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Swiprosin-1: Its Expression and Diverse Biological Functions

Ramesh P. Thylur [1*] Raghavendra Gowda,[2] Sumita Mishra,[3] and Chang-Duk Jun[1]

[1] School of Life Science, Gwangju Institute of Science and Technology (GIST), 123 Cheomdangwagi-ro, Buk-gu, Gwangju 61005, Republic of Korea

[2] Department of Pharmacology, Pennsylvania State University College of Medicine, Hershey, Pennsylvania

[3] Department of Pediatrics, Division of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland

ABSTRACT

Swiprosin-1/EFhd2 is a Ca^{2+} binding adapter protein involved in the various cellular functions. Swiprosin-1 is significantly upregulated in a number of pathological conditions of inflammation, neurodegeneration, and cancer. Swiprosin-1 associated with actin and its expression level amplifies the production of proinflammatory mediators and modulates the activation of transcription factor during immune cells activation. This review aims at providing an overview of the expression and function of swiprosin-1/EFhd2 in various pathophysiological conditions. We also discussed the key role of swiprosin-1 in immune cell activation, cell migration, apoptosis, humoral immunity, cancer invasion and metastasis, neuronal transport, and major signaling cascades. J. Cell. Biochem. 119: 150–156, 2018.

KEY WORDS: SWIPROSIN-1; RECEPTOR SIGNALING; IMMUNE CELLS ACTIVATION; PROTEIN KINASE

Swiprosin-1 or SWSI, also known as EFHD2, is an EF-hand and coiled-coil-containing adopter protein that plays a role in lymphocyte physiology [Vuadens et al., 2004; Avramidou et al., 2007; Schulz et al., 2007 Kim et al., 2013]. Swiprosin-1 is a 240 amino acid protein, with molecular weights of 27 kDa (predicted) and 33 kDa (apparent) [Vuadens et al., 2004; Avramidou et al., 2007]. It consists of four putative myristoylation sites (lipid modifications), three binding sites for SH3-domain containing proteins, two EF-hand domains, and a coiled-coil domain at the C-terminus revealed by primary and secondary protein structure analysis (Fig. 1A and B) [Vuadens et al., 2004; Avramidou et al., 2007]. Swiprosin-1 is broadly expressed in different cells or tissues of different species and significantly it is upregulated in a number of pathological situations like inflammation (acute and chronic), neurodegeneration, dementia, schizophrenia, and cancer [Huh et al., 2015]. Swiprosin-1 was first recognized in human lymphocytes, predominantly in $CD8^+$ T, $CD4^+$ T, and $CD19^+$ B lymphocytes [Vuadens et al., 2004] and later they identified in other immune cells, mast cells, epithelial cells, endothelial cells, and macrophages [Fechheimer and Taylor, 1984; Mielenz et al., 2005; Avramidou et al., 2007; Schulz et al., 2007; Williams, 2007; Checinska et al., 2009; Kroczek et al., 2010; Xu et al., 2010; Hagen et al., 2012; Kim et al., 2013]. More importantly, Swiprosin-1 is also playing a key role in delivery membrane scaffold that is

Abbreviations: Arp2/3, Actin-related protein 2/3; BCR, B Cell Receptor; Ca^{2+}, Calcium ion; DNP-HAS, Dinitrophenyl-human serum albumin; ΔPR, Deletant of proline rich; EFhd2, EF-hand domain 2; ERM, Ezrin radixin moesin; EGFR, Epidermal growth factor receptor; GFP, Green fluorescent protein; GTPase, Guanosine triphosphatase; HMC-1, Human mast cells-1; I-κB-α, Inhibitor of kappa B-alpha; IL, Interleukin; IgE, Immunoglobulin E; IgM, Immunoglobulin M; MAP2, Microtubule-associated Protein 2; $\Delta\Psi_m$, Mitochondrial membrane potential; NK, Natural killer; NF-κB, Nuclear Factor Kappa B; NF-AT, Nuclear factor of activated T-cells; PBMA, Peripheral Blood Mononuclear Cell; PKC-βI/η, Protein kinase C-beta/eta; PKC-θ, Protein kinase C-thea; PLC-γ2, Phospholipase C-gamma-2; PMA, Phorbol myristate acetate; PSD-95, Postsynaptic density protein 95; RANK-L, Receptor Activator of Nuclear Factor Kappa B Ligand; RBL-2H3, Rat Basophilic Leukemia-2H3; Syk, spleen tyrosine kinase; SLP-65, SH2 domain-containing leukocyte adaptor protein of 65 kDa; SH3, SRC Homology 3 Domain; SDF-1α, stromal cell-derived factor 1 alpha; TNF-α, Tumor Necrosis Factor-alpha; VCA, Verprolin, cofilin and acidic; WA*SP*, Wiskott–Aldrich syndrome protein.

