**What enhances the inflammatory response: new players and unexpected roles**



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* [1](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us)



Highlights

* Cytosolic PRRs activate IRF-related genes
* NLRC5 activates the inflammasome in conjunction with NLRP3
* Oxidative burst triggers NET formation
* Endogenous TLR ligands have implications for myocarditis, atherosclerosis, and Alzheimer's disease
* miRNAs regulate resolution by interfering with the NF-κB signaling pathway

[Introduction](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#Introduction)
[The acute response to microbial infection: new pattern recognition receptors (PRRs)](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#acute)
[The neutrophil response: TNF-triggered IL-18 and the role of the oxidative burst in NET formation](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#neutrophil)
[Monocytes: an emerging role for microparticles in endothelial activation](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#Monocytes)
[The sterile tissue response: endogenous TLR ligands and a new indirect TLR signaling mechanism](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#sterile)
[Maresins and miRNAs: agents of resolution](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#Maresins)
[Conclusions](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#Conclusions)
[References](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#References)

[**Back to top**](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#topOfPage)**Introduction**

Recent research has clarified the roles of pathogen sensors like NLRC5, AIM2, and Ku70 in initiating the inflammatory response via induction of proinflammatory cytokines. Cutting-edge discoveries shed light on how oxidative burst, a mechanism that neutrophils use to kill internalized microbes, initiates another key microbicidal mechanism, the neutrophil extracellular traps (NETs). Additionally, a role is emerging for monocyte produced microparticles in activating the endothelium during infection-initiated inflammation.
Sterile inflammation, the inflammatory response to cell and tissue damage, is also yielding fresh insights. Novel endogenous Toll-like receptor (TLR) ligands have been discovered with implications for hemolysis and myocarditis, and CD36 orchestrates an unexpected route for indirect TLR signaling in response to atherosclerotic and Alzheimer's plaque components. Finally, the emergence of new players in the resolution process, the series of events that end inflammation and return the tissue to homeostasis, offers intriguing targets for examining why inflammation sometimes spirals out of control.

[**Back to top**](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#topOfPage)**The acute response to microbial infection: new pattern recognition receptors (PRRs)**

PRRs recognize molecules that are broadly shared by pathogens, but distinguishable from host molecules. Cytosolic DNA sensors remained elusive for many years, but recently, several of these receptors have finally been identified (see figure Cytosolic DNA Sensing). DNA-dependent activator of IFN-regulatory factors, or DAI, was discovered by Takaoka and colleagues in 2007. Induced in response to double-stranded DNA, DAI responds by triggering induction of Type I IFNs through interferon regulatory factor-3 (IRF3) (1). More recently, absent in melanoma-2 (AIM-2) and IFI16, the so-called AIM2-like receptors (ALRs), were also shown to respond to intracellular DNA, leading to inflammasome-mediated IL-1beta activation and IFN-beta induction, respectively (2, 3). Intriguingly, a newly identified cytosolic DNA sensor, Ku70, induces Type III rather than Type I interferons through activation of IRF-1 and IRF-7 (4).

Another PRR, the nuclear oligomerization domain-like receptor (NLR) family member NLRC5, has gained attention due to widespread interest in the inflammasome, a protein complex responsible for maturation of several inflammation-related cytokines. Recent work reveals that NLRC5 helps activate the inflammasome in conjunction with NLRP3, for processing proinflammatory cytokines in response to both pathogen- and danger-associated molecular patterns (5). Additionally, Kuenzel et al showed that knocking NLRC5 down during viral infection impairs IFN- induction (6). This receptor may also exert anti-inflammatory effects, however; in 2010, Cui and colleagues found that NLRC5 prevents phosphorylation of IKK and IKK , blocking downstream expression of the genes for proinflammatory cytokines TNF-α and IL-6, and that it also prevents Type I IFN induction by interfering with RIG-I and MDA5 (7). Nevertheless, Kumar et al later demonstrated that NLRC5-deficient DCs produce normal levels of TNF-α and IL-6 following LPS stimulation (8).

