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How Does Oxidative Stress Affect Inflammasome Activation?

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The innate immune system activated as a first line of response to host defense during bacterial infections and injury. It plays a key role in the initial recognition followed by the production of pro-inflammatory cytokines and chemokines to halt invading pathogens [1]. The innate immune response relies on recognition of evolutionarily conserved structures of pathogens, known as pathogen-associated molecular patterns (PAMPs), through a limited number of germ line-encoded pattern recognition receptors (PRRs) [2]. Among these, the family of Toll-like receptors (TLRs) has been studied most extensively for immune response [3]. Bacterial cell wall components such as lipopolysaccharide (LPS) are the most potent PAMPs known and responsible for the inflammatory response observed during bacterial infections. PAMPs trigger innate immune response by producing the major inflammatory cytokines such as IL-1b and IL-18 which by autocrine and paracrine manner generates a number of other cytokines leading to chronic inflammation, profound vasodilatation, organ failure and dysfunction [4-7]. IL-1b and IL-18 are essential for host defense, innate immune response, and mediate the pathogenesis of many inflammatory diseases such as sepsis [8]. Generally, cytokines such as IL-1b, IL-18 and IL-33, lack a signal peptide for the classic endoplasmic reticulum-mediated release of proteins by exocytosis, are synthesized as an inactive precursor by NF-κB-mediated signalosome [9]. In order to be activated, these cytokines need to be cleaved by an intracellular cysteine protease called caspase-1. For example, activation of caspase-1 cleaves 31 kDa precursor form of IL-1b into a bioactive 17-kDa form [10]. However, caspase-1 is itself synthesized as a zymogen which needs to be processed in to 20 and 10 kDa subunits to form an active enzyme. Activation of caspase-1 is mediated by recently discovered multi-protein complex called inflammasome. In response to microbial stimuli or injury, a major NOD like receptor (NLR) family member assembles in a large multi-protein complex in association with ASC and pro-caspase-1 leading to autocatalytic activation of caspase-1 [11]. NLR family proteins such as NALP1, NALP3 and NALP4 (also called NLRP1, NLRP2 and NLRP4) and a cytoplasmic protein AIM2 (absent in melanoma 2; which does not belong to NLR family) recruit CARD domain containing protein called PYCARD (or ASC) and pro-caspase-1 to from active inflammasome for the processing of inflammatory cytokines [11]. Out of these known inflammasomes, NALP3 inflammasome is extensively investigated and found to be involved in a number of inflammatory pathologies. In fact, recent emerging studies indicate that inhibition of NALP3 inflammasome -mediated innate immune response could be a novel therapeutic strategy for the prevention of inflammatory complications such as sepsis, arthritis, Crohn's disease, Alzheimer's, gout and atherosclerosis [12,13].

There are number of oxidative stress stimuli that trigger assembly of the inflammasomes and initiate innate immune response. However, the underlying molecular mechanisms of their activation are still not clearly understood. The identification of how inflammasome is activated is of immense significance since it can help to prevent or cure a number of inflammatory complications where innate immune response plays a major role. Recent studies indicate that reactive oxygen species (ROS) generated by the PAMPs such as endotoxins on one hand, activate synthesis of inflammasome protein complex proteins by activating NF-κB signalosome. On the other hand, ROS directly or indirectly could activate the formation of inflammasome complex that is required for the activation of caspase-1 and processing of innate immune response cytokines. Recent studies confirm a definite role of ROS in activation of inflammasome [14]. Superoxide dismutase (SOD) deficient macrophages specifically inhibit caspase-1 activation and SOD–knockout mice have been shown to be less susceptible to endotoxemia due to low levels of inflammasome- mediated processing of IL-1b [15]. Even though, ROS can modulate both signalosome and inflammasome pathways leading to deregulated immune response, the mechanisms by which ROS regulate activation of inflammasome and processing of inflammatory cytokines are still not clear. The ROS are formed during mitochondrial electron transport chain and by the specific enzymes such as NADPH oxidase and xanthine oxidase. It is well known that through activation of several protein kinase cascades, ROS can activate transcription factors such as NF-κB and AP1 which are involved in the synthesis of IL-1b and IL-18 and others. Now the question is how ROS activates NALP3 inflammasome? There are few hypotheses that indicate how ROS could activate inflammasome; 1) since K^+ efflux causes the formation of inflammasome assembly, it could be possible that ROS can directly mobilize intracellular K^+ ions, 2) by modulating Ca^{2+} influx ROS could modulate K^+ efflux, 3) by interacting with specific protein kinases such as syk and PI3K, ROS could change intracellular IP3 levels which regulate $Ca2^+$ and K^+ levels, 4) ROS generated aldehydes could act as endogenous danger signals that regulate K^+ levels by interacting with protein kinases, 5) ROS and lipid aldehydes could regulate the processing of cytokines by directly binding to caspase-1 and modulating its enzyme activity, and 6) by activating membrane-bound receptors or receptor tyrosine kinases, ROS could activate downstream protein kinases such as MAPKs which can regulate inflammasome –mediated processing of IL-1b. Some of these possibilities are supported by the recent findings. A recent study shows that suppression of NALP3 inflammasome when mitochondrial activity is deregulated by inhibition of the voltage-dependent anion channel [16]. Another study has demonstrated that autophagic proteins regulate NALP3-dependent immune response by preserving mitochondrial integrity [17]. Further, suppression of NADPH oxidase (p22) has been shown to prevent activation of NALP3-inflammasome [18]. In contrast, another study reports that NAPDH oxidase is not required for the release of IL-1b in the human peripheral- blood

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mononuclear cells [19]. It is also shown that ROS production could activate NALP3 inflammasome through the dissociation of ROS-sensitive NLRP3 ligand thioredoxin-interacting protein from its inhibitor thioredoxin [20]. All these studies and several other studies undoubtedly demonstrated that ROS are involved in the activation of inflammasomes by the bacterial endotoxins, infectious agents, nanoparticles, cigarette smoke, asbestos and silica.

