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MYCOBACTERIAL SURVIVAL IN ALVEOLAR MACROPHAGES AS A RESULT OF CORONIN-1A INHIBITION OF AUTOPHAGOSOME FORMATION

Sh intaro Seto, Kunio Tsujimura, Toshinobu Horii, Yukio Koide

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ABSTRACT

Alveolar macrophages are the first line of defense of the lung against infection by pathogenic microbes. Despite this, *Mycobacterium tuberculosis* can proliferate in alveolar macrophages by inhibiting phagolysosome biogenesis. Differential recruitment of Rab GTPases, which regulate phagosome maturation, to mycobacterial phagosomes contributes to the inhibition of phagolysosome biogenesis. Recruitment of Coronin-1a, an actin binding protein, to mycobacterial phagosomes is also thought to inhibit their fusion with lysosomes. Host defense mechanisms exploit autophagy to control the proliferation of intracellular pathogens, including *M. tuberculosis*. On the other hand, several intracellular bacteria can evade the elimination induced by the autophagic process. *M. tuberculosis* also escapes being targeted for autophagosomal uptake. We have demonstrated that the depletion of Coronin-1a inhibits mycobacterial survival in macrophages, since Coronin-1a depletion facilitates the formation of autophagosomes around mycobacterial phagosomes. These results suggest that Coronin-1a inhibits autophagosome formation to *M. tuberculosis*, thereby allowing mycobacterial survival in alveolar macrophages.

INTRODUCTION

Mycobacterium tuberculosis, the causative pathogen of tuberculosis, is latent in one-third of the world's population. Worldwide tuberculosis causes approximately 1.4 million deaths per year. *M. tuberculosis* bacilli, as well as other pathogenic microbes inhaled into the lung, are phagocytosed by alveolar macrophages. However, *M. tuberculosis* can survive and persist within phagocytosed macrophages (Russell, 2001). Mycobacteria gain this ability by inhibiting phagolysosome biogenesis (Armstrong and Hart, 1971). Intracellular pathogens are known to disrupt the normal membrane trafficking pathways of the host cell; this alteration is likely to produce more hospitable intracellular conditions for their growth and multiplication. Rab GTPases regulating the endocytic pathway play pivotal roles in phagosome maturation. Therefore, the activity and localization of these regulatory proteins may be targeted by intracellular pathogens to establish a niche for their proliferation (Brumell and Scidmore, 2007). In this issue, we describe that the differential recruitment of Rab GTPases to mycobacterial phagosomes contributes to arrest phagosome maturation, leading to the inhibition of phagolysosome biogenesis (Seto *et al.*, 2009, 2010, 2011; Sugaya *et al.*, 2011).

Intracellular parasite invasion triggers autophagy induction, thereby protecting host cells (Deretic and Levine, 2009). The proliferation of *M. tuberculosis* in macrophages has also been shown to be controlled by autophagy (Kumar *et al.*, 2010; Gutierrez *et al.*, 2004). The physiological or pharmacological induction of autophagy usually restrains mycobacterial survival. However, *M. tuberculosis* can evade the elimination by autophagy at the static state (Gutierrez *et al.*, 2004) by unknown mechanisms. Recently, we found that the depletion of Coronin-1a, an actin-binding protein, promotes autophagosome formation around *M.*

tuberculosis-containing phagosomes, thereby decreasing mycobacterial survival in macrophages (Seto *et al.*, 2012). Coronin-1a was originally identified to inhibit the fusion of mycobacterial phagosomes with lysosomes (Pieters, 2008). Herein we further discuss the mechanisms by which Coronin-1a inhibits the autophagosome formation to *M. tuberculosis*.