[**Back to top**](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#topOfPage)**The neutrophil response: TNF-triggered IL-18 and the role of the oxidative burst in NET formation**

The neutrophil response: TNF-triggered IL-18 and the role of the oxidative burst in NET formation It is well known that TNF-α primes neutrophils, the first cells to arrive at the inflammation site after PRR-mediated pathogen recognition, to enhance their microbicidal activity (9). A new study by Silliman and colleagues implicates the proinflammatory cytokine IL-18 in this process. They demonstrate that IL-18 is preformed in the neutrophil cytoplasm, and that TNF induces its release. When TNF is used as a priming agent, its ability to enhance fMLP-induced neutrophil oxidase activity is severely diminished in the presence of IL-18 binding protein, suggesting that TNF priming is dependent on this cytokine (10).
For a few years, it has been known that reactive oxygen species are also required for formation of neutrophil extracellular traps (NETs) (11), DNA-protease mixtures that kill microbes, but until recently the mechanism was undefined. A study by Papayannopoulos et al helps clarify the process behind this observation, demonstrating that ROS stimulate the release of azurophilic granule proteases, elastase and myeloperoxidase, to the nucleus. The enzymes drive the decondensation of chromatin, leading to the production of NETs (12).

[**Back to top**](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#topOfPage)**Monocytes: an emerging role for microparticles in endothelial activation**

Monocytes, which arrive at the inflammation site in response to factors produced by neutrophils, have multiple roles in inflammation. Monocyte-produced microparticles (MP) have been observed during inflammatory processes such as bacterial infections, and were recently shown to induce apoptosis in endothelial cells (13). A new study by Wang et al extends these findings, demonstrating that MP from monocytes contain inflammasome components, and that those from LPS-treated cells also carry IL-1beta. Binding of these latter MP to endothelial cells leads to activation of NF-κB and ERK1/2 signaling pathways and upregulation of adhesion molecules (14). Further research will be needed to determine if this also occurs in vivo, and which receptors mediate the MP-endothelial cell binding event.

[**Back to top**](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#topOfPage)**The sterile tissue response: endogenous TLR ligands and a new indirect TLR signaling mechanism**

Danger-associated molecular patterns (DAMPs) are thought to trigger the inflammatory response during sterile inflammation by signaling through TLR ligands15. Recent studies have identified novel DAMPs with implications for a host of diseases. Monteiro and colleagues showed that free heme is capable of directly stimulating LTB4 production by macrophages, eliciting neutrophil influx (16). Additionally, Zhang and colleagues found that human cardiac myosin signals through TLRs 2 and 8, stimulating production of the proinflammatory cytokines IL-6, IL-8, and TNF-α (17). An intriguing new twist in this phenomenon was observed by Stewart et al, who noted that oxidized LDL and amyloid-beta, components of atherosclerotic and Alzheimer's plaques respectively, initiate heterotrimeric assembly of their common receptor, CD36, with TLRs 4 and 6 to stimulate proinflammatory responses (18).

[**Back to top**](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#topOfPage)**Maresins and miRNAs: agents of resolution**

Lipid mediators, including lipoxins, resolvins, and protectins, are major players in dismantling the inflammatory response, a process called inflammatory resolution. A new class of molecules, maresins, has also been identified in this process. Serhan et al reported that these mediators are derived by macrophages from the omega-3 fatty acid DHA, and can diminish neutrophil accumulation at inflammation sites as well as enhance phagocytosis in macrophages (19).

Intriguingly, recent studies have also implicated miRNAs in the resolution of inflammation, due to their ability to regulate inflammatory mediators in macrophages. This regulation is achieved through interference with components of the NF-kappaB signaling pathway in the case of miR-146, which is induced by LPS and resolvin D1. Macrophage stimulation with LPS also leads to production of miR-21, which downregulates an inhibitor of the anti-inflammatory cytokine IL-10 (20).

