The role of inflammasome modulation in virulence

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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

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 Nlep1b gene were shown to alter anthrax lethal toxin-induced macrophage cell death responses.5,13 Notably, NLRP1b inflammasome-induced
macrophage cell death confers resistance to infection with *B. anthracis* spores in vivo, demonstrating the importance of pyroptosis for host defense. 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.

NLRC4 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 NLRC4 is activated by such a diverse range of agents is still under investigation but activation of NLRC4 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. Subsequent exposure to microbial pore-forming toxins and ionophores such as listeriolysin O, streptolysin O, α-hemolysin, nigericin or maitotoxin then fully activate the NLRP3 inflammasome. 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). 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.

The NLRC4 inflammasome detects bacterial flagellin from Legionella and the Prgl family of proteins that comprise the basal body rod component of bacterial type III secretion systems (TTSS) of *Salmonella*, *Pseudomonas* and *Shigella* species. In addition to the secretion of IL-1β and IL-18, the Nlr4 inflammasome also induces pyroptotic cell death in order to clear flagellin-expressing bacteria such as *L. pneumophila* and *B. thailandensis*. 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. It should be noted, however, that several earlier studies reported that NAIP5 was dispensable or only partially required 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. 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.

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. In the case of *S. pneumoniae*, AIM2 is the predominant sensor, but NLRP3 is also capable of inflammasome activation. 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. 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. 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. 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. 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. 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.

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. 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. Intra-cerebral injection of gp120 activates caspase-1 and leads to IL-1β maturation as well as cell death in the neocortex of rats. This pathology can be reduced by treatment with inhibitors of caspase-1 or IL-1 receptor antagonist. 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. During dengue virus infection of mice, caspase-1 expression increases and inflammasome activation results in pyroptotic cell death. However, treatment...
with the caspase-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 mediated 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). **55 For example, baculovirus protein p35 is capable of binding to and directly inhibiting a wide variety of caspases, including caspase-1, in its natural insect hosts and mammalian cells. **56,59 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 Intrauterine 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 **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
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.\textsuperscript{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-1\textbeta and IL-18.\textsuperscript{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.\textsuperscript{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-1\textbeta and IL-18 processing but also leads to reduced virus reactivation and progeny virus production.\textsuperscript{78}

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

\textbf{Indirect inflammasome inhibition.} Influenza A/PR/8/34 H1N1 virus (PR8) NS1 protein, in addition to blocking type-I interferon responses, is also capable of blocking inflammasome
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. 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. 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 Zn²⁺ 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. The ExoU and ExoS proteins of P. aeruginosa inhibit the NLRC4 inflammasome upon TTSS delivery to the cytosol and are required for pathogenicity. ExoU was shown to indirectly inhibit the NLRC4 inflammasome through its phospholipase A₂ activity; however, it is not altogether clear how this enzymatic activity of ExoU inhibits caspase-1 activation. ExoS similarly inhibits caspase-1 activation through its ADP ribosyltransferase activity through an undefined mechanism. 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 RhoA and Rho-GTPase Rac-1. 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

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    | NLRP4                   | unknown                  | Downregulates NLRP4 and ASC                             | 79         |
| Indirect inhibition: | | | | |
| Influenza A       | NLRP3                   | NS1                      | Exact mechanism unknown, PKR                            | 80–81      |
| M. tuberculosis   | NLRP3                   | Zmp1                     | Zn⁺⁺ metalloprotease, blocks superoxide production       | 82         |
| P. aeruginosa     | NLRP3, NLRC4            | ExoU                     | Phospholipase A₂ activity, unknown mechanism             | 83         |
|                   |                         | ExoS                     | ADP ribosyltransferase activity, unknown mechanism       | 84         |
| Y. enterocolitica | NLRP3, NLRC4            | YopE                     | Inhibits caspase-1 oligomerization through Rac-1        | 85         |
|                   |                         | YopT                     | Inhibits caspase-1 oligomerization through RhoA          | 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  |
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-acetylttransferase 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 mannann, 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.

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