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

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,
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 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) 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).

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(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 curA 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 pneumophila, 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 concanavolin 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; Shio 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 (Shio 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 Ca²⁺/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 Ca²⁺- 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 Ca²⁺ 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., Rybakin 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 as well as 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., Rybakin 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 Ca²⁺- 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 Ca²⁺/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.

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