Published in final edited form as:
Shock. 2012 January ; 37(1): 124–125. doi:10.1097/SHK.0b013e31823b7643.

WHAT IS THE ROLE FOR THE INFLAMMASOME IN BURN INJURY AND SEPSIS?

Lori F. Gentile and **Lyle L. Moldawer**
Department of Surgery, University of Florida College of Medicine, Gainesville, Florida

Since the discovery of the inflammasome and its first report in the literature nearly 10 years ago, the inflammasome complex has been emerging as a key modulator of the innate immune response via inflammatory cytokine production and pyroptosis (1). The inflammasome is a large multiprotein complex thought to be assembled around Nod-like receptor protein complexes that detect microbial pathogen-associated molecular patterns and damage-associated molecular patterns in intracellular compartments, very similar to the role of Toll-like receptors on the cell surface or within endosomes (2). The inflammasome ultimately leads to the activation of caspase 1, which activates downstream effectors and proinflammatory cytokines interleukin 1β (IL-1β) and IL-18 in macrophages, dendritic cells, and epithelial cells. It is presumed that the activation of such proinflammatory cytokines that, when excessive, promotes organ injury and ultimately mortality related to sepsis and injury.

Despite a growing body of evidence examining the inflammasome's components and mechanisms, many questions remain regarding the exact signaling pathways leading to activation of the inflammasome complex (3). Moreover, the role the inflammasome plays in response to injury remains hotly debated. To date, dysregulated activation of the inflammasome has been implicated in several human diseases including systemic lupus erythematosus, rheumatoid arthritis, and gout, as well as in hereditary Muckle-Wells syndrome (a periodic fever syndrome) and diabetes mellitus. As these entities are associated with excess IL-1β production, there has been some therapeutic success in human trials with IL-1 antagonists in these conditions (3), thus the interest in the inflammasome as a more proximal therapeutic target.

In this issue of *Shock*, Osuka and colleagues (4) demonstrate significant caspase 1 activation in macrophages, dendritic cells, and natural killer cells in mice following burn injury and surmise that inflammasome activation plays a protective role in the host response to burn injury, as burned mice had a higher rate of mortality when caspase 1 activity was blocked with the caspase 1–specific inhibitor Ac.YVAD.cmk. There is a paucity of work investigating the role of the inflammasome *in vivo* following burn injury, and this continues a long line of investigation by the Lederer group. Interestingly, the findings from this novel study appear contrary to several previous published reports in other acute inflammation models, which in general have demonstrated a protective effect of caspase 1 blockade. For example, caspase 1 knockout mice have a survival advantage in endotoxin-induced shock (5) and bacteria-induced sepsis, independent of IL-1β and IL-18 production (6). Interestingly, Giamarellos-Bourboulis et al (7) showed that activated caspase 1 was nearly

absent in peripheral blood mono-nuclear cells from patients with sepsis, suggesting that pharmaceutical inactivation of caspase 1 in this setting would be irrelevant.

The studies of Osuka and colleagues (4) are clearly well conducted and present convincing findings that activation of the inflammasome is protective in this setting of burns. There is strong precedent for the observation that inflammatory responses can be protective under some conditions and detrimental under others. This is the conundrum of the injury response that has bedeviled investigators seeking novel therapeutics. For example, endogenous IL-10 production in severe polymicrobial sepsis or endotoxicosis can be protective because of its anti-inflammatory properties (8) but, as Kelly et al (9) have ably shown in the past, can also inhibit T-cell function after burn injury.

One worries that the protective effects of caspase 1 blockade seen in burn injury may be unique to these experimental conditions. The same concern exists regarding their potential mechanisms. Is the beneficial caspase 1 effect reported by Osuka et al (4) due to the inhibition of IL-1/IL-18 processing, without any effect on apoptosis? Perhaps, but that is not clear. Sarkar et al (6) reported that the caspase 1 knockout mice sustained significantly less splenic cell apoptosis than their wild-type counterparts following bacterial-induced sepsis. Likewise, in a study examining the role of the inflammasome following traumatic spinal cord injury, mice that had caspase 1 blocked with AC-YVAD-CMK had significantly less neuronal cell apoptosis than their control counterparts (10).

