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REVIEW

Spectrin-based skeleton as an actor in cell signaling

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Abstract This review focuses on the recent advances in functions of spectrins in non-erythroid cells. We discuss new data concerning the commonly known role of the spectrin-based skeleton in control of membrane organization, stability and shape, and tethering protein mosaics to the cellular motors and to all major filament systems. Particular effort has been undertaken to highlight recent advances linking spectrin to cell signaling phenomena and its participation in signal transduction pathways in many cell types.

Keywords Spectrin · Cell signaling · Spectrin-based skeleton · Membrane skeleton

Spectrins: several genes and numerous isoforms widely distributed in all metazoan cells

Spectrins are large flexible molecules that exist mainly as heterotetramers made of various α and β subunit isoforms. The α and β subunits are assembled side to side in an antiparallel fashion to form rod-like αβ dimers that in turn self-associate head to head to form tetramers. Tetramer formation involves the N-terminus of each α subunit with the C-terminus of each β subunit. The β-spectrin chains can also exist as homopolymeric complexes in skeletal muscle [1] and possibly in the Golgi apparatus [2, 3]. Each extremity of tetramers binds actin microfilaments via β-spectrin, allowing spectrin to form cross-links between actin filaments, thus generating an extended network.

Spectrins are expressed in all metazoan cells arising from numerous genes. Therefore, in mammals, the different spectrin isoforms originate by extensive mRNA splicing from seven genes. Two genes, *SPTA1* and *SPTAN1*, encode αI- and αII-spectrin subunits, respectively. In contrast to *SPTA1*, the *SPTAN1* gene codes for several αII-spectrin isoforms present in all non-erythroid cells, resulting from three alternative splicing processes [4–6]. Five genes code for β-spectrins: four "conventional" β genes, *SPTB*, *SPTBN1*, *SPTBN2*, *SPTBN4*, encoding the βI–βIV spectrins, respectively, and one gene, *SPTBN5*, encoding one large βV-spectrin (β-Heavy) [7, 8]. The expression of the diverse isoforms is regulated in a complex tissue- and developmental stage time-specific manner (Tables 1, 2).

Invertebrates have a smaller repertoire of spectrin genes. The *Caenorhabditis elegans* and *Drosophila melanogaster* genomes include a single gene coding for an α-spectrin closed to the mammalian αII-spectrin [*spc-1* and *I(3)dre3*, respectively] [9, 10] and two genes coding for β-spectrin; one codes for a β_G protein resembling the mammalian βII-spectrin referred to as "conventional β-spectrin" (*Unc-70/bgs-1* and *β-Spc*) [11], and the other (*sma 1* in *C. elegans* and *karst* in *D. melanogaster*) encodes βH-spectrin (β-Heavy similar to mammalian βV) [12, 13]. Greater sequence conservation is observed between spectrins from

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Table 1 Spectrin genes and their expression in mammalian tissue

Subunit	Gene	Chromosome	Tissue expression	Ref.
Homo sapiens				
αI	*SPTA1*	1q21–q23	Isoform αIΣ1 RBC and isoform (αIΣ*) in brain	[7, 8]
αII	*SPTAN1*	9q33–q34	Several isoforms present in all non-erythroid cells	[4, 5, 132]
βI	*SPTB*	14q22–q23.2	βIΣ1 erythrocytes, βIΣ2 isoforms in brain and muscle, βI-spectrin was also detected in lymphocytes	[8, 18, 50, 100]
βII	*SPTBN1*	2q21	All nucleated cells	[8, 50, 100]
βIII	*SPTBN2*	11q13	Golgi and vesicular membrane skeletons, plasma membrane in neurons and epithelial cells	[49, 113]
βIV	*SPTBN4*	19q13.13	Neurons (axon, initial segment, nodes of Ranvier) and pancreatic islets, nucleus	[6, 130]
βV	*SPTBN5*	15q21	Low level in many tissues, outer segments of photoreceptor rods and cones, basolateral membrane of gastric epithelial cells and outer hair cell (OHC)	[59, 60]

