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# Zizimin and Dock guanine nucleotide exchange factors in cell function and disease

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**Zizimin proteins belong to the Dock (dedicator of cytokinesis) superfamily of guanine nucleotide exchange factor (GEF) proteins. This family of proteins plays a role in the regulation of Rho family small GTPases. Together the Rho family of small GTPases and the Dock/Zizimin proteins play a vital role in a number of cell processes including cell migration, apoptosis, cell division and cell adhesion. Our recent studies of Zizimin proteins, using a simple biomedical model, the eukaryotic social amoeba *Dictyostelium discoideum,* have helped to elucidate the cellular role of these proteins. In this article, we discuss the domain structure of Zizimin proteins from an evolutionary viewpoint. We also compare what is currently known about the mammalian Zizimin proteins to that of related Dock proteins. Understanding the cellular functions of these proteins will provide a better insight into their role in cell signaling, and may help in treating disease pathology associated with mutations in Dock/Zizimin proteins.**

**Keywords:** *Dictyostelium*, RacGEFs, Zizimins, Dock proteins, Rho small GTPases

**Abbreviations:** cAMP, cyclic adenosine monophosphate; Dock, dedicator of cytokinesis; GEF, guanine nucleotide exchange factor; DHR, Dock-homology region; PH, Plekstrin homology. $PIP_2$, phosphatidylinositol-(4,5)-bisphosphate; $PIP_3$, phosphatidylinositol-(3,4,5)-trisphosphate

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## Introduction

Zizimins are guanine nucleotide exchange factor (GEF) proteins, which specifically regulate the cycling of Rho family of small GTPases (Rac, Rho and Cdc42) from an inactive to an active state. Since these small GTPases have a crucial role in regulating the cytoskeleton in many important cellular processes such as cell migration, proliferation, cytokinesis and phagocytosis,[1-3] Zizimins therefore play central role in regulating a broad spectrum of cellular functions. Zizimins are related to Dock proteins, which have a similar domain topology and together they constitute the Dock superfamily of proteins (**Fig. 1A**). There are five human Dock and six human Zizimin proteins which are subdivided into four subclasses: consisting of the Zizimin (Ziz), Zizimin-related (Zir), Dock4 and the Dock180 subfamilies, based on their domain structure and sequence similarity. Within these groupings, our current understanding of cellular role of Ziz and Zir proteins is the most limited and our recent study of these proteins has provided some new insights.[4]

Dock and Zizimin proteins are characterized by their common domains; the Dock Homology Region 1 (DHR1) and Dock Homology Region 2 (DHR2).[5,6] Although the role of the DHR1 domain is unclear, it has been and is also associated with lipid binding activity [phosphatidylinositol-(3,4,5)-trisphosphate (PtdIns(3,4,5)$P_3$)].[5,7,8] The DHR2 domain is responsible for GEF activity.[6,9,10] The Zizimin subfamily, but not the Zizimin-related subfamily, contains a Plekstrin Homology (PH) domain involved in membrane localization through phospholipid binding.[11]

## Phylogeny of Domain Structure

Zizimin proteins are widespread throughout eukaryotes. They are found in all kingdoms of the eukaryotic tree. Dock proteins are much more sparse. They are notably absent from plants and Chromalveolates. This begs the question whether Zizimins may have evolved first.

