P R E F A C E 17th international conference on Brain Edema and Cellular Injury

Jerome Badaut, John Zhang

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PREFACE

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Brain edema is frequently observed in various cerebral and non-cerebral disorders, including traumatic brain injury (TBI), cerebral ischemia, brain tumors, cardiac arrest, altitude sickness, and liver failure. Brain edema is acutely life threatening and part of the pathophysiology of brain insults. The development of new neuroimaging tools, as well as new molecular tools, has provided a new way to examine the process by which edema develops longitudinally and in real time both in preclinical models and in patients. The recent work in this field of research was presented at the 17th international conference on Brain Edema (2017), held on December 8–10, 2017 in the beautiful city of Guangzhou, China. Professor Anding Xu, a Neurologist from Jinnan University hospital, chaired the meeting. It was a unique occasion to gather many leading brain edema researchers from Asia, Europe, and North America for a 2-day meeting.

The present special issue is a compilation of articles illustrating the scientific presentations during these 2 days of meetings. This special issue, comprising 19 articles, including reviews and original clinical and preclinical studies, presents the latest developments in the cellular and molecular complexity of brain edema and cellular injuries. In the first part, we present a collection of papers reviewing recent developments in molecular and cellular mechanisms of edema, neuroinflammation as well as the role of immune cells in various acute brain injuries. The second part of the special issue is a collection of original studies presenting new therapeutic approaches in addition to the molecular mechanisms of the secondary injuries in preclinical models. Three papers present the use of neuroimaging for prognostic factor and the quality of care for patient with subarachnoid hemorrhage (SAH).

1 | EDEMA, NEUROINFLAMMATION, AND THE IMMUNE SYSTEM IN SECONDARY INJURY PATHOPHYSIOLOGY

Edema, neuroinflammation, and the immune system are involved in post-injury pathophysiology. Researchers developed a better knowledge of the sequence of events post-injury with the emergence of new molecular and imaging tools. New evidence focusing on water channels, extracellular matrix glycoproteins, and transcription factors as well as circular RNAs are presented in the following reviews:

First, the function of the central nervous system requires a fine-tuned and complex control of the cellular and ionic environment. It engages a plethora of complex molecular and cellular mechanisms to maintain correct brain homeostasis. These molecular mechanisms might contribute to the pathological accumulation of water in the brain after injury. In this regard, astrocytic water channels, aquaporins (AQPs), have been proposed to be a key player in water accumulation and thought to be a potential candidate for drug development to limit edema formation post-injury (Clement, Rodriguez-Grande, & Badaut, 2018). Due to the molecular complexity of injury, water channel inhibition is not suitable at all time points or in all injury subtypes. Moreover, AQP4 is coupled with other ionic channels or with gap junctions and participate in water accumulation and in neuroinflammation, adding another layer of intricacy (Clement, Rodriguez-Grande, & Badaut, 2018). In the theme of edema and neuroinflammation, several preclinical studies that identify molecular targets in the potential treatment of TBI are discussed in a review by Sulhan and collaborators (Sulhan, Lyon, Shapiro, & Huang, 2018). Edema and neuroinflammation engage the blood–brain barrier (BBB) properties, which involve several molecular mechanisms including the major facilitator superfamily domain-containing protein 2a (Mfsd2a) (Eser Ocak, Ocak, Sherchan, Zhang, & Tang, 2018). Mfsd2a contributes to various biological functions including transport, cell fusion, cell cycle, inflammation, and regeneration. Mfsd2a has been shown to contribute to the performance of other organs with barrier functions and in response to injury (Eser Ocak et al., 2018).

BBB dysfunction includes extracellular matrix alterations as well. In this regard, tenascin C (TNC) is an inducible, nonstructural, secreted, and multifunctional matricellular glycoprotein, and its role in global edema after SAH is reviewed (Suzuki et al., 2018). In the absence of TNC, decreased edema and brain injury have been observed (Suzuki et al., 2018). Very interestingly, more severe SAH increases TNC expression in cerebrospinal fluid (CSF) and peripheral blood, which could be a surrogate marker of SAH injury to predict the outcomes (Suzuki et al., 2018).

