Abstract

The receptor for advanced glycation endproducts (RAGE) plays central roles in the immune/inflammatory response. RAGE is expressed on monocytes/macrophages, T and B lymphocytes, and dendritic cells. Previous studies illustrated that homozygous RAGE−/− mice subjected to overwhelming bacterial sepsis displayed normal clearance of pathogenic bacteria and significantly increased survival. In this issue of Critical Care, Lutterloh and colleagues confirm these findings and provide evidence that blocking antibodies to RAGE afford similar protection in mice, even when administration of anti-RAGE is delayed by 24 hours. Furthermore, these authors illustrate that deletion of RAGE is remarkably protective in mice infected with the intracellular pathogen Listeria monocytogenes. In this Commentary, we consider these findings and propose possible mechanisms by which RAGE exacts a heavy toll on the host in response to polymicrobial sepsis and L. monocytogenes.

In confirming the results of others in RAGE−/− mice [4], these authors showed that homozygous or heterozygous deletion of the RAGE gene was strongly protective in mice subjected to cecal ligation and puncture. Furthermore, administration of blocking monoclonal antibodies to RAGE, even when delayed by 24 hours, afforded survival benefit in mice subjected to this procedure. These data provide compelling evidence that RAGE is not required for fundamental innate responses that clear bacteria. Rather, RAGE may mediate hyperinflammatory responses to the invading bacteria that are injurious to the host. Clues that this is a likely explanation have come from the novel findings of Lutterloh and colleagues in L. monocytogenes-challenged RAGE−/− mice.

These authors challenged mice with L. monocytogenes and report that RAGE−/− mice or RAGE+/− mice displayed an LD50 (median lethal dose) that was more than two orders of magnitude higher than that of wild-type mice. In BALB/c mice, administration of anti-RAGE antibody offered significant protection against listeriosis. Importantly, bacterial counts did not differ among RAGE−/− and antibody-treated mice compared with controls.

HMGB-1 = high-mobility group box-1; Myd88 = myeloid differentiation factor 88; RAGE = receptor for advanced glycation end products.
As recently reviewed by Pamer [5], in the first few days of Listeria infection, the innate response is critical for early bacterial clearance and host survival. The adaptive response instead is required for controlling chronic, but not acute, infection since SCID (severe combined immunodeficiency disease) mice survive early listeriosis normally, but ultimately this infection is lethal due to long-term failure to clear the organism [6,7]. In the initial phase of infection, Listeria binds to splenic macrophages and is internalized; Listeria produces products that activate nuclear factor-kappa B and upregulate innate immune molecules such as CC-chemokine ligand CCL2 [5]. Infected macrophages then release microbial products and engage Toll-like receptors (TLRs). Via myeloid differentiation factor 88 (Myd88), these macrophages differentiate into TNF (tumor necrosis factor)- and iNOS (inducible nitric oxide synthase)-producing cells that directly promote bacterial killing. Innate immune responses are thoroughly essential for host survival to Listeria as mice deficient in Myd88 are exquisitely vulnerable to this bacterium [8]. Interestingly, mice deficient in either TLR-2 or TLR-4 display relatively normal resistance to Listeria [6,9], suggesting that compensation by other TLRs may override the loss of a single TLR and permit macrophage activation and bacterial killing. Unlike the TLRs, RAGE is not likely to be activated directly by microbial products. However, RAGE ligands inductively expressed upon macrophage activation may potentiate initial innate activation and the systemic inflammatory response.

It is well established that in listeriosis, production of interferon-γ presumably by natural killer cells or T lymphocytes is critical for macrophage activation and initial bacterial clearance as well as for promotion of long-term protective cellular immunity [10]. Herein lies an intriguing piece of the puzzle; RAGE−/− mice displayed strikingly decreased levels of interferon-γ compared with wild-type mice in listeriosis yet were significantly protected from the injurious effects of the microorganism. In addition to revealing that production of this cytokine is not absolutely linked to the initial clearance of L. monocytogenes, these findings are consistent with the notion that the RAGE-induced proinflammatory state may be deleterious in the early stages of infection yet may ultimately promote protective adaptive Th1 cellular immunity. Thus, we may predict that deletion of RAGE or RAGE blockade suppresses interferon-γ-propagated macrophage activation and the hyperinflammation response that injures the host. However, since RAGE is critical for the Th1 adaptive response [3], it will be important to address the effect of RAGE deficiency or blockade on long-term anti-Listeria immunity. Note that Lutterloh and colleagues examined interferon-γ levels at 48 hours post-infection and in plasma only, not tissue. Thus, it remains possible that levels of this cytokine in RAGE−/− mice might have been different at distinct sites or time points in the infection.

How may RAGE signaling pathways be specifically recruited in listeriosis? Adaptive RAGE-dependent mechanisms may contribute to production of interferon-γ. What, then, overrides the otherwise protective effects of interferon-γ production? We propose that stimulated macrophages, in addition to releasing microbial products in the early response to infection...
release the RAGE ligand HMGB-1 [12,13]. HMGB-1, which may engage TLR-2 and TLR-4 [14], as well as RAGE, might activate signaling systems that stimulate hyperinflammatory responses (Figure 1).

In conclusion, in polymicrobial sepsis and in response to L. monocytogenes, genetic deletion of RAGE is remarkably protective. RAGE is not directly required for bacterial clearance, but the compelling experiments of Lutterloh and colleagues confirm that RAGE action mediates tissue damage initiated in response to overwhelming bacterial infection. Future studies must dissect the precise mechanisms by which RAGE exacts a heavy toll on the host during efforts to combat pathogenic bacteria.

Competing interests
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