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Autor	ALESSANDRA AMARAL DE VASCONCELLOS
Orientador	DIOGO ONOFRE GOMES DE SOUZA

Peripheral blood mononuclear cells drive astrocyte energetic failure in acute sepsis

Aluno: Alessandra Amaral de Vasconcellos

Orientador: Prof. Dr. Diogo Onofre Gomes de Souza

Instituição: Departamento de Bioquímica, UFRGS

Introduction: Sepsis is characterized by a severe and disseminated inflammation. When inflammation spreads to the central nervous system it promotes neuronal dysfunction and permanent cognitive impairment. Astrocytes are specialized immune-competent cells involved in brain surveillance that have been gaining considerable attention in this context. However, the communication between peripheral immune system and astrocytes during acute sepsis still remains unclear. We hypothesized that peripheral blood mononuclear cells (PBMCs) are able to affect the brain, eliciting astrocyte reactivity, during an episode of acute sepsis.

Methods: Wistar rats (90 days old) were submitted to cecal ligation and perforation (CLP) to induce sepsis. 24 h later, animals were examined *in vivo* via Micro-PET [^{18}F]FDG imaging. Metabolic brain networks were constructed by computing Pearson correlation coefficients based on 10000 bootstrap samples. Primary astrocyte cultures were obtained from 1-2 days old rats and treated with PBMC conditioned media (PBMC CM) from septic or sham rats (10% v/v) and/or 10 µM LY294002 [a phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) inhibitor] for 72 h.

Results: Whole brain [^{18}F]FDG hypometabolism was observed in the CLP group. Additionally, sepsis changed multiple connections within the metabolic network, promoting a widespread metabolic hyposynchronicity. Graph measures demonstrated a consistent reorganization in the brain metabolic network indexed by lower density, reduced global efficiency, assortativity and small-worldness. *Ex vivo* analyses demonstrated astrocyte reactivity along with reduced capacity of taking up glutamate. Also, by exposing cultured astrocytes to PBMC CM from CLP animals, we reproduced the energetic failure observed *in vivo*. Finally, by pharmacologically inhibiting PI3K, a central metabolic pathway, we mimicked PBMCs effect on glutamate uptake but not on glucose metabolism.

Conclusions: These results suggest that PBMCs are capable of directly mediating astrocyte reactivity and contribute to the brain energetic failure observed in acute sepsis. Moreover, the evidence of PI3K participation in this process indicates a potential target for therapeutic modulation.