Table 2 Examples of spectrin functions in cellular processes and signaling

Spectrin isoforms	Function in cellular processes/signaling	Ref.
αI	Supports RBC shape and maintains cell membrane integrity and its mechanical properties	[14, 51, 52, 131]
αII	Engaged in maintaining cell architecture, morphology, and plasma membrane stability	[53–55]
	Engaged in regulation of neurite outgrowth stimulated by NCAM	[64]
	Participates in the organization of specialized membranes—TRPC4 channels	[65, 66]
	Engaged in cell adhesion and spreading, regulation of actin dynamics	[84, 91]
	Modifies cell cycle by altering cell adhesion	[84]
	Engaged in DNA interstrand cross-links repair, connected to maintaining chromosomal stability	[85–87, 90]
βI	Supports RBC shape and maintains cell membrane integrity and its mechanical properties	[51, 52]
	Contributes to the formation of TCR complexes in lymphocytes	[99, 100, 109]
	Involved in early cellular apoptotic events	[110, 111]
βII	Engaged in cell morphology and mechanical properties, compaction and accumulation of E-cadherin in the epithelial cell-cell contact	[56, 57]
	Delivery of proteins and phospholipids to the membrane	[3, 30, 31, 47]
	Cell cycle regulation by involvement in TGFβ signaling	[75, 76, 80–82]
βIII	Participates in the organization of the glutamate transporter EAAT4 in Purkinje cells	[70, 71]
	Facilitates membrane protein transport via the secretory and endocytic pathways	[112–114]
βIV	Regulates localisation of voltage-gated channels at the axon initial segment and node of Ranvier, synchronizes action potentials, provides multifunctional regulatory platform for sodium channels, plays an important role in the structure and stability of excitable membranes in heart and brain	[72, 73, 133]
	Involved in targeting of critical structural and regulatory proteins	[134]
βV	Engaged in cell flexibility	[59]
	Engaged in OHCs' electromotility	[60]

Drosophila and non-erythroid spectrin than between the erythroid and non-erythroid forms within the mammalian organism. Sequence analyses suggest that the erythroid spectrin genes arose during vertebrate evolution, and some of the sequence changes may correspond to neo-functionalization of the erythroid spectrin genes [14–16].

Despite the diversity of the genes, each spectrin subunit is made up of a succession of triple helical motifs called spectrin repeats (roughly 106 amino acid residues long), flanked by non-homologous N- and C-terminal sequences [7, 17, 18]. α-Spectrins contain 20 spectrin repeats (α1-α20), β-spectrins are made of 17 spectrin repeats (β1-β17), while the heavy βV-spectrins contain 30 repeats.

