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A re-evaluation of the role of B cells in protective immunity to *Chlamydia* infection

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Abstract

Chlamydia trachomatis is the etiological agent of the most commonly reported bacterial sexual transmitted infection (STI) in North America and Europe. The control of *Chlamydia* infection is hindered by the asymptomatic nature of initial infection but the consequence of untreated infection seriously threatens the reproductive health of young women. Unfortunately, there is no licensed vaccine for *Chlamydia* vaccine, in part due to our incomplete understanding of the immune response to *Chlamydia* urogenital infection. It has been well established that T cell-mediated immunity plays a dominant role in protective immunity against *Chlamydia* and thus the importance of B cells is somewhat underappreciated. Here, we summarize recent progress on understanding the role of B cells during *Chlamydia* genital tract infections and discuss how B cells and humoral immunity make an effective contribution to host defense against important intracellular pathogens, including *Chlamydia*.

Keywords

Chlamydia; intracellular infections; B cells; antibody

1. Introduction

Chlamydia trachomatis is a gram-negative, obligate intracellular bacterium that causes the most prevalent sexual transmitted infection (STI) worldwide. According to the Centers for Disease Control (CDC), *Chlamydia* is now the most commonly reported infectious disease in the United States with more than 3 million cases occurring annually [1,2]. Unfortunately most women with urogenital *Chlamydia* experience a subclinical infection, yet these untreated *Chlamydia* infections can lead to severe reproductive problems such as pelvic inflammatory disease (PID), ectopic pregnancy and involuntary infertility, meaning that *Chlamydia* infections represent a growing threat to the reproductive health of young women [3]. Despite the implementation of a *Chlamydia* screening and treatment program in many

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high-income countries over the past decade, the prevalence of *Chlamydia* infection has continued to increase every year [4]. There is now a consensus among the medical and research community that an effective *Chlamydia* vaccine is required [5,6]. However, for this to become a reality, a greater understanding of the mechanisms of *Chlamydia* pathogenesis and the induction of host protective immunity will be required.

Chlamydia is an obligate intracellular pathogen and it is commonly thought that protective immunity to this class of pathogen is largely conferred by an appropriate cell-mediated immune (CMI) response. Indeed, it is generally accepted that CD4 T cells plays a predominant role in protective immunity to *Chlamydia* infection, whereas the requirement for antibody and/or B cells is limited [3,7,8]. Although there is certainly a collection of evidence to support the protective contribution of Th1 cells in a variety of intracellular infections [9–12], the easy assumption that intracellular organisms are outside the reach of the humoral immune responses deserves careful consideration [13]. Indeed, there is emerging evidence to support a prominent role for B cell-mediated immunity in several intracellular infection models, including *Chlamydia*, challenging the paradigm that such pathogens are beyond the reach of the humoral response. In this review, we attempt to highlight the progress made over the past few years to further define the role of antibody and B cells in *Chlamydia* genital tract infection models and also in vaccination studies with this pathogen.

2. Historical paradigms

Before the availability of gene-deficient mice, the role of B cells in *Chlamydia* infection was examined using reagents that suppressed humoral immunity in small animal models. When the humoral immune response was suppressed in Guinea pigs by cyclophosphamide treatment, genital infection with Guinea Pig Inclusion Conjunctivitis (GPIC, also called *Chlamydia caviae*) failed to resolve [14]. Similarly, treatment with cyclophosphamide was able to diminish host protective immunity against secondary *Chlamydia* infection [15]. Consistent with these observations, the passive transfer of immune serum from previously infected animals was able to significantly reduce bacterial shedding from the genital tract of naïve guinea pigs [16]. Conversely, in murine models, the depletion of B cells using anti-IgM antibody suggested no clear role for B cells in the resolution of primary and secondary infection with *Chlamydia muridarum* (a natural mouse pathogen closely related to *Chlamydia* trachomatis) [17]. Despite the discordant findings in these two models, both groups of infected animals developed long-lasting antibody responses reflected by high titers of *Chlamydia*-specific IgGs in the serum [18,19].

