# *Yersinia* Activation of Type I Interferon

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## Introduction

Three *Yersinia* species are pathogenic to mammals and are part of the Enterobacteriaceae family of eubacteria. *Yersinia enterocolitica* causes gastroenteritis, a normally self-limiting infection that has been associated with significant outbreaks of yersiniosis in humans and animals throughout the world [1, 2]. *Yersinia pseudotuberculosis* causes less severe infection and is less commonly associated with foodborne outbreaks but is more closely related to the deadly *Yersinia pestis*, which diverged approximately 3,000 years ago [3]. *Y. pestis* is the causative agent of bubonic plague, a flea borne disease which is characterized by a late stage bacteremia that seeds multiple tissues including the lungs [4]. *Y. pestis* infection of the respiratory tract leads to a fulminant bronchopneumonia which can be spread through respiratory secretions.

Enhanced virulence through systemic infection and the flea life cycle of *Y. pestis* are due to the acquisition of two plasmids as well as genetic reduction, loss of function mutations that in some cases reduced the activity of virulence factors conserved in the other *Yersinia* species [5]. Importantly, all three pathogens employ temperature-dependent changes in LPS composition such that the immunostimulatory hexacylated lipid A is down-regulated at the mammalian host temperature of 37 °C [6]. Tetraacylated LPS from *Yersinia* grown at 37 °C provides little to no stimulation of TNFα secretion. Hypoacetylation of *Y. pestis* LPS at 37 °C makes a significant contribution to virulence by providing evasion from toll-like receptor 4 (TLR4) signaling, thereby limiting the activation of NF-κB [7]. This structure also contributes to evasion of inflammasome activation [8]. Nevertheless, in spite of this and other immune evasive strategies used to control inflammatory responses,

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*Y. pestis* still induces the production of type I interferon (IFN) [9]. In this chapter, we will review signaling pathways that may induce type I IFN and the phenotypic outcome of IFN signaling during *Yersinia* infection.

## Extracellular Bacteria Evade Activation of Interferon Responses

Extracellular *Yersinia* target phagocytic cells for the injection of anti-host proteins, known as Yops, by the type III secretion system (T3SS) [10]. Yop activities result in inhibition of phagocytosis and production of proinflammatory cytokines and lead to host cell death in vitro [11] (Fig. 1). *Yersinia* that makes intimate contact with a host cell will insert a translocation pore into its plasma membrane through which effector Yops are transported. Pore formation can be detected by the cell's inflammasome machinery, which includes cytoplasmic nucleic acid pattern recognition receptors. In the absence of Yop effectors, MyD88- and TRIF-independent production of type I

