Species-specific interactions of Src family tyrosine kinases regulate Chlamydia intracellular growth and trafficking.

Cherilyn A Elwell, Arlinet Kierbel, Joanne N Engel

To cite this version:

HAL Id: pasteur-00685238
https://hal-riip.archives-ouvertes.fr/pasteur-00685238
Submitted on 25 Jun 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Species-Specific Interactions of Src Family Tyrosine Kinases Regulate Chlamydia Intracellular Growth and Trafficking

Cherilyn A. Elwell, Arlinet Kierbel and Joanne N. Engel

Updated information and services can be found at:
http://mbio.asm.org/content/2/3/e00082-11.full.html

This article cites 22 articles, 7 of which can be accessed free at:
http://mbio.asm.org/content/2/3/e00082-11.full.html#ref-list-1

Receive: RSS Feeds, eTOCs, free email alerts (when new articles cite this article), more>>
COMMENTS

Species-Specific Interactions of Src Family Tyrosine Kinases Regulate Chlamydia Intracellular Growth and Trafficking

Cherilyn A. Elwell, Arlin Kierbel, and Joanne N. Engel

Departments of Medicine and Microbiology and Immunology, Microbial Pathogenesis and Host Defense Program, University of California, San Francisco, California, USA, and Institut Pasteur de Montevideo, Montevideo, Uruguay

ABSTRACT Src family kinases (SFKs) regulate key cellular processes and are emerging as important targets for intracellular pathogens. In this commentary, we briefly review the role of SFKs in bacterial pathogenesis and highlight new work on the role of SFKs during the intracellular cycle of Chlamydia species.

Src family tyrosine kinases (SFKs) are cytoplasmic tyrosine kinases that participate in a vast range of physiological functions, including cell proliferation and survival, regulation of the cytoskeleton, cell shape control, maintenance of normal intercellular contacts, cell matrix adhesion dynamics, motility, and migration. Although some family members are ubiquitously expressed (e.g., c-Src, Yes, and Fyn), others show more restricted patterns of expression. Many cell types express multiple SFKs. Selective tyrosine phosphorylation allows SFK members to switch between an inactive “closed” conformation and a catalytically active “open” configuration, releasing the Src homology (SH) domains, SH2 and SH3, from intramolecular interactions. In the open conformation, the SH2 and SH3 domains bind to heterologous molecular partners and enables the kinase domain tyrosine phosphorylate substrates.

SFKs play key roles in the pathogenesis of diverse intracellular pathogens, including viruses, parasites, and bacteria. For example, SFK-mediated phosphorylation of cortactin plays a role in Shigella entry and the internalization of Listeria monocytogenes. Upon binding of enteropathogenic Escherichia coli (EPEC) to host cells, the translocated EPEC receptor TIR is phosphorylated by c-Fyn, triggering actin polymerization and pedestal formation. Src and Lyn have been shown to tyrosine phosphorylate the Helicobacter pylori type IV-secreted effector CagA, allowing it to bind and activate the tyrosine phosphatase SHP-2, resulting in changes in the host cell morphology. Thus, SFKs are targeted by numerous pathogens in order to achieve an array of consequences ranging from inducing local actin polymerization to altering cell morphology.

SFKs are also important during many steps of infection by the obligate intracellular parasite Chlamydia. Upon bacterial attachment, Chlamydia trachomatis uses its type III secretion apparatus to inject a multifunctional protein with actin-nucleating activity, called TARP (translocated actin-recruiting phosphoprotein), which is phosphorylated by SFKs and other tyrosine kinases, such as Abi kinase. Although tyrosine phosphorylation of TARP is not required for bacterial internalization, it is postulated to allow the protein to function as a scaffold for recruitment of host proteins that modulate actin dynamics as well as for recruitment of host proteins that regulate signaling events necessary during early development.

