



From Phagocytes to Immune Defense: Roles for Coronin Proteins in *Dictyostelium* and Mammalian Immunity

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Microbes have interacted with eukaryotic cells for as long as they have been co-existing. While many of these interactions are beneficial for both the microbe as well as the eukaryotic cell, several microbes have evolved into pathogenic species. For some of these pathogens, host cell invasion results in irreparable damage and thus host cell destruction, whereas others use the host to avoid immune detection and elimination. One of the latter pathogens is *Mycobacterium tuberculosis*, arguably one of the most notorious pathogens on earth. In mammalian macrophages, *M. tuberculosis* manages to survive within infected macrophages by avoiding intracellular degradation in lysosomes using a number of different strategies. One of these is based on the recruitment and phagosomal retention of the host protein coronin 1, that is a member of the coronin protein family and a mammalian homolog of coronin A, a protein identified in *Dictyostelium*. Besides mediating mycobacterial survival in macrophages, coronin 1 is also an important regulator of naïve T cell homeostasis. How, exactly, coronin 1 mediates its activity in immune cells remains unclear. While in lower eukaryotes coronins are involved in cytoskeletal regulation, the functions of the seven coronin members in mammals are less clear. *Dictyostelium* coronins may have maintained multiple functions, whereas the mammalian coronins may have evolved from regulators of the cytoskeleton to modulators of signal transduction. In this minireview, we will discuss the different studies that have contributed to understand the molecular and cellular functions of coronin proteins in mammals and *Dictyostelium*.

Keywords: coronins, *Dictyostelium discoideum*, *Mycobacterium*, phagocytes, immune cells

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Received: 13 October 2017

Accepted: 27 February 2018

Published: 22 March 2018

Citation:

Mori M, Mode R and Pieters J (2018)
From Phagocytes to Immune Defense:
Roles for Coronin Proteins in
Dictyostelium and Mammalian
Immunity.
Front. Cell. Infect. Microbiol. 8:77.
doi: 10.3389/fcimb.2018.00077

INTRODUCTION

All eukaryotes are surrounded by microorganisms that on the one hand fulfill important roles in providing symbiotic support for eukaryotic life, and at the same time can pose a threat in the form of virulent bacteria, causing infections, disease and death.

For both lower eukaryotes such as the amoeba *Dictyostelium discoideum*, as well as mammalian macrophages, the first encounter with microbes, especially bacteria, results in the activation of phagocytic processes leading to engulfment of the bacteria within phagosomes, followed by lysosomal digestion (Flannagan et al., 2012). When bacteria serve as nutrients, as is the case for *Dictyostelium*, lysosomal degradation will allow the availability of amino acids,

lipids, and other molecules that serve the need for *Dictyostelium* growth (Allen and Aderem, 1996). In case of bacteria being phagocytosed by mammalian cells such as dendritic cells and macrophages, the end point is usually inactivation of the pathogen, as well as presentation of pathogen fragments to the immune system in order to activate effector lymphocytes (T cells) for the generation of adaptive immune responses (Pieters, 2000; Blum et al., 2013).

Phagocytosis is an ancient and evolutionary conserved mechanism (Aderem and Underhill, 1999). Indeed, the basic mechanisms regulating the formation of a phagocytic cup, internalization of the bacteria and the transfer from phagosomes to lysosomes are conserved from lower eukaryotes such as *Dictyostelium* to mammalian phagocytes, including macrophages, neutrophils and dendritic cells. Phagocytosis involves cell surface recognition through different plasma membrane receptors that transmit signals through a variety of pathways to the cytoskeleton in order to allow plasma membrane deformation to accommodate the incoming particles/bacteria (Flannagan et al., 2012).

Virulence Strategies Employed by Pathogenic Microbes

Whereas the encounter of mammalian phagocytes with bacteria most often results in its destruction and activation of specific immunity, many pathogenic bacteria have evolved a diverse array of strategies to circumvent phagocytosis and lysosomal destruction. For example, several pathogens, including *Neisseria* spp., *Pseudomonas* spp., *Streptococcus* spp., and *Salmonella* spp. are known to avoid phagocytic uptake (Sarantis and Grinstein, 2012). Also, certain pathogens, including *Listeria* spp. and *Shigella* spp. are engulfed by phagocytic cells but rapidly transfer to the cytosol where they can proliferate and spread (Hamon et al., 2012; Mellouk and Enninga, 2016). Yet other bacilli such as *Brucella* spp. and *Salmonella* spp. enter the phagocyte through phagocytosis but divert to the endoplasmic reticulum (*Brucella* spp.) or the Golgi (*Salmonella* spp.) instead of being delivered to lysosomes (Celli and Gorvel, 2004; Escoll et al., 2016). Furthermore, some pathogens are phagocytosed and delivered to lysosomes and subsequently withstand the hostile environment of the lysosomal pathway through the release of neutralizing factors (Voth and Heinzen, 2007).

