Cell. Mol. Life Sci. 65 (2008) 2688 – 2701
1420-682X/08/172688-14
DOI 10.1007/s00018-008-8080-8
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Cellular and Molecular Life Sciences

Review

α-Actinin structure and regulation

B. Sjöblom[a], A. Salmazo[a] and K. Djinović-Carugo[a,b,*]

[a] Department for Biomolecular Structural Chemistry, Max F. Perutz Laboratories, University of Vienna, Campus Vienna Biocenter 5, 1030 Vienna (Austria), Fax: +43-1-4277-952,
e-mail: kristina.djinovic@univie.ac.at
[b] Department of Biochemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana (Slovenia)

Received 13 February 2008; received after revision 13 April 2008; accepted 15 April 2008
Online First 19 May 2008

Abstract. Alpha-actinin is a cytoskeletal actin-binding protein and a member of the spectrin superfamily, which comprises spectrin, dystrophin and their homologues and isoforms. It forms an anti-parallel rod-shaped dimer with one actin-binding domain at each end of the rod and bundles actin filaments in multiple cell-type and cytoskeleton frameworks. In non-muscle cells, alpha-actinin is found along the actin filaments and in adhesion sites. In striated, cardiac and smooth muscle cells, it is localized at the Z-disk and analogous dense bodies, where it forms a lattice-like structure and stabilizes the muscle contractile apparatus. Besides binding to actin filaments alpha-actinin associates with a number of cytoskeletal and signaling molecules, cytoplasmic domains of transmembrane receptors and ion channels, rendering it important structural and regulatory roles in cytoskeleton organization and muscle contraction. This review reports on the current knowledge on structure and regulation of alpha-actinin.

Keywords. α-Actinin, binding actin filaments, structure, regulation.

Introduction

The cytoskeleton consists of filamentous systems composed of polymers of actin, tubulin or intermediate filament proteins. The basic organizational principle of all these filamentous systems is that large complex structures are built from small, simpler components – either from multi-subunit or single peptide constituents, forming therefore intermediate filaments, microtubules or actin filaments. Their filamentous nature supplies the cell with networks of structures that are both highly dynamic as well as very stable. These highly organized structures are involved in a number of important functions: maintenance of cell's internal scaffold, provision of mechanical stability, locomotion, intracellular transport of organelles, as well as chromosome separation in mitosis and meiosis.

In migrating cells the dynamic assembly/disassembly of actin network drives cell motility, while in a muscle a stable actomyosin system composes the contractile apparatus (for review see [1, 2]). Actin filaments are assembled in two general types of structures: bundles and networks. Many actin-binding proteins are necessary for the formation, organization and customized functioning of the actin cytoskeleton. Actin-binding proteins, in particular their size, molecular architecture and flexibility, dictate the formation of either structure since they cross-link actin filaments.

α-Actinin is a ubiquitously conserved protein that cross-links actin filaments. It belongs to a highly

* Corresponding author.

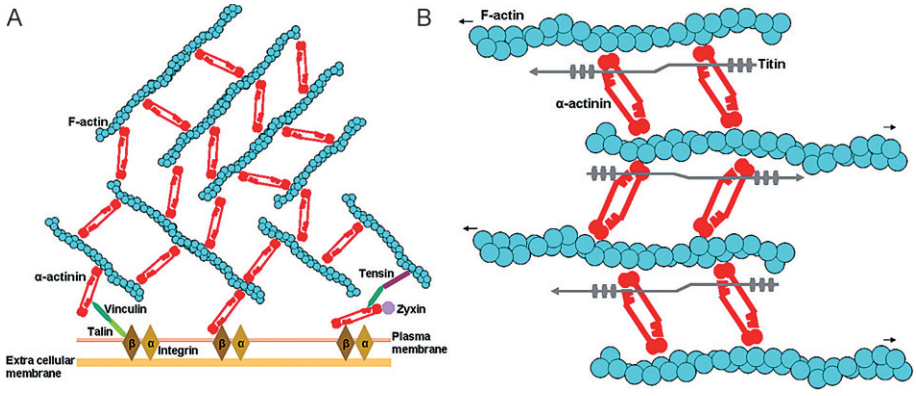

Figure 1. Schematic view of α-actinin interactions in focal adhesions and in striated muscle. (*A*) Representation of the cytoskeleton in focal contacts showing α-actinin (red) linking actin (blue) to membrane-associated structures, like vinculin (dark green), talin (light green), integrin (brown) and tensin (purple). (*B*) Representation of sarcomeric Z-disk where α-actinin (red) cross-links anti-parallel actin filaments (blue) and also interacts with titin.

