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Highlights

# The inflammasome: Friend or foe in Chlamydia infection?

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ABSTRACT

In this issue of the Biomedical Journal, we take a look at the still somewhat perplexing role of the inflammasome in Chlamydia infection. We also highlight findings suggesting a link between structural changes to arteries in the brain and the onset of depression. Finally, we learn about some of the implications of co-morbidity between diabetes and infectious diseases.

## Spotlight on reviews

### *The inflammasome: friend or foe in Chlamydia infection?*

As the most common bacterial cause of sexually-transmitted infection and preventable blindness worldwide [1,2], *Chlamydia trachomatis* is a major public health problem. This obligate intracellular pathogen is able to subvert host immune defenses and keep infected cells alive by interfering with cell death pathways [3], leading to chronic inflammation and substantial damage to local tissues. Recently however, much progress has been made in the understanding of the relationship between important inflammation-associated pathways and *Chlamydiae* species. In this issue of the *Biomedical Journal*, Pettengill et al. [4] outline the recent developments on two of these pathways, and in particular, the perplexing role of the inflammasome.

*Chlamydiae* species including *C. trachomatis*, *Chlamydophila pneumoniae* and *Chlamydophila psittaci* cause a spectrum of human and zoonotic infections characterized by one consistent hallmark: chronic, localized inflammation. The chronic and excessive production of inflammatory cytokines is thought to be the main cause of pathology associated with infection [5], such as pelvic inflammatory disease which develops in women with untreated genital tract infections and is a common cause of pregnancy complications and infertility [6]. Therefore, it is very important to understand the relationship between inflammatory signaling and the pathogen.

Like most bacteria, *C. trachomatis* is detected by host pattern recognition receptors (PRRs) which recognize pathogen associated molecular patterns (PAMPs). These PRRs can be membrane-bound, like the Toll-like receptors (TLRs), which sample the extracellular environment or the interior of endosomes, or cytosolic, like the nucleotide-binding and

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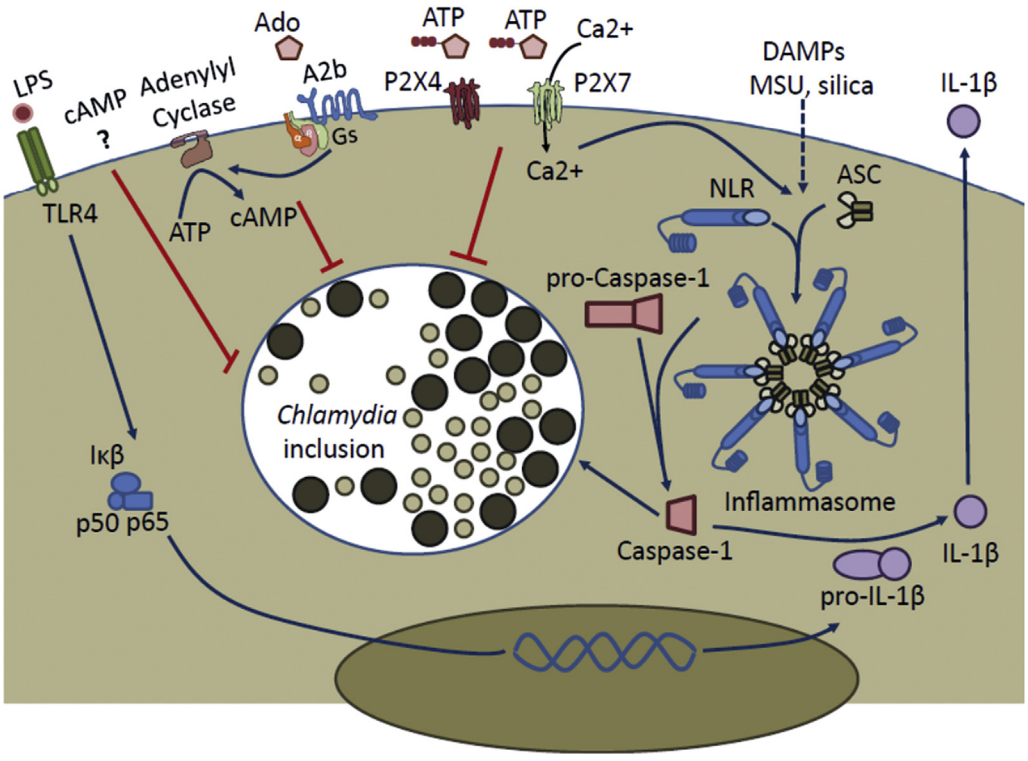


Fig. 1 – **Inflammasome activation and purinergic signaling in *Chlamydia*-infected cells**. *Chlamydia* consists of two forms: elementary bodies (EB; small light brown circles) and reticulate bodies (RB, large dark brown circles). EBs are the dispersive form of the bacteria, capable of invading host-epithelial cells and establishing a new cellular compartment called an inclusion (white circle). It is here that EBs differentiate into RBs, the replicative and metabolically active form of the pathogen. After accumulating in number, RBs differentiate back into EBs, eventually leading to cell lysis and a new round of infection. Chlamydia infection activates the inflammasome, which in turn activates caspase-1 leading to cleavage of pro-IL-1β into its mature, active form. Infection also activates another inflammation pathway, purinergic signaling (see Ref. [4] for more details). Figure kindly provided by Pettengill et al. [4]

oligomerization domain (NOD)-like receptors (NLRs). These NLRs are capable of recognizing not only PAMPs but also danger associated molecular patterns (DAMPs) [7] like ATP, which are released by damaged host cells. NLRs are also components of a macromolecular complex called the inflammasome, which activates caspase-1, in turn leading to the generation of potent inflammatory cytokines IL-1β and IL-18 [Fig. 1].

These cytokines are so potent that their production must be carefully regulated. The NLRP3 inflammasome, which is the most extensively studied inflammasome to date, requires signals from PAMPs and DAMPs for its activation. Some intracellular pathogens like *C. trachomatis* provide both signals, and caspase-1 is indeed activated during chlamydial infection in a manner dependent on NLRP3 [8]. Human monocytes infected with *C. trachomatis* secrete IL-1β following the assembly of NLRP3 and caspase-1 activation [9]. Whether the engagement of the inflammasome is helpful or harmful however is still debatable. Mice lacking caspase-1 showed reduced clearance of *C. pneumoniae* and increased mortality [10]. However, blocking the activity of caspase-1 with an inhibitor in lung fibroblasts actually makes them more resistant to infection [11]. Perhaps the key lies in the context of infection. Monocytes and macrophages are geared towards the production of pro-inflammatory cytokines following the activation of caspase-1, but this is not the case for epithelial cells. Instead, inflammasome activation in these cells leads to the caspase-1-dependent destruction of the Golgi apparatus [12]. As an obligate pathogen with a substantially reduced genome, *Chlamydia* species must scavenge many nutrients from its host. Breakdown of the Golgi liberates lipids produced by the host but required by the bacterium, which may explain why caspase-1 is actually needed for optimal *C. trachomatis* growth in epithelial cells [8].

Thus, as the driver behind the production of pro-inflammatory cytokines and potential sustainer of *Chlamydia* growth in epithelial cells, the situation looks pretty incriminating for the inflammasome in the pathology of *Chlamydia* infections. There are however likely to be important nuances to the relationship that require further investigation.

## Spotlight on original articles

### *Structural changes to brain blood vessels correlate with depression*

The "vascular depression hypothesis" postulates that cerebrovascular disease can predispose to depressive symptoms in older adults [13]. In this issue of the *Biomedical Journal*,