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Jordan Wesolowski
Thomas Jefferson University

Fabienne Paumet
Thomas Jefferson University

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REVIEW

Taking control: reorganization of the host cytoskeleton by *Chlamydia* [version 1; referees: 5 approved]

Jordan Wesolowski, Fabienne Paumet 

Department of Microbiology and Immunology, Thomas Jefferson University, Philadelphia, PA, 19107, USA

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Abstract

Both actin and microtubules are major cytoskeletal elements in eukaryotic cells that participate in many cellular processes, including cell division and motility, vesicle and organelle movement, and the maintenance of cell shape. Inside its host cell, the human pathogen *Chlamydia trachomatis* manipulates the cytoskeleton to promote its survival and enhance its pathogenicity. In particular, *Chlamydia* induces the drastic rearrangement of both actin and microtubules, which is vital for its entry, inclusion structure and development, and host cell exit. As significant progress in *Chlamydia* genetics has greatly enhanced our understanding of how this pathogen co-opts the host cytoskeleton, we will discuss the machinery used by *Chlamydia* to coordinate the reorganization of actin and microtubules.

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Corresponding author: Fabienne Paumet (Fabienne.Paumet@jefferson.edu)

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Introduction

The *Chlamydiaceae* constitute a family of obligate intracellular bacteria that encompasses numerous species. With ~92 million new cases/year worldwide, *Chlamydia trachomatis* is the most frequent cause of bacterial sexually transmitted infections and is the leading cause of preventable infectious blindness called trachoma^{1–3}. Trachoma is a significant problem in the developing world, where access to healthcare is limited and antibiotics are scarce. *Chlamydia* infections are also associated with chronic diseases and increased risk for cervical cancer^{4,5}, making this infection a significant socioeconomic and medical burden in both developed and developing countries.

Chlamydiae exhibit a unique biphasic life cycle, cycling between a metabolically inactive but infectious small elementary body (EB ~200 nm) and a noninfectious metabolically active and dividing large reticulate body (RB ~800 nm)⁶. *Chlamydia* spends the majority of its life as an intracellular RB. Soon after invasion, EBs differentiate into RBs and replicate within a membrane-bound compartment called an “inclusion”. This obligate intracellular lifestyle required *Chlamydia* to develop an effective strategy to manipulate host cell pathways in order to ensure its survival and replication. Among the many pathways that *Chlamydia* co-opts, a common and intriguing target for all *Chlamydia* species has emerged: the host cytoskeleton⁷. We will discuss the recent advances concerning the role played by the host cytoskeleton in the growth and structural maintenance of the chlamydial inclusion (see Figure 1).

***Chlamydia trachomatis* recruits actin to enter its host cell and uses microtubules to travel to the microtubule-organizing center**

Because of their obligate intracellular nature, Chlamydiae have evolved very efficient ways to enter eukaryotic cells (Figure 1A). During infection, EBs attach to the host cell surface via a relatively weak electrostatic interaction with heparan sulfate moieties⁸. Then a stronger and more specific binding to a cellular receptor takes place, during which the majority of the EBs are internalized via an actin-dependent event⁹. While a number of receptors have been identified, including PDGFR β , β 1-integrin, and Ephrin A2, depletion of a single receptor is not sufficient to block entry, suggesting that *Chlamydia* utilizes more than one receptor to invade its host cell^{10,11}.

To promote entry into non-phagocytic epithelial cells, *C. trachomatis* delivers a translocated actin-recruiting phosphoprotein (Tarp, also known as CT456)^{12–14} into the host cytoplasm (Figure 1A). In a phosphorylation-dependent manner, Tarp recruits guanine nucleotide exchange factors that activate Rac1, a member of the Rho family of GTPases^{9,10,13,15}. Whereas *Chlamydia caviae* uses both Rac1 and Cdc42 to promote its entry, *C. trachomatis* recruits only Rac1, and not Cdc42 or RhoA^{16,17}. Hijacking only one Rho GTPase family member is unique to *C. trachomatis*, as other intracellular bacteria including *Salmonella* and *Shigella* usually use multiple isoforms such as RhoA and Cdc42^{18–20}. In addition to its Rac1 recruitment function, Tarp also directly binds to actin monomers and nucleates new unbranched actin filaments^{21,22}. These linear filaments are then branched via the host Arp2/3 complex, which is activated by the

Rac1 signaling pathway^{9,13}. Thus, Tarp functions as both an actin nucleator and a signaling platform to locally remodel the actin cytoskeleton and promote *Chlamydia* invasion.