When gene-deficient mice with immunological defects became available [20,21], Su *et al* confirmed that the duration and intensity of *Chlamydia muridarum* primary infection was indistinguishable in wild-type and B cell deficient mice (μMT), as determined by bacterial shedding measured by vaginal swabs [20]. However, in response to a secondary infection with the same pathogen, μMT mice exhibited a small, but significant, increase in infection susceptibility [20]. These data suggested a minor role for B cells in secondary protective immunity. In marked contrast, numerous studies demonstrated a major role for CMI in the clearance of *Chlamydia* infection. Thus, mice lacking T cells (athymic nude mice, TCR$\beta^{-/-}$),

or MHC class II-restricted CD4 T cells ($MHCII^{-/-}$ mice), developed chronic *Chlamydia* infection that did not resolve [22–24]. Together, these findings from gene-deficient mice provided support for a conceptual framework that pointed to CMI responses mediating protection against intracellular infections and minimal contribution from B cells and antibody.

3. B cells and *Chlamydia* infection: mouse model revisited

While the studies outlined above support a major role for T cells in *Chlamydia* clearance, they do not completely rule out the possibility that B cells actively participate in bacteria clearance [13]. As noted above, mice lacking B cells show increased susceptibility to secondary infection, indicating some protective role for B cells. Furthermore, the studies of T cell-deficient mice rarely considered the fact these animals also lacked T cell dependent antibody, meaning that increased susceptibility could also reflect a major defect in humoral immunity. In an effort to unravel the contribution of these different arms of adaptive immunity during secondary *Chlamydia* infection, Morrison and colleagues conducted a series of important antibody-depletion experiments in wild-type and B-cell deficient mice. By removing either CD4 or CD8 T cells, or both populations, they were able to demonstrate that when antibody-mediated immunity (AMI) is intact, neither CD4 T cells nor CD8 T cells are absolutely required for the resolution of secondary *Chlamydia* infection. In contrast, when similar experiments were conducted in B cell-deficient mice, these mice were unable to resolve secondary infection in the absence of CD4 T cells [25,26]. Together, these findings suggest a fundamental difference between the mechanisms of protective immunity against primary and secondary *Chlamydia* infection. While the resolution of *Chlamydia* primary infection seems to be dependent on the response of CD4 T cells, secondary protection against *Chlamydia* infection can be conferred by CD4 T cells or B cells. The predominant role of antibody in protective immunity against *Chlamydia* reinfections was further supported by a follow-up study by Morrison and colleagues demonstrating that the passive transfer of immune convalescent serum to B cell-deficient mice conferred full protection to the host against *Chlamydia* reinfection in the absence of CMI [27].

An additional aspect to consider is that there is increasing evidence for B cell effector functions beyond simply producing pathogen-specific antibody [28]. More recently, our laboratory addressed whether B cells can act as antigen presenting cells during a primary host response to *Chlamydia* genital tract infection by revisiting the μMT mouse model. The issue being examined was whether the lack of B cells in these animals directly affected the clonal expansion of *Chlamydia*-specific CD4 T cells. Using *Chlamydia*-specific MHC class-II tetramers, we demonstrated that the endogenous, antigen-specific CD4 T cell responses to *Chlamydia* infection is significantly reduced within the local draining iliac lymph nodes of B cell-deficient mice. Strikingly, while the kinetics of bacterial shedding from the genital tract remained unaltered by the absence of B cells, μMT mice displayed a transient disseminated infection in the spleen and peritoneal cavity and developed ascites, a phenotype that actually closely resembles human peritonitis and severe PID associated with *C. trachomatis* genital tract infection [29–32]. Surprisingly, this disseminated infection in μMT mice correlated with a robust systemic immune response in both the spleen and peritoneal cavity, perhaps representing a compensatory response by the host defending against disseminated bacteria

[33]. The exact mechanism underlying this unexpected requirement for B cells in early primary bacterial containment in the reproductive tract is under active investigation, but these findings reveal an unexpected but indispensable role of B cells in *Chlamydia* primary infection.

