

## Response to “HMGB1 Mediates Cognitive Impairment in Sepsis Survivors”

The letter from Dal-Pizzol *et al.* (1) addresses the question of brain cell activation in sepsis survivors. The data demonstrate that RAGE (receptor for advanced glycation end products) expression in the hippocampus and in the prefrontal cortex is significantly increased 4 wks after septic insult. This is an interesting observation because it indicates that altered expression of specific brain proteins can be sustained for weeks after sepsis. The significance of these findings can be considered in light of our recent report showing that HMGB1 (high mobility group box 1), one of the putative RAGE ligands, mediates memory loss in sepsis survivors (2).

The novel findings by Dal-Pizzol *et al.* (1), combined with Chavan *et al.* (2), raise additional questions: What is the time course for the elevation of RAGE levels? Is it an immediate increase after septic insult, indicating a direct link between sepsis-mediated systemic inflammation and increased RAGE expression? Alternatively, is it a late effect, suggesting it is caused by sepsis-induced changes in brain physiology and not by the systemic inflammation? Which molecular cascade induces RAGE expression? What sustains the high expression of RAGE? Do receptors besides RAGE mediate HMGB1-dependent alteration of memory function, as suggested in a recent report by Mazarati *et al.* (3)? Which brain cells express RAGE? Is HMGB1 directly affecting neurons, or is it altering glial cell biology? A recent report by Pedrazzi *et al.* (4) shows that HMGB1 potentiates N-methyl-D-aspartate receptor activation, a process that might be critical for memory formation. This finding is consistent with the hypothesis that HMGB1 acts directly on

neurons, but it may also activate glial cells, which in turn can modulate neuronal signaling via other cytokine networks. Finally, it is worth mentioning that HMGB1 may be deleterious to neurons or may function to compensate for previous injury. In sum, we agree with the authors of the letter that this is an important area of research with significant implications for medical practice.

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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.

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