Actin Cytoskeleton and Related Proteins
Role During Immune Cells Migration, Polarity and Activation: An Overview

Claudio Vieira da Silva
Instituto de Ciências Biomédicas, Universidade Federal de Uberlândia, Brazil

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ABSTRACT

Immune cells migration, polarity and activation are essential during host immune response. Upon recognition of specific peptides presented by Human Leukocyte Antigen (HLA) molecules on Antigen Presenting Cells (APC), lymphocytes execute subset-related functions such as killing, help and regulation. These cells travel through the organism in a succession of steps, including entry into tissues, interstitial migration, APC scanning, synapse formation and tissue exit. Such ability is possible because of a plastic motility behavior, which is highly controlled in time and space. The scope of this review is to discuss recent data pointing to the key role of regulators of actin cytoskeleton remodeling in tuning migration, polarity and activation of immune cells during host immune response. We believe that the more complete understanding of actin and related proteins recruitment during these processes the better to obtain novel targets for establishing strategies to control immune responses.

Keywords: Actin Cytoskeleton, Immune Cells, Activation, Migration, Immune Response

1. INTRODUCTION

The actin cytoskeleton is a dynamic structure that plays a fundamental role in diverse processes in all eukaryotic cells. Actin-dependent cellular processes are typically associated with membrane dynamics and the coordinated polymerization of actin filaments against cellular membranes provides the force for these processes. Probably the most thoroughly characterized of such processes are cell migration and endocytosis.

During cell migration, precisely coordinated polymerization of actin filaments against the plasma membrane induces the formation of plasma membrane protrusions and consequent advancement of the leading edge of the cell. Similar membrane protrusions, in the absence of retraction of the trailing edge of the cell, drive cell elongation during morphogenetic processes such as neuronal outgrowth (Chhabra and Higgs, 2007).

During endocytosis, actin polymerization provides the force for generating membrane invaginations and for the scission of the endocytic vesicles from the plasma membrane (Kaksonen et al., 2006).

The structure and dynamics of the actin cytoskeleton in cells are regulated by a vast number of actin-binding proteins. These include proteins that promote nucleation of new actin filaments (Arp2/3 complex, formins, Cobl, Spire, leiomodin) and proteins that enhance actin filament severing and depolymerization (e.g., ADF/cofilins, gelsolin) (Chesarone and Goode, 2009; Ono, 2007).

Also, proteins that regulate actin filament polymerization either by interacting with actin monomers (e.g., profilin, twinfilin, β-thymosins) or with filament barbed ends (e.g., capping protein, Eps8, Ena/VASP) play crucial roles in actin dynamics in cells. Finally, actin dependent cellular processes typically rely on the organization of actin filaments to desired three-dimensional structures through a large number of actin filament bundling and cross-linking proteins (e.g., α-actinin, fascin) (Cooper and Sept, 2008; Disanza et al., 2004; Drees and Gertler, 2008; Le Clainche and Carlier, 2008; Paavilainen et al., 2004).
Fundamental studies by the Carlier laboratory revealed that the minimal set of actin-binding proteins required for actin-based motility in vitro consists of ADF/cofilin, profilin, activated Arp2/3 complex and capping protein (Loisel et al., 1999). However, most cellular processes driven by actin filament treadmilling depend on a significantly larger number of actin-associated proteins and their regulators. The activities of actin-binding proteins are controlled through various signaling pathways to ensure proper spatial and temporal regulation of actin dynamics in cells.

The most thoroughly characterized regulators of actin binding proteins are the Rho-family small GTPases. In mammals, these include, e.g., RhoA that induces the formation of contractile stress fibers, Rac1 that drives the formation of lamellipodial actin filament network at the leading edge of motile cells, as well as Cdc42 and Rif that induce the formation of thin actin-rich filopodial protrusions at cell periphery (Hall, 1998; Heasman and Ridley, 2008; Pellegrin and Mellor, 2005).

### 1.1. Actin Cytoskeleton Dynamics During Immune Cell Migration and Polarity

Cell migration plays a key role for the function of the immune system: Maturation of cells of the innate and adaptive immune system takes place in distinct, anatomical compartments and immunological effector functions have to be operative wherever the integrity of the organism is challenged. Thus, immune cells are constantly “en route” to complete their maturation and to exert their effector functions. Migration of cells is orchestrated by a complex interplay of interactions of cell-surface receptors with their respective cognate ligands (Von Andrian and Mempel, 2003).

