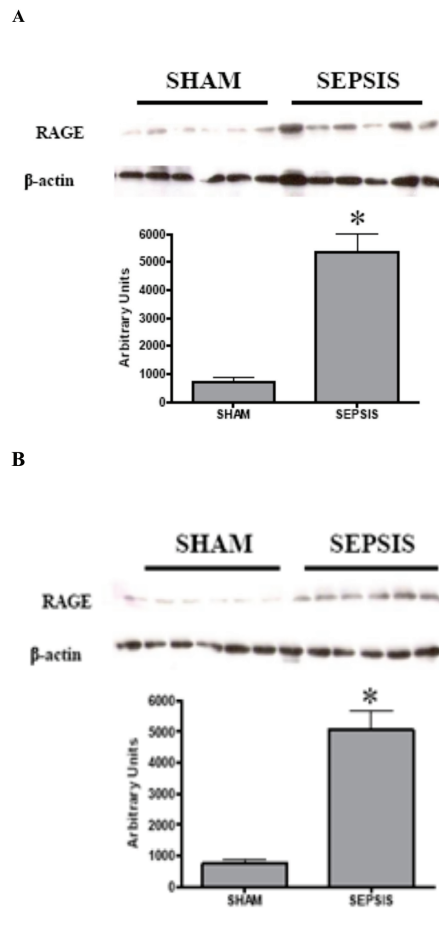


## Is There a Role for High Mobility Group Box 1 and the Receptor for Advanced Glycation End Products in the Genesis of Long-term Cognitive Impairment in Sepsis Survivors?

Recently, Chavan *et al.* (1) demonstrated the major role of high mobility group box 1 (HMGB1) in cognitive dysfunction in sepsis survivors. By using a severe sepsis mice model, they clearly showed that serum HMGB1 levels were elevated 4 wks after sepsis (1). In addition, these animals had significant long-term impairments in learning and memory that were reversed by the administration of anti-HMGB1 antibody (1). The fact that HMGB1 can be one of the major mediators that leads to cognitive impairment suggests that some of its receptors can be a therapeutic target in this context. The interactions involving HMGB1, Toll-like receptors (TLRs) and the receptor for advanced glycation end products (RAGE) are considered relevant in some diseases (2), and these are one of the postulated mechanisms raised by Chavan *et al.* (1) to explain their results. In fact, TLR upregulation was demonstrated after endotoxemia (3), but no direct evidence of an upregulation of RAGE was found in the literature. Thus, by using a rat model of sepsis (4), we looked for the content of RAGE in the brain 30 d after sepsis, when these animals presented impairments of learning and memory (5,6). RAGE content was determined by Western blot by using anti-RAGE antibodies (R5278; Sigma, St. Louis, MO, USA). RAGE content, in hippocampus and prefrontal cortex, of septic animals was increased when compared with sham animals (Figures 1A, B).



**Figure 1.** Immunoccontent of RAGE in the hippocampus and prefrontal cortex of sepsis survivor animals. Sepsis was induced by cecal ligation and perforation and, after 30 d, the immunoccontent of RAGE was evaluated in samples from the hippocampus (A) and prefrontal cortex (B). Representative immunoblots of individual samples from different animals from sham and sepsis groups are shown, and the bar graphs represent mean values  $\pm$  standard error normalized by  $\beta$ -actin immunoccontent. Data were analyzed by *t* test. \*Difference from sham group ( $p < 0.05$ ).  $n = 15$  for each group.

It is well described that HMGB1 can bind RAGE, and the activation of RAGE in the central nervous system has been increasingly implicated in the progression of neurodegeneration (7). The neurotoxicity related to RAGE signaling in the brain is believed to be associated with mechanisms that enhance RAGE ex-

pression and/or the production and secretion of RAGE ligands (8). One of the main intracellular targets of RAGE activation is the transcription factor nuclear factor (NF)- $\kappa$ B, which activates microglia, thus perpetuating brain inflammatory response (9). Thus, taken together, these results pointed to a role of HMGB1-RAGE signaling activation as a major pathway for the long-term cognitive impairment observed in sepsis survivors. A great effort must be done to clearly demonstrate the relevance of HMGB1-TLR-RAGE signaling as the major mediator of long-term cognitive impairment in sepsis survivors.

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## DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

## REFERENCES

1. Chavan SS, et al. (2012) HMGB1 mediates cognitive impairment in sepsis survivors. *Mol. Med.* 18:930–7.
2. Nogueira-Machado JA, Volpe CM, Veloso CA, Chaves MM. (2011) HMGB1, TLR and RAGE: a functional tripod that leads to diabetic inflammation. *Expert. Opin. Ther. Targets.* 15:1023–35.
3. Chakravarty S, Herkenham M. (2005) Toll-like receptor 4 on nonhematopoietic cells sustains CNS inflammation during endotoxemia, independent of systemic cytokines. *J. Neurosci.* 25:1788–96.
4. Ritter C, et al. (2003) Oxidative parameters and mortality in sepsis induced by cecal ligation and perforation. *Intensive Care Med.* 29:1782–9.
5. Barichello T, et al. (2006) Oxidative variables in the rat brain after sepsis induced by cecal ligation and perforation. *Crit. Care Med.* 34:886–9.
6. Tuon L, et al. (2008) Time-dependent behavioral recovery after sepsis in rats. *Intensive Care Med.* 34:1724–31.
7. Yan SD, Bierhaus A, Nawroth PP, Stern DM. (2009) RAGE and Alzheimer's disease: a progression factor for amyloid-beta-induced cellular perturbation? *J. Alzheimers Dis.* 16:833–43.
8. Zhang L, Postina R, Wang Y. (2009) Ectodomain shedding of the receptor for advanced glycation end products: a novel therapeutic target for Alzheimer's disease. *Cell Mol. Life Sci.* 66:3923–35.
9. Du Yan S, et al. (1997) Amyloid-beta peptide-receptor for advanced glycation endproduct interaction elicits neuronal expression of macrophage-colony stimulating factor: a proinflammatory pathway in Alzheimer disease. *Proc. Natl. Acad. Sci. U. S. A.* 94:5296–301.