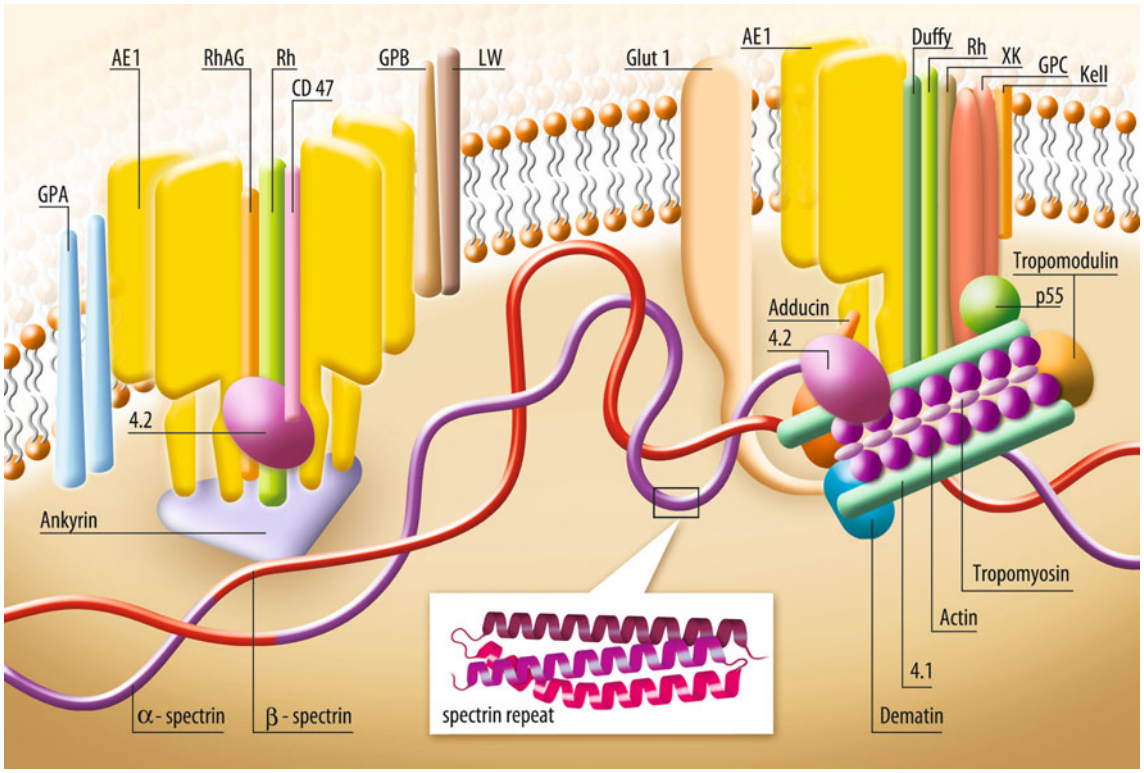

Fig. 1 A model of the human red cell membrane. The spectrin-actin interaction is modulated by accessory proteins such as protein 4.1, together with dematin, adducin, tropomyosin and tropomodulin. Their functions are to stabilize the actin-spectrin complex, to maintain actin filament length (adducin acts as a capping protein), and to bind the spectrin-based network to the transmembrane proteins (the glycophorin C, the anion exchanger AE1) via adapter proteins (protein p55 and protein 4.2). Another major binding site to membrane is mediated via ankyrin, which binds to β-spectrin and the anion exchanger AE1. The Rh/RhAG-ankyrin complex can be also a link between the red cell membrane and the spectrin-based skeleton. Spectrins also interact directly with phospholipids such as phosphatidylserine and phosphatidylethanolamine, membrane components actively confined to the inner leaflet of the lipid bilayer. The aminophospholipid-binding sites in β-spectrin are localized in close proximity to the attachment sites for both ankyrin and 4.1, the proteins engaged in spectrin links to the membrane. *AE1* anion exchanger, *GPA* glycophorin A, *GPB* glycophorin B, *GPC* glycophorin C, *GLUT 1* glucose transporter 1, *Rh* rhesus factor, *RhAG* Rh-associated glycoprotein

The structure of the repeat unit (folded in a triple α-helical coiled-coil structure) and their interconnection are thought to be closely associated with spectrin flexibility [19]. When stretched, spectrin tetramer filaments can reach $\sim$200 nm in length. Besides roles in the structure and the flexibility of spectrins, spectrin repeats can be considered as an interaction platform. Some spectrin repeats are involved in the formation of spectrin dimers and tetramers, such as the α17–α20 repeats with β1–β4 repeats, and the first helix of α-spectrin with the last incomplete β17 repeat of β-spectrin, respectively [20–22]. Moreover, they are also essential to the binding of the spectrin-based membrane skeleton to the membrane bilayer (Fig. 1). In erythrocytes, the β14–15 repeat region is bound to the anion exchanger (AE1) via ankyrin [23]. Another major membrane bilayer binding site is the protein 4.1 complex, which includes actin, dematin, adducin, tropomyosin and tropomodulin. This complex binds the spectrin-based network to glycophorin C and the anion AE1 by adapter proteins p55 and 4.2 [24–27]. The 4.1 complex also stabilizes the actin–spectrin interaction and maintains actin filament length. Spectrins also interact directly with phospholipids such as phosphatidylserine and phosphatidylethanolamine, a component actively confined to the inner leaflet of the lipid bilayer [28–34]. All these interactions are crucial for maintaining membrane mechanical properties. Recent data revealed that α-spectrin repeats can directly interact with membrane proteins such as the adhesion molecules Lu/BCAM (involving the α4 repeat) [35, 36]. Furthermore, there are still unexplained relationships between proteins exported by the malaria parasite *Plasmodium* and α-spectrin repeats (for a review, see [37].