Nascent *C. trachomatis*-containing inclusions then use the minus-end-directed microtubule motor dynein to move from the cell periphery to the microtubule-organizing center (MTOC), where the inclusion resides for the duration of the life cycle²³ (Figure 1B). This is a pathogen-driven event in which the inclusion protein CT850 is involved through its interaction with the dynein light chain DYNLT1²⁴. At the MTOC, Src family kinases control the tight association between inclusions and centrosomes²⁵. Additional inclusion proteins including IncB, CT101, and CT222 are concentrated at these contact points between inclusions and centrosomes, suggesting their potential contribution to the transport of the inclusion²⁴. In fact, during *Chlamydia psittaci* infection, IncB has been shown to interact with Snapin, which also binds dynein, thus connecting the inclusion to the microtubule network²⁶. The association of inclusions with the MTOC is a common characteristic for a number of *Chlamydia* species, suggesting that this event is essential for *Chlamydia*'s life cycle. One possibility is that the MTOC brings host organelles and chlamydial inclusions in close proximity, thus facilitating the transfer of nutrients and lipids from the host to the inclusion. Additionally, the clustering of the inclusions at the MTOC is necessary for the homotypic fusion of inclusions to take place during *C. trachomatis* infection, as the dissociation of the inclusions from the MTOC inhibits this fusion event²⁷. Homotypic fusion is critical for *C. trachomatis* pathogenicity, as non-fusing mutants grow significantly slower than their wild-type counterparts^{28,29}. In particular, *C. trachomatis* strains that do not undergo homotypic fusion are also replication-defective and cause significantly milder disease in humans^{28–30}. Given the importance of microtubule-based transport of the inclusion in *Chlamydia* development, additional unidentified *Chlamydia* effectors are likely involved in this process.

***Chlamydia* creates microtubule cages to support the development of its inclusion**

Around 12 hours post-infection (PI), microtubules likely assemble around the inclusion under the control of the chlamydial effector CT223/IPAM, which has been shown to alter microtubule organization through the host centrosomal protein of 170 kDa (CEP170) in transfected cells³¹ (Figure 1C). There, microtubules encasing the inclusion are stabilized, which allows them to undergo post-translational modifications (PTMs), including detyrosination and acetylation^{32,33} (Figure 1D). These PTMs influence microtubule structure and depolymerization rates³⁴ and have been implicated in the relocation of the Golgi apparatus around the chlamydial inclusion^{32,33}. In most cells, dynamic microtubules have a half-life of about 5–10 minutes, while modified microtubules can persist for hours³⁵, suggesting that *Chlamydia* uses these PTM microtubules to establish a stable long-term relationship with its host. Detyrosination is the best-characterized modification and involves the removal of the carboxy-terminal tyrosine from α -tubulin by tubulin carboxypeptidase, thus exposing a glutamic acid as the new C-terminus³⁶.