A direct consequence of neuroinflammation and edema is the decrease in cerebral blood perfusion, leading to hypoxia. Both neuroinflammation and edema induce increases in hypoxia-inducible factor (HIF) transcription factors, which are critically reviewed (Ostrowski & Zhang, 2018). HIF regulates various genes, including some associated with energy metabolism, but has also been recently shown to

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contribute to epigenetic changes. Similarly, endoplasmic reticulum (ER) stress causes oxidative damage and cell death (Doycheva, Kaur, Tang, & Zhang, 2019). The role of Bax Inhibitor-1 (BI-1), an evolutionarily conserved protein encoded by the Transmembrane Bax inhibitor Motif, has been proposed to be protective from ER stress. The neuroprotective properties of BI-1 are examined as a potential drug intervention (Doycheva et al., 2019). In the last decade, noncoding RNAs have been investigated as having a potential role in gene regulation in secondary injury. Circular RNAs (circRNAs), one of noncoding RNAs, act as a miRNA sponge to repress miRNA function and interact with RNA-binding proteins in order to participate in splicing of target genes, and translate genes into protein in the post-injury pathophysiology process (Zang, Lu, & Xu, 2018). The timing and the brain location of the complex molecular mechanisms (HIF, BI-1, circRNAs, etc.) need to be carefully understood in order to plan future therapeutic interventions.

Brain disorders are also known to induce an immune response, which can be part of the processes accelerating edema pathophysiology. The role of the immune system might not be designed to handle severe injuries such as polytrauma or severe stroke. Therefore, severe injuries are potentially associated with exaggerated/deregulated inflammatory response, which may cause more damage than initial pathology (Duris & Jurajda, 2019). Several signaling molecules and metabolic derangements result in the disruption of the BBB, leading to an extravasation of immune cells and cerebral edema are described by Sulhan and colleagues. The timeline and pathophysiology of the delayed, secondary injury allows for a window of possible therapeutic options summarized in the review paper from Huang and collaborators (Sulhan et al., 2018).

There are various cell types involved in the post-injury neuroinflammation events from immune cells to microglia, although they also contribute to pathology resolution. In the case of germinal matrix hemorrhage and hydrocephalus from premature infants, induction of fibrosis and gliosis in the periventricular and subarachnoid spaces disrupt normal CSF dynamics (Klebe et al., 2019). The review by Klebe and colleagues focuses first on microglia/macrophage's role in hematoma clearance, before discussing a new hydrodynamic theory, involving redistribution of vascular pulsations and disruption of Starling forces in brain microcirculation (Klebe et al., 2019).

2 | NEW MOLECULAR PATHWAYS AND TREATMENTS FOR SECONDARY INJURIES

The collection of papers with original data provides results presenting new molecular pathways, potential treatments, and prognostic factors for the outcomes in preclinical models and clinical applications. The papers cover various brain injuries such as TBI, ICH-SAH, and stroke.

- The temporal evolution of TBI pathophysiology is dependent on the primary injury severity, which influences patient's outcomes. Neuroimaging, in particular multimodal magnetic resonance imaging (MRI), can provide additional diagnostic information, including edema and hemorrhage. The importance of edema and the presence of blood using MRI after juvenile TBI have been evaluated in correlation to neuronal cell death in mild, moderate, and severe controlled cortical impact models (Badaut, Adami, Huang, & Obenaus, 2019). Increased cellular death is associated with increasing TBI severity, and the presence of extravascular blood (Badaut, Adami, Huang, & Obenaus, 2019). Neuroimaging represents a key tool in order to classify the patients for clinical trials in the new therapeutic approaches.
- After the primary mechanical injury in TBI, delayed secondary injury involves a variety of neuroinflammatory processes. Specifically, increase in heme oxygenase-1 (HO-1) expression is correlated with edema formation after TBI (Jullienne et al., 2019). Very interestingly, intranasal osteopontin (OPN) administration after TBI increases the number of activated microglia paralleled with a weaker correlation between edema formation and HO-1 expression. Thus, OPN treatment may limit the secondary consequences of TBI at a later time point by an early increase in activated microglia and HO-1 response (Jullienne et al., 2019).
- The role of kynurenine 3-monooxygenase (KMO) and neurotoxic quinolinic acid (QUIN) has been studied in surgically induced brain injury (SBI) (Zakhary, Sherchan, Li, Tang, & Zhang, 2019). SBI is known to be a postoperative complication after neurosurgical procedures, with the presence of brain edema and neuronal apoptosis in peri-lesion brain tissue. The inhibition of KMO reduced brain water content, QUIN expression, the apoptotic markers, and improved long-term neurological function after SBI, suggesting that KMO inhibition may be a potential postoperative therapy following neurosurgical procedures (Zakhary et al., 2019).
- Intracerebral hemorrhage (ICH) and SAH are life-threatening diseases with frequently massive edema formations and no pharmacological treatments. Neuroinflammation and brain edema are present after ICH. The annexin A1 pathway has previously been shown to be protective in stroke models and in a new study was tested in the ICH mouse model. Annexin-A1 agonist injection mitigates brain edema and improves neurological functions after ICH by activating microglia. The benefits of Annexin A1 on memory at 28 days after ICH possibly involve AnxA1/FPR2 signaling via p38-associated inflammatory cascade (Ding et al., 2019).
- Ischemic stroke is frequently associated with edema formation as well as changes in the brain homeostasis with early alterations in acid/base and electrolyte concentrations at the onset of stroke (Martha et al., 2019). In their study, Dr. Martha and collaborators used 18-month-old male and female rats to observe a significant difference in acid/base balance and electrolyte levels in venous blood samples from aged rats after ischemic stroke using a middle cerebral artery occlusion (MCAO) model. Very interestingly, changes in pH, sodium, and ionized calcium were predictors of the final infarct and edema volumes. The authors suggest that these venous biomarkers may be useful in the human condition (Martha et al., 2019).