Several pathogens use more than one of these strategies to circumvent host cell destruction; in fact, one of the most notorious pathogens, *Mycobacterium tuberculosis*, has evolved multiple mechanisms to avoid killing by immune cells as well as recognition by the adaptive immune system. For example, *M. tuberculosis* manipulates the host ability to detect and internalize the bacilli through pathogen-associated molecular patterns (PAMPs) (Stamm et al., 2015). Also, once inside the host cell, *M. tuberculosis* uses a range of strategies to avoid destruction, including manipulation of V-ATPase levels to avoid lysosomal acidification (Rohde et al., 2007), expression of genes that allow the bacilli to withstand the low pH of the endosomal/lysosomal pathway (Vandal et al., 2008), neutralizing reactive nitrogen and oxygen species (Shiloh and Nathan, 2000),

resisting delivery to autophagosomes (Deretic, 2005; Romagnoli et al., 2012), counter-balancing iron depletion encountered upon phagocytosis (Weiss and Schaible, 2015) and interfering with lysosomal delivery following phagocytosis (Pieters, 2008; Gengenbacher and Kaufmann, 2012).

Inhibition of lysosomal delivery is an important trait of pathogenic mycobacteria, and the bacilli devote considerable efforts toward achieving that goal (Rohde et al., 2007; Pieters, 2008). This is achieved through the release of molecules, both signaling molecules, lipids and proteins (Cowley et al., 2004; Walburger et al., 2004; Hmama et al., 2015; Lovewell et al., 2016), as well as through the recruitment of host factors allowing mycobacterial escape from lysosomal degradation.

Role for Coronin 1 in the Interaction of *M. tuberculosis* With Macrophages

One of the host proteins co-opted by *M. tuberculosis* to avoid lysosomal killing is coronin 1 (encoded by the *coro1a* gene; for a discussion on the coronin nomenclature see; Pieters et al., 2013), a ~51 kD protein that is located in the macrophage cytosol and cell cortex. Coronin 1, also known as P57 or TACO, for Tryptophan Aspartate containing Coat protein, was identified in a search for host components potentially involved in the intracellular survival of mycobacteria within macrophages (Ferrari et al., 1999). Coronin 1 is a member of the highly conserved family of coronin proteins whose members are expressed across the eukaryotic kingdom and are characterized by the presence of a central WD (tryptophan-aspartate) 40 repeat that in coronin 1-folds in a 7-bladed beta propeller (Suzuki et al., 1995; Okumura et al., 1998; Gatfield et al., 2005; Appleton et al., 2006). Coronin 1 is highly expressed in all hematopoietic cells as well as to a lower degree in neurons (Ferrari et al., 1999; Nal et al., 2004; Jayachandran et al., 2014). Upon entry of pathogenic mycobacteria into macrophages, coronin 1 is retained on phagosomes containing viable, but not killed mycobacteria and its retention on phagosomes prevents intracellular killing of *M. tuberculosis* through activation of the Ca^{2+} /calcineurin pathway (Jayachandran et al., 2007). Apart from *M. tuberculosis*, *M. leprae* as well as virulent *H. pylori* recruit coronin 1 to their intracellular niche, although the exact consequences of coronin 1 retention for pathogen survival in these latter cases remain unclear (Zheng and Jones, 2003; Suzuki et al., 2006).

CORONINS IN DICTYOSTELIUM

Coronin was initially isolated as a 55 kD actin/myosin-interacting molecule from *Dictyostelium discoideum* lysates (de Hostos et al., 1991). Subsequently, it was realized that *Dictyostelium* also expresses a so-called “tandem” coronin containing a duplicated tryptophan-aspartate repeat-containing region, now referred to as coronin B (Shina et al., 2010). Coronin B assembles with actin and deletion of this coronin in *Dictyostelium* was shown to both enhance as well as reduce phagocytosis, dependent on the particles to be internalized (Shina et al., 2010). Coronin B was proposed to act upstream of the suppressor of cAMP receptor (SCAR) and Wiskott-Aldrich syndrome protein

(WASp) (Swaminathan et al., 2015) which connect signals from G protein-coupled receptors and cell surface tyrosine receptors to the actin cytoskeleton, respectively (Bear et al., 1998; Pollitt and Insall, 2009).

