**Chlamydia trachomatis**
- T4SS apoptosis
- Autophagy
- Beclin-1
- ROS
- AnkA
- Ats-1
- IL-8
- Lymphohistiocytic infiltrates in the liver
- Neutrophil recruitment
- IFN-γ
- CD8+
- CD4+ Th1
- Macrophage activation
- NKT
- CYBB
- CXCR2
- IL-8

**Anaplasma phagocytophilum**
- T4SS apoptosis
- Autophagy
- Beclin-1
- ROS
- AnkA
- Ats-1
- IL-8
- Neutrophil recruitment
- Lymphohistiocytic infiltrates in the liver
- IL-10
- CD8+
- CD4+ Th1
- Macrophage activation
- NKT
- CYBB
- CXCR2
- IL-8

**Coxiella burnetii**
- CD4+ Th1
- IFN-γ
- Macrophage activation
- T4SS apoptosis
- Chronic infection
- Tregs
- NF-kB
- IL-6
- TNF-α
- TNF-α produced by infected macrophages

**Ehrlichia spp.**
- CD4+ Th1
- IFN-γ
- CD8+
- Fe limited
- PRRs
- TRPs
- NF-kB
- IL-10
- Toxic shock
- Ec survival

**Rickettsia spp.**
- CD4+ Th1
- IFN-γ
- CD8+
- Macrophage activation
- T4SS T1SS T5SS
- Host actin hijacking
- TLRs
- IL-6
- TNF-α
- Type I IFN
- Endothelial dysfunction

**Orientia tsutsugamushi**
- CD4+ Th2
- CD4+ Th1
- IFN-γ
- CD8+
- iNOS
- IL-10
- Macrophage activation
- T4SS T1SS
- Apoptosis
- NOD-1
- ASC
- IL-33 mediated activation
- Endothelial dysfunction
- Lesions and inflammatory infiltrates in the liver, lung, heart, and brain
Obligates must remodel the host environment through effectors secreted through the type 1, type 2, type 3, type 4, and type 5 secretion systems (TXSS). Secreted effectors, which include inclusion proteins (Inc)s, ankryin repeat domain-containing proteins (Anks), and tandem repeat containing proteins (TRPs), among others, interact with eukaryotic host cell processes to inhibit apoptosis, induce autophagy, modulate host gene transcription, co-opt host signaling pathways, manipulate vesicle trafficking, and hijack host actin polymerization. Host immune responses against obligates generally involve the activation of innate pattern recognition receptors (PRRs), including Toll-like (TLRs), NOD-like (NLRs), and cytosolic DNA-sensing molecules (for example, stimulator of interferon genes (STING)), which leads to the secretion of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, type I interferons (IFN) and IL-1. Innate responses activate the host adaptive immune responses, which against obligates, is largely comprised of a CD4+ T helper cell (Th)1 response. The hallmark of a Th1 response is the production of IFN-γ by CD4+ T cells, as well as CD8+ T cells, natural killer (NK), and NKT cells. Cytotoxic CD8+ lymphocytes also directly kill infected cells. IFN-γ further serves to activate macrophages, which upregulate antimicrobial genes, leading to the production of reactive oxygen species (ROS) and nitric oxide, and to limit nutrient availability (for example, iron and tryptophan). While essential to control pathogen burden, immune activation in excess can lead to tissue destruction, cytokine storm, inflammatory infiltrates into organs, and endothelial dysfunction. Indeed, the symptoms of obligate infection can largely be attributed to immunopathology triggered by a dysregulated immune response. Although cellular immunity is the major player in obligate defense, antibodies against obligates are also observed, indicating that a humoral response also participates in infection clearance. The ability of several obligates to vary the composition of their outer membrane proteins represents an effective immune evasion strategy.

Bacterial proteins are in orange and secreted effectors are highlighted in yellow. Cytokines are colored red. Ank, Ankyrin repeat containing protein; ASC, apoptosis-associated speck-like protein containing a carboxy-terminal CARD; Ats-1, Anaplasma-translocated substrate-1; CXCR2, C-X-C motif chemokine receptor 2; CYBB, cytochrome B subunit β; GBP, guanylate binding protein; Fe, iron; IFN, interferon; IL, interleukin; iNOS, inducible nitrogen oxide synthase; ISG, interferon stimulated gene; NF-kB, nuclear factor-kappa B; NK, natural killer; NLRP3, NLR Family Pyrin Domain Containing 3; NOD, nucleotide oligomerization binding domains; PRR, pattern recognition receptor; ROS, reactive oxygen species; STING, stimulator of interferon genes; TLR, Toll-like receptor; Treg; T regulatory cell; TRPs, tandem repeat proteins; TXSS, type X secretion system.

REFERENCES