Besides the spectrin repeats, spectrins contain additional sequences that can facilitate some protein-protein or protein-lipid interactions. α-Spectrins contain an SH3 domain within the α9-spectrin repeat, which is well known to be engaged in cell signaling mainly by interacting with proline-rich stretches [38]. At the C-terminal end they also

contain two EF-hand motifs related to calmodulin and involved in calcium binding [39–41]. αII-Spectrin differs from αI-spectrin by a 35-residue insert in the α10 repeat, which bears a Ca^{2+}-dependent binding site for calmodulin [42] and cleavage sites for both caspases (2 and 3) [43] and for m and μ calpains [44]. All β-spectrins contain an actin-binding domain in their N-terminal region composed of a tandem of two CH (calponin homology) domains, which is present in many spectrin-related and unrelated skeletal proteins [45, 46]. The C-terminal region of the "long" isoforms of β-spectrins contains a PH (pleckstrin homology) domain responsible for phosphoinositide binding [47–49].

While mammalian erythrocytes contain only one type of spectrin tetramer made of αI and βI subunits, located at the inner surface of the membrane, nucleated cells can contain several spectrin species. Numerous isoforms of α- and β-spectrins derived from different genes are located in diverse cellular compartments (membrane, Golgi apparatus, endoplasmic reticulum, vesicles and nucleus). Some isoforms have a specific expression according to cell type or to cell organelle with very specific functions. The inactivation of the genes encoding canonical spectrin in *D. melanogaster* or in *C. elegans* indicated that these proteins are essential for the survival and normal development of these organisms (for review see [50]).

Spectrins are multifunctional proteins involved in regulation of cell morphology and mechanical properties

In erythrocytes the spectrin-based network supports cell shape, and maintains cell membrane integrity and its mechanical properties (for reviews, see [51, 52]). The role of spectrin in determining the physical properties of red blood cell membrane was clearly documented in hereditary hemolytic anemia associated with mutations in both αI- and βI-spectrins. Indeed molecular defects in erythroid spectrins are associated with abnormal shape, increased membrane fragility and reduced erythrocyte deformability.

Similarly, in nucleated cells the spectrin-based skeleton is involved in cell architecture, morphology, and plasma membrane stability [53–55]. In epithelial cells, knockdown of either βII-spectrin or ankyrin G results in loss of the lateral membrane, expansion of the apical and basal membrane area, and conversion of cells from columnar to squamous morphology [56, 57]. Both proteins are required for compaction and accumulation of E-cadherin in the epithelial cell-cell contact, and the delivery of proteins and phospholipids to the lateral membrane [56]. Recent data suggest that in *Drosophila*, β_H-spectrin (homolog to mammal βV-spectrin) at the apical membrane coordinates the interaction between cadherin-based zonula adherens, with the immunoglobulin cell adhesion molecule Roughest during eye morphogenesis [4, 58].

Spectrins also participate in cell flexibility outside the red blood cells. This property is conferred by mammalian βV-spectrin and its homologs (β_H spectrin in *D. melanogaster* and Sma-1 in *C. elegans*). These βV spectrin homologs have independently maintained an unusual 30-repeat length throughout evolution, which helps to cross-link membrane actin and confers extensive flexibility in cells [19, 59]. In the outer hair cells (OHC) αII-, βII- and βV-spectrins together with F-actin form the cortical network involved in the sound-induced electromotility. The main function of this spectrin-actin network is to provide flexible properties required for lateral wall contraction-elongation cycles. While βII-spectrin is restricted to the cuticular plate, a dense apical network of actin filaments, βV-spectrin is concentrated at the cortical lattice and is directly involved in the OHCs' electromotility [60].

