Persistent infection of Chlamydia in reactive arthritis

M Rihl, L Köhler, A Klos, H Zeidler

Unravelling the molecular mechanisms

A number of bacteria have been implicated as causing reactive arthritis. In epidemiological studies, Chlamydia have been identified as the most common bacteria triggering reactive arthritis in Western countries. Only 1–3% of patients acquiring infection at the urogenital tract as the primary site of infection develop Chlamydia-induced arthritis.

It has been shown that Chlamydia reaches the joint from the urogenital system through circulating monocytes and that monocytes/macrophages are the common host cells for persistent organisms during long term infection, with a major role in the induction of inflammation (fig 1). Most patients will achieve clinical remission within 6 months after infection. However, a chronic disease course occurs with intermittent relapses and periods of remission despite the presence of persistent bacteria in the joint. To date, there is no explanation for this clinical heterogeneity, but it is probably related to the genetic background of the host as well as to bacterial factors, such as the ability of Chlamydia to modify its life cycle.

CURRENT UNDERSTANDING OF THE AETIOPATHOGENESIS OF REACTIVE ARTHRITIS

During the past decade, significant progress has been made in understanding the aetiopathogenesis of reactive arthritis. Convincing evidence suggests that bacteria and microbial antigens triggering reactive arthritis persist in the joints and other reservoirs such as the entry site of the infection. Owing to intensive immunological and immunogenetic research into reactive arthritis over past decades, the present view of the disease mechanisms is mainly based on the potential role of the immune response. A cytokine imbalance and the interaction between bacteria and HLA-B27 are thought to have a major role in the failure to eliminate the triggering bacteria and the microbial antigen, leading to the disease manifestations and chronicity. In contrast, the microbiological and molecular aetiopathogenesis of the persistence of the bacteria is less well understood, although some insights into the persistent state of Chlamydia have been obtained over recent years.

In the case of Chlamydia, it has been shown that viable metabolically active organisms exist for extended periods in the joints of patients with reactive arthritis. Chlamydia has a special life cycle determined by an infectious stage (elementary bodies) outside the cells and a non-infectious stage (reticular bodies) inside the cells. Most intriguingly, the intracellular viable non-replicating Chlamydia found within monocytes isolated from the synovial fluid and the synovial membrane of patients with Chlamydia-induced arthritis showed an aberrant morphology, typical of neither the reticulate nor the elementary bodies.

‘Initial hopes of eradicating Chlamydia by antibiotic treatment have been dashed’

When Chlamydia were first identified in joints there were great hopes that antibiotic treatment would eradicate the bacteria and cure the disease, but clinical studies performed so far have been equivocal or disappointing. Recently, however, positive results have been reported from a combination of antibiotics (doxycycline plus rifampicin) and a combination of synovectomy with 3 months azithromycin in patients with spondyloarthritis and postvenereal reactive arthritis, including patients with chlamydial infections. The lack of efficacy of the antibiotics is probably due to the altered metabolic and persistent state of the organism. Thus, more detailed knowledge of the host bacteria interaction is crucial for development of more efficacious and new therapeutic concepts.

The work by Gérard et al presented in this issue and further delineated in this editorial is adding important new information in elucidating the molecular mechanisms underlying chlamydial persistence.
15 minutes after contact with C trachomatis, tyrosine phosphorylation of host cell proteins occurs. However, drastic changes in the expression pattern of the infected host cell start after several hours, reaching a maximum after ∼24 hours. Thus, Chlamydia induce a plethora of transcription factors, signal transduction molecules, apoptosis related genes, adhesion molecules, and cytokines in the infected cells.

In epithelial cells, chlamydial persistence can be induced within several days by various modes, such as by the use of interferon gamma, penicillin G, or deprivation of essential nutrients, leading to different gene expression patterns. In the interferon gamma model, responses of persistently infected host cells to Chlamydia and other stimuli are attenuated, probably permitting the bacteria to escape immune responses (unpublished observations).

NEW APPROACH TO ELUCIDATION OF GENE REGULATION SUPPORTING CHLAMYDIAL PERSISTENCE

Another organism with a known full genomic sequence, which also causes persistent infection, is Mycobacterium tuberculosis. As opposed to C trachomatis, this bacterium is available for genetic manipulation. Thus, the mechanisms underlying mycobacterial persistence have been studied more extensively. In a study by Sassetti et al, 194 genes required for mycobacterial growth and persistence in vivo were identified.

