nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

SUPPLEMENTARY INFORMATION

In format as provided by the authors

Inflammasomes in the gastrointestinal tract: infection, cancer and gut microbiota homeostasis

Si Ming Man

https://doi.org/10.1038/s41575-018-0054-1

Table 1 | Expression of inflammasome sensors and related molecules in humans and mice

Cell type	Inflammasome sensors and related molecules	Refs
Human		
Enterocytes	NLRP6, NLRP9, Caspase-1, Caspase-4, Caspase-5, IL-18,	[1-5]
Gastric cells	AIM2, NLRC4, NLRP1, NLRP3, NLRP6, ASC, Caspase-1	[6,7]
Keratinocytes	AIM2, NLRP1, Caspase-4, ASC, IL-1β	[5,8-10]
Kupffer cells	AIM2, NLRP3, ASC, Caspase-1, IL-1β, IL-18	[11]
Monocytes (blood-derived)	AIM2, NLRC4, NLRP3, Pyrin, Caspase-1, Caspase-4, Caspase-5, ASC, IL-1β	[5,12-18]
Macrophages (monocyte-derived)	AIM2, NAIP, NLRC4, NLRP1, NLRP3, NLRP7, Pyrin, ASC, Caspase-1, Caspase-4, Caspase-5, IL-1β, IL-18	[13,15,19-30]
Neutrophils (blood-derived)	NLRC4, NLRP1, NLRP3, NLRP6, NLRP12, ASC, Caspase-1, IL-1β	[17,31,32]
Peripheral blood mononuclear cells	NAIP, NLRC4, NLRP3, NLRP6, NLRP12, Pyrin, ASC, Caspase-1, IL-1β	[4,17,32-37]
Mouse		
Dendritic cells (bone-marrow-derived)	NAIPs, NLRC4, NLRP3, NLRP6, ASC, Caspase-1, Caspase-11, gasdermin D, IL-1β, IL-18	[33,38-41]
Enterocytes	AIM2, NAIPs, NLRC3, NLRC4, NLRP6, NLRP9b, ASC, Caspase-1, Caspase-11, gasdermin D, IL-1β, IL-18	[1-4,40,42-50]
Hepatocytes	NLRP3, NLRP6, ASC, Caspase-1, IL-1β	[40,51]
Gastric epithelium	ASC, IL-1β, IL-18	[7]
Goblet cells	NLRP6, ASC, Caspase-1, IL-18	[47,52]
Intestinal endothelial cells	NLRP6	[40]
Intestinal myofibroblasts	NLRP6	[40]
Intestinal phagocytes	NAIPs, NLRC4, NLRP3, ASC, Caspase-1, Caspase-11, IL-1β, IL-18	[53,54]
Lamina propria inflammatory monocytes	NLRP3, NLRP6, ASC, Caspase-1, IL-1β, IL-18	[55,56]
Liver immune cells and Kupffer cells	NLRP3, ASC, Caspase-1, IL-1β,	[51]
Macrophages (bone-marrow-	AIM2, NAIPs, NLRC3, NLRC4, NLRP1a–c, NLRP3, NLRP6,	[18,22-25,34,35,48,49,57-65]

derived)	NLRP12, Pyrin, ASC, Caspase-1, Caspase-11, gasdermin D, IL-1β, IL-18	
Neutrophils	AIM2, NLRC4, NLRP1a, NLRP3, NLRP12, Caspase-1, gasdermin D, IL-1β, IL-18	[17,32,41,66]

AIM2, Absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a caspase activation and recruitment domain; IL-1β, interleukin-1β; IL-18, interleukin-18; NAIP(s), Neuronal apoptosis inhibitory protein(s); NLRC, nucleotide-binding domain, leucine-rich repeat containing protein containing a caspase activation and recruitment domain; NLRP, nucleotide-binding domain, leucine-rich repeat containing protein containing a pyrin domain.