The exact location of the root of the eukaryotic tree is still debated, but a

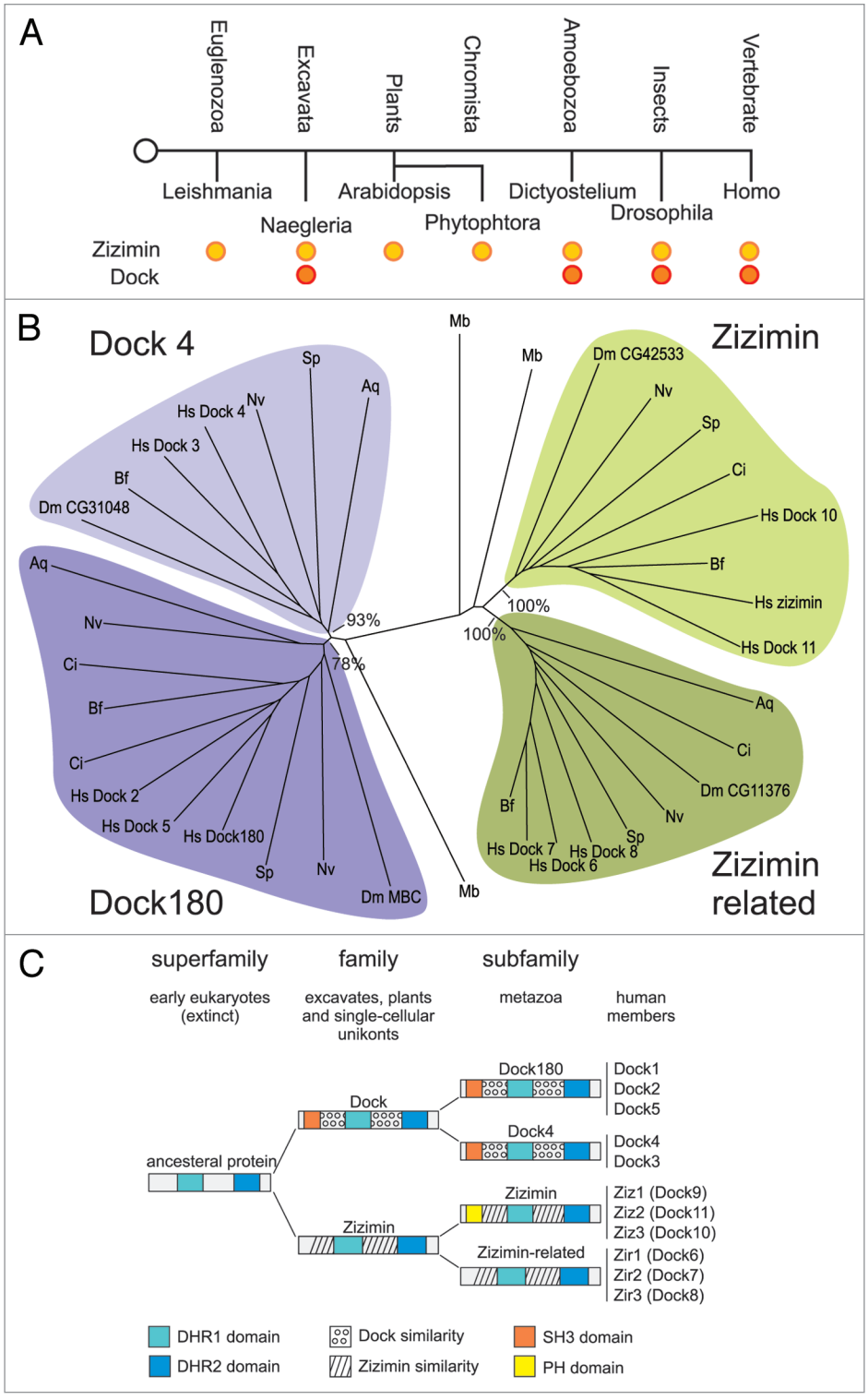


**Figure 1.** Nomenclature and evolution of the Dock and Zizimin protein families. (**A**) Schematic representation of eukaryotic evolution. The root of the tree is on the left. The presence of Zizimin (orange) and Dock (red) genes in the genomes of respective organisms is indicated. (**B**) Full length sequences of Dock and Zizimin homologs of indicated species were aligned and a bootstrapped (n = 1000) tree was drawn. Bootstrap values of the branches that separate the different subfamilies are indicated. Hs, *Homo sapiens*; Bf, *Branchiostoma floridae*; Sp, *Strongylocentrotus purpuratus*; Dm, *Drosophila melanogaster*; Ci, *Ciona intestinalis*; Nv, *Nematostella vectensis*; Aq, *Amphimedon queenslandica;* Mb, *Monosiga brevicollis*. (**C**) Most likely sequence of events that lead to the current distribution of Dock and Zizimin isoforms in human.

**Table 1.** Mammalian Zizimin cellular functions

| Name | Alternative name | Function | Substrate | Mammalian cell type | Refs. |
|---|---|---|---|---|---|
| Zizimin-related1 | Dock6 | Lamellipodia formation, Filopodia formation, Regulate neuronal outgrowth | Cdc42 Rac1 | N1E-115 Neuroblastoma cells | 1 |
| Zizimin-related2 | Dock7 | Microtubule localization, Neuronal axon formation, OE causes multiple axons, KO suppresses axon formation, Cell migration | Rac1 Rac3 | Hippocampal Neurons, Schwann cells | 45 |
| Zizimin-related3 | Dock8 | Lamellipodia formation, Cell migration, Proliferation, adhesion | Cdc42 Rac1 | Dendritic cells | 24, 35 |
| Zizimin1 | Dock9 | Filopodia formation | Cdc42 | NIH-3T3 cells, COS-7 cells | 7, 10 |
| Zizimin2 | Dock11 | Filopodia formation, Cell migration | Cdc42 | 293T cells, Dendritic cells | 23, 10 |
| Zizimin3 | Dock10 | Amoeboid invasion | Cdc42 | A375M2 Melanoma Cells | 44 |

