Virulence 3:3, 262–270; May/June 2012; © 2012 Landes Bioscience

The role of inflammasome modulation in virulence

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Keywords: inflammasome, caspase-1, immune evasion, immunopathology, virulence, pathogenicity

Abbreviations: TTSS, type III secretion system; NS1, nonstructural protein 1; PRR, pattern recognition receptors; ASC, apoptosis-associated speck-like protein containing a CARD; NLR, NOD-like receptor; LRR, leucine-rich repeat; AIM2, absent in melanoma 2; IL-1β, interleukin-1β; IL-18, interleukin-18; HAD, HIV-1 associated dementia; CPAF, chlamydial protease-like activity factor; KSHV, Kaposi sarcoma-associated herpes virus; VV, vaccinia virus; vIL-1βR, IL-1β scavenger receptor; PR8, Influenza A/PR/8/34 H1N1 virus

Pathogens frequently exist in an immunological balancing act with their host. Pathogens must not only replicate within a host but also transmit effectively between hosts to perpetuate their species. On the other hand, the host seeks to maintain homeostasis by clearing pathogens. The inflammasome is a multi-protein complex that can induce cell death and processes IL-1β and additional proinflammatory substrates. In this review we discuss the pathogen specific modulation of inflammasome activation and the role this plays in virulence and disease pathology.

Introduction

Host-pathogen interactions are essential for modulation of immunity. As the host evolves the ability to defend itself from invasion, the pathogen must adapt. Some pathogen adaptations lead to enhancement or suppression of the host immune system, often with severe pathological consequences or even death. Innate immunity to infection is the first line of host defense and is initiated by a group of diverse pattern recognition receptors (PRR) that recognize proteins, sugars or nucleic acid structures present only in pathogens and not the host. One such innate immune pathway, the inflammasome, has been studied extensively in recent years and yet our understanding of the full range of inflammasome sensors, activators and repressors continues to grow. As inflammasome signaling is important for both innate and adaptive immunity, a more detailed understanding of how the inflammasome is perturbed by pathogen-derived proteins will facilitate the design or implementation of new therapeutic treatments or vaccine adjuvants that modulate these same pathways.

The inflammasome is a large molecular complex consisting of caspase-1, ASC (apoptosis-associated speck-like protein containing a CARD), and an upstream activator such as an NLR (nucleotide-binding domain and leucine-rich repeat containing) or PYHIN (pyrin and HIN domain containing) family member. Bioinformatics studies have discovered 22 NLR genes in the human genome and 34 NLR genes in the mouse genome.[1-3] The NLRs NLRP1, NLRP3 and NLRC4 and the PYHIN family member AIM2 have been shown to assemble inflammasomes in response to a range of ligands of microbial, environmental or endogenous origin. The role of inflammasomes is to process interleukin-1β (IL-1β) and IL-18 from their immature pro-forms into active forms that are released from the cells. Caspase-1 activation also leads to a form of cell death known as pyroptosis, which is important for the clearance of several intracellular pathogens.[4-6] Recently, the caspase-1 related inflammatory protease caspase-11 was shown to play a significant role in inflammasome signaling and is essential for caspase-1 processing and IL-1β production by *E. coli*, *C. rodentium* and *V. cholerae*.[7]

In general, inflammasome activation and subsequent pyroptosis or release of proinflammatory substrates is required for efficient clearance of pathogens. In addition to its role in pathogen clearance, inflammasome activation can also lead to inflammatory pathology, which is detrimental to the host but may play a role in facilitating dissemination of the pathogen. Modulation of inflammasome activation is therefore an integral part of virulence. In this review, we discuss the mechanisms by which the host recognizes and activates the inflammasome in response to invading pathogens. In addition, we discuss the pathogen encoded activators and inhibitors of inflammasomes which regulate their virulence.

Inflammasome Activation

A wide variety of microbial, environmental and endogenous ligands have been shown to trigger inflammasome complex formation. AIM2 is activated by cytosolic dsDNA derived from a wide variety of pathogens in the cytosol of infected immune cells.[8-12] The NLRP1b inflammasome responds to *B. anthracis* lethal toxin in the cytosol, and mutations in the *Nlrp1b* gene were shown to alter anthrax lethal toxin-induced macrophage cell death responses.[5,13] Notably, NLRP1b inflammasome-induced

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Submitted: 12/23/11; Revised: 03/31/12; Accepted: 04/04/12
http://dx.doi.org/10.4161/viru.20266

macrophage cell death confers resistance to infection with *B. anthracis* spores in vivo, demonstrating the importance of pyroptosis for host defense.[5] Although AIM2 and NLRP1b are activated by single ligands, the molecular mechanisms leading to activation of the NLRC4 and NLRP3 inflammasomes by specific stimuli are less clear.

NLRP3 is the best-studied sensor of the NLR family and is activated by a wide range of pathogens or endogenous/exogenous danger or damage causing agents. The exact mechanism by which NLRP3 is activated by such a diverse range of agents is still under investigation but activation of NLRP3 is generally thought to comprise a two-step process involving priming with Toll-like receptor (TLR) or NLR ligands, which activate NFκB and enhance the expression level of pro-IL-1β and NLRP3.[14] Subsequent exposure to microbial pore-forming toxins and ionophores such as listeriolysin O,[15] streptolysin O,[16] α-hemolysin,[17] nigericin or maitotoxin then fully activate the NLRP3 inflammasome.[18,19] The NLRP3 inflammasome also responds indirectly to invading pathogens by monitoring potassium egress from the cell, through phagosomal destabilization following phagocytosis of large particles (especially crystalline particles) or through the generation of mitochondrial reactive oxygen species (ROS).[19,20] It should be noted that many bacterial, viral and fungal pathogens are capable of providing both the priming and activation signals for the NLRP3 inflammasome.[19,20]

The NLRC4 inflammasome detects bacterial flagellin from Legionella and the PrgJ family of proteins that comprise the basal body rod component of bacterial type III secretion systems (TTSS) of *Salmonella*, *Pseudomonas* and *Shigella* species.[18,21-23] In addition to the secretion of IL-1β and IL-18, the Nlrc4 inflammasome also induces pyroptotic cell death in order to clear flagellin-expressing bacteria such as *L. pneumophila* and *B. thailandensis*.[4] One ongoing question is how NLRC4 can recognize multiple bacterial ligands. Two independent groups recently published that NAIP (NLR family, apoptosis inhibitory protein) family members NAIP5 and NAIP6 specifically recognize flagellin and that NAIP2 recognizes TTSS rod components. These NAIPs then bind NLRC4 to induce inflammasome activation.[23-26] It should be noted, however, that several earlier studies reported that NAIP5 was dispensable[27] or only partially required[28] for NLRC4 inflammasome activation. These differences may be due to partial redundancy between NAIP5 and NAIP6 or may indicate that low levels of NAIP5 are sufficient for NLRC4 activation, as the A/J mouse strain containing mutations in NAIP5 is not completely deficient for NAIP5 protein.[29] It was also recently shown that NAIP5 may only be required in response to certain pathogens or that only the C-terminal portion of flagellin activates NAIP5, whereas the N terminus of flagellin utilizes another pathway.[25]

Finally, as pathogens are continuously evolving and evading detection, it is important to note the overlap that exists between different inflammasomes and pathogen detection. As an example of redundancy in the host, the NLRP3 inflammasome also contributes to host defense during systemic *S.* Typhimurium infection when flagellin expression is inhibited and NLRC4 can no longer be activated.[4,30] In the case of *S. pneumoniae*, AIM2 is the predominant sensor, but NLRP3 is also capable of inflammasome activation.[31] These findings highlight the complexity of the relationship between the host and the pathogen.

