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Editorial:

Pathogenesis and cell corruption by intracellular bacteria

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Current knowledge on intracellular bacteria has been gathered at a slower pace than with many other bacterial human pathogens, due the many difficulties that we face when studying their biology. First, they are *de facto* interacting with host cells and their phenotype, including the expression of virulence traits may be different when grown axenically or in eukaryotic cells; in addition, significant differences are observed when a given bacterial strain is investigated in different cell lines. Moreover, as nicely illustrated in the review by O. Disson and M. Lecuit on *Listeria monocytogenes*, several important pathogenic mechanisms such as those implicated in bacterial crossing of the placental or intestinal barriers of this Gram-positive bacilli may only be identified by in vivo analyses (1).

Second, some of the bacteria discussed in this special issue, such as *Ehrlichia, Anaplasma, Chlamydia* and *Waddlia,* are strictly intracellular and their study is further impaired by the absence of a straightforward genetic system to manipulate their genomes. However, these difficulties have been largely overcome since the recent availability of genomic data, and by using a large diversity of modern functional genomics approaches, recently summarized by de Barsy et al. (2). Thus, during the last 10 years, a bulk of new informations have been gathered on intracellular bacteria thank to cell biology, molecular biology and “omics” approaches. These new data are summarized in this special issue by experts in the field.

In the first article of this special issue, Disson and Lecuit provide a very nice overview of the respective importance of both internalin proteins (InlA and InlB) in the entry of *Listeria monocytogenes,* and their different cell and hosts specificities (1). This comprehensive review also discusses the importance of several other virulence factors of *Listeria* such as listeriolysin and ActA (1), including the recently uncovered role of ActA in the aggregation of *Listeria monocytogenes* in the intestinal tract and on *Listeria* shedding (3).

In the second article of this special issue, Julie Allombert et al. reviewed how *Legionella* adapted to survive phagocytic cells (4). The T4SS is of course a central player that uses more than 275 different secreted effectors to corrupt the host cell at its own advantage (4).

Alike *Legionella*, *Francisella tularensis* (another proteobacteria) is able to survive to macrophages microbicidal effectors. The interaction of this Gram-negative bacterium with macrophages is extensively reviewed by M. Barel and A. Charbit in the third article of this special issue (5). After a short overview on the mechanisms implicated in the entry of *F. tularensis*, the authors nicely

illustrate (i) how the bacteria survives to the significant oxidative stress present in phagocytic cells, and (ii) how *F. tularensis* might delay or block autophagy (5). Again, cell corruption and access to essential host cell components (including nutrients) are possible thank to various secretion systems, and are further facilitated by the exit of the bacteria in the eukaryotic cytosol (5). Altogether, the many recent data accumulated on the pathogenesis of this zoonotic pathogen are encouraging given the relatively few number of groups working on this BSL-3 level agent.

Another important pathogenic zoonotic agent that should only be studied in BSL-3 laboratories is *Brucella*. In the 4th article of the present special issue, Charles Van der Henst et al. propose a fascinating outlook on the asymmetrical division of *Brucella* species (6). Although many questions remain unanswered, the concept that polar growth may lead to functionally different daughter cells is highly interesting, since (i) this may help *Brucella* to adapt to different environments the bacteria may encounter, and (ii) this highlights the importance to study bacterial pathogens at “single cell” level, to cope with the intrinsic heterogeneity of clonal bacterial populations due to asymmetrical division. Noteworthy, such an asymmetrical division is not only present in *Brucella* but, as outlined by Van der Henst et al. (6), is also documented for different other alpha-proteobacteria including the free-lining bacteria *Caulobacter crescentus*, which is widely used as a model organizer to study bacterial division (7). Interestingly, the strict intracellular bacteria *Ehrlichia chaffeensis* (another alpha-proteobacteria), also possesses some genes implicated in asymmetrical division although their role remains to be defined (6).

The main determinants of the interactions between *E. chaffeensis* and mononuclear phagocytes are described by P.S. Dunphy et al. in the fifth review of this special issue (8). Again, this member of the *Rickettsiales* order uses a large variety of effectors to manipulate the host cell at his own advantage. As for some other intracellular bacterial pathogens, proteins containing Ankyrin repeats and tandem repeat proteins appear to be highly important to interact with host proteins, and to modulate host transcriptional response by acting as nucleomodulins directly binding to host chromatin (8).

The sixth article of this special issue, by H.K. Truchan et al., is nicely summarizing current knowledge on *Anaplasma phagocytophilum*, another member of the *Rickettsiales* order (9). More specifically, they describe the host cell receptors involved in the entry of this bacterium, and summarize how the bacterium gets nutrients from its host cell. Moreover, they report on new tools that will help studying this obligate intracellular bacterium.

Alike *Rickettsiales*, members of the *Chlamydiales* order are also very difficult to study given their strict intracellular lifestyle and the absence of a genetic system to manipulate chlamydial genomes.

These difficulties led chlamydiologists to use a variety of indirect approaches to study the role of a given protein. For one of them, CPAF, a conserved secreted protease, it has been recently shown that most of its previous identified host targets were not true targets due to artifacts caused by inaccurate methodological approaches (10, 11). Conrad et al., in this special issue, are reviewing current knowledge on CPAF, and clarify how erroneous interpretations have been made (11). They also recommend using forward genetics to more precisely define the true role of this protease, which should be very important, since CPAF is also encoded on the genomes of other members of the *Chlamydiales* order including *W. chondrophila, Simkania negevensis* and *Parachlamydiaceae* (12-14), which diverged from *Chlamydiaceae* more than 700 million years ago (15).

The last article of this special issue, written by de Barsy and Greub (16), is summarizing knowledge on the biology of *Waddlia chondrophila*, a *Chlamydia*-related bacteria, which has been recently identified as an agent of miscarriage in humans (17, 18).

We hope that this special issue on the Biology of eight different intracellular pathogens will help the readers to appreciate the huge diversity of tricks used by intracellular bacteria to corrupt the host cell for their own benefit.

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