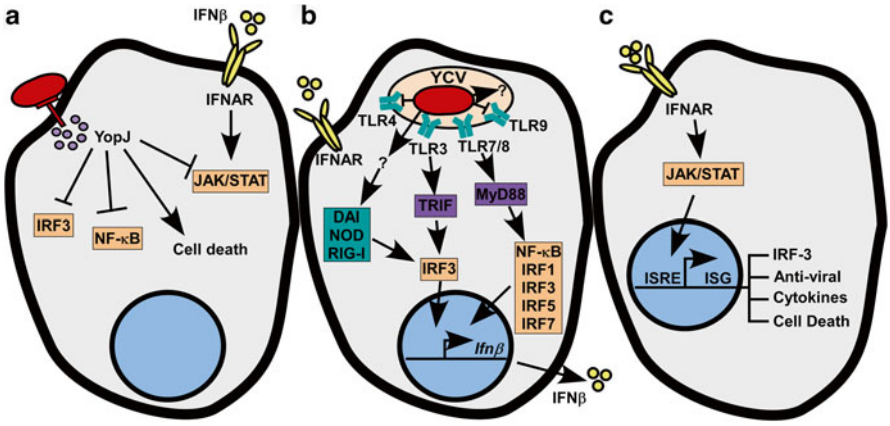


**Fig. 1** *Yersinia* activation of type I IFN in macrophages and other phagocytic cells, with possible downstream signaling outcomes. (**a**) Macrophages making intimate contact with *Yersinia* (*red*) are injected with Yops by the T3SS. One effector, YopJ blocks activation of major pro-inflammatory signaling pathways mediated by IRF3, NF-κB, and p38 kinase, and promotes apoptosis. Signaling from IFNAR (*yellow*) is probably blocked in these cells, but this has not yet been directly shown. (**b**) Intracellular bacteria reside in a *Yersinia* containing vacuole (YCV) where they may prevent signaling by TLR4 and TLR9. In addition, YCV may secrete proteins or other products into the cytoplasm or vacuole lumen that might activate one or more intracellular PRRs (*blue*, DAI, NOD, RIG-I or TLR3, TLR7, respectively). Signaling can be through MyD88, TRIF (*purple*) or independent of either, leading to induction of one or more transcription factors (*orange*) and the expression of IFN-β. Cells carrying intracellular *Yersinia* may also respond to IFN-β through IFNAR in an unknown manner. (**c**) Uninfected immune cells residing in different sites such as the bone marrow, may also respond to IFN-β through IFNAR, inducing interferon stimulated gene (ISG) expression that may upregulate an anti-viral response, IRF3, inflammatory cytokines, and/or cell death genes

IFN were observed following insertion of the type III translocation pore by *Y. pseudotuberculosis* [12]. MyD88-/TRIF-independent induction of IFN was not blocked by the inhibition of phagocytosis suggesting that extracellular, rather than intracellular, bacteria were detected by macrophages. Deletion of the type III secretion system translocator YopB resulted in no detectable type I IFN production in vitro. These data suggest that host sensing of insertion of the type III translocation pore leads to expression of IFN-β through a cytoplasmic receptor. One or more Yop effectors may prevent expression of IFN-β either within the cell or by producing anti-inflammatory molecules that prevent cells from responding to cytokine signals.

YopJ/P is a deubiquitinase and an acetylase that primarily targets MAP2 kinases, and prevents activation of master inflammatory regulators such as NF-κB, AP-1, and IRF3 (Fig. 1a) [13–16]. During infection of macrophages in vitro, YopJ/P inactivation of NF-κB not only prevents production of proinflammatory cytokines, but it also induces apoptosis due to suppression of the NF-κB-dependent expression of anti-apoptotic proteins Bid and t-Bid [17]. Given these activities, it seems likely that YopJ injection would prevent the expression of IFN-β either due to acetylation of IRF3, NF-κB or even another cytoplasmic target required for signaling from the translocation pore. Even though deletion of *yopJ* results in loss of immune suppression of macrophages in vitro, there appears to be only a small contribution of YopJ to virulence in mouse models of disease [18, 19].

## *Yersinia* Evades TLR4 Activation

TLR4 is a host pattern recognition receptor that in conjunction with MD-2 can recognize the Gram-negative bacterial cell membrane component LPS [20–22]. Activation of TLR4 can occur at the plasma membrane or in the endosome, with different outcomes [23]. Upon binding LPS at the plasma membrane, the scaffold protein TIRAP (MAL) is recruited via its TIR domain. TIRAP binding results in recruitment of MyD88, which leads to the activation of the transcription factor NF-κB and the production of proinflammatory cytokines such as TNFα and IL-6. Alternatively, when TLR4 activation occurs in the endosomal compartment after, for example, the phagocytosis of Gram-negative bacteria, the downstream adapter molecule TRIF mediates the activation of the transcription factor IRF3 and induces the expression of IFN-β.