References:

1 Knodler, L. A. *et al.* Noncanonical Inflammasome Activation of Caspase-4/Caspase-11 Mediates Epithelial Defenses against Enteric Bacterial Pathogens. *Cell Host Microbe* **16**, 249-256, doi:10.1016/j.chom.2014.07.002 (2014).

2 Kempster, S. L. *et al.* Developmental control of the Nlrp6 inflammasome and a substrate, IL-18, in mammalian intestine. *American journal of physiology. Gastrointestinal and liver physiology* **300**, G253-263, doi:10.1152/ajpgi.00397.2010 (2011).

3 Elinav, E. *et al.* NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis. *Cell* **145**, 745-757, doi:S0092-8674(11)00480-6 [pii]10.1016/j.cell.2011.04.022 (2011).

4 Zhu, S. *et al.* Nlrp9b inflammasome restricts rotavirus infection in intestinal epithelial cells. *Nature*, doi:10.1038/nature22967 (2017).

5 Shi, J. *et al.* Inflammatory caspases are innate immune receptors for intracellular LPS. *Nature* **514**, 187-192, doi:10.1038/nature13683 (2014).

6 Li, S. *et al.* MiR-22 sustains NLRP3 expression and attenuates H. pylori-induced gastric carcinogenesis. *Oncogene*, doi:10.1038/onc.2017.381 (2017).

7 Jenkins, B. J. *et al.* Inflammasome adaptor ASC suppresses apoptosis of gastric cancer cells by an IL-18 mediated inflammation-independent mechanism. *Cancer Res*, doi:10.1158/0008-5472.CAN-17-1887 (2017).

8 Zhong, F. L. *et al.* Germline NLRP1 Mutations Cause Skin Inflammatory and Cancer Susceptibility Syndromes via Inflammasome Activation. *Cell* **167**, 187-202 e117, doi:10.1016/j.cell.2016.09.001 (2016).

9 Dombrowski, Y. *et al.* Cytosolic DNA triggers inflammasome activation in keratinocytes in psoriatic lesions. *Science translational medicine* **3**, 82ra38, doi:10.1126/scitranslmed.3002001 (2011).

10 Reinholz, M. *et al.* HPV16 activates the AIM2 inflammasome in keratinocytes. *Arch Dermatol Res* **305**, 723-732, doi:10.1007/s00403-013-1375-0 (2013).

11 Zannetti, C. *et al.* Characterization of the Inflammasome in Human Kupffer Cells in Response to Synthetic Agonists and Pathogens. *Journal of immunology* **197**, 356-367, doi:10.4049/jimmunol.1502301 (2016).

12 Gaidt, M. M. *et al.* The DNA Inflammasome in Human Myeloid Cells Is Initiated by a STING-Cell Death Program Upstream of NLRP3. *Cell* **171**, 1110-1124 e1118, doi:10.1016/j.cell.2017.09.039 (2017).