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*Correspondence to: Dr. Ramesh P. Thylur, Department of Biochemistry and Molecular Biology, The Pennsylvania State University College of Medicine, 500 University Drive, Hershey, PA 17033, E-mail: rameshthylur@gmail.com

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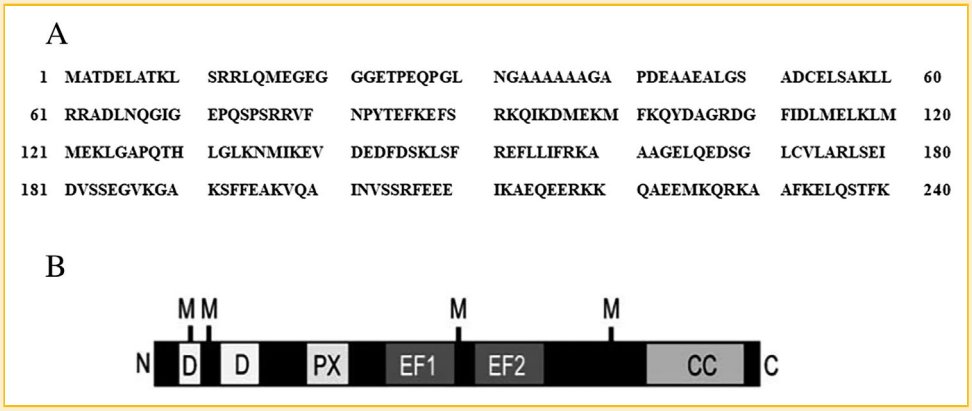

Fig. 1. Predicted amino acid sequence (A) and secondary structure (B) of swiprosin-1. M, myristylation site; PX, proline-rich elements (potential SH3 domain-binding sites); EF, EF hands; CC, coiled coil domain; D, disordered region.

essential for the Syk-, SLP-65, and PLC-gamma2-dependent B-cell receptor (BCR)-induced calcium flux [Vuadens et al., 2004; Avramidou et al., 2007; Schulz et al., 2007; Kim et al., 2013). However, the functions of swiprosin-1 are still largely unknown. Swiprosin-1 functions as a small adaptor protein that associates with lipid rafts and is involved in Ca^{2+} signaling suggesting that swiprosin-1 might have a pivotal role in the cytotoxic cellular pathway. Swiprosin-1 regulates PKC-βI/η, PKC-θ, and NF-κB signaling pathways in HMC-1 and Jurkat T cells [Thylur et al., 2009]. Furthermore, swiprosin-1 induction is faster in RBL-2H3 cells via FcεRI cross-linking than in HMC-1 and Jurkat T cells. [Ramesh et al., 2009]. Finally, swiprosin-1 is induced during osteoblast differentiation from human mesenchymal stem cells [Zhang et al., 2007], also during differentiation of the murine RAW264 macrophage cell line into osteoclasts after treatment with RANK-L (receptor activator of NF-κB ligand or tumor necrosis factor ligand superfamily member 11) [Nomiyama et al., 2005] and it is highly up-regulated in mice megakaryocytic (MKs) platelets during sepsis [Freishtat et al., 2009], and in rat and human platelets upon thrombin stimulation [Yu et al., 2010]. This review discusses the multifaceted role of swiprosin-1 in regulating the process of the various biological function will be highlighted. Finally, the future implications of swiprosin-1 research will also be explored.

