Unraveling neutrophil–Yersinia interactions during tissue infection [version 1; peer review: 3 approved]

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Abstract

The human and animal pathogens Yersinia pestis, which causes bubonic and pneumonic plague, and Yersinia pseudotuberculosis and Yersinia enterocolitica, which cause gastroenteritis, share a type 3 secretion system which injects effector proteins, Yops, into host cells. This system is critical for virulence of all three pathogens in tissue infection. Neutrophils are rapidly recruited to infected sites and all three pathogens frequently interact with and inject Yops into these cells during tissue infection. Host receptors, serum factors, and bacterial adhesins appear to collaborate to promote neutrophil–Yersinia interactions in tissues. The ability of neutrophils to control infection is mixed depending on the stage of infection and points to the efficiency of Yops and other bacterial factors to mitigate bactericidal effects of neutrophils. Yersinia in close proximity to neutrophils has higher levels of expression from yop promoters, and neutrophils in close proximity to Yersinia express higher levels of pro-survival genes than migrating neutrophils. In infected tissues, YopM increases neutrophil survival and YopH targets a SKAP2/SLP-76 signal transduction pathway. Yet the full impact of these and other Yops and other Yersinia factors on neutrophils in infected tissues has yet to be understood.

Keywords

Yersinia pestis, Yersinia enterocolitica, Yersinia pseudotuberculosis, neutrophils, polymorphonuclear cells, YadA, Ail, Invasin, type 3 secretion system, Yops, SKAP2
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**Introduction**

The study of the Gram-negative bacterial pathogens *Yersinia pestis*, *Yersinia pseudotuberculosis*, and *Yersinia enterocolitica* has been at the forefront of cellular and molecular pathogenesis for over four decades. *Y. pestis*, a recently emerged pathogen evolved from *Y. pseudotuberculosis*, is the causative agent of bubonic and pneumonic plagues and has produced several pandemics in the past 10,000 years. These infections are associated with high mortality rates of 30% and over 90%, respectively, if not treated rapidly with antibiotics. Transmission of *Y. pestis* to cause bubonic plague occurs via flea bite into the intradermal skin layer, whereas transmission of pneumonic plague occurs via inhalation of *Y. pestis* into lungs. By contrast to the highly lethal infections caused by *Y. pestis* in humans, *Y. pseudotuberculosis* and *Y. enterocolitica* generally cause self-limiting gastroenteritis and mesenteric lymph adenitis in most otherwise-healthy humans, rarely spreading to cause systemic disease or fatal infections. Infections normally occur through ingestion of contaminated foods or liquids. All three *Yersinia* species infect a variety of mammals, including rodents and ungulates, and the enteric pathogens can be found in birds. Thus, the *Yersiniae* are “generalists”, adept at surviving in many different hosts, and so have evolved virulence factors and pathogenic strategies that counteract immune systems of a variety of animals.

Over the past 35 years, the study of the *Yersinia* virulence factors—including bacterial adhesins, the type 3 secretion system (T3SS), effector proteins (Yops), Pla protease in *Y. pestis*, and iron acquisition systems—has revealed critical features of host–pathogen interactions (reviewed in 2–5). Notable recent advances include uncovering aspects of innate immunity that are triggered or suppressed (or both) by the T3SS and Yops in macrophages and reconstructing the recent evolutionary progression from *Y. pseudotuberculosis* to *Y. pestis*. Another critical feature of *Yersinia*–host cell interaction garnering attention is its interactions with neutrophils during various types of tissue infection. Neutrophils are critical cells of the innate immune system and both sense pathogens resulting in release of signaling molecules, such as cytokines and alarmins, and kill invading microbes through a variety of mechanisms. These killing mechanisms include phagocytosis, generation of reactive oxygen species, degranulation, and formation of neutrophil extracellular traps. Effector Yops hamper a number of these processes in isolated neutrophils, observations which are further driving current interest in how neutrophils interact with *Yersinia* in the context of infected tissues and other cell types. This mini-review highlights recent studies involving *Yersinia*–neutrophil interactions in murine tissues.