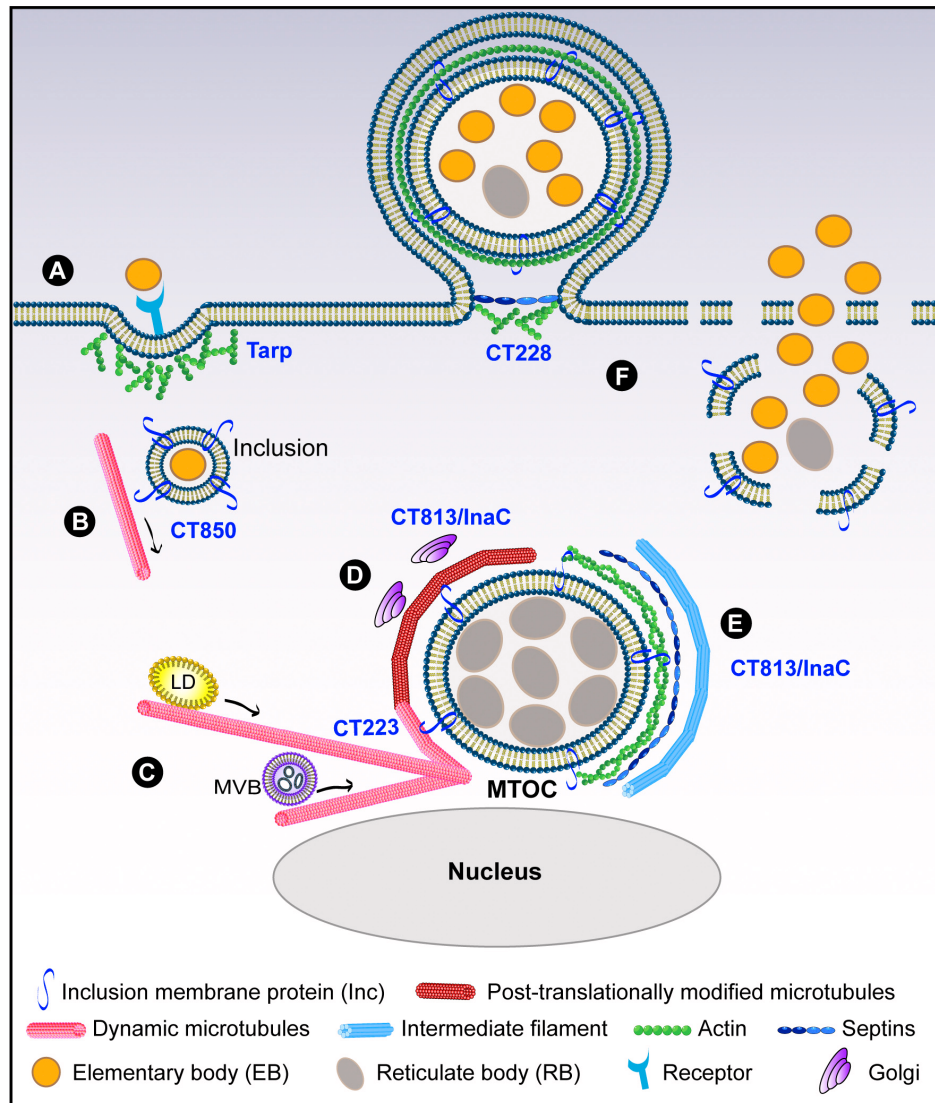


Figure 1. Reorganization of the host cytoskeleton during *Chlamydia trachomatis* infection. (A) Entry during which a translocated actin-recruiting phosphoprotein (Tarp) induces actin polymerization; (B) transport of the nascent inclusion to the microtubule-organizing center (MTOC) using CT850; (C) formation of microtubule cages around the inclusion, in which CT223 is likely involved, and microtubule-dependent movement of lipid droplets (LDs) and multi-vesicular bodies (MVBs) towards the inclusion; (D) post-translational modifications of microtubule cages and positioning of Golgi mini-stacks around the inclusion controlled by CT813/InaC; (E) structural scaffolds of actin, septins, and intermediate filaments reinforce the growing inclusion membrane in a CT813-dependent manner; (F) *Chlamydia* exits the host cell using CT228-dependent extrusion (left) or through cell lysis (right).

Interestingly, stable microtubules are involved in the repositioning of organelles. During infection, the Golgi is a major source of host lipids, including sphingomyelin and cholesterol^{37–40}. To enhance access to these lipids, *Chlamydia* induces the fragmentation of the Golgi into mini-stacks, which are then recruited around the inclusion in a microtubule-dependent manner^{32,41} (Figure 1D). In addition to controlling Golgi positioning, deetyrosinated microtubules are involved in other trafficking events, including the recycling of endocytosed transferrin⁴²

and the dispersal of lipid droplets⁴³, which are also co-opted by *Chlamydia*^{39,44}. Lipid droplets and multi-vesicular bodies are redirected towards the chlamydial inclusion along microtubules to provide fatty acids, which are important for *Chlamydia* replication^{39,40,44,45} (Figure 1C). The endoplasmic reticulum (ER) has also been associated with stable microtubules, in particular acetylated microtubules, along which ER tubules slide⁴⁶. *Chlamydia* hijacks the ER and promotes the formation of ER-inclusion contact sites, which are important for the transfer

of lipids to the inclusion^{47–49}. During *Chlamydia* infection, the acetylated microtubules that surround the inclusion could enable the ER to slide towards the inclusion, thus allowing IncD/CERT to interact with the ER-resident proteins VAPA/VAPB and form ER-inclusion contact sites^{47,48}. Although treatment with nocodazole, which disrupts microtubules, failed to prevent ER accumulation around the inclusion⁴⁹, acetylated microtubules are notoriously resistant to nocodazole treatment and may still be present following treatment.