Yet, it appears that TLR4 signaling does not play a major role during *Y. pestis* infection, as *Tlr4*$^{-/-}$ mice challenged with wild-type *Y. pestis* are not more susceptible to infection [7]. All three *Yersinia* species modulate their lipid A structure in response to temperature which is believed to result in poor stimulation of TLR4 during infection. The TLR4–MD-2 complex binds hexaacylated lipid A but does not recognize hypoacetylated forms [23]. Hexaacylated lipid A is the most common form of Gram-negative LPS and the predominant species when *Yersiniae* are growing in the flea or environment. At 37 °C, the bacterial genes encoding lipid IV acetylases LpxL and LpxM are down-regulated and newly synthesized LPS incorporates

tetraacylated lipid A. While the hexacylated lipid A that predominates at lower temperatures stimulates TLR4, the tetraacylated form does not stimulate TLR4 on human or murine macrophages [24]. All three *Yersinia* species down-regulate the expression of hexaacylated lipid A at 37 °C and even though each expresses a unique LPS structure, none of these is stimulatory to TLR4 [25]. In summary, *Y. enterocolitica*, *pseudotuberculosis*, and *pestis* share dominant virulence factors of hypoacetylated LPS and injection of immunomodulatory Yops by the T3SS. These virulence factors combine to provide for evasion of TLR4 and the expression of pro-inflammatory cytokines during infection. Yet in spite of these dominant immune modulatory mechanisms, host type I IFN signaling pathways appear to be active during infection.

## Susceptibility of Mice to Yersiniosis and Plague is Affected by Type I Interferon Signaling

TRIF is required during *Y. enterocolitica* infection and its signaling led to protective responses in a murine model of yersiniosis. *Trif*$^{-/-}$ mice were found to be defective in phagocytosis of bacteria, which may have contributed to an increase in bacterial dissemination and elevated titers [26]. *Trif*$^{-/-}$ mice produced reduced amounts of IFN-β and IFN-γ during *Y. enterocolitica* infection suggesting that both cytokines depended on TRIF signaling for production. Although IFN-γ activates macrophages to up-regulate bactericidal mechanisms, it is unclear if this would be sufficient to have an impact on the infection since the closely related *Y. pestis* resists killing by activated macrophages [27, 28]. In addition, previous work showed a requirement for TRIF in inducing apoptosis in macrophages following infection by *Y. enterocolitica* [29]. TLR4 was required for TRIF-dependent apoptosis but not MyD88. Together these data suggest that *Y. enterocolitica* may induce type I IFN expression through TLR4 activation of TRIF from the phagosomal membrane rather than the cell surface. This hypothesis is at odds with the observation that LPS from *Y. enterocolitica* does not induce inflammatory cytokine production, and additional work is needed to understand how TRIF is stimulated during infection. Whether the TRIF-dependent cell death, phagocytosis or inflammatory responses required type I IFN signaling has not yet been reported. Furthermore, the phenotype of *Trif*$^{-/-}$ mice in a plague infection model has not yet been reported and it is unclear if host defense against other *Yersinia* would also require TRIF.

IRF3 is a transcription factor that is activated downstream of the adaptors TRIF, MyD88, or STING leading to expression of *Ifnb* and other interferon-stimulated genes. Although the sensitivity of *Trif*$^{-/-}$ mice to plague has not yet been reported, *Irf3*$^{-/-}$ mice have been tested in a murine model of pneumonic plague. *Irf3*$^{-/-}$ mice were more susceptible to the non-pigmented mutant *Y. pestis*, but not fully virulent bacteria [9]. Similar to *Trif*$^{-/-}$ mice, *Irf3*$^{-/-}$ macrophages were defective for phagocytosis of *Y. pestis* which may have contributed to accelerated growth and

progression of the infection. However, bone marrow derived macrophages from *Ifnar*$^{-/-}$ mice were not defective for phagocytosis indicating that type I IFN is not involved this process. In fact, *Ifnb* expression was found in infected lung homogenate in WT and *Irf3*$^{-/-}$ mice suggesting that IRF3 is not required for *Ifnb* expression. Furthermore, unlike the *Trif*$^{-/-}$ mice infected with *Y. enterocolitica*, *Ifng* expression was not dependent on IRF3 and was absent until late stage infection in the presence or absence of IRF3. These results do not rule out signaling through IRF3 or TRIF as contributing to the type I IFN response, and additional data is needed to identify the signaling cascade induced by *Yersinia* for expression of type I IFN.

