Filamin A and Big2

A shared endocytic pathway

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Neural proliferation, migration and differentiation require reorganization of the actin cytoskeleton and regulation of vesicle trafficking to provide stability in maintaining cell adhesions, allow for changes in cell shape, and establishing cell polarity. Human disorders involving the actin-binding Filamin A (FLNA) and vesicle trafficking Brefeldin-associated guanine exchange factor 2 (BIG2 is encoded by the *ARFGEF2* gene) proteins are implicated in these various developmental processes, resulting in a malformation of cortical development called periventricular heterotopia (nodules along the ventricular lining) and microcephaly (small brain). Here we discuss several recent reports from our laboratory that demonstrate a shared role for both proteins in actin-associated vesicle trafficking, which is required to maintain the expression and stability of cell adhesion and cell cycle associated molecules during cortical development. While changes in FLNA and BIG2 have first been linked to disorders involving the central nervous system, increasing reports suggest they are associated with aberrant development of various other organ systems in the body. These studies suggest that vesicle trafficking defects in FLN-GEF dependent pathways may contribute to a much broader phenotype than previously realized.

Introduction

Dynamic changes in the actin cytoskeleton are required for fundamental processes that drive cell adhesion and

migration.^{1,2} Filamins are actin-binding proteins that regulate the cytoskeleton by serving as a scaffold for stabilizing actin filaments and linking them to the cell membrane to allow for signal transduction.³ Filamin A (FLNA) is one of three isoforms (the others being FLNB and FLNC) and has been most intensely studied. FLNA is a 280 kD protein that undergoes both homo and heterodimerization with other filamins.⁴ It is comprised of an actin-binding N terminus, followed by 24 Ig-like repeats with β -pleated sheet units. The end C-terminal repeat 24 is responsible for dimerization, whereas repeats 16–23 largely mediate binding to over 90 interacting partners.¹ In general, FLNA effects have largely been thought to occur through its regulation of adhesion molecules/receptors and changes in actin filaments, predominantly through actin effectors such as the RhoGTPases. The cell biological changes observed following disruption of filamin with the various interactors have not necessarily translated into human disease phenotypes nor have they given insight into which pathways are most physiologically relevant. Here we focus on a FLNA-associated human and mouse disease phenotypes in providing insight into actin-associated processes that would contribute to this disorder and review recently discovered interactions between FLNA and another protein BIG2, causal for the same disease, in effecting membrane trafficking and subsequent cell adhesion, migration, and proliferation.

FLNA and BIG2 in Human Malformations of Cortical Development

Characterization of the human phenotype in disorders associated with *FLNA* mutations provides a means with which to identify the most relevant *FLNA*-dependent biological pathways. Loss of *FLNA* function leads to periventricular heterotopia (PH), a malformation of cortical development characterized by ectopic nodules of neurons along the neuroependyma of the lateral ventricles. During normal development, proliferating neural progenitors along the neuroependyma undergo a decision pathway to become post-mitotic neurons/intermediate progenitors or to remain as a primary progenitor. With transformation to the intermediate or post-mitotic state, neural cells migrate from the ventricular zone to the cortical plate. Failure in initial migration due to *FLNA*-dependent defects in the actin cytoskeleton was initially thought to cause PH.⁵ *FLNA* dependent PH is an X-linked disorder such that heterozygous females harbor the PH phenotype, and males are generally embryonic lethal. Loss of *FLNA* function leads to cell autonomous defects in neural motility, although many cells reached their appropriate destination in the cortical plate.^{6,7} These findings raised the possibility that some fraction of neural progenitors harboring the mutant *FLNA* did not migrate properly whereas those expressing the normal *FLNA* protein had no migratory impairment.

