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Perspective

Yersinia Proteins That Target Host Cell Signaling Pathways

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Yersinia pestis, the causative agent of bubonic plague, is one of the most virulent bacterial pathogens known to mankind. This gram-negative bacterium is usually transmitted to humans by an infected rodent flea. After infection, the pathogen invades lymphatic tissue and proliferates in the lymph nodes. The two other human pathogenic species of *Yersinia*, *Y. enterocolitica* and *Y. pseudotuberculosis*, cause enteric infections that usually are self-limiting. These orally transmitted pathogens also proliferate in lymphatic tissue, and their primary site of infection is the lymphoid follicles of the small intestine. For a long time, *Yersinia* was considered to be an intracellular pathogen, but recent findings have shown that the pathogen proliferates in the extracellular fluid during infection and prevents its uptake process by professional phagocytes, a mechanism termed antiphagocytosis (1). This is a major virulence mechanism that is shared by the three pathogenic species, which possess a common conserved virulence plasmid that encodes ~ 11 secreted proteins, collectively called Yops (*Yersinia* outer proteins).[1] These Yops serve different functions during infection; some are directly involved as effector proteins attacking the host cell to prevent phagocytosis while other Yop proteins have regulatory functions. Thus, the Yops are key elements in *Yersinia* virulence enabling the pathogen to obstruct the nonspecific immune defense of the host.

The Yops are secreted to the surface of the bacteria by a plasmid encoded secretion system (*ysc*). This secretion apparatus constitutes ~ 22 proteins and recognizes a short NH_2-terminal signal sequence of the Yops that is not processed during secretion. The Ysc proteins show striking similarity with gene products involved in secretion of virulence determinants from a large variety of bacteria species including *Salmonella* and *Shigella* (1, 2). Interestingly, the secretion systems in *Salmonella*, *Shigella*, and *Yersinia* are functionally conserved (3, 4), indicating that these enteropathogens have evolved a common strategy to deliver virulence determinants attacking the host cell.

Upon contact with the eukaryotic cell, *Yersinia* translocates the Yop effectors across the plasma membrane into the cytosol while remaining bound to the host cell surface, implying that the Yop effectors have their respective molecular targets within the eukaryotic cell (5, 6). Although the pathogen is extracellularly located, the Yop effectors are solely found in the cytosol of the target cell (7). Therefore, it has been concluded that the secretion of the Yops is polarized and occurs only at the zone of contact between the pathogen and the eukaryotic cell. Accordingly, the pathogen senses the contact with the eukaryotic cell surface and transmits a signal focusing the secretion of Yop effectors to the zone of contact. The translocation process can be divided into three consecutive steps: (*a*) sensing target cell contact; (*b*) secretion of Yops from the bacterium to the site of interaction with the target cell; and (*c*) translocation of Yop effectors through the target cell plasma membrane.

Mutants of *Yersinia* have been isolated that have lost their ability to secrete and translocate the Yop effectors in a polarized manner, and they expel the Yops to the extracellular milieu. These mutants are defective in the expression of one particular Yop protein, YopN (1). It has been proposed that this surface-located protein gates the secretion apparatus and that physical contact between the pathogen and its target cell mediates the opening of the secretion channel only at the zone of contact between the cells (7). Thus, YopN may be a surface protein sensing the interaction between the bacterium and the eukaryotic cell. Moreover, intimate contact between the pathogen and the eukaryotic cell results in increased expression of Yop proteins. This cross-talk requires a functional secretion system linking the polarized Yop secretion with Yop regulation. One negative *yop* gene regulator, LcrQ, is secreted via the secretion apparatus, and based on this observation, the following model for the contact-dependent Yop regulation has been proposed. Contact between the pathogen and its target cell results in the opening of the gated secretion apparatus which allows rapid secretion of LcrQ. Consequently, the intracellular concentration of LcrQ is lowered, and the LcrQ-mediated repression of *yop* gene expression is thereby relieved resulting in increased Yop expression (8). This model explains how the bacterium coordinates polarized secretion with upregulation of Yop expression and suggests that these two regulatory events are controlled by the same YopN-mediated sensing mechanism.