MATURATION ARREST OF MYCOBACTERIAL PHAGOSOMES

The engulfment of pathogens by macrophages is an important initial step in the innate immune response. Pathogens phagocytosed by macrophages are enclosed into phagocytic vacuoles and processed by a series of interactions with early and late endosomal vesicles. This process is termed phagosome maturation. During the maturation process, phagosomes acquire degradative and microbicidal properties. Phagosomes ultimately fuse with lysosomes, thereby becoming phagolysosomes. Several regulators of the endocytic pathway, including Rab GTPases, play pivotal roles in phagosome maturation and phagolysosome biogenesis (Vieira *et al.*, 2002). Rab5 is associated with early phagosomes and recruits the effector proteins EEA1 and the Class III phosphatidylinositol 3-kinase (PI3-kinase) VPS34. The phosphatidylinositol 3-phosphate (PI3P) produced by VPS34 is important in phagosome maturation because NADPH oxidase and other effector proteins including EEA1 interact with PI3P, resulting in their recruitment to the phagosome. NADPH oxidase generates superoxide in the phagosome to assist in the elimination of the ingested pathogens. Rab7 appears on the phagosome membrane after the dissociation of Rab5, and it resides there during the subsequent phagosome maturation. RILP (Rab7-interacting lysosomal protein) interacts with the active form of Rab7 and mediates the fusion of endosomes with lysosomes. RILP recruits the

minus-end motor complex dynein-dynactin to phagosomes, resulting in the migration of phagosomes to the microtubule-organizing center, where late endosomal and lysosomal compartments accumulate. During the phagosome maturation process an acidic environment is established within phagosomes (Vieira *et al.*, 2002). This acidification is achieved by the localization of the vacuolar-type proton transport ATPase (v-ATPase) to phagosomes, and supports the activity of lysosomal digestive enzymes.

Localization of Rab7 to mycobacterial phagosomes

It was widely accepted that *M. tuberculosis* arrests the maturation of its containing phagosome at the stage of Rab5-Rab7 conversion, leading to the inhibition of phagolysosome biogenesis (Vergne *et al.*, 2004). This hypothesis was supported by the observations that Rab7 does not localize to mycobacterial phagosomes in macrophages: Rab7 was shown to be absent at the time when its recruitment would usually occur, while Rab5 remained on mycobacterial phagosomes (Kelley and Schorey, 2003; Via *et al.*, 1997). On the other hand, opposite observations have been reported; i.e. Rab7 localized to mycobacterial phagosomes (Sun *et al.*, 2007; Clemens *et al.*, 2000). More recently, we have demonstrated that *M. tuberculosis*-containing phagosomes acquire Rab7 molecules by their association with Rab7-containing vesicles immediately after infection, but that this association is inhibited during the later stages of infection (Seto *et al.*, 2009, 2011). We further demonstrated that Rab7 mobility is restricted on mycobacterial phagosomes (Sugaya *et al.*, 2011). These results suggest that either *M. tuberculosis* halts Rab7 recruitment or it inhibits the fusion of Rab7-containing endosomal vesicles and thereby blocks the subsequent phagosome maturation and phagolysosome biogenesis.

Differential localization of Rab GTPases to mycobacterial phagosomes

Rab GTPases, encoded by a family of over 70 genes, regulate membrane trafficking (Schwartz *et al.*, 2007). Their functions in phagocytosis are being elucidated. Proteomic analyses have revealed that several Rab GTPases are recruited to both latex bead- and mycobacteria-containing phagosomes (Lee *et al.*, 2010; Garin *et al.*, 2001). Both Rab14 and Rab22a have been demonstrated to be involved in mycobacterial phagosome maturation arrest (Kyei *et al.*, 2006; Roberts *et al.*, 2006). Rab10 which also regulates phagosome maturation does not localize to mycobacterial phagosomes (Cardoso *et al.*, 2010). However, there is currently insufficient information concerning the role of Rab GTPases in professional phagocytotic cells to understand how *M. tuberculosis* manages to subvert membrane trafficking and survive within infected macrophages.