SWIPROSIN-1 IN IMMUNE CELLS ACTIVATION

The immune responses are regulated by a broad range of cell type specific, and shared activating and inhibitory receptors that are responsive to signals from extrinsic or intrinsic [Pearce and Pearce, 2013]. These responses in immune cells modulates expression of large numbers of genes leads to the high output production of cytokines, lipid mediators, tissue remodeling enzymes, toxic gases, and the ability to migrate through tissues and/or undergo cellular division [Pearce and Pearce, 2013]. In earlier studies we have demonstrated the ectopic expression of swiprosin-1 amplifies pro-inflammatory cytokines (TNF-α and IL-3), chemokines (IL-8) and histamine secretion during activation of mast cells (HMC-1) [Thylur et al., 2009]. Besides, Kim et al. [2013] showed that swiprosin-1 shows temporal over induction to phorbol ester in cultured immune cells (HMC-1, Jurkat-T) [Thylur et al., 2009]. In addition, they have also studied the upregulation in rat mast cell line RBL-2H3 through FcεRI cross-linking by stimulation with IgE and DNP-HAS, and in in-vivo model tissues of passive cutaneous anaphylaxis and atopic dermatitis [Ramesh et al., 2009; Thylur et al., 2009].

Signaling elements like spleen tyrosine kinase (SYK), important in both adaptive immunity and innate immunity [Dutting et al., 2011]. Interestingly, signaling molecules of innate immune cells in higher organisms are even shared in drosophila where they control processes like the removal of necrotic tissue [Mocsai et al., 2010]. Although, insects do not possess an adaptive immune system but rely solely on their innate immune system and they utilize ITAMs (immunoreceptor tyrosine-based activation motifs) [Flaswinkel et al., 1995]. Kroczek et al. demonstrated that in the murine WEHI231 cell, swiprosin-1 acts as a positive regulator of Syk activity in response to BCR stimulation [Kroczek et al., 2010].

Insect hemocytes act as crucial players of immune surveillance by migrating through the body, phagocytizing invading pathogens, and secreting antimicrobial peptides [Williams, 2007]. Plasmatocytes are a form of hemocytes which resembles mammalian monocytes and macrophages [Williams, 2007]. EFhd exhibits phagocytic activity when expressed in differentiated macrophages like the hemocytes of drosophila [Henikoff et al., 2009; Dutting et al., 2011] and the drosophila S2 cell line [Williams, 2007]. Many hematopoietic factors have been conserved across taxonomic groups [Mocsai et al., 2010]. Likewise, swiprosin-1/EFhd2 was found to be express in murine monocyte cell line RAW264 [Nomiyama et al., 2005], human PBMC [Xu et al., 2010], microglia cells [Reynolds et al., 2008], and in NK-like cells [Meng and Wilkins, 2005]. It gets upregulated along with actin in response to stimulation of the human monocyte cell line THP-1

with a recombinant mycobacterium bovis strain. This stimulation improved the antigen presenting capacity of THP-1 cells, the $CD8^+$ immune response, and TNF-α production [Xu et al., 2010]. Hence, swiprosin-1 expressed across species in many cell types of the innate and adaptive immune system. It would be interesting to investigate if swiprosin-1 is participating in phagocytosis.

SWIPROSIN-1 IN APOPTOSIS

Apoptosis is a process of cellular suicide executed by chemotherapeutic agents, ionizing radiation, or mitochondrial damages, a family of cysteine proteases like caspases [Checinska et al., 2009]. Swiprosin-1 expressed WEHI231 cells induces the apoptosis via the caspase-7 pathway and decreases the Bcl-xL level, but interestingly Bcl-xL protein was three-fold more abundant in absence of swiprosin-1 compared to control during BCR activation. Furthermore, ectopic expression of swiprosin-1 shows decreased $\Delta\Psi_m$ under normal culture conditions, suggesting that swiprosin-1 abundance may regulate the amount of Bcl-xL on the transcriptional level and thereby influences proapoptotic BCR signaling in B cells [Avramidou et al., 2007]. Blagoev et al. [2004] and Mielenz et al.[2005] demonstrated that swiprosin-1 found to be associated with an inactive caspase-9 during BCR and EGFR signal transduction. Further, Checinska et al. [2009] speculated that swiprosin-1 binds to caspase-9 via ERM proteins, which are cross-linkers between integral membrane proteins and actin filaments, which are known to associate with caspase-9. Furthermore, the presence of two potential EF-hand domains of swiprosin-1 may regulates calcium-dependent activation of caspase-9 during apoptosis.

