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Bailliere's Clinical Infectious Diseases International Practice and Research Volume 1/Number 2 Strategies for Intracellular Survival of Microbes

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This is the second issue in a new series being developed by Bailliere Tindall covering various topics in clinical infectious diseases. The editorial board have selected 12 contributions to the overall theme, *Strategies for Intracellular Survival of Microbes*, which is divided into four sections—*Microbial adherence and host cell entry*; *Establishment and maintenance of the pathogen containing compartment*; *Escape from the vacuole and survival in the host-cell cytosol*; and *Maintenance of infection and modulation of immune surveillance*.

Within each of these sections, a selection of topics has been chosen which displays considerable breadth in the subject matter with examples being drawn from diseases caused by plasmodia, leishmania, toxoplasma, histoplasma, theileria, listeria and mycobacteria. In each case, experts (predominantly from the USA) have presented comprehensive detailed information about the molecular mechanisms used by these parasites in their quest to enter host cells and proliferate therein. It is a difficult task to try to encompass the wealth of knowledge contained in each article in a review of this kind. However, it is hoped that by summarising some of the main features, the reader will gain a favourable impression of the advances being made in this exciting field of research.

In the first section, there are three articles. The first deals with the invasion of erythrocytes by merozoites of *Plasmodium* sp. (Ward, Chitnis and Miller). Although the morphological features have been well described, the molecular mechanisms are much less well understood. However, this article goes a long way to provide the reader with important information about the key elements of the invasion process such as the role of rhoptries, micronemes, merozoite plasma membrane and parasite-encoded proteases. In addition, we are given an insight into how the parasite might use and integrate the various components during invasion to recognise and attach to the erythrocyte, to generate the intracellular signals necessary to continue cell-cell interaction, induce formation of the parasitophorous vacuole and finally to penetrate into the erythrocyte.

The complexities of intracellular parasitism are again highlighted in a review of the life cycle of the dimorphic protozoan, *Leishmania* (Mosser and Rosenthal). The promastigotes are internalised by macrophages via receptor-mediated phagocytosis before differentiation into a non-flagellate amastigote form which can then replicate prior to release extracellularly. Within the sandfly, these amastigotes differentiate through a non-infective to an infective promastigote in which form the parasite is transmitted to another host in a blood meal of the infected sandfly. This chapter concentrates on the interaction of macrophage receptors and parasite-derived ligands involved in phagocytosis of leishmania.

Species-specific differences are recognised in some aspects of leishmania binding to macrophages even in the absence of exogenous opsonins. Promastigote binding is less efficient than that of amastigotes with a lipophosphoglycan providing the main surface component needed for this interaction. A member of the leukocyte integrin family, MAC-1 or CR3, is important in adhesion of leishmania promastigotes to macrophages and the authors have dissected the nature of this interaction in some detail before proceeding to examine

the contribution of serum factors to the adhesion process. Major species differences are apparent but complement activation and binding of C₃ is important. Finally, a short discussion of the ability of leishmania to multiply within the phagolysosomes probably by their ability to block superoxide production is included.

The role of the invasion genes of yersiniae (*inv*, *ail* and *Yad A*) are reviewed in terms of the ability of *Yersinia enterocolitica* and *Y. pseudotuberculosis* to cause gastrointestinal infections (V. L. Miller and J. C. Pepe). In tissue culture cells as a model system, each of these genes have been shown to contribute to invasiveness. The *inv* gene of *Y. pseudotuberculosis* encodes a 108-kDa protein that is localised in the outer membrane. The C terminal 192 amino acids encode the binding-internalisation domain that interacts with the β_1 integrin receptor. The *ail* gene encodes a 17-kDa outer-membrane protein. Both of these genes are chromosomally located. The *Yad A* gene is found on the virulence plasmid and controls resistance to serum killing as well as binding to various substrates.

Section Two contains three contributions on the intracellular survival mechanisms used by various microorganisms. D. G. Russell compares *Leishmania* spp. and *Mycobacterium* spp. in terms of the ways in which they may subvert the normal host responses and, in particular, the characteristics of the parasitophorous vacuole of leishmania-infected macrophages and the intracellular vacuole surrounding mycobacteria. In the former, lysosomal fusion can take place but not in the latter. It is suggested that liparabinomannan in the cell wall of mycobacteria is involved which can induce both up- and down-regulation of macrophage activation with consequent changes in cytokine expression. Modulation of the macrophage-T cell interface is likely to account for the success of these intracellular pathogens and the apparent absence of an immunological response to infection.

Intracellular survival of *Toxoplasma gondii* (L. D. Sibley *et al.*), as with mycobacteria, is dependent on failure of phagosome-lysosome fusion. However, in the presence of antibody, fusion may take place. The parasitophorous vacuole is extensively modified by secretion of parasite proteins during invasion. One important role of these section proteins may be to process host cell components that serve as nutrients for parasite growth.