conserved family of actin-binding proteins – the spectrin superfamily, which also contains the spectrins and dystrophin [3]. α-Actinin isoforms have been found and characterized genetically and/or biochemically from a large variety of taxa, from protists [4], invertebrates [5, 6], birds [7] and mammals [8, 9]. During evolution, alternative splicing and gene duplication have lead to a substantial functional assortment within the α-actinin protein family. This diversity is most marked in mammalian cells where four α-actinin encoding genes produce at least six different protein products, each found within a specific tissue type and expression profile [8–12]. Regarding their expression patterns, biochemical characteristics, tissue and subcellular location, these proteins can be grouped into two distinct classes: muscle (calcium insensitive) and non-muscle cytoskeletal (calcium sensitive) isoforms [3, 13, 14].

Both non-muscle isoforms (1 and 4) are commonly associated with focal contacts (Fig. 1A) and stress fibers [3, 15–17], but their distribution differs at least in highly motile cells. α-Actinin isoform 4 is more concentrated in circular dorsal ruffles, while the α-actinin isoform 1 is evenly distributed along the actin stress fibers in motile cells [9, 18, 19]. In contrast, skeletal, cardiac, and smooth muscle isoforms (2 and 3) are localized in the Z-disk and analogous dense bodies. In the Z-disk – the boundary between sarcomeres in striated muscle – the predominant component is α-actinin where it cross-links actin filaments form adjacent sarcomeres, forming a lattice-like structure that stabilizes the muscle contractile apparatus (Fig. 1B) [20, 21]. α-Actinin-2 is a major isoform in the cardiac and oxidative skeletal muscle, while α-actinin-3 is largely expressed in glycolytic skeletal muscle fibers [12].

Apart from its mechanical role, α-actinin plays multiple important roles in the cell: it links the cytoskeleton to different transmembrane proteins in a variety of junctions, it regulates the activity of a number of receptors, and it serves as a scaffold to connect the cytoskeleton to diverse signaling pathways (see below and review [16]).

This review discusses and summarizes the current knowledge and recent advances on structure and regulation of α-actinin family of proteins.

Domain structure and molecular architecture

All members of the spectrin superfamily have at their N-terminus a characteristic actin-binding domain (ABD), composed of two consecutive calponin homology (CH) domains, followed by multiple spectrin repeats (SR), the number of which determines the length and flexibility of the actin-binding protein and therefore the nature of actin-filament cross-links. α-Actinin is a functional anti-parallel dimer, composed of an ABD, connected *via* a flexible neck region to four spectrin repeats forming the central rod that is followed by a C-terminal calmodulin (CaM)-like domain [22–24]. Such a molecular architecture results in the formation of a rod-shaped molecule with functional domains (ABD and CaM) at both ends (Fig. 2A), allowing to cross-link actin filaments in bundles.

Structure and regulation

Rod domain

The central rod region of α-actinin is typically composed of four consecutive spectrin repeats. The number of the repeats has changed during evolution and the rod appears to be the least conserved region of the α-actinin: all known vertebrate α-actinins contain four SR, while protozoan *Entamoeba histolytica*, the fungus *Schizosaccharomyces pombe* and the parasite *Trichomonas vaginalis* have one [25, 26], two [27, 28] or five [29] such repeats, respectively. The phylogenetic analysis shows that an α-actinin like precursor has given rise to the members of spectrin superfamily