Elucidation of redox signaling is critical for understanding multiple diseases, and for developing novel therapeutic interventions. Hence, investigating the mechanisms that control inflammasome pathways has intense significance for understanding and managing a wide array of inflammatory complications. Recent studies provided NALP3 inflammasome as an attractive therapeutic target for autoimmune, infectious diseases and cancer. Although, the studies on the role of inflammasome activation in various cancers are limited, identification of how deregulated innate immune response could contribute to various cancers is very exciting. Accordingly, potential novel strategies are required to control ROS mediated progression of inflammatory complications. Emerging studies indicate that ROS could act as essential signaling intermediates in the activation of inflammasomes and processing of initial cytokines, which triggers innate immune response. However, extensive investigations are further required to identify the mechanisms though which oxidative stress-induced ROS play a major role in the mediation of innate immune response via activation of inflammasome mediated processing of pro-inflammatory cytokines. It is also important to know how autocrine and paracrine signals of cytokines such as IL-1b and IL-18 contributes feedback formation of ROS that activates immune response. Better understandings of the signaling pathways engaged by ROS -generated lipid aldehydes contribute to inflammasome activation are essential to understand the link between cellular redox metabolism and inflammasome-mediated pathological consequences. Promising results from such studies will shed new light on the fundamental mechanisms regulating inflammasomes as well as lay down the foundation for future studies to devise strategies for clinical implications.

References

1. Medzhitov R, Janeway C Jr (2000) Innate immunity. N Engl J Med 343: 338-344.
2. Mogensen TH (2009) Pathogen recognition and inflammatory signaling in innate immune defenses. Clin Microbiol Rev 22: 240-273.
3. Akira S, Uematsu S, Takeuchi O (2006) Pathogen recognition and innate immunity. Cell 124: 783-801.
4. Netea MG, Simon A, van de Veerdonk F, Kullberg BJ, Van der Meer JW, et al. (2010) IL-1beta processing in host defense: beyond the inflammasomes. PLoS Pathog 6: e1000661.
5. Martinon F (2010) Signaling by ROS drives inflammasome activation. Eur J Immunol 40: 616-619.
6. Liao PC, Chao LK, Chou JC, Dong WC, Lin CN, et al. (2012) Lipopolysaccharide/adenosine triphosphate-mediated signal transduction in the regulation of NLRP3 protein expression and caspase-1-mediated interleukin-1β secretion. Inflamm Res.
7. Rubartelli A (2012) Redox control of NLRP3 inflammasome activation in health and disease. J Leukoc Biol.
8. Davis BK, Wen H, Ting JP (2011) The inflammasome NLRs in immunity, inflammation, and associated diseases. Annu Rev Immunol 29: 707-735.
9. Arend WP, Palmer G, Gabay C (2008) IL-1, IL-18, and IL-33 families of Cytokines. Immunol Rev 223: 20-38.
10. Denes A, Lopez-Castejon G, Brough D (2012) Caspase-1: is IL-1 just the tip of the ICEberg? Cell Death Dis 3:e338.
11. Broz P, von Moltke J, Jones JW, Vance RE, Monack DM (2010) Differential requirement for Caspase-1 autoproteolysis in pathogen-induced cell death and cytokine processing. Cell Host Microbe 8: 471-483.
12. Lamkanfi M, Dixit VM (2012) Inflammasomes and Their Roles in Health and Disease. Annu Rev Cell Dev Biol.
13. Blomgran R, Patcha Brodin V, Verma D, Bergström I, Söderkvist P, et al. (2012) Common genetic variations in the NALP3 inflammasome are associated with delayed apoptosis of human neutrophils. PLoS One 7: e31326.
14. Martinon F, Mayor A, Tschopp J (2009) The inflammasomes: guardians of the body. Annu Rev Immunol 27: 229-265.
15. Hirota SA, Ng J, Lueng A, Khajah M, Parhar K, et al. (2011) NLRP3 inflammasome plays a key role in the regulation of intestinal homeostasis. Inflamm Bowel Dis 17: 1359-1372.
16. Zhou R, Yazdi AS, Menu P, Tschopp J (2011) A role for mitochondria in NLRP3 inflammasome activation. Nature 469: 221-225.
17. Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, et al. (2011) Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 12: 222-230.
18. Leemans JC, Cassel SL, Sutterwala FS (2011) Sensing damage by the NLRP3 inflammasome. Immunol Rev 243: 152-162.
19. van Bruggen R, Köker MY, Jansen M, van Houdt M, Roos D, et al. (2010) Human NLRP3 inflammasome activation is Nox1-4 independent. Blood 115: 5398-5400.
20. Strowig T, Henao-Mejia J, Elinav E, Flavell R (2012) Inflammasomes in health and disease. Nature 481: 278-286.