In addition to a motility problem, recent studies suggest that *FLNA* loss leads to a proliferative defect. While microcephaly is not seen in heterozygous females with *FLNA* mutations (likely due to mosaicism), hemizygous males have been reported to have thinner cortices, and loss of cortical convolutions consistent with underlying microcephaly.⁸ Loss of *FLNA* function in homozygous mice leads to microcephaly and a reduction in neural progenitor proliferation over time.⁹ Characterization of null *FLNA* mouse progenitors has shown that the decreased proliferation is not due to an increase in cell death, but rather a decrease in production due to a prolongation in the cell cycle time of progression through G2-M and G1-S phases. *FLNA*

inhibition leads to impaired degradation of several cyclinB/cdk1 associated proteins. A slowing in the cell cycle ultimately causes a delay and reduction in progenitor production over time. Moreover, M phase (mitosis) occurs along the neuroependymal lining, suggesting that a common process might mediate neuroependymal integrity, initial migration and brain size.

While coordinating the actin cytoskeleton through *FLNA* assists in many basic cell processes, identification of a second gene causal for PH suggest that disruption of actin filaments alone is not responsible for the disease phenotype. Autosomal recessive mutations in the human gene *ADP-ribosylation Factor Guanine Exchange Factor 2* (*ARFGEF2*, encodes for BIG2) also cause PH and microcephaly.¹⁰⁻¹² Brefeldin A guanine exchange factor 2 (BIG2) is a 180 kDa protein which belongs to a family of three highly conserved large molecular weight mammalian Sec7-GEFs (the others being GBF1, BIG1/2), characterized by their sensitivity to the fungal metabolite Brefeldin-A (BFA).¹³⁻¹⁵ A highly conserved Sec7 domain in these GEFs directs GDP-to-GTP exchange and activation of the ADP-ribosylation factors (ARFs).¹⁶⁻²⁰ ARFs regulate vesicular traffic through recruiting coat proteins.²¹ The N-terminal of BIG2 binds Exo70, a member of the exocyst complex involved in vesicle exocytosis.²² Several AKAP (A-kinase anchoring protein) binding sites are located within the Exo70 binding region. BIG2 residues 27–48 interact with PKA (Protein Kinase A) subunits RI α and RI β residues 284–301 interact with subunits RII α and RII β , and residues 517–538 interact with subunits RI α , RI α , and RII β .²³ Finally, at its C-terminal, BIG2 has been shown to bind the β subunit of GABA receptors.²⁴ As a kinase anchoring protein, BIG2 is implicated in the spatiotemporal activation of cAMP signaling, and PKA-dependent phosphorylation also appears to regulate BIG2 activation of the ARFs.^{25,26} Given that vesicle trafficking is in part mediated through the actin cytoskeleton, some interplay between these two genes is likely most relevant in disease pathogenesis and understanding their primary functions.

Comparisons between the human disease phenotypes and animal models associated with the two causal PH genes

provide several key insights. First, PH due to *ARFGEF2* mutations is an autosomal recessive disorder, indicating that all the neural progenitors harbor the genetic mutation.¹¹ Thus a cell-autonomous migratory defect alone from disruption in actin-dependent cell morphology is not sufficient to explain PH formation since many neurons in this disorder migrate appropriately into a normal appearing, overlying cortex. Recent studies suggest that loss in cell-cell adhesion along the neuroependyma leads to a disruption in ventricular neuroepithelium, alters radial glial fibers, and disrupts migration out of the ventricular zone.²⁷⁻²⁹ This impairment in cell-cell adhesion is likely a primary cause of the heterotopia. Both loss of *FLNA* and *Big2* function in mice, however, also demonstrate impairments in neural motility.^{30,31} A migratory defect might be more pronounced near the end of cortical development as a slower migratory rate might influence the ability of the latest born neurons to reach their final destination. In this context, shared biological mechanisms that regulate cell adhesion and cell migration in progenitors along the neuroepithelial lining are likely most relevant for discerning *FLNA* and *BIG2* function. Second, both genes also lead to microcephaly in mice.^{9,31} The impairment in degradation of various cell-cycle associated proteins seen with loss of *FLNA* function would be indicative of a problem in vesicle trafficking, involving endocytosis and/or lysosomal degradation. Third, both proteins show strong overlapping expression along the neuroependymal lining.³² Thus, a trafficking defect within progenitors along the neuroepithelium could disrupt the lining (from loss in cell-cell contacts), disrupt initial migration (from loss in cell-ECM contacts) and alter proliferation (from impaired trafficking of cell receptors and intracellular signaling molecules).