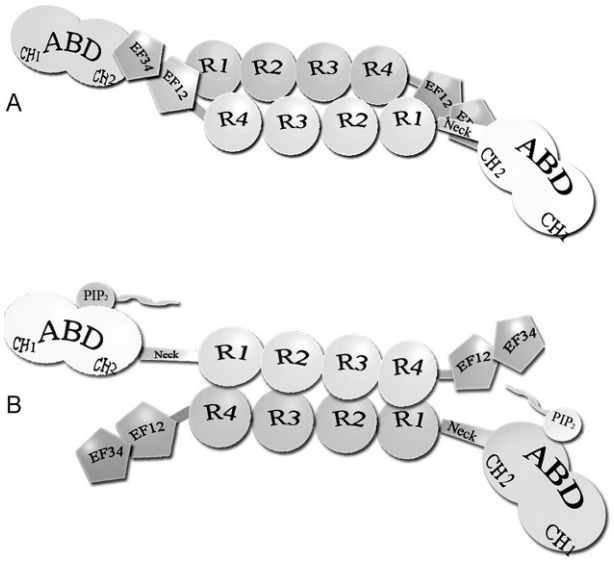

Figure 2. Schematic drawing showing the domain structure of α-actinin and model for its regulation. (*A*) Inactive form with the calmodulin (CaM)-like domain bound to the neck between actin-binding domain (ABD) and rod domain. (*B*) Addition of phosphatidylinositol 4,5-biphosphate (PiP2) to muscle isoforms releases the CaM-like domain to interact with titin; this conformational change also increases α-actinin's affinity for actin.

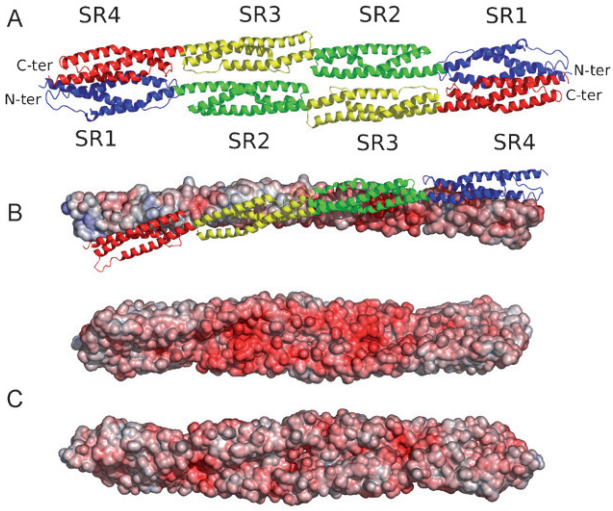

Figure 3. Dimer organization and electrostatic potential mapped on the solvent accessible surface of the rod domain of α-actinin. (*A*) Schematic drawing of the rod domain with the spectrin repeats 1–4 colored blue, green, yellow, and red, respectively. (*B*) The model is rotated 90° around the long axis of the rod relative to (*A*). The surface representation of one monomer is colored according electrostatic potential and the other monomer is drawn as a ribbon. (*C*) Solvent accessible surface of the entire dimer colored according to electrostatic potential. The upper picture shows the concave surface of the dimer in the same orientation as in (*A*). The lower picture is rotated 180° around the long axis of the rod showing the convex surface.

proteins [30–33], and that the modern vertebrate form of α-actinin consisting of four SR arouse from a simple molecule containing only one spectrin repeat, *via* two intragenic duplication events [25, 34].

The three-dimensional structure of a single spectrin repeat adopts a triple helix coiled-coil bundle. Such a structure of the repeating unit was predicted on the basis of amino acid sequence analysis of spectrin [35], and has until now been observed in a number of structures coming from the spectrin superfamily of proteins [36–43]. Spectrin repeats are protein modules well suited to build extended molecules of variable length, and serve to separate other functional domains. In the spectrin superfamily of proteins they are employed to dictate a specific distance between the domains at the N and/or C termini [44] and, therefore, the length and the flexibility of the linker, which in turn determines the nature of the cross-link of the actin filaments.

α-Actinin rod domain forms an anti-parallel homodimer [39] with an overall length of 240 Å and width of 40–50 Å (Fig. 3A). The repeating units are connected by short, rigid, helical linkers, which render structural rigidity to the subunit and to the dimer, a feature required for its primary function – bundling of actin filaments. Conversely, structure determination of the same repeat pair of α-spectrin in multiple crystal lattice conditions [40] and subsequent studies on different double and triple spectrin repeat constructs [41, 42] revealed inherent flexibility between repeats, a characteristic long assumed from the flexible nature of the erythrocyte membranes [45].

A marked feature of the α-actinin rod is its 90° twist along the long axis of the dimer (Fig. 3C). An analysis of the inter-subunit interface shows an extensive list of polar (42 %) and non-polar (58 %) contacts, burying about 11 % of the solvent accessible area of the monomer [39]. This is in line with the high affinity of dimer formation with K_d of 10 pM [46, 47]. The electrostatic potential of the interface surface shows a gradient from basic in repeat 1 to acidic in repeat 4 (Fig. 3B). A customized complementarity of the interacting surfaces in terms of productive electrostatic interactions between subunits drives the formation of a perfectly aligned anti-parallel dimer. The specific and tight intersubunit contacts deem torsional flexibility of the rod unlikely, suggesting that the twist is an intrinsic feature of the α-actinin rod [39], as also observed in electron microscopy studies of the full-length α-actinin [48].