Two additional Yop proteins, YopB and YopD, are essential for the translocation of the Yop effector proteins across the plasma membrane of the eukaryotic cell (5, 9). Thus, *yopB/D* mutants can secrete but cannot deliver the Yops into the cytosol. Instead, the Yop effectors are trapped between the bacterium and the target cell surfaces. While little is known about the functional role of YopD, the functional significance of YopB in the Yop translocation process has been identified.

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1. *Abbreviations used in this paper:* FAK, focal adhesion kinase; Yops, *Yersinia* outer proteins.

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Table I. Yop Proteins Involved in Virulence

	Protein	Molecular mass	Function
Translocated effector proteins	YopE	25 kD	Contact-dependent cytotoxin. Depolymerizes actin microfilament.
	YopH	51 kD	Protein tyrosine phosphatase. Dephosphorylates $p130^{Cas}$ and FAK.
	YpkA	82 kD	Serine/Threonine kinase.
	YopM	51 kD	Leucine-repeat protein. Protein–protein interactions?
Polarized transfer control/escort proteins	YopN	33 kD	Controls polarized secretion. Senses target cell contact? Gates the secretion channel?
	YopB	44 kD	Essential for translocation of Yops. Pore former.
	YopD	34 kD	Essential for translocation of Yops.

YopB contains two putative membrane-spanning regions which set it apart from other Yops, and additionally, YopB shows sequence similarities to pore-forming proteins of the repeat toxin (RTX) family of hemolysins and leukotoxins (10). In accordance with these observations, YopB affects the membrane integrity of eukaryotic cells and mediates a contact-dependent lysis of erythrocytes. It has been shown that YopB forms a pore in the target cell membrane (9). This observation has lead to the suggestion that the Yop effectors are translocated through this pore structure.

The Yop effector proteins YopH, YopE, YopM, and YpkA (Table I) are translocated into the eukaryotic target cell. All of these are essential for the virulence of the bacteria, and they are thought to interfere with different signal transduction pathways within the target cell. YpkA shares considerable sequence similarities with eukaryotic serine/threonine kinases (11). This effector localizes to the inner surface of the target cell plasma membrane and causes a contraction of the target cell while some peripheral attachment sites remain attached to the underlying substratum giving the affected cell a stellate shape (12). Although the molecular target for this kinase has not been identified, it is predicted to be a membrane-associated molecule involved in cytoskeletal regulation.

The Yop proteins directly involved in antiphagocytosis are YopE and YopH (1). These Yops affect a general phagocytic mechanism, including uptake involving β1-integrin interactions as well as uptake mediated via Fc receptors and complement receptors (13, 14). This blocking effect of *Yersinia* is not restricted to professional phagocytes; other normally nonphagocytic cells are affected in a similar manner by the pathogen. For instance, plasmid-cured strains of *Y. pseudotuberculosis* are internalized by HeLa cells, whereas strains that express, secrete, and translocate YopH and YopE block the uptake and remain bound to the external surface of the cell (7, 15).

YopE possess considerable sequence similarities to the NH_2-terminal noncatalytical region of the ADP-ribosylating enzyme exoenzyme S of *Pseudomonas aeruginosa* (16). This Yop effector disrupts the F-actin network of the target cell, but the molecular mechanisms underlying this effect are not known. Since there is no direct effect of YopE on F-actin in vitro (15), it has been suggested that this effector targets an F-actin regulatory molecule. Given the homology with exoenzyme S, it is possible that YopE targets small GTP-binding proteins, since exoenzyme S has been shown to modify these signaling molecules (17).

The other effector involved in antiphagocytosis, YopH, is homologous to eukaryotic tyrosine phosphatases (18) and has the highest activity of all tyrosine phosphatases known today (19). High expression of YopH alone is sufficient to block internalization of the bacteria (20). Individual bacteria are responsible for blocking their own internalization, and therefore, the YopH-mediated effect occurs immediately after the pathogen has attached to the target cell surface. In the absence of YopH, the bacterium is internalized, and the uptake is mediated by a mechanism that involves the interaction between the chromosomally encoded bacterial protein invasin and β1-integrins of the eukaryotic cell (13, 21, 22). Notably, the uptake of *Yersinia* by nonphagocytic cells resembles that of professional phagocytes in being a tyrosine kinase–dependent process (21, 23). Therefore, it is likely that YopH acts by dephosphorylating phosphotyrosine proteins involved in the initial signal transduction events triggering the uptake of bacteria.

