Cause

The life cycle of *Dermacentor variabilis* and *Dermacentor andersoni* ticks (Family *Ixodidae*)

Rocky Mountain spotted fever, like all rickettsial infections, is classified as a *zoososis*. Zoonoses are diseases of animals that can be transmitted to humans. Some zoonotic diseases require a *vector* (e.g., a mosquito, tick, or flea) to be transmitted from the animal host to the human host. In the case of Rocky Mountain spotted fever, ticks are the natural hosts, serving as both reservoirs and vectors of *R. rickettsii*. Ticks transmit the organism to *vertebrates* primarily by their bites. Less commonly, infections may occur following exposure to *crushed tick tissues, fluids, or tick feces*.

*A female tick can transmit R. rickettsii to her eggs* in a process called *transovarial transmission*. Ticks can also become infected with *R. rickettsii* while feeding on blood from the host in either the larval or nymphal stage. After the tick develops into the next stage, the *R. rickettsii* may be transmitted to the second host during the feeding process. Furthermore, *male ticks may transfer R. rickettsii to female ticks through body fluids or spermatozoa* during the mating process. These types of transmission represent how generations or life stages of infected ticks are maintained. Once infected, the tick can carry the pathogen for life.

Rickettsiae are transmitted to a vertebrate host through saliva while a tick is feeding. It usually takes about 24 hours of attachment and feeding before the rickettsiae are transmitted to the host. In general, about one to three percent of the tick population carries *R. rickettsii*, even in areas where the majority of human cases are reported. Therefore, the risk of exposure to a tick carrying *R. rickettsii* is low.

Vectors include the American dog tick *Dermacentor variabilis*, *Dermacentor andersoni*, *Rhipicephalus sanguineus*, and *Amblyomma cajennense*. Not all of these are of equal importance, and most are restricted to certain geographic areas.

The two major vectors of *R. rickettsii* in the United States are the *American dog tick* (*Dermacentor variabilis*) and the *Rocky Mountain wood tick* (*Dermacentor andersoni*). American dog ticks are widely distributed east of the Rocky Mountains and they also occur in limited areas along the Pacific Coast. Dogs and medium-sized mammals are the preferred hosts of an adult American dog ticks, although it feeds readily on other large mammals, including *human beings*. This tick is the most commonly identified species responsible for transmitting *R. rickettsii* to humans. Rocky Mountain wood ticks (*Dermacentor andersoni*) are found in the Rocky Mountain states and in southwestern Canada. The life cycle of this tick may require up to three years for its completion. The adult ticks feed primarily on large mammals. The larvae and nymphs feed on small rodents.
Other tick species have been shown to be naturally infected with \textit{R. rickettsii} or serve as experimental vectors in the laboratory. These species are likely to play only a minor role in the ecology of \textit{R. rickettsii}.

**Mechanism of pathogenicity**

**Entry into host**

\textit{Rickettsia rickettsii} can be transmitted to human hosts through the bite of an infected tick. As with other bacterium transmitted via ticks, the process generally requires a period of attachment of 4 to 6 hours. However, in some cases a \textit{Rickettsia rickettsii} infection has been contracted by contact with tick tissues or fluids. Then, the bacteria induce their internalization into host cells via a receptor-mediated invasion mechanism.

Researchers believe that this mechanism is similar to that of \textit{Rickettsia conorii}. This species of \textit{Rickettsia} uses an abundant cell surface protein called OmpB to attach to a host cell membrane protein called Ku70. It has previously been reported that Ku70 migrates to the host cell surface in the presence of "Rickettsia". Then, Ku70 is ubiquitinated by c-Cbl, an E3 ubiquitin ligase. This triggers a cascade of signal transduction events resulting in the recruitment of Arp2/3 complex, CDC42, protein tyrosine kinase, phosphoinositide 3-kinase, and Src-family kinases then activate Arp2/3. This causes the alteration of local host cytoskeletal actin at the entry site as part of a zipper mechanism. Then, the bacteria is phagocytosized by the host cell and enveloped by a phagosome.

Studies have suggested that rOmpB is involved in this process of adhesion and invasion. Both rOmpA and rOmpB are members of a family of surface cell antigens (Sca) which are autotransporter proteins; they act as ligands for the Omp proteins and are found throughout the \textit{rickettsiae}.

**Escape from the phagosome and then the host cell**

The cytosol of the host cell contains nutrients, adenosine triphosphate, amino acids, and nucleotides which are used by the bacteria for growth. For this reason, as well as to avoid phagolysosomal fusion and death, \textit{rickettsiae} must escape from the phagosome. To escape from the phagosome, the bacteria secrete phospholipase D and hemolysin C. This causes disruption of the phagosomal membrane and allows the bacteria to escape. Following generation time in the cytoplasm of the host cells, the bacteria utilizes actin-based motility to move through the cytosol.

RickA, expressed on the rickettsial surface, activates Arp2/3 and causes actin polymerization. The \textit{rickettsiae} use the actin to propel themselves throughout the cytosol to the surface of the host cell. This causes the host cell membrane to be deformed outward and then it invaginates into the adjacent cell. The bacteria are then able to spread from cell to cell.

**Consequences of infection**

\textit{Rickettsia rickettsii} migrate to vital organs such as the brain, skin, and the heart following infection. The subsequent binary replication causes perforation of the vessel walls within the host cells. Bacteria inflict damage resulting in hyperplasia and then apoptosis of the infected cell.

People can develop permanent disabilities including "cognitive deficits, ataxia, hemiparesis, blindness, deafness, or amputation following gangrene."