IMMUNE RESPONSE

Rocky Mountain Spotted Fever

INNATE and ADAPTIVE IMMUNE RESPONSE

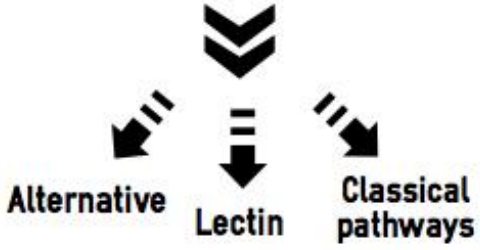
- Spread to humans by ixodid (hard) ticks
- The skin is considered the pathogen carrying tick-host interface.
- Tick bites elicit an inflammatory immune response in the skin, which includes the accumulation of eosinophils at the tick-bit site

Tick laceration and the creation of a pool-like feeding site in the skin initiates 5 key responses:

1. Inflammatory response
2. Proliferation
3. Migration
4. Contraction
5. Migration

Ixodid tick saliva contains a complex mixture of active molecules that potentiate transmission of pathogens

The primary lines of defense against infectious agents



INNATE RESPONSE

Alternative Pathway:

- Most common target for tick modulation
- Proteins, called C3, made by the liver, are present at high concentrations in blood and tissues
- C3 gets cleaved into C3b, which is very reactive and binds to amino or hydroxyl groups on the surface of bacteria

- C3bBb molecule (a convertase) cleaves other C3 molecules to make more C3 - cleaving C5 to make C5b.
- Combination of these proteins with other complement proteins (C6, C7, C8, and C9) make up the membrane attack complex (MAC). anchor themselves to the cell wall
- To opsonize bacteria they work together and anchor themselves to the cell wall of host.

Inflammatory Response:

- Passive leakage of neutrophils from damaged blood
- Mast cells release chemokines and cytokines (TNF-a and IFNy), which helps continue the recruitment of neutrophils and macrophages from nearby blood vessels
- Cytokines trigger the expression of selectins, which control the rolling and tethering of leukocytes to the vessel wall and facilitate crossing of the endothelial barrier.
- Enhanced by the vessel dilation from histamine released by mast cells. Neutrophils play an important role in killing the invading microorganisms by using bursts of reactive oxygen species (ROS)

IMMUNE RESPONSE

ADAPTIVE RESPONSE

Based on the antigen specific responses of the T and B lymphocytes

B cells adapt to bind specific soluble molecules through their cell-surface immunoglobulins (Ig). They internalize the antigens bound by their Ig receptors and display peptide fragments on their MHC II complexes which induces CD4 T cell differentiation into T helper cells (Th)

Involve the destruction of intracellular pathogens by macrophages, which are activated by Th1 cells.

- Th1 cells are involved in humoral immunity by inducing the production of opsonizing antibodies
- Th2 cells are involved in activating naïve B cells to secrete IgM, IgG, IgA, and IgE
- Helper T-cell memory appear abruptly and is at its maximal level after 5 days, whereas memory B cells appear some days later, because B-cell activation can't begin until after helper-T cells are activated. B cells enter a phase of proliferation and selection in the lymphoid tissue.

The OmpA and OmpB proteins on the bacteria's outer membrane are recognized by the OMP antibodies (IgG2a).

- The antibodies have the ability to eliminate the bacteria from tissues within 24 hours after the infection.

