to-date reference in the field, discusses currently used methods to study protein-protein interactions *in vivo, in vitro* and *in silico*. Interaction methods are essential to identify binding partners of tau protein and other vulnerable brain proteins experimentally. This can lead to validation of predicted physiological as well as pathological mechanisms.

Neurodegeneration caused by ageing and acute or chronic CNS injuries requires innovative therapies combined with rehabilitation. In spite of enormous effort, the treatment of CNS neurons still lacks the progress we would like to see. One of the promising therapies is the use of stem cells and/or the conditioned culture media for the treatment. Humenik et al. (2021) characterised the effect of mesenchymal stem cells on CNS neurons in an animal model and showed stimulated neurite growth, the indicator of neuroregeneration. Spinal cord injury in animal models represents a unique way for understanding of mechanisms and development of treatment. Baciak et al. (2021) describe magnetic resonance and especially diffusion tensor imaging in animal models as a technique of choice for observation and quantification of changes in spinal cord after the injury as well as during treatment.

Traumatic brain injury (TBI) is generally considered a critical risk factor for development of neurodegeneration.

In this context, the analysis of early phases of etiopathogenesis is crucial for identification of promising biomarkers and therapeutic targets, especially in high-risk patients. The pool of noncoding RNAs is a "high-information-content" component of peripheral fluids and may contain a code for identification of critically important molecules. First step on this journey should be a comprehensive analysis of microRNA profiles in mild-TBI patients as it is provided by Matyasova at al. (2021). The authors used a validated bioinformatic pipeline for meta-analysis of big data sets and identified deregulated genes of specific molecular pathways. They also identified a network of validated interacting proteins that are associated with neurodegenerative signalling and provided the set of genes as novel candidates for experimental validation of post-TBI events. One of the practical problems in TBI research is a collection of well-characterized samples. It is therefore important to design a way to get a sufficient number of samples for experimental analyses. In the paper of Majdan et al. (2021) the authors focussed on epidemiological analysis of brain injury cases in ice hockey players. They have reported data on frequency of concussions in ice-hockey leagues in Slovakia; their data identified the most critical phases of the game and can be a source of useful data in the injury prevention.

Modern neuroimmunology evolved beyond its traditional focus on CNS autoimmunity in the discipline that synthesizes the interactions of the nervous and immune systems. We believe that better understanding the brain and immune functions in one entity may lead to successful treatment of severe human brain diseases.

References

Apetri A, Crespo R, Juraszek J, Pascual G, Janson R, Zhu X, Zhang H, Keogh E, Holland T, Wadia J, et al. (2018): A common antigenic motif recognized by naturally occurring human VH5-51/VL4-1 anti-tau antibodies with distinct functionalities. Acta Neuropathol. Commun. **6,** 43 https://doi.org/10.1186/s40478-018-0543-z

Baciak L, Melichercik L, Mate V, Murgoci AN, Smolek T, Juranek I, Gogola D, Hudakova N, Cizek M, Cizkova D (2021): Improved tissue integrity after alginate treatment in rat spinal cord injury: evidence from ex vivo diffusion tensor imaging. Gen. Physiol. Biophys. **40,** 561-568

Baloyannis SJ (2016): Galen and the Neurosciences. J. Neurol. Stroke **4,** 00116 https://doi.org/10.15406/jnsk.2016.04.00116

Cehlar O, Bagarova O, Hornakova L, Skrabana R (2021): The structure of the unstructured: mosaic of tau protein linear motifs obtained by high-resolution techniques and molecular simulation (Review). Gen. Physiol. Biophys. **40,** 479-493

Cente M, Smolek T, Zorad S, Fialova L, Paulenka Ivanovova N, Krskova K, Balazova L, Skrabana R, Filipcik P (2021): Hypertension does not alter disturbances in leptin signalling observed in experimental model of tauopathy. Gen. Physiol. Biophys. **40,** 577-584

Crivellato E, Ribatti D (2007): Soul, mind, brain: Greek philosophy and the birth of neuroscience. Brain Res. Bull. **71,** 327-336 https://doi.org/10.1016/j.brainresbull.2006.09.020

Csicsatkova N, Szalay P, Matyasova K, Mate V, Cente M, Smolek T, Brezovakova V, Kawecka L, Zilka N, Jadhav S (2021): Transcriptomic signature of Alzheimer's disease tau seed-induced pathology. Gen. Physiol. Biophys. **40,** 541-549

Fujita Y, Yamashita T (2019): The effects of leptin on glial cells in neurological diseases. Front Neurosci. **13,** 828 https://doi.org/10.3389/fnins.2019.00828

Humenik F, Jego S, Hornakova L, Maloveska M, Valencakova-Agyagosova A, Vikartovska Z, Mudronova D, Hudakova N, Zilkova M, Cizek M, Cizkova D (2021): Impact of mesenchymal stem cells derived conditioned media on neural progenitor cells. Gen. Physiol. Biophys. **40,** 551-559