The electrostatic potential on the surface of α-actinin rod is largely acidic on the concave part and well conserved throughout the isoforms and species [39] (Fig. 3C). The targeting of α-actinin to the plasma membrane is mediated *via* interactions with phospholipids and with cytoplasmic regions of transmembrane receptors [49–62]. The sequences of segments impli-

cated in interactions have been reported to be largely of basic nature and demonstrate high propensity for α-helical secondary structure. It has been proposed that the extended acidic surface of the α-actinin rod acts as a docking platform, offering two binding sites at a time due to the internal symmetry of the rod [39].

In skeletal and cardiac muscle α-actinin cross-links anti-parallel actin filaments coming from adjacent sarcomeres (Fig. 1B). In non-muscle and smooth muscle cells actin filaments are not part of an organized lattice, and can therefore assume very diverse orientations (Fig. 1A). To carry out bundling in such an array of actin filaments some intrinsic structural plasticity in the molecule is required. Electron microscopy studies have shown that the ABD can adopt variable conformations with respect to the rigid rod region [48, 63, 64], which are connected by a neck region. The inherent flexibility of this linker region has been also observed through its sensitivity to the proteolytic cleavage [65]. On the basis of the observed structural rigidity of the twisted rod domain, it was proposed that it is the inbuilt flexibility in the neck region that allows for variable orientations of ABD and renders α-actinin a versatile cross-linker of actin filaments arranged in diverse arrays: from highly ordered anti-parallel lattice in the Z-disk of striated muscles to variable orientations in non-muscle and smooth muscle cells.

Actin-binding domain

The ABD of α-actinins is the most conserved domain within the protein family, reflecting the evolutionary very high conservation of its binding partner – actin [66]. ABD consists of a tandem pair of type 1 and type 2 CH domains (CH1, CH2), and is also found in a number of other actin-binding proteins, including most of the spectrin superfamily proteins, but also in fimbrins and parvins/actopaxins/affixins (reviewed in [67]).

The crystal structures of ABDs from several actin-binding proteins have already been determined: *Arabidopsis thaliana* and *S. pombe* fimbrin [68, 69], utrophin [70], dystrophin [71], human and mouse plectin [72, 73], as well as human α-actinin 1, 3, and 4 [74–76]. In all structures except for fimbrin from *A. thaliana*, which has unique mutations at the CH1/CH2 interface, the ABD adopts a closed conformation (Fig. 4A), which is achieved by an extensive inter-domain interaction interface of about 700–900 $Å^2$ [74, 75]. In two reported structures, from utrophin and dystrophin [70, 71], the closed conformation is attained *via* a domain swapping between two molecules, a crystal artifact observed and recognized in macromolecular crystallography [77]. Nevertheless, the ABD from utrophin is monomeric in solution [78], while the dystrophin ABD is found in monomer-dimer equilibrium in solution [71]. Given the above observations and the fact that both utrophin and dystrophin are functional monomers in a living cell [79], it is believed that most of the ABDs assume a closed conformation in the unbound state.

Each individual CH domain is composed of four principal helices (A, C, E and G) that form the core of the domain. Helices C and G are parallel to each other and are sandwiched between the N-terminal helix A and helix E (Fig. 4A). Out of three minor helices observed in the spectrin CH domain structure [80] only B and F are present in the α-actinin ABD.

The closed arrangement of CH1-CH2 in ABD is achieved in a similar manner in all ABDs: helices A and G of CH1 pack against the C-terminal region of CH2 (helices F and G and the E–F linker) (Fig. 4A). The nature of the CH1-CH2 domain interface is semipolar, with in part hydrophobic and in part polar contacts stabilizing the interaction (Fig. 4B) [74, 75]. Indicators of the complementarity of the two surfaces involved the inter-domain interface, in particular the gap index [81], show that they are highly tuned to match each other, to the level typically observed in permanent hetero-complexes, which form together with the enzyme-inhibitor complexes the most complementary interfaces [81].