Endothelial cells limit the emigration rate of leukocytes. Being located between blood and tissues, they permit or deny the passage. The exact mechanism of this process called diapedesis is not solved yet. Leukocytes can principally traverse either between cells (paracellularly) or directly through an individual endothelial cell (transcellularly). The transcellular way has recently gained experimental support, but it is not clear how the endothelial cytoskeleton manages to open and close a transmigratory channel. During this process, the endothelial cell turned out to become softer in a confined region strictly underneath the leukocyte that rearranges the endothelial cytoskeleton to form transmigratory channels (Isac et al., 2011).

Along leukocyte migration, different F-actin-related proteins are activated. In this sense, Protease-Activated Receptor-2 (PAR-2) promotes activation of the actin filament severing protein cofilin, which is crucial for the reorganization of the actin cytoskeleton and chemotaxis. PAR-2 promotes the formation of a complex containing β-arrrestins, cofilin and chronophin (CIN) in primary leukocytes and cultured cells. Both association of cofilin with CIN and cell migration are inhibited in leukocytes from β-arrestin-2-/-mice. In response to PAR-2 activation, β-arrestins scaffold cofilin with its upstream activator CIN, to facilitate the localized generation of free actin barbed ends, leading to membrane protrusion (Zoudilova et al., 2010). Hence, providing evidences for an important role of β-arrestins in chemotaxis of PAR-2-stimulated immune.

Moreover, authors have shown that The Wiskott-Aldrich Syndrome Protein (WASP) plays an important role in the locomotion of lymphocytes, DC and granulocytes in vitro and in vivo and thus, reveal a crucial role of WASP in physiological trafficking of various hematopoietic cell lineages (Snapper et al., 2005). Likewise, Cybr, a scaffold protein highly expressed in the hematopoietic/immune system, binds to cytohesin-1, a guanine nucleotide exchange factor for the ARF GTPases, which affects actin cytoskeleton remodeling during cell migration. In this context, Cybr was found to play a role in leukocyte trafficking in response to proinflammatory cytokines in stress conditions (Coppola et al., 2006).

The large GTPase Guanylate-Binding Protein-1 (GBP-1) was found as a novel member within the family of actin remodeling proteins, specifically mediating IFN-γ-dependent defense strategies (Ostler et al., 2013).

Concerning B cells migration, authors have shown that SWAP-70, a Rac-interacting protein involved in actin rearrangement (Pearce et al., 2006) and ezrin, a member of the membrane-cytoskeleton cross-linking ezrin-radixin-moesin proteins (Parameswaran et al., 2011) play important role during B cells chemotaxis. In addition, Rap-1 and -2 GTPases play an important role in mediating adhesion and cytoskeletal reorganization during SDF-1a-dependent B cell migration (McLeod et al., 2002; 2004; Durand et al., 2006; Chen et al., 2008).

Establishment of cell polarity is crucial for the migration of immature and mature leukocytes across vascular endothelial barriers and provides the basis for Hematopoietic Stem and Progenitor Cell (HSC/HPC) homing. Directional cues for the migration of leukocytes to the sites of inflammation are provided by the
chemokine family members (Kitano et al., 2008) and are promptly executed via intrinsic signaling pathways downstream of chemokine receptors. Similarly, chemokines have been implicated in controlling HSC/HPC homing (Luster, 1998). In both contexts, cells switch from spherical to polarized phenotypes in response to polarization cues. These morphological changes are accompanied by an orchestrated compartmentalization of certain cell surface associated molecules (Lapidot et al., 2005; Serrador et al., 1998; Dustin and Chan, 2000). Additionally, cytoskeletal reorganization (Giebel et al., 2004; Serrador et al., 1999), lateral compartmentalization of functional membrane microdomains (Merwe et al., 2000; Gomez-Mouton et al., 2001) and redistribution of some cellular proteins have been observed (Del Pozo et al., 1998).