We examined the localization of 42 Rab GTPases to mycobacterial phagosomes and found that 22 Rab GTPases were recruited to *S. aureus*-containing phagosomes. 17 of those Rab GTPases showed different localization kinetics on *M. tuberculosis*-containing phagosomes (Seto *et al.*, 2011). We also found that some of the Rab GTPases localizing to phagosomes regulated the recruitment of cathepsin D as well as phagosomal acidification (Seto *et al.*, 2011). Rab7, Rab20, Rab22b, Rab32, Rab34, Rab38 and Rab43 were involved in the recruitment of cathepsin D to the phagosomes, and Rab7, Rab20 and Rab39 regulated the acidification of the phagosomes. Of these Rab GTPases, Rab7, Rab20, Rab32, Rab34, Rab38 and Rab39 were dissociated from mycobacterial phagosomes. Rab7 is a well-known late endosomal marker protein (Vieira *et al.*, 2002), which regulates the trafficking of cathepsin D to the phagosome as well as phagosomal acidification (Seto *et al.*, 2009,

2010). Rab34 interacts with RILP as well as Rab7 and is involved in the promotion of phagolysosome biogenesis, suggesting that the dissociation of these Rab GTPases directly inhibits phagolysosome biogenesis. Rab32, Rab34 and Rab38 regulate membrane trafficking in the trans-Golgi network (TGN) (Schwartz *et al.*, 2007), suggesting that the direct transport of cathepsin D from TGN to mycobacterial phagosomes is inhibited by the dissociation of these Rab GTPases. Rab20 localizes to the endoplasmic reticulum, co-localizing with v-ATPases (Schwartz *et al.*, 2007). Recently, the function of Rab20 in phagosome maturation was further examined (Egami and Araki, 2012). Rab39 co-localizes with lysosomes (Seto *et al.*, 2011). Considering its recruitment kinetics, Rab39 seems to maintain phagosomal acidification during the later stages of phagocytosis. These observations, taken together, suggest that these Rab GTPases differentially regulate phagosome maturation, at the various stages of phagocytosis. Hence, the failure of the recruitment of these Rab GTPases to mycobacterial phagosomes may contribute to phagosome maturation arrest and the inhibition of phagolysosome biogenesis (Figure 1).

Localization of lysosomal marker proteins to mycobacterial phagosomes

Lysosomal glycoproteins LAMP-1, LAMP-2 and CD63 show only limited recruitment to live mycobacterial phagosomes, indicating that phagolysosome biogenesis is inhibited in mycobacteria-infected macrophages (Clemens and Horwitz, 1995). However, a recent study demonstrated that these lysosomal proteins are recruited to mycobacterial phagosomes in human monocyte derived macrophages and dendritic cells (van der Wel *et al.*, 2007). We re-examined the localization of LAMP-2 and CD63 in mycobacteria-infected macrophages. We found that large

numbers of *M. tuberculosis*-containing phagosomes are associated with both lysosomal marker proteins (Seto *et al.*, 2009, 2010). Proteomic analysis also revealed that mycobacterial phagosomes associate with these lysosomal marker proteins (Lee *et al.*, 2010). We also assessed the localization of two other lysosomal proteins, cathepsin D and RILP, in mycobacteria-infected macrophages (Seto *et al.*, 2009, 2010). Cathepsin D became associated with *M. tuberculosis*-containing phagosomes immediately after infection, but later dissociated. RILP was absent from the majority of *M. tuberculosis*-containing phagosomes. These results suggest that mycobacterial phagosomes selectively fuse with lysosomal vesicles with heterogeneous properties. A similar model was proposed by Rohde *et al.*: that phagosomes fuse with a subset of lysosomal vesicles that contain distant sets of digestive enzymes or membrane transporters (Rohde *et al.*, 2007). Our observations would support this model and provide critical evidence concerning the heterogeneous lysosome compartments.

CORONIN-1A RECRUITMENT TO MYCOBACTERIAL PHAGOSOMES INHIBITS PHAGOLYSOSOME BIOGENESIS

The ability of mycobacteria to block phagolysosome biogenesis is also demonstrated by the active recruitment of Coronin-1a to their phagosomes in macrophages (Pieters, 2008). Coronin-1a shows 30% homology with *Dictyostelium* coronin, which, in growth phase cells, localizes to crown-shaped surface projections of F-actin filaments (de Hostos, 1999). Coronin-1a in mammalian cells has three distinct domains: an N-terminal domain, which contains the 5 WD repeats and two additional stretches composed of four short β-strands. This domain makes up the 7-bladed propeller structure. C-terminal domain is a coiled coil segment, which is rich in α-helices. Coronin-1a molecules assemble into trimers using this domain. A linker