13 Baker, P. J. *et al.* NLRP3 inflammasome activation downstream of cytoplasmic LPS recognition by both caspase-4 and caspase-5. *Eur J Immunol* **45**, 2918-2926, doi:10.1002/eji.201545655 (2015).
14 Vigano, E. *et al.* Human caspase-4 and caspase-5 regulate the one-step non-canonical inflammasome activation in monocytes. *Nature communications* **6**, 8761, doi:10.1038/ncomms9761 (2015).
15 Netea, M. G. *et al.* Differential requirement for the activation of the inflammasome for processing and release of IL-1beta in monocytes and macrophages. *Blood* **113**, 2324-2335, doi:10.1182/blood-2008-03-146720 (2009).
16 Gaidt, M. M. *et al.* Human Monocytes Engage an Alternative Inflammasome Pathway. *Immunity* **44**, 833-846, doi:10.1016/j.immuni.2016.01.012 (2016).
17 Chen, K. W. *et al.* The neutrophil NLRC4 inflammasome selectively promotes IL-1beta maturation without pyroptosis during acute *Salmonella* challenge. *Cell reports* **8**, 570-582, doi:10.1016/j.celrep.2014.06.028 (2014).
18 Xu, H. *et al.* Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome. *Nature* **513**, 237-241, doi:10.1038/nature13449 (2014).
19 Khare, S. *et al.* An NLRP7-containing inflammasome mediates recognition of microbial lipopeptides in human macrophages. *Immunity* **36**, 464-476, doi:S1074-7613(12)00049-0 [pii]10.1016/j.immuni.2012.02.001 (2012).
20 Kortmann, J., Brubaker, S. W. & Monack, D. M. Cutting Edge: Inflammasome Activation in Primary Human Macrophages Is Dependent on Flagellin. *Journal of immunology* **195**, 815-819, doi:10.4049/jimmunol.1403100 (2015).
21 Reyes Ruiz, V. M. *et al.* Broad detection of bacterial type III secretion system and flagellin proteins by the human NAIP/NLRC4 inflammasome. *Proc Natl Acad Sci U S A* **114**, 13242-13247, doi:10.1073/pnas.1710433114 (2017).
22 Fernandes-Alnemri, T., Yu, J. W., Datta, P., Wu, J. & Alnemri, E. S. AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA. *Nature* **458**, 509-513, doi:nature07710 [pii]10.1038/nature07710 (2009).
23 Hornung, V. *et al.* AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature* **458**, 514-518, doi:nature07725 [pii]10.1038/nature07725 (2009).
24 Burckstummer, T. *et al.* An orthogonal proteomic-genomic screen identifies AIM2 as a cytoplasmic DNA sensor for the inflammasome. *Nat Immunol* **10**, 266-272, doi:10.1038/ni.1702ni.1702 [pii] (2009).
25 Roberts, T. L. *et al.* HIN-200 proteins regulate caspase activation in response to foreign cytoplasmic DNA. *Science* **323**, 1057-1060, doi:10.1126/science.11698411169841 [pii] (2009).
26 Gavrilin, M. A. *et al.* Activation of the pyrin inflammasome by intracellular *Burkholderia cenocepacia*. *Journal of immunology* **188**, 3469-3477, doi:jimmunol.1102272 [pii]10.4049/jimmunol.1102272 (2012).
27 Romberg, N. *et al.* Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation. *Nat Genet* **46**, 1135-1139, doi:10.1038/ng.3066 (2014).
28 Canna, S. W. *et al.* An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. *Nat Genet* **46**, 1140-1146, doi:10.1038/ng.3089 (2014).
29 Kitamura, A., Sasaki, Y., Abe, T., Kano, H. & Yasutomo, K. An inherited mutation in NLRC4 causes autoinflammation in human and mice. *J Exp Med* **211**, 2385-2396, doi:10.1084/jem.20141091 (2014).

