Interleukin-1{beta} (IL-1{beta}) Processing Pathway
Axel Weber, Peter Wasiliew and Michael Kracht (19 January 2010)
Science Signaling **3** (105), cm2. [DOI: 10.1126/scisignal.3105cm2]

IMMUNOLOGY

Interleukin-1β (IL-1β) Processing Pathway

Axel Weber[1], Peter Wasiliew[1], Michael Kracht[1]*

Published 19 January 2010; Volume 3 Issue 105 cm2

The innate immune system senses molecular patterns from invading microorganisms. Once activated, it orchestrates the inflammatory response by secreting proinflammatory cytokines, such as interleukin-1 (IL-1)–type cytokines, in particular IL-1β. IL-1 mediates the expression of a vast array of genes involved in secondary inflammation. IL-1–responsive genes coordinate all aspects of local inflammation and also attract and activate cells of the adaptive immune system at sites of infection. Moreover, the innate immune system can also sense a wide range of nonmicrobial molecular patterns that represent danger or damage signals. These signals activate the NALP3-inflammasome pathway, which plays a central role in acute and chronic sterile inflammation. Here, we describe the essential components of the NALP3-inflammasome that control processing and release of IL-1β.

Description

Stimuli that activate the NALP3 inflammasome. NALP [NACHT-, leucine-rich repeat (LRR)– and PYD-containing protein] 3 belongs to the large family of intracellular NOD-like receptors (NLRs) that sense pathogen-associated molecular patterns (PAMPs), such as viral DNAs, bacterial peptidoglycans, and toxins (*1, 2*). NALP3 also senses nonmicrobial danger or damage signals (DAMPs), such as monosodium urate crystals (MSU) or calcium pyrophosphate dihydrate (*3*), low potassium (*4*), ATP (*5*), amyloid-β (*6*), reactive oxygen species (ROS) (*7*), DNA (*8*), heat shock proteins (HSP90) (*9*), aluminum salts (*10*), asbestos and silica crystals (*7, 11, 12*), skin irritants (*13*), and ultraviolet (UV) irradiation (*14*).

The central role of NALP3 in processing and release of IL-1β. The relation of NALP3 to the IL-1 pathway was based on the discovery of inflammasomes. The first inflammasome, the NALP1 inflammasome, was identified in 2002 by the Tschopp lab as a high-molecular-weight complex that participated in the activation of the inflammatory proteases caspase-1 and -5 and in subsequent maturation of interleukin-1β (IL-1β) (*15*). Through analysis of a gain-of-function mutation in the related gene encoding NALP3 that produced an amino acid substitution of Arg^{260} to Trp (R260W), NALP3 was subsequently identified as the cause of increased inflammasome activity and enhanced IL-1β release associated with Muckle-Wells disease, a rare febrile human disease (*16, 17*). Alternative names for the NALP3 gene or the encoded protein are cold-induced autoinflammatory syndrome 1 (CIAS1), cryopyrin, and pyrin-containing Apaf-1–like (PYPAF1).

Structure of NALP3-inflammasome components. The core structure of the NALP3 inflammasome is formed by three proteins: NALP3, the adaptor protein ASC [apoptosis-associated specklike protein containing a caspase recruitment domain (CARD)], and caspase-1. Caspase-1 was initially discovered as an interleukin-1β–converting enzyme (ICE) (*18, 19*). Mice deficient in this enzyme are defective in production of mature IL-1β and are resistant to endotoxic shock (*20, 21*).

Like other NLRs, NALP3 is a multidomain protein containing a C-terminal LRR region, a central nucleotide domain called the NACHT domain [domain present in neuronal apoptosis inhibitory protein (NAIP), the major histocompatibility complex (MHC) class II transactivator (CIITA), HET-E, and TP1], a NAD (NACHT-associated) domain, and a PYRIN (PYR) domain, which is the N-terminal effector domain (*2, 22*).

