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 Chlamydia 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
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 their 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,
Farmar and Prasad [14] provide intriguing evidence that this hypothesis may be relevant to understanding depression in individuals showing no physical manifestations of neurodegenerative disease.

Depressive disorders have been linked to functional changes in several brain regions on neuroimaging, including the prefrontal cortex, anterior cingulate cortex, the basal ganglia and brain stem, the limbic areas (notably the amygdala and hippocampus) [15]. Although the neural basis of depression is far from understood, it has been consistently shown that these functional abnormalities are associated with altered cerebral blood flow [16]. Yet, the histochorarchitecture of the arteries that supply the brain regions involved in depression has never been investigated closely.

To investigate whether functional changes correlate with architectural changes in depression, Parmar and Prasad focused on the basilar artery, which supplies many of the brain areas shown to be involved in depression. By histological staining they examined several variables relating to the structure of the basilar artery, in 20 individuals who had committed suicide and 20 age-matched control individuals who had died of non-head related injuries, including arterial diameter, the thickness of its constituent layers, and the volume fraction of collagen. All of the variables measured were lower in suicide persons than in the control group, and in the case of the thickness of the tunica media (middle arterial layer) and the volume fraction of collagen, these differences were statistically significant.

This analysis reveals that the architecture of blood vessels serving brain regions important for depression is altered in individuals who have committed suicide, thus establishing a firm correlation between structural changes to the vascular circuitry, altered blood flow and brain function. These findings are reminiscent of the vascular depression hypothesis [13]. Specifically, Parmar and Prasad postulate that a loss of collagen and elastic fibers in the arterial wall leads to a failure to distribute appropriately muscle tension around the vessel, which is likely to affect hemodynamics and blood flow. These changes in turn affect the regions supplied by the artery. Of course correlation does not amount to causation, but nonetheless, if substantiated, these findings could provide a useful framework for the understanding vascular depression outside of the context of the physical signs of neurodegeneration.

Review articles

Purinergic signaling in infectious and autoimmune disease

Purinergic signaling is a highly conserved form of cell-cell communication involving extracellular ATP, adenosine and other purines. It plays a key role in modulating inflammatory responses, and as such many pathogens have developed to mechanisms to manipulate the pathway to their advantage [17–19]. In this issue of the Biomedical Journal, Silva [20] reviews another example of this interplay involving the parasitic worm Schistosoma. Not restricted to infectious disease, perturbation to purinergic signaling may also occur in the context of autoimmune disease. Di Virgilio and Giuliani [21] outline the role of purinergic signaling during systemic lupus erythematosus and in particular that of the P2X7 receptor, which when activated by ATP, leads to the processing and release of the pro-inflammatory cytokine IL-1β.

Original articles

Virulent strain of Helicobacter pylori linked to cellular damage in cardiac syndrome X

Patients with cardiac syndrome X (CSX) experience chest pain during exercise even though coronary arteries appear normal on an angiogram. It is thought that CSX is caused by endothelial dysfunction of the coronary microcirculation, although the pathological mechanisms are not completely understood. This heterogeneous condition has been linked to infection with the stomach-dwelling pathogen Helicobacter pylori [22] which despite its location, has been implicated in several extra-intestinal disorders [23]. In particular, strains carrying the cytotoxin-associated gene A (CagA+) elicit heightened inflammatory responses [24]. Rasmie et al. [25] investigated the levels of markers of endothelial dysfunction in CSX patients with or without H. pylori infection. Their findings suggest that H. pylori, especially strains carrying CagA, promote endothelial dysfunction in CSX.

Malaria affects leptin levels differently in diabetics and non-diabetics

Patients with co-morbidities are becoming the norm rather than the exception for health care systems and it is no longer sufficient to study and treat diseases in isolation. In this report, Acquah et al. [26] investigate the coexistence of two diseases of major global burden: type 2 diabetes mellitus (T2DM) and falciparum malaria in a prospective study involving 200 individuals. Specifically they address how infection with falciparum affects the levels of the adipocytokines leptin and adiponectin, both of which are thought to protect against T2DM [27,28]. Following infection, adiponectin levels were increased in both study groups whereas leptin levels were increased in diabetics and decreased in non-diabetics. These findings could have implications for patient management.

Investigating micronutrient levels in diabetic patients with tuberculosis

Diabetics have a higher risk of developing tuberculosis than non-diabetics, and once infected, have a higher risk of treatment failure [29]. This association is probably explained in part by the effect of diabetes on cell-mediated immunity [30], although other mechanisms may be involved. Ginnadjar et al. [31] investigate a possible link with nutrition in 62 patients with tuberculosis and find that those with poor blood glucose control also show altered levels of vitamin E.

Also in this issue:

Treatment of immature necrotic teeth: which method is best?

Internal damage to young permanent teeth is notoriously difficult to treat, in large part because death of the dental pulp halts root formation, leaving a wide open apex. The traditional method for treating such injuries is apexification, in which an inert material is used to stimulate hard tissue to form at the apex, but is not thought to promote root growth. By contrast, regenerative endodontic treatment aims to stimulate continued growth of the immature root (either by replacing damaged tissue in the pulp chamber with live cells or bioactive substances or encouraging organized healing in other ways). In this retrospective study of 38 patients, Chen et al. [32] compare the outcome of these techniques with up to one year of follow-up in children with necrotic dental pulp injuries. Surprisingly, there was no statistical difference in radiographic outcome or root development between the two techniques, suggesting that this new treatment trend should be further validated in larger studies.

Conflicts of interest

The author declares that there are no conflicts of interest.

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