Endosomal Trafficking in Phenotypes Associated with PH

Several studies have implicated *BIG2* and *FLNA* in endosomal vesicle trafficking in cortical development. Although *BIG2* is mainly associated with trafficking through the trans-Golgi network,

it also regulates recycling endosomes through class1 ARFs.³³ ARFs have been shown to reside at the cell surface with ARF1 and ARF3 mediating endocytosis.^{21,34} Further, BIG2 dependent recycling of the integrin receptor at the cell membrane has been thought to mediate neuronal migration.³⁵ While FLNA has been linked to multiple cell functions (receptors, intracellular signaling pathways), the actin binding protein is directly involved in trafficking. FLNA binds to the protease furin, can direct the rate of internalization of this protein, and directs sorting of furin from the early endosome to the trans-Golgi network. FLNA also is required for appropriate localization of late endosomes and lysosomes.³⁶ Mechanistically, furin co-localizes with caveolin, an integral membrane protein involved in receptor independent endocytosis.³⁷ Caveolin binds FLNA, and FLNA phosphorylation and its binding to actin are required for caveolin dependent endocytosis.³⁸⁻⁴⁰ Phosphorylation of caveolin is involved in integrin-regulated caveolae trafficking and also in signaling at focal adhesions in migrating cells.⁴¹ Transient inhibition of integrin binding and signaling disrupts the attachment of apical processes along the ventricular lining, alters internuclear kinetic migration and alters the cleavage orientation of dividing cells.⁴² Collectively, these studies provide a common endocytic pathway between FLNA and BIG2 in causing the PH phenotypes.

Endocytosis relies on vesicle formation for maintenance of protein localization, expression, and function, and actin for vesicle movement.^{43,44} A fundamental question lies in whether FLNA and BIG2 act separately or in some coordinated fashion during endocytosis. Our recent studies have shown that Big2 and FlnA physically interact and both are expressed in the Golgi and along the cell membrane.^{31,32} Loss of Big2 in transgenic mice results in a consequent increase in both FlnA and phosphoFlnA at serine 2152. FlnA overexpression impairs neural migration by altering the number and size of paxillin focal adhesions. Conversely, loss of FlnA expression similarly impairs neural migration, in part, through changes in paxillin stability at

the
cell

Figure 1. Endosomal recycling through Big2 and FlnA. FlnA phosphorylation localizes Big2 to the cell membrane, thereby activating the Arfs. Arfs are required for vesicle formation. Disruption of endocytosis leads to disruption of cell-cell adhesion molecules, giving rise to periventricular heterotopia. Impaired turnover of integrin receptors alters neural migration. Impaired signaling through cadherin/catenins alters neural proliferation.

membrane. Further, both enhanced or loss of FlnA expression has been shown to cause PH in humans.^{5,45} Taken in this context, Big2 could alter FlnA stability and expression through endocytosis, raising the possibility that FlnA alone serves as a final common pathway in this disease.

More recent studies provide another potential explanation for FlnA-Big2 interactions. Loss of FlnA leads to a reciprocal, enhanced expression of Big2, suggestive of a compensatory feedback.³⁰ We have also found that Big2 localization is dependent on FlnA, with FlnA phosphorylation leading to redistribution of Big2 from the Golgi apparatus to the membrane. Arf1 activation through Big2 at the membrane is dependent on FlnA.

Thus, loss of FlnA not only affects migration, cell adhesion and proliferation by disrupting formation of actin filaments, but also by indirectly disrupting vesicle trafficking through Big2-dependent Arf1 activation. The increase in Big2 following FlnA loss would be consistent with cellular attempts to promote Big2 redistribution to the membrane to activate Arf1. Further, the increase in FlnA and phosphoFlnA after Big2 loss would reflect a cellular response, favoring Big2 localization to the cell periphery and Arf1 activation. Overall, these studies suggest that disruption in vesicle trafficking and endocytosis with indirect consequential effects on cell-cell and cell-ECM molecules are primarily responsible for the PH phenotypes.