Osuka et al (4) were able to segregate apoptosis from caspase 1 activation in the burn model. They observed significant increases in annexin V binding in splenic cells of mice on day 1 following burn injury, without similar increases in caspase 1 expression (via p10 and p20 expression), concluding that cells undergoing apoptosis after burns were not dependent on caspase 1.

No single study can definitively answer one question, let alone two. The importance of this study is in its demonstration that apoptosis is not dependent on caspase 1 activity in burns and that inhibition of caspase 1 is protective. We are left, however, with the unanswered questions; what are the mechanisms behind the survival advantage associated with caspase 1 blockade, and why are these findings so different from more lethal models of infection or sepsis? Clearly, these findings are important, and they just reconfirm how little we know about the role of the inflammasome in burns and infections, and whether its activation is either protective or detrimental or both. The answers are undoubtedly more complex than the authors would suggest in this preliminary investigation.

References

1. Lamkanfi M. Emerging inflammasome effector mechanisms. Nat Rev Immunol. 2011; 11(3):213–220. [PubMed: 21350580]
2. Vande Walle L, Lamkanfi M. Inflammasomes: caspase-1–activating platforms with critical roles in host defense. Front Microbiol. 2011; 2:3. [PubMed: 21687402]
3. Tschopp J, Schroder K. NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production? Nat Rev Immunol. 2010; 10(3):210–215. [PubMed: 20168318]
4. Osuka A, Hanschen M, Stoecklein V, Lederer JA. A protective role for inflammasome activation following injury. Shock. 2011; 37(1):47–55. [PubMed: 21921832]

5. Li P, Allen H, Banerjee S, Franklin S, Herzog L, Johnston C, McDowell J, Paskind M, Rodman L, Salfeld J, et al. Mice deficient in IL-1 beta–converting enzyme are defective in production of mature IL-1 beta and resistant to endotoxic shock. Cell. 1995; 80(3):401–411. [PubMed: 7859282]

6. Sarkar A, Hall MW, Exline M, Hart J, Knatz N, Gatson NT, Wewers MD. Caspase-1 regulates *Escherichia coli* sepsis and splenic B cell apoptosis independently of interleukin-1beta and interleukin-18. Am J Respir Crit Care Med. 2006; 174(9):1003–1010. [PubMed: 16908867]

7. Giamarellos-Bourboulis EJ, van de Veerdonk FL, Mouktaroudi M, Raftogiannis M, Antonopoulou A, Joosten LA, Pickkers P, Savva A, Georgitsi M, van der Meer JW, et al. Inhibition of caspase-1 activation in Gram-negative sepsis and experimental endotoxemia. Crit Care. 2011; 15(1):R27. [PubMed: 21244670]

8. van der Poll T, Marchant A, Buurman WA, Berman L, Keogh CV, Lazarus DD, Nguyen L, Goldman M, Moldawer LL, Lowry SF. Endogenous IL-10 protects mice from death during septic peritonitis. J Immunol. 1995; 155(11):5397–5401. [PubMed: 7594556]

9. Kelly JL, O'Suilleabhain CB, Soberg CC, Mannick JA, Lederer JA. Severe injury triggers antigen-specific T-helper cell dysfunction. Shock. 1999; 12(1):39–45. [PubMed: 10468050]

10. Karaoğlan A, Kaya E, Akdemir O, Sağvmanligil A, Bilguvar K, Cirakoğlu B, Sahan E, Erdoğan N, Barut AE, Colak A. Neuroprotective effects of Ac.YVAD.cmk on experimental spinal cord injury in rats. Surg Neurol. 2008; 69(6):561–567. [PubMed: 18262241]