domain, which has little secondary structure, joins the N- and C-terminal domains. A *Dictyostelium* coronin-null mutant shows deficiencies in cell locomotion, phagocytosis and cytokinesis; suggesting that coronin regulates F-actin-based cellular processes in *Dictyostelium*. In mammals, Coronin-1a is predominantly expressed in leukocytes. Coronin-1a functions in T cell receptor signal transduction, where Coronin-1a is required to activate the calcium-dependent phosphatase calcineurin (Mueller *et al.*, 2008). However, no defects in F-actin cytoskeleton or F-actin-mediated cellular processes are apparent in coronin-1a depleted macrophages (Jayachandran *et al.*, 2007, 2008).

Ferrari *et al.* (1999) reported that in macrophages live mycobacteria actively recruit Coronin-1a proteins to their phagosomes. They compared the protein profiles of phagosomal fractions containing either live or dead mycobacteria. They found that a WD repeat-rich molecule termed TACO, which is identical to Coronin-1a, is associated with live mycobacterial phagosomes, but not with dead ones. They also found that Coronin-1a localizes to both live and dead mycobacterial phagosomes immediately after phagocytosis. Coronin-1a remained associated with live mycobacterial phagosomes, but was released from dead ones. Moreover, they demonstrated that mycobacterial phagosomes fuse with lysosomes in Kupffer cells, which do not express Coronin-1a. These results suggest that the active recruitment of Coronin-1a to mycobacterial phagosomes inhibits phagolysosome biogenesis.

Recently, Jayachandran *et al.* (2007, 2008) demonstrated that, in macrophages, mycobacterial phagosomes fuse with lysosomes upon the genetical depletion of Coronin-1a. Because Coronin-1a is known to be required for the activation of calcineurin, they proposed that it was the activation of calcineurin that blocks phagolysosome biogenesis, thereby allowing mycobacterial survival in the wild type

macrophages. They confirmed that the treatment with calcineurin inhibitors stimulated the fusion of mycobacterial phagosomes with lysosomes in macrophages. However, this observation conflicts with an earlier one: that mycobacterial lipoarabinomannan inhibits phagosome maturation via interfering the calmodulin signal pathways (Vergne *et al.*, 2004). Further investigation is thus required to clarify the mechanisms by which Coronin-1a inhibits phagolysosome biogenesis.

CORONIN-1A INHIBITS AUTOPHAGOSOME FORMATION TO MYCOBACTERIA

We hypothesized that inhibition of autophagy induction may account for the mechanism by which Coronin-1a allows mycobacterial survival. This is because the treatment with autophagic inhibitors or autophagy-related gene silencing restored mycobacterial survival in Coronin-1a-knockdown Raw264.7 macrophages (Seto *et al.*, 2012). To assess this hypothesis, we examined the localization of LC3 and found that it was recruited to *M. tuberculosis*-containing phagosomes in Coronin-1a-knockdown Raw264.7 macrophages. Thin-section electron microscopy also revealed that in Coronin-1a-knockdown macrophages mycobacterial phagosomes were surrounded by characteristic autophagic membrane structures (Figure 2). We also found that depletion of Coronin-1a induced autophagosome formation around *M. tuberculosis*-containing phagosomes, in both alveolar and bone marrow derived macrophages. These results suggest that Coronin-1a inhibits autophagosome formation around *M. tuberculosis*-containing phagosomes in various types of macrophages.

Treatment with autophagic inhibitors or silencing of autophagy-related genes interfered with LC3 recruitment to mycobacterial phagosomes in Coronin-1a-knockdown macrophages (Seto *et al.*, 2012). We further showed that p62,

ubiquitin and LAMP1 localized to LC3-positive mycobacterial phagosomes in Coronin-1a-knockdown macrophages during infection. This therefore implies the involvement of the ubiquitin-mediated autophagic degradation system. Considering that the delivery of anti-bactericidal protein and/or peptides to mycobacterial phagosomes depends on the induction of autophagy (Yuk *et al.*, 2009), these results suggest that the inhibition of mycobacterial proliferation in Coronin-1a-knockdown macrophages is caused by the autophagosome formation to mycobacterial phagosomes and subsequent bactericidal effector mechanisms.