Open Questions

While Big2 activation leads to Arf1 dependent formation of vesicles, it is unclear whether and how actin cytoskeletal changes through FlnA actually regulate vesicle trafficking. FlnA does bind the Rho GTPases which direct actin cytoskeletal changes and have been shown to mediate endocytosis.^{46,47} The Rho GTPases comprise a small family of G proteins that regulate actin dynamics, Cdc42, Rac1, and RhoA being the most studied. They interact with over 60 effectors, some of which are involved in actin nucleation and vesicle trafficking. None, however, have been specifically linked to FlnA. Identification of a shared Rho-FlnA effector is necessary to further elucidate the disease-causative pathway.

Although PH involves altered cell-cell adhesion effecting the neuroependymal lining and cell migration, other studies suggest that disruption of either Big2 or FlnA impairs proliferation. Loss of FlnA causes changes in the rate of degradation of several cell cycle proteins involved in G2-M and to a lesser degree G1-S phases of the cell cycle. These findings suggest that PH genes are likely involved in progression from endocytosis to lysosomal degradation. This possibility is consistent with the finding that the localization of both late endosomal and lysosomal compartments is dependent on FlnA.³⁶ Finally, mutations in two additional genes, atypical cadherin receptor ligands (involved in cell cell adhesion) *FAT4* and *DCHS1* have recently been shown to cause periventricular heterotopia, with nodules along the lateral ventricle and altered progenitor proliferation.⁴⁸ *FAT* and *DCHS* have been implicated in the Hippo signaling pathway, which controls organ size through regulation of cell proliferation and apoptosis through cyclin E (Cdk2) during G1-S phase.^{49,50} It will be of interest to see whether the regulation of these receptors follows a *FLNA* and *BIG2* dependent pathway from endocytosis to lysosomal degradation.