Both α- and β-spectrins are required during nervous system development. β-Spectrin interacts directly with the neural cell adhesion molecule NCAM, a synaptic adhesion molecule involved in mechanical stabilization of neuronal contacts [61, 62]. Genetic variations of NCAM are considered a risk factor in bipolar affective disease and schizophrenia [63]. In another way, αII-spectrin (α12 repeat) phosphorylation-dependent interaction with 14-3-3, a protein involved in neuronal migration and synaptic plasticity, acts as a switch between positive and negative regulation of neurite outgrowth stimulated by NCAM [64].

This short survey of published data presented in this paragraph suggests that various spectrins are strongly involved in supporting cell architecture and morphology in non-erythroid cells.

Spectrins are a structural platform for stabilization and activation of membrane microdomains

The spectrin-based skeleton participates in the organization of specialized membranes. When spectrin or its binding partner ankyrin is lost from or defective in cells, their interacting membrane partners do not accumulate at the appropriate site within the membrane (for review, see [65]). The surface expression and activation of the hTRPC4 channel (human Transient Receptor Potential Channel 4) is partially regulated by way of a direct interaction with spectrin. In αII-spectrin-depleted cells, the TRPC4 channels failed to undergo membrane insertion [66]. Mutations in βIII-spectrin are the cause of spinocerebellar ataxia type 5 (SCA5) and neurodegenerative disease [49, 67–69]. βIII-Spectrin defects are associated with mislocation of the glutamate transporter EAAT4 at the surface of the plasma

membrane in Purkinje cells [70, 71]. βIV-Spectrin knockout mice exhibit tremors and contraction of the hindlimbs. Loss of βIV-spectrin observed in quivering mice with hearing loss is associated with mislocation of voltage-gated channels at the axon initial segment and node of Ranvier. Alterations in the location of sodium and potassium channels at myelinated nerves slow propagation and desynchronize action potentials [72, 73]. So, βIV-spectrin acts as a multifunctional regulatory platform for sodium channels, and has important roles in the structure and stability of excitable membranes in heart and brain, targeting critical structural and regulatory proteins. In *Drosophila*, loss of β-spectrin led to the loss of Na^+K^+-ATPase from the basolateral domain of epithelial cells [74]. In an extreme case, loss of a variant of βII-spectrin in mice led to death in utero [75].

As described above, the spectrin-based membrane skeleton controls the disposition of selected membrane channels, receptors, transporters and adhesion molecules. Defects in spectrins result in destabilization of the membrane structure, lead to serious neurodegenerative diseases and are involved in pathological processes.

Spectrins, cell cycle and DNA repair

Other studies suggest the participation of spectrin in cell cycle regulation. Spectrin might be involved in TGFβ signaling. Proteomic studies revealed the presence of spectrin in a complex including TGFβ-R1 (transforming growth factor β receptor-1) [76]. The loss of β-spectrin results in defective TGFβ signaling as manifested by mislocation of proteins that modulate the activity of TGFβ—smads 3 and 4 [75]. Spectrins are also components of the G-protein-coupled receptor (GPCR) complex [77] and the synaptic multiprotein complex [29, 78, 79]. These data indicate that spectrins are involved in the cell cycle by regulating the expression of membrane receptors. It is also noteworthy that in a mouse model, downregulation of expression of ELF, an isoform of βII-spectrin, confers susceptibility to tumorigenesis: βII-Sp+/− mutant mice develop frequent tumors associated with deregulation of cell cycle control at the G1/S transition and defective TGFβ signaling [80–82]. Moreover, these βII-Sp+/− mice are born with many phenotypic characteristics observed in Beckwith-Wiedemann syndrome (BWS), a hereditary stem cell cancer syndrome. These include dramatic visceromegaly, followed in later months by the development of multiple cancers, including carcinomas of the gastrointestinal tract, as well as renal and adrenal adenocarcinomas. Epigenetic silencing of βII-spectrin expression in human BWS could be a potential causal factor in this stem cell disorder [83].