SWIPROSIN-1 IN NF-κB PATHWAY

NF-κB is a prototypical proinflammatory signaling pathway modulates the expression of proinflammatory mediators like cytokines, chemokines, and adhesion molecules [Lawrence, 2009]. Swiprosin-1 acts dual role as negative regulator of NF-κB activation in BCR signaling pathway [Avramidou et al., 2007] and as a positive regulator of the NF-κB activation in PKC βI/η signaling pathway [Thylur et al., 2009]. In earlier studies, we have revealed that the ectopic expression of swiprosin-1 significantly increases the transcriptional activity of NF-κB and I-κB degradation in HMC-1 cells treated with PMA/A23187, which augments level of swiprosin-1 abundance increases the expression of proinflammatory cytokines, chemokines, and histamine releases [Thylur et al., 2009; Kim et al., 2013]. Furthermore, Rawlings et al. demonstrated that NF-κB activation through the Carma1/Bcl10/MALT1 complex by PKCβ pathway which is also activated by the BCR downstream of PLCγ2/Ca^{2+} signaling [Rawlings et al., 2006]. In addition, Avramidou et al. showed in BCR stimulation of murine B-cell line WEHI231, absence of swiprosin-1 induces strong I-κB-α phosphorylation and I-κB-α degradation but surprisingly it was not observed in control cells or in ectopically expressed swiprosin-1 cells [Avramidou et al., 2007].

SWIPROSIN-1 IN CA^{2+} SIGNALING

Many of Ca^{2+} mediated events occurs when the released Ca^{2+} binds to and activates the regulatory protein calmodulin [Kretsinger and Nockolds, 1973]. Alterations of Ca^{2+} ions are often transmitted through Ca^{2+} binding proteins of the EF-hand family [Kretsinger and Nockolds, 1973], such as calmodulin that activates NF-AT through the Ca^{2+}/calmodulin dependent phosphatase calcineurin [Clipstone and Crabtree, 1992]. In murine WEHI231 B cells, deletion of ΔPR, ΔLC, and ΔEF1 swiprosin-1 mutants did not restore the BCR elicited Ca^{2+} flux as compared with wild-type swiprosin-1 and also absence of swiprosin-1 shows lower calcium flux, suggest that two putative SH3 binding motifs (proline-rich domain, amino acids 72–82) of swiprosin-1 are responsible for BCR induced calcium flux [Hagen et al., 2012].

Swiprosin-1 deficient mice platelets showed normal Ca^{2+} store release when stimulated with major platelet agonists like CRP and thrombin [Morowski et al., 2014]. Further, a hydrophobicity plot of murine swiprosin-1 (Q9D8Y0) according to Kyte and Doolittle reveals that EF-hand 1 (EF1) of swiprosin-1 is more hydrophilic than EF-hand 2 (EF2). Therefore, deletion of EF1 may render the protein more hydrophobic. Ca^{2+} binding by EF hands is mediated by a 12 canonical amino acid loop that connects the two helices of the EF-hand. The classical consensus motif of the 12 amino acid Ca^{2+} binding loop of EF hands is also present in swiprosin-1 (EFhd2) as well as the related swiprosin-2 (EFhd1) [Dutting et al., 2011]. In swiprosin-1, conserved glutamic acid residues, namely E116 and E152 are located at position −Z of EF1 and EF2, respectively. Since Ca^{2+} binding to each of the single mutants was reduced by half and abolished in the double mutant E116A/E152A, thus both residues E116A of EF1 and E152A of EF2 were accounted for most of the Ca^{2+} binding to swiprosin-1 [Hagen et al., 2012].

Swiprosin-1 contains three actin-binding sites (69–96, 96–163, and 163–199) situated between 70 and 199 amino acids (Fig. 2). Very weak or no actin-binding site was identified in the first N-terminal region (amino acids 1–69) and C-terminal coiled-coil region (amino acids 200–240), however, these sites were required for the actin-binding affinity was regulated by swiprosin-1. Fechheimer et al. shows that calcium can affect cellular dynamics by regulating actin bundling by binding to actin bundling proteins [Fechheimer and Taylor, 1984]. Further, the deletion of EF-hand motifs (D97–163, M2) of swiprosin-1 showed less actin bundling activity, but deletion of the coiled-coil domain (1–163, M1) abolished the actin bundling activity than wild type swiprosin-1, suggesting that Ca^{2+} changes affected the bundling activity specifically Lys-rich region (218–240) is essential for swiprosin-1 induced actin bundling [Kwon et al., 2013], except actin binding activity was not significantly different among the coiled-coil mutants.