Conclusion

Our studies provide a hypothetical model for PH formation (Fig. 1). First the primary anatomical defect leading to the PH phenotype (loss in neuroependymal integrity, impaired migration, and reduced proliferation) occurs within neural progenitors along the neuroepithelial lining. Genes implicated in PH (*FLNA*, *Big2*) regulate the stability, turnover and degradation of cell adhesion molecules (β -catenin, N-cadherin, *Fat4*, *Dchs1*) and cell-ECM receptors (integrins, paxillin adaptor proteins). *FlnA* phosphorylation targets *Big2* to the membrane, allowing for Arf-dependent activation and vesicle formation. Endocytosis occurs through a caveolin dependent mechanism leading to internalization of catenin/cadherin/protocadherins and integrins. Specificity for some of these molecules extends from their binding of filamins. The downstream mechanisms that mediate endosomal processing in contributing to PH are not known, and remain a focus of continued research. Lastly, human phenotypes associated with mutations in *FLNA* and *ARFGEF2* extend beyond neurological disorders. Disruption of *FLNA* leads to impairments in virtually every organ system, from skin to skeleton, whereas *BIG2* defects have been associated with obstructive cardiomyopathy, recurrent infections and feeding difficulties.^{10,51} The increasingly broad genotype-phenotype correlations reiterate the significant role actin and vesicle trafficking play in human development and disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Nakamura F, Stosel TP, Hartwig JH. The filamins: organizers of cell structure and function. *Cell Adh Migr* 2011; 5:160-9; PMID:21169733; <http://dx.doi.org/10.4161/cam.5.2.14401>
2. Razinia Z, Mäkelä T, Ylännä J, Calderwood DA. Filamins in mechanosensing and signaling. *Annu Rev Biophys* 2012; 41:227-46; PMID:22404683; <http://dx.doi.org/10.1146/annurev-biophys-050511-102252>
3. Zhou AX, Hartwig JH, Akyürek LM. Filamins in cell signaling, transcription and organ development. *Trends Cell Biol* 2010; 20:113-23; PMID:20061151; <http://dx.doi.org/10.1016/j.tcb.2009.12.001>
4. Sheen VL, Feng Y, Graham D, Takafuta T, Shapiro SS, Walsh CA. Filamin A and Filamin B are co-expressed within neurons during periods of neuronal migration and can physically interact. *Hum Mol Genet* 2002; 11:2845-54; PMID:12393796; <http://dx.doi.org/10.1093/hmg/11.23.2845>
5. Fox JW, Lamperti ED, Eksioğlu YZ, Hong SE, Feng Y, Graham DA, Scheffer JE, Dobyns WB, Hirsch BA, Radtke RA, et al. Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. *Neuron* 1998; 21:1315-25; PMID:9883725; [http://dx.doi.org/10.1016/S0896-6273\(00\)80651-0](http://dx.doi.org/10.1016/S0896-6273(00)80651-0)
6. Feng Y, Chen MH, Moskowitz IP, Mendonza AM, Vidali L, Nakamura F, Kwiatkowski DJ, Walsh CA. Filamin A (FLNA) is required for cell-cell contact in vascular development and cardiac morphogenesis. *Proc Natl Acad Sci U S A* 2006; 103:19836-41; PMID:17172441; <http://dx.doi.org/10.1073/pnas.0609628104>
7. Calderwood DA, Huttenlocher A, Kiosses WB, Rose DM, Woodside DG, Schwartz MA, Ginsberg MH. Increased filamin binding to beta-integrin cytoplasmic domains inhibits cell migration. *Nat Cell Biol* 2001; 3:1060-8; PMID:11781567; <http://dx.doi.org/10.1038/ncb1201-1060>
8. Guerrini R, Mei D, Sisodiya S, Sicca F, Harding B, Takahashi Y, Dorn T, Yoshida A, Campistol J, Krämer G, et al. Germline and mosaic mutations of FLN1 in men with periventricular heterotopia. *Neurology* 2004; 63:51-6; PMID:15249610; <http://dx.doi.org/10.1212/01.WNL.0000132818.84827.4D>
9. Lian G, Lu J, Hu J, Zhang J, Cross SH, Ferland RJ, Sheen VL. Filamin A regulates neural progenitor proliferation and cortical size through Wee1-dependent Cdk1 phosphorylation. *J Neurosci* 2012; 32:7672-84; PMID:22649246; <http://dx.doi.org/10.1523/JNEUROSCI.0894-12.2012>
10. Tanyalçin I, Verhelst H, Halley DJ, Vanderhasselt T, Villard L, Goizet C, Lissens W, Mancini GM, Jansen AC. Elaborating the phenotypic spectrum associated with mutations in *ARFGEF2*: case study and literature review. *Eur J Paediatr Neurol* 2013; 17:666-70; PMID:23755938; <http://dx.doi.org/10.1016/j.ejpn.2013.05.002>
11. Sheen VL, Ganesh VS, Topcu M, Sebire G, Bodell A, Hill RS, Grant PE, Shugart YY, Imitola J, Khoury SJ, et al. Mutations in *ARFGEF2* implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex. *Nat Genet* 2004; 36:69-76; PMID:14647276; <http://dx.doi.org/10.1038/ng1276>
12. de Wit MC, de Co IF, Halley DJ, Lequin MH, Mancini GM. Movement disorder and neuronal migration disorder due to *ARFGEF2* mutation. *Neurogenetics* 2009; 10:333-6; PMID:19384555; <http://dx.doi.org/10.1007/s10048-009-0192-2>