Inflammasome Induced Pathology

Although the role of inflammation is to clear or limit the spread of an invading pathogen, there is frequently collateral damage associated with the somewhat nonspecific nature of the innate immune response. Inflammasome activation leads to the pro-inflammatory pyroptotic form of cell death, which kills the infected cell but leads to tissue damage and inflammation.[4] Furthermore, IL-1β and IL-18 release participate in the recruitment of macrophages and neutrophils that help to eliminate the pathogen but also cause tissue damage. In the case of *Chlamydia trachomatis* infection, an ex vivo human Fallopian tube organ culture system showed that inflammation can lead to tissue damage and potentially infertility through an IL-1 mediated mechanism.[32] NLRP3 inflammasome activation and IL-1β production by *C. trachomatis* have also been shown to lead to inflammation and cell death in the THP-1 human monocytes cell line.[33] In a model of corneal infection with *Pseudomonas aeruginosa*, caspase-1 deficient mice had reduced cytokine and chemokine production with reduced polymorphonuclear leukocytes (PMN) infiltration and subsequently less corneal damage, thus demonstrating the negative consequences of unchecked inflammasome mediated inflammation.[34] Recently in a mouse model of pneumonia, the *rhsT* gene of *P. aeruginosa* was shown to activate the inflammasome which enhanced lung pathology and facilitated bacterial colonization, as bacteria lacking *rhsT* were cleared but WT *P. aeruginosa* persisted, which resulted in enhanced lethality.[35] Finally, infection with *Mycobacterium marinum* in mice demonstrated that the Esx-1 (type VII) secretion system activates the NLRP3 inflammasome. However, inflammasome activation leads to increased tissue damage but does not resolve the infection.[36]

Another common pathology associated with inflammasome activation is neuronal damage. Pneumococcal meningitis results in inflammasome activation and IL-1β release in the cerebral spinal fluid, which correlates with the severity of disease. In a mouse model of pneumococcal meningitis, caspase-1 deficient mice, or mice treated with inflammasome inhibitors, showed reduced neuronal damage and improved clinical outcomes.[37] HIV-1 associated dementia (HAD) is the result of virus dissemination to the central nervous system where increased apoptosis of neuronal cells and resident immune cells is thought to mediate disease. Interestingly, the HIV surface glycoprotein gp120 alone is capable of activating the inflammasome.[38] Intra-cerebral injection of gp120 actives caspase-1 and leads to IL-1β maturation as well as cell death in the neocortex of rats.[39] This pathology can be reduced by treatment with inhibitors of caspase-1 or IL-1 receptor antagonist.[40-42] Ectromelia virus also activates caspase-1 in brain tissue of infected mice and this may play a role in inflammation and pyroptosis induced cell death.[43] During dengue virus infection of mice, caspase-1 expression increases and inflammasome activation results in pyroptotic cell death. However, treatment

with the caspsase-1 inhibitor YVAD reduced cell death without significantly enhancing virus replication.[44] These findings suggest that, especially in the case of encephalitis, inhibition of inflammasome activation may prevent nerve damage and host death.

In addition to bacteria and viruses, the intracellular parasite Plasmodium, which includes the causative agent of malaria, also activates the NLRP3 inflammasome through the production of a heme metabolite called hemozoin. Intriguingly, NLRP3 inflammasome or IL-1β deficient mice survive longer than wildtype mice during infection with *Plasmodium chabaudi adami* DS.[45] Furthermore, *Plasmodium berghei* infection in mice results in cerebral malaria and NLRP3 inflammasome deficient mice had reduced cerebral inflammation and improved survival.[46]

Due to the negative effects of inflammasome activation by certain pathogens, treatment of severe inflammation with inflammasome inhibitors has promising therapeutic potential. Indeed, treatment with the caspase-1 inhibitor glyburide was able to delay death in a mouse model of endotoxic shock.[47] As discussed above, treatment of encephalitis with YVAD provides a proof of principle for reduced neuronal death. However, there are many factors that will likely affect the utility of such treatments including the effect of inflammasome inhibition on pathogen burden and eventual clearance, as well as the ability of inhibitors to cross the blood brain barrier. Combination of treatments with antimicrobial agents and inflammasome inhibitors will therefore likely provide the greatest therapeutic potential.

Pathogen-Mediated Inflammasome Activation in Virulence

As inflammasome activation leads to inflammation, most pathogens seek to avoid or suppress inflammasome activation. However, some pathogens are able to replicate despite inflammasome activation and still others require inflammasome activation for efficient replication or dissemination. It was demonstrated for *C. trachomatis* that inflammasome activation within infected HeLa cells is required for efficient bacterial replication.[48] It should be noted that epithelial cells, though they possess an inflammasome and make substantial amounts of IL-18, generally express minimal levels of IL-1β, and therefore do not induce the same inflammatory signaling that macrophages containing an activated inflammasome are capable of producing.[32,49,50] Alternatively, another group recently published that chlamydial protease-like activity factor (CPAF) inhibition results in breakdown of the *C. trachomatis* vacuole in HeLa cells or mouse lung fibroblasts and subsequent inflammasome mediate cell death with concurrent inhibition of pathogen replication.[51] It is therefore unclear what role inflammasome activation may play in clearance or growth of *C. trachomatis*, but one possibility that explains the differences observed between these group may be the level of caspase-1 activation, as one group inhibited caspase-1 and the other induced its activation through blockade of CPAF. Some inflammasome activation may be beneficial, but too much may be detrimental. Finally, another *Chlamydia* species, *C. pneumoniae*, has also been shown to benefit from inflammasome activation and cell death.[52] In this instance, inflammasome mediated cell death in T cells during pulmonary infection in mice leads to both the persistence of inflammation as well as impaired T cell mediated clearance of the pathogen. In all, it appears that some level of inflammasome activation during Chlamydia infection may be beneficial to the pathogen, but further studies are clearly needed.

Another instance of a pathogen benefiting from inflammasome activation is during Salmonella infection. Gastrointestinal infection with Salmonella leads to macrophage infection and the subsequent delivery of the sipB virulence factor via the bacterial TTSS, which activates the NLRC4 inflammasome and induces cell death.[53,54] This results in inflammation and damage to the intestinal epithelium in a murine model and allows for colonization of Peyer's patches and disseminated infection.[55,56]

Pathogen-Mediated Inflammasome Inhibition in Virulence

Direct inhibition of caspase-1. As obligate intracellular pathogens, it is not surprising that many viruses evade or inhibit the inflammasome to preserve the life of their host cells. Several viruses are known to encode proteins capable of interfering with inflammasome signaling (**Table 1**). Not surprisingly, inflammasome signaling is generally disrupted at the adaptor protein ASC or caspase-1 itself (**Fig. 1**).[57] For example, baculovirus protein p35 is capable of binding to and directly inhibiting a wide variety of caspases, including caspsase-1, in its natural insect hosts and mammalian cells.[58,59] Poxviruses also encode a variety of serpine like protease inhibitors. The CrmA protein (also known as SPI-2) of cowpox virus inhibits several caspases, including caspase-1, through a direct but reversible inhibition of the enzymatic active site.[60,61] This subsequently inhibits cleavage of pro-IL-1β.[62,63] Pulmonary infection of mice with CrmA mutants of cowpox or SPI-2 mutants of rabbit poxvirus demonstrated that they are attenuated in inflammation and viral replication compared with wild type viruses.[64] Intradermal infection with CrmA mutant cowpox also resulted in rapid viral clearance but with a more robust inflammatory response.[65] Additional pox viruses also encode CrmA homologs. Serp2 is the CrmA homolog found in myxoma virus.[66] Deletion of Serp2 results in severe attenuation of the virus in rabbits.[67] Vaccinia virus (VV) has been shown to activate both the NLRP3[68] and AIM2[10,69] inflammasomes. VV also encodes a SPI-2 protein (B13R) which is able to inhibit caspase-1 activation in a cell free assay; however, VV B13R mutants were not attenuated.[70,71] Instead, fever reduction and weight loss were dependent on VV encoded IL-1β scavenger receptor (vIL-1βR).[70] Finally, ectromelia virus SPI-2 protein also inhibits caspase-1 activation, though what role this may play in vivo has not been examined.[72] It is apparent that poxviruses have a variety of inhibitors for inflammasomes. The differential requirement for SPI-2 family proteins may, therefore, be the result of differentially encoded additional inhibitors or the result of different natural host ranges of these viruses, as rodents are the natural host for cowpox but not VV.[73]