A detailed analysis of the inter-domain interface and of the conservation of amino acid residues involved revealed a critical and highly conserved interaction between Trp128 (helix G, CH1) and Lys236 (helix G, CH2) (Fig. 4A) [75, 82] (numbering of human α-actinin-1), which form extensive hydrophobic interactions, and sporadically also π-interactions [83], that seem to govern the domain interface. This has been corroborated by the observation of a non-compact ABD conformation of *A. thaliana* fimbrin, where these two amino acid residues are mutated [69, 75]. Interestingly, the crystal structure of α-actinin-4 ABD mutant Lys255Glu (Lys255 corresponds to the position 236 in isoform 1), involved in familial focal segmental glomerulosclerosis, displays the same closed conformation as observed in other ABDs [76], suggesting that the compact conformation is a highly stable structure in classical actin-binding domains.

A number of mutational, cross-linking, and NMR studies have consistently identified three major actin-binding sites (ABS1–3) on ABDs from different proteins [84–91]. These sites map to the N-terminal A helix of CH1 (ABS1: residues 48–57), the C-terminal G helix of CH1 (ABS2: residues 123–147) and to the interdomain linker flanked by the N-terminal segment of CH2 domain (ABS3: residues 153–172), comprising helix A (Fig. 5) (numbering corresponds to human α-actinin-3).

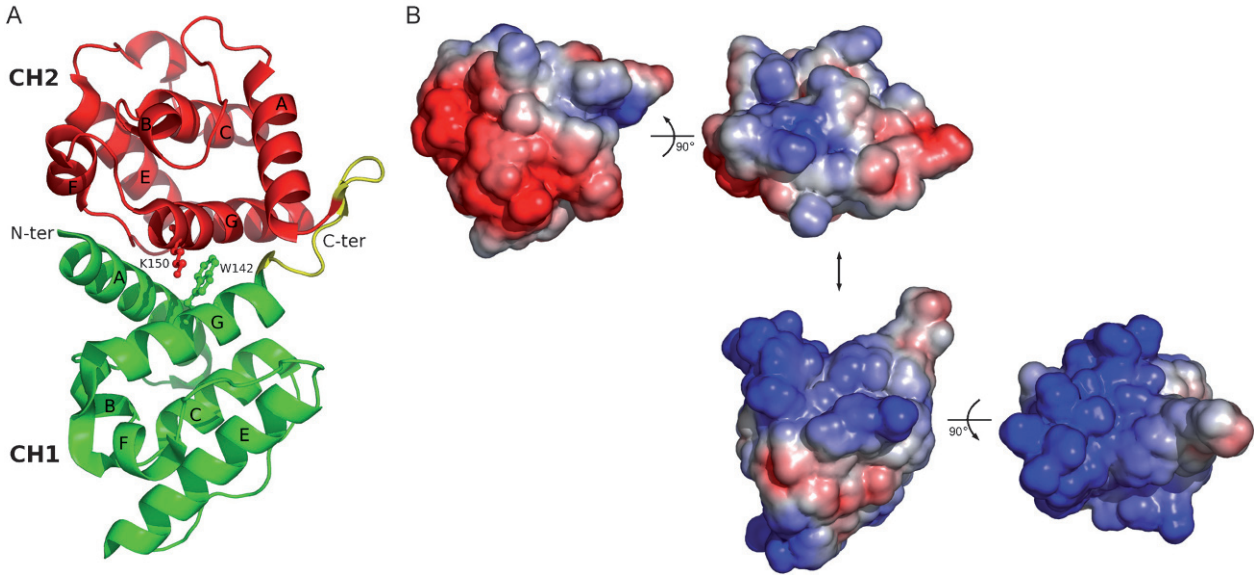

Figure 4. Domain organization and electrostatic potential mapped on the solvent accessible surface of the individual calponin homology (CH) domains of ABD. (*A*) Schematic drawing of ABD from human α-actinin-3 in closed conformation. CH1 is colored green, CH2 red and the connecting linker yellow. Highlighted with a ball and stick model are Lys 150 and Trp142, two conserved residues critical to the interaction of the two CH domains. (*B*) Middle: surface representation of the ADB in the same orientation as in (*A*) but the molecule was cut between the two CH domains and moved apart then rotate 90° (left and right) to show the complementarity of the interacting surfaces.