13. Shin HW, Morinaga N, Noda M, Nakayama K. BIG2, a guanine nucleotide exchange factor for ADP-ribosylation factors: its localization to recycling endosomes and implication in the endosome integrity. *Mol Biol Cell* 2004; 15:5283-94; PMID:15385626; <http://dx.doi.org/10.1091/mbc.E04-05-0388>
14. Achstetter T, Franzosoff A, Field C, Schekman R. SEC7 encodes an unusual, high molecular weight protein required for membrane traffic from the yeast Golgi apparatus. *J Biol Chem* 1988; 263:11711-7; PMID:3042778
15. Sata M, Donaldson JG, Moss J, Vaughan M. Brefeldin A-inhibited guanine nucleotide-exchange activity of Sec7 domain from yeast Sec7 with yeast and mammalian ADP ribosylation factors. *Proc Natl Acad Sci U S A* 1998; 95:4204-8; PMID:9539714; <http://dx.doi.org/10.1073/pnas.95.8.4204>
16. Togawa A, Morinaga N, Ogasawara M, Moss J, Vaughan M. Purification and cloning of a brefeldin A-inhibited guanine nucleotide-exchange protein for ADP-ribosylation factors. *J Biol Chem* 1999; 274:12308-15; PMID:10212200; <http://dx.doi.org/10.1074/jbc.274.18.12308>
17. Pacheco-Rodriguez G, Moss J, Vaughan M. BIG1 and BIG2: brefeldin A-inhibited guanine nucleotide-exchange proteins for ADP-ribosylation factors. *Methods Enzymol* 2002; 345:397-404; PMID:11665623; [http://dx.doi.org/10.1016/S0076-6879\(02\)45032-X](http://dx.doi.org/10.1016/S0076-6879(02)45032-X)
18. Jones HD, Moss J, Vaughan M. BIG1 and BIG2, brefeldin A-inhibited guanine nucleotide-exchange factors for ADP-ribosylation factors. *Methods Enzymol* 2005; 404:174-84; PMID:16413268; [http://dx.doi.org/10.1016/S0076-6879\(05\)04017-6](http://dx.doi.org/10.1016/S0076-6879(05)04017-6)
19. Shinotsuka C, Waguri S, Wakasugi M, Uchiyama Y, Nakayama K. Dominant-negative mutant of BIG2, an ARF-guanine nucleotide exchange factor, specifically affects membrane trafficking from the trans-Golgi network through inhibiting membrane association of AP-1 and GGA coat proteins. *Biochem Biophys Res Commun* 2002; 294:254-60; PMID:12051703; [http://dx.doi.org/10.1016/S0006-291X\(02\)00456-4](http://dx.doi.org/10.1016/S0006-291X(02)00456-4)
20. Shinotsuka C, Yoshida Y, Kawamoto K, Takatsu H, Nakayama K. Overexpression of an ADP-ribosylation factor-guanine nucleotide exchange factor, BIG2, uncouples brefeldin A-induced adaptor protein-1 coat dissociation and membrane tubulation. *J Biol Chem* 2002; 277:9468-73; PMID:11777925; <http://dx.doi.org/10.1074/jbc.M112427200>
21. Dong C, Zhang X, Zhou F, Dou H, Duvernay MT, Zhang P, Wu G. ADP-ribosylation factors modulate the cell surface transport of G protein-coupled receptors. *J Pharmacol Exp Ther* 2010; 333:174-83; PMID:20093398; <http://dx.doi.org/10.1124/jpet.109.161489>
22. Xu KF, Shen X, Li H, Pacheco-Rodriguez G, Moss J, Vaughan M. Interaction of BIG2, a brefeldin A-inhibited guanine nucleotide-exchange protein, with exocyst protein Exo70. *Proc Natl Acad Sci U S A* 2005; 102:2784-9; PMID:15705715; <http://dx.doi.org/10.1073/pnas.0409871102>
23. Li H, Adamik R, Pacheco-Rodriguez G, Moss J, Vaughan M. Protein kinase A-anchoring (AKAP) domains in brefeldin A-inhibited guanine nucleotide-exchange protein 2 (BIG2). *Proc Natl Acad Sci U S A* 2003; 100:1627-32; PMID:12571360; <http://dx.doi.org/10.1073/pnas.0337678100>
24. Charych EI, Yu W, Miralles CP, Serwanski DR, Li X, Rubio M, De Blas AL. The brefeldin A-inhibited GDP/GTP exchange factor 2, a protein involved in vesicular trafficking, interacts with the beta subunits of the GABA receptors. *J Neurochem* 2004; 90:173-89; PMID:15198677; <http://dx.doi.org/10.1111/j.1471-4159.2004.02481.x>