MAP kinase signaling pathway

We sought the key events necessary for the induction of autophagosome formation around mycobacterial phagosomes in Coronin-1a-knockdown macrophages. As *M. tuberculosis* is thought to prevent the induction of autophagy by inhibiting PI3-kinase activation (Vergne *et al.*, 2004), it would have to be a strong promoter to drive autophagosome formation to infected mycobacteria. Because mitogen activated protein (MAP) kinase signaling has previously been shown to be involved in autophagy induction in macrophages (Yuk *et al.*, 2009) we went on to examine its involvement in autophagosome formation to mycobacteria in Coronin-1a-knockdown macrophages. We assessed phosphorylation status throughout the MAP kinase pathways and found that only the p38 MAP kinase pathway was specifically activated by *M. tuberculosis* infection in Coronin-1a-knockdown macrophages. An inhibitor for p38 MAP kinase activation also inhibited autophagosome formation around mycobacterial phagosomes in Coronin-1a-knockdown macrophages. These results suggest that Coronin-1a blocks the signals that activate p38 MAP kinase in response to mycobacterial infection.

ESX-1 is required for autophagosome formation

A recent report demonstrated ESX-1-dependent LC3 recruitment to *Mycobacterium marinum*-containing phagosomes (Lerena and Colombo, 2011). ESAT-6 homolog of *M. marinum* has pore formation activity in phagosomal membranes and assists the bacilli to escape from phagosomes to the cytosol, where it then moves along by an actin-based motility. *M. tuberculosis* is also reported to translocate from its containing phagosomes to the cytosol in infected monocytes, dependent on an active ESX-1 secretion system (van der Wel *et al.*, 2007). This therefore suggests that the secreted proteins produced by the ESX-1 system, including ESAT-6, damage the phagosomal membranes. To asses this hypothesis, we infected *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) lacking ESX-1 secretion system into Coronin-1a-knockdown macrophages, and found that autophagosomes were not formed around BCG-containing phagosomes at all (Seto *et al.*, unpublished data). Since Coronin-1a interacts with F-actin to stabilize the structure, it is likely that the localization of Coronin-1a to mycobacterial phagosomes (Ferrari *et al.*, 1999) supports the phagosomal membranes. Therefore, depletion of Coronin-1a would increase the susceptibility of the phagosomal membranes to ESAT-6 secreted by *M. tuberculosis*. The damage to the membrane of *M. tuberculosis*-containing phagosomes may induce the autophagosome formation seen in Coronin-1a-knockdown macrophages.

CONCLUDING REMARKS

M. tuberculosis bacilli inhaled into human lungs are phagocytosed by alveolar macrophages as well as other pathogenic microbes. Phagocytosed pathogens by

macrophages are surrounded by a phagosomal membrane to form phagosomes, which subsequently fuse with endosomal and lysosomal vesicles. During phagosomal maturation and phagolysosome biogenesis, phagocytosed microbes are killed and digested. Autophagosome formation also contributes to traffic bactericidal peptides/protein to the phagosomes. *M. tuberculosis* can escape from these mechanisms ingeniously and proliferate within infected macrophages. *M. tuberculosis* modulates the differential recruitment of Rab GTPases to its containing phagosome, leading the failure of phagosome maturation and phagolysosome biogenesis. Active recruitment of Coronin-1a, an actin binding protein to mycobacterial phagosomes, also participates in the mechanism by which mycobacterial phagosomes avoid phagolysosome biogenesis. We have demonstrated that Coronin-1a has another function in promoting mycobacterial survival in macrophages: Coronin-1a inhibits autophagosome formation around *M. tuberculosis*-containing phagosomes and assists in its survival in macrophages (Figure 3). Our results further suggest that Coronin-1a represents a possible therapeutic and/or vaccine target against tuberculosis.

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REFERENCES

Armstrong, J.A. and Hart, P.D. (1971) Response of cultured macrophages to Mycobacterium tuberculosis with observations on fusion of lysosomes with phagosomes. J. Exp. Med. 134: 713-740.

