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MINI-REVIEW

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ARHGAP21 as a master regulator of multiple cellular processes

Lucas R. O. Rosa | Gabriela M. Soares | Leonardo R. Silveira | Antonio C. Boschero | Helena C. L. Barbosa-Sampaio

Department of Structural and Functional Biology, Obesity and Comorbidities Research Center (OCRC), Institute of Biology, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil

Correspondence
Helena C. L. Barbosa-Sampaio, Department of Structural and Functional Biology, Obesity and Comorbidities Research Center (OCRC), Institute of Biology, University of Campinas (UNICAMP), Carl Von Linaeus, 2-238Cidade Universitária, Campinas SP 13083-864, Brazil.
Email: bsampaio@unicamp.br

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The cellular cytoskeleton is involved with multiple biological processes and is tightly regulated by multiple proteins and effectors. Among these, the RhoGTPases family is one of the most important players. RhoGTPAses are, in turn, regulated by many other elements. In the past decade, one of those regulators, the RhoGAP Rho GTPase Activating Protein 21 (ARHGAP21), has been overlooked, despite being implied as having an important role on many of those processes. In this paper, we aimed to review the available literature regarding ARHGAP21 to highlight its importance and the mechanisms of action that have been found so far for this still unknown protein involved with cell adhesion, migration, Golgi regulation, cell trafficking, and even insulin secretion.

KEYWORDS
ARHGAP21, cell dynamics, cytoskeleton, membrane trafficking

1 | INTRODUCTION

RhoGTPases are small proteins, a subfamily of the Ras superfamily, whose actions are crucial in cytoskeleton-related processes. This is demonstrated by the roles of its members, such as Rho, Rac, and cell division control protein 42 homolog (Cdc42), in multiple processes (Hall, 2012). They act like molecular switches, cycling between a guanosine diphosphate (GDP)–bound (inactive) form and a guanosine triphosphate (GTP)–bound (active) form. When GTP-bound, RhoGTPases interact with effectors, they trigger cellular processes. The first and most important result of RhoGTPase signaling is the reorganization of the cellular cytoskeleton, mostly through their interaction with mDia and Rho-associated kinase (ROCK), as well as activation of actin related proteins 2/3 (Arp2/3) (Hall, 2012). The cytoskeleton, in turn, is an important element in multiple cellular processes, including migration, proliferation, adhesion, endocytosis, and exocytosis (Figure 1).

Because to their importance, RhoGTPase activity is strictly regulated through three factors: Guanine nucleotide exchange factors (RhoGEFs), guanosine nucleotide dissociation inhibitors (RhoGDIs), and RhoGTPAse activating proteins (RhoGAPs; Hodge & Ridley, 2016). GEF activity leads to the exchange of GDP to GTP, acting as positive controllers that stimulate RhoGTPase action. GDIs act as negative controllers by sequestering the GDP-bound form of RhoGTPases, impairing GEFs's ability to activate them. Finally, GAPs also act as inhibitors of RhoGTPases by promoting the catalysis of GTP into GDP, inactivating the RhoGTPase after their activation by GEFs, and promoting the cycling necessary for correct RhoGTPase function.

Among the multiple existing RhoGAPs, this review will focus on Rho GTPase Activating Protein 21 (ARHGAP21), an overlooked and understudied member of the family with documented relevancy in multiple biological processes ranging from cellular migration to insulin secretion. ARHGAP21 (also known as ARHGAP10) was identified by Basseres, Tizzei, Duarte, Costa, and Saad (2002) and was found to be expressed in multiple tissues; notably, the brain, heart, skeletal muscle, and placenta presented the highest levels of expression, according to the study.