A table showing the conserved functions and substrate specificity of the mammalian Zizimin/Zizimin-related subfamilies of Dock proteins.

recent paper puts the root close to the Euglenozoa.[12] A schematic based on the proposed eukaryotic tree in this paper is drawn in **Figure 1A** and the presence and absence of Docks and Zizimin genes was indicated. Interestingly, a Zizimin gene is found in Leishmania, a member of the Euglenozoa. The excavate Naegleria, which falls on the next branch of the tree encodes both Zizimin and Dock proteins. As such, the Dock gene must have been lost in Plants and Chromalveolates, which share a single branch. Both Dock and Zizimin proteins are well conserved throughout unikont evolution, as both genes are found in Amoebozoa, insects and vertebrates. Taking the uncertainty of the location of the root of the eukaryotic tree into account, the most likely sequence of events is that the Dock and Zizimin families split before the eukaryotic last common ancestor (**Fig. 1C**).

To investigate the further split of Dock and Zizimin into the Dock180/Dock4 and Zizimin/Zizimin-related subfamilies that are found in human and Drosophila,[13,14] Dock and Zizimin genes were collected from various metazoan species and the Choanoflagellate Monosiga. Sequences were aligned using ClustalX and a phylogenetic tree was constructed from the results (**Fig. 1B**). All metazoan Dock/Zizimin homologs fall into the indicated Dock180/Dock4 and Zizimin/Zizimin-related subfamilies, demonstrating that these subfamilies must have split at the onset of metazoan evolution. In agreement with this, the Dock/Zizimin proteins from the Choanoflagellate Monosiga do not group with any of the subfamilies.

The widespread distribution of Zizimin genes even in evolutionarily ancient eukaryotes signifies its importance in basic cellular function. Similarly, the split of the Dock180/Dock4 and Zizimin/Zizimin-related in early metazoa indicates that the different isoforms may be involved in elementary organization of multicellular tissues. The conserved domain sequence and domain structure of Docks and Zizimins suggest that their cellular functions are also conserved. The function of these proteins, the cellular localization mechanisms and the role of specific domains is now slowly being uncovered.

## What are Docks Doing?

The human genome encodes five Dock subfamily paralogues (numbered Dock1–5, **Fig. 1**). All of these proteins are exchange factors for Rac1, although Dock2 has also been shown to also catalyze GTP exchange in Cdc42.[15] The initial discovery of mammalian Dock1 (also known as Dock180) first identified a role of Dock proteins in controlling cell morphology.[16] This function is shared with its closest homologs, Dock5, that regulates spreading and migration of epithelial cells,[17] Dock2 regulates motility and polarity during neutrophil chemotaxis[15,18] and the related Dock3 that induces axonal outgrowth by stimulating membrane recruitment of the WAVE complex.[15,19] Expression of encoded proteins also varies, with Dock2 showing expression in neutrophils,[15] Dock3 is expressed in neurons,[15,19] and Dock1 is expressed in a range of human tissue, but highest in kidney and placenta.[16] Thus, our understanding of human Dock proteins suggests that they are commonly involved in regulating cell shape and movement, and membrane protrusions. This functional role of Dock proteins is evolutionary conserved since our recent study has shown that the single celled amoeba, *Dictyostelium discoideum,* expresses three Dock paralogues that have both a DHR1 and a DHR2 domain. All three proteins are recruited to the leading edge of moving cells and disruption of the genes leads to a decrease in cell speed[20] and our unpublished observations suggest that the functional role of Dock proteins is evolutionary conserved.

## What are Zizimins Doing?

The name Zizimin originates from the Hebrew word, "Zizim," meaning spike.[10] The mammalian Zizimin and Zizimin-related proteins have been shown to have a range of functions including lamellipodia and filopodia formation, microtubule localization and cell migration[10,21-23] (**Table 1**). Studies in Zir3 knockout mice (Dock8 null) showed that the Zir3 protein regulates actin dynamics during cell migration in dendritic cells, through the activation of Cdc42.[24] In mouse neuronal

