Commentary

Targeting RAGE in sepsis

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See related review by Bopp *et al*., http://ccforum.com/content/12/1/201

Abstract

The receptor of advanced glycation endproducts (RAGE) is a multiligand receptor that upon activation causes sustained activation of multiple inflammatory pathways. Recent evidence, summarized in a review by Bopp and colleagues in this issue of *Critical Care*, has implicated RAGE as a potential therapeutic target in sepsis. Here, we discuss several open issues that need to be addressed before anti-RAGE strategies can enter the sepsis clinical trial arena.

In a review in this issue of *Critical Care*, Bopp and colleagues [1] summarize current knowledge on the receptor of advanced glycation endproducts (RAGE) and its potential as a new therapeutic target in sepsis. RAGE is expressed in many cell types involved in the innate immune system and is able to recognize a wide range of endogenous molecules that are released during various conditions of inflammation and/or injury. Collectively, these endogenous molecules, which warn the host of imminent danger, have been called alarmins or danger-associated molecular patterns [2]. An important example of an alarmin and an established ligand for RAGE with relevance for sepsis is high-mobility group box 1 (HMGB1) [3].

Activation of RAGE results in sustained activation of nuclear factor-kappa B (NF-κB), thereby converting transient pro-inflammatory responses into lasting cellular dysfunction [4]. The evidence that inhibition of RAGE may be beneficial in sepsis is derived from what is, thus far, a limited number of studies. In a hallmark study published in 2004, Liliensiek and colleagues [5] reported that RAGE-deficient mice were strongly protected against lethality due to polymicrobial sepsis caused by cecal ligation and puncture (CLP). The protection provided by the lack of RAGE was associated with a strongly reduced activation of NF-κB in the peritoneum and lungs, which in wild-type mice was abundantly present, suggesting that the absence of excessive NF-κB activation in RAGE-deficient mice might have contributed to their reduced mortality [5]. In addition, RAGE deficiency resulted in a diminished accumulation of inflammatory cells in the peritoneum, which is in line with an earlier investigation by the same group of authors identifying RAGE as a counter-receptor for the β2-integrin Mac-1 (CD11b/CD18) and thereby as a mediator of leukocyte recruitment and adhesion [6]. Moreover, other authors have demonstrated that RAGE-deficient mice are partially protected against lethality due to endotoxin shock [7]. It is likely that the protective effect of RAGE inhibition in experimental sepsis is due, at least in part, to inhibition of one of its ligands, HMGB1. Indeed, HMGB1 is released in the circulation during experimental and clinical sepsis and an anti-HMGB1 antibody protected against endotoxin- and CLP-induced lethality [8,9]. Importantly, HMGB1 can activate not only RAGE but also other receptors, most notably Toll-like receptors 2 and 4 [3], and anti-HMGB1 treatment caused an additional survival benefit in RAGE-deficient mice injected with high-dose endotoxin, suggesting that HMGB1 acts only partially via RAGE during endotoxin shock [7].

Which questions remain to be answered to further establish a role for RAGE in sepsis and to obtain further support for the notion that RAGE may be a therapeutic target in this syndrome? When addressing this question, one needs to consider that the historic concept of the pathogenesis of sepsis implicating mortality as the consequence of an uncontrolled hyperinflammatory response of the host has

CLP = cecal ligation and puncture; HMGB1 = high-mobility group box 1; NF-κB = nuclear factor-kappa B; RAGE = receptor of advanced glycation endproducts.

been modified. The scientific community now agrees that this paradigm is oversimplified and only partially true [10]. The extent and duration of hyperinflammation likely vary due to differences in the comorbidity, nutritional status, age, and genetic background of the patient, on the one hand, and the initial source of the infection, the virulence of the causing organism, and the size of the infectious inoculum on the other hand. In most if not all patients who survive the acute phase of sepsis, a prolonged state of immune suppression evolves; this condition is referred to as immunoparalysis [11]. Moreover, experimental studies have indicated that a certain degree of inflammation is necessary to mount an effective innate immune response to invading pathogens. As such, RAGE inhibition may be ineffective or even harmful in some infectious conditions. Therefore, more research is required to situate RAGE in a position that warrants clinical trials in patients with sepsis. In this respect, one could think of studies on RAGE inhibition in pneumonia, considering that the lung not only is the most frequent cause of sepsis in humans [12] but also represents an organ in which RAGE is abundantly expressed [13]. In addition, experiments in which anti-RAGE treatment is delayed until after bacterial infection (peritonitis and pneumonia) and combined with antibiotic therapy should be considered. Moreover, more studies need to be conducted on the role of RAGE in critical organ derangements implicated in the pathogenesis of sepsis, including activation of the coagulation system and the complement system. Until then, RAGE remains a potential yet promising therapeutic target in sepsis which awaits further research.

Competing interests

The authors declare that they have no competing interests.

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