Antagonists to inflammasome assembly. Poxviruses have evolved multiple inhibitors that interfere with innate and adaptive immunity (**Table 1 and Fig. 1**).[74] The myxoma virus M13L and

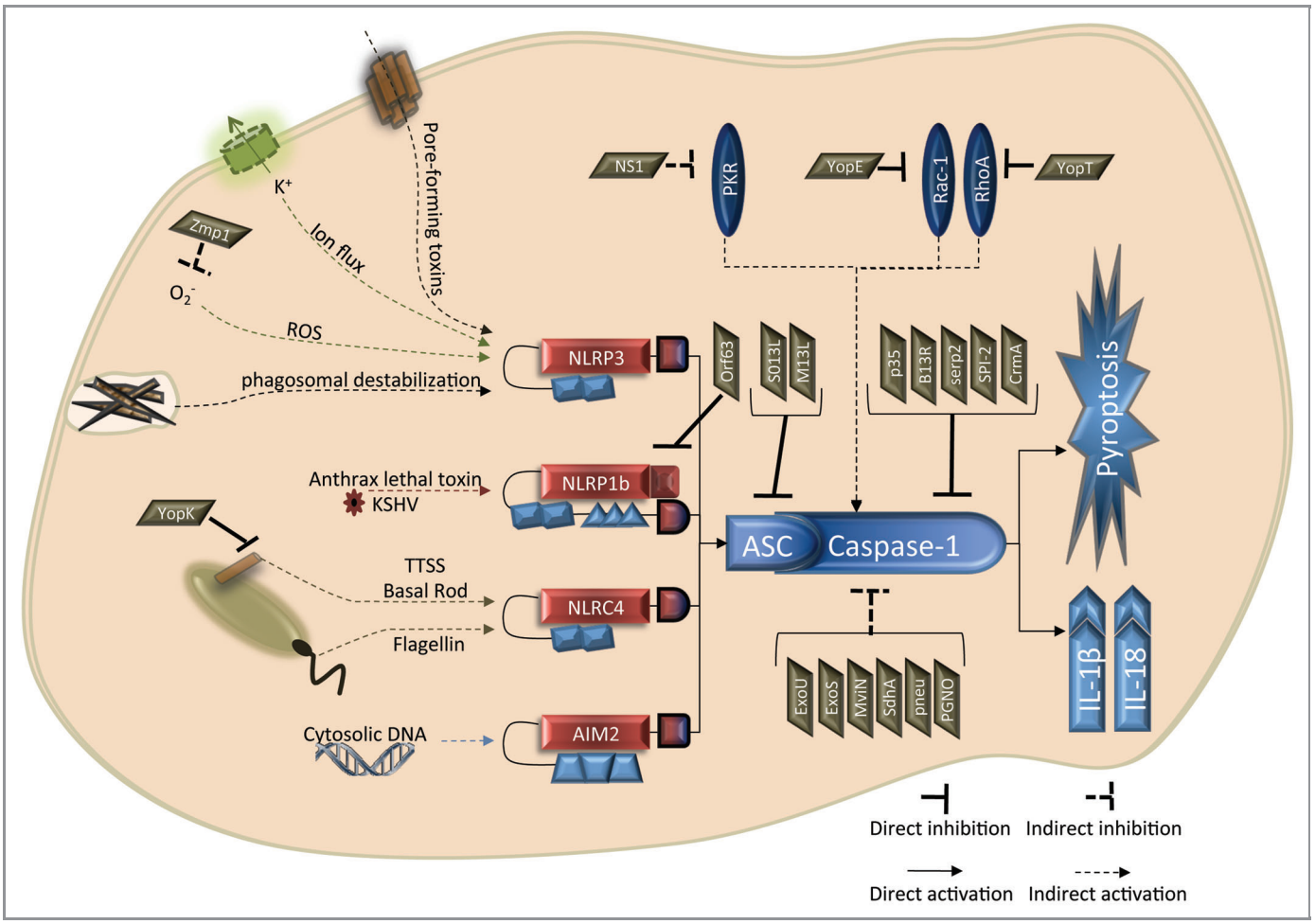

Figure 1. Pathogen activation and repression pathways of the inflammasome. The host has evolved a complex and multilayered pathogen and damage sensing pathway which regulates inflammasome activation. Activation sensors include NLRs, NAIPs and PYHIN (AIM2) family members, which converge on the adaptor ASC. The pathway culminates with caspase-1 activation and inflammatory cytokine processing (IL-1β/IL-18) as well as cell death (pyroptosis). Pathogens employ a surprising array of mechanisms to inhibit inflammasomes. It is also interesting to note that certain groups of pathogens, particularly pox viruses, appear to have evolved more direct inhibitory pathways which are common to the entire family of pox viruses.

Shope fibroma virus S013L proteins contain a pyrin domain (PYD) and interact with ASC to suppress inflammasome activation by blocking the ability of ASC to bid to and activate caspase-1.[75,76] M13L-PYD is required for pathogenesis of myxoma virus and deletion results in severe attenuation in vivo characterized by decreased viremia due to inefficient replication in lymphocytes and leukocytes and increased inflammation at the initial site of infection. In cell culture, myxoma virus lacking M13L-PYD increases activation of caspase-1 and increases the levels of IL-1β and IL-18.[76] Although M13L could theoretically inhibit any inflammasome due to direct inhibitory action on ASC, the NLRP3 inflammasome appears to be most critical during myxoma virus infection.[77] Poxvirus PYD proteins therefore inhibit inflammasomes at the level of the adaptor ASC and potentially prevent all upstream PRRs from efficiently activating inflammasomes. Orf63 of Kaposi's sarcoma-associated herpesvirus (KSHV) was shown to encode an antagonistic NLR homolog which inhibits the NLRP1 inflammasome. In addition, Orf63 could interact with other NLRs, NLRP3 and NLRC2, potentially indicating multiple inhibitory roles for this protein in the KSHV life-cycle. Mutation of this Orf not only leads to increased inflammasome activation, IL-1β and IL-18 processing but also leads to reduced virus reactivation and progeny virus production.[78]

Gene expression modulation. It was recently discovered that the NLRP3 inflammasome requires increased expression of NLRP3 for full activation,[14] thus implicating gene expression as one potential mechanism for inflammasome inhibition. Indeed, inflammasome activation by *Legionella pneumophila* infection is suppressed due to reduced NLRC4 and ASC mRNA and subsequent protein expression (**Table 1**). The downregulation of these genes allows *L. pneumophila* to suppress inflammasome activation and replicate in human macrophages.[79] However, it is unclear how *L. pneumophila* inhibits production of NLRC4 and ASC mRNA.