ARHGAP21 possesses a RhoGAP domain, a pleckstrin homology (PH) domain, and a PDZ domain. The RhoGAP domain is the one

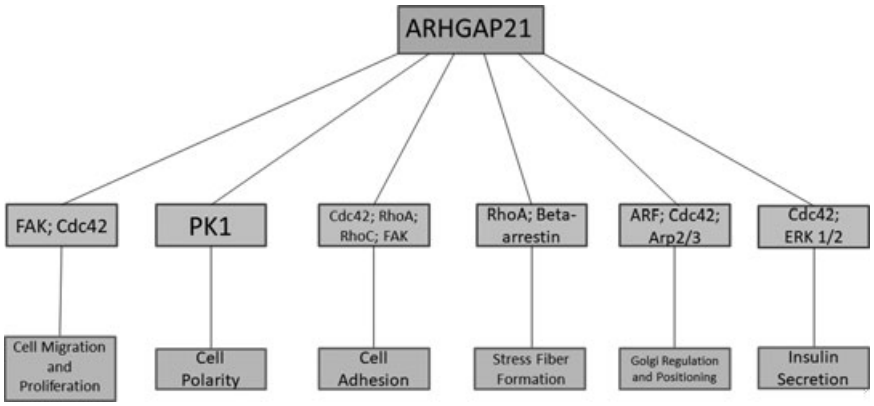

FIGURE 1 ARHGAP21, the interactive partners and their respective biological processes. FAK: focal adhesion kinase; PK1: Prickle 1

through which ARHGAP21 performs its most important action-regulating RhoGTPase proteins. Specifically, ARHGAP21 has been shown to have a GAP action over Ras homolog gene family member A (RhoA) and Ras homolog gene family member C (RhoC) in cancer cells (Lazarini et al., 2013), and Cdc42 in human prostate cancer cell line DU145 (Barcellos et al., 2013).

The function of the PH domain, in contrast, is less clear, thanks to the fact the properties of this kind of domain remains elusive. PH domains were initially found to bind with phosphoinositides (Lemmon, 2007; Scheffzek & Welti, 2012); however, with increasing research carried out, it became apparent that this interaction was an exception, not a rule, being present in only 10% of PH domains (Lemmon, 2007) and, in fact, is not a function of ARHGAP21's PH domain (Dubois et al., 2005). Since then, PH domains have been shown to have a multitude of roles in protein–protein interactions (Scheffzek & Welti, 2012). Notably, PH domains have also been shown to be capable of interaction with filamentous actin directly in Bruton's tyrosine kinase, and this could help PH domain–containing proteins to be recruited to their proper locations (Yao et al., 1999). ARHGAP21 also contains an Arf-binding domain (ArfBD) adjacent to its PH region (Menetrey et al., 2007); the interaction between ArfBD and Arfs promotes conformational changes in the PH domain, which, according to Menetrey et al. (2007), explains why ARHGAP21's PH domain does not bind to phosphoinositides.

Finally, PDZ domains mediate protein–protein interactions (Saras & Heldin, 1996). PDZ domains can bind with each other, assembling multimeric complexes (Saras & Heldin, 1996). Notably, most proteins that contain a PDZ domain seem to be associated with cytoskeletal functions (Fanning & Anderson, 1996), and the domain has been shown to interact with important cytoskeletal proteins that bind to actin, like protein 4.1, and the MERM family (Fanning & Anderson, 1996; Murthy et al., 1998; Saras & Heldin, 1996). PDZ domains are also present in multiple GEF proteins, and both GEFs and GAPs might be recruited to adhesion sites through interactions on their PDZ domain (Fukata & Kaibuchi, 2001). ARHGAP21 was the first protein to be found (not merely predicted) to have both a RhoGAP domain and a PDZ domain (Basseres et al., 2002), and ARHGAP21's PDZ domain possesses a peculiar characteristic: A P-loop, which suggests that ARHGAP21 could interact with GTP and ATP directly (Basseres et al., 2002). In fact, this makes it possible for ARHGAP21 to bind to GTP through the P-loop while still regulating the cellular GTP content through the RhoGAP domain (Basseres et al., 2002).

ARHGAP21 is found localized primarily on the nucleus, peri-nuclear regions, and the cytoplasm in multiple cell types (Barcellos et al., 2013; Bigarella, Borges, Costa, & Saad, 2009; Lazarini et al., 2013), but has been shown to be able to be recruited to other regions, such as the Golgi, possibly due to the binding of ArfBD to ADP ribosylation factor 1 (ARF) (Menetrey et al., 2007), and cellular junctions after cell adhesion (Barcellos et al., 2013). Thus, ARHGAP21 is able to act in multiple places within the cell.