30 Martinon, F., Burns, K. & Tschopp, J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell* **10**, 417-426, doi:S1097276502005993 [pii] (2002).
31 Perez-Figueroa, E. *et al.* Activation of NLRP3 inflammasome in human neutrophils by *Helicobacter pylori* infection. *Innate immunity* **22**, 103-112, doi:10.1177/1753425915619475 (2016).
32 Mankan, A. K., Dau, T., Jenne, D. & Hornung, V. The NLRP3/ASC/Caspase-1 axis regulates IL-1beta processing in neutrophils. *Eur J Immunol* **42**, 710-715, doi:10.1002/eji.201141921 (2012).
33 Semper, R. P. *et al. Helicobacter pylori*-induced IL-1beta secretion in innate immune cells is regulated by the NLRP3 inflammasome and requires the cag pathogenicity island. *Journal of immunology* **193**, 3566-3576, doi:10.4049/jimmunol.1400362 (2014).
34 Park, Y. H., Wood, G., Kastner, D. L. & Chae, J. J. Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. *Nat Immunol* **17**, 914-921, doi:10.1038/ni.3457 (2016).
35 Van Gorp, H. *et al.* Familial Mediterranean fever mutations lift the obligatory requirement for microtubules in Pyrin inflammasome activation. *Proc Natl Acad Sci U S A* **113**, 14384-14389, doi:10.1073/pnas.1613156113 (2016).
36 Villani, A. C. *et al.* Common variants in the NLRP3 region contribute to Crohn's disease susceptibility. *Nat Genet* **41**, 71-76, doi:ng.285 [pii]10.1038/ng.285 (2009).
37 Grenier, J. M. *et al.* Functional screening of five PYPAF family members identifies PYPAF5 as a novel regulator of NF-kappaB and caspase-1. *FEBS letters* **530**, 73-78 (2002).
38 Koch, K. N. *et al. Helicobacter* urease-induced activation of the TLR2/NLRP3/IL-18 axis protects against asthma. *The Journal of clinical investigation* **125**, 3297-3302, doi:10.1172/JCI79337 (2015).
39 Kim, D. J., Park, J. H., Franchi, L., Backert, S. & Nunez, G. The Cag pathogenicity island and interaction between TLR2/NOD2 and NLRP3 regulate IL-1beta production in *Helicobacter pylori* infected dendritic cells. *Eur J Immunol* **43**, 2650-2658, doi:10.1002/eji.201243281 (2013).
40 Normand, S. *et al.* Nod-like receptor pyrin domain-containing protein 6 (NLRP6) controls epithelial self-renewal and colorectal carcinogenesis upon injury. *Proc Natl Acad Sci U S A* **108**, 9601-9606, doi:10.1073/pnas.1100981108 1100981108 [pii] (2011).
41 Heilig, R. *et al.* The Gasdermin-D pore acts as a conduit for IL-1beta secretion in mice. *Eur J Immunol*, doi:10.1002/eji.201747404 (2017).
42 Sellin, M. E. *et al.* Epithelium-Intrinsic NAIP/NLRC4 Inflammasome Drives Infected Enterocyte Expulsion to Restrict *Salmonella* Replication in the Intestinal Mucosa. *Cell Host Microbe* **16**, 237-248, doi:10.1016/j.chom.2014.07.001 (2014).
43 Rauch, I. *et al.* NAIP-NLRC4 Inflammasomes Coordinate Intestinal Epithelial Cell Expulsion with Eicosanoid and IL-18 Release via Activation of Caspase-1 and -8. *Immunity* **46**, 649-659, doi:10.1016/j.immuni.2017.03.016 (2017).
44 Man, S. M. *et al.* Critical Role for the DNA Sensor AIM2 in Stem Cell Proliferation and Cancer. *Cell* **162**, 45-58, doi:10.1016/j.cell.2015.06.001 (2015).
45 Wilson, J. E. *et al.* Inflammasome-independent role of AIM2 in suppressing colon tumorigenesis via DNA-PK and Akt. *Nature medicine* **21**, 906-913, doi:10.1038/nm.3908 (2015).