Recently, we have shown that the chlamydial protein CT813 (also called InaC⁵⁰) is critical for promoting microtubule modifications during infection through its interaction with and activation of the small host GTPases ARF1 and ARF4³³, supporting prior data showing interactions between CT813 and ARF proteins⁵⁰ (Figure 1D). It is unclear how the CT813:ARF complex is able to influence microtubule PTMs. However, inhibitors of RhoA and ROCK (Rho-associated protein kinase) decrease the number of inclusions associated with stable microtubules, suggesting that both of these proteins are involved in this process³². There is evidence demonstrating that RhoA triggers microtubule stabilization via its interaction with the mammalian homolog of Diaphanous (mDia). The activation of mDia generates capped microtubules, thus preventing catastrophic microtubule disassembly^{51,52}. Interestingly, DIAPH2 was identified in an RNAi screen in *Drosophila* S1 cells as important for chlamydial inclusion development¹⁰. It would be interesting to determine whether *C. trachomatis* co-opts mDia to stabilize microtubules and generate the post-translationally modified microtubule cages around the inclusion, particularly since mDia is also involved in actin polymerization⁵³.

***Chlamydia trachomatis* builds actin scaffolds around its inclusion to promote inclusion stability**

As the inclusion continues to grow, actin and intermediate filaments associate with the inclusion⁵⁴ (Figure 1E). This association increases progressively from ~20 hours PI until the end of *Chlamydia*'s intracellular life cycle. Disruption of the actin cytoskeleton results in the rupture of the inclusion membrane and the leakage of *C. trachomatis* into the host cytoplasm, demonstrating that the maintenance of the inclusion's integrity requires intact actin cages⁵⁴. Interestingly, RhoA—but not ROCK—also plays a major role in this event, as it is recruited to the inclusion and its depletion results in a substantial loss of actin scaffolds around the inclusion⁵⁴.

The chlamydial protein CT813 is the only effector identified to date to regulate actin recruitment around the inclusion^{33,50} (Figure 1E). Interestingly, this function of CT813 appears to be independent of its role in regulating post-translationally modified microtubule cages, as the overexpression of CT813 in wild-type *Chlamydia* results in the loss of post-translationally modified microtubules but not actin cages³³. Together, these data suggest that both CT813 and RhoA participate in actin cage formation and microtubule stabilization. While microtubule stabilization also depends on ARF1/ARF4 and ROCK, actin polymerization

does not require ROCK. The role of ARF in the formation of actin cages remains unclear, as depletion of ARF does not affect actin polymerization³³.

Recently, the actin cytoskeleton has been implicated in Golgi reorganization during infection. Using chemical mutagenesis, it has been suggested that CT813 organizes Golgi mini-stacks around the inclusion through the formation of actin cages⁵⁰. However, a CT813-overexpressing *Chlamydia* strain that has actin but no post-translationally modified microtubule cages displays a defect in Golgi organization around the inclusion. This suggests that it is the CT813-dependent induction of post-translationally modified microtubule cages that controls Golgi organization³³. Therefore, the exact role of the actin cytoskeleton in organelle repositioning during *Chlamydia* infection is still unclear.

***Chlamydia* uses the actin cytoskeleton to exit host cells by extrusion**

Chlamydia exits the host cell through two mutually exclusive mechanisms: extrusion and cell lysis (Figure 1F, left and right, respectively). Note that to exit their host cells using the lytic process, *Chlamydia* must extricate themselves from the cytoskeleton structures that encase the inclusion, in particular the actin scaffold⁵⁵. Pgp4, a transcription factor encoded by the chlamydial plasmid, is essential for actin depolymerization prior to cell exit, as the deletion of this regulatory gene prevents actin disassembly and completely blocks *Chlamydia* exit⁵⁵. The chlamydial protease activity factor, which cleaves intermediate filaments, is also involved in cell exit, but it does not play a role in actin disassembly^{54–56}.