Ever since its discovery, ARHGAP21 has been the subject of only a few studies, despite being associated with multiple cellular processes (Dubois et al., 2005; Ferreira et al., 2015; Lazarini et al., 2013; Menetrey et al., 2007; Wang et al., 2012). Our aim with this paper is to assess the current knowledge about ARHGAP21, providing a clear picture of studies moving forward.

2 | ARHGAP AS A REGULATOR OF CYTOSKELETAL PROCESSES IN CANCER CELLS

A significant amount of the available literature deals with the role of ARHGAP21 in many cancer-related subjects such as migration and adhesion, indicating that the protein might be a tumoral suppressor. ARHGAP21 has been identified as a cancer-related gene (Katoh & Katoh, 2004), and is overexpressed in head and neck squamous carcinomas (Carles et al., 2006). The same study found multiple splice variants in the proteome of these cells, and the authors suggested that this might be important for tumorigenesis (Carles et al., 2006).

ARHGAP21 depletion also increased cell migration in cervical carcinoma cell lines (Bigarella et al., 2009). In this study, ARHGAP was found to interact with focal adhesion kinase (FAK), and this interaction occurs at the C-terminal region of FAK and can occur at both portions of ARHGAP21 (Bigarella et al., 2009). The loss of ARHGAP21–FAK interaction led to increased FAK and Cdc42 activation and, thus, increase in migration (Bigarella et al., 2009). Thus, ARHGAP21 was identified as a potential tumor suppressor, being able to control the progression of the disease. ARHGAP21 depletion was also found to increase cell migration and decrease

proliferation in prostate adenocarcinoma cell line (PC3) (Lazarini et al., 2013). The increase in migration was attributed to its RhoGAP action over RhoC, as the lack of ARHGAP21 resulted in increased RhoC activity, which in turn led to increased migration (Lazarini et al., 2013). The modulation of proliferation in ARHGAP21-silenced PC3 cells was attributed to a modulation of the expression of multiple genes, notably the endothelin-1 signaling pathway through the inhibition of the expression of the endothelin-A receptor (Lazarini et al., 2013). Many members of the endothelin-1 pathway are ARHGAP21 partners, such as RhoA, FAK, and β-arrestin1, which have been previously implied to regulate endothelin-A receptor signaling (Lazarini et al., 2013). Thus, the lack of ARHGAP21 seems to have perturbed this pathway.

A recently discovered signaling pathway, named "Lateral Signaling," was also found to be related to migration in multiple cancer cell lines, with ARHGAP21 playing a key role (Zhang & Wrana, 2016; Zhang et al., 2016). This lateral signaling pathway controls cell polarity and morphology, which affects migration. This pathway consists of Prickle 1 (Pk1), an important cell polarity protein, and ARHGAP21. ARHGAP21 interacts with Pk1 and regulates RhoA (Zhang & Wrana, 2016), thus controlling the volatility of cell shape, which in turn regulates cell motility (Zhang & Wrana, 2016).

Another important process in the development of cancer is cell adhesion—or, rather, the lack of it (Okegawa, Pong, Li, & Hsieh, 2004), and ARHGAP21 plays a role in normal cell–cell adhesion. ARHGAP21 moves from the nucleus to the cellular junctions during cell adhesion, reducing Cdc42 activity in MDCK kidney cells and DU145 human prostate cancer cell lines (Barcellos et al., 2013). Knockdown of ARHGAP21 (which results in increased Cdc42 activation due to the loss of ARHGAP21's RhoGAP inhibitory activity over Cdc42) reduced the strength of cell–cell adhesion and, consequentially, increased migration (Barcellos et al., 2013). ARHGAP21 is a necessary protein for α-tubulin acetylation, possibly by aiding the organization and stabilization of tubulin, and the study pointed the lack of α-tubulin acetylation as a contributing factor for the alterations of migration behavior in cells lacking ARHGAP21 (Barcellos et al., 2013). The study also found that the ARHGAP21-deficient cells displayed reduced ability to undergo epithelial–mesenchymal transition (EMT) in response to hepatocyte growth factor stimulation (Barcellos et al., 2013). EMT is a process in which epithelial cells lose their adhesion properties and become more invasive and migratory. The effect of ARHGAP21 in EMT was also attributed to α-tubulin acetylation (Barcellos et al., 2013). ARHGAP21 is, therefore, important for both adhesion and migration, and has an interesting relationship with α-tubulin (Barcellos et al., 2013). Another study, by Pirot et al. (2014), showed that lymphoblastic leukemia associated hematopoiesis regulator 1 (LYL1) knockdown mice led to a reduction of ARHGAP21 gene expression and, consequentially, increased vascular permeability in the lungs of mice. LYL1 is a protein involved with the maturation of endothelial junctions. The reduction in ARHGAP21 resulted in an increase of RhoA activity and, finally, stress fiber formation. This suggests a pathway in which LYL1 regulates ARHGAP21, which in turn regulates RhoA to ensure proper endothelial adhesion in lung blood vessels. Therefore, ARHGAP21 is implicated in multiple cytoskeleton-related processes, such as adhesion, proliferation, and migration, through its modulation of Cdc42, RhoA, RhoC, and FAK.