These domains fulfill specific tasks. The LRR is involved in ligand sensing of PAMPs and DAMPs and in autoregulation (*2*). The NACHT domain is involved in oligomerization to form a high-molecular-weight active inflammasome. With the NACHT domain, NALP3 binds ATP and dATP, which is released from damaged cells (*5*). Nucleotide binding is necessary for oligomerization of the NACHT domain (*23*).

CARD and PYR domains are "death-fold" domains that facilitate dimerization or trimerization by homotypic interactions with corresponding CARD or PYR domains in other proteins (*2*).

The C-terminal PYD domain of NALP3 interacts with and recruits the adaptor ASC through PYD-PYD interactions. ASC contains an N-terminal PYD and a C-terminal CARD and is required for inflammasome formation. Caspase-1 contains a CARD domain followed by a domain containing the catalytic cysteine residue. The CARD domain within ASC binds the CARD domain of caspase-1 and thereby recruits caspase-1 to the inflammasome (*5, 15*).

Formation of the inflammasome through interactions mediated by the death-fold domains promotes dimerization or oligomerization of caspase-1, which leads to the formation of an active enzyme that cleaves the cytosolic 33-kD pro-IL-1β precursor at the site Tyr-Val-His-Asp (*16*) /Ala (*17*). Cleavage results in the 17-kD mature IL-1 protein (*18, 19, 24, 25*).

Efficient secretion of mature IL-1β requires not only processing of the IL-1β precursor by active caspase-1 but also regulation of its release (Fig. 1). Extracellular ATP promotes the secretion of mature IL-1β and thus

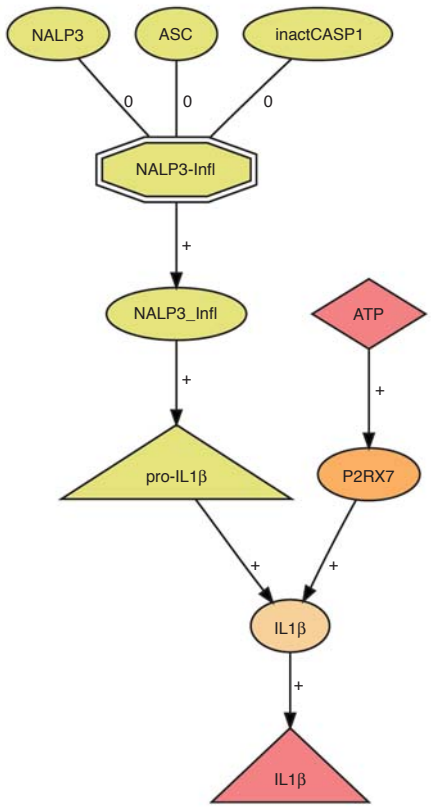

Fig. 1. Pathway image captured from the dynamic graphical display of the information in the Database of Cell Signaling on 21 December 2009. For a key to the colors and symbols and to access the underlying data, please visit the pathway (http://stke.sciencemag.org/cgi/cm/stkecm;CMP_21962).

[1]Rudolf-Buchheim-Institute of Pharmacology, Justus-Liebig-University Giessen, 35392 Giessen, Germany

*Corresponding author. E-mail, michael.kracht@pharma.med.uni-giessen.de

provides an additional signal for efficient secretion of IL-1β. ATP acts through the nucleotide receptor P2X7. Absence of P2X7 receptors impairs IL-1β secretion (*5, 26-30*).

Relevance of the NALP3-inflamamsome pathway for human disease. Studies in mice deficient in NALP3, ASC, or caspase-1 confirm its crucial role in processing of pro-IL-1β (*3, 5, 13, 31-33*). Mutations in NALP3 are found in a number of inflammatory human diseases that are characterized by increased systemic levels of IL-1β (*2, 16, 17, 34*). These syndromes and also more common inflammatory conditions, such as gout or type II diabetes, can be treated successfully with recombinant IL-1 receptor antagonist (IL-1RA, commercially known as Anakinra) (*35, 36*) or the IL-1 Trap (Rilonacept) (*37, 38*), proving that IL-1 and the inflammasomes are at the apex of complex inflammatory syndromes.

