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Commentary

Medium-chain Fatty Acids as Biomarkers of Mitochondrial Dysfunction in Traumatic Brain Injury

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Traumatic brain injury (TBI) is a complex disorder with variable etiology and severity that nowadays stands as a major cause of death and disability worldwide, principally among children and young people. Despite the implementation of intensive care strategies at early stages following the injury, long-term morbidity of severe TBI still remains high, and many patients may show significant neurologic sequelae even after recovery, which usually persist for years. For this reason, there is a critical need to get a deeper insight into pathological mechanisms occurring in brain after trauma and discover potential biomarkers that could help in diagnosis, staging disease severity, monitoring disease progression, the identification of complications, as well as the development of better strategies for treatment and rehabilitation after injury. TBI pathology begins with a mechanical brain damage, which is followed by complex and dynamic perturbations in multiple molecular pathways in glia and neurons. Thus, holistic approaches such as metabolomics stand out as suitable tools for characterizing these metabolic alterations. Metabolomics can be defined as the comprehensive study of the entire set of metabolites from a cell, tissue, organ, body fluid or organism at a specific time, as well as of the metabolic changes observed in response to a genetic or environmental perturbation. However, only a few authors have previously reported the application of metabolomic techniques for investigating TBI pathogenesis, usually by employing nuclear magnetic resonance (^{1}H-NMR) to study the brain and blood metabolome from different animal models (Viant et al., 2005; Bahado-Singh et al., 2016a; Bahado-Singh et al., 2016b). Thereby, it was demonstrated that numerous significant disturbances in TBI might be associated with oxidative stress, membrane disruption, failures in energy metabolism and neuronal injury, among other pathological processes.

In the current issue of EBioMedicine, Orešič et al. (2016) describe the application of a metabolomic platform based on bi-dimensional gas chromatography coupled to high-resolution mass spectrometry (GC × GC-TOF-MS) to identify biomarkers in serum samples that could associate with disease severity and predict the outcomes of TBI patients. For this purpose, two independent cohorts were enrolled with the aim to validate results obtained in the discovery phase, comprising mild, moderate and severe TBI patients as well as orthopedic controls. Various metabolomic alterations were detected in serum samples, following the same pattern in all patients but with a proportional degree of change depending on the disease severity, thus suggesting that TBI is characterized by a specific metabotype. Moreover, some of these metabolites could be also associated with patient clinical outcomes, which were then employed to build a predictive model with good accuracy. Significant changes were observed in serum levels of different hydroxyl-acids, sugar-derived metabolites as well as amino acids and related compounds. Furthermore, many of these metabolites were highly correlated with their content in brain microdialysates, thus evidencing a possible disruption of the blood brain barrier. However, the most relevant finding was the increase of two medium chain fatty acids (MCFA), including octanoic and decanoid acids, whose levels remain high in most patients during the first week following the injury, and could be associated with poor outcomes in TBI patients. The accumulation of MCFAs, together with their corresponding acyl-carnitines, is the typical feature of medium-chain acyl-coenzyme A dehydrogenase deficiency, the most frequent fatty acid oxidation disorder, and one of the most recognizable inborn errors of metabolism (Rinaldo and Matern, 2002). Nevertheless, recent studies have also associated this metabolic signature with other heterogeneous diseases, such as Alzheimer's disease (González-Domínguez et al., 2014), schizophrenia (Liu et al., 2014) and different types of cancer (Hori et al., 2011; Crotti et al., 2016), all of them characterized by impaired mitochondrial function. Furthermore, it has been demonstrated that these fatty acids can provoke significant failures in various pathways related to energy metabolism, including the oxidative phosphorylation and the creatine kinase system, and may elicit lipid and protein oxidative damage (Schuck et al., 2009). Thereby, there is considerable evidence that suggests the potential of these circulating MCFAs as biomarkers of mitochondrial dysfunction.

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Therefore, it is noteworthy that octanoic and decanoic acids could play a major role in energy crisis associated with mitochondrial failures occurring in traumatic brain injury. However, it remains unclear if these metabolic changes are causative performers of the pathophysiology observed or, on the contrary, they are a consequence of these impairments. Thus, a better understanding of pathological mechanisms underlying to these perturbations is necessary to obtain a deeper knowledge about the relationships between TBI and medium-chain fatty acids. To this end, future studies should be undertaken with complementary metabolomic approaches such as reversed phase liquid chromatography-mass spectrometry in order to elucidate the relevance of lipid metabolism and fatty acid β-oxidation in pathogenesis of traumatic brain injury.

Disclosure

The author declares no conflicts of interest.

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