- Hyperglycemia and diabetes are known to be risk factors for hemorrhagic transformation after ischemic stroke, and contribute to a worsening of outcomes. Disintegrins from *Crotalus atrox* venom have been tested after MCAO in hyperglycemic rats. The authors showed that disintegrins from the venom attenuate hemorrhagic transformation by preventing activation of matrix metalloproteinase (McBride, Gren, Kelln, Hayes, & Zhang, 2018).
- There is a clinical need to improve recovery from coma. Two rodent models have been used to induce unconsciousness using ketamine or ethanol and to test hyperbaric oxygen (HBO) treatment (Bian et al., 2019). HBO (100% O_2 at 3 ATA) was administered immediately after animals were unconscious for 1 hr. Loss of righting reflex test and Garcia test were used to evaluate the duration of unconsciousness and neurological deficits. Bian and collaborators concluded that HBO exerted arousal-promoting effects on unconscious rats, and the underlying mechanism may be due to ATP/orexin A upregulation. HBO may become a practical clinical approach to accelerate unconsciousness recovery in patients.
- The final two papers focus on clinical prognosis and assessment of the quality of care. In clinic, perihematomal edema (PHE) is a radiological marker of secondary injury following ICH and becoming increasingly used as a proof-of-concept surrogate measure to assess the potential efficacy of various therapeutic interventions in clinical trials (Selim & Norton, 2018). Dr. Selim reviewed the pathophysiology of PHE, its prognostic significance for clinical outcomes, and irregularity in PHE measurement methods in order to determine the advantages of exploiting PHE as a marker to evaluate the efficacy of interventions aiming to decrease secondary injury in ICH (Selim & Norton, 2018). With regard to assessing the quality of care, the 30-day readmission rates can be used as a quantitative measurement. This metric has been studied for SAH patients in order to evaluate the quality of care provided (Ng & Du, 2019). Interestingly, the 30-day readmission rate primarily captures values such as the number of comorbidities, disease severity, and discharge dispositions for the SAH patients. There is little association between SAH 30-day readmission rates and mortality (Ng & Du, 2019).

3 | SUMMARY

The current special issue in the *Journal of Neuroscience Research* updates the current developments in the field of brain edema in relation to brain injuries and neuroinflammation. The Brain Edema Society board member meeting was held on December 9, 2017, during which Professor Anding Xu was elected to serve as the chair. Professor Nikolaus Plesnila (Ludwig-Maximilians-University Munich LMU, Germany) was elected as the incoming chair, starting from 2019. The new board members of the Brain Edema Society include Jerome Badaut (France), Ross Bullock (USA), Oliver Kempski (Germany), Toshihiko Kuroiwa (Japan), Takeshi Maeda (Japan), Robert Ostrowski (Poland), Nikolaus Plesnila (Germany), Hidenori Suzuki (Japan), Guohua Xi (USA), and John Zhang (USA). The Emeritus Advisory Board members are Alexander Baethmann (Germany), Umeo Ito (Japan), Zbigniew Czernicki (Poland), Yoichi Katayama (Japan), and David Mendelow (UK).

The 18th international conference on Brain Edema and Cellular Injury will be on October 5–7th, 2020 in Berlin Germany, and will be chaired by Prof Nikolaus Plesnila (Ludwig-Maximilians-University Munich LMU, Germany). We look forward to seeing you in Germany 2020.

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Jerome Badaut[1,2]
John Zhang[2,3]

[1]*CNRS UMR 5287, University of Bordeaux, Bordeaux, France*
[2]*Basic Sciences, Loma Linda University School of Medicine, Loma Linda, CA, USA*
[3]*Department of Physiology, Basic Sciences, Loma Linda University School of Medicine, Loma Linda, CA, USA*

Correspondence
Jerome Badaut, CNRS UMR 5287, University of Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux cedex, France.
Email: jerome.badaut@u-bordeaux.fr

John Zhang, Department of Physiology, Basic Sciences, Loma Linda University School of Medicine, Loma Linda, CA, USA.
Email: johnzhang3910@yahoo.com

ORCID

Jerome Badaut https://orcid.org/0000-0001-8475-0519
John Zhang https://orcid.org/0000-0002-4319-4285

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