25. Wong W, Scott JD. AKAP signalling complexes: focal points in space and time. *Nat Rev Mol Cell Biol* 2004; 5:959-70; PMID:15573134; <http://dx.doi.org/10.1038/nrm1527>
26. Kuroda F, Moss J, Vaughan M. Regulation of brefeldin A-inhibited guanine nucleotide-exchange protein 1 (BIG1) and BIG2 activity via PKA and protein phosphatase 1gamma. *Proc Natl Acad Sci U S A* 2007; 104:3201-6; PMID:17360629; <http://dx.doi.org/10.1073/pnas.0611696104>
27. Ferland RJ, Batiz LF, Neal J, Lian G, Bundock E, Lu J, Hsiao YC, Diamond R, Mei D, Banham AH, et al. Disruption of neural progenitors along the ventricular and subventricular zones in periventricular heterotopia. *Hum Mol Genet* 2009; 18:497-516; PMID:18996916; <http://dx.doi.org/10.1093/hmg/ddn377>
28. Sarkisian MR, Bartley CM, Chi H, Nakamura F, Hashimoto-Torii K, Torii M, Flavell RA, Rakic P. MEKK4 signaling regulates filamin expression and neuronal migration. *Neuron* 2006; 52:789-801; PMID:17145501; <http://dx.doi.org/10.1016/j.neuron.2006.10.024>
29. Caraballona A, Beguin S, Pallesi-Pocachard E, Buhler E, Pellegrino C, Arnaud K, Hubert P, Oualha M, Siffroi JP, Khantane S, et al. A glial origin for periventricular nodular heterotopia caused by impaired expression of Filamin-A. *Hum Mol Genet* 2012; 21:1004-17; PMID:22076441; <http://dx.doi.org/10.1093/hmg/ddr531>
30. Zhang J, Neal J, Lian G, Hu J, Lu J, Sheen V, Filamin A. Filamin A regulates neuronal migration through brefeldin A-inhibited guanine exchange factor 2-dependent Arf1 activation. *J Neurosci* 2013; 33:15735-46; PMID:24089482; <http://dx.doi.org/10.1523/JNEUROSCI.1939-13.2013>
31. Zhang J, Neal J, Lian G, Shi B, Ferland RJ, Sheen V. Brefeldin A-inhibited guanine exchange factor 2 regulates filamin A phosphorylation and neuronal migration. *J Neurosci* 2012; 32:12619-29; PMID:22956851; <http://dx.doi.org/10.1523/JNEUROSCI.1063-12.2012>
32. Lu J, Tiao G, Folkerth R, Hecht J, Walsh C, Sheen V. Overlapping expression of ARFGEF2 and Filamin A in the neuroependymal lining of the lateral ventricles: insights into the cause of periventricular heterotopia. *J Comp Neurol* 2006; 494:476-84; PMID:16320251; <http://dx.doi.org/10.1002/cne.20806>
33. Shin HW, Shinotsuka C, Nakayama K. Expression of BIG2 and analysis of its function in mammalian cells. *Methods Enzymol* 2005; 404:206-15; PMID:16413271; [http://dx.doi.org/10.1016/S0076-6879\(05\)04020-6](http://dx.doi.org/10.1016/S0076-6879(05)04020-6)
34. Kondo Y, Hanai A, Nakai W, Katoh Y, Nakayama K, Shin HW. ARF1 and ARF3 are required for the integrity of recycling endosomes and the recycling pathway. *Cell Struct Funct* 2012; 37:141-54; PMID:22971977; <http://dx.doi.org/10.1247/csf.12015>
35. Shen X, Li CC, Aponte AM, Shen RF, Billings EM, Moss J, Vaughan M. Brefeldin A-inhibited ADP-ribosylation factor activator BIG2 regulates cell migration via integrin β 1 cycling and actin remodeling. *Proc Natl Acad Sci U S A* 2012; 109:14464-9; PMID:22908276; <http://dx.doi.org/10.1073/pnas.1211877109>
36. Liu G, Thomas L, Warren RA, Enns CA, Cunningham CC, Hartwig JH, Thomas G. Cytoskeletal protein ABP-280 directs the intracellular trafficking of furin and modulates proprotein processing in the endocytic pathway. *J Cell Biol* 1997; 139:1719-33; PMID:9412467; <http://dx.doi.org/10.1083/jcb.139.7.1719>