Brumell, J.H. and Scidmore, M.A. (2007) Manipulation of rab GTPase function by intracellular bacterial pathogens. Microbiol. Mol. Biol. Rev. 71: 636-652.

Cardoso, C.M., Jordao, L. and Vieira, O.V. (2010) Rab10 regulates phagosome maturation and its overexpression rescues Mycobacterium-containing phagosomes maturation. Traffic. 11: 221-235.

Clemens, D.L. and Horwitz, M.A. (1995) Characterization of the Mycobacterium tuberculosis phagosome and evidence that phagosomal maturation is inhibited. J. Exp. Med. 181: 257-270.

Clemens, D.L., Lee, B.Y. and Horwitz, M.A. (2000) Mycobacterium tuberculosis and Legionella pneumophila phagosomes exhibit arrested maturation despite acquisition of Rab7. Infect. Immun. 68: 5154-5166.

de Hostos, E.L. (1999) The coronin family of actin-associated proteins. Trends. Cell Biol. 9: 345-350.

Deretic, V. and Levine, B. (2009) Autophagy, immunity, and microbial adaptations. Cell Host. Microbe. 5: 527-549.

Egami, Y. and Araki, N. (2012) Rab20 regulates phagosome maturation in RAW264 macrophages during Fc gamma receptor-mediated phagocytosis. PLoS One 7: e35663.

Ferrari, G., Langen, H., Naito, M. and Pieters, J. (1999) A coat protein on phagosomes involved in the intracellular survival of mycobacteria. Cell. 97: 435-447.

Garin, J., Diez, R., Kieffer, S., Dermine, J.F., Duclos, S., Gagnon, E., Sadoul, R., Rondeau, C. and Desjardins, M. (2001) The phagosome proteome: insight into

phagosome functions. J. Cell Biol. 152: 165-180.

Gutierrez, M.G., Master, S.S., Singh, S.B., Taylor, G.A., Colombo, M.I. and Deretic, V. (2004) Autophagy is a defense mechanism inhibiting BCG and Mycobacterium tuberculosis survival in infected macrophages. Cell. 119: 753-766.

Jayachandran, R., Gatfield, J., Massner, J., Albrecht, I., Zanolari, B. and Pieters, J. (2008) RNA interference in J774 macrophages reveals a role for coronin 1 in mycobacterial trafficking but not in actin-dependent processes. Mol. Biol. Cell. 19: 1241-1251.

Jayachandran, R., Sundaramurthy, V., Combaluzier, B., Mueller, P., Korf, H., Huygen, K., Miyazaki, T., Albrecht, I., Massner, J. and Pieters, J. (2007) Survival of mycobacteria in macrophages is mediated by coronin 1-dependent activation of calcineurin. Cell. 130: 37-50.

Kelley, V.A. and Schorey, J.S. (2003) Mycobacterium's arrest of phagosome maturation in macrophages requires Rab5 activity and accessibility to iron. Mol. Biol. Cell. 14: 3366-3377.

Kumar, D., Nath, L., Kamal, M.A., Varshney, A., Jain, A., Singh, S. and Rao, K.V. (2010) Genome-wide analysis of the host intracellular network that regulates survival of Mycobacterium tuberculosis. Cell. 140: 731-743.

Kyei, G.B., Vergne, I., Chua, J., Roberts, E., Harris, J., Junutula, J.R. and Deretic, V. (2006) Rab14 is critical for maintenance of Mycobacterium tuberculosis phagosome maturation arrest. EMBO J. 25: 5250-5259.

Lee, B.Y., Jethwaney, D., Schilling, B., Clemens, D.L., Gibson, B.W. and Horwitz, M.A. (2010) The Mycobacterium bovis bacille Calmette-Guerin phagosome proteome. Mol. Cell. Proteomics. 9: 32-53.

Lerena, M.C. and Colombo, M.I. (2011) Mycobacterium marinum induces a marked

LC3 recruitment to its containing phagosome that depends on a functional ESX-1 secretion system. Cell. Microbiol. 13: 814-835.