SWIPROSIN-1 IN CANCER INVASION AND METASTASIS

Cancer invasion and metastasis are landmark events that transform a locally growing tumor into a systemic, metastatic, and live

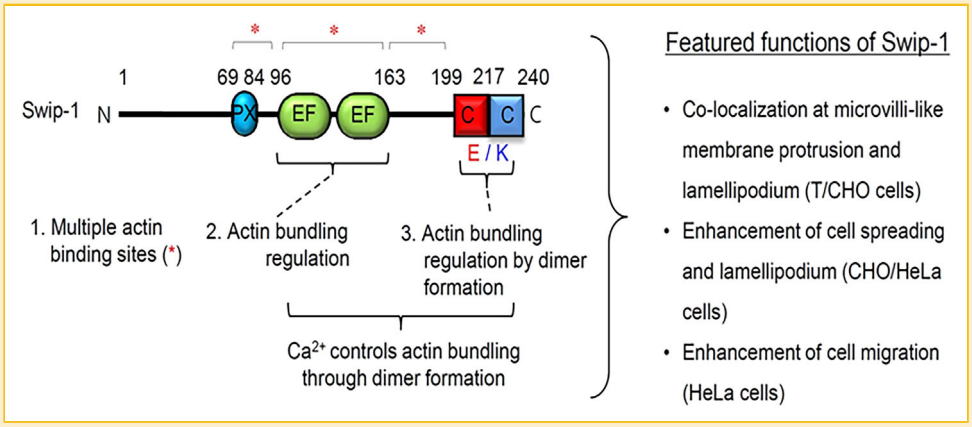

Fig. 2. Schematic diagrams of the putative domains of swiprosin-1 and their specific roles in regulating actin organization (Adopted from Ref [Kwon et al., 2013]).

threatening disease [Friedl and Alexander, 2011]. Mice injected with B16F10 cells stably expressing GFP-Swiprosin-1 shows significantly increased the number (~4 times) and size of black nodules in lung as indicative of pulmonary metastases, compared to those injected with GFP-control. Moreover, in B16F10 cells a stable transduced shRNA-Swiprosin-1 injected mouse, pulmonary metastasis was dramatically decreased the size, and number of pulmonary nodules [Huh et al., 2015]. These few studies in cancer indicate a deleterious role in cancer progression gives a glimpse at the role of swiprosin-1 in various stages of metastasis, but there is still a significant amount of work to be done in this field. Is swiprosin-1 involved in the silencing of anticancer pathways; does it primarily promote migration, invasion, and other cancer-promoting roles; which genes are involved in the observed responses; what is involved in, and how can we influence, the balance of tumor promoting vs. tumor suppressing roles? These are just some of the questions for future research (Fig. 3).

SWIPROSIN-1 ASSOCIATES WITH ACTIN CYTOSKELETON, AND REGULATES LAMELLIPODIA AND CELL MIGRATION

Cytoskeleton is an intracellular matrix plays a several fundamental roles in the cell including, organizing the spatial arrangement of subcellular organelles, regulating cell dynamics and motility, providing a platform for interaction with neighboring cells, and ultimately defining overall cell shape [McKayed and Simpson, 2013]. Cell migration begins with the formation of membrane protrusions, such as lamellipodia, filopodia, and membrane ruffles are dependent on actin dynamics, which are regulated by a variety of actin-binding proteins acts cooperatively to reorganize actin filaments [Huh et al., 2013, 2015]. Members of the Rho family of guanosine triphosphatases (GTPase) (RhoA, Rac1, and Cdc42) function in multiple signaling pathways leading to cell adhesion, migration, proliferation, and transformation. For instance, the Cdc42 is required for cellular polarity and formation of filopodia, Rac1 is required for lamellipodia, ruffle formation and cell migration, whereas RhoA is required to retract the trailing edge of migrating cells [Dutting et al., 2011; Huh et al., 2015].

F-actin is known to be enriched in the microvilli-like region (lamellipodia formation) [Ramesh et al., 2009], whereas swiprosin-1 is localized in microvilli like protrusions of HMC-1 cells and membrane apical ridge area of 293T cells. Additionally, swiprosin-1 re-localized along with the movement of F-actin in COS-7 and B16F10 cells, when the cells were stimulated with PMA and EGF respectively [Ramesh et al., 2009; Dutting et al., 2011; Huh et al., 2013; Kwon et al., 2013]. Kwon et al. [2013] observed similarly swiprosin-1 was recruited to the actin-rich region in Jurkat T or human primary T cells during T cell activation. On the other hand swiprosin-1 did not promote actin polymerization mediated by the Arp2/3 complex and VCA domain of WASP, a cofactor of Arp2/3 complex and did not function as a cofactor like VCA domain, but the phosphorylation of swiprosin-1 at Ser183 inhibits cofilin-mediated actin depolymerization by blocking its access to F-actin, suggesting that dynamic exchange of phosphorylation/dephosphorylation of swiprosin-1 play a key role in regulating membrane dynamics [Huh et al., 2013].