[**Back to top**](http://www.qiagen.com/spotlight-pages/newsletters-and-magazines/articles/reviews-online-inflammatory-response/?utm_content=QFDKPR140804JL%20Toll-Like%20Receptors_us#topOfPage)**Conclusions**

Inflammation is a complex, multi-faceted process that is important in a variety of disease states. Studying inflammation-related gene expression with pathway-focused PCR arrays can help elucidate how the inflammatory response functions and why it sometimes goes awry.

**References**

1. Takaoka, A. et al. (2007) DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response. Nature **448**, 501.
2. Burckstummer, T. et al. (2009) An orthogonal proteomic-genomic screen identifies AIM2 as a cytoplasmic DNA sensor for the inflammasome. Nat. Immunol. **10**, 266.
3. Unterholzner, L. et al. (2010) IFI16 is an innate immune sensor for intracellular DNA. Nat. Immunol. **11**, 997.
4. Zhang, X. et al. (2011) Cutting edge: Ku70 is a novel cytosolic DNA sensor that induces Type III rather than Type I IFN. J. Immunol. **186**, 4541.
5. Davis, B.K. et al. (2011) Cutting edge: NLRC5-dependent activation of the inflammasome. J. Immunol. **186**, 1333.
6. Kuenzel, S. et al. (2010) The nucleotide-binding oligomerization domain-like receptor NLRC5 is involved in IFN-dependent antiviral immune responses. J. Immunol. **184**, 1990.
7. Cui, J. et al. (2010) NLRC5 negatively regulates the NF-kB and type I interferon signaling pathways and antiviral immunity. Cell **141**, 483.
8. Kumar, H. et al. (2011) NLRC5 deficiency does not influence cytokine induction by virus and bacteria infections. J. Immunol. **186**, 994.
9. Smith, J.A. (1994) Neutrophils, host defense, and inflammation: a double-edged sword. J. Leukoc. Biol. **56**, 672.
10. Silliman, C.C. et al. (2010). Tumor necrosis factor-alpha causes release of cytosolic interleukin-18 from human neutrophils. Am. J. Physiol. Cell. Physiol. **298**, C714.
11. Fuchs, T.A. et al. (2007) Novel cell death program leads to neutrophil extracellular traps. J. Cell. Biol. **176**, 231.
12. Papayannopoulos, V., Metzler, K.D., Hakkim, A. and Zychlinsky, A. (2011) Neutrophil elastase and myeloperoxidase regulate the formation of neutrophil extracellular traps. J. Cell Bio. **191**, 677.
13. Aharon, A., Tamari, T. and Brenner, B. (2008) Monocyte-derived microparticles and exosomes induce procoagulant and apoptotic effects on endothelial cells. Thromb. Haemost. **100**, 878.
14. Wang, J.G., Williams, J.C., Davis, B.K., Jacobson, K., Doerschuk, C.M., Ting, J.P.Y. and Mackman, N. (2011) Monocytic microparticles activate endothelial cells in an IL-b-dependent manner. Blood **118**, 2366.
15. Piccinini, A.M. and Midwood, K.S. (2010) DAMPening inflammation by modulating TLR signalling. Mediators Inflamm. Article ID 672395.
16. Monteiro, A.P.T. et al. (2011) Leukotriene B4 mediates neutrophil migration induced by heme. J. Immunol. **186**, 6562.
17. Zhang, P., Cox, C.J., Alvarez, K.M. and Cunningham, M.W. (2009) Cutting Edge: Cardiac Myosin Activates Innate Immune Responses through TLRs. J. Immunol. **183**, 27.
18. Stewart, C. R. et al. (2010) CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. Nat. Immunol. **11**, 155.
19. Serhan, C.N. et al. (2009) Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions. J. Exp. Med. **206**, 15.
20. Alam, M.M. and O'Neill, L.A. (2011) MicroRNAs and the resolution phase of inflammation in macrophages. Eur. J. Immunol. **41**, 2482.
21. Sharma, S. et al. (2011) Innate immune recognition of an AT-rich stem-loop DNA motif in the Plasmodium genome. Immunity **35**, 194.

