New insights into a persistent problem — chlamydial infections

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Tissue tropism of clinical ocular and genital Chlamydia trachomatis strains is shown to be linked to the tropophan synthase genotype (see related article beginning on page 1757). It is suggested that, in the presence of IFN-γ, which depletes available tropophan, there exist unique host-parasite interactions that may contribute to persistent chlamydial infection.


Chlamydia infections are noted for the broad array of clinically distinct manifestations that they produce, ranging from acute self-limiting ocular and genital infections to chronic inflammatory diseases that result in blindness or infertility. Trachoma, an ocular infection, is caused by Chlamydia trachomatis serovars A–C and is a primary cause of preventable blindness. The majority of C. trachomatis serovars (D–K) cause urogenital infection, which can progress to serious genital tract disease in men and women. A genetic basis for the remarkable tissue tropism of the various chlamydial serovars (i.e., ocular vs. urogenital strains) was first proposed by Fehlner-Gardiner et al., based upon their analysis of the tropophan synthase gene cluster (trpRBA) of laboratory strains of chlamydiae (1). They found that the tropophan synthase genotype is closely linked to the tissue tropism of ocular and genital chlamydial strains; urogenital serovars possess a functional tropophan synthase and are capable of utilizing indole as a substrate for tropophan synthesis, whereas ocular isolates possess a nonfunctional tropophan synthase. In this issue of the JCI, Caldwell et al. have extended that earlier work to include the characterization of tropophan synthase genes from hundreds of clinical isolates, thereby confirming the correlation between chlamydial tropophan synthase genotype and tissue tropism (2).

Between the extremes of acute self-limiting infection and chronic inflammatory disease lies the notion of persistent and/or chronic states of chlamydial infection. Cell culture systems have been used for a number of years to demonstrate and study chlamydial persistence in vitro (3). However, the experimental demonstration of persistent infection in the human host and of the mechanisms of in vivo persistence has been a much greater challenge. A particularly intriguing hypothesis put forth by the authors is that tropophan synthase genes function as chlamydial virulence factors and may be involved in the maintenance of persistent/chronic chlamydial infection. That hypothesis is shown to be linked to the tryptophan synthase genotype (see related article beginning on page 1757). It is suggested that, in the presence of IFN-γ, which depletes available tropophan, there exist unique host-parasite interactions that may contribute to persistent chlamydial infection.
esis is particularly relevant when one considers the key role played by IFN-γ in host defense against chlamydial infection. Caldwell et al. propose a mechanism by which genital chlamydial strains may counter the growth inhibitory effects of IFN-γ by utilizing indole produced by vaginal microbial flora as a substrate for tryptophan synthesis, thus allowing for the continued survival of chlamydiae within a growth-inhibiting environment (2).

The intracellular developmental cycle of Chlamydia
Key to understanding the pathophysiology of chlamydial disease is an appreciation of the chlamydial developmental cycle (Figure 1) (4). Chlamydial infection is initiated by the attachment of the infectious EB to the host cell, followed by entry of the EB into a membrane-bound vesicle, termed an inclusion. The inclusion evades fusion with host lysosomes, and the EB rapidly differentiates into an RB that replicates by binary fission within the inclusion. Following several rounds of replication, the RBs reorganize and form infectious EBs, which are released from the cell. Under certain conditions, such as in an inflammatory environment where IFN-γ is produced, the intracellular growth of ocular and urogenital chlamydial strains may be altered. IFN-γ induces cellular IDO, which results in a marked decrease in available tryptophan. Depletion of tryptophan either results in chlamydiae cell death or causes chlamydiae to adopt a noninfectious, nonreplicating form that retains viability (persistence). The outcome is dependent on the level and duration of tryptophan depletion and the tryptophan synthase genotype of the infecting chlamydial strain. Persistent forms of chlamydiae can redifferentiate into infectious EBs upon removal of IFN-γ and subsequent replenishing of intracellular tryptophan pools. Alternatively, even in an IFN-γ-rich environment, strains of chlamydiae that possess a functional tryptophan synthase (i.e., genital strains) may use indole (perhaps produced by local microbial flora) as a substrate for tryptophan synthesis to counter the growth inhibitory effects of IFN-γ. This model is far from complete, and the biological processes involved are likely much more complex and interrelated than depicted here. However rudimentary, though, the proposed model provides a reasonable representation of our current understanding.