Actin cytoskeletal rearrangement during directional migration is a highly conserved and well documented process in amoeboid cells (Gerisch et al., 1993; Chung et al., 2001; Parent et al., 1998) and leukocytes display the characteristic leading and trailing edges. While the leading edge is marked by a concentration of F-actin (Del Pozo et al., 1998; Gerisch et al., 1993) and chemokine receptors (Gomez-Mouton et al., 2001; Parent et al., 1998; Gomez-Mouton et al., 2004), the trailing edge, termed uropod, is marked by the accumulation of several adhesion molecules (Serrador et al., 1998; Giebel et al., 2004; Del Pozo et al., 1997), the hyaluron receptor (Ariel et al., 2000; Del Pozo et al., 1995), sialoglycoproteins (Serrador et al., 1998; Gubina et al., 2002; Savage et al., 2002) and the ERM family of proteins (Serrador et al., 1999). Lipids also show different polarization patterns during lymphocyte migration (Giebel et al., 2004; Gomez-Mouton et al., 2001).

Along similar lines, insights into the importance of lipid rafts or membrane microdomains in the process of chemokine-induced polarization have been provided by recent studies (Gubina et al., 2002; Millan et al., 2002; Manes et al., 2001). However, none of the molecules implicated in either chemokine-induced polarization or raft residency show asymmetric localization under resting conditions that could impart pre-polarization cues. A recent study has shown that the lipid microdomain resident proteins, flotillin-1 and -2 (Salzer and Prohaska, 2001; Babuke and Tikkanen, 2007), confer intrinsic polarity to leukocytes by their asymmetric localization (Rajendran et al., 2003). Authors have also shown that flotillin-1 and -2 accumulate at uropods and co-localize with CD43, CD44 and moesin and presented evidence for the distinct spatial and temporal localization of flotillin platforms with respect to the actin cytoskeleton upon chemokine-induced migration. Moreover, flotillins were accumulated at the central supramolecular Activation Cluster (c-SMAC) during immunological synapse formation concomitant with membrane ordering in these regions. Based on these results, authors proposed that a subset of lipid microdomains provide pre-polarization cues for hematopoietic cell polarization (Rajendran et al., 2009).

1.2. Actin Cytoskeleton Dynamics During Immune Cells Activation

Immune cells activation is a process triggered by different pathogens and compounds (Gomez-Flores et al., 2005). On the other hand, drugs, such as methamphetamine inhibits β-chemokines and costimulatory molecules by dendritic cells (Nair et al., 2007). However, it is not known whether this activity relies on impairing the activation of actin cytoskeleton related proteins.

The molecular basis for the adaptable motility behavior of T lymphocytes is only starting to be unraveled and this subject was recently reviewed (Lafaouresse et al., 2013; Beemiller and Krummel, 2013).

Actin polymerization plays a critical role in activated T lymphocytes both in regulating T Cell Receptor (TCR)-induced Immunological Synapse (IS) formation and signaling. Using gene targeting, authors demonstrated that the hematopoietic specific, actin- and Arp2/3 complex-binding protein coronin-1A contributes to both processes. Coronin-1A links cytoskeleton plasticity with the functioning of TCR signaling components (Mugnier et al., 2008). T cells express drebrin, a neuronal actin-binding protein, that co-localizes with the chemokine receptor CXCR4 and F-actin at the peripheral supramolecular activation cluster in the immune synapse. Drebrin interacts with the cytoplasmic tail of CXCR4 and both proteins redistribute to the immune synapse with similar kinetics (Perez-Martinez et al., 2010).

RLIP76, a multifunctional transporter protein, is necessary for activation, membrane trafficking and functional maturation of Dendritic Cells (DC) (Borvak et al., 2010). Further exploration of the role of RLIP76 in DC biology is warranted and may provide promising means in DC-based immunotherapies.

Formation of IS between T cells and Antigen Presenting Cell (APC-DC, macrophages and B cells) requires multiple rearrangements in the actin cytoskeleton and selective receptor accumulation in Supramolecular Activation Clusters (SMAC). The inner cluster (central SMAC) contains the TCR/CD3 complex.
The outer cluster (peripheral SMAC) contains the integrin LFA-1 and Talin. Sustained LFA-1 clustering in the IS is a consequence of the combined activities of the actin-bundling protein L-Plastin (LPL) and calmodulin (Wabnitz et al., 2010).

Natural Killer (NK) cells discriminate between healthy and unhealthy target cells through a balance of activating and inhibitory signals at direct immune synapses. Authors have brought together the vast literature on this subject, the number of different ways in which the cytoskeleton is important becomes evident. The dynamics of filamentous actin is critical in (i) creating the nanometer-scale organization of NK cell receptors, (ii) establishing cellular polarity, (iii) coordinating immune receptor and integrin-mediated signaling and (iv) directing secretion of lytic granules and cytokines (Lagrue et al., 2013).