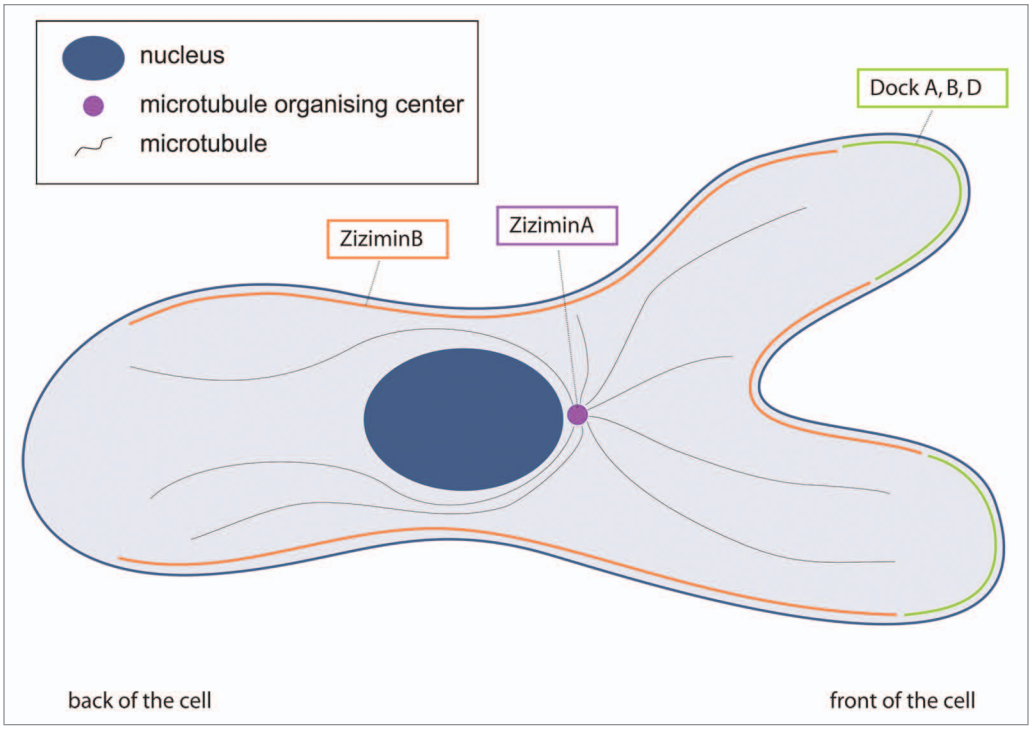


**Figure 2.** A schematic diagram representing the localization of the *Dictyostelium* Dock superfamily of proteins. Within the Zizimin family, Zizimin A localizes to the microtubule organizing center (MTOC) (purple) and Zizimin B (orange) localizes to the front and sides of the cell. Within the Dock family, Dock A, B and D (green) all localize to the leading edge (pseudopods) of the cell.

cells, Zir1 (Dock6) has been shown to regulate neuronal outgrowth through Rac1 and Cdc42 activation, as well as promoting lamellipodia and filopodia formation.[25] The Zizimin-related protein in Drosophila has been implicated in the cellular immune response.[13,14] Other studies show that Ziz1 (Dock9) regulates neuronal growth and filopodia formation through Cdc42 activation.[10,26] Although Ziz and Zir proteins are involved in a diverse range of cell functions, the common trend involves the formation of filopodia and cell migration through regulation of the actin cytoskeleton. This is not surprising considering the small GTPases, Cdc42 and Rac1 are mainly involved in regulating actin cytoskeletal dynamics, with Cdc42 specifically regulating F-actin dynamics during filopodia formation. Two of the most highly expressed *Dictyostelium* Zizimin paralogues have recently been characterized, providing new insights into the role of these proteins.[4]

### *Dictyostelium Discoideum*

*Dictyostelium* is a unicellular social amoeba that inhabits forest soil, feeding on yeast and bacteria.[27] When conditions are unfavorable, the surrounding cells communicate with each other via pulses of extracellular cAMP.[28] These signals act as a chemoattractant initiating aggregation by chemotaxis. Cells aggregate together forming mounds which differentiate into multi-cellular spore producing fruiting bodies within 24 h. When the environmental conditions subsequently become favorable for growth, spores released from the fruiting body germinate and reproduce as single cells.[27] This chemotaxis and development process can be easily mimicked in a laboratory by artificially pulsing cells with cAMP, creating a simple model system to examine cell movement and development, and a range of intriguing biomedical questions.[29,30]

### Zizimins in *Dictyostelium*

There are four Zizimin family proteins in *Dictyostelium* (ZizA-ZizD) and the roles of ZizB and ZizA have been recently investigated.[4] In this study, isogenic cell lines in which these proteins are either overexpressed or knocked-out were used to localize the protein and to determine potential roles in cell movement and development.[4] ZizB-GFP shows enrichment in the cortex, while ZizA-GFP localizes to the Microtubule Organizing Centre (MTOC) (**Fig. 2**). This localization is distinct to that of the *Dictyostelium* Dock family proteins, which localize exclusively to the leading edge of the cell during movement,[20] suggesting that the Zizimin proteins have a different functional role.