Indirect inflammasome inhibition. Influenza A/PR/8/34 H1N1 virus (PR8) NS1protein, in addition to blocking type-I interferon responses, is also capable of blocking inflammasome

Table 1. Pathogen virulence factors that inhibit or evade inflammasomes

Pathogen	Inflammasome activation	Pathogen inhibitory gene	Inhibitor function	References
Direct caspase-1 inhibition:				
Baculovirus	unknown	p35	Directly binds and inhibits caspase-1	58–59
Cowpox virus	unknown	CrmA	Competitive inhibitor of caspase-1	60–65
Rabbit pox virus	unknown	SPI-2	Competitive inhibitor of caspase-1	64
Myxoma virus	NLRP3	Serp2	Competitive inhibitor of caspase-1	66–67
Vaccinia virus	NLRP3, AIM2	B13R	Competitive inhibitor of caspase-1	10, 68–71
Ectromelia virus	unknown	SPI-2	Competitive inhibitor of caspase-1	72
Inflammasome antagonists:				
Shope Fibroma virus	unknown	S013L	PYD blocks ASC/caspase-1 interaction	75
Myxoma virus	NLRP3	M13L	PYD blocks ASC/caspase-1 interaction	76–77
KSHV	NLRP1	Orf63	Antagonistic NLRP1 homolog	78
Modulation of genes:				
L. pneumophila	NLRC4	unknown	Downregulates NLRC4 and ASC	79
Indirect inhibition:				
Influenza A	NLRP3	NS1	Exact mechanism unknown, PKR	80–81
M. tuberculosis	NLRP3	Zmp1	Zn^{2+} metalloprotease, blocks superoxide production	82
P. aeruginosa	NLRP3, NLRC4	ExoU ExoS	Phospholipase A_2 activity, unknown mechanism ADP ribosyltransferase activity, unknown mechanism	83 84
Y. enterocolitica	NLRP3, NLRC4	YopE YopT	Inhibits caspase-1 oligomerization through Rac-1 Inhibits caspase-1 oligomerization through RhoA	85 85
Y. pseudotuberculosis	NLRP3, NLRC4	YopK	Interacts with TTSS, exact mechanism unknown	86
Antigenic stealth:				
S. aureus	NLRP3	PGN O-Acetyltransferase A	Masks ligands, prevents PGN cleavage	87
F. novicida	AIM2	MviN (etc.)	Membrane/cell wall integrity	88–89
S. pneumoniae	NLRP3, AIM2	Pneumolysin	Exact mechanism unknown	90
L. pneumophila	NLRC4	SdhA	Maintains replication vacuole	91
Fungi	NLRP3, NLRC4		Spores sequester PAMPs	95, 97–99

activation. The N-terminus of PR/8 NS1 possesses an inflammasome inhibitory function and PR8 lacking the N-terminus of NS1 is attenuated in cell culture and induces higher levels of IL-1β and pyroptosis. This caspase-1 inhibitory function appears to be indirect, as blocking the RNA dependent protein kinase PKR in PR/8 NS1 mutants was able to suppress renewed caspase-1 activation.[80] However, the ability of NS1 to block inflammasome activation appears to be strain specific, as NS1 from highly pathogenic H5N1 bird flu reportedly activates caspases and induce apoptosis.[81] It is interesting to speculate that the ability of the NS1 protein from different strains of influenza A virus to inhibit caspase-1 may play a role in host range and zoonotic transmission; with those viruses adapting the ability to inhibit human caspase-1 being able to more efficiently transmit between humans.

In the case of *Mycobacterium tuberculosis* (Mtb), the zmp1 protein is a potential Zn^{2+} metalloprotease which represses inflammasome activation likely through the regulation of superoxide, an NLRP3 coactivator. Zmp1 mutant Mtb are cleared faster from the lungs of infected mice and more efficiently activate macrophages leading to phagosomal maturation and bacterial killing.[82] The ExoU and ExoS proteins of *P. aeruginosa* inhibit the NLRC4 inflammasome upon TTSS delivery to the cytosol and are required for pathogenicity.[83,84] ExoU was shown to indirectly inhibit the NLRC4 inflammasome through its phospholipase A_2 activity; however, it is not altogether clear how this enzymatic activity of ExoU inhibits caspase-1 activation.[83] ExoS similarly inhibits caspase-1 activation through its ADP ribosyltransferase activity through an undefined mechanism.[84] Additional bacterial inhibitors include the YopT, YopE and YopK proteins from various *Yersinia* species, which are delivered to the cytosol via the TTSS. YopE and YopT inhibit inflammasome activation through an indirect mechanism that involves inhibiting oligomerization and self cleavage of caspase-1 through the Rho-GTPase Rac-1 and LIM kinase-1.[85] This inhibitory mechanism is particularly intriguing as it may indicate the requirement for cytoskeletal proteins in the induced proximity required for caspase-1 self cleavage upon inflammasome activation. In the case of YopK, indirect inhibition or masking of the TTSS appear to be involved, as YopK cannot block inflammasome activation in Trans and

YopK directly interacts with the TTSS which is recognized by NLRC4.[86]

Antigenic stealth. During infection, some pathogens use stealth to avoid inflammasome activation (**Table 1**). One example of stealth is the *S. aureus* enzyme PGN O-acetyltransferase A, which acetylates peptidoglycan in the bacterial cell wall and prevents lysosomal degradation of the cell wall and subsequent sensing of the bacteria by NLRs.[87] *Francisella novicida* deficient in membrane-associate proteins like MviN (a lipid II flippase) or proteins required for cell wall synthesis are also known to more efficiently activate the inflammasome; however, this appears to be due to increased bacterial lysis, due to insufficient cell wall synthesis or instability of the cell wall/membrane, and not from any direct inhibitory mechanism.[88,89] Another example is that of *S. pneumoniae* pulmonary infection, where bacteria lacking pneumolysin, or possessing non-hemolytic pneumolysin, are not detected by the NLRP3 inflammasome and become more invasive.[90] *L. pneumophila* also employs an antigen masking strategy through its SdhA protein which is important for maintaining the *L. pneumophila* replication vacuole and preventing cytosolic recognition of antigens by the inflammasome.[91] In all, a diverse range of inflammasome repression mechanisms are utilized by an equally diverse group of pathogens to evade immune detection and allow for pathogen dissemination.

Inflammasome Modulation during Fungal Infection

Many examples of inflammasome activation or inhibition from bacterial or viral pathogens have been shown to regulate virulence. However, much less is known regarding the ability of fungal pathogens to inhibit or enhance inflammasome activation. Multiple fungal pathogens have been shown to activate the NLRP3 inflammasome through the activation of cell surface Dectin receptors and the tyrosine kinase Syk including *Saccharomyces cerevisiae*,[92] *Candida albicans*[93,94] and *Aspergillus fumigatus*.[95] In addition, the NLRC4 inflammasome in epithelial cells was recently reported to be required for the efficient clearance of *C. albicans* during mucosal infections.[96] In all of these infections, inflammasome activation is critical for fungal clearance. It does not appear from the current literature, however, that fungi actively suppress inflammasome activation to perpetuate or enhance their infectivity in the same manner as viruses or bacteria. The one mechanism that is apparent is stealth. Most fungal spores mask their PAMPs, such as zymosan or mannan, thus avoiding inflammasome activation (**Table 1**).[95,97] Once the spores or yeast mature into hyphae, the signals for inflammasome activation are exposed and the fungi are rapidly cleared through an inflammasome dependent Th17 mediated immune response.[98,99] Therefore, fungal infections are generally only pathogenic in immunocompromised hosts such as transplant recipients or chemotherapy patients. However, there are some polymorphisms in the NLRP3 gene that have been linked to recurrent vulvovaginal candidiasis which result in reduced IL-1β secretion.[100] Thus, genetic polymorphisms in the host that result in reduced inflammasome activation or IL-1β signaling may predispose patients to fungal infections.

Conclusion

In all, it is apparent that inflammasome modulation is a critical component of pathogen virulence. The host has developed a multitude of inflammasome activators and regulatory mechanisms to control inflammasome activation and, in general, inflammasome activation facilitates pathogen clearance and is beneficial to the host. However, pathogens modulate inflammasomes differently according to their specific niche to promote immune evasion or enhance inflammation, which allows for optimal dissemination. In some instances, inflammasome activation appears to be detrimental to the host and inflammasome inhibition in these situations may be therapeutically useful.

As seen with influenza, overt inflammation can occur following transmission from birds to humans with one possible cause being the inability of the virus to effectively inhibit inflammasome activation in humans.[81] Further research into the field of emerging infectious diseases will likely be of interest to determine if differences in virulence between the natural host and humans is the result of inflammasome modulation. Continued research in the area of therapeutics which target the inflammasome, or its downstream substrates, will also improve our understanding of the importance of inflammasome modulation in infectious disease.

Acknowledgments

We would like to thank John Lukens for helpful comments on the manuscript. This work was supported by the US National Institutes of Health grants (AR056296, AI1010935) and the American Syrian Lebanese Associated Charities to T.-D.K.