Figure 1
Chlamydial infection is initiated by the attachment of the infectious EB to the host cell, followed by entry of the EB into a membrane-bound vesicle, termed an inclusion. The inclusion evades fusion with host lysosomes, and the EB rapidly differentiates into an RB that replicates by binary fission within the inclusion. Following several rounds of replication, the RBs reorganize and form infectious EBs, which are released from the cell. Under certain conditions, such as in an inflammatory environment where IFN-γ is produced, the intracellular growth of ocular and urogenital chlamydial strains may be altered. IFN-γ induces cellular IDO, which results in a marked decrease in available tryptophan. Depletion of tryptophan either results in chlamydiae cell death or causes chlamydiae to adopt a noninfectious, nonreplicating form that retains viability (persistence). The outcome is dependent on the level and duration of tryptophan depletion and the tryptophan synthase genotype of the infecting chlamydial strain. Persistent forms of chlamydiae can redifferentiate into infectious EBs upon removal of IFN-γ and subsequent replenishing of intracellular tryptophan pools. Alternatively, even in an IFN-γ-rich environment, strains of chlamydiae that possess a functional tryptophan synthase (i.e., genital strains) may use indole (perhaps produced by local microbial flora) as a substrate for tryptophan synthesis to counter the growth inhibitory effects of IFN-γ. This model is far from complete, and the biological processes involved are likely much more complex and interrelated than depicted here. However rudimentary, though, the proposed model provides a reasonable representation of our current understanding.
tryptophan by IDO essentially starves chlamydiae of this essential amino acid, rendering them incapable of differentiating into infectious EBs (Figure 1) (10, 11). As noted by Caldwell et al., the resistance pattern of the various chlamydial strains to the inhibitory effects of IFN-γ correlates to polymorphisms in tryptophan synthase genes (2). Thus, ocular serovars, which have a nonfunctional tryptophan synthase and are unable to synthesize tryptophan, are more sensitive to IFN-γ-mediated inhibition than genital serovars, which have a functional tryptophan synthase and are capable of utilizing indole as a substrate for tryptophan synthesis.

Clinical persistence
Persistence of chlamydial infection in the human host is at best incompletely defined (12, 13). Chlamydial infections are known to be particularly insidious, and chronic inflammatory conditions are a frequent consequence of untreated chlamydial infection. Because chlamydiae respond to a variety of environmental stimuli that alter their growth characteristics (e.g., IFN-γ), there exists the potential for chlamydiae to establish a chronic or persistent relationship with the host. If persistent or chronic infections are established, then those infections may serve as a reservoir for new infections, contribute to the immunopathological consequences of infection, or require alternative therapeutic approaches. Thus, understanding the consequences of persistent chlamydial infection could be important to the control and prevention of chlamydial disease.

IFN-γ is an important mediator of protective immunity to chlamydial infection (14). Consequentially, the possibility that chlamydiae may grow in an environment rich in IFN-γ and the potential for chlamydiae to establish persistent or chronic infections in the presence of IFN-γ are two infection outcomes that could have important clinical implications. Caldwell et al. discuss quite eloquently how genital strains of chlamydiae could utilize indole produced by vaginal microbes to survive in an IFN-γ-rich, tryptophan-limiting environment (Figure 1) and how survival under such conditions might facilitate the development of chronic infections (2). Moreover, if the in vitro observation of IFN-γ-mediated persistent infection holds for human infection, then perhaps in an IFN-γ-rich environment, chlamydiae could persist as morphologically aberrant, nonculturable forms. If so, would those persistent chlamydiae be susceptible to therapeutic doses of antimicrobials typically prescribed to treat infection? Although apparent treatment failures have been reported, there is no direct in vivo evidence to support the notion that those failures resulted from persistent chlamydiae being more refractory to antimicrobial chemotherapy. However, recent studies using an in vitro cell culture system suggest that persistent forms of chlamydiae are more refractory to antimicrobial therapy than chlamydiae grown under normal cell culture conditions (P. Wyrick, personal communication).

Much remains to be learned about the pathogenesis of chlamydial disease, but the study by Caldwell et al. represents a seminal contribution to our understanding of chlamydiae-host interactions (2). Further characterization of the polymicrobial environment of the female genital tract during chlamydial infection and the development of experimental animal models of defined polymicrobial infections will be needed to assess the full impact of tryptophan synthase gene polymorphisms on the pathogenesis of chlamydial disease. Additional studies will also be needed to more fully understand why ocular strains have lost functional tryptophan synthase activity even though they face the same IFN-γ selection pressure as genital strains and to define what other biological differences may exist between ocular and genital strains that might contribute to tissue tropism and disease pathogenesis. Investigating the interplay between chlamydiae and its environment will impart a more thorough understanding of host-microbial interactions and may provide important insight into novel approaches for the treatment and prevention of chlamydial disease.

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