1.3. Future Research

Here, we reviewed different aspects of actin and actin related proteins during immune cells activation. Although many progresses in this research field was achieved, it is important to highlight the need of novel studies devoted to understand the kinetics of actin and actin related proteins recruitment during the different steps comprising immune cell differentiation, migration, phagocytosis and activation. We strongly believe that a more detailed comprehension of these processes may help researchers from different field to develop approaches to interfere and regulate immune response against different targets.

2. CONCLUSION

Actin is essential for the survival of most cells. The actin cytoskeleton is a dynamic structure that plays a fundamental role in diverse processes in all eukaryotic cells. Actin-dependent cellular processes are typically associated with membrane dynamics and the coordinated polymerization of actin filaments against cellular membranes provides the force for these processes. A demanding task of medicine is to understand and control the immune system. Central players in the cellular immune response are the leukocytes that leave the blood stream for host defense. In this context, the understanding the physiological role of these cells and their products along as the actin rearrangements and actin associated proteins role during immune activation are crucial to establish immune based methods to control immune response. The more complete understanding of actin and related proteins recruitment during these processes the better to obtain novel targets for establishing strategies to control immune response.

3. REFERENCES

Ariel, A., O. Lider, A. Brill, L. Cahalon and N. Savion et al., 2000. Induction of interactions between CD44 and hyaluronic acid by a short exposure of human T cells to diverse pro-inflammatory mediators. Immunology, 100: 345-351. DOI: 10.1046/j.1365-2567.2000.00059.x

Babuke, T. and R. Tikkanen, 2007. Dissecting the molecular function of reggie/flotillin proteins. Eur. J. Cell. Biol., 86: 525-532. DOI: 10.1016/j.ejcb.2007.03.003

Beemiller, P. and M.F. Krummel, 2013. Regulation of T-cell receptor signaling by the actin cytoskeleton and poroelastic cytoplasm. Immunol. Rev., 256:148-159. PMID: 24117819

Borvak, J., M. Sahu, V. Joy, J. Singhal and S. Yadav et al., 2010. Ral-binding protein is required for the maturation and function of dendritic cells. Am. J. Immunol., 6: 29-42. DOI: 10.3844/ajisp.2010.29.42

Chen, Y., M. Yu, A. Podd, R. Wen and M. Chrzanowska-Wodnicka et al., 2008. A critical role of Rap1b in B-cell trafficking and marginal zone B-cell development. Blood, 111: 4627-4636. DOI: 10.1182/blood-2007-12-128140

Chesarone, M.A. and B.L. Goode, 2009. Actin nucleation and elongation factors: Mechanisms and interplay. Curr. Opin. Cell. Biol., 21: 28-37. DOI: 10.1016/j.cub.2008.12.001

Chhabra, E.S. and H.N. Higgs, 2007. The many faces of actin: Matching assembly factors with cellular structures. Nat. Cell. Biol., 9: 1110-1121. DOI: 10.1038/ncb1007-1110

Chung, C.Y., S. Funamoto and R.A. Firtel, 2001. Signaling pathways controlling cell polarity and chemotaxis. Trends Biochem. Sci., 26: 557-566. DOI: 10.1016/S0968-0004(01)01934-X

Cooper, J.A. and D. Sept, 2008. New insights into mechanism and regulation of actin capping protein. Int. Rev. Cell. Mol. Biol., 267: 183-206. DOI: 10.1016/S1937-6448(08)00604-7

Coppola, C., C.A. Barrick, S. Bobisse, M.C. Rodriguez-Galan and M. Pivetta et al., 2006. The scaffold protein cybr is required for cytokine-modulated trafficking of leukocytes in vivo. Mol. Cell. Biol., 2: 5249-5258. DOI: 10.1128/MCB.02473-05
Del Pozo, M.A., C. Cabanas, M.C. Montoya, A. Ager and P. Sanchez-Mateos et al., 1997. ICAMs redistributed by chemokines to cellular uropods as a mechanism for recruitment of T lymphocytes. J. Cell Biol., 137: 493-508. DOI: 10.1083/jcb.137.2.493

Del Pozo, M.A., M. Nieto, J.M. Serrador, D. Sancho and M. Vicente-Manzanares et al., 1998. The two poles of the lymphocyte: Specialized cell compartments for migration and recruitment. Cell Adhes. Commun., 6: 125-133. DOI: 10.3109/15419069809004468