Furthermore, in αII-spectrin-depleted melanoma cells, increased expression of p21 (an inhibitor of cyclin-dependent kinase) was observed, which was associated with cell cycle arrest in the G1 phase. Spectrin depletion could secondarily modify the cell cycle by altering cell adhesion [84]. Although the detailed roles of spectrins in cell cycle regulation remain to be elucidated, spectrins should be considered as important elements in transduction pathways of extracellular signals controlling the cell cycle.

αII-Spectrin is present in nuclei of human cells and could play an important role in the repair of DNA interstrand cross-links. αII-Spectrin is deficient in cells from patients with Fanconi anemia (FA) [85]. It colocalizes with the cross-link repair protein XPF and FANCA, one of the Fanconi anemia proteins, in cross-link-induced nuclear foci [86, 87]. Another FA protein, FANCG, contains a motif that interacts directly with the SH3 domain of αII-spectrin. It plays a role in maintaining αII-spectrin stability in the cell [88]. αII-Spectrin could be particularly important in some of the initial steps of the cross-link repair process, which involves incision and unhooking of the cross-link via XPF/ERCC1 [89]. After cell damage, αII-spectrin binds to DNA at the sites of damage and acts as a scaffold, contributing to the recruitment of repair proteins. Moreover, αII-spectrin is involved in maintaining chromosomal stability. Depletion of αII-spectrin in normal human cells results in chromosomal instability, as evidenced by an increased number of interchromatid exchanges, fusions/radials and breaks. It leads to decreased cell growth and survival [90]. These studies demonstrate the importance of αII-spectrin in the repair of DNA interstrand cross-links.

Spectrin contributes with actin to cell adhesion and spreading

A newly proven role of α-spectrin is its participation in cell adhesion and spreading via its SH3 domain. αII-Spectrin is present in a specialized type of calpain-induced β3 integrin signaling complexes. The SH3 domain appears to transmit signals required for Rac activation and lamellipodia extension [91]. Cells overexpressing the SH3 domain adhered to the substratum, and their calpain-induced integrin signaling complexes were formed, but Rac activation, lamellipodia extension and cell spreading were inhibited. Spreading was restored by overexpressing constitutively active Rac. Other data supported the involvement of αII-spectrin in actin reorganization [84]. Spectrin loss by siRNA impaired cell adhesion and spreading. Spectrin-depleted cells exhibited modifications of the actin cytoskeleton, such as loss of stress fibers, alterations of focal contacts and modified expression of some integrins. Spectrin via its SH3 domain interacts with two members of

the Ena/VASP (enabled/vasodilator-stimulated phosphoprotein) family: VASP [92] and EVL (Ena/VASP-like) [93, 94]. Ena/VASP proteins are found in focal contacts, cell-cell contacts and highly dynamic membrane regions such as lamellipodia. These proteins appear to regulate adhesion and to control actin dynamics. Proteins of the Ena/VASP family are essential for actin remodeling upon T cell activation, formation and extensions of lamellipodia. Ena/VASP proteins bind the adapter protein ADAP (expressed in T cells and myeloid cells), which participates in LFA-1 integrin clustering. Spectrin also interacts with other proteins involved in actin dynamics, such as Abi1 [95, 96] and proteins of the WASP (Wiskott-Aldrich syndrome protein) family. The T cells from patients with Wiskott-Aldrich syndrome show characteristic cytoskeletal defects [97] and impaired function [98].

Thus, these recent data pointed out an unexpected role of αII-spectrin in transmission of signals leading to Rac activation, adhesion, lamellipodia extension, and cell spreading through several ligands and partners regulating actin dynamics.