37. Mayer G, Boileau G, Bendayan M. The proprotein convertase furin colocalizes with caveolin-1 in the Golgi apparatus and endosomes of hepatocytes. *Cell Tissue Res* 2004; 316:55-63; PMID:14986103; <http://dx.doi.org/10.1007/s00441-004-0866-x>
38. Sverdllov M, Shinin V, Place AT, Castellon M, Minshall RD. Filamin A regulates caveolae internalization and trafficking in endothelial cells. *Mol Biol Cell* 2009; 20:4531-40; PMID:19759182; <http://dx.doi.org/10.1091/mbc.E08-10-0997>
39. Stahlhut M, van Deurs B. Identification of filamin as a novel ligand for caveolin-1: evidence for the organization of caveolin-1-associated membrane domains by the actin cytoskeleton. *Mol Biol Cell* 2000; 11:325-37; PMID:10637311; <http://dx.doi.org/10.1091/mbc.11.1.325>
40. Muriel O, Echarrri A, Hellriegel C, Pavón DM, Beccari L, Del Pozo MA. Phosphorylated filamin A regulates actin-linked caveolae dynamics. *J Cell Sci* 2011; 124:2763-76; PMID:21807941; <http://dx.doi.org/10.1242/jcs.080804>
41. Salanueva IJ, Cerezo A, Guadamillas MC, del Pozo MA. Integrin regulation of caveolin function. *J Cell Mol Med* 2007; 11:969-80; PMID:17979878; <http://dx.doi.org/10.1111/j.1582-4934.2007.00109.x>
42. Loulier K, Lathia JD, Marthens V, Relucio J, Mughal MR, Tang SC, Coksangyan T, Hall PE, Chigurupati S, Patton B, et al. beta1 integrin maintains integrity of the embryonic neocortical stem cell niche. *PLoS Biol* 2009; 7:e1000176; PMID:19688041; <http://dx.doi.org/10.1371/journal.pbio.1000176>
43. Smythe E, Ayscough KR. Actin regulation in endocytosis. *J Cell Sci* 2006; 119:4589-98; PMID:17093263; <http://dx.doi.org/10.1242/jcs.03247>
44. Howell GJ, Holloway ZG, Cobbold C, Monaco AP, Ponnambalam S. Cell biology of membrane trafficking in human disease. *Int Rev Cytol* 2006; 252:1-69; PMID:16984815; [http://dx.doi.org/10.1016/S0074-7696\(06\)52005-4](http://dx.doi.org/10.1016/S0074-7696(06)52005-4)
45. Lachlan KL, Collinson MN, Sandford RO, van Zyl B, Jacobs PA, Thomas NS. Functional disomy resulting from duplications of distal Xq in four unrelated patients. *Hum Genet* 2004; 115:399-408; PMID:15338277; <http://dx.doi.org/10.1007/s00439-004-1175-x>
46. Ohta Y, Suzuki N, Nakamura S, Hartwig JH, Stossel TP. The small GTPase RalA targets filamin to induce filopodia. *Proc Natl Acad Sci U S A* 1999; 96:2122-8; PMID:10051605; <http://dx.doi.org/10.1073/pnas.96.5.2122>
47. Lamaze C, Chuang TH, Terlecky LJ, Bokoch GM, Schmid SL. Regulation of receptor-mediated endocytosis by Rho and Rac. *Nature* 1996; 382:177-9; PMID:8700210; <http://dx.doi.org/10.1038/382177a0>
48. Cappello S, Gray MJ, Badouel C, Lange S, Einsiedler M, Srouf M, Chitayat D, Hamdan FF, Jenkins ZA, Morgan T, et al. Mutations in genes encoding the cadherin receptor-ligand pair DCHS1 and FAT4 disrupt cerebral cortical development. *Nat Genet* 2013; 45:1300-8; PMID:24056717; <http://dx.doi.org/10.1038/ng.2765>
49. Matakatsu H, Blair SS. Separating planar cell polarity and Hippo pathway activities of the protocadherins Fat and Dachsous. *Development* 2012; 139:1498-508; PMID:22399682; <http://dx.doi.org/10.1242/dev.070367>
50. Sadeqzadeh E, de Bock CE, Thorne RF. Sleeping giants: emerging roles for the fat cadherins in health and disease. *Med Res Rev* 2014; 34:190-221; PMID:23720094; <http://dx.doi.org/10.1002/med.21286>
51. Sheen VL. Periventricular Heterotopia: Shuttling of Proteins through Vesicles and Actin in Cortical Development and Disease. *Scientifica (Cairo)*; 2012:480129.