*Dictyostelium* cells are chemotactically sensitive to cAMP. A common way to analyze the response of proteins to cAMP stimulation is the sudden perfusion of cells with a saturating concentration of cAMP. In resting cells, prior to stimulation, ZizB-GFP is enriched in the cortex, but this enrichment is transiently lost following cAMP stimulation, and returns to the membrane after eight seconds.[4] This behavior is opposite to that of the *Dictyostelium* Dock family proteins, which move from the cytosol onto the membrane upon cAMP stimulation. The localization of ZizB is similar to that of that of cortical actin filaments. These filaments help reinforce the membrane integrity in the

resting state, but their rigidity impairs the formation of new protrusions. Our observations suggest that ZizB may be involved in cortex stabilization and that activation of chemoattractant receptors may inhibit ZizB to locally reduce cortical tension.[4] It remains to be determined if the localization signal is a phospholipid, such as phosphatidylinositol-(4,5)-bisphosphate [PtdIns(4,5)$P_2$], or if the localization domain on ZizB is within DHR1 domain.

Consistent with a role in cortex stabilization for ZizB, *Dictyostelium* cell lines lacking ZizB showed defects in cell migration, development, cytokinesis and growth,[4] and a reduced response to environmental stress induction (data not shown). These divergent processes would all be expected to be regulated by cortex integrity.[31-33]

Overexpression of ZizB-GFP results in an increase in filopodia formation. This behavior is common to mammalian Ziz and Zir proteins,[10,25,26] through Rac1 and/or Cdc42 activation. Identification of the binding partners of ZizB confirmed that the protein binds to *Dictyostelium* Rac1 in vivo, multiple Rac proteins in vitro and a variety of actin and myosin associated proteins, including, ForminA, Arp2/3 subunits, Cap32/34 subunits and Severin.[4] The cellular localization and binding partners of ZizB therefore strongly support a conserved role for the protein in *Dictyostelium* and mammalian systems.

In contrast to ZizB, the ZizA-GFP protein is recruited to the MTOC and does not show chemoattractant-induced localization or cause any alterations in cell movement or filopod formation.[4] A role for the protein in cell function is thus likely to be related to microtubule organization, which was confirmed by preliminary immunoprecipitation data that suggests an interaction between ZizA and tubulin. These factors indicate a divergent role for ZizA in *Dictyostelium*, with the potential mammalian homologs still to be defined.

## Zizimin and Dock Proteins in Disease

Zizimin and Dock family proteins have been implicated in a number of human diseases. Multiple deletions and single mutations in Zir3 have resulted in an immunodeficiency syndrome,[34] and an autosomal-recessive form of hyper-IgE syndrome,[35,36] presenting with eosinophilia (increased eosinophil count in peripheral blood), increased serum IgE levels and recurrent pneumonia, skin abscesses and viral infections. Furthermore, reduced Zir3 gene expression has also been associated with squamous cell lung cancer and has been investigated in the various lung cancer cell lines.[37] Truncated Zir1 leads to Adams-Olivers syndrome leading to sever developmental defects.[38] Single nucleotide polymorphisms in Ziz1 have been associated with an increased risk of bipolar disorder.[39] Dock1 and Dock4 have been implicated in tumorigensis[40,41] and the latter is associated with autism and dyslexia.[42] Dock3 has recently been found to play a critical role in integrating neuronal death signals by presenilin proteins in Alzheimer disease.[43]

Understanding the mechanisms of these proteins in each condition is thus likely to help in treatment. Since *Dictyostelium* has been identified as a suitable research model for over 33 human diseases,[29,30] and both the Dock and Zizimin family of proteins show conserved structure and function between *Dictyostelium* and mammalian systems, this model may provide a robust system to investigate the conserved function of these proteins in the pathophysiology of Dock/Zizimin-associated diseases.

## Conclusion

The cellular functions outlined in this article show that Zizimin proteins play a role in regulating the cytoskeleton. Mammalian Zizimins show a common role in the regulation of filopodia formation, although little is known about the molecular mechanisms. In *Dictyostelium*, two Zizimin proteins have so far been partly characterized: ZizA, which localizes to the MTOC and binds tubulin; and ZizB which shows more stereotypical Zizimin characteristics through localizing to the cortex, regulating and stabilizing the actin filament network and filopod formation. These roles suggest that *Dictyostelium* Zizimin family proteins have a more diverse function than the Dock family proteins. The advanced techniques for cell biology analysis in this model may therefore enable a better understanding of the multiple roles of Zizimin and Dock-related proteins in human disease.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.


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