Sepsis and sepsis syndrome are leading causes of mortality throughout the world. It is widely held that sepsis represents a dysregulated innate immune response to an offending pathogen. This immune response is often initiated via microbial products signaling through TLRs expressed on host immune cells. There is increasing evidence that this innate response can be dramatically influenced by the cellular redox state, and thus a better understanding of oxidative regulation of innate immunity could lead to new treatments for sepsis. In this issue of the *JCI*, Thimmulappa et al. show that nuclear factor-erythroid 2–related factor 2 (Nrf2), a member of the “cap’n’collar” family of basic region–leucine zipper transcription factors, which has previously been shown to be involved in the transcription of antioxidant gene expression in response to xenobiotic stress, is also a critical regulator of cellular oxidative stress in sepsis (see the related article beginning on page 984).
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Despite decades of advances in antibiotic treatment, sepsis remains an elusive killer, with over 750,000 cases per year in North America (1) with a 40–50% mortality rate in adults. Sepsis is mediated by infectious stimuli, and many of the clinical findings of sepsis can be replicated in experimental animal models using specific bacterial products such as LPS (2). The last decade of immunological research has revolutionized how scientists understand the initiation of the innate immune response to invading pathogens. For many offending agents, the TLR family of proteins functions as the host sentinels to invading pathogens. This was first demonstrated in Drosophila melanogaster in 1996 (3), where Toll was shown to regulate the production of the antifungal molecule dorosphycin, and later in mammals, when positional cloning revealed Tlr4 to be the Lps gene product (4). An additional 10 human TLRs have been described that recognize other bacterial products as well as fungi and viruses. These receptors signal via their Toll/IL-1 receptor (TIR) domains containing adaptor proteins: (a) MyD88; (b) TIR domain–containing adaptor inducing IFN-β (TRIF); (c) MyD88–like/TIR-associated protein (MAL/TIRAP); and (d) TRIF-related adaptor molecule (TRAM) (2). In the case of LPS signaling through TLR4, the MyD88-dependent pathway is critical for NF-kB activation and the production of TNF-α whereas the MyD88-independent, TRIF-dependent pathway is required for type I IFN production. Based on the fact that 10 human TLRs signal via 4 adaptors and 2 predominant kinases to subsequently regulate the expression of hundreds of genes, the innate immune response has been proposed to be shaped like an hourglass (Figure 1). The top of the hourglass is wide, indicating that 10 TLR proteins recognize a variety of potential offending pathogens, then the hourglass narrows to represent a smaller number of highly conserved TLR adaptor proteins and initial kinases, and then it widens again to reflect the increased number of genes that are transcriptionally activated by NF-kB and other transcription factors (2). This notion is further supported by the fact that this signaling pathway is markedly conserved among mammalian species, and mutations in this pathway in humans that lead to defective TLR signaling are associated with the development of invasive meningococcal (5) or Legionella

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**Oxidative stress in sepsis: a redox redux**

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**Nonstandard abbreviations used:** IKK, inhibitor of κB kinase; IRAK, IL-1 receptor–associated kinase; IRF-3, IFN regulatory factor 3; NAC, N-acetyl cysteine; Nrf2, nuclear factor-erythroid 2-related factor 2; TIR, Toll/IL-1 receptor; TRIF, TIR domain–containing adaptor inducing IFN-β.  

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Infections (6). The work by Thimmulappa et al. (7) in this issue of the JCI suggests that this hourglass may not be so narrow at its center, as many of the kinases active downstream of TLR signaling can be regulated through oxidant (redox)–dependent posttranslational modifications, resulting in an additional level of control of TLR signaling (Figure 1).

**Nrf2 and oxidative stress**

Redox-dependent control of TLR4 signaling stems from the fact that many of the kinases, transcription factors, and subsequent gene products induced by the TLR4 ligand, LPS, can be posttranslationally modified by ROS (Figure 1). In fact, this has been well studied in the context of NF-κB translocation to the nucleus and activation of activator protein 1 (AP-1) — 2 transcription factors that regulate gene expression after LPS stimulation of macrophages (8, 9). Due to the many sources of ROS within the cell, it has been difficult to take a reductionist approach to identify the critical regulatory factors that control oxidant production at the subcellular level. Moreover, the molecular targets of ROS are...
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In the current study, mice deficient in Nrf2 displayed increased mortality in both a sterile (LPS administration) and a nonsterile (cecal ligation and puncture) model of sepsis (7). Moreover, Nrf2 deficiency resulted in increased levels of TNF and lung injury in Nrf2−/− mice (7). These data confirm the critical role of the cellular redox state in regulating innate immune responses and support the contention that the transcriptional regulation of the antioxidant response is critical in regulating the cellular response to external stressors. Thus, polymorphisms may exist in the Nrf2 gene that may identify subjects at risk for more severe sepsis. In a recent clinical trial, NAC was shown to reduce NF-κB activation as well as IL-8 secretion in patients with sepsis (19). However, in a subsequent randomized trial of 34 patients, NAC failed to improve end-organ function or microalbuminuria (20). This underlying reason for the failure of antioxidant therapy may be similar to that observed for the failure of other anti-inflammatory approaches: the timing of these interventions may be too late to adequately interfere with the induction of the inflammatory cascade. Thus, early administration of antioxidant-based therapy is likely critical. A potential advantage of an antioxidant approach is that restoration of normal cellular glutathione levels should leave basal innate immunity intact. However, it remains unclear which subcellular stores of glutathione need to be restored.

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