4. Protective role of B cells and antibody in *Chlamydia* infection

The mechanism by which B cells and/or antibody protect the host against *Chlamydia* infection is not completely clear. Numerous in vitro studies have documented a definitive role of antibody in *Chlamydia* neutralization and complement activation [34–39]. Indeed, adoptive transfer of monoclonal antibodies against immunodominant epitopes, such as MOMP (major outer membrane protein), can protect mice against *Chlamydia* genital tract infection [37,40]. In contrast, antibodies against other antigens such as hsp60 (heat-shock protein 60) are not protective and some have even been associated with the development of immune-mediated pathology [27,41,42]. An interesting study by Caldwell and colleagues has demonstrated that pre-existing antibodies against major surface antigens such as MOMP and LPS can block the binding of a more protective antibody against PmpD (polymorphic membrane protein D) [43]. Therefore, given the unique intracellular biphasic developmental cycle and temporal regulation of gene expression of *Chlamydia* [44], the contribution of different antibody responses to protection or inhibiting protection adds an additional layer of complexity to the overall antibody response. The importance of complement fixation is also less clear from in vivo studies than historically has been observed in vitro. Nevertheless, recent reports have shed some light on the role of different complement components during *Chlamydia* infection. It has been demonstrated that C3 and C3aR both play a protective role in *Chlamydia psittaci* lung infection, whereas C5 but not C3 contribute to development of immunopathology at the mouse upper genital tract [45–47].

Despite the possibility for direct antibody-dependent neutralization or complement-mediated killing, these mechanisms are unlikely to account for antibody-mediated protection during secondary infection. This conclusion is based on the observation that the passive transfer of immune serum is only able to protect antigen-experienced hosts, rather than naïve animals [44]. Morrison et al, has suggested that this unique feature of the model reflects “CD4 T cell-mediated adaptive changes” that occur in the local genital tract tissue during initial infection, and that these modifications are required for protective antibody to elicit an effector function. This model suggests that interaction of antibody with Fc receptors on non-CD4 T cells is required for antibody-mediated protective immunity. In line with this hypothesis, Moore et al, have reported that *Chlamydia*-specific antibody can enhance antigen presentation of $FcR^{+/+}$ but not $FcR^{-/-}$ antigen presenting cells (APCs) [48,49].

Early infection of the genital mucosa presents a crucial “window of opportunity” for the host to restrict pathogen spread [50]. The disseminated infection during the early phase of primary *Chlamydia* infection of μMT mice points to an indispensable role of B cells in local pathogen containment [33]. The marked reduction in antigen-specific CD4 T cell priming within the draining iliac lymph nodes could suggest that B cells participate directly in antigen presentation during the earliest stages of primary infection. Although direct evidence from mice lacking MHC class-II expression specifically on B cells would required to

support this idea, additional studies using the *C. muridarum* lung infection model have demonstrated that mice lacking B cells fail to initiate an efficient CD4 T cell response to intranasal infection [51]. Despite the attractiveness of B cells participating as antigen-presenting cells, several alternative possibilities are equally viable (Figure 1). First, as a major component of secondary lymphoid organs (SLOs), B cells are known to be essential for the maintenance of the lymphoid architecture. Thus, the defective *Chlamydia*-specific CD4 T cell response that is observed in μMT mice could be a consequence of disrupted lymphoid structure leading to inefficient antigen presentation to T cells. Second, a recent study has suggested that B cells are essential for the maintenance of sub-capsular sinus (SCS) macrophages in the draining lymph node. The lack of SCS macrophages explains the inability of μMT mice to defend against some viral infections [52]. A similar mechanism involving a requirement for SCS macrophages could therefore account for disseminated infection in μMT mice after *Chlamydia* infection. Third, B cells can elicit effector functions by producing various cytokines in response to microbial stimulation and these cytokines may contribute to local defense in the lymph node that prevents bacterial dissemination. Lastly, a very early antibody response to *Chlamydia* infection may contribute to bacteria containment within the draining lymph node and local tissues. This possibility is supported by the notion that unlike the well-characterized high-affinity antibody that usually developed later during primary infection and can confer protection to reinfections, a rapid extra-follicular B cell response can result in antibody development very early during a primary infection [53]. Further studies are required to determine which of these alternative hypotheses explains the contribution of B cells to preventing bacterial dissemination during primary *Chlamydia* infection.