The molecular targets for YopH were recently identified as $p130^{Cas}$ (Crk-associated substrate) and focal adhesion kinase (FAK) using HeLa cells as a model system (20). YopH, lacking tyrosine phosphatase activity, was shown to interact with tyrosine phosphorylated forms of $p130^{Cas}$ and FAK, while wild-type YopH specifically dephosphorylated these proteins. In agreement with this observation, the YopH mutant protein colocalizes with $p130^{Cas}$ and FAK proteins at the peripheral focal adhesion structures, whereas active YopH rapidly disrupts these structures (20).

Both FAK and $p130^{Cas}$ are known as focal adhesion proteins that become tyrosine phosphorylated upon β1-integrin stimulation (24–26). Focal adhesions are multimolecular complexes that link integrins bound to extracellular ligands to the underlying cytoskeleton. In these complexes, the clustered integrins are associated with a large number of cytoplasmic-derived molecules that exhibit structural or signaling functions (27). The components participate in a variety of signaling events stimulated by ligand-mediated clustering of integrins.

FAK is a focal adhesion protein involved in the integrin-mediated signaling cascade (28). This kinase interacts with and mediates phosphorylation of several proteins and therefore is

believed to function as a signal amplifier/transmitter. The localization of FAK to focal adhesions is mediated by its COOH-terminal domain, which is distinct from its integrin-binding domain. Targeting of FAK to focal adhesions is a phosphotyrosine-independent event, and the activity of the kinase is stimulated by a mechanism involving interactions with integrins (28). FAK binds to p130^{Cas} via an interaction between its proline-rich sequence and a COOH-terminal SH3-domain of p130^{Cas} (29). The p130^{Cas} protein is an adaptor protein that in addition to this SH3-domain contains SH3-binding sites and several putative tyrosine phosphorylation sites that can serve as binding sites for SH2-containing molecules (30). Accordingly, these structural features allow p130^{Cas} to regulate the assembly of a variety of signaling complexes (31).

The fact that p130^{Cas} and FAK constitute targets for YopH indicates that they are important players in the mechanism mediating uptake of *Yersinia.* The interaction between the invasin-expressing bacteria and the target cell results in occupancy and clustering of the β1-integrin receptors, a condition that generates a phosphotyrosine signal that is essential for linkage of β1-integrins to F-actin via focal adhesion-like structures (27). Interestingly, infection with *Yersinia,* which interacts with β1-integrins located at the edges of HeLa cells (15), stimulates an invasin-dependent tyrosine phosphorylation of both p130^{Cas} and FAK. Furthermore, this phosphorylation is associated with the recruitment of these proteins to the focal adhesion structures lining the edges of the cell (20). The infection-induced tyrosine phosphorylation of p130^{Cas} and FAK and the associated recruitment of these proteins to sites close to where the bacteria bind strengthen the hypothesis that phosphorylated forms of these proteins participate in the uptake of bacteria. It could be hypothesized that the assembly of p130^{Cas} and FAK into these sites mediates signaling to the underlying cytoskeleton resulting in actin reorganization that enables uptake of the bacteria (Fig. 1). Notably, enrichment of focal adhesion proteins in complexes lining the cell periphery represents focal adhesions under formation, and interesting in this context is the recent finding that inhibition of FAK tyrosine phosphorylation impairs formation of such structures (32). In the presence of active YopH, the bacteria remain bound to the outer surface of the affected cells, p130^{Cas} and FAK are dephosphorylated, and the recruitment of these proteins to peripheral focal adhesion structures is totally abolished (20). This suggests that the site of action of YopH is focal adhesion structures under formation. This formation occurs in regions close to where the bacterium binds and injects the tyrosine phosphatase into the target cell. This is in line with previous findings showing that endogenous disassembly of focal adhesion structures involves tyrosine phosphatase activity and occurs during processes that require cells to detach from the interacting surface (33).

