FEMS MICROBIOLOGY REVIEWS

EDITORIAL

Persistent intracellular pathogens

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Intracellular pathogens live and replicate either within endosomal compartments or in the cytosol of diverse host cells such as macrophages, dendritic cells, neutrophils, fibroblasts, epithelial or endothelial cells or erythrocytes. Examples not only include all viruses, which represent obligate intracellular pathogens in the strictest sense, but also many different bacterial pathogens as well as certain protozoa and fungi that display either an obligate or at least facultative intracellular lifestyle in mammalian cells.

One of the hallmarks of many intracellular pathogens is their ability to persist for long periods, if not lifelong, in their mammalian hosts. Persistent infections are typically initiated with an acute infection associated with disease symptoms of different severity. If the pathogen is not eradicated during the spontaneous or drug-induced resolution of active infection, it transits to a persistent state, which depending on the pathogen and the triggered immune response can manifest differently. Some pathogens continue to replicate during the persistent infection stage and cause chronic debilitating diseases (e.g. *Brucella* spp., *Mycobacterium leprae*, *Trypanosoma cruzi*, HIV). Other pathogens retreat to an immunologically protected niche where they typically persist in a non-replicative dormant state. Some pathogens may spontaneously seed active infection from this persistence niche, thus causing relapsing active disease (e.g. uropathogenic *Escherichia* = UPEC, herpes simplex virus). Other pathogens are more efficiently kept in check by an immune response that controls pathogen replication, but is inefficient in pathogen eradication, leading to an asymptomatic persistence state (e.g. *Toxoplasma gondii*, hepatitis C virus, measles virus, *Mycobacterium tuberculosis*, *Salmonella* spp.). In the latter case, weakening of the immune system may lead again to acute forms of infectious disease.

The phenomenon of persistence of intracellular pathogens raises a number of important questions: (1) What are the infection mechanisms of these pathogens and the provoked host responses that facilitate extended if not lifelong persistent infection? (2) How do pathogens manage to escape their elimination by immune effector mechanisms? (3) Does pathogen persistence bear any benefit for the host organism, facilitating co-evolution of persistent pathogens and the mammalian immune system? (4) How are persistent intracellular pathogens reactivated to cause active disease after long periods of dormancy? (5) How is the capacity of a given pathogen to cause persistent infection in a given host affected by genetic variation in the pathogen or the host?

This Thematic Issue covers persistence mechanisms of intracellular pathogens in a broad manner. While the Editors do not aim for a comprehensive representation of this complex topic, they include prominent examples from viruses (hepatitis C virus, herpex simplex virus, HIV, measles virus), bacteria (*Salmonella*, *Bartonella*, *Brucella*, *M. tuberculosis*, UPEC) and protozoa (*Trypanosoma*, *Toxoplasma*, Microsporidia). These examples illustrate the diversity of pathogenicity mechanisms involved in establishing a persistent state and highlight common features in the host immune responses triggered. The pathogenicity mechanisms are complex and involve mostly pathogen-specific virulence factors that encompass: (1) passive protection against toxic effector molecules of the host; (2) remodeling of intracellular compartments as safe niches and (3) active modulation of the innate and adaptive immune response at multiple levels. The Editors sincerely hope that, further to enlightening the paradigms of persistent intracellular infection at the molecular and cellular level, this Thematic Issue will also stimulate the development of new anti-infectives to combat the emerging or re-emerging infectious diseases that are related to persistent infections.

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