In *Dictyostelium*, coronin A is involved in a diverse array of activities, including cell motility, cAMP-mediated chemotaxis, and cytokinesis (de Hostos et al., 1993; Nagasaki et al., 2002). Given the initial isolation of coronin A with actin/myosin, the roles for coronin A in the above-mentioned activities have been attributed to the capacity of *Dictyostelium* coronin A in modulating the F-actin cytoskeleton. Coronin A is localized within regions of actin turnover (Maniak et al., 1995; Heinrich et al., 2008), leading to the conclusion that *Dictyostelium* coronin A is a regulator of the F-actin cytoskeleton, thereby modulating chemotaxis, cell motility and cytokinesis; it should however be noted that *Dictyostelium* lacking coronin A do not show an obvious alteration in the assembly or localization of actin filaments (de Hostos et al., 1993). Separate work using yeast coronin (Crn1) has shown that while deletion of yeast Crn1 does not result in an aberrant F-actin cytoskeleton (Heil-Chapdelaine et al., 1998; Goode et al., 1999), Crn1 binds to and bundles F-actin *in vitro* (Goode et al., 1999) as well as can modulate F-actin polymerization either positively (Liu et al., 2011) or negatively (Humphries et al., 2002) in an actin-related protein 2/3 (ARP2/3) complex-dependent manner. Indeed, yeast Crn1 possesses a number of regions of homology with actin- and tubulin-binding proteins, including microtubule- and F-actin/ARP2/3-interacting domains (Liu et al., 2011), that are lacking in most other coronins (Eckert et al., 2011).

More recent work that revisited the role for coronin A in *Dictyostelium* found that coronin A is important for the initiation of multicellular differentiation following deprivation of nutrients (Vinet et al., 2014); in *Dictyostelium*, nutrient starvation induces the aggregation of individual amoebae into a multicellular structure ultimately forming a fruiting body. Such aggregation is mediated by the second messenger cAMP, that functions both as a chemoattractant as well as an intracellular signal mediating gene transcription. Aggregation is initiated by cell density and nutrient-sensing factors released by the starving culture that induce the expression of genes involved in multicellular aggregation (Devreotes, 1989; Loomis, 2014). It was found that coronin A plays an essential role in the initiation of this developmental program by being involved in the response to factors secreted during the transition from growth to development of the cells. Since application of cAMP to coronin A-deficient cells is sufficient to restore chemotaxis and multicellular aggregation, coronin A appears to be dispensable for the cAMP relay as well as for processes downstream of cAMP. Also, the fact that folate chemotaxis occurs normally in the absence of coronin A argues against an exclusive role for coronin A in cytoskeletal remodeling (Vinet et al., 2014). Furthermore, consistent with earlier results showing that F-actin rearrangement is not required for the initiation of cAMP signaling (Parent et al., 1998; Kriebel et al., 2008), coronin A-dependent induction of genes required for development such as *aca* and *carA* does not require F-actin-based rearrangement (Vinet et al., 2014).

These data suggests that instead of modulating F-actin, coronin A is responsible for the sensing of factors secreted in the conditioned medium (Vinet et al., 2014). Coronin A may function downstream of conditioned medium factor (CMF) (Jain et al., 1992; Yuen et al., 1995), or possibly other, as yet undefined factors that are essential for the initiation of cAMP-dependent chemotaxis and aggregation. Whether the motility and cytokinesis defects observed upon coronin A deletion (de Hostos et al., 1993; Vinet et al., 2014) are related to a possible function of coronin A in the modulation of the cAMP pathway or linked to a role for coronin A in F-actin-mediated processes remains to be clarified. In this context, it is interesting to note that in *Dictyostelium*, myosin-independent cytokinesis (one of the two types of cytokinesis, the other one being myosin-II-dependent, see Nagasaki et al., 2002; Li, 2007) has been linked to both coronin A as well as AmiA (also known as Pianissimo, a target of rapamycin complex (TORC) 2-associated protein) that in *Dictyostelium* is a cytosolic regulator of adenylate cyclase (Pergolizzi et al., 2002). Furthermore, recent work implicated coronin A in regulating the availability of GTP-Rac through a domain with homology to a Cdc42- and Rac-interactive binding (CRIB) motif for activation of downstream effectors, thereby being responsible for myosin II disassembly (Swaminathan et al., 2014). Interestingly, this CRIB-like domain was found to be dispensable for the role of coronin A in cytokinesis, since expression of a mutant coronin A lacking Rac binding activity rescued the cytokinesis defect of coronin A-deficient cells (Swaminathan et al., 2014). This suggest that coronin A domains distinct from the CRIB-like motif are involved in the regulation of cytokinesis.