Del Pozo, M.A., P. Sanchez-Mateos, M. Nieto and F. Sanchez-Madrid, 1995. Chemokines regulate cellular polarization and adhesion receptor redistribution during lymphocyte interaction with endothelium and extracellular matrix. Involvement of cAMP signaling pathway. J. Cell Biol., 131: 495-508. DOI: 10.1083/jcb.131.2.495

Disanza, A., M.F. Carlier, T.E. Stradal, D. Didry and E. Frittoli et al., 2004. Eps8 controls actin-based motility by capping the barbed ends of actin filaments. Nat. Cell. Biol., 6: 125-133. DOI: 10.1016/j.conb.2008.05.007

Drees, F. and F.B. Gertler, 2008. Ena/VASP: Proteins at the tip of the nervous system. Curr. Opin. Neurobiol., 18: 53-59. DOI: 10.1016/j.conb.2008.05.007

Durand, C.A., J. Westendorf, K.W. Tse and M.R. Gold, 2006. The rap GTPases mediate CXCL13- and sphingosine1-phosphate-induced chemotaxis, adhesion and Pyk2 tyrosine phosphorylation in B lymphocytes. Eur. J. Immunol., 36: 2235-2249. DOI: 10.1002/eji.200535004

Dustin, M.L. and A.C. Chan, 2000. Signaling takes shape in the immune system. Cell, 103: 283-294. DOI: 10.1016/S0092-8674(00)01200-3

Gerisch, G., R. Albrecht, E. De Hostos, E. Wallraff and C. Heizer et al., 1993 Actin associated proteins in motility and chemotaxis of Dictyostelium cells. Symp. Soc. Exp. Biol., 47: 297-315. PMID: 8165772

Giebel, B., D. Corbeil, J. Beckmann, J. Hohn and D. Freund et al., 2004. Segregation of lipid raft markers including CD133 in polarized human hematopoietic stem and progenitor cells. Blood, 104: 2332-2338. DOI: 10.1182/blood-2004-02-0511

Gomez-Flores, R., D. Caballero-Hernandez, R.J. Weber, R. Tamez-Guerra and P. Tamez-Guerra et al., 2005. In vitro activation of human and rat lymphocyte and macrophage functions by norepinephrine. Am. J. Immunol., 1: 148-153. DOI: 10.3844/ajisp.2005.148.153

Gomez-Mouton, C., J.L. Abad, E. Mira, R.A. Lacalle and E. Gallardo et al., 2001. Segregation of leading-edge and uropod components into specific lipid rafts during T cell polarization. Proc. Natl. Acad. Sci. USA., 98: 9642-9647. DOI: 10.1073/pnas.171160298

Gomez-Mouton, C., R.A. Lacalle, E. Mira, S. Jimenez-Baranda and D.F. Barber et al., 2004. Dynamic redistribution of raft domains as an organizing platform for signaling during cell chemotaxis. J. Cell Biol., 164: 756-768. DOI: 10.1083/jcb.200409101

Gubina, E., T. Chen, L. Zhang, E.F. Lizzie and S. Kozlowski, 2002. CD43 polarization in unprimed T cells can be dissociated from raft coalescence by inhibition of HMG CoA reductase. Blood, 99: 2518-2525. DOI: 10.1182/blood.V99.7.2518

Hall, A., 1998. Rho GTPases and the actin cytoskeleton. Science, 279: 307-314. DOI: 10.1126/science.279.5350.475

Heasman, S.J. and A.J. Ridley, 2008. Mammalian Rho GTPases: New insights into their functions from in vivo studies. Nat. Rev. Mol. Cell Biol., 9: 690-701. DOI: 10.1038/nrm2476

Isac, L., G. Theolking, A. Schwah, H. Oberleithner and C. Riethmuller, 2011. Endothelial f-actin depolymerization enables leukocyte transmigration. Anal. Bioanal. Chem., 399: 2351-2358. DOI: 10.1007/s00216-010-3997-5

Kaksonen, M., C.P. Toret and D.G. Drubin, 2006. Harnessing actin dynamics for clathrin-mediated endocytosis. Nat. Rev. Mol. Cell Biol, 7: 404-414. DOI: 10.1038/nrm1940