References

1. Harton JA, Linhoff MW, Zhang J, Ting JP. Cutting edge: CATERPILLER: a large family of mammalian genes containing CARD, pyrin, nucleotide-binding, and leucine-rich repeat domains. J Immunol 2002; 169:4088-93; PMID:12370334
2. Inohara N, Nuñez G. The NOD: a signaling module that regulates apoptosis and host defense against pathogens. Oncogene 2001; 20:6473-81; PMID: 11607846; http://dx.doi.org/10.1038/sj.onc.1204787
3. Ting JP, Lovering RC, Alnemri ES, Bertin J, Boss JM, Davis BK, et al. The NLR gene family: a standard nomenclature. Immunity 2008; 28:285-7; PMID: 18341998; http://dx.doi.org/10.1016/j.immuni.2008.02.005
4. Miao EA, Leaf IA, Treuting PM, Mao DP, Dors M, Sarkar A, et al. Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria. Nat Immunol 2010; 11:1136-42; PMID:21057511; http://dx.doi.org/10.1038/ni.1960
5. Terra JK, Cote CK, France B, Jenkins AL, Bozue JA, Welkos SL, et al. Cutting edge: resistance to Bacillus anthracis infection mediated by a lethal toxin sensitive allele of Nalp1b/Nlrp1b. J Immunol 2010; 184:17-20; PMID:19949100; http://dx.doi.org/10.4049/jimmunol.0903114
6. Lamkanfi M, Dixit VM. Manipulation of host cell death pathways during microbial infections. Cell Host Microbe 2010; 8:44-54; PMID:20638641; http://dx.doi.org/10.1016/j.chom.2010.06.007
7. Kayagaki N, Warming S, Lamkanfi M, Vande Walle L, Louie S, Dong J, et al. Non-canonical inflammasome activation targets caspase-11. Nature 2011; 479:117-21; PMID:22002608; http://dx.doi.org/10.1038/nature10558
8. Bürckstümmer T, Baumann C, Blüml S, Dixit E, Dürnberger G, Jahn H, et al. An orthogonal proteomic-genomic screen identifies AIM2 as a cytoplasmic DNA sensor for the inflammasome. Nat Immunol 2009; 10:266-72; PMID:19158679; http://dx.doi.org/10.1038/ni.1702