While the lytic pathway requires actin depolymerization to proceed, extrusion is regulated by an acto-myosin-mediated mechanism^{57,58}. Extrusion involves the protrusion of the intact membrane-bound inclusion out of the cell and the pinching off of the inclusion into a separate compartment. The resulting extruded inclusion is surrounded by the actin cytoskeleton⁵⁹, the host plasma membrane, and a thin layer of cytoplasm between plasma and inclusion membranes⁵⁷. Extrusion requires N-WASP-mediated actin polymerization and myosin II-dependent contraction of stable actin filaments^{57,58}. The septin family of cytoskeletal proteins regulates actin fiber formation on the inclusion membrane⁶⁰ through an unknown mechanism. Interestingly, RhoA is also involved in this process, where it specifically regulates the final stage of extrusion—pinching off and separation of the extrusion from the host cell⁵⁷.

The signals that dictate whether *Chlamydia* exits the host cell by lysis or extrusion are not well understood. However, the Chlamydial inclusion protein CT228 has been shown to play a central role in this process⁵⁸. CT228 recruits the MYPTI subunit of myosin phosphatase to microdomains on the inclusion membrane early during infection. MYPTI-mediated phosphorylation of myosin light chain II (MLC2) favors extrusion-mediated exit, while the depletion or dephosphorylation of MLC2 shifts the balance

towards the lytic pathway. Thus, *Chlamydia* establishes local cytoskeletal signaling networks on the inclusion membrane to direct its escape from the host cell.

Concluding remarks

Chlamydia has evolved efficient mechanisms to hijack essential components of the host cytoskeleton. The successful establishment of *Chlamydia*'s intracellular niche and dissemination of infectious progeny relies on the proper spatial and temporal control of both actin and microtubules. To orchestrate this balance, *Chlamydia* employs effector proteins to recruit host proteins to the inclusion membrane and modulate the activity of host cytoskeletal signaling networks. Recent work has only begun to shed light on the identity of these chlamydial effector proteins.

Almost a decade ago, an RNAi screen in *C. trachomatis*-infected *Drosophila* cells revealed the importance of numerous host cytoskeleton-associated proteins in inclusion development, supporting the critical role of the cytoskeleton during infection¹⁰. However, limited mechanistic information regarding the role of chlamydial effector proteins in this process was available owing to the intractability of *Chlamydia* to genetic manipulation. Recent advances in *Chlamydia* genetics and the expansion of the

Chlamydia genetic toolbox now provide the tools necessary to dissect the molecular pathways and the chlamydial effectors that control the interactions between the chlamydial inclusion and the host cytoskeleton. Identifying these mechanisms is important not only for understanding *Chlamydia* pathogenesis and developing novel therapeutics but also because it has the potential to identify new host cellular pathways that regulate the cytoskeleton.

Competing interests

The authors declare that they have no competing interests.