Kitano, M., M. Nakaya, T. Nakamura, S. Nagata and M. Matsuda, 2008. Imaging of Rab5 activity identifies essential regulators for phagosome maturation. Nature, 453: 241-245. DOI: 10.1038/nature06857

Lafouresse, F., Z. Vasconcelos, V. Cotta-de-Almeida and L. Dupre, 2013. Actin cytoskeleton control of the comings and goings of T lymphocytes. Tissue Antigens, 82: 301-311. DOI: 10.1111/tan.12193
Lagrange, K., A. Carisey, A. Oszmiana, P.R. Kennedy and D.J. Williamson et al., 2013. The central role of the cytoskeleton in mechanisms and functions of the NK cell immunesynapse. Immunol. Rev., 256: 203-221. PMID: 24117823

Lapidot, T., A. Dar and O. Kollet, 2005. How do stem cells find their way home? Blood, 106: 1901-1910. DOI: 10.1182/blood-2005-04-1417

Le Clair, C. and M.F. Carlier, 2008. Regulation of actin assembly associated with protrusion and adhesion in cell migration. Physiol. Rev., 88: 489-513. DOI: 10.1152/physrev.00021.2007

Loisel, T.P., R. Boujemaa, D. Pantaloni and M.F. Carlier, 1999. Reconstitution of actin-based motility of Listeria and Shigella using pure proteins. Nature, 401: 613-616. DOI: 10.1038/44183

Luster, A.D., 1998. Chemokines-chemotactic cytokines that mediate inflammation. N. Engl. J. Med., 338: 436-445. DOI: 10.1056/NEJM199802123380706

Manes, S., R.A. Lacalle, C. Gomez-Mouton, G. del Real and E. Mira et al., 2001. Membrane raft microdomains in chemokine receptor function. Semin. Immunol., 13: 147-157. DOI: 10.1006/smim.2000.0306

McLeod, S.J., A.H. Li, R.L. Lee, A.E. Burgess and M.R. Gold, 2002. The Rap GTPases regulate B cell migration toward the chemokine stromal cell derived factor-1 (CXCL12): Potential role for Rap2 in promoting B cell migration. J. Immunol., 169: 1365-1371. PMID: 12133960

McLeod, S.J., A.J. Shum, R.L. Lee, F. Takei and M.R. Gold, 2004. The Rap GTPases regulate integrin-mediated adhesion, cell spreading, actin polymerization and Pyk2 tyrosine phosphorylation in B lymphocytes. J. Biol. Chem., 279: 12009-12019. DOI: 10.1074/jbc.M313098200

Merwe, P.A.V.D., S.J. Davis, A.S. Shaw and M.L. Dustin, 2000. Cytoskeletal polarization and redistribution of cell-surface molecules during T cell antigen recognition. Semin. Immunol., 12: 5-21. DOI: 10.1006/smim.2000.0203

Millan, J., M.C. Montoya, D. Sancho, F. Sanchez-Madrid and M.A. Alonso, 2002. Lipid rafts mediate biosynthetic transport to the T lymphocyte uropod subdomain and are necessary for uropod integrity and function. Blood, 99: 978-984. DOI: 10.1182/blood.V99.3.978

Mugnier, B., B. Nal, C. Verthuy, C. Boyer and D. Lam et al., 2008. Coratin-1A links cytoskeleton dynamics to TCR alpha beta-induced cell signaling. PLoS One, 3: e3467-e3467. DOI: 10.1371/journal.pone.0003467

Nair, M.P.N., J.W. Rodriguez, I.M. Borodowsky, S. Mahajan and N. Nair et al., 2007. Methamphetamine inhibits β-Chemokines and Co-Stimulatory molecule expression by dendritic cells. Am. J. Infect. Dis., 3: 217-224. DOI: 10.3844/ajidsp.2007.217.224

Ono, S., 2007. Mechanism of depolymerization and severing of actin filaments and its significance in cytoskeletal dynamics. Int. Rev. Cytol., 258: 1-82. DOI: 10.1016/S0074-7696(07)58001-0

Ostler, N., N. Britzen-Laurent, A. Liebl, E. Naschberger and G. Lochnit et al., 2013. IFN-γ-induced guanylate binding protein-1 is a novel actin cytoskeleton remodeling factor. Mol. Cell Biol. PMID: 24190970