9. Fernandes-Alnemri T, Yu JW, Datta P, Wu J, Alnemri ES. AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA. Nature 2009; 458:509-13; PMID:19158676; http://dx.doi.org/10.1038/nature07710
10. Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, et al. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. Nature 2009; 458:514-8; PMID:19158675; http://dx.doi.org/10.1038/nature07725
11. Roberts TL, Idris A, Dunn JA, Kelly GM, Burnton CM, Hodgson S, et al. HIN-200 proteins regulate caspase activation in response to foreign cytoplasmic DNA. Science 2009; 323:1057-60; PMID:19131592; http://dx.doi.org/10.1126/science.1169841
12. Tsuchiya K, Hara H, Kawamura I, Nomura T, Yamamoto T, Daim S, et al. Involvement of absent in melanoma 2 in inflammasome activation in macrophages infected with Listeria monocytogenes. J Immunol 2010; 185:1186-95; PMID:20566831; http://dx.doi.org/10.4049/jimmunol.1001058
13. Boyden ED, Dietrich WF. Nalp1b controls mouse macrophage susceptibility to anthrax lethal toxin. Nat Genet 2006; 38:240-4; PMID:16429160; http://dx.doi.org/10.1038/ng1724
14. Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, et al. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J Immunol 2009; 183:787-91; PMID:19570822; http://dx.doi.org/10.4049/jimmunol.0901363
15. Hara H, Tsuchiya K, Nomura T, Kawamura I, Shoma S, Mitsuyama M. Dependency of caspase-1 activation induced in macrophages by Listeria monocytogenes on cytolysin, listeriolysin O, after evasion from phagosome into the cytoplasm. J Immunol 2008; 180:7859-68; PMID:18523249
16. Harder J, Franchi L, Muñoz-Planillo R, Park JH, Reimer T, Núñez G. Activation of the Nlrp3 inflammasome by Streptococcus pyogenes requires streptolysin O and NF-kappa B activation but proceeds independently of TLR signaling and P2X7 receptor. J Immunol 2009; 183:5823-9; PMID:19812205; http://dx.doi.org/10.4049/jimmunol.0900444
17. Craven RR, Gao X, Allen IC, Gris D, Bubeck Wardenburg J, McElvania-Tekippe E, et al. Staphylococcus aureus alpha-hemolysin activates the NLRP3-inflammasome in human and mouse monocytic cells. PLoS One 2009; 4:e7446; PMID:19826485; http://dx.doi.org/10.1371/journal.pone.0007446
18. Lamkanfi M, Dixit VM. The inflammasomes. PLoS Pathog 2009; 5:e1000510; PMID:20041168; http://dx.doi.org/10.1371/journal.ppat.1000510
19. Tschopp J, Schroder K. NLRP3 inflammasome activation: The convergence of multiple signalling pathways on ROS production? Nat Rev Immunol 2010; 10:210-5; PMID:20168318; http://dx.doi.org/10.1038/nri2725
20. Lamkanfi M, Kanneganti TD. Nlrp3: an immune sensor of cellular stress and infection. Int J Biochem Cell Biol 2010; 42:792-5; PMID:20079456; http://dx.doi.org/10.1016/j.biocel.2010.01.008
21. Suzuki T, Franchi L, Toma C, Ashida H, Ogawa M, Yoshikawa Y, et al. Differential regulation of caspase-1 activation, pyroptosis, and autophagy via Ipaf and ASC in Shigella-infected macrophages. PLoS Pathog 2007; 3:e111; PMID:17696608; http://dx.doi.org/10.1371/journal.ppat.0030111
22. Miao EA, Mao DP, Yudkovsky N, Bonneau R, Lorang CG, Warren SE, et al. Innate immune detection of the type III secretion apparatus through the NLRC4 inflammasome. Proc Natl Acad Sci U S A 2010; 107:3076-80; PMID:20133635; http://dx.doi.org/10.1073/pnas.0913087107
23. Zhao Y, Yang J, Shi J, Gong YN, Lu Q, Xu H, et al. The NLRC4 inflammasome receptors for bacterial flagellin and type III secretion apparatus. Nature 2011; 477:596-600; PMID:21918512; http://dx.doi.org/10.1038/nature10510
24. Lightfield KL, Persson J, Brubaker SW, Witte CE, von Moltke J, Dunipace EA, et al. Critical function for Naip5 in inflammasome activation by a conserved carboxy-terminal domain of flagellin. Nat Immunol 2008; 9:1171-8; PMID:18724372; http://dx.doi.org/10.1038/ni.1646
25. Lightfield KL, Persson J, Trinidad NJ, Brubaker SW, Kofoed EM, Sauer JD, et al. Differential requirements for NAIP5 in activation of the NLRC4 inflammasome. Infect Immun 2011; 79:1606-14; PMID:21282416; http://dx.doi.org/10.1128/IAI.01187-10
26. Kofoed EM, Vance RE. Innate immune recognition of bacterial ligands by NAIPs determines inflammasome specificity. Nature 2011; 477:592-5; PMID:21874021; http://dx.doi.org/10.1038/nature10394
27. Lamkanfi M, Amer A, Kanneganti TD, Muñoz-Planillo R, Chen G, Vandenabeele P, et al. The Nod-like receptor family member Naip5/Birc1e restricts Legionella pneumophila growth independently of caspase-1 activation. J Immunol 2007; 178:8022-7; PMID:17548639
28. Miao EA, Ernst RK, Dors M, Mao DP, Aderem A. Pseudomonas aeruginosa activates caspase 1 through Ipaf. Proc Natl Acad Sci U S A 2008; 105:2562-7; PMID:18256184; http://dx.doi.org/10.1073/pnas.0712183105
29. Wright EK, Goodart SA, Growney JD, Hadinoto V, Endrizzi MG, Long EM, et al. Naip5 affects host susceptibility to the intracellular pathogen Legionella pneumophila. Curr Biol 2003; 13:27-36; PMID:12526741; http://dx.doi.org/10.1016/S0960-9822(02)01359-3
30. Broz P, Newton K, Lamkanfi M, Mariathasan S, Dixit VM, Monack DM. Redundant roles for inflammasome receptors NLRP3 and NLRC4 in host defense against Salmonella. J Exp Med 2010; 207:1745-55; PMID:20603313; http://dx.doi.org/10.1084/jem.20100257
31. Fang R, Tsuchiya K, Kawamura I, Shen Y, Hara H, Sakai S, et al. Critical roles of ASC inflammasomes in caspase-1 activation and host innate resistance to Streptococcus pneumoniae infection. J Immunol 2011; 187:4890-9; PMID:21957143; http://dx.doi.org/10.4049/jimmunol.1100381
32. Hvid M, Baczynska A, Deleuran B, Fedder J, Knudsen HJ, Christiansen G, et al. Interleukin-1 is the initiator of Fallopian tube destruction during Chlamydia trachomatis infection. Cell Microbiol 2007; 9:2795-803; PMID:17614966; http://dx.doi.org/10.1111/j.1462-5822.2007.00996.x
33. Abdul-Sater AA, Saïd-Sadier N, Padilla EV, Ojcius DM. Chlamydial infection of monocytes stimulates IL-1beta secretion through activation of the NLRP3 inflammasome. Microbes Infect 2010; 12:652-61; PMID:20434582; http://dx.doi.org/10.1016/j.micinf.2010.04.008
34. Thakur A, Barrett RP, McClellan S, Hazlett LD. Regulation of Pseudomonas aeruginosa corneal infection in IL-1 beta converting enzyme (ICE, caspase-1) deficient mice. Curr Eye Res 2004; 29:225-33; PMID:15590467; http://dx.doi.org/10.1080/02713680490516710
35. Kung VL, Khare S, Stehlik C, Bacon EM, Hughes AJ, Hauser AR. An rhs gene of Pseudomonas aeruginosa encodes a virulence protein that activates the inflammasome. Proc Natl Acad Sci U S A 2012; 109:1275-80; PMID:22232685; http://dx.doi.org/10.1073/pnas.1109285109
36. Carlsson F, Kim J, Dumitru C, Barck KH, Carano RA, Sun M, et al. Host-detrimental role of Esx-1-mediated inflammasome activation in mycobacterial infection. PLoS Pathog 2010; 6:e1000895; PMID:20463815; http://dx.doi.org/10.1371/journal.ppat.1000895
37. Koedel U, Winkler F, Angele B, Fontana A, Flavell RA, Pfister HW. Role of Caspase-1 in experimental pneumococcal meningitis: Evidence from pharmacologic Caspase inhibition and Caspase-1-deficient mice. Ann Neurol 2002; 51:319-29; PMID:11891827; http://dx.doi.org/10.1002/ana.10103
38. Corasaniti MT, Bilotta A, Strongoli MC, Navarra M, Bagetta G, Di Renzo G. HIV-1 coat protein gp120 stimulates interleukin-1beta secretion from human neuroblastoma cells: evidence for a role in the mechanism of cell death. Br J Pharmacol 2001; 134:1344-50; PMID:11704656; http://dx.doi.org/10.1038/sj.bjp.0704382
39. Corasaniti MT, Turano P, Bilotta A, Malorni W, Stringaro AR, Nisticò R, et al. Evidence that increases of mitochondrial immunoreactive IL-1beta by HIV-1 gp120 implicate in situ cleavage of pro-IL-1beta in the neocortex of rat. J Neurochem 2001; 78:611-8; PMID:11483664; http://dx.doi.org/10.1046/j.1471-4159.2001.00441.x
40. Corasaniti MT, Russo R, Amantea D, Gliozzi M, Siviglia E, Stringaro AR, et al. Neuroprotection by the caspase-1 inhibitor Ac-YVAD-(acyloxy)mk in experimental neuroAIDS is independent from IL-1beta generation. Cell Death Differ 2005; 12(Suppl 1):999-1001; PMID:15846371; http://dx.doi.org/10.1038/sj.cdd.4401644
41. Corasaniti MT, Bellizzi C, Russo R, Colica C, Amantea D, Di Renzo G. Caspase-1 inhibitors abolish deleterious enhancement of COX-2 expression induced by HIV-1 gp120 in human neuroblastoma cells. Toxicol Lett 2003; 139:213-9; PMID:12628757; http://dx.doi.org/10.1016/S0378-4274(02)00436-8
42. Bagetta G, Corasaniti MT, Berliocchi L, Nisticó R, Giammarioli AM, Malorni W, et al. Involvement of interleukin-1beta in the mechanism of human immunodeficiency virus type 1 (HIV-1) recombinant protein gp120-induced apoptosis in the neocortex of rat. Neuroscience 1999; 89:1051-66; PMID:10362294; http://dx.doi.org/10.1016/S0306-4522(98)00363-7
43. Krzyzowska M, Cymerys J, Winnicka A, Niemiałtowski M. Involvement of Fas and FasL in Ectromelia virus-induced apoptosis in mouse brain. Virus Res 2006; 115:141-9; PMID:16169110; http://dx.doi.org/10.1016/j.virusres.2005.08.001
44. Nasirudeen AM, Liu DX. Gene expression profiling by microarray analysis reveals an important role for caspase-1 in dengue virus-induced p53-mediated apoptosis. J Med Virol 2009; 81:1069-81; PMID:19382257; http://dx.doi.org/10.1002/jmv.21486
45. Shio MT, Eisenbarth SC, Savaria M, Vinet AF, Bellemare MJ, Harder KW, et al. Malarial hemozoin activates the NLRP3 inflammasome through Lyn and Syk kinases. PLoS Pathog 2009; 5:e1000559; PMID:19696895; http://dx.doi.org/10.1371/journal.ppat.1000559
46. Dostert C, Guarda G, Romero JF, Menu P, Gross O, Tardivel A, et al. Malarial hemozoin is a Nalp3 inflammasome activating danger signal. PLoS One 2009; 4:e6510; PMID:19652710; http://dx.doi.org/10.1371/journal.pone.0006510