In the aspects of cell migration, Huh et al. showed ectopic expression of swiprosin-1 translocate to the leading edge of motile B16F10 cells, induced the formation of membrane ruffles, microspikes, and lamellipodia, and also enhances the Rac1 and Cdc42 activity, but reduces the RhoA activity in B16F10 cells [Huh et al., 2015]. The deletion of the coiled-coil domain and EF-hand motifs of swiprosin-1 showed a dramatic reduced lamellipodia formation and cell spreading, were observed mainly in the cytosolic region but no significant localization at the F-actin rich region at the cell periphery, suggesting a connection between actin bundling activity and lamellipodium formation at the cell periphery [Kwon et al., 2013]. Furthermore, Kwon et al. [2013] demonstrated that swiprosin-1 enhances SDF-1α-mediated T cell spreading and the phosphorylation site(s) in N-terminal region of swiprosin-1 has the regulatory function of lamellipodia formation, thereby modulating cell spreading and migration through remodeling of the actin cytoskeleton with the Rho family of GTPase.

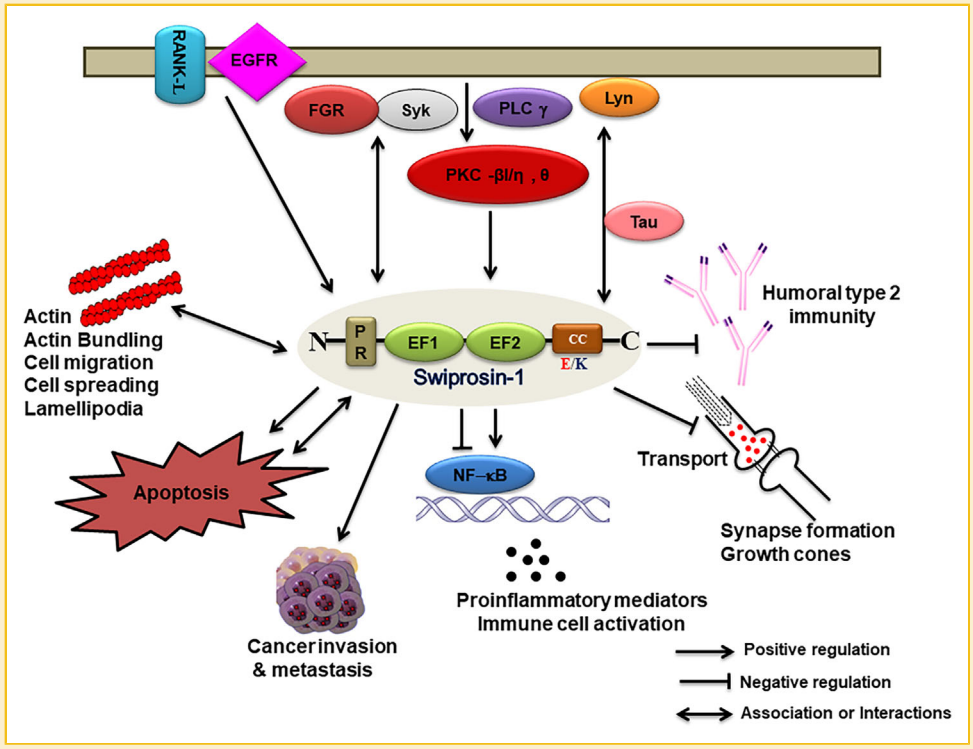

Fig. 3. Swiprosin-1 associated signaling pathways and functions. Expression of swiprosin-1 regulated by RANK-L, PKCβ1/η, PKCθ, and EGFR. It increases the constitutive association of the BCR μHC, Syk, and PLCγ2 with membrane rafts. It also stabilizes the association of BCR with tyrosine-phosphorylated Syk and PLCγ2, and enhances the constitutive interaction of Syk and PLCγ2 with Lyn [Kroczek et al., 2010]. The N-terminal half of swiprosin-1 and/or Ca^{2+} binding to EF1 (residues E116A and E152A) is the regulators of BCR elicited Ca^{2+} flux. Swiprosin-1 exhibited dual role as negative regulator of NF-κB activation by apoptosis and neurodegeneration, and as positive regulator of the NF-κB activation by release of proinflammatory mediators and immune cells activation. During apoptosis it associates with caspase-9 complex and regulates the cancer invasion and metastasis by increasing Rho. Swiprosin-1 interacts with actin/cytoskeleton, and its EF-hand motifs and coiled-coil domain (Lys-rich region) regulates the actin bundling and also modulates the cell migration (cell spreading and lamellipodium). Swiprosin-1 associates with tau in mouse and also in alzheimer's patients. Swiprosin-1 negatively regulates the kinesin-mediated anterograde microtubule transport and formation of synapses either directly through its effect on actin remodeling and a potential function in growth cones other than neurite outgrowth or indirectly through its negative impact on microtubule transport. Finally, swiprosin-1 negatively regulated the germinal center dependent humoral type-2 immunity.

SWIPROSIN-1 IN NEURON AXONAL TRANSPORT

