

## **PATHOGENESIS OF RICKETTSIAL DISEASES**

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Human rickettsioses are caused by numerous named pathogens: *Rickettsia rickettsii* (Rocky Mountain spotted fever), *R. conorii* (Mediterranean spotted fever), *R. africae* (African tick bite fever), *R. akari* (rickettsialpox), *R. sibirica* (North Asian tick typhus and lymphangitis-associated rickettsiosis), *R. australis* (Queensland tick typhus), *R. japonica* (Japanese spotted fever), *R. honei* (Flinders Island spotted fever), *R. prowazekii* (epidemic typhus), *R. typhi* (murine typhus), and several emerging unnamed diseases (*R. massiliae*, *R. aeschlimannii*, *R. monacensis*, *R. helvetica*, and *R. amblyommii*). Rickettsiae are small obligately intracellular gram negative bacteria that reside in an arthropod host as its ecologic niche during at least a portion of their natural history. They have small genomes resulting from reductive evolution and rely upon the host cell for synthesis of numerous nutrients and building blocks for growth.

Rickettsiae are transmitted in the saliva of infected ticks and mites or feces of infected fleas and lice, and spread via lymphatic vessels to the regional lymph nodes and hematogenously to endothelium throughout the body. Life-threatening lesions are interstitial pneumonia/noncardiogenic pulmonary edema and meningoencephalitis associated with extensive rickettsial infection of pulmonary and cerebral endothelium. The pathologist may observe only subtle perivascular edema prior to the onset of adaptive immunity. The perivascular infiltration of mononuclear cells actually comprises the CD8 and CD4 T lymphocytes and macrophages that mediate immune clearance of the pathogen.

The crucial pathophysiologic effect of rickettsial endothelial infection is increased microvascular permeability resulting from discontinuities in interendothelial adherens junctions, the effects of TNF $\alpha$ , IFN $\gamma$ , IL-1 $\beta$ , and VEGF, and COX-2 dependent production of PGE $_2$  and PGI $_2$ . The pathogenic mechanisms of endothelial injury include endothelial cell production of toxic reactive oxygen species, damage to the cell membrane upon rickettsial exit, and cytotoxic T lymphocyte-induced apoptosis of infected endothelial cells. Rickettsial infections cause a procoagulant state, but only very rarely disseminated intravascular coagulation. Thrombi comprise non-occlusive hemostatic plugs that are appropriately located at foci of severe endothelial damage and prevent severe hemorrhage and rarely cause ischemic necrosis. Host factors play an important role in severity of illness, including older age, male gender, G6PD deficiency, diabetes, alcoholism, and IFN $\gamma$  SNP genetic polymorphism.

Rickettsiae adhere to target cells by outer membrane autotransporter proteins OmpA, OmpB, Sca1, and Sca2. Ku70 is a host cell receptor for OmpB, triggering actin rearrangement and induced phagocytosis. Rickettsiae rapidly escape from the phagosome, most likely via secretion of membranolytic phospholipase D and hemolysin C. Spotted fever group rickettsiae effect host actin-based mobility through rickettsial proteins RickA and Sca2 with actin tails propelling them into filopodia for extracellular release or cell-to-cell spread. Rickettsial manipulation of its host cell also includes activation of NF- $\kappa$ B, which inhibits apoptosis, prolonging the life of the rickettsial niche.

Innate immunity is triggered by TLR4-dependent activation of dendritic cells that, in turn, activate NK cells to produce infection-dampening IFN $\gamma$ . Adaptive immunity is effected by cytokine-activated endothelial cells, macrophages, and hepatocytes which kill intracellular rickettsiae in association with autophagy by producing nitric oxide and reactive oxygen species and by indoleamine-2,3-dioxygenase mediated degradation of tryptophan. These effectors are induced not only in experimental animals, but also in the sites of immune control in infected humans. The ultimate clearance of rickettsiae is mediated by cytotoxic T lymphocyte-induced apoptotic death of the remaining infected cells. Lethal infection is associated with rickettsial antigen-specific immunosuppression mediated by induced T regulatory cells.

Future therapeutic advances that might improve survival of severely ill patients who are diagnosed late in the course, include blocking the pathogenic mechanisms such as rickettsia-induced oxidative stress and modulation of the pathologic effects of the immune response such as T regulatory cell mediated immunosuppression.