Paavlaainen, V.O., E. Bertling, S. Falck and P. Lappalainen, 2004. Regulation of cytoskeletal dynamics by actin-monomer-binding proteins. Trends Cell Biol., 14: 386-394. DOI: 10.1016/j.tcb.2004.05.002

Parameswaran, N., K. Matsui and N. Gupta, 2011. Conformational switching in ezrin regulates morphological and cytoskeletal changes required for B cell chemotaxis. J. Immunol., 186: 4088-4097. DOI: 10.4049/jimmunol.1001139

Parent, C.A., B.J. Blacklock, W.M. Froehlich, D.B. Murphy and P.N. Devreotes, 1998. G protein signaling events are activated at the leading edge of chemotactic cells. Cell, 95: 81-91. DOI: 10.1016/S0092-8674(00)81784-5

Pearce, G., V. Angeli, G.J. Randolph, T. Junt and U. Von Andrian et al., 2006. Signaling protein SWAP-70 is required for efficient B cell homing to lymphoid organs. Nat. Immunol., 7: 827-834. DOI: 10.1038/nm1365

Pellegrin, S. and H. Mellor, 2005. The Rho family GTPase Rif induces filopodia through mDia2. Curr. Biol., 15: 129-133. DOI: 10.1016/j.cub.2005.01.011

Perez-Martinez, M., M. Gordon-Alonso, J.R. Cabrero, M. Barrero-Villar and M. Rey et al., 2010. F-actin-binding protein drebrin regulates CXCR4 recruitment to the immune synapse. J. Cell Sci., 123: 1160-1170. PMID: 20215400
Rajendran, L., J. Beckmann, A. Magenau, E.M. Boneberg and K. Gaus et al., 2009. Flotillins Are involved in the polarization of primitive and mature hematopoietic cells. PLoS ONE, 4: e8290-e8290. DOI: 10.1371/journal.pone.0008290

Rajendran, L., M. Masilamani, S. Solomon, R. Tikkanen and C.A. Stuermer et al., 2003. Asymmetric localization of flotillins/reggies in preassembled platforms confers inherent polarity to hematopoietic cells. Proc. Natl. Acad. Sci. USA., 100: 8241-8246. DOI: 10.1073/pnas.1331629100

Salzer, U. and R. Prohaska, 2001. Stomatin, flotillin-1 and flotillin-2 are major integral proteins of erythrocyte lipid rafts. Blood, 97: 1141-1143. DOI: 10.1182/blood.V97.4.1141

Savage, N.D., S.L. Kimzey, S.K. Bromley, K.G. Johnson and M.L. Dustin et al., 2002. Polar redistribution of the sialoglycoprotein CD43: Implications for T cell function. J. Immunol., 168: 3740-3746. PMID: 11937524

Serrador, J.M., M. Nieto and F. Sanchez-Madrid, 1999. Cytoskeletal rearrangement during migration and activation of T lymphocytes. Trends Cell Biol., 9: 228-233. DOI: 10.1016/S0962-8924(99)01553-6

Serrador, J.M., M. Nieto, J.L. Alonso-Lebrero, M.A. del Pozo and J. Calvo et al., 1998. CD43 interacts with moesin and ezrin and regulates its redistribution to the uropods of T lymphocytes at the cell-cell contacts. Blood, 91: 4632-4644. PMID: 9616160

Snapper, S.B., P. Meelu, D. Nguyen, B.M. Stockton and P. Bozza et al., 2005. WASP deficiency leads to global defects of directed leukocyte migration in vitro and in vivo. J. Leukoc. Biol., 77: 993-998. DOI: 10.1189/jlb.0804444

Von Andrian, U.H. and T.R. Mempel, 2003. Homing and cellular traffic in lymph nodes. Nat. Rev. Immunol., 3: 867-878. DOI: 10.1038/nri1222

Wabnitz, G.H., P. Lohneis, H. Kirchgessner, B. Jahraus and S. Gottwald et al., 2010. Sustained LFA-1 cluster formation in the immune synapse requires the combined activities of L-plastin and calmodulin. Eur. J. Immunol., 40: 2437-49. DOI: 10.1002/eji.201040345

Zoudilova, M., J. Min, H.L. Richards, D. Carter and T. Huang et al., 2010. β-Arrestins scaffold cofilin with chronophin to direct localized actin filament severing and membrane protrusions downstream of protease-activated receptor-2. J. Biol. Chem., 285: 14318-14329. DOI: 10.1074/jbc.M109.055806