Control of activation of transmembrane proteins

The other example of spectrin participation in cell signaling is its contribution to the formation of TCR (T cell receptor) complexes in lymphocytes. It has been clearly demonstrated that the spectrin-based skeleton via its two major proteins, spectrin and ankyrin, directly binds CD45 in lymphocytes [99, 100]. CD45 plays a pivotal role in antigen-stimulated proliferation of T lymphocytes and in thymic development. The catalytic activity of CD45 is required for TCR signaling and regulation. Human mutations in the CD45-encoding gene are the cause of severe combined immunodeficiencies (SCID) [101–103]. CD45-deficient mice are severely immune-deficient, with very few peripheral T lymphocytes, defective thymocyte development and failed receptor-mediated activation [104]. The direct binding of spectrin to CD45 stimulates the PTPase activity of CD45 and also facilitates the movement of CD45 and CD3 to the lymphocyte surface [100].

In lymphoid-derived cell lines, spectrin is distributed in the cytoplasm, but appears very often as large aggregates [105]. These spectrin-rich large aggregates in lymphocytes contain several proteins, such as hsp70, receptor for activated C kinase-1 (RAC-1) and PKCθ (Ca^{2+}-independent subfamily of serine/threonine specific protein kinase C) [106, 107]. Activation of lymphocytes by phorbol 12-myristate 13-acetate (PMA), T-receptor cross-linking and mild hyperthermia resulted in the formation of cytoplasmic spectrin aggregates [108]. Recruitment of intracellular proteins to the plasma membrane is a well-known event required for the initiation of signal transduction; the participation of spectrin in this event may indicate its signaling function in lymphocytes. These facts imply that occurrence of aggregation of spectrin and PKCθ in chemically and physically stimulated lymphocytes and formation of a large signaling complex at the site of TCR clustering in immunological synapses may be related phenomena [109].

Spectrin aggregation may also be associated with early cellular apoptotic events preceding a loss of membrane aminophospholipid asymmetry [110]. Concomitant PKCθ rearrangement in lymphocytes implies its relationship to spectrin aggregation and its participation in regulating early steps of apoptosis [111]. The redistribution of spectrin and PKCθ into a polar aggregate has also been observed in Jurkat T and HL60 cell lines during early apoptosis-induced by cytostatics. These changes seem to be restricted to spectrin and not to concern other cytoskeletal proteins such as actin or vimentin. Although spectrins are potential caspase -3, -7 and -8 substrates, these proteases exhibited minor involvement in the early apoptotic rearrangement of spectrin/PKCθ. Moreover, spectrin aggregation was shown to be at least partially dependent on PKCθ activity.

Taken together, we may state that spectrin also plays an important role in various pathways of regulation of cellular processes and signaling in lymphocytes, such as TCR formation, activation and early steps of apoptosis.

Spectrins interact with proteins involved in intracellular traffic

The multifunctional spectrin-based skeleton participates in the complexes linking various structures or organelles to the motors involved in microtubule-directed transport, and in the facilitation of membrane protein transport via the secretory and endocytic pathways [112]. βIII-Spectrin is present in the Golgi and vesicle membranes [49], and binds to the dynactin subunit ARP1, suggesting a possible role in transport [113]. In patients exhibiting spinocerebellar ataxia type 5 (SCA5), a mutation found in the calponin homology domain (CH) alters the interaction of βIII-spectrin with ARP1 and consequently affects the stabilization of membrane protein, or may cause alterations in EAAT4 transport by disrupting the binding to ARP1 and dynein motor complex. Cell culture studies reveal that the L253P mutant of βIII-spectrin, instead of being found at the cell membrane, appears trapped in the cytoplasm associated with the Golgi apparatus. Moreover, L253P βIII-spectrin prevents correct localization of wt βIII-spectrin and prevents EAAT4 from reaching the plasma membrane. These data provide evidence for a dominant-negative effect of an SCA5 mutation and show that trafficking of both βIII-spectrin and

EAAT4 from the Golgi is disrupted through failure of the L253P mutation to interact with ARP1 [114].

Spectrin functions can be regulated by posttranslational modifications

Several pathways of spectrin posttranslational regulation have been correlated to apoptosis/necrosis [115] as well as to secretion/endocytosis, vertebrate lens development [116] and pathologies in the central nervous system [117, 118].