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References

1. WHO: **World Health Organization: Global prevalence and incidence of selected curable sexually transmitted infections overview and estimates.** Geneva, WHO. 2005.
2. Gerbase AC, Rowley JT, Mertens TE: **Global epidemiology of sexually transmitted diseases.** *Lancet.* 1998; 351 Suppl 3: 2–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. CDC: **Sexually Transmitted Disease Surveillance 2011.** Atlanta: US Department of Health and Human Services. 2012: 1–184.
[Reference Source](#)
4. Romano Carratelli C, Nuzzo I, Cozzolino D, et al.: **Relationship between *Chlamydia pneumoniae* infection, inflammatory markers, and coronary heart diseases.** *Int Immunopharmacol.* 2006; 6(5): 848–53.
[PubMed Abstract](#) | [Publisher Full Text](#)
5. Ezzahiri R, Stassen FR, Kurvers HR, et al.: ***Chlamydia pneumoniae* infections augment atherosclerotic lesion formation: a role for serum amyloid P.** *APMIS.* 2006; 114(2): 117–26.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Abdelrahman YM, Belland RJ: **The chlamydial developmental cycle.** *FEMS Microbiol Rev.* 2005; 29(5): 949–59.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Scidmore MA: **Recent advances in *Chlamydia* subversion of host cytoskeletal and membrane trafficking pathways.** *Microbes Infect.* 2011; 13(6): 527–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. Su H, Raymond L, Rockey DD, et al.: **A recombinant *Chlamydia trachomatis* major outer membrane protein binds to heparan sulfate receptors on epithelial cells.** *Proc Natl Acad Sci U S A.* 1996; 93(20): 11143–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. Carabeo RA, Grieshaber SS, Fischer E, et al.: ***Chlamydia trachomatis* induces remodeling of the actin cytoskeleton during attachment and entry into HeLa cells.** *Infect Immun.* 2002; 70(7): 3793–803.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
10. Elwell CA, Ceasay A, Kim JH, et al.: **RNA interference screen identifies Abl kinase and PDGFR signaling in *Chlamydia trachomatis* entry.** *PLoS Pathog.* 2008; 4(3): e1000021.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
11. Subbarayal P, Karunakaran K, Winkler A, et al.: **EphrinA2 receptor (EphA2) is an invasion and intracellular signaling receptor for *Chlamydia trachomatis*.** *PLoS Pathog.* 2015; 11(4): e1004846.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
12. Clifton DR, Fields KA, Grieshaber SS, et al.: **A chlamydial type III translocated protein is tyrosine-phosphorylated at the site of entry and associated with recruitment of actin.** *Proc Natl Acad Sci U S A.* 2004; 101(27): 10166–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
13. Jewett TJ, Miller NJ, Dooley CA, et al.: **The conserved Tarp actin binding domain is important for chlamydial invasion.** *PLoS Pathog.* 2010; 6(7): e1000997.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
14. Parrett CJ, Lenoci RV, Nguyen B, et al.: **Targeted Disruption of *Chlamydia trachomatis* Invasion by in Trans Expression of Dominant Negative Tarp Effectors.** *Front Cell Infect Microbiol.* 2016; 6: 84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
15. Jiwani S, Alvarado S, Ohr RJ, et al.: ***Chlamydia trachomatis* Tarp harbors distinct G and F actin binding domains that bundle actin filaments.** *J Bacteriol.* 2013; 195(4): 708–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. Carabeo RA, Grieshaber SS, Hasenkrug A, et al.: **Requirement for the Rac GTPase in *Chlamydia trachomatis* invasion of non-phagocytic cells.** *Traffic.* 2004; 5(6): 418–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Subtil A, Wyplosz B, Balaña ME, et al.: **Analysis of *Chlamydia caviae* entry sites and involvement of Cdc42 and Rac activity.** *J Cell Sci.* 2004; 117(Pt 17): 3923–33.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Hänisch J, Kölm R, Wozniczka M, et al.: **Activation of a RhoA/myosin II-dependent but Arp2/3 complex-independent pathway facilitates *Salmonella* invasion.** *Cell Host Microbe.* 2011; 9(4): 273–85.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
19. Suzuki T, Mimuro H, Miki H, et al.: **Rho family GTPase Cdc42 is essential for the actin-based motility of *Shigella* in mammalian cells.** *J Exp Med.* 2000; 191(11): 1905–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)