Finally, ARHGAP21 inhibits the formation of stress fibers (Anthony et al., 2011; Pirot et al., 2014). In RhoA-mediated stress fiber formation upon angiotensin stimulation, ARHGAP21 modulation of RhoA can be controlled by its interaction with β-arrestin in human embryonic kidney HEK293 cells (Anthony et al., 2011). β-Arrestin1 is capable of binding to the GAP domain of ARHGAP21, thus inhibiting its action. When the β-arrestin–ARHGAP21 complex was disrupted, ARHGAP21 activity increased, leading to RhoA inhibition, and less stress fiber formation and actin reorganization (Anthony et al., 2011).

3 | ARHGAP21, CELLULAR TRANSPORT, AND GOLGI

ARHGAP21 is also involved in the regulation of the Golgi apparatus and in the transport of substances—endogenous or exogenous—within the cell. ARHGAP21 was identified as a link between ARF and the downstream activation of Cdc42 in the regulation of Golgi function, which then leads to the modulation of Arp2/3 and F-actin in HeLa and MCF-7 cell lines (Dubois et al., 2005). The interaction between ARHGAP21 and GTP-bound ARF1 or ARF6 was mediated by a C-terminal PH-domain region (Dubois et al., 2005). It has been suspected for a long time that ARF coordinated Cdc42 and RhoA for the regulation of Golgi but the connection between them had eluded researchers until this study came out (D'Souza-Schorey & Chavrier, 2006; Stamnes, 2002). The team was able to demonstrate that ARHGAP21 interacts with both ARF and Cdc42, establishing the link; ARHGAP21 interaction with GTP-bound ARF is required for its localization to and association with the Golgi complex (Dubois et al., 2005), where it will act as a RhoGAP for Cdc42 to affect Golgi organization (Dubois et al., 2005). A subsequent study reinforced that ARHGAP21 physically interacts with ARF through its PH domain and an adjacent α-helix (Menetrey et al., 2007). ARHGAP21 depletion reduced Golgi's ability to be positioned correctly (Hehnly, Xu, Chen, & Stamnes, 2010). This positioning process is dependent on dynein and on microtubule and is controlled by Cdc42, which is, in turn, modulated by ARHGAP21, ARF1, and a vesicle-coating protein coatomer.

On top of its direct action over Golgi-related processes, ARHGAP21 is also involved in the traffic of substances within the cell. The retrograde transport of *Escherichia coli*'s Shiga toxin through the secretory pathway is modulated by RhoGTPase activity, especially Cdc42 (Hehnly, Longhini, Chen, & Stamnes, 2009). ARHGAP21 knockdown (or the constitutive activation of Cdc42 resulted in the same action, i.e., increased cdc42 action) in monkey kidney Vero cell lines inhibited the transport of Shiga toxin, and the addition of the toxin by itself lowered the levels of Cdc42 due to the increase in ARHGAP21; thus, ARHGAP21 seems to be important for the transport of the toxin within the cell, through its modulation of

Cdc42 (Hehnly et al., 2009). The transport of influenza virus neuraminidase was also modulated by ARHGAP21 (Wang et al., 2012). The intracellular transport of influenza virus neuraminidase is crucial for the virus' life cycle, and the depletion of ARHGAP21 (or the constitutive activation of Cdc42) stimulated neuraminidase transport to the cell membrane. Silencing ARHGAP21 led to the increase in viral replication (Wang et al., 2012). Thus, ARHGAP21 modulation over Cdc42 signaling appears to be important in influenza virus infection through its influence over neuraminidase transport.