The precise role for *Dictyostelium* coronins in the modulation of bacterial uptake and survival is less clear. A role for coronin A in phagocytosis appears to be dependent on the type of cargo that is internalized; upon coronin A deletion, phagocytosis of *E. coli* and yeast particles is reduced, while uptake of *Mycobacterium marinum* is enhanced (Maniak et al., 1995; Solomon et al., 2003). Also, it should be noted that yeast phagocytosis is increased upon coronin B deletion (Shina et al., 2011). Furthermore, while coronin A becomes enriched on newly formed phagosomes, it is rapidly dissociated once the bacteria have been fully internalized (Maniak et al., 1995; Rauchenberger et al., 1997; Lu and Clarke, 2005; Hagedorn and Soldati, 2007). For both *M. marinum* as well as *Legionella pneumoniae*, deletion of coronin A renders *Dictyostelium* more permissive for intracellular bacterial growth (Solomon et al., 2000, 2003). These data suggest that in *Dictyostelium* coronin A may play a protective role for the host, although the mechanisms involved remain unclear.

CORONIN 1 FUNCTION IN MAMMALIAN LEUKOCYTES

As described above, in resting macrophages, the only role for coronin 1 appears to be the modulation of the intracellular trafficking and survival of *M. tuberculosis* (Jayachandran et al., 2007, 2008). Given the proposed role for *Dictyostelium* coronin A in the modulation of F-actin-dependent processes such as

chemotaxis and cytokinesis, it was initially anticipated that its mammalian homolog in macrophages, coronin 1, also modulates F-actin. However, in macrophages depleted for coronin 1 either by short interference (si)RNA or gene ablation, actin-dependent functions appear to be unperturbed as judged by the analysis of cell motility, macropinocytosis and membrane ruffling (Jayachandran et al., 2007, 2008). In contrast to studies using macrophages from coronin 1-deficient mice (Jayachandran et al., 2007) or J774 macrophages depleted for coronin 1 by siRNA (Jayachandran et al., 2008), TAT-mediated transduction of the WD repeat domain of coronin 1 in RAW 264.7 macrophages and neutrophils was shown to affect early phagocytosis (Yan et al., 2005, 2007); this may reflect differences in the experimental setup (such as time to allow uptake) or differential requirements for coronin 1 in phagocytosis in different macrophage and/or cell types; alternatively, especially given the propensity of coronin 1 mutants to cause aggregation, the introduction of misfolded protein domains may compromise cellular functions such as chemotaxis and phagocytosis (Gatfield et al., 2005). Whereas coronin 1 does not appear to be required for the functionality of resting macrophages, during an inflammatory stimulus coronin 1 is responsible for reprogramming the uptake pathway from phagocytosis to macropinocytosis in order to rapidly eliminate pathogens, a function that is dependent on activation of phosphoinositol (PI)-3-kinase (Bosedasgupta and Pieters, 2014). Furthermore, coronin 1 is largely dispensable for the functioning of B cells, mast cells, dendritic cells and natural killer cells, although the latter have been described to be affected by coronin 1 mutation in human (Moshous et al., 2013; Mace and Orange, 2014; Jayachandran and Pieters, 2015; Tchang et al., 2017). Also, coronin 1 was found to be dispensable for neutrophil function and recruitment in an *in vivo* model of liver injury and concanavalin A-induced hepatitis (Combaluzier and Pieters, 2009; Siegmund et al., 2013); in humans, coronin 1 has been associated with neutrophil survival and recent work has implicated coronin 1 in integrin-mediated functioning (Moriceau et al., 2009; Pick et al., 2017).

The in-depth analysis of coronin 1-deficient mice revealed that besides protecting intracellular mycobacteria from degradation within macrophages, a major function of coronin 1 is to regulate peripheral naïve T cell homeostasis; upon depletion of coronin 1, naïve T cells are virtually absent despite a normal development and selection in the thymus (Föger et al., 2006; Haraldsson et al., 2008; Mueller et al., 2008; Shiow et al., 2008; Lang et al., 2017). The role for coronin 1 in maintaining peripheral naïve T cells is conserved in humans: deletion or mutation of the *coro1a* gene has been reported to result in a selective depletion of naïve T cells (Moshous et al., 2013; Yee et al., 2016), or, when *coro1a* deletion or mutation is combined with other genetic aberrations, in more complex phenotypes including B and NK cell deficits besides the naïve T cell depletion (Shiow et al., 2009; Mace and Orange, 2014; Stray-Pedersen et al., 2014; Punwani et al., 2015; Yee et al., 2016). The mechanism underlying coronin 1-dependent naïve T cell survival remains controversial; in one study, coronin 1 was suggested to modulate the F-actin cytoskeleton, thereby regulating T cell survival (Föger et al., 2006); however, separate studies showed that altered