20. Patel JC, Galán JE: Investigating the function of Rho family GTPases during *Salmonella*/host cell interactions. *Meth Enzymol*. 2008; 439: 145–58.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Jewett TJ, Fischer ER, Mead DJ, *et al.*: Chlamydial TARP is a bacterial nucleator of actin. *Proc Natl Acad Sci U S A*. 2006; 103(42): 15599–604.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
22. Jiwani S, Ohr RJ, Fischer ER, *et al.*: *Chlamydia trachomatis* Tarp cooperates with the Arp2/3 complex to increase the rate of actin polymerization. *Biochem Biophys Res Commun*. 2012; 420(4): 816–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Grieshaber SS, Grieshaber NA, Hackstadt T: *Chlamydia trachomatis* uses host cell dynein to traffic to the microtubule-organizing center in a p50 dynamitin-independent process. *J Cell Sci*. 2003; 116(Pt 18): 3793–802.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
24. Mital J, Lutter EI, Barger AC, *et al.*: *Chlamydia trachomatis* inclusion membrane protein CT850 interacts with the dynein light chain DYNLT1 (Tctex1). *Biochem Biophys Res Commun*. 2015; 462(2): 165–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
25. Mital J, Hackstadt T: Role for the SRC family kinase Fyn in sphingolipid acquisition by chlamydiae. *Infect Immun*. 2011; 79(11): 4559–68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Böcker S, Heurich A, Franke C, *et al.*: *Chlamydia psittaci* inclusion membrane protein IncB associates with host protein Snapin. *Int J Med Microbiol*. 2014; 304(5–6): 542–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
27. Richards TS, Knowlton AE, Grieshaber SS: *Chlamydia trachomatis* homotypic inclusion fusion is promoted by host microtubule trafficking. *BMC Microbiol*. 2013; 13: 185.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Pannekoek Y, Spaargaren J, Langerak AA, *et al.*: Interrelationship between polymorphisms of incA, fusogenic properties of *Chlamydia trachomatis* strains, and clinical manifestations in patients in The Netherlands. *J Clin Microbiol*. 2005; 43(5): 2441–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Pannekoek Y, van der Ende A, Eijk PP, *et al.*: Normal IncA expression and fusogenicity of inclusions in *Chlamydia trachomatis* isolates with the incA I47T mutation. *Infect Immun*. 2001; 69(7): 4654–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. Suchland RJ, Rockey DD, Bannantine JP, *et al.*: Isolates of *Chlamydia trachomatis* that occupy nonfusogenic inclusions lack IncA, a protein localized to the inclusion membrane. *Infect Immun*. 2000; 68(1): 360–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
31. Dumoux M, Menny A, Delacour D, *et al.*: A *Chlamydia* effector recruits CEP170 to reprogram host microtubule organization. *J Cell Sci*. 2015; 128(18): 3420–34.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
32. Al-Zeer MA, Al-Younes HM, Kerr M, *et al.*: *Chlamydia trachomatis* remodels stable microtubules to coordinate Golgi stack recruitment to the chlamydial inclusion surface. *Mol Microbiol*. 2014; 94(6): 1285–97.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Wesolowski J, Weber MM, Nawrotek A, *et al.*: *Chlamydia* Hijacks ARF GTPases To Coordinate Microtubule Posttranslational Modifications and Golgi Complex Positioning. *mBio*. 2017; 8(3): pii: e02280-16
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. Peris L, Wagenbach M, Lafanechère L, *et al.*: Motor-dependent microtubule disassembly driven by tubulin tyrosination. *J Cell Biol*. 2009; 185(7): 1159–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
35. Webster DR, Gundersen GG, Bulinski JC, *et al.*: Differential turnover of tyrosinated and detyrosinated microtubules. *Proc Natl Acad Sci U S A*. 1987; 84(24): 9040–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
36. Westermann S, Weber K: Post-translational modifications regulate microtubule function. *Nat Rev Mol Cell Biol*. 2003; 4(12): 938–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Carabeo RA, Mead DJ, Hackstadt T: Golgi-dependent transport of cholesterol to the *Chlamydia trachomatis* inclusion. *Proc Natl Acad Sci U S A*. 2003; 100(11): 6771–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
38. Hackstadt T, Rockey DD, Heinzen RA, *et al.*: *Chlamydia trachomatis* interrupts an exocytic pathway to acquire endogenously synthesized sphingomyelin in transit from the Golgi apparatus to the plasma membrane. *EMBO J*. 1996; 15(5): 964–77.
[PubMed Abstract](#) | [Free Full Text](#)
39. Kumar Y, Cocchiaro J, Valdivia RH: The obligate intracellular pathogen *Chlamydia trachomatis* targets host lipid droplets. *Curr Biol*. 2006; 16(16): 1646–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Beatty WL: Trafficking from CD63-positive late endocytic multivesicular bodies is essential for intracellular development of *Chlamydia trachomatis*. *J Cell Sci*. 2006; 119(Pt 2): 350–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Heuer D, Rejman Lipinski A, Machuy N, *et al.*: *Chlamydia* causes fragmentation of the Golgi compartment to ensure reproduction. *Nature*. 2009; 457(7230): 731–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