47. Lamkanfi M, Mueller JL, Vitari AC, Misaghi S, Fedorova A, Deshayes K, et al. Glyburide inhibits the Cryopyrin/Nalp3 inflammasome. J Cell Biol 2009; 187:61-70; PMID:19805629; http://dx.doi.org/10.1083/jcb.200903124
48. Abdul-Sater AA, Koo E, Häcker G, Ojcius DM. Inflammasome-dependent caspase-1 activation in cervical epithelial cells stimulates growth of the intracellular pathogen Chlamydia trachomatis. J Biol Chem 2009; 284:26789-96; PMID:19648107; http://dx.doi.org/10.1074/jbc.M109.026823
49. Gurcel L, Abrami L, Girardin S, Tschopp J, van der Goot FG. Caspase-1 activation of lipid metabolic pathways in response to bacterial pore-forming toxins promotes cell survival. Cell 2006; 126:1135-45; PMID:16990137; http://dx.doi.org/10.1016/j.cell.2006.07.033
50. VanderBrink BA, Asanuma H, Hile K, Zhang H, Rink RC, Meldrum KK. Interleukin-18 stimulates a positive feedback loop during renal obstruction via interleukin-18 receptor. J Urol 2011; 186:1502-8; PMID:21855933; http://dx.doi.org/10.1016/j.juro.2011.05.046
51. Jorgensen I, Bednar MM, Amin V, Davis BK, Ting JP, McCafferty DG, et al. The Chlamydia protease CPAF regulates host and bacterial proteins to maintain pathogen vacuole integrity and promote virulence. Cell Host Microbe 2011; 10:21-32; PMID:21767809; http://dx.doi.org/10.1016/j.chom.2011.06.008
52. Olivares-Zavaleta N, Carmody A, Messer R, Whitmire WM, Caldwell HD. Chlamydia pneumoniae inhibits activated human T lymphocyte proliferation by the induction of apoptotic and pyroptotic pathways. J Immunol 2011; 186:7120-6; PMID:21543647; http://dx.doi.org/10.4049/jimmunol.1100393
53. Hoffmann C, Galle M, Dilling S, Käppeli R, Müller AJ, Songhet P, et al. In macrophages, caspase-1 activation by SopE and the type III secretion system-1 of S. typhimurium can proceed in the absence of flagellin. PLoS One 2010; 5:e12477; PMID:20814576; http://dx.doi.org/10.1371/journal.pone.0012477
54. Hersh D, Monack DM, Smith MR, Ghori N, Falkow S, Zychlinsky A. The Salmonella invasin SipB induces macrophage apoptosis by binding to caspase-1. Proc Natl Acad Sci U S A 1999; 96:2396-401; PMID:10051653; http://dx.doi.org/10.1073/pnas.96.5.2396
55. Guiney DG. The role of host cell death in Salmonella infections. Curr Top Microbiol Immunol 2005; 289:131-50; PMID:15791954; http://dx.doi.org/10.1007/3-540-27320-4_6
56. Monack DM, Hersh D, Ghori N, Bouley D, Zychlinsky A, Falkow S. Salmonella exploits caspase-1 to colonize Peyer's patches in a murine typhoid model. J Exp Med 2000; 192:249-58; PMID:10899911; http://dx.doi.org/10.1084/jem.192.2.249
57. Johnston JB, Rahman MM, McFadden G. Strategies that modulate inflammasomes: insights from host-pathogen interactions. Semin Immunopathol 2007; 29:261-74; PMID:17717669; http://dx.doi.org/10.1007/s00281-007-0080-5
58. Crook NE, Clem RJ, Miller LK. An apoptosis-inhibiting baculovirus gene with a zinc finger-like motif. J Virol 1993; 67:2168-74; PMID:8445726
59. Zhou Q, Krebs JF, Snipas SJ, Price A, Alnemri ES, Tomaselli KJ, et al. Interaction of the baculovirus anti-apoptotic protein p35 with caspases. Specificity, kinetics, and characterization of the caspase/p35 complex. Biochemistry 1998; 37:10757-65; PMID:9692966; http://dx.doi.org/10.1021/bi980893w
60. Zhou Q, Snipas S, Orth K, Muzio M, Dixit VM, Salvesen GS. Target protease specificity of the viral serpin CrmA. Analysis of five caspases. J Biol Chem 1997; 272:7797-800; PMID:9065443; http://dx.doi.org/10.1074/jbc.272.12.7797
61. Callus BA, Vaux DL. Caspase inhibitors: viral, cellular and chemical. Cell Death Differ 2007; 14:73-8; PMID:16946729; http://dx.doi.org/10.1038/sj.cdd.4402034
62. Ray CA, Black RA, Kronheim SR, Greenstreet TA, Sleath PR, Salvesen GS, et al. Viral inhibition of inflammation: cowpox virus encodes an inhibitor of the interleukin-1 beta converting enzyme. Cell 1992; 69:597-604; PMID:1339309; http://dx.doi.org/10.1016/0092-8674(92)90223-Y
63. Komiyama T, Ray CA, Pickup DJ, Howard AD, Thornberry NA, Peterson EP, et al. Inhibition of interleukin-1 beta converting enzyme by the cowpox virus serpin CrmA. An example of cross-class inhibition. J Biol Chem 1994; 269:19331-7; PMID:8034697
64. Thompson JP, Turner PC, Ali AN, Crenshaw BC, Moyer RW. The effects of serpin gene mutations on the distinctive pathobiology of cowpox and rabbitpox virus following intranasal inoculation of Balb/c mice. Virology 1993; 197:328-38; PMID:8212568; http://dx.doi.org/10.1006/viro.1993.1594
65. MacNeill AL, Moldawer LL, Moyer RW. The role of the cowpox virus crmA gene during intratracheal and intradermal infection of C57BL/6 mice. Virology 2009; 384:151-60; PMID:19056101; http://dx.doi.org/10.1016/j.virol.2008.10.041
66. Petit F, Bertagnoli S, Gelfi J, Fassy F, Boucraut-Baralon C, Milon A. Characterization of a myxoma virus-encoded serpin-like protein with activity against interleukin-1 beta-converting enzyme. J Virol 1996; 70:5860-6; PMID:8709205
67. Messud-Petit F, Gelfi J, Delverdier M, Amardeilh MF, Py R, Sutter G, et al. Serp2, an inhibitor of the interleukin-1beta-converting enzyme, is critical in the pathobiology of myxoma virus. J Virol 1998; 72:7830-9; PMID:9733819
68. Delaloye J, Roger T, Steiner-Tardivel QG, Le Roy D, Knaup Reymond M, Akira S, et al. Innate immune sensing of modified vaccinia virus Ankara (MVA) is mediated by TLR2-TLR6, MDA-5 and the NALP3 inflammasome. PLoS Pathog 2009; 5:e1000480; PMID:19543380; http://dx.doi.org/10.1371/journal.ppat.1000480
69. Rathinam VA, Jiang Z, Waggoner SN, Sharma S, Cole LE, Waggoner L, et al. The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses. Nat Immunol 2010; 11:395-402; PMID:20351692; http://dx.doi.org/10.1038/ni.1864
70. Kettle S, Alcamí A, Khanna A, Ehret R, Jassoy C, Smith GL. Vaccinia virus serpin B13R (SPI-2) inhibits interleukin-1beta-converting enzyme and protects virus-infected cells from TNF- and Fas-mediated apoptosis, but does not prevent IL-1beta-induced fever. J Gen Virol 1997; 78:677-85; PMID:9049422
71. Kettle S, Blake NW, Law KM, Smith GL. Vaccinia virus serpins B13R (SPI-2) and B22R (SPI-1) encode M(r) 38.5 and 40K, intracellular polypeptides that do not affect virus virulence in a murine intranasal model. Virology 1995; 206:136-47; PMID:7831769; http://dx.doi.org/10.1016/S0042-6822(95)80028-X
72. Turner SJ, Silke J, Kenshole B, Ruby J. Characterization of the ectromelia virus serpin, SPI-2. J Gen Virol 2000; 81:2425-30; PMID:10993930
73. Chantrey J, Meyer H, Baxby D, Begon M, Bown KJ, Hazel SM, et al. Cowpox: reservoir hosts and geographic range. Epidemiol Infect 1999; 122:455-60; PMID:10459650; http://dx.doi.org/10.1017/S0950268899002423
74. Seet BT, Johnston JB, Brunetti CR, Barrett JW, Everett H, Cameron C, et al. Poxviruses and immune evasion. Annu Rev Immunol 2003; 21:377-423; PMID:12543935; http://dx.doi.org/10.1146/annurev.immunol.21.120601.141049
75. Dorfleutner A, Talbott SJ, Bryan NB, Funya KN, Rellick SL, Reed JC, et al. A Shope Fibroma virus PYRIN-only protein modulates the host immune response. Virus Genes 2007; 35:685-94; PMID:17676277; http://dx.doi.org/10.1007/s11262-007-0141-9
76. Johnston JB, Barrett JW, Nazarian SH, Goodwin M, Ricciuto D, Wang G, et al. A poxvirus-encoded pyrin domain protein interacts with ASC-1 to inhibit host inflammatory and apoptotic responses to infection. Immunity 2005; 23:587-98; PMID:16356857; http://dx.doi.org/10.1016/j.immuni.2005.10.003
77. Rahman MM, McFadden G. Myxoma virus lacking the pyrin-like protein M013 is sensed in human myeloid cells by both NLRP3 and multiple Toll-like receptors, which independently activate the inflammasome and NF-κB innate response pathways. J Virol 2011; 85:12505-17; PMID:21957307; http://dx.doi.org/10.1128/JVI.00410-11
78. Gregory SM, Davis BK, West JA, Taxman DJ, Matsuzawa S, Reed JC, et al. Discovery of a viral NLR homolog that inhibits the inflammasome. Science 2011; 331:330-4; PMID:21252346; http://dx.doi.org/10.1126/science.1199478
79. Abdelaziz DH, Gavrilin MA, Akhter A, Caution K, Kotrange S, Khweek AA, et al. Apoptosis-associated speck-like protein (ASC) controls Legionella pneumophila infection in human monocytes. J Biol Chem 2011; 286:3203-8; PMID:21097506; http://dx.doi.org/10.1074/jbc.M110.197681
80. Stasakova J, Ferko B, Kittel C, Sereinig S, Romanova J, Katinger H, et al. Influenza A mutant viruses with altered NS1 protein function provoke caspase-1 activation in primary human macrophages, resulting in fast apoptosis and release of high levels of interleukins 1beta and 18. J Gen Virol 2005; 86:185-95; PMID:15604446; http://dx.doi.org/10.1099/vir.0.80422-0
81. Lam WY, Tang JW, Yeung AC, Chiu LC, Sung JJ, Chan PK. Avian influenza virus A/HK/483/97(H5N1) NS1 protein induces apoptosis in human airway epithelial cells. J Virol 2008; 82:2741-51; PMID:18199656; http://dx.doi.org/10.1128/JVI.01712-07
82. Master SS, Rampini SK, Davis AS, Keller C, Ehlers S, Springer B, et al. Mycobacterium tuberculosis prevents inflammasome activation. Cell Host Microbe 2008; 3:224-32; PMID:18407066; http://dx.doi.org/10.1016/j.chom.2008.03.003
83. Sutterwala FS, Mijares LA, Li L, Ogura Y, Kazmierczak BI, Flavell RA. Immune recognition of Pseudomonas aeruginosa mediated by the IPAF/NLRC4 inflammasome. J Exp Med 2007; 204:3235-45; PMID:18070936; http://dx.doi.org/10.1084/jem.20071239
84. Galle M, Schotte P, Haegman M, Wullaert A, Yang HJ, Jin S, et al. The Pseudomonas aeruginosa Type III secretion system plays a dual role in the regulation of caspase-1 mediated IL-1beta maturation. J Cell Mol Med 2008; 12(5A):1767-76; PMID:18081695; http://dx.doi.org/10.1111/j.1582-4934.2007.00190.x
85. Schotte P, Denecker G, Van Den Broeke A, Vandenabeele P, Cornelis GR, Beyaert R. Targeting Rac1 by the Yersinia effector protein YopE inhibits caspase-1-mediated maturation and release of interleukin-1beta. J Biol Chem 2004; 279:25134-42; PMID:15060067; http://dx.doi.org/10.1074/jbc.M401245200
86. Brodsky IE, Palm NW, Sadanand S, Ryndak MB, Sutterwala FS, Flavell RA, et al. A Yersinia effector protein promotes virulence by preventing inflammasome recognition of the type III secretion system. Cell Host Microbe 2010; 7:376-87; PMID:20478539; http://dx.doi.org/10.1016/j.chom.2010.04.009