5. B cells and intracellular infections: lesson learned from others

While the exact mechanism of B cell-mediated protective immunity is currently unclear for *Chlamydia* genital tract infection, some lesson can learned from the study of B cells in other intracellular pathogen models. For example, it has been established that defined monoclonal antibodies (mAbs) are able to protect the host against *Mycobacterium tuberculosis* (Mtb) infection [54–56]. Moreover, as constituents of ectopic germinal centers in the lung, B cells are able to modulate the inflammatory response during Mtb infection and have recently been shown to regulate host neutrophilia by affecting IL-17 responses [57,58].

The protective role of B cell in *Salmonella* infection has been described as involving antibody-dependent and antibody-independent mechanisms [59–61]. For example, it has been shown that an early isotype-switched antibody response that is established as early as 3 days after *Salmonella* infection is able to impair colonization of *Salmonella* in the spleen and reduce bacteremia [62]. Other studies suggest a regulatory function of B cells during *Salmonella* infection as manifested by B cell-dependent cytokine production that alters the effector function of CD4 T cells to make IFN-γ and IL-17 [63,64]. Lastly, although serum transfers can reduce bacterial loads [60,65], it has been demonstrated that B cell production of antibody is not actually essential to the protective effect of B cells upon the host response [61]. Indeed, Th1 responses are found to be significantly reduced in *Salmonella*-infected B cell-deficient mice [59,61], demonstrating a prominent role for non-antibody-dependent mechanisms in this model.

There is also a growing body of evidence for antibody-mediated protection against other obligate intracellular pathogens. Passive transfer of immune serum protects naïve immune competent hosts from *Coxiella burnetii*, the etiological agent for Q fever [66], although the exact protective mechanism in this model remains unclear since both Fc receptor and complement seem to be dispensable [67]. Interestingly, in an effort to find the protective mechanism mediated by a *C. burnettii* phase I vaccine (PI-V) strain, Zhang et al demonstrated that a switched IgG response to PI-V lipopolysaccharide (LPS) provided significant protection to the host to an extent comparable to PI-V vaccination against *C. burnetii* infection [68]. Similar observations have also been made in obligate intracellular *Ehrlichia chaffeensis* infections, where antibody recognizing the major outer membrane protein (OMP)-1g of *E. chaffeensis* protects SCID mice from ehrlichiosis, a vector-borne disease [69].

How might antibody mediate protection against an obligate intracellular pathogen? The discovery of protective antibody to *E. chaffeensis* infection led Li et al to uncover an extracellular phase in the *Ehrlichia* life cycle [70]. Although this may not be relevant for *Chlamydia*, it does imply that for an obligate intracellular bacterium, even brief exposure outside host cells can make them vulnerable to antibody-mediated defense mechanisms. Alternatively, rather than provide a killing mechanism extra-cellularly, it is possible that some antibodies can find their way inside infected cells. Recent discovery of intracellular Fc receptor, TRIM21 has suggested an intracellular defending mechanism for antibody-mediated protection to viral and bacteria infections [71,72].

6. Concluding remarks

The increasing prevalence of *Chlamydia* STI, the asymptomatic nature of *Chlamydia* infection in young women, and the irreversible disease sequelae, all argue for the development of an effective *Chlamydia* vaccine [5]. While the majority of vaccine studies in the past two decades have focused on using the whole organism or a handful of immunodominant proteins, recent attempts have examined subunit vaccines that are able to elicit robust CD4 T cell responses [73–75]. Nevertheless, even in these vaccine models, the fact that the native conformation of the immune-dominant proteins is essential for protective immunity might suggest that B cells actively participate in the protective immunity conferred by vaccination [76–78]. The murine model of *Chlamydia* genital tract infection has provided an invaluable system for immunologists to understand the host immune response to this infection and as noted above, recent data support a previously unappreciated role of B cells in preventing bacteria dissemination from the genital tract reinfection. Fortunately, with recent advances in proteomics, the screening of large numbers of antigens using serum samples from previously infected mice, non-human primates, and human patients has lead to discovery of a new array of antigen targets in *Chlamydia* [79–81]. Although the understanding of the role of B cells and antibody in *Chlamydia* infection is still in its infancy, the recent progress discussed in this review supports the idea that this population play an important role in the adaptive immune response to infection and thus may be key to the development of a novel vaccine for *Chlamydia*.