**Yersinia spps target Yop injection to neutrophils during infection of tissues**

*Yersinia* spps use the highly conserved T3SS to inject six or seven effector Yop proteins in host cells to cause disease in mammals. In tissue infections using a β-lactamase reporter system, studies with *Y. pestis*, *Y. enterocolitica*, and *Y. pseudotuberculosis* have demonstrated that neutrophils are a major—and, typically, the primary—cell target for Yop injection. That neutrophils are a significant target holds true regardless of whether the route of infection is oral, intravenous, or intranasal and the tissues examined are Peyer’s patches, mesenteric lymph nodes, spleens, or lungs.

There are, however, several exceptions, most notably early after tissue infection. For example, 6 hours after intranasal infection with the virulent *Y. pestis* CO92 strain, alveolar macrophages are the primary injected cell type and comprise over 50% of injected cells whereas neutrophils comprise about 15% of the injected population. This balance shifts by 12 hours when neutrophils start invading tissues at higher numbers and become over 70% of the injected population. Similarly, 1 day after intravenous infection with *Y. enterocolitica*, macrophages are more highly targeted in the spleen but by day 2 neutrophils become equally targeted. After oral infection with *Y. pseudotuberculosis*, levels of injected macrophages and neutrophils in the mesenteric lymph nodes are comparable 5 days after oral gavage. Finally, in splenic infections, while neutrophils are enriched significantly for injection, frequently a comparable or even higher absolute number of B cells are injected with *Yersinia* species. The high injection levels of B cells may occur because they comprise the majority of total cells in spleens—over 60% compared with the much lower numbers of neutrophils and macrophages—so *Yersinia* may stochastically encounter them more than any other cell type. For insights into the Yop interactions with B and T cells, readers are referred to the following.

What factors are important for *Yersinia* targeting Yops into neutrophils?

**Proximity**

There are both physiological and molecular explanations for why neutrophils are a major target of *Yersinia* Yop injection during infection. One significant reason is location of the cells to the bacteria since tight binding of *Yersinia* to cells is required for Yop injection, and neutrophils migrate to inoculation sites within hours or days after infection and are typically the closest cell type associated with the bacteria. After infection with the enteric *Yersinia* pathogens, neutrophils migrate to and eventually encase the bacterial colonies in the Peyer’s patches or spleens between 24 and 72 hours after oral or intravenous infection. In these tissues, pyogranulomas containing tightly packed *Y. pseudotuberculosis* immediately surrounded by neutrophils with macrophages forming an outer ring of cells. It is noteworthy that, in some cases, neutrophils associate more rapidly with yop mutants than with wild-type *Yersinia*. For instance, within a day after oral inoculation with wild-type *Y. pseudotuberculosis*, *Y. enterocolitica*, or yop mutants, more neutrophils are found in association with the yop mutants than the wild-type *Yersinia*, indicating that early interactions of wild-type *Yersinia* with resident tissue cells delay chemotaxis of neutrophils to the bacteria.

After intradermal inoculation, by either a flea bite or needle inoculation, neutrophils are detected within 50 minutes to 7 hours of inoculation. Likewise, in lung infections with *Y. pestis* or *Y. pseudotuberculosis*, neutrophils migrate to tissue sites within 12 to 48 hours, depending on the strain.
Yet several lines of evidence suggest that proximity is not the only factor critical for the preponderance of neutrophils found injected with Yops. In one study, in which neutrophils and inflammatory monocytes were depleted from tissues, fewer overall cells are targeted for injection rather than different cell populations. This suggests that the nature of bacterial growth within tissues or interactions with the remaining innate immune cells in tissues (or both) play a role in the number of injected cells during tissue infection.

Receptors, adhesins, and serum factors
Ex vivo studies show that the selectivity for injection into neutrophils is recapitulated in single-cell splenic and lung homogenates infected with Yersinia when bacteria are limiting, indicating that there are specific receptor–ligand interactions that are favored between the Yersinia and neutrophils. Blockage of complement receptor 3 (CR3) on neutrophils from ex vivo splenic homogenates significantly reduced injection into neutrophils by Y. pestis in splenocytes, demonstrating that Y. pestis uses this receptor and suggesting that the CR3 receptor, which is enriched in neutrophils, plays a role in promoting Y. pestis–neutrophil interactions over other cell types in these lysates. This has yet to be evaluated in a mouse model of infection with Y. pestis. But findings with Y. pseudotuberculosis also show a role for complement or serum factors in directing injection of Yops into neutrophils in isolated mouse splenocytes and in mouse infections in spleens after intravenous but not in intranasal infections. Elegant in vivo studies with β1-depleted mice demonstrate that Y. enterocolitica uses β1 integrins to inject Yops into many different cell types in infected spleens, although this receptor usage was not specific to neutrophils.

