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Tyrosine kinases required for *Pseudomonas aeruginosa*invasion

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Keywords

CFTR, epithelial cells, invasion, *P. aeruginosa*, Src-like tyrosine kinases

Context

The mechanism by which *Pseudomonas aeruginosa* invades host epithelial cells is not known. Other bacterial pathogens have been shown to co-opt the host cells' tyrosine kinase signalling, particularly Src-like tyrosine kinase pathways, probably to induce cytoskeletal remodelling. A previous study by Evans et al (see Additional information) implicated Src tyrosine kinases in *P. aeruginosa* invasion of corneal epithelium. The specific aim of this study was to demonstrate the role of Src-like tyrosine kinases in P. aeruginosa invasion of human epithelial cells.

Significant findings

Invasion of conjuctival or pulmonary epithelial cells by *P. aeruginosa* induced rapid, marked tyrosine phosphorylation of several proteins. Phosphorylation of p59Fyn and p60Src was demonstrated to increase fourfold to fivefold within 10 min of infection and to peak within 15-45 min. Tyrosine phosphorylation was specific to invasion of the host cells, and not simply a consequence of generalized bacterial adherence. Preincubation of bacteria with an invasion-specific receptor (cystic fibrosis transmembrane regulator [CFTR]) peptide blocked both invasion and phosphorylation without preventing attachment of bacteria to epithelial cells. The Src-like tyrosine kinase inhibitor compounds herbimycin A and PP1 significantly reduced bacterial entry for all tested bacterial strain/cell type/drug combinations. The authors concluded the following: firstly, both p60Src and p59Fyn are involved in invasion of human epithelial cell lines by *P. aeruginosa*; secondly, the specific binding of bacteria to CFTR is a prerequisite for invasion; and, thirdly, that tyrosine kinase activation is required for (but not a result of) entry since blocking phosphorylation abrogates internalization of the bacteria.

Comments

Evans *et al* showed that invasive strains of *P. aeruginosa* induce tyrosine phosphorylation in host cells. This work confirms their observations and links the requirement for binding to CFTR (as opposed to generalized adhesion) to initiation of the internalization event. There are definitely some missing links remaining, however; in similar bacterial systems, injection of specific proteins into the host cell via type III secretion systems is necessary to trigger activation of the tyrosine kinases and subsequent internalization events. While the authors acknowledge the potential involvement of type III secretion, it would be interesting to see this type of work performed with defined type III secretion mutants in an attempt to further discriminate the events leading to invasion. Also, the relevance of the requirement for CFTR binding for invasion with respect to cystic fibrosis (where CFTR is often missing) needs to be further explored. As an interesting parallel to this work, interaction of epithelial cells with *P. aeruginosa* lipopolysaccharide (which also binds CFTR) was previously shown by, Li *et al*, (see Additional information), to result in upregulation of mucin production via a Src-dependent pathway.

Methods

Cell culture, polymyxin protection assays, phosphotyrosine western blot and immunoprecipitation

Additional information

Evans DJ, Frank DW, Finck-Barbancon V, Wu C, Fleiszig SM: ***Pseudomonas aeruginosa*** **invasion and cytotoxicity are independent events, both of which involve protein tyrosine kinase activity.**

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Li J-D, Feng W, Gallup M, Kim J-H, Gum J, Kim Y, Basbaum C: **Activation of NF-?B via a Src-dependent Ras-MAPK-pp90rsk pathway is required for *Pseudomonas aeruginosa* -induced mucin overproduction in epithelial cells.**

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