In striking contrast to *Irf3*$^{-/-}$ mice, *Ifnar*$^{-/-}$ mice were more resistant to plague suggesting that IFN-β signaling is immunopathogenic [9]. No changes in pro-inflammatory cytokines were associated with *Ifnar*$^{-/-}$ mice. Instead, IFN-dependent sensitivity to infection manifested under conditions of high bacterial burden, where the IFNAR-expressing mice lost control over bacterial growth while the *Ifnar*$^{-/-}$ mice cleared the infection. Neutrophil populations appeared depleted in the bone marrow and periphery of WT mice which may have led to their poor outcome. Together the data suggested that IFN signaling during *Y. pestis* infection caused an increase in neutrophil cell death or a decrease in maturation of cells in the bone marrow. The sensitivity of *Ifnar*$^{-/-}$ mice to *Y. enterocolitica* has not yet been reported and it remains unclear if a similar mechanism of neutrophil depletion is a common feature of the type I IFN response to *Yersinia*.

## Activation of Intracellular PRRs by Intracellular *Yersinia*?

Although *Yersinia* has a predominantly extracellular life cycle, it also has the ability to invade phagocytic and non-phagocytic cells and will survive and grow in macrophages, eventually causing their death [30, 31, 27, 32]. The T3SS is not required for the intracellular life cycle, being only weakly expressed, and the role of hypoacylated LPS in the intracellular compartment has not been rigorously examined. Following phagocytosis or invasion, bacteria have been observed to localize in spacious vacuoles known as *Yersinia* containing vacuoles (YCV) which have cell surface markers found on late endosomes and autophagosomes (Fig. 1b) [33]. Survival in the YCV depends on the bacterial 2-component signaling pathway PhoPQ which is activated in low magnesium or low pH environments [34]. PhoP is also required for virulence of *Y. pestis* suggesting that intracellular survival is important to pathogenesis [35]. Little evidence has been presented supporting cytoplasmic localization of *Yersinia*. However, genome annotation of all three *Yersinia* pathogens has revealed the presence of multiple secretion systems, some of which could be utilized in the intracellular compartment to facilitate nutrient uptake or escape from the vacuole or cell. Overall, these data suggest that intracellular bacteria could be detected by cytoplasmic or endosomal PRRs, any number of which could result in expression of type I IFN.

While TLR4 is a major PRR for detection of bacteria that leads to type I IFN expression, TLR3 is activated primarily by viruses and double-stranded RNA in phagolysosomes, leading to type I IFN expression and an anti-viral response. Evidence suggests that TLR3 may also recognize bacteria. Gut epithelial cells expressing TLR3 can be stimulated by Gram-positive bacteria in the microbiota resulting in an anti-viral response that may serve to suppress the inflammatory response to commensal bacteria [36, 37]. TLR3 activation as a host defense mechanism against bacteria has not yet been reported but it is nevertheless clear that bacteria can be recognized by TLR3. *Y. pestis*-derived tetraacylated LPS has previously been shown to reduce activation of signaling through the TLR2 and TLR3 pathways [38]. This data demonstrates the ability of *Y. pestis* to actively suppress the innate immune response through receptor crosstalk and suggests that TLR3 may also be neutralized during infection due to the *Yersinia* LPS structure.