The enteric Yersinia bacterial adhesins YadA, Invasin, or Ail (or a combination of these) are important for injection in mouse tissues. Under conditions where adhesin-mutants and the wild-type strain were recovered at comparable numbers, a ΔailΔinvΔyadA triple mutant in Y. pseudotuberculosis and a yadA mutant in Y. enterocolitica injected fewer cells after intravenous infection than the isogenic wild-type strains. In the case of Y. enterocolitica, very few neutrophils are detected in tissues correlating with very few injected cells and this is similar to findings with Y. pseudotuberculosis. After infection with the ΔailΔinvΔyadA triple mutant in Y. pseudotuberculosis, the spectrum of injected cells was not changed. However, treatment with cobra venom factor both restores virulence of the triple mutant and causes a significant shift in spectrum of cells targeted by the triple-mutant but not the wild-type strain. Specifically, in mice treated with cobra venom factor (which is a complement-activating protein that depletes complement regulatory proteins and ultimately complement), the triple mutant injects more B cells and fewer neutrophils. This result shows that a combination of serum factors and bacteria adhesins influences cells targeted for injection in Y. pseudotuberculosis. However, it remains to be determined whether the nature of the pyogranuloma formed under these conditions is the same as or different from that formed by the wild-type strain and whether this explains the altered spectrum of injected cells. Nonetheless, Ail and YadA have long been recognized in in vitro studies to interact with serum factors and to bind cells and promote injection; these in vivo studies demonstrate their importance for injection of Yops in tissue infection.

Do neutrophils matter in tissue infection?
Given that Yersinia expends energy injecting Yops into neutrophils and appears to have co-opted CR3 or serum factors (or both) in mouse tissues to enhance injection into neutrophils, the question arises “Are neutrophils important to contain Yersinia infection?” If neutrophils are important, one would predict increased colony-forming units (CFUs), increased disease symptoms, and decreased time to morbidity in their absence. At first glance, the results of the classic approach of depleting neutrophils and measuring infection outcomes are mixed.

In intradermal models of infected mice depleted of neutrophils with 1A8, an antibody recognizing Ly6G found on mature neutrophils, the CFUs of Y. pestis in the skin increase significantly in the absence of neutrophils, yet the total number of bacteria replicating in the draining lymph node does not change. Likewise, CFUs of Y. pestis in lymph tissues remain constant after depletion with RB6-8C5, an antibody that depletes Gr-1–expressing cells, including mature and immature neutrophils and subsets of inflammatory monocytes, dendritic cells, and T cells. These results support the ideas that neutrophils are important for curbing bacterial growth in the skin, but not the lymph nodes, and that neutrophils are not essential for dissemination from skin to lymph tissues. Some debate exists about whether Y. pestis disseminates from skin to lymph nodes by hitchhiking in neutrophils, macrophages, or dendritic cells or a combination of these (reviewed in 67). But these most recent studies support the idea that Y. pestis can disseminate to lymph nodes independently of neutrophils.

Depletion of neutrophils with 1A8 in lung infection with Y. pestis, as with lymph node infection, does not result in changes in bacteria counts 24 or 48 hours after infection. Surprisingly, symptoms of disease progression and time to death are reduced in the absence of neutrophils, although the difference in time to death is not statistically significant. Consistent with these findings, the histopathology of mice treated with 1A8 showed less damage to lungs with intact alveoli structure whereas untreated mice had necrotizing pneumonia. However, artificially increasing the number of neutrophils in lungs prior to infection significantly attenuates Y. pestis infection. Combined, these results show that, early after infection, high levels of neutrophils stop infection, but once Y. pestis reaches a certain stage—either in number or in modulating early host responses or both—the bactericidal activities of neutrophils are effectively nullified and, in fact, their continued migration into lungs wrought the damage observed during infection.