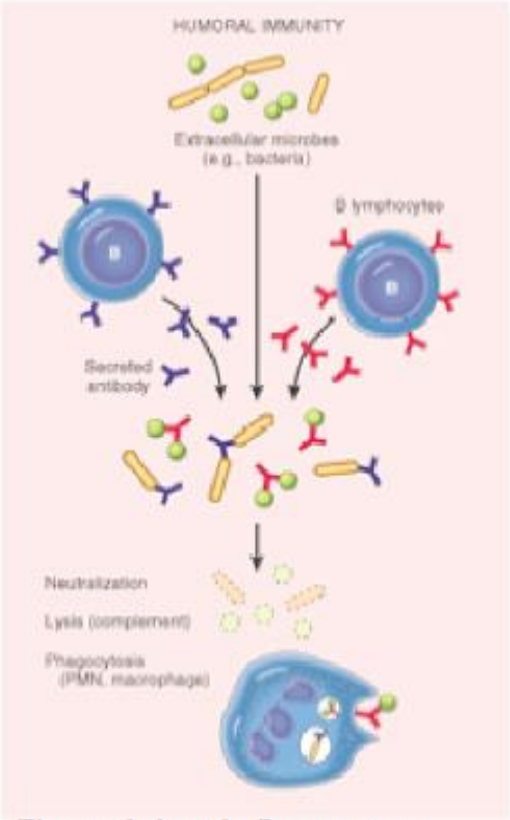


Figure 1. Innate Response

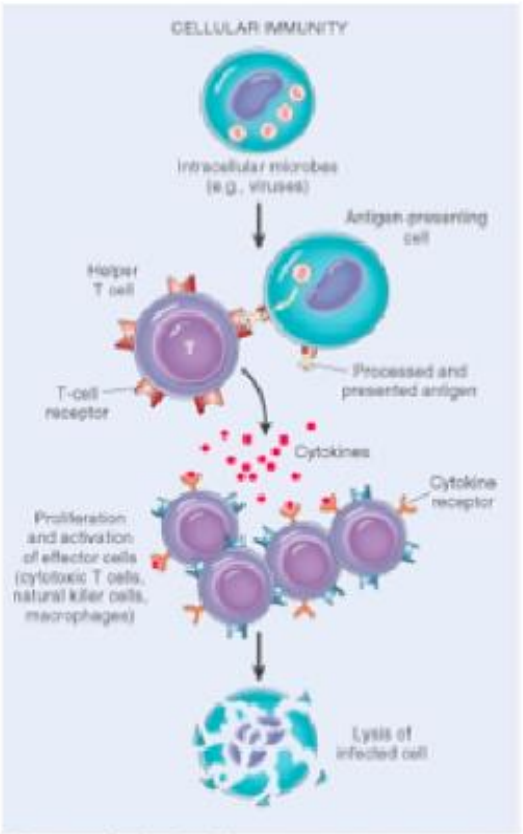


Figure 2. Adaptive response

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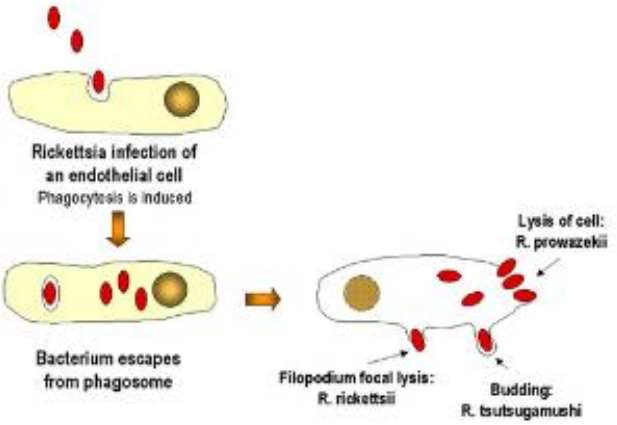


Host Damage

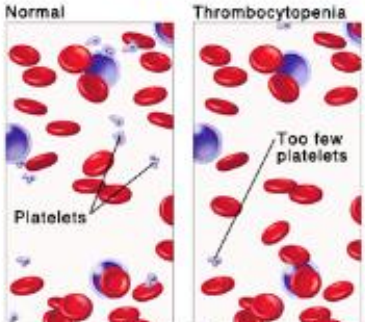
Pathogenic infection is responsible for activating host immune components which cause damage to self.

TNF alpha and IFN gamma induce the production of chemically reactive oxygen species (ROS) in neutrophils: superoxide anion, hydrogen peroxide, and hydroxyl radical products

Bacterial Invasion: → Epithelial cells produce reactive species, yielding lipid peroxidation of the host cell membrane causing damage and death to endothelial cells, leaking of plasma into peripheral tissues, a decrease in blood volume, and overall shock.

R. rickettsia grow in small or medium sized blood vessels throughout the human body in the brain, skin, and heart; causing damage and death to the cells which they multiply and replicate in.

- Causes hyperplasia (blood leakage into peripheral tissues via holes) and a blood flow obstructing thrombus to form
- Thrombosis (blood clot formation) can ultimately result in deficiencies to circulation



Key responses which prolong the inflammatory response, and yield damage to self tissues are:

- Neutrophil phagocytosis and entry into blood vessels
- Mast cells secrete factors and mediators such as histamine which dilate blood vessels
- Macrophage phagocytosis and cytokine/chemokine secretion

Damage from these immune responses results in widespread edema, low blood volume, reduced perfusion of organs, and the potential for resultant tissue function disorders.