Pathway Details

Scope: Canonical

Pathway URL: http://stke.sciencemag.org/cgi/cm/stkecm;CMP_21962

References

1. E. Meylan, J. Tschopp, M. Karin, Intracellular pattern recognition receptors in the host response. *Nature* **442**, 39–44 (2006).
2. F. Martinon, A. Mayor, J. Tschopp, The inflammasomes: Guardians of the body. *Annu. Rev. Immunol.* **27**, 229–265 (2009).
3. F. Martinon, V. Pétrilli, A. Mayor, A. Tardivel, J. Tschopp, Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* **440**, 237–241 (2006).
4. V. Pétrilli, S. Papin, C. Dostert, A. Mayor, F. Martinon, J. Tschopp, Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration. *Cell Death Differ.* **14**, 1583–1589 (2007).
5. S. Mariathasan, D. S. Weiss, K. Newton, J. McBride, K. O'Rourke, M. Roose-Girma, W. P. Lee, Y. Weinrauch, D. M. Monack, V. M. Dixit, Cryopyrin activates the inflammasome in response to toxins and ATP. *Nature* **440**, 228–232 (2006).
6. A. Halle, V. Hornung, G. C. Petzold, C. R. Stewart, B. G. Monks, T. Reinheckel, K. A. Fitzgerald, E. Latz, K. J. Moore, D. T. Golenbock, The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. *Nat. Immunol.* **9**, 857–865 (2008).
7. C. Dostert, V. Pétrilli, R. Van Bruggen, C. Steele, B. T. Mossman, J. Tschopp, Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science* **320**, 674–677 (2008).
8. D. A. Muruve, V. Pétrilli, A. K. Zaiss, L. R. White, S. A. Clark, P. J. Ross, R. J. Parks, J. Tschopp, The inflammasome recognizes cytosolic microbial and host DNA and triggers an innate immune response. *Nature* **452**, 103–107 (2008).
9. A. Mayor, F. Martinon, T. De Smedt, V. Pétrilli, J. Tschopp, A crucial function of SGT1 and HSP90 in inflammasome activity links mammalian and plant innate immune responses. *Nat. Immunol.* **8**, 497–503 (2007).
10. S. C. Eisenbarth, O. R. Colegio, W. O'Connor, F. S. Sutterwala, R. A. Flavell, Crucial role for the Nalp3 inflammasome in the immunostimulatory properties of aluminium adjuvants. *Nature* **453**, 1122–1126 (2008).
11. V. Hornung, F. Bauernfeind, A. Halle, E. O. Samstad, H. Kono, K. L. Rock, K. A. Fitzgerald, E. Latz, Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat. Immunol.* **9**, 847–856 (2008).
12. S. L. Cassel, S. C. Eisenbarth, S. S. Iyer, J. J. Sadler, O. R. Colegio, L. A. Tephly, A. B. Carter, P. B. Rothman, R. A. Flavell, F. S. Sutterwala, The Nalp3 inflammasome is essential for the development of silicosis. *Proc. Natl. Acad. Sci. U.S.A.* **105**, 9035–9040 (2008).
13. F. S. Sutterwala, Y. Ogura, M. Szczepanik, M. Lara-Tejero, G. S. Lichtenberger, E. P. Grant, J. Bertin, A. J. Coyle, J. E. Galán, P. W. Askenase, R. A. Flavell, Critical role for NALP3/CIAS1/Cryopyrin in innate and adaptive immunity through its regulation of caspase-1. *Immunity* **24**, 317–327 (2006).
14. L. Feldmeyer, M. Keller, G. Niklaus, D. Hohl, S. Werner, H. D. Beer, The inflammasome mediates UVB-induced activation and secretion of interleukin-1beta by keratinocytes. *Curr. Biol.* **17**, 1140–1145 (2007).
15. F. Martinon, K. Burns, J. Tschopp, The inflammasome: A molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol. Cell* **10**, 417–426 (2002).