42. Lin SX, Gundersen GG, Maxfield FR: Export from pericentriolar endocytic recycling compartment to cell surface depends on stable, detyrosinated (glu) microtubules and kinesin. *Mol Biol Cell*. 2002; 13(1): 96–109.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Herms A, Bosch M, Reddy BJ, *et al.*: AMPK activation promotes lipid droplet dispersion on detyrosinated microtubules to increase mitochondrial fatty acid oxidation. *Nat Commun*. 2015; 6: 7176.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
44. Cocchiaro JL, Kumar Y, Fischer ER, *et al.*: Cytoplasmic lipid droplets are translocated into the lumen of the *Chlamydia trachomatis* parasitophorous vacuole. *Proc Natl Acad Sci U S A*. 2008; 105(27): 9379–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
45. Gambarte Tudela J, Capmany A, Romao M, *et al.*: The late endocytic Rab39a GTPase regulates the interaction between multivesicular bodies and chlamydial inclusions. *J Cell Sci*. 2015; 128(16): 3068–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
46. Friedman JR, Webster BM, Mastrorade DN, *et al.*: ER sliding dynamics and ER-mitochondrial contacts occur on acetylated microtubules. *J Cell Biol*. 2010; 190(3): 363–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
47. Agaisse H, Derré I: STIM1 Is a Novel Component of ER-*Chlamydia trachomatis* Inclusion Membrane Contact Sites. *PLoS One*. 2015; 10(4): e0125671.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
48. Derré I, Swiss R, Agaisse H: The lipid transfer protein CERT interacts with the *Chlamydia* inclusion protein IncD and participates to ER-*Chlamydia* inclusion membrane contact sites. *PLoS Pathog*. 2011; 7(6): e1002092.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
49. Dumoux M, Clare DK, Saibil HR, *et al.*: *Chlamydiae* assemble a pathogen synapse to hijack the host endoplasmic reticulum. *Traffic*. 2012; 13(12): 1612–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
50. Kokes M, Dunn JD, Granek JA, *et al.*: Integrating chemical mutagenesis and whole-genome sequencing as a platform for forward and reverse genetic analysis of *Chlamydia*. *Cell Host Microbe*. 2015; 17(5): 716–25.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
51. Palazzo AF, Cook TA, Alberts AS, *et al.*: mDia mediates Rho-regulated formation and orientation of stable microtubules. *Nat Cell Biol*. 2001; 3(8): 723–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
52. Wen Y, Eng CH, Schmoranz J, *et al.*: EB1 and APC bind to mDia to stabilize microtubules downstream of Rho and promote cell migration. *Nat Cell Biol*. 2004; 6(9): 820–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
53. Copeland JW, Treisman R: The diaphanous-related formin mDia1 controls serum response factor activity through its effects on actin polymerization. *Mol Biol Cell*. 2002; 13(11): 4088–99.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. Kumar Y, Valdivia RH: Actin and intermediate filaments stabilize the *Chlamydia trachomatis* vacuole by forming dynamic structural scaffolds. *Cell Host Microbe*. 2008; 4(2): 159–69.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
55. Yang C, Starr T, Song L, *et al.*: Chlamydial Lytic Exit from Host Cells Is Plasmid Regulated. *mBio*. 2015; 6(6): e01648–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. Snaveley EA, Kokes M, Dunn JD, *et al.*: Reassessing the role of the secreted protease CPAF in *Chlamydia trachomatis* infection through genetic approaches. *Pathog Dis*. 2014; 71(3): 336–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
57. Hybiske K, Stephens RS: Mechanisms of host cell exit by the intracellular bacterium *Chlamydia*. *Proc Natl Acad Sci U S A*. 2007; 104(27): 11430–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. Lutter EI, Barger AC, Nair V, *et al.*: *Chlamydia trachomatis* inclusion membrane protein CT228 recruits elements of the myosin phosphatase pathway to regulate release mechanisms. *Cell Rep*. 2013; 3(6): 1921–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
59. Chin E, Kirker K, Zuck M, *et al.*: Actin recruitment to the *Chlamydia* inclusion is spatiotemporally regulated by a mechanism that requires host and bacterial factors. *PLoS One*. 2012; 7(10): e46949.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. Volceanov L, Herbst K, Biniossek M, *et al.*: Septins arrange F-actin-containing fibers on the *Chlamydia trachomatis* inclusion and are required for normal release of the inclusion by extrusion. *MBio*. 2014; 5(5): e01802–14.
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- 1 **Rey Carabeo** Washington State University, Pullman, WA, USA
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- 1 **Thomas Meyer , Munir Al-Zeer** Max Planck Institute for Infection Biology, Berlin, Germany
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- 1 **Joanne Engel** Department of Medicine, University of California, San Francisco, San Francisco, CA, USA
Competing Interests: No competing interests were disclosed.
- 1 **Kenneth Fields** University of Kentucky, Lexington, KY, USA
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