Mueller, P., Massner, J., Jayachandran, R., Combaluzier, B., Albrecht, I., Gatfield, J., Blum, C., Ceredig, R., Rodewald, H.R., Rolink, A.G. and Pieters, J. (2008) Regulation of T cell survival through coronin-1-mediated generation of inositol-1,4,5-trisphosphate and calcium mobilization after T cell receptor triggering. Nat. Immunol. 9: 424-431.

Pieters, J. (2008) Coronin 1 in innate immunity. Subcell. Biochem. 48: 116-123.

Roberts, E.A., Chua, J., Kyei, G.B. and Deretic, V. (2006) Higher order Rab programming in phagolysosome biogenesis. J. Cell Biol. 174: 923-929.

Rohde, K., Yates, R.M., Purdy, G.E. and Russell, D.G. (2007) Mycobacterium tuberculosis and the environment within the phagosome. Immunol. Rev. 219: 37-54.

Russell, D.G. (2001) Mycobacterium tuberculosis: here today, and here tomorrow. Nat. Rev. Mol. Cell. Biol. 2: 569-577.

Schwartz, S.L., Cao, C., Pylypenko, O., Rak, A. and Wandinger-Ness, A. (2007) Rab GTPases at a glance. J. Cell Sci. 120: 3905-3910.

Seto, S., Tsujimura, K. and Koide, Y. (2011) Rab GTPases regulating phagosome maturation are differentially recruited to mycobacterial phagosomes. Traffic. 12: 407-420.

Seto, S., Tsujimura, K. and Koide, Y. (2012) Coronin-1a inhibits autophagosome formation around Mycobacterium tuberculosis-containing phagosomes and assists mycobacterial survival in macrophages. Cell. Microbiol. 14: 710-727.

Seto, S., Matsumoto, S., Tsujimura, K. and Koide, Y. (2010) Differential recruitment of CD63 and Rab7-interacting-lysosomal-protein to phagosomes containing

Mycobacterium tuberculosis in macrophages. Microbiol. Immunol. 54: 170-174.

Seto, S., Matsumoto, S., Ohta, I., Tsujimura, K. and Koide, Y. (2009) Dissection of Rab7 localization on Mycobacterium tuberculosis phagosome. Biochem. Biophys. Res. Commun. 387: 272-277.

Sugaya, K., Seto, S., Tsujimura, K. and Koide, Y. (2011) Mobility of late endosomal and lysosomal markers on phagosomes analyzed by fluorescence recovery after photobleaching. Biochem. Biophys. Res. Commun. 410: 371-375.

Sun, J., Deghmane, A.E., Soualhine, H., Hong, T., Bucci, C., Solodkin, A. and Hmama, Z. (2007) Mycobacterium bovis BCG disrupts the interaction of Rab7 with RILP contributing to inhibition of phagosome maturation. J. Leukoc. Biol. 82: 1437-1445.

van der Wel, N., Hava, D., Houben, D., Fluitsma, D., van Zon, M., Pierson, J., Brenner, M. and Peters, P.J. (2007) M. tuberculosis and M. leprae translocate from the phagolysosome to the cytosol in myeloid cells. Cell. 129: 1287-1298.

Vergne, I., Chua, J., Singh, S.B. and Deretic, V. (2004) Cell biology of Mycobacterium tuberculosis phagosome. Annu. Rev. Cell. Dev. Biol. 20: 367-394.

Via, L.E., Deretic, D., Ulmer, R.J., Hibler, N.S., Huber, L.A. and Deretic, V. (1997) Arrest of mycobacterial phagosome maturation is caused by a block in vesicle fusion between stages controlled by rab5 and rab7. J. Biol. Chem. 272: 13326-13331.

Vieira, O.V., Botelho, R.J. and Grinstein, S. (2002) Phagosome maturation: aging gracefully. Biochem. J. 366: 689-704.

Yuk, J.M., Shin, D.M., Lee, H.M., Yang, C.S., Jin, H.S., Kim, K.K., Lee, Z.W., Lee, S.H., Kim, J.M. and Jo, E.K. (2009) Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. Cell Host. Microbe. 6: 231-243.