The impact of neutrophils on restraining infection by the enteric Yersinia pathogens is equally mixed. In an oral infection model of Y. pseudotuberculosis, depletion of neutrophils with 1A8 or RB6-8C5 resulted in significantly more growth at day 1 post-infection with wild-type and yopE, yopH, and yopK
mutant strains, and disease symptoms were worse on subsequent
days. Likewise, increasing the numbers of neutrophils in
Peyer’s patches or increasing their activation in spleens by
depletion of dendritic cells results in increased clearance of
wild-type Y. enterocolitica. Increasing neutrophils in tissues
also suppresses Y. pseudotuberculosis yop mutant colonization but
not wild-type colonization in oral infection. Although these
results point to some differences between the enteric Yersin-
iae interactions with neutrophils, they indicate that neutrophils
can control early seeding or dissemination events in infection
(or both). However, neutrophil depletion does not always
increase Y. pseudotuberculosis growth in tissues. Three days
after oral inoculation, fewer wild-type Y. pseudotuberculosis
were detected overall in neutrophil-depleted mice (by lumi-
nescence) compared with non-depleted tissues despite worse
neutrophil disease symptoms. After intravenous infection with
Y. pseudotuberculosis, the number of bacteria recovered 3 days
from mock-depleted, 1A8-treated or RB6-8C5–treated mice was
comparable despite the observation that 1A8- or RB6-8C5–
treated mice appeared more ill and reached morbidity faster.
Thus, although the growth of Y. pseudotuberculosis is not
always increased in the tissues examined in the absence of
neutrophils, the overall health of the mice typically worsens.

Overall, these results are consistent with the idea that Yersinia
handles intimate interactions with neutrophils effectively once
infection in a tissue is established, but the bacteria are more
susceptible to neutrophils early in infection, such as soon after
inoculation or when disseminating to new tissues. Supporting
the idea that Yersinia spp are well designed to withstand
neutrophil onslaught in tissues is the observation that a number
of attenuated Yersinia mutants grow significantly better in
neutrophil-depleted mice, indicating that the function of these
proteins is to inactivate neutrophils or withstand the bactericidal
activities of neutrophils. Importantly, adhesin mutants yadA
and ail and several yop mutants such as yopH, yopE, and yopK
mutants all conform significantly better in some tissues
in neutrophil-depleted mice than in wild-type mice. (Not every
mutant is restored for growth in the absence of neutrophils;
for example, some are restored in the absence of both neutrophils
and inflammatory monocytes and some have been tested
only in the absence of both.)

What are the consequences to neutrophils after Yop
injection in mouse infections?

Several elegant studies have examined the transcriptome of cells
surrounding Yersinia microcolonies by using RNA sequencing
(RNA-seq) when dual-tissue RNA-seq was used to evaluate
the host cell and bacterial responses to infection of
Y. pseudotuberculosis in the Peyer’s patches, a number of host
transcripts associated with infection were strongly induced; this
is indicative of the pronounced neutrophil infiltrate that occurs
after infection. These included metal ion sequestration,
inflammatory responses, acute-phase responses, and coagulat-
ive activities. These findings shed light into the overall host
response to infection in tissues which are composed predomi-
nately of neutrophils, but the findings do not distinguish the
cells specifically in contact with bacterial microcolonies. The

β-lactamase reporter system can also be used to dis-
tinguish and isolate injected from non-injected neutrophils
in infected tissues. Via such an approach, YopH, a tyrosine
phosphatase, was found to target the Slp-76/SKAP-2/PRAM
pathway in neutrophils during tissue infection. This pathway is
critical for reactive oxygen production of neutrophils after
integrin stimulation, providing a possible role for YopH. This
approach can be further exploited to determine direct from
indirect consequences of Yersinia–neutrophil interactions in
tissues.

