

## Sepsis worsens the neurological outcome of traumatic brain injury: role of sialic acids related to glial activation

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Microglial cells are the brain resident macrophages that, in response to brain injury, changes its phenotype from ramified to “activated” ameboid, increase motility to the site of damage and secrete soluble factors that modulate surrounding environment [1]. Astrocytes are the predominant glial cell type in the CNS that play a central role in forming the inhibitory glial scar contributing to neuroprotection and repair. As well as microglia they change morphology after injury, undergoing to hypertrophy and forming a dense network bordering the lesion site [2]. Both, in healthy and damaged CNS, these processes are controlled by intracellular interactions of glial cells with several components of the brain microenvironment [3]. Between them sialic acids are one of the most important glycans expressed at the cell surface and recently it has been demonstrated that polysialic acid (PSA), a linear homopolymer attached to the neural cell adhesion molecule (NCAM), has a central role in restoring adult injured tissue by creating conditions permissive for architectural remodeling. The aim of this study was to evaluate the glial cells sialic acids expression pattern in a rat model of traumatic brain injury complicated by sepsis.

PSA content was evaluated by immunohistochemistry, whereas expression of sialic acid and the different types of sialic acid residues was evidenced by fluorescent lectin histochemistry. Experiments were performed on adult male rats assigned to four groups: 1) sham-operated; 2) Caecal Ligation and Puncture (CLP) (clinically model of polymicrobial infection that mimics human sepsis); 3) Controlled Cortical Impact (CCI) (clinically model of brain cortical injury); 4) sepsis superimposed to traumatic brain injury (CLP + CCI). The evaluations were carried out 14 days from CLP, CCI or CCI+CLP. Our results showed that in the lesional region sepsis associated with CCI causes a significant increase in sialic acid linked  $\alpha$ 2,3 (MALI) and  $\alpha$ 2,6 to galactose/galactosamine (SNA) in respect to sham, CLP, and CCI rats ( $P < 0.001$ ). As regards the CCI group both sialic acids increase their pattern of expression in respect to control group, whereas the CLP group showed a significant increase ( $P < 0.001$ ) in respect to the sham group only for the SNA lectin reactivity. PSA expression in the lesioned cortex evidenced an overexpression in the CCI group in respect to all the other groups of animals ( $P < 0.001$ ). Interestingly, the sepsis (CLP and CLP+CCI) seems to induce a downregulation of PSA expression level compared to sham or to CCI alone ( $P < 0.001$ ). As regards the colocalization studies, our results revealed that the cells showing the lectin reactivity (MALI and SNA) were strongly positive also for the Iba-1 immunoreactivity, whereas the astrocytes immunoreactivity did not show a correlation with the lectin expression. On the contrary, PSA co-localized both with microglia and astrocytes. Our findings suggest that the sepsis-dependent PSA downregulation may be implied in the delay of tissue repair processes. Moreover, the changes in sialic acids expression could be involved in maintaining glia activation.

### References

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