16. L. Agostini, F. Martinon, K. Burns, M. F. McDermott, P. N. Hawkins, J. Tschopp, NALP3 forms an IL-1 beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. *Immunity* **20**, 319–325 (2004).
17. E. Aganna, F. Martinon, P. N. Hawkins, J. B. Ross, D. C. Swan, D. R. Booth, H. J. Lachmann, R. Gaudet, P. Woo, C. Feighery, F. E. Cotter, M. Thome, G. A. Hitman, J. Tschopp, M. F. McDermott, Association of mutations in the NALP3/CIAS1/PYPAF1 gene with a broad phenotype including recurrent fever, cold sensitivity, sensorineural deafness, and AA amyloidosis. *Arthritis Rheum.* **46**, 2445–2452 (2002).
18. D. P. Cerretti, C. J. Kozlosky, B. Mosley, N. Nelson, K. Van Ness, T. A. Greenstreet, C. J. March, S. R. Kronheim, T. Druck, L. A. Cannizzaro, K. Huebner, R. A. Black, Molecular cloning of the interleukin-1 beta converting enzyme. *Science* **256**, 97–100 (1992).
19. N. A. Thornberry, H. G. Bull, J. R. Calaycay, K. T. Chapman, A. D. Howard, M. J. Kostura, D. K. Miller, S. M. Molineaux, J. R. Weidner, J. Aunins, K. O. Elliston, J. M. Ayala, F. J. Casano, J. Chin, G. J.-F. Ding, L. A. Egger, E. P. Gaffney, G. Limjuco, O. C. Palyha, S. M. Raju, A. M. Rolando, J. P. Salley, T.-T. Yamin, T. D. Lee, J. E. Shively, M. MacCross, R. A. Mumford, J. A. Schmidt, M. J. Tocci, A novel heterodimeric cysteine protease is required for interleukin-1 beta processing in monocytes. *Nature* **356**, 768–774 (1992).
20. P. Li, H. Allen, S. Banerjee, S. Franklin, L. Herzog, C. Johnston, J. McDowell, M. Paskind, L. Rodman, J. Salfeld, E. Towne, D. Tracey, S. Wardwell, F.-Y. Wei, W. Wong, R. Kamen, T. Seshadri, Mice deficient in IL-1 beta-converting enzyme are defective in production of mature IL-1 beta and resistant to endotoxic shock. *Cell* **80**, 401–411 (1995).
21. K. Kuida, J. A. Lippke, G. Ku, M. W. Harding, D. J. Livingston, M. S. Su, R. A. Flavell, Altered cytokine export and apoptosis in mice deficient in interleukin-1 beta converting enzyme. *Science* **267**, 2000–2003 (1995).
22. F. Martinon, O. Gaide, V. Pétrilli, A. Mayor, J. Tschopp, NALP inflammasomes: A central role in innate immunity. *Semin. Immunopathol.* **29**, 213–229 (2007).
23. J. A. Duncan, D. T. Bergstralh, Y. Wang, S. B. Willingham, Z. Ye, A. G. Zimmermann, J. P. Ting, Cryopyrin/NALP3 binds ATP/dATP, is an ATPase, and requires ATP binding to mediate inflammatory signaling. *Proc. Natl. Acad. Sci. U.S.A.* **104**, 8041–8046 (2007).
24. K. P. Wilson, J.-A. F. Black, J. A. Thomson, E. E. Kim, J. P. Griffith, M. A. Navia, M. A. Murcko, S. P. Chambers, R. A. Aldape, S. A. Raybuck, D. J. Livingston, Structure and mechanism of interleukin-1 beta converting enzyme. *Nature* **370**, 270–275 (1994).
25. A. D. Howard, M. J. Kostura, N. Thornberry, G. J. Ding, G. Limjuco, J. Weidner, J. P. Salley, K. A. Hogquist, D. D. Chaplin, R. A. Mumford, IL-1-converting enzyme requires aspartic acid residues for processing of the IL-1 beta precursor at two distinct sites and does not cleave 31-kDa IL-1 alpha. *J. Immunol.* **147**, 2964–2969 (1991).
26. C. A. Gabel, P2 purinergic receptor modulation of cytokine production. *Purinergic Signal.* **3**, 27–38 (2007).