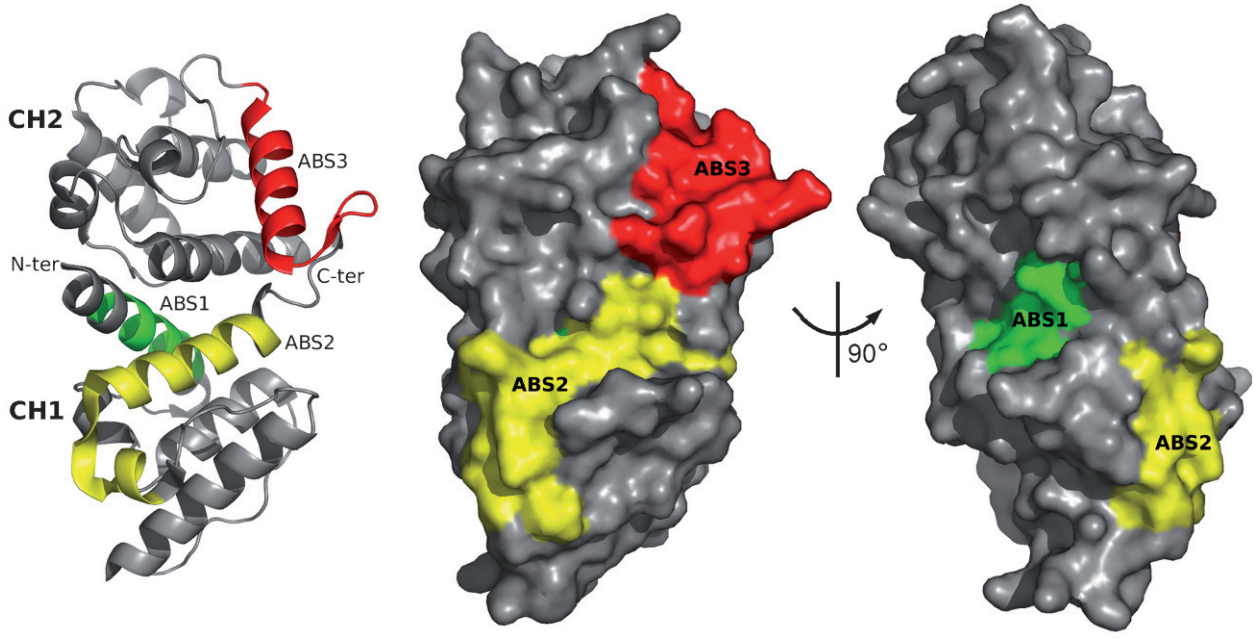

Figure 5. Actin-binding sites on ABD of α-actinin. Actin-binding sites 1–3 in green, yellow and red, respectively, mapped onto a ribbon drawing of the ABD (left) and to the solvent accessible surface (middle and right). Note that ABS2 and 3 form a continuous patch on the surface, while ABS1 is partially buried in the interface between CH1 and CH2.

Biochemical characterization of the CH1 and CH2 domains of utrophin, dystrophin, beta-spectrin and α-actin showed that they together confer high affinity binding to actin filaments, but are not functionally equivalent. The highest affinity binding is achieved by the tandem CH domains; while CH1 domain can still bind actin filament with lower affinity, the CH2 domain alone is not sufficient to bind actin filaments [67, 80, 92–95].

Mapping the binding sites ABS1–3 on the molecular surface of the ABD shows that ABS2 and ABS3 form a contiguous region on the surface of the domain

(Fig. 5), while ABS1 remains, in part, buried in the interface between the two tandem CH domains in the closed conformation. Analysis of conservation of solvent-exposed amino acid residues implicated in ABS1–3 sites or close to them shows conserved hydrophobic patches on ABS2 (helix G, CH1), E–F loop of CH1, ABS3 (helix A, CH2), and the A-B linker of the CH2 [75, 82]. The conservation at the amino acid level is in line with the fact that actin is one of the most conserved proteins in nature, imposing therefore evolutionary pressure on the actin-binding sites of the interacting proteins, and with the accepted paradigm that the force driving the interaction with actin filaments is at least partly hydrophobic [92]. No conserved solvent exposed residues can be observed on ABS1, which is partially buried in the CH1-CH2 interface. This is reminiscent of a need for a conformational rearrangement of the CH1 and CH2 domains promoted upon binding to actin filaments so as to render the ABS1 accessible for the interaction [73]. Indeed, a conserved patch of exposed residues can be observed also on ABS1 when taking into account a more open ABD conformation in which ABS1 would become fully solvent accessible [75].