F-actin levels do not correlate with T cell viability nor are other actin-dependent leukocyte functions affected by coronin 1 deletion (Jayachandran et al., 2007; Mueller et al., 2011). Instead, coronin 1-deficient T cells were shown to be unable to respond to a range of T cell stimuli and the defect was narrowed down to be at the level of activation of the Ca^{2+} /calcineurin pathway (Haraldsson et al., 2008; Mueller et al., 2008).

Further analysis of mice lacking coronin 1 revealed an important function of this coronin family member in neurons, where it regulates Ca^{2+} - and cAMP-dependent signaling thereby modulating various neuronal activities, including cognition and behavior as well as target innervation (Jayachandran et al., 2014; Suo et al., 2014). It is also interesting to note that *M. tuberculosis* is known to subvert host cAMP signaling (Agarwal et al., 2009), and retention of coronin 1 at the phagosomal membrane may be part of this strategy. Whether and how Ca^{2+} and cAMP signaling are interconnected and whether coronin 1-dependent cAMP signaling plays a role in T cell homeostasis and mycobacterial survival within macrophages remains to be analyzed.

A CONCERTED ROLE FOR CORONINS IN *DICTYOSTELIUM* AND MAMMALS?

The available information on the role for coronins in *Dictyostelium* and mammals suggests that these proteins play diverse roles in a number of physiological processes. The hallmark of all coronin protein family members is their central WD40 repeat, that folds into a beta propeller structure. Beta-propellers, also known as beta-transducin repeats, form structural domains that are involved in protein-protein interaction (Smith, 2008). Both in *Dictyostelium* as well as in mammalian cells, several coronin family members colocalize with and are associated with actin (de Hostos et al., 1991; Shina et al., 2010; Pieters et al., 2013) whereas for a number of mammalian coronin proteins (coronin 2, 5, and 7) actin binding remains unclear (see e.g., Rybakina et al., 2004; Cai et al., 2007). It of course remains possible, especially in mammals with up to 7 coronin molecules being expressed, that the role for coronins in actin rearrangement is redundant and therefore single deletions may not result in an actin-dependent phenotype. On the other hand, it could be that the interaction of coronin molecules with the actin cytoskeleton ensures a local source of coronin molecules to allow conversion of extracellular signals into local changes in the cortical actin cytoskeleton (Wang et al., 1998; Eichinger et al., 1999; Gatfield et al., 2005). Such a role for coronins is consistent not only with their sequence as well as structural homology with the beta subunit of trimeric G proteins that function downstream of G protein-coupled receptor molecules (de Hostos et al., 1991; Gatfield et al., 2005; Appleton et al., 2006), but also with the activities of *Dictyostelium* coronin A and mammalian coronin 1 in the modulation of Ca^{2+} - and cAMP-dependent signal transduction pathways (Jayachandran et al., 2014; Suo et al., 2014; Vinet et al., 2014). Also, recent work linking coronins to the activation of small GTP binding proteins, that are well known regulators of the actin cytoskeleton (Berzat and Hall, 2010; Castro-Castro et al., 2011; Swaminathan et al., 2014), suggests

that coronins may be placed upstream of F-actin reorganization. Interestingly, in both *Dictyostelium* as well as mammalian cells, the role for coronin in the activation of Ca^{2+} /cAMP signaling could be separated from a potential involvement in F-actin rearrangement (Mueller et al., 2007, 2011; Jayachandran et al., 2014; Vinet et al., 2014). How, exactly, coronin molecules are being regulated is unknown. Also, the molecules upstream of coronin 1 possibly involved in the sensing of extracellular signals remain to be identified. In light of the here described roles for mammalian and *Dictyostelium* coronins in the trafficking and survival of intracellular pathogens, elucidation of these upstream receptor molecules may also shed light on the intricate relationship of pathogenic microbes and their eukaryotic hosts.

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AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

We thank Rajesh Jayachandran and Tohnyui Ndinyanka Fabrice for critical comments on the manuscript. Work in the Pieters Laboratory is supported by the Swiss National Science Foundation, the Swiss Multiple Sclerosis Society, the Novartis Foundation for Medical-Biological Research, the Gebert Ruff Foundation and the Canton of Basel.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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