Neurons are regionally differentiated cells and axonal transports occur in two directions from the cell body to the terminal (anterograde) and from terminals to the cell body (retrograde) [Schwartz, 1979]. Axonal transport can be affected by alterations of various components of the transport machinery and contributes to the pathogenesis of neurodegenerative diseases [Millecamps and Julien, 2013]. In Nogo-A knockout mice, downregulated swiprosin-1 expression increased the neurite growth and regeneration potential when compared to the wild type mice [Dimou et al., 2006]. Martins-de-Souza et al. observed that swiprosin-1 is upregulated together with microtubule-associated proteins in the frontal cortex of schizophrenic patients [Martins-de-Souza et al., 2009]. These data's suggested that swiprosin-1 might participate in neurodegenerative diseases and neuronal regeneration. On the other hand, in murine neurites, co-localization of swiprosin-1 with tau, MAP2, synapsin 1a/b, and PSD-95 signifying that swiprosin-1 could be also associated with transport vesicles delivering synaptic proteins and it serve as a synaptic protein. For example, swiprosin-$1^{-/-}$ mice increases the speed of axonal transport but its presence inhibited the KIF5A (kinesin) mediated MT (microtubules) gliding in a dose-dependent manner [Purohit et al., 2014]. Similarly, Borger et al. also showed knockdown of swiprosin-1 facilitates the development of a larger number of synapses in neurons but did not affect their ability to convert to mature synapses by recruiting postsynaptic densities [Borger et al., 2014].

SWIPROSIN-1 IN HUMORAL IMMUNITY

Humoral immunity leads to the antibody production, Th2 activation, cytokine production, germinal center formation, isotype switching, affinity maturation, and memory cell generation [Erard et al., 1993; Achatz-Straussberger et al., 2009; Harris and Gause, 2011]. The activated B cells are selected for antibody specificity and isotype switching in germinal centers which are regulated by their checkpoints or apoptosis [Reth, 1992]. Swiprosin-1 can promote apoptosis in activated B cells [Kroczek et al., 2010]. EFhd2$^{-/-}$ (swiprosin-1) mice does not affect B-cell responses to T-cell independent immunization with TI1 (Nitrophenol-Ficoll) and TI2 (Trinitrophenol-LPS) antigens but it strongly elicits a T-cell

dependent Th2 cell mediated IgE and IgM production in response to the mice infected with helminth Nippostrongylus brasiliensis as compared to the EFhd2$^{+/+}$ mice. After 7 days of immunization with sheep red blood cells and Nippostrongylus brasiliensis, the germinal center area, B-cell numbers, and antibodies production of multiple isotopes were significantly increased in EFhd2$^{-/-}$ mice, suggesting that swiprosin-1 acts as a negative regulator of germinal center dependent humoral type 2 immunity [Brachs et al., 2014].

CONCLUSIONS

Although many important questions remain regarding the development of specific inhibitors or the design of interaction blockers, we believe that swiprosin-1 are attractive targets for the number of pathological situations like inflammation (acute and chronic), neurodegeneration, dementia, schizophrenia and cancer. The challenges for the future will be elucidating the complexity and variability of the swiprosin-1 network in the inflammatory disorders, and understanding the protective and adaptive immunity, and its corresponding regulatory mechanisms.

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