Cryo-electron microscopy was used to study filamentous actin decorated with the ABD of chick smooth muscle α-actinin [96]. Electron density for ABD was found to be bell shaped with a base measuring 38 Å and a height of 42 Å, which is smaller than the dimensions of the ABD in a closed conformation ($55\times35\times20$ Å^3). The base was centered on subdomain 2 of actin and in contact with two neighboring subdomains 1 along the long-pitch helical strands. Similar electron microscopy studies on actin filaments decorated with the ABD from other members of the spectrin family as fimbrin, utrophin and dystrophin [97–100] have not led to a uniform picture of how the ABD interacts with actin filaments. One reason for this could be that, although all ABDs are composed of two consecutive CH domains, their mode of binding is truly variable for functional and structural reasons.

CaM-like domain

EF hands are helix-loop-helix motifs involved in binding intracellular calcium. Generally, EF-hands come in side-by-side pairs, forming a globular domain capable of coordinating up to two calcium ions [101]. Calcium binding triggers a major conformational change of the globular domain from a closed into an open state, causing a rearrangement of the α-helices and exposure of hydrophobic residues to the surface of the protein, allowing the protein to interact with specific targets [102]. In a subset of EF-hand family of proteins, motifs have diverged to the extent that they have partially or entirely lost the capacity of chelating calcium ions [103]. These proteins retain the protein-recognition and -binding capacity, but are no longer regulated by calcium.

The C-terminal CaM-like domain of α-actinin is composed of four EF hand motifs, which display functional divergence between α-actinin isoforms. In non-muscle (cytoskeletal) isoforms of α-actinin (1 and 4), the EF hands bind calcium, exerting regulatory control over the actin-binding activity of the adjacent ABD and to other proteins [13, 104].

Solved EF-hand structures from the spectrin family proteins non-erythroid α-spectrin [23, 105] and from dystrophin (as part of a larger construct including a WW domain) [106] are essentially similar, but display distinct structural features. The α-spectrin EF-hands can bind calcium ions, while the WW-EF structure of dystrophin revealed a new functional role of EF-hands: structural support without binding either calcium or a target peptide/protein, where WW was found embedded by a helical region containing two EF-hands.

The actin-binding property of the non-muscle α-actinins is reduced or even abolished at calcium concentration of $>10^{-7}$ M and pH > 7 [4, 107–109]; at lower concentrations the viscosity of F-actin is significantly increased by α-actinin non-muscle isoforms [3, 16]. Recent biochemical and genetic studies on ancestral α-actinins from *E. histolytica* have shown that the calcium interferes with the ability of binding to actin filaments [26, 27] and corroborated the thesis that the calcium binding and calcium non-binding forms evolved at the point of the vertebrate-invertebrate divergence during evolution [25, 110]. Nevertheless, the atomic detail on the mechanism of calcium and α-actinin interaction is still unknown.

On the other hand, muscle isoforms have lost their ability to bind calcium due to several mutations of residues engaged in calcium coordination [3, 4, 8]. It could be speculated that during evolution of α-actinin, the ancestral gene encoded a calcium-sensitive isoform, while the calcium-insensitive isoforms arose with the development of the muscle tissue, where the actin-binding regulation should be independent of calcium flux [3]. The regulation of muscle isoforms (2 and 3) is achieved upon binding of the phospholipid phosphatidylinositol 4,5-biphosphate (PiP2) [111–115].

The CaM-like domain of muscle specific α-actinin isoforms 2 and 3 is involved in targeting the α-actinin to the Z-disk *via* binding to titin (and other proteins) in striated muscle [116, 117]. Titin is a giant multi-domain protein that spans from the Z-disk to the M-line of the sarcomere [118–120]. Titin acts as a molecular ruler organizing the actin cytoskeleton *via* interactions with many sarcomeric proteins, including

α-actinin [121]. The region of titin that binds to the CaM-like domain of α-actinin consists of a series of repeated sequence motifs of about 45 residues, termed Z-repeats [122, 123]. This interaction, primarily responsible of targeting α-actinin specifically to the Z-disk, is conformationally controlled. The current model for muscle isoform regulation proposed by Young and Gautel [117] implies that the CaM-like domain of one subunit interacts with the neck [the region between the ABD and the first spectrin repeat (SR1) of the opposing subunit], therefore preventing CaM from binding to different partners (Fig. 2A, B). However, in the presence of phosphoinositide PiP2, conformational changes are trigged that release this inter-subunit interaction and render CaM free to bind to its partners like titin [116, 124, 125] and PDZ domain of ZASP [126, 127], and even enhancing the actin-binding properties of the molecule [117].