Recent exciting studies by Mital and coworkers indicate that SFK recruitment to the inclusion is not conserved in all species of Chlamydia. Rather, SFK recruitment appears to be a feature shared only by the human-adapted species C. pneumoniae and C. trachomatis and not by Chlamydia muridarum or Chlamydia caviae (GPIC), which infect mice or guinea pigs, respectively. In a recent issue of mBio, Mital and Hackstadt extended their studies and reported that the strain-dependent recruitment of SFKs to human-adapted chlamydial species exhibits unique requirements for SFKs throughout their developmental cycle.

Published 17 May 2011
Copyright © 2011 Elwell et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported License, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original author and source are credited.
Address correspondence to Joanne N. Engel, jengel@medicine.ucsf.edu.
creased activation of SFKs. Although SFKs are not required for binding and entry of C. trachomatis or for Inc microdomain formation, the authors show that SFKs are required for microtubule-dependent trafficking of the inclusion to the MTOC and for intracellular growth. Of note, the requirement of SFKs for intracellular growth is separate from the requirement of SFKs for trafficking along microtubules. This observation suggests that SFKs may serve multiple functions during C. trachomatis infection. Remarkably, the two nonhuman species, C. caviae and C. muridarum, which fail to display active SFK recruitment to inclusions, also do not traffic to the MTOC, prompting the hypothesis that SFK recruitment correlates with trafficking to the MTOC. Furthermore, C. caviae and C. muridarum do not display the developmental defects observed with C. trachomatis in SFK-deficient cells. Instead, inhibition of SFKs actually enhances the intracellular replication of C. caviae and C. muridarum, suggesting that the growth of nonhuman strains may instead be restricted by SFKs. The authors speculate that species-specific utilization of SFKs may represent a novel mechanism for defining host tropism.

These new observations raise several interesting questions. First, how do SFKs regulate microtubule-dependent trafficking to the MTOC? Src and Fyn have been shown to interact with gamma-tubulin and to regulate microtubule nucleation from membranes (Fyn) and from centrosomes (Src) (21–23). It is possible that SFKs cooperate with both host and bacterial proteins within the specialized microdomains on the inclusion surface to control trafficking along microtubules and to promote proper positioning of the inclusion at the centrosome. Second, how are SFKs activated and recruited to the inclusion, and what accounts for their unusual distribution to a few discrete subdomains on the inclusion? Do the Incs interact directly with activated SFKs, or are other proteins involved in their interactions? Is SFK activity required for interaction with dynein and/or centrosomes? One attractive hypothesis is that one or more of the Incs present in the microdomains recruit active SFKs to the inclusion, thus promoting microtubule nucleation and dynein-dependent movement toward the MTOC, where upon arrival, Inc850 then binds centrosomes for proper positioning. Third, what accounts for the species specificity? The diverse requirements of SFKs for human versus nonhuman strains are particularly exciting because genomic comparisons of Chlamydia species have yielded little insight into specific virulence determinants associated with disease. It will be interesting to determine whether the specific Incs that colocalize with SFKs within the microdomains display species-specific binding and activation of Src and/or Fyn or are differentially expressed in the nonhuman strains, as this could account for the observed SFK dependencies. Fourth, what is the nature of the developmental defect observed in the absence of SFKs for the human-adapted strains? Finally, how do SFKs restrict the growth of nonhuman species? Do active SFKs enhance the innate immune response, affect accessibility to nutrients, or regulate general host protein trafficking during infection of the nonhuman strain?

Studying the role of SFKs during Chlamydia infection will likely lead to a better understanding of how SFKs regulate microtubule-dependent trafficking in normal host cells and shed light on the unique ways that pathogens subvert host cell signaling. Furthermore, the ability of Chlamydia to alter centrosome positioning and cause deregulation of centrosome duplication (20, 24) may also provide insights into the pathways leading to chromosome instability during deregulated states, such as cancer. Once again, pathogens serve as tutors to help us understand complex but fundamental cellular processes.

REFERENCES