“One third of C trachomatis genes tested were orthologous to genes related to mycobacterial persistence”

Now, a new approach is introduced in a study by Gérard et al as published in the current issue. The authors used the mycobacterial genome as scaffolding and compared it with chlamydial sequences in order to identify transcriptionally up regulated chlamydial genes supporting persistence. Of the 194 mycobacterial genes originally reported by Sassetti et al, 67 (35%) chlamydial orthologous genes were identified by BLAST search, a computational alignment, and direct comparison of the two sequences.

Orthologues are defined as genes in different species directly evolving from the same ancestral locus. The chlamydial orthologues of mycobacterial persistence related genes fell into generally similar categories, such as genes encoding for cell envelope synthesis, synthesis of cofactors, transport translation, other cellular processes, regulatory functions, and uncategorised transcripts. To confirm in vitro that genes were up regulated not only during persistent infection but also during active infection, 16 orthologues from the various categories were selected for real time RT-PCR; they were tested during both infection states in C trachomatis infected normal human monocytes. All 16 genes were found to be transcribed at 12 hours after infection, the active infection state. Twelve orthologues also showed fairly strong up regulation in persistent infection assayed 5 days after infection, consistent with the mycobacterial study, whereas four genes showed no or only minimal transcriptional regulation.

To go further and demonstrate clinical relevance, the actual in vivo transcription was verified by measuring the 16 genes in the synovial biopsy specimens of patients with arthritis who were PCR

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**Figure 1**  Pathogenetic concept of Chlamydia-induced arthritis. (1) Primary urogenital infection; (2) dissemination of the bacteria into the joint; (3) intracellular persistence of the bacteria (a) and subsequent synthesis of antigens (AG) out of phagosomes or antigens (b) detected by T cells, which in turn activate monocytes through multiple cytokines; (4) production and release of proinflammatory mediators by the activated monocytes establishing and sustaining the actual inflammation.
positive for C trachomatis in their synovial tissue. Likewise, the genes showing transcription in the monocytic model were also up regulated in the synovial samples. However, the four transcripts showing no up regulation in the in vitro model were up regulated at least to some extent in the synovial samples. Apart from the attempt to define the genes and the molecular mechanisms of persistent C trachomatis infection, this report provides further important information: in contrast with M tuberculosis, probably because of its much smaller genome, C trachomatis does not dispose of a set of genes solely inducing and maintaining a persistent infection state. Thus, it seems obvious that C trachomatis merely adapts and adjusts its level of gene expression in order to elicit this particular state of infection.

FUTURE DIRECTIONS

A number of questions remain:

- Given that the persistence of C trachomatis does induce reactive arthritis, what are the mechanisms that prevent the organism from being eliminated from the host and the joint?
- What is the exact role of the native and the adaptive immune system that prevents the organism from detection within the blood and the joint?
- How do Chlamydia modulate between normal and persistent growth?

Future research should not only attempt to answer these key questions but also needs to establish a more detailed picture of the genome-wide transcript pattern underlying chlamydial persistence in monocytic and other host cells, as well as the overall metabolic characteristics of persistence for the organism resulting from the particl gene expression pattern. Full transcriptome analysis of the monocyte model of chlamydial persistence and synovial tissue samples from patients who are PCR positive for C trachomatis at that site are promising steps, contributing to the unravelling of the molecular mechanisms that determine the pathogenesis of reactive arthritis.1 10

Moreover, the role of HLA-B27 and other genes in the induction, maintenance, and recurrence of Chlamydia-induced arthritides still has to be elucidated. Finally, therapeutics that directly target persistent Chlamydia are urgently needed to cure reactive arthritides and other chronic chlamydial infections.

CONCLUSIONS

Despite the importance of C trachomatis as a major causative agent of sexually transmitted diseases and as one of the most common bacteria involved in reactive arthritides, our knowledge of the molecular mechanisms used by Chlamydia to persist in the host and in the joint has increased very little in recent years. The success of C trachomatis as an arthritogenic pathogen is due, in part, to its ability to survive in macrophages and to establish long term persistent infection in both the host and the joint during clinically symptomatic and asymptomatic periods of infection. Recent studies have shown that several chlamydial genes of known function are differentially expressed in persistent and active infection. The present study of Gerard et al shows a gene expression profile potentially determining and/or causing chlamydial persistence by comparing and extrapolating gene expression from a classically persisting organism, M tuberculosis.11 Further characterisation of the factors and molecular mechanisms underlying chlamydial persistence and the host-parasite interaction in the persistent state is needed to establish a better understanding of the aetiopathogenesis of Chlamydia-induced arthritis, and to help identify new therapeutic targets, allowing elimination of C trachomatis and, eventually, determination of a cure for the arthritis. Ann Rheum Dis 2006;65:281–284. doi: 10.1136/ard.2005.044966

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