

## Forum

A Deadly Path:  
Bacterial Spread  
During Bubonic  
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***Yersinia pestis* causes bubonic plague, a fulminant disease where host immune responses are abrogated. Recently developed *in vivo* models of plague have resulted in new ideas regarding bacterial spread in the body. Deciphering bacterial spread is key to understanding *Y. pestis* and the immune responses it encounters during infection.**

## Evolving Portrait of a Deadly Pathogen

*Y. pestis* is arguably the most feared pathogen of the bacterial world. The bacterium causes plague, a re-emerging infectious disease that can kill a host (including humans) in less than a week. The bacterium survives in sylvatic animal reservoirs, mainly in rodents. These animal reservoirs are the source of modern plague outbreaks.

The field of plague pathogenesis focuses on how *Y. pestis* infects a host, and how infection results in disease and death. Much progress has been made in the identification of genes the bacterium might use during infection. The plasmid pCD1, the most studied genetic determinant of *Y. pestis*, is essential for infection. pCD1 encodes proteins of the *Yersinia* type III secretion system, a syringe-like molecular apparatus responsible for secretion of proteins that interfere with host cellular functions. Other genetic determinants have been regarded as essential for *Y. pestis* infection but most of them have been tested only *in vitro*. By far the biggest challenge in the field is the widespread use

of *in vitro* approaches to build a picture of what occurs during infection. Addressing infection with *in vivo* models and fully virulent strains is challenging, but this is a challenge the field needs to embrace to advance.

Bubonic plague develops after *Y. pestis* enters the body via the skin, typically through the bite of an infectious flea. During infection the bacterium disseminates from the dermis to draining lymph nodes (dLNs), and from dLNs to the systemic circulation [1,2]. Notably, movement from tissue to tissue is not directly dependent on the bacterium as *Y. pestis* is nonmotile (i.e., it lacks flagella).

How *Y. pestis* disseminates inside the body during bubonic plague, and what host–pathogen interactions accompany this process, are two prominent questions in the field. Here, we address these questions by paying particular, if not exclusive, attention to work done *in vivo* (i.e., using animal models) and with fully virulent *Y. pestis* strains.

## Escape from the Skin and Initiation of Infection

Before entering the host, *Y. pestis* survives in the digestive tract of a flea. Infected fleas deposit bacteria in the dermal layer of the skin while obtaining a blood meal [3]. The bacterial population inoculated in the dermis can be divided into two: a large population that remains in the skin, and a very small population that leaves this tissue [4]. The bacteria that remain in the skin trigger the recruitment of neutrophils [4–6], which can be seen in close proximity to the bacteria, or engulfing them. Neutrophils arrest bacterial proliferation in the skin but are unable to clear infection in this tissue [3,4]. Accordingly, *Y. pestis* must interfere, at least to some extent, with the normal function of neutrophils. pCD1 has been implicated as a key player in this process [5].

We propose that the bacterial population in the skin and the host–pathogen

interactions at this site are not crucial in the development of disease. Instead, we hypothesize that the bacteria that escape from the skin are responsible for host colonization and disease. The bacterial population that escapes from the skin travels to the dLNs through lymphatic vessels and, most likely, contrary to prevailing models [7,8], without the need of a phagocyte (i.e., macrophage, dendritic cell (DC), or neutrophil) [4]. Because the latter statement goes against long-lasting dogma it is important to review the most relevant evidence that supports it (Box 1).

The mechanisms behind phagocyte-independent transport to dLNs are unknown; however, it is likely that transport is driven by lymph flow. We propose that movement from the skin into the dLN is the key step for *Y. pestis* to successfully colonize the host and that this process depends almost exclusively on the fluidics of lymph.

## The Lymph Node (LN), a Killer's Heaven

When traceable, genetically tagged *Y. pestis* are inoculated intradermally (ID) (~20 CFU/tag) into the skin; only a few of the tags are detected in the dLN, while most of them persist in the skin [4]. This bottleneck in bacterial dissemination from skin to dLN might form in part because only a fraction of the bacteria are dissemination-competent (i.e., are free to enter lymphatic vessels). Bacterial killing in the LN early after arrival also may contribute to bottleneck formation. This hypothesis predicts that any process contributing to bacterial escape from the skin (e.g., reduced bacterial adhesion) or bacterial survival would result in a weaker bottleneck.

The very few individual bacteria that pass the bottleneck colonize the LN at remarkably high rates. Approximately  $10^4$ – $10^5$  CFU/LN can be detected 24 h after ID inoculation of ~200 CFU [3]. This number increases to ~ $10^8$  CFU/LN around 48 h after inoculation. As opposed to the skin, the LN environment might represent a 'special niche' that favors proliferation by

**Box 1. In or Out?**

*Yersinia pestis* traditionally has been thought to require an intracellular stage to disseminate from skin to dLN [7,8]. However, the points listed below argue against this hypothesis.

*Y. pestis* is detected in the dLN minutes after intradermal (ID) inoculation [4,12]. Phagocytes reach LNs in hours, not minutes.