Harris MG, Hulseberg P, Ling C, Karman J, Clarkson BD, Harding JS, Zhang M, Sandor A, Christensen K, Nagy A, et al. (2014): Immune privilege of the CNS is not the consequence of limited antigen sampling. Sci. Rep. **4,** 4422 https://doi.org/10.1038/srep04422

Kaufmann SHE (2019): Immunology's coming of age. Front. Immunol. **10,** 684 https://doi.org/10.3389/fimmu.2019.00684

Li Q, Barres BA (2018): Microglia and macrophages in brain homeostasis and disease. Nat. Rev. Immunol. **18,** 225-242 https://doi.org/10.1038/nri.2017.125

Llinas RR (2003): The contribution of Santiago Ramon y Cajal to functional neuroscience. Nat. Rev. Neurosci. **4,** 77-80 https://doi.org/10.1038/nrn1011

Louveau A, Harris TH, Kipnis J (2015): Revisiting the mechanisms of CNS immune privilege. Trends Immunol. **36,** 569-577 https://doi.org/10.1016/j.it.2015.08.006

Majdan M, Toth I, Barila P, Peracek P, Perackova J, Parnican S, Cente M, Filipcik P (2021): Head impacts in youth national hockey leagues in Slovakia: a retrospective analysis of four seasons. Gen. Physiol. Biophys. **40,** 569-576

Matyasova K, Csicsatkova N, Filipcik P, Jurisica I, Cente M (2021): Peripheral microRNA alteration and pathway signaling after mild traumatic brain injury. Gen. Physiol. Biophys. **40,** 523-539

Medawar PB (1948): Immunity to homologous grafted skin; the fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. Br. J. Exp. Pathol. **29,** 58-69

Mihaljevic S, Michalicova A, Bhide M, Kovac A (2021): Pathophysiology of the choroid plexus in brain diseases (Review). Gen. Physiol. Biophys. **40,** 443-462

Naylor C, Petri WA, Jr. (2016): Leptin regulation of immune responses. Trends Mol. Med. **22,** 88-98 https://doi.org/10.1016/j.molmed.2015.12.001

Novak M (1994): Truncated tau protein as a new marker for Alzheimer's disease. Acta Virol. **38,** 173-189

Novak P, Zilka N (2021): The manifold works of Prof. Michal Novak. Gen. Physiol. Biophys. **40,** 439-442

Nutma E, Willison H, Martino G, Amor S (2019): Neuroimmunology – the past, present and future. Clin. Exp. Immunol. **197,** 278-293 https://doi.org/10.1111/cei.13279

Palova D, Turic Csokova N, Markova K, Kontsekova E, Kovacech B, Zilkova M (2021): The engagement of microglia in tau-targeted immunotherapy in Alzheimer's disease (Review). Gen. Physiol. Biophys. **40,** 463-478

Papadopoulos Z, Herz J, Kipnis J (2020): Meningeal lymphatics: from anatomy to central nervous system immune surveillance. J. Immunol. **204,** 286-293 https://doi.org/10.4049/jimmunol.1900838

Pichlerova K, Hanes J (2021): Technologies for the identification and validation of protein-protein interactions (Review). Gen. Physiol. Biophys. **40,** 495-522

Rustenhoven J, Drieu A, Mamuladze T, de Lima KA, Dykstra T, Wall M, Papadopoulos Z, Kanamori M, Salvador AF, Baker W, et al. (2021): Functional characterization of the dural sinuses as a neuroimmune interface. Cell **184,** 1000-1016 https://doi.org/10.1016/j.cell.2020.12.040

Salvador AF, de Lima KA, Kipnis J (2021): Neuromodulation by the immune system: a focus on cytokines. Nat. Rev. Immunol. **21,** 526-541 https://doi.org/10.1038/s41577-021-00508-z

Schiller M, Ben-Shaanan TL, Rolls A (2021): Neuronal regulation of immunity: why, how and where? Nat. Rev. Immunol. **21,** 20-36 https://doi.org/10.1038/s41577-020-0387-1

Sevigny J, Chiao P, Bussiere T, Weinreb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, et al. (2016): The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. Nature **537,** 50-56 https://doi.org/10.1038/nature19323

Silverstein AM (1989): A History of Immunology. Academic Press, San Diego

Stolp HB, Liddelow SA, Sa-Pereira I, Dziegielewska KM, Saunders NR (2013): Immune responses at brain barriers and implications for brain development and neurological function in later life. Front. Integr. Neurosci. **7,** 61 https://doi.org/10.3389/fnint.2013.00061

Zilka N, Kazmerova Z, Jadhav S, Neradil P, Madari A, Obetkova D, Bugos O, Novak M (2012): Who fans the flames of Alzheimer's disease brains? Misfolded tau on the crossroad of neurodegenerative and inflammatory pathways. J. Neuroinflammation **9,** 47 https://doi.org/10.1186/1742-2094-9-47