Increased vascular permeability (TNF-a induced adhesion molecules increase vascular permeability) results from the immune responses damage to blood vessels via epithelial cells production of ROS.

The mechanism of ROS-mediated damage involves:

- The accumulation of reactive oxygen species in the host cell, which yields lipid peroxidation generates a large host cell stress that depletes vital host components
- A cytoplasmic increase in [catalase] (antioxidant enzyme which yields further damage) for defense against the ROS products; an internal struggle causing injury to blood vessels

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Bacterial Evasion

Bacterial evasion occurs in six different ways:

1. Evade the Host Apoptotic Defense

R. rickettsii interacts with NF-kB in its inactive form, causing activation and inducing the transcription of its regulated genes. ➡ This activation is key to R. rickettsii survival, because the bacteria utilizes NF- κB as an inhibitor of the apoptotic defense activated in host cells.

- Using NF-kB, R. rickettsia is able to maintain an intracellular environment essential for its replication and spread
- NF- κB allows the maintenance of mitochondrial integrity inside the host cell

2. Phagosome Escape

R. rickettsii are able to escape the phagosome, by lysing the phagosomal membrane, to avoid lysozymes that would usually degrade it. ➡ R. rickettsii secretes phospholipase D and heamolysin C, encoded in these genes are tlyC and pld, which then disrupt the phagosomal membrane, allowing escape.

3. Invasion of Non-Phagocytic Cells

The bacteria are able to invade non-phagocytic host cells with the use of its surface protein, OmpB. This protein acts as a ligand for Ku70, a subunit of a DNA-dependant protein kinase. The interaction that occurs between Ku70 and OmpB, mediates invasion of nonphagocytic cells.

4. Use of Actin Systems

R. rickettsii utilize host actin systems to gain mobility and facilitate rapid escape from host cells. In the cytosol, R. rickettsii expresses a surface protein, Sca2 that has the ability to recruit an Arp2/3 complex, allowing induction of host actin polymerization.

This actin tail formation helps the bacterium through the cell and across cell membranes into adjacent endothelial cells or extracellular

5. Arthropod Vector Support in Evasion

Bacteria are able to evade the host immune system by being transferred through an arthropod vector's saliva.

Tick saliva contains molecules that help block components of the alternative complement pathway such as displacing C3b from factor Bb and cleaving C3b.

In addition, C5a production by the cleavage of C5 is also used to inhibit the creation of the membrane attack complex.

Natural killer cell activity is also downregulated by components of the tick saliva, therefore reducing inflammation and the ability of the innate immune response to induce the adaptive response.

6.Use of T4SS

R. rickettsii utilize the host cells type IV secretion system, to promote survival by transport of virulence factors/effector proteins, as well as synthesize nutrients from the host cell

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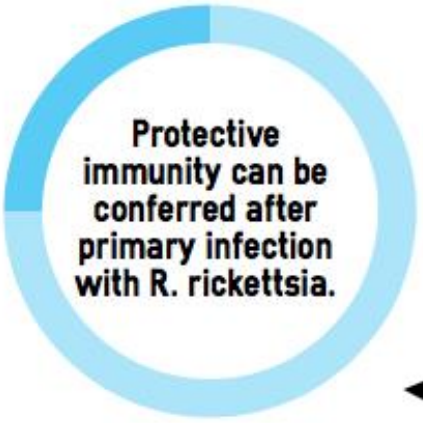
Outcome: Is the bacteria completely removed?

With prompt and appropriate antibiotic treatment full recovery and elimination of bacteria is quite common

If the R. rickettsii infection remains untreated, there is a mortality rate of 20-25%

In some cases, longer antibiotic treatment may be required, and some long-term health problems may surface such as: partial paralysis of the lower extremities, gangrene requiring amputation of fingers, toes, or arms or legs, hearing loss, loss of bowel or bladder control, movement disorders, and language disorders



- IgG2a provides protective immunity with recognition of Adr2, a surface antigen on the bacteria.
- This antibody supports a strong immune response, with rapid activation of T-cells and innate immune cells.