Mini Review
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The hijacking of host endocytic trafficking by the bacterial pathogen

Abstract

Phagocytes utilize an Endocytic process to engulf and degrade microbes that produce an immune response against pathogens. Immune cells in our bodies rely on functional vesicle trafficking and fusion to send out substances including cytokines and immunologic effector molecules that mediate innate and adaptive immune responses. It is clear that vesicle trafficking is important for general cell function as it mediates many intracellular processes. Moreover, appreciation for the vesicular trafficking within the cell has been addressed after the 2013 Nobel Prize in Physiology or Medicine was awarded to James Rothman, Randy Schekman, and Thomas Südof. Their work provided the footsteps and showed the importance of Endocytic trafficking in host cellular responses. This review will focus our interconnected knowledge of cell biology with microbiology and immunology that will help to understand the fate of a bacterial pathogen after going inside the host cells.

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Rama F Pranadinata, Salony Roongta Pranadinata, Soumita Das
Department of Pathology, University of California San Diego, USA

Correspondence: Soumita Das, Department of Pathology, University of California San Diego, 9500 Gilman Drive, BRFII, 5217 JJ, San Diego, CA, Tel 858-822-5523, Email sodas@ucsd.edu

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Introduction

Two endo membrane systems; the secretory pathway and the Endocytic pathway both utilize vesicular trafficking to control movement in and out of the cell. In the secretory pathway, proteins synthesized in the Endoplasmic Reticulum (ER) are Trans located to the plasma membrane. In Endocytic pathway, the endosomal and phagosomal trafficking to lysosome occurs via the early to late endosomal pathway. In the Endocytic pathway, the endosomal and phagosomal trafficking to lysosome follows a maturation process of early to late endosome/phagosome in which similar protein players are involved. As it is understood now, phagosome trafficking to the lysosome is a modified version of endosomal trafficking.[1] In most of the microbial infection, after 5min of phagocytosis early phagosomes are marked with a pH 6, Transferrin receptor, EEA1, Rab5, PI (3) P. Early Phagosome proceeds towards the late phagosome in around 20min with pH 5-6 marked with Mannose-6-phosphate receptor, LAMP1/2, Rab7, Rab9, and lyso(bis)phosphatidic acid. Approximately 1 h after infection, phagolysosomes is generated by the fusion of the late phagosomes with lysosomes, with the marker of LAMP1/2 and matures Cathepsins D.

A series of additional events must consecutively take place for proper endosomal maturation into late endosome (LE) stage and consequent LE-lysosome fusion. Several protein players important for this pathway have been identified: GTPases; trafficking protein complexes between the trans-Golgi network (TGN) and the endosome; V-ATPases; and motor proteins.[1,2] The most seemingly well-known players in endosomal maturation are the GTPases Rab5 and Rab7 which participate in the "Rab switch".[1,3] Rab5 associates first with the early endosome (EE) and as the endosome matures to LE, Rab5 is exchanged for Rab7. This switch is required for proper endosomal maturation and lysosome fusion [1]. Moreover, these GTPases are used as markers for various stages in endosome maturation; Rab5 and Rab7 for EE and LE respectively. In addition, Rab9 mediates retrograde trafficking of mannose-6 phosphate receptors (MPRs) from the endosome to the TGN, a process shared by another protein complex known as the retromer.[4] This retrograde trafficking is important in recycling MPRs for subsequent loading of hydrolases to the LE. Another marker the vacuolar-type V-ATPase, present on LE plays an important role in the acidification that is necessary for lysosome fusion and hydrolase activity.[1,5] Motor proteins such as dynein, once recruited by GTP-bound Rab7 and RILP (Rab Interacting Lysosomal Protein) complex, act in motility control of the LE to the lysosome.[1] Moreover, bacterial effectors from several pathogens (*Coxiella; Helicobacter pylori; Legionella pneumophila; Listeria monocytogenes; Mycobacteria; Salmonella*) utilize Rab GTPases to evadedegradation, direct transport to specific intracellular locations and control host vesicles that are required for a stable niche and/or bacterial growth and differentiation.[6]

Inconventionalphagocytosis,alargevarietyofmicrobesareengulfed by a zipper-like process involving several ligands and phagocytic receptors interacting with a tightly fitting pseudopodia formation which moves circumferentially and symmetrically around the particle. Pathogens like *Francisella*, *Salmonella* and *Legionella* resides inside the spacious vacuole to provide the microbes a protective niche. After phagocytosis by macrophages, the bacteria-containing phagosome may fuse with LAMP-1 (lysosomal-associated membrane protein 1)-positive lysosomes to generate a phago-lysosome. The abundant series of steps that must take place for correct endosomal maturation are necessary for segregating the LE from the recycling pathway of the EE, prepping the LE for lysosome fusion and for excluding endosomal membrane proteins not intended for lysosomal degradation. Nonetheless, these many checkpoints allow for many possible areas of disruption by pathogens and thus the exploitation of the endosomal pathway to create safe niches within host-maintained vesicles. Rab5 and Rab7 both have key roles in the maturation of the phagosome and fusion with the lysosome.[7] Phagolysosome fusion is a very important method host cells use to combat infection and inhibit the survival of intracellular pathogens. Intracellular pathogens like *Mycobacterium tuberculosis* avoid lysosomal fusion through the manipulation of host signaltransductionpathways.[8]Thebacteria-containingvacuolesacquire endosomal marker but subsequently inhibits phagosomal maturation or lysosomal degradation. For example, *Salmonella* containing vacuole (SCV) has markers of Endocytic trafficking with reduced lysosomal hydrolytic enzymes transported by Mannose 6 phosphate receptor (M6PR). *Salmonella* effector protein SifA abrogates proper MPR recycling from the endosome to the TGN with attenuated lysosomal enzymatic activity.[9] *Francisella tularensis*vacuole transiently acquires early endosomal markers, but, by using limited amountsof lysosome-associated membrane glycoproteins (CD63, LAMP-1 and LAMP-2), does not fuse with lysosomes or acquire lysosomal markers such as Cathepsin D. With time, all markers of

the Endocytic pathway are lost and *F. tularensis* escapes into the host cell cytoplasm.[10] In *Listeria* infection, the secretion of listeriolysin (LLO) by *Listeria* decreases phagosomal calcium concentration and increases pH, which impedes phago-lysosomal fusion. The secreted effector, Lmo2459, blocks the maturation of the phagosome via the inhibition of Rab 5.[11] *Legionella* containing vacuoles (LCV) inside phagocytic cells avoid fusion with lysosomes, yet the pathogen vacuole extensively communicates with the endosomal, secretory, and retrograde vesicle trafficking pathways, as well as with the endoplasmic reticulum (ER).[12]

Functions of the Endocytic trafficking and phagosomal maturation/ lysosomal degradation control the destruction of pathogens and instruction of the developing adaptive immune response through expression of cytokines and chemokines. The effects of secreted vesicles on immune responses and their potential use as therapeutic agents in various conditions provide exciting lines of investigation for the future.

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Conflicts of interest

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