Other toll-like receptors, such as TLR7 and TLR9, also localize to the phagosomal membrane where they can be activated upon recognition of microbial nucleic acids. TLR7 and TLR9 signal downstream to MyD88 to activate NF-κB, IRF1, IRF3, IRF5, and/or IRF7 to induce the expression of IFN-β [39–43]. TLR9 binds unmethylated dinucleotides to induce a downstream signal transduction pathway involving MyD88 and resulting in activation of *Ifnb* expression [23]. Active stimulation of TLR9 prior to infection improved clearance of non-pigmented *Y. pestis* in a murine respiratory infection model [44]. Since IFN-β signaling was previously associated with immunopathology, these data suggest that the protective effect of TLR9 signaling may not be related to IFN-β and TLR9 may not be principally responsible for *Ifnb* expression. Furthermore, these data suggest that *Y. pestis* may even prevent TLR9 activation. All three *Yersinia* pathogens have similar capability for intracellular survival and replication and there is evidence that live bacteria prevent acidification of the phagolysosome, which is necessary for the localization and activation of TLR7 in this compartment [33]. Together, the data suggest that live *Yersiniae* are likely to prevent signaling from the nucleic acid sensors of the phagosome. It may be that bacteria that lyse in a small percentage of macrophages are detected by nucleic acid PRRs and the resulting type I IFN signal is amplified by neighboring cells (Fig. 1c). Furthermore, intracellular *Y. pestis* eventually kill their host cells in an active process that requires intracellular survival. Perhaps the mechanism that is used to cause host cell death from the phagosome also induces expression of IFN-β from cytoplasmic PRRs. Overall, the mechanism underlying *Yersinia* activation of type I interferon remains incompletely understood and may be a critical part of its pathogenesis.

## Concluding Remarks

*Yersinia* are potentially recognized throughout their infectious life cycle from an early intracellular phase to later anti-phagocytic, rapid growth phase and therefore are likely to interact with PRRs on the plasma and phagosomal membranes as well

as within the cytoplasm [32]. Although all three species of pathogenic *Yersinia* have in common two major virulence factors, an atypical LPS that is not stimulatory to TLR4 and the T3SS, only one causes severe sepsis with multi-organ failure while the others cause self-limiting gastroenteritis. The differences are presumably caused at least in part by different host responses to infection, originating with PRRs or downstream adaptor molecules. All three *Yersinia* species that are pathogenic to mammals suppress PAMPs at 37 °C that would otherwise stimulate activation of TLR2, -3, -4, -5, and possibly -9, thereby disabling recognition of intracellular and extracellular bacteria [45].

Nevertheless, *Yersinia* are detected by the mammalian innate immune system and mice that lack components of type I IFN signaling pathways have altered sensitivity to infection. The complex *Yersinia* lifecycle in the mammalian host includes the display of many PAMPs: insertion of the type III translocation pore, injection of bacterial proteins in the host cytoplasm, modification of intracellular trafficking to permit growth and survival within the YCV, and promoting escape of intracellular bacteria by host cell lysis. PRRs at the plasma membrane, phagosomal membrane and even cytoplasm have the opportunity to see *Yersinia* during infection.

The adaptor TRIF is required for *Yersinia* YopJ-induced apoptosis through caspase 8 and 9 and it is tempting to speculate that TRIF-dependent type I IFN signaling contributes to the control of apoptosis or other forms of programmed cell death as it does following viral infection [29]. During *Salmonella* infection, type I IFN signaling led to activation of necroptosis in infected macrophages which enhanced virulence [46]. The bacterial and host proteins that were responsible for this were not identified leaving it unknown whether *Yersinia* infection could have a similar effect on neutrophils, macrophages or even hematopoetic precursor cells. For the plague model, IFN pathology manifests during late stage disease when bacteria have spread to distal sites where they grow logarithmically. Thus it may well be that only infected cells are responding poorly to type I IFN.

Type I IFN is used as a therapeutic to induce anti-viral and anti-cancer mechanisms in humans and the data gathered to date on the role of type I IFN during *Yersinia* infection suggests that this type of treatment could generate an increased risk of disease [47, 48]. Conversely, it seems likely that blocking type I IFN signaling might improve the outcome of late stage plague. Perhaps single ISGs are responsible for IFN-related pathology and could be specifically targeted as an anti-plague therapeutic. Given the dependence of viral clearance on the type I IFN response, it would be preferred to target one or a few ISGs as this would be less likely to generate an increase in susceptibility to viruses. Future experiments to identify ISGs associated with pathology or host defense against *Yersinia* may result in important advances in interferon therapies for humans.

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