4 | ARHGAP21 AND GLUCOSE HOMEOSTASIS

The second phase of insulin secretion (which is less intensive but longer lasting than the first phase) is a process that depends on actin rearrangement (Kalwat & Thurmond, 2013). The cortical actin acts as a barrier that prevents the passage of insulin granules coming from the cytoplasm to the membrane and, thus, this cytoskeletal barrier needs to be rearranged. Glucose stimulation of the pancreatic β cell promotes that rearrangement through multiple pathways, one of the most important involving Cdc42 (Nevins & Thurmond, 2003).

Considering the involvement of the actin cytoskeleton in insulin secretion and the importance of RhoGTPases in the modulation of actin (and the already established role of Cdc42 in insulin secretion; Kowluru, 2010), it was not a stretch to imagine that ARHGAP21 could play a role in insulin secretion; thus, our group decided to investigate the possible involvement. We found that ARHGAP21 is present in the β cell of neonatal mice and MIN6 cell line (Ferreira et al., 2015), and ARHGAP21 knockdown increased basal insulin secretion but not glucose-stimulated insulin secretion, as expected. ARHGAP21 knockdown also led to an increase in extracellular signal-regulated kinases 1/2 (ERK 1/2) phosphorylation, which was previously implied in actin rearrangement during insulin secretion (Kalwat & Thurmond, 2013; Longuet et al., 2005). These findings suggest, therefore, that ARHGAP21 seems to be involved in insulin secretion, possibly through a modulation of ERK1/2.

A recent paper from our group examined ARHGAP21's effects on overall glucose homeostasis (Soares et al., 2018). The study used haplodeficient mice, with 50% less ARHGAP21 than wild-type mice, and was fed high-fat diet (HFD). Surprisingly, ARHGAP21-deficient mice showed a protection against the deleterious effects of HFD, with lower body weight gain, better glucose tolerance, and insulin sensitivity, and lower insulin secretion and β-cell area (Soares et al., 2018). In addition, haplodeficient mice fed on a regular diet also presented lower body weight, reduced white adipose tissue, and increased brown adipose tissue, which implies that ARHGAP21 may play a role in controlling body composition, energy expenditure, and overall glucose homeostasis (Soares et al., 2018). However, the underlying molecular mechanisms involved in these processes still remain unclear, as this study was mostly descriptive.

5 | CONCLUDING REMARKS

As shown in this review, ARHGAP21 appears to be an important protein in multiple processes, especially those linked with the actin cytoskeleton, including migration, adhesion, intracellular transport, and insulin secretion. Through ARHGAP21's modulation of RhoGTPases, especially RhoA and Cdc42, and its interaction with other proteins, such as β-arrestin1, ARFs, ERK, and FAK, which usually serve to either localize ARHGAP21 for RhoGAP action or modulate its activity, ARHGAP21 positions itself as a key member in the regulation of those processes. It is still unclear how ARHGAP21 specificity occurs—that is, why ARHGAP21 seems to be able to affect multiple processes independently through the same mechanism (RhoGAP action of RhoA, RhoC, and Cdc42). Localization of its RhoGAP action is probably one answer for this conundrum, with certain interactions (like its interaction with ARF1 and ARF6) serving to localize ARHGAP21 to the sites in which its RhoGAP activity is required (in this case, the Golgi complex); however, other, still unknown, mechanisms might play a role in this specificity process as well. Unfortunately, very little is understood about how external stimuli might control ARHGAP21's expression and action—most of the studies focus on observing the effects of ARHGAP21 modulation (like silencing) on cellular processes and not so much on the mechanisms through which external conditions might modulate ARHGAP21 action.

Despite its importance, ARHGAP21 has been a neglected protein since its discovery and holds an incredible potential yet to be clarified by future studies.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ORCID

Helena C. L. Barbosa-Sampaio http://orcid.org/0000-0002-5244-889X

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