46 Bergstrom, K. *et al.* Defective Intestinal Mucin-Type O-Glycosylation Causes Spontaneous Colitis-Associated Cancer in Mice. *Gastroenterology* **151**, 152-164 e111, doi:10.1053/j.gastro.2016.03.039 (2016).
47 Wlodarska, M. *et al.* NLRP6 inflammasome orchestrates the colonic host-microbial interface by regulating goblet cell mucus secretion. *Cell* **156**, 1045-1059, doi:10.1016/j.cell.2014.01.026S0092-8674(14)00078-6 [pii] (2014).
48 Man, S. M., Karki, R. & Kanneganti, T. D. AIM2 inflammasome in infection, cancer, and autoimmunity: Role in DNA sensing, inflammation, and innate immunity. *Eur J Immunol* **46**, 269-280, doi:10.1002/eji.201545839 (2016).
49 Allam, R. *et al.* Epithelial NAIPs protect against colonic tumorigenesis. *J Exp Med* **212**, 369-383, doi:10.1084/jem.20140474 (2015).
50 Wang, P. *et al.* Nlrp6 regulates intestinal antiviral innate immunity. *Science* **350**, 826-830, doi:10.1126/science.aab3145 (2015).
51 Petrasek, J. *et al.* IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. *The Journal of clinical investigation* **122**, 3476-3489, doi:10.1172/JCI60777 (2012).
52 Birchenough, G. M., Nystrom, E. E., Johansson, M. E. & Hansson, G. C. A sentinel goblet cell guards the colonic crypt by triggering Nlrp6-dependent Muc2 secretion. *Science* **352**, 1535-1542, doi:10.1126/science.aaf7419 (2016).
53 Franchi, L. *et al.* NLRC4-driven production of IL-1beta discriminates between pathogenic and commensal bacteria and promotes host intestinal defense. *Nat Immunol* **13**, 449-456, doi:ni.2263 [pii]10.1038/ni.2263 (2012).
54 Filardy, A. A., He, J., Bennink, J., Yewdell, J. & Kelsall, B. L. Posttranscriptional control of NLRP3 inflammasome activation in colonic macrophages. *Mucosal immunology* **9**, 850-858, doi:10.1038/mi.2015.109 (2016).
55 Seo, S. U. *et al.* Distinct Commensals Induce Interleukin-1beta via NLRP3 Inflammasome in Inflammatory Monocytes to Promote Intestinal Inflammation in Response to Injury. *Immunity* **42**, 744-755, doi:10.1016/j.immuni.2015.03.004 (2015).
56 Seregin, S. S. *et al.* NLRP6 function in inflammatory monocytes reduces susceptibility to chemically induced intestinal injury. *Mucosal immunology* **10**, 434-445, doi:10.1038/mi.2016.55 (2017).
57 Gao, W., Yang, J., Liu, W., Wang, Y. & Shao, F. Site-specific phosphorylation and microtubule dynamics control Pyrin inflammasome activation. *Proc Natl Acad Sci U S A* **113**, E4857-4866, doi:10.1073/pnas.1601700113 (2016).
58 Mariathasan, S. *et al.* Cryopyrin activates the inflammasome in response to toxins and ATP. *Nature* **440**, 228-232, doi:nature04515 [pii]10.1038/nature04515 (2006).
59 Mariathasan, S. *et al.* Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. *Nature* **430**, 213-218, doi:10.1038/nature02664 (2004).
60 Ulland, T. K. *et al.* Nlrp12 mutation causes C57BL/6J strain-specific defect in neutrophil recruitment. *Nature communications* **7**, 13180, doi:10.1038/ncomms13180 (2016).
61 Zaki, M. H., Man, S. M., Vogel, P., Lamkanfi, M. & Kanneganti, T. D. *Salmonella* exploits NLRP12-dependent innate immune signaling to suppress host defenses during infection. *Proc Natl Acad Sci U S A* **111**, 385-390, doi:10.1073/pnas.1317643111317643111 [pii] (2014).
62 Sastalla, I. *et al.* Transcriptional analysis of the three Nlrp1 paralogs in mice. *BMC Genomics* **14**, 188, doi:10.1186/1471-2164-14-188 (2013).
63 Anand, P. K. *et al.* NLRP6 negatively regulates innate immunity and host defence against bacterial pathogens. *Nature* **488**, 389-393, doi:nature11250 [pii]10.1038/nature11250 (2012).

64 Kayagaki, N. *et al.* Caspase-11 cleaves gasdermin D for non-canonical inflammasome signaling. *Nature* **526**, 666-671, doi:10.1038/nature15541 (2015).
65 Shi, J. *et al.* Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature* **526**, 660-665., doi:10.1038/nature15514 (2015).
66 Zamoshnikova, A. *et al.* NLRP12 is a neutrophil-specific, negative regulator of in vitro cell migration but does not modulate LPS- or infection-induced NF-kappaB or ERK signalling. *Immunobiology* **221**, 341-346, doi:10.1016/j.imbio.2015.10.001 (2016).