27. J. M. Labasi, N. Petrushova, C. Donovan, S. McCurdy, P. Lira, M. M. Payette, W. Brissette, J. R. Wicks, L. Audoly, C. A. Gabel, Absence of the P2X7 receptor alters leukocyte function and attenuates an inflammatory response. *J. Immunol.* **168**, 6436–6445 (2002).
28. M. Solle, J. Labasi, D. G. Perregaux, E. Stam, N. Petrushova, B. H. Koller, R. J. Griffiths, C. A. Gabel, Altered cytokine production in mice lacking P2X(7) receptors. *J. Biol. Chem.* **276**, 125–132 (2001).
29. D. G. Perregaux, P. McNiff, R. Laliberte, M. Conklyn, C. A. Gabel, ATP acts as an agonist to promote stimulus-induced secretion of IL-1 beta and IL-18 in human blood. *J. Immunol.* **165**, 4615–4623 (2000).
30. M. G. Netea, C. A. Nold-Petry, M. F. Nold, L. A. Joosten, B. Opitz, J. H. van der Meer, F. L. van de Veerdonk, G. Ferwerda, B. Heinhuis, I. Devesa, C. J. Funk, R. J. Mason, B. J. Kullberg, A. Rubartelli, J. W. van der Meer, C. A. Dinarello, Differential requirement for the activation of the inflammasome for processing and release of IL-1beta in monocytes and macrophages. *Blood* **113**, 2324–2335 (2009).
31. T. D. Kanneganti, N. Ozören, M. Body-Malapel, A. Amer, J. H. Park, L. Franchi, J. Whitfield, W. Barchet, M. Colonna, P. Vandenabeele, J. Bertin, A. Coyle, E. P. Grant, S. Akira, G. Núñez, Bacterial RNA and small antiviral compounds activate caspase-1 through cryopyrin/Nalp3. *Nature* **440**, 233–236 (2006).
32. M. Yamamoto, K. Yaginuma, H. Tsutsui, J. Sagara, X. Guan, E. Seki, K. Yasuda, M. Yamamoto, S. Akira, K. Nakanishi, T. Noda, S. Taniguchi, ASC is essential for LPS-induced activation of procaspase-1 independently of TLR-associated signal adaptor molecules. *Genes Cells* **9**, 1055–1067 (2004).
33. S. Mariathasan, K. Newton, D. M. Monack, D. Vucic, D. M. French, W. P. Lee, M. Roose-Girma, S. Erickson, V. M. Dixit, Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. *Nature* **430**, 213–218 (2004).
34. S. Farasat, I. Aksentijevich, J. R. Toro, Autoinflammatory diseases: Clinical and genetic advances. *Arch. Dermatol.* **144**, 392–402 (2008).
35. C. A. Dinarello, Immunological and inflammatory functions of the interleukin-1 family. *Annu. Rev. Immunol.* **27**, 519–550 (2009).
36. A. So, T. De Smedt, S. Revaz, J. Tschopp, A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res. Ther.* **9**, R28 (2007).
37. R. Goldbach-Mansky, S. D. Shroff, M. Wilson, C. Snyder, S. Plehn, B. Barham, T. H. Pham, F. Pucino, R. A. Wesley, J. H. Papadopoulos, S. P. Weinstein, S. J. Mellis, D. L. Kastner, A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 Trap) in patients with familial cold autoinflammatory syndrome. *Arthritis Rheum.* **58**, 2432–2442 (2008).
38. H. M. Hoffman, M. L. Throne, N. J. Amar, M. Sebai, A. J. Kivitz, A. Kavanaugh, S. P. Weinstein, P. Belomestnov, G. D. Yancopoulos, N. Stahl, S. J. Mellis, Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: Results from two sequential placebo-controlled studies. *Arthritis Rheum.* **58**, 2443–2452 (2008).

10.1126/scisignal.3105cm2

Citation: A. Weber, P. Wasiliew, M. Kracht, Interleukin-1β (IL-1β) processing pathway. *Sci. Signal.* **3**, cm2 (2010).