Also in macrophages, the inactive YopH protein specifically recognizes and interacts with tyrosine phosphorylated p130^{Cas} (Carballeira, N., and M. Fällman, unpublished data). This is of particular interest since YopH, in addition to inhibiting invasin-stimulated phagocytosis, also blocks phagocytosis mediated by either complement receptors (β2-integrin receptors; 14) or Fc receptors (13). Interestingly, these receptors also mediate phosphorylation of FAK or p130^{Cas} upon stimulation (34, 35). Consequently, p130^{Cas} seems to be a key protein involved in a general phagocytic mechanism important for the uptake of bacteria by professional as well as nonprofessional phagocytes. Tellingly enough, *Yersinia* has chosen this adaptor protein as a suitable target to obstruct phagocytosis.

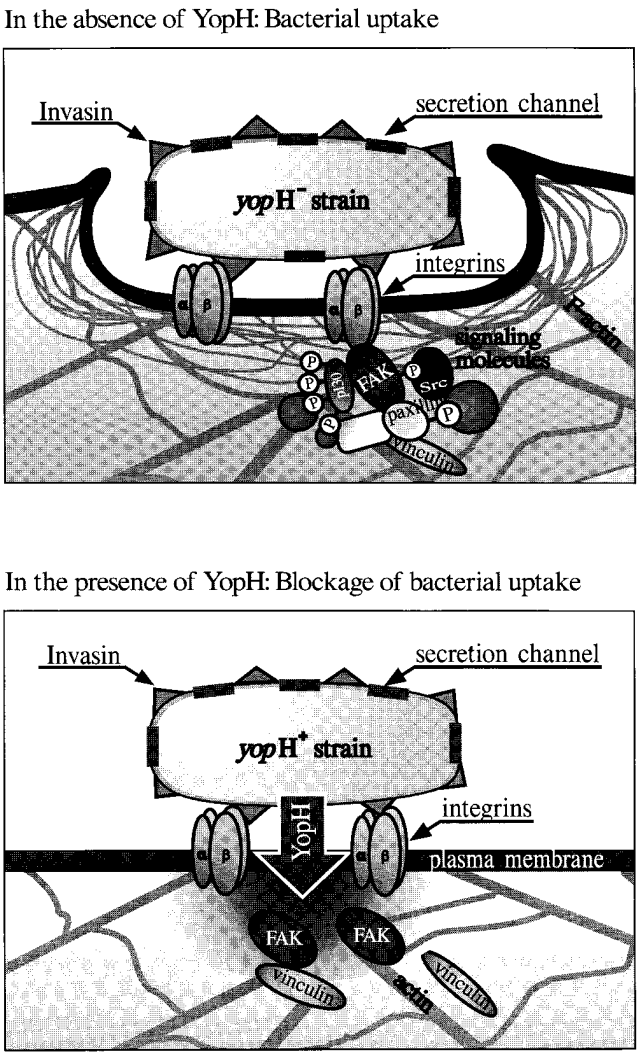

Figure 1. Yersinia block uptake of bacteria by eukaryotic cells. In the absence of YopH the bacterium is internalized, and the uptake is stimulated by interactions of the bacterial protein invasin with β1-integrins on the surface of the target cell. These interactions result in clustering of the integrins and at least two focal adhesion proteins, FAK and p130^{Cas}, are tyrosine phosphorylated and recruited to focal adhesion structures in the vicinity of the bacteria. The assembly of these structures mediates a signal that results in actin reorganization enabling uptake of the bacteria. Upon infection with a *Yersinia* strain that expresses YopH, the bacterium binds to the eukaryotic cell surface from where it secretes and translocates Yops across the plasma membrane only at the zone of contact. YopH is injected into the cytosol at the site of interaction between the pathogen and the cell, and p130^{Cas} and FAK are rapidly dephosphorylated. Consequently, p130^{Cas} and FAK are not recruited to the site of interaction and the bacterial uptake is abolished.

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