Macrophages are, in general, regarded as poor migratory cells. In addition, macrophage recruitment to the skin is very low after *Y. pestis* inoculation [5].

Neutrophil depletion does not affect *Y. pestis* loads in the dLN [4,5].

DC recruitment in the skin is very low after *Y. pestis* inoculation, and bacterial loads in the dLN are not affected in a model where DC trafficking to dLNs is abrogated [5].

*Y. pestis* that associate with skin lymphatic vessels immediately after inoculation are not associated with phagocytic cells [4].

Colonization of the dLN by *Y. pestis* begins in its periphery and not in the cortex, where trafficking phagocytes bring engulfed antigen [1].

*Y. pestis* is observed extracellularly during early stages of LN colonization [1].

Nevertheless, an intracellular phase might be required beyond early stages of infection (late disseminators). This idea has not been addressed experimentally with fully virulent strains.

In one of the very few studies reporting on septicemic stages of bubonic plague, intravenous injections confirmed that pCD1 is essential for bacterial proliferation in blood [11]. Other studies have implicated additional *Y. pestis* genetic determinants to be important as well, but their methods cannot exclude the possibility of effects on earlier stages of infection (e.g., LN colonization) rather than a specific effect in the blood.

The study of *Y. pestis* in the bloodstream is probably the area of plague pathogenesis where research has invested the least. This is paradoxical as severe disease and death from bubonic plague directly derive from bacterial systemic colonization.

**Concluding Remarks**

Much remains to be uncovered to paint a clear portrait of *Y. pestis* dissemination in the body and effective transmission to a new flea. The questions presented with the model in Figure 1 remain unanswered

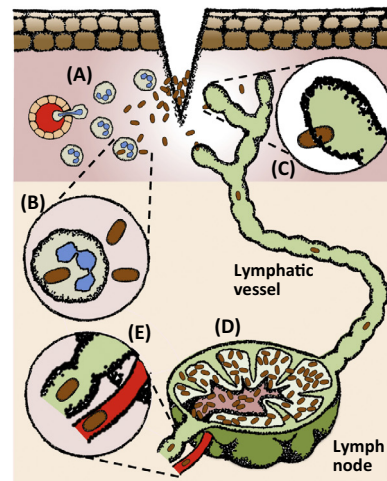
triggering replication and/or the synthesis of proteins to fight host defenses. One of these proteins might be the protease Pla, regarded as critical for *Y. pestis* proliferation in the dLN [9].

reach the bloodstream. Bacterial dissemination into blood results in sepsis, a systemic inflammatory response that can lead to septic shock and death.

The LN is the organ most associated with *Y. pestis* and bubonic plague. We propose that it is in this tissue (and not in the skin) where the fate of an infected individual is defined. For this reason, we propose that elucidating LN colonization is a high priority for the field.

**Escaping Heaven to Cause Havoc**

*Y. pestis* must escape the LN and enter systemic circulation as only then can a naïve flea acquire the bacterium and transmit it to a new host [10]. How *Y. pestis* escapes the dLN is unknown. However, two possible mechanisms are (i) escape through efferent lymphatic vessels, to eventually drain into the subclavian vein, and (ii) escape through the LN vasculature, ruptured as a result of LN colonization. The use of genetically tagged bacteria revealed a reduction in the number of tags in the spleen (used to assess systemic dissemination) in comparison with tags in the LN [3]. This second bottleneck is a barrier the bacteria pass to



- Do the bacteria that remain in the skin play a role during infection?
- How do neutrophils control bacterial proliferation in the skin and how do the bacteria prevent infection clearance at this site?
- What are the mechanisms that drive formation of each of the two dissemination bottlenecks?
- What host and bacterial factors account for the differences in bacterial proliferation between LN and skin?
- What host cells interact with *Y. pestis* in the dLN and how do these interactions affect the outcome of infection?
- How does *Y. pestis* escape the LN?
- What bacteria–host interactions occur in blood during systemic spread and how do they contribute to disease?

Trends in Microbiology

**Figure 1. Dissemination of *Yersinia pestis* in the Body during Bubonic Plague.** (1) Inoculation of *Y. pestis* (brown rods) into the dermal layer of the skin triggers the recruitment of neutrophils (light green cells with blue nuclei). The dermis (pink) appears below the epidermis (brown cuboidal cells). (2) In the dermis, *Y. pestis* interacts mostly with neutrophils. These cells control *Y. pestis* proliferation in the dermis but are unable to eliminate infection. (3) Dissemination-competent bacteria escape from the skin immediately after inoculation via lymphatic vessels (green) to reach the draining lymph node (dLN). (4) *Y. pestis* colonizes the lymph node (LN) at very high rates. (5) The bacteria escape the lymph node compartment into systemic circulation through efferent lymphatic vessels or via blood vessels (red). The questions at the right of the figure summarize areas of the field that need to be explored to obtain a more detailed picture of how *Y. pestis* disseminates in the body.

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