87. Shimada T, Park BG, Wolf AJ, Brikos C, Goodridge HS, Becker CA, et al. Staphylococcus aureus evades lysozyme-based peptidoglycan digestion that links phagocytosis, inflammasome activation, and IL-1beta secretion. Cell Host Microbe 2010; 7:38-49; PMID: 20114027; http://dx.doi.org/10.1016/j.chom.2009.12.008
88. Ulland TK, Buchan BW, Ketterer MR, Fernandes-Alnemri T, Meyerholz DK, Apicella MA, et al. Cutting edge: mutation of Francisella tularensis mviN leads to increased macrophage absent in melanoma 2 inflammasome activation and a loss of virulence. J Immunol 2010; 185:2670-4; PMID:20679532; http://dx.doi.org/10.4049/jimmunol.1001610
89. Peng K, Broz P, Jones J, Joubert LM, Monack D. Elevated AIM2-mediated pyroptosis triggered by hypercytotoxic Francisella mutant strains is attributed to increased intracellular bacteriolysis. Cell Microbiol 2011; 13:1586-600; PMID:21883803; http://dx.doi.org/10.1111/j.1462-5822.2011.01643.x
90. Witzenrath M, Pache F, Lorenz D, Koppe U, Gutbier B, Tabeling C, et al. The NLRP3 inflammasome is differentially activated by pneumolysin variants and contributes to host defense in pneumococcal pneumonia. J Immunol 2011; 187:434-40; PMID:21646297; http://dx.doi.org/10.4049/jimmunol.1003143
91. Creasey EA, Isberg RR. The protein SdhA maintains the integrity of the Legionella-containing vacuole. Proc Natl Acad Sci U S A 2012; 109:3481-6; PMID: 22308473; http://dx.doi.org/10.1073/pnas.1121286109
92. Kumar H, Kumagai Y, Tsuchida T, Koenig PA, Satoh T, Guo Z, et al. Involvement of the NLRP3 inflammasome in innate and humoral adaptive immune responses to fungal beta-glucan. J Immunol 2009; 183:8061-7; PMID:20007575; http://dx.doi.org/10.4049/jimmunol.0902477
93. Gross O, Poeck H, Bscheider M, Dostert C, Hannesschläger N, Endres S, et al. Syk kinase signalling couples to the Nlrp3 inflammasome for anti-fungal host defence. Nature 2009; 459:433-6; PMID:19339971; http://dx.doi.org/10.1038/nature07965
94. Joly S, Sutterwala FS. Fungal pathogen recognition by the NLRP3 inflammasome. Virulence 2010; 1:276-80; PMID:21178453; http://dx.doi.org/10.4161/viru.1.4.11482
95. Saïd-Sadier N, Padilla E, Langsley G, Ojcius DM. Aspergillus fumigatus stimulates the NLRP3 inflammasome through a pathway requiring ROS production and the Syk tyrosine kinase. PLoS One 2010; 5:e10008; PMID:20368800; http://dx.doi.org/10.1371/journal.pone.0010008
96. Tomalka J, Ganesan S, Azodi E, Patel K, Majmudar P, Hall BA, et al. A novel role for the NLRC4 inflammasome in mucosal defenses against the fungal pathogen Candida albicans. PLoS Pathog 2011; 7:e1002379; PMID:22174673; http://dx.doi.org/10.1371/journal.ppat.1002379
97. Joly S, Ma N, Sadler JJ, Soll DR, Cassel SL, Sutterwala FS. Cutting edge: Candida albicans hyphae formation triggers activation of the Nlrp3 inflammasome. J Immunol 2009; 183:3578-81; PMID:19684085; http://dx.doi.org/10.4049/jimmunol.0901323
98. Cheng SC, van de Veerdonk FL, Lenardon M, Stoffels M, Plantinga T, Smeekens S, et al. The dectin-1/inflammasome pathway is responsible for the induction of protective T-helper 17 responses that discriminate between yeasts and hyphae of Candida albicans. J Leukoc Biol 2011; 90:357-66; PMID:21531876; http://dx.doi.org/10.1189/jlb.1210702
99. van de Veerdonk FL, Joosten LA, Shaw PJ, Smeekens SP, Malireddi RK, van der Meer JW, et al. The inflammasome drives protective Th1 and Th17 cellular responses in disseminated candidiasis. Eur J Immunol 2011; 41:2260-8; PMID:21681738; http://dx.doi.org/10.1002/eji.201041226
100. Lev-Sagie A, Prus D, Linhares IM, Lavy Y, Ledger WJ, Witkin SS. Polymorphism in a gene coding for the inflammasome component NALP3 and recurrent vulvovaginal candidiasis in women with vulvar vestibulitis syndrome. Am J Obstet Gynecol 2009; 200:303, e1-6; PMID:19254587; http://dx.doi.org/10.1016/j.ajog.2008.10.039