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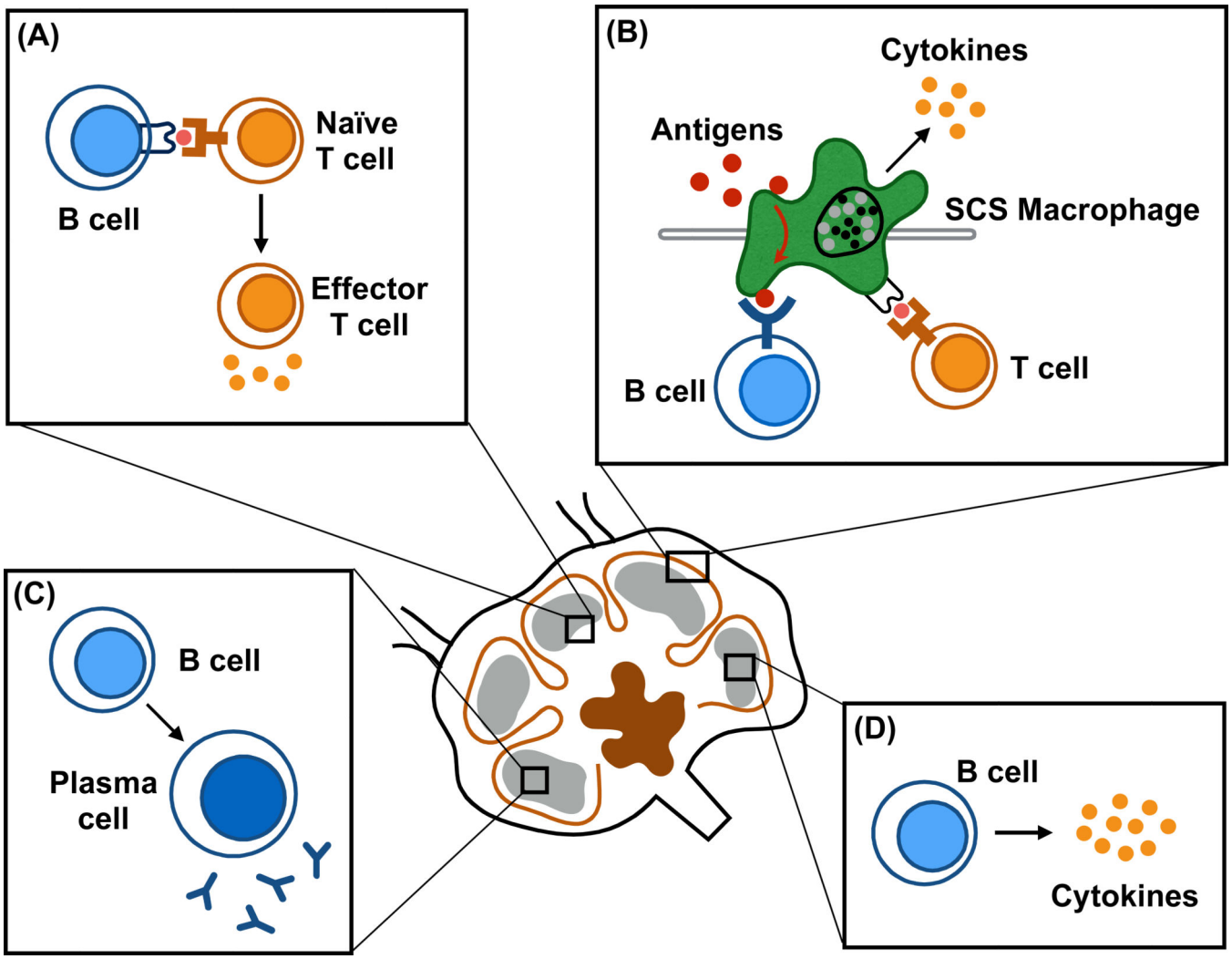

Figure 1.

Potential role of B cells in the draining iliac lymph nodes during *Chlamydia* genital tract infection. (A) B cells might act directly as antigen presenting cells to T cells, (B) help maintain the lymphoid architecture perhaps to allow SCS macrophages to function in anti-bacterial immunity upon active *Chlamydia* infection, (C) directly contribute to early defense by producing inflammatory cytokines in response to bacterial ligands or, (D) rapidly produce antibody in the draining lymph node that hinders pathogen spread.