Via laser capture microdissection, the inflammatory lesions
in the lungs induced by Y. pestis were parsed on the basis of proximal
(and presumably containing many cells injected with Yops) and distal areas to Y. pestis microcolonies. These transcriptomes were compared with each other and with the transcriptome of bone marrow neutrophils from uninfected
(representing not activated) and infected mice. Remark-
ably, the transcriptomes of cells proximal to the bacteria are
most similar to bone marrow neutrophils from uninfected
mice; that is, both resemble non-activated cells with higher
expression of pro-survival signals and lower expression of
chemotaxis/migration genes than the more distally located
cells. Strikingly, YopM expression changes the physiology of
neutrophils in tissue infection but not the bacterial burden. In
histological sections of mice infected with a yopM mutant,
cells appear anucleated and express more apoptotic markers,
indicating that YopM contributes to the pro-survival state of
the neutrophils yet this is not sufficient to impact bacterial survival.

What are the consequences to Yersinia after contact
with neutrophils in mouse tissues?

Changes to Y. pseudotuberculosis and Y. pestis gene expression in
lymph tissues that contain high numbers of neutrophils have been
analyzed by microarray analysis and RNA-seq, respectively. Notably, genes required for metal ion acquisition, nitric oxide
(NO) stress responsiveness, and (in Y. pseudotuberculosis) carbohydrate use were mostly highly upregulated in tissues
with neutrophils (representing not activated) and infected mice. Many of these pathways are also critical for survival of Y. pestis in a rat bubo model. Collectively, these results point toward a local lymph
environment where the bacteria experience high NO stress and restrictive ion and metabolic conditions. Y. pestis and Y. pseudotuberculosis respond to this restrictive metabolic environment in different ways; Y. pseudotuberculosis induces
carbohydrate use genes and the upper part of glycolysis,
whereas Y. pestis uses anaerobic respiration.

Direct observation of Y. pseudotuberculosis expressing fluorescent reporter constructs that are responsive to different environmental cues has permitted further dissection of bacterial responses in tissues. Specifically, at the periphery of micro-
colonies, Y. pseudotuberculosis expresses higher levels from the
lmp promoter, an NO responsive gene, and yopE, a T3SS gene. Higher NO expression is more uniformly observed in the outer ring of the microcolony, yet inducible nitric oxide synthase (iNOS) was not detected in the immediately adjacent
cells, indicating that NO diffuses from a distance. By
contrast, high expression from the yopE promoter was sporadically observed in individual cells on the periphery, suggesting that these cells are in direct contact with neutrophils and therefore upregulating yopE transcription\(^4\). These findings are consistent with increased copy number of the plasmid containing the T3SS upon contact with host cells\(^5\).

**Emerging models: Yersinia–neutrophil interactions in murine tissues**

Many facets of *Yersinia*–neutrophil interactions have yet to be unraveled, but a working model of *Yersinia*–neutrophil interactions in infected tissues is beginning to emerge. Neutrophils are recruited rapidly to infected tissues, albeit sometimes after a delay relative to recruitment by a *yop* mutant. This delay suggests that very early Yop injection into resident tissue cells may modulate chemokine and cytokine release, delaying neutrophil recruitment. However, neutrophils rapidly become the most proximal cell type to *Yersinia*, surround them, and in turn are efficiently injected with Yops by *Yersinia*. Higher expression of stress response genes and T3SS promoters is observed in line with increases in copy number of the pYV plasmid and increases in ion sequestration genes in host cells. Injection disarms neutrophils without triggering significant cell death. Rather, the immediately adjacent cells adopt a pro-survival and low migration state that fails to reduce bacterial growth.

Understanding how different Yops collaborate to modulate neutrophil activities in tissue infection is ongoing. Because it is easier to obtain human primary neutrophils in large quantities relative to mice, most studies investigating *Yersinia*–neutrophil interactions have used isolated human neutrophils\(^3,29,32–38\). It is important to be aware that murine and human neutrophils have notable differences and thus findings in one system cannot be inferred to occur in another\(^4,26\). Furthermore, human neutrophils are typically harvested from peripheral blood whereas mouse neutrophils are collected from either the bone marrow or the peritoneal cavity after being elicited by an irritant, such as casein or thioglycolate. Therefore, these cells are in different stages of development and have the potential to respond to bacteria differently. Nonetheless, studies in either system are important to understand how *Yersinia*, through manipulation of neutrophils, thwarts the orchestrated mammalian host cell response to infection at an organismal, tissue, cellular, and molecular level.

**Author contributions**

The author reviewed the literature and drafted and edited the review.

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