The regulatory pathways affecting spectrin include the action of calcium ions, calmodulin and Ca^{2+}-activated proteolysis. Proteolysis of spectrin leads to destabilization of the membrane scaffold and membrane remodeling. This process is under the control of several proteases—m- and μ-calpains (Ca^{2+}-activated proteases) and caspases 2, 3 and 7 (activated during apoptosis)—and is highly regulated by Ca^{2+}/calmodulin and tyrosine phosphorylation. αII-Spectrin cleavage is highly influenced by Ca^{2+} homeostasis and calmodulin, which therefore represent a potential regulatory pathway for the stability and plasticity of the spectrin-based skeleton [43, 44]. In fusion of placental trophoblast cells, caspases rather than calpains mediate remodeling of the spectrin skeleton [119]. As was found recently, during early apoptosis, caspase 8 releases an N-terminal fragment containing ABD as well as a C-terminal fragment of βII-spectrin. The proteolysis in the N-terminal region depends on 4.1 protein (Kołodziejczyk, Dubielecka 2011 in preparation).

The other regulatory pathway important during membrane skeleton remodeling is spectrin phosphorylation. β-Spectrin phosphorylation was reported to be essential in destabilization of the erythrocyte membrane skeleton [120–122], disassembly of the skeleton during mitosis [123] and the control of Golgi stability [124]. Likewise, αII-spectrin is an important subject of tyrosine phosphorylation. Tyrosine phosphorylation/dephosphorylation in the calpain cleavage site of αII-spectrin by kinases and phosphatases is a mechanism that regulates this spectrin subunit's sensitivity to cleavage [44, 125]. Spectrin is a key point of signal convergence between tyrosine/phosphatase and Ca^{2+}-mediated signal cascades. This kind of control may be particularly important in vesicle trafficking, endocytosis, neurite outgrowth and NMDA receptor activation [126]. However, a study on homozygous mice expressing a mutant αII-spectrin designed to resist calpain and caspase cleavage questions the functional importance of this process in vivo [127].

Moreover, βIV-spectrin might be involved in a regulatory mechanism for Na+ channels (Nav1.5), via direct phosphorylation by βIV-spectrin targeted calcium/calmodulin-dependent kinase II [128]. These findings provide evidence for an unexpected yet commanding molecular platform involving spectrin that determines vertebrate membrane excitability.

Concluding remarks

The role of different spectrin subunits and domains has been studied and explained progressively. The first discovered role of αIβI-spectrin was to define the cell shape and to maintain cell membrane integrity and stability in erythrocytes. Defects in these skeletal proteins in red cells lead to hereditary hemolytic anemia.

In nucleated cells the functions of spectrins still remain to be elucidated. The occurrence of a variety of spectrin isoforms in different cells indicates that its functions may vary among different cells as a result of their specializations. In most cells spectrins are known to be engaged in determination of the cell shape, in maintaining cell flexibility, cell-cell contact, cell polarity and proliferation.

Moreover, spectrins are engaged in the organization and function of membrane integral proteins, such as ion channels, receptors and adhesion molecules in specialized membrane domains. The β-spectrin mutations induce destabilization of the membrane structure and mislocation of membrane receptors and channels, often leading to serious diseases, such as spinocerebellar ataxia and neurodegenerative diseases. Recent data have revealed that αII-spectrin mutations are associated with West syndrome, an epileptic encephalopathy [129]. Defects in this ortholog in *Drosophila melanogaster* and *Caenorhabditis elegans* larvae are lethal. These facts corroborate the crucial role of this protein. In the last few years, more and more reports providing new data concerning the previously unrecognized role of α-spectrins in signaling pathways have appeared. The SH3 domain of spectrin plays an essential role in Rac activation, initiation of actin network formation, adhesion, lamellipodia extension, cell spreading and DNA repair. The spectrins are also engaged in different pathways of cell transduction and signaling in lymphocytes, such as TCR formation, activation and early steps of apoptosis.

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