The final contribution to this section concerns the interplay between *Histoplasma capsulatum* and its host cells (L. G. Eissenberg and W. E. Goldman). This interplay begins with the lining cells of the respiratory tract facilitating the conversion of inhaled conidia or mycelia into yeast forms. Subsequently, polymorphonuclear leucocytes prevent growth but do not kill the pathogen which then enters its preferred host cell, the macrophage. Multiplication of the yeasts within the macrophage probably alters antigen presentation as well as the triggering of the arachidonic acid cascade. The ability of *H. capsulatum* to undergo various morphological changes *in vivo* may be due to the continual change of host environment seen in infections with this organism.

Section Three covers parasite release from the intracellular vacuole and survival within the host cell cytosol with *Listeria monocytogenes* and *Trypanosoma cruzi* as examples. *L. monocytogenes* has been shown to invade both phagocytic and non-phagocytic cells such as epithelial cells and hepatocytes (P. Cossart). After escape from the phagosome, the bacteria multiply in the cytoplasm and start moving in the cytosol. Movement is coupled to actin polymerisation at the rear of the bacterium and results in the incorporation of

bacteria into long protrusions of the plasma membrane which then become internalised by neighbouring cells as double-membrane bound vacuoles. Following lysis, a second round of replication, movement and spread takes place. Several genes which control this process have been identified including *inlA* and *inlB* for entry into epithelial cells, *hly* and *plcA* for escape from the phagosome, *actA* for intra- and inter-cellular movement and *plcB* for lysis of the double-membrane vacuoles.

T. cruzi invades various mammalian cells by receptor-ligand interactions in a process that depends on energy production by the parasite and on lysosome recruitment to the periphery of the host cell. Three molecules are implicated in *T. cruzi* invasion: trans-sialidase, penetrin and a haemolysin. The trans-sialidase promotes adhesion by reacting with an α -2, 3-linked sialic acid on the surface of cell receptors and may also promote escape from the lysosomes. Penetrin promotes adhesion by reacting with heparin-like host cell receptors and the haemolysin appears to form pores in the cell membrane of the lysosome perhaps because of its similarity to C9 of the complement system.

Section Four, which looks at persistence of infection, comprises four chapters—three of which complement some material in earlier chapters. For example, the catabolism of haemoglobin involving two aspartic proteases and one cysteine protease by intra-erythrocytic *Plasmodium* sp. for nutritional purposes is described (D. E. Goldberg). Genes for all three have been cloned and the enzymes characterised. The degradative process releases toxic haem which is sequestered by a haem polymerase as haem ozoin.

Theileria spp. have a complex life cycle (L. G. Tilney, M. S. Tilney and M. K. Shaw) with three distinct stages (sporogony, merogony and the piroplasm stage) ultimately leading to a multinucleate syncytium in the salivary gland of the tick which then infects the animal host. Most of the detailed information about *Theileria* spp. concerns the animal host phase in which the parasite survives within lymphocytes and red blood cells of cattle. There are differences in the invasion mechanism of this parasite compared to *Toxoplasma* spp. or *Plasmodium* spp. with involvement of MHC Class I in recognition, binding and internalisation.

Further information on the immunological aspects of leishmania infection are also included (P. M. Kaye) with a

comparative picture of their interaction with macrophages affecting antigen presentation. There are some differences between the different species in terms of their ability to stimulate cytokine production, MHC surface expression and signal transduction. In particular, the role of cytokines in NK cell and T cell activation is described in some detail. *Leishmania donovani* fails to trigger early NK cell cytokine production whereas T cell-derived IL2 is necessary for IFN production by NK cells. Such a pattern of infection clearly separates leishmania from other bacterial and protozoal parasites and suggests that it has become truly adapted to its host. The net result is that host T cells may simply not see infected macrophages through Class II MHC inhibition. There remain several unanswered questions as to how this parasite evades the host in each of the different forms of disease.

Last but not least, I. M. Orme examines some experimental models of chronic mycobacterial disease with particular reference to *M. tuberculosis*, some of the atypical mycobacteria and *M. leprae*. Within the immunocompetent host, infections with these bacteria give rise to chronic disease but as soon as immunocompetence fails, the disease becomes active and often fatal. Such a change is not only due to loss of T cell competence but to several other more subtle changes. As described in an earlier chapter, liparabinomannan seems to play an important role in protecting the organism from the products of the host's oxidative burst. In addition, it seems to impair the triggering of TNF production. Production of reactive oxygen scavenger proteins is also important in intracellular survival.

Changes of CD4 T cell and CD8 T cell activity in the course of *M. tuberculosis* infection appear to be critical in maintaining the chronicity of infection by this bacterium. Hence, the radical changes that occur in an HIV-positive individual with marked alteration in the CD4/CD8 T cell ratio.

I have tried to provide an overview of the key issues highlighted in each of the chapters of this excellent book. There is much to interest both the active research worker and the general microbiologist and I am sure that the attempt to bring together comparative aspects of intracellular survival mechanisms of such diverse parasites has been successful. This book is to be commended.

C. G. GEMMELL