The structure of human α-actinin-2 EF hands 3 and 4 was solved in complex with the titin Z-repeat 7 [124], which binds to the groove formed by the two semi-open lobes of the two EF hands (Fig. 6). Such a binding mode was proposed to be a general solution for calcium-independent target recognition. Upon complex formation with EF34-hands, Z-repeat 7, which is natively unfolded, adopts an α-helical structure and binds with nanomolar affinity [125, 128].

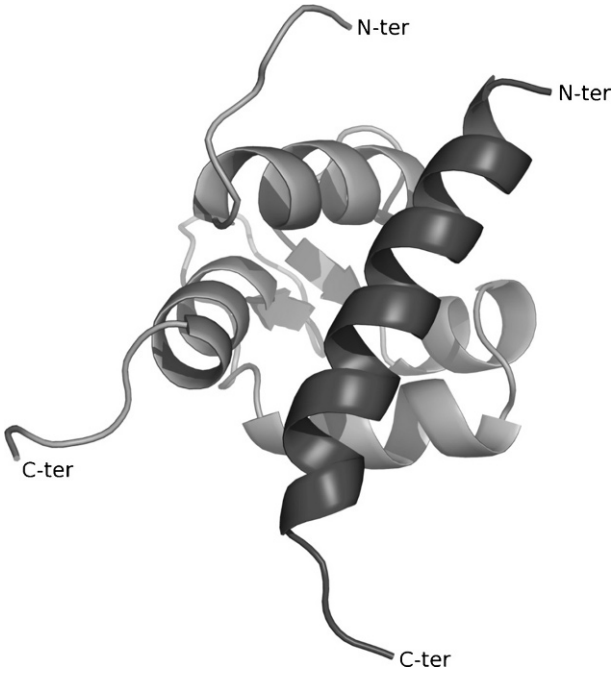

Figure 6. α-Actinin EF34-hands in complex with titin Z-repeat 7. Structure of EF34-hands from human α-actinin-2 (light gray) in complex with the titin Z-repeat 7 (dark gray).

A detailed molecular mechanism of the manner of how PiP2 relieves the interaction between the CaM-like domain and the neck connecting the ABD and SR1 is not yet known. It was proposed that its hydrophobic tail disrupts the binding of the CaM-like domain to the neck (Fig. 2A, B) [117], while the head group of the PiP2 interacts with the CH2 domain of ABD. It was shown that the phosphate groups in position 4 and 5 are important for the interaction with α-actinin [113] and the binding site was mapped by immunoassays and direct point mutations to the CH2 domain [115]. According to this work the PiP2 binding site corresponds to the amino acids 168–184 (the numbering corresponds to the sequence of chicken skeletal muscle α-actinin isoform) [115], which map to the loop connecting helices A and B in the CH2 domain, just after the ABS3 in the primary amino acid sequence and follow the three-dimensional and sequence pattern observed in other complexes between proteins and phospholipids head group [74].

Correlation of the predicted PiP2-binding amino acid residues with the three-dimensional structural information on the ABD of the human isoform 3 [74], based on solvent accessibility and on three-dimensional arrangement of positively charged residues suitable for binding of a defined pattern of phosphate groups presented by PiP2 polar head, suggested a slightly different set of residues: Arg170, Arg176 and Arg199 (Fig. 7). These residues are present only in the CH2 domains of α-actinin isoforms [67] and flank the ABS3 region in primary and tertiary structure of ABD.

It is known that PiP2 is present in low abundance in Z-disk and that the enzyme phosphatidylinositol-4-phosphatase-5-OH-kinase (PiP-4P-5k) is required for PiP2 biosynthesis and consequently regulation of actin cytoskeleton [117, 129]. Immunofluorescence assays were therefore performed to check if PiP-4P-5k and Z-disk are associated at any stage of myofibrillogenesis. The PiP-4P-5k kinase was detected in association with the Z-disk of neonatal rat cardiomyocytes, suggesting that the requirement of PiP2 for activation of α-actinin is necessary during the Z-disk formation in developing muscle [117].

There are still some open questions about the regulation of α-actinin: not only PiP2 is involved on this regulation as described above but also the phosphatidylinositol 3,4,5-triphosphate (PiP3). Moreover, it has been shown that in non-muscle cells the incorporation of α-actinin to the cytoskeleton is also regulated by phosphoinositides; however, for these cells, the binding of PiP2 or PiP3 decreases the actin binding properties of the molecule [113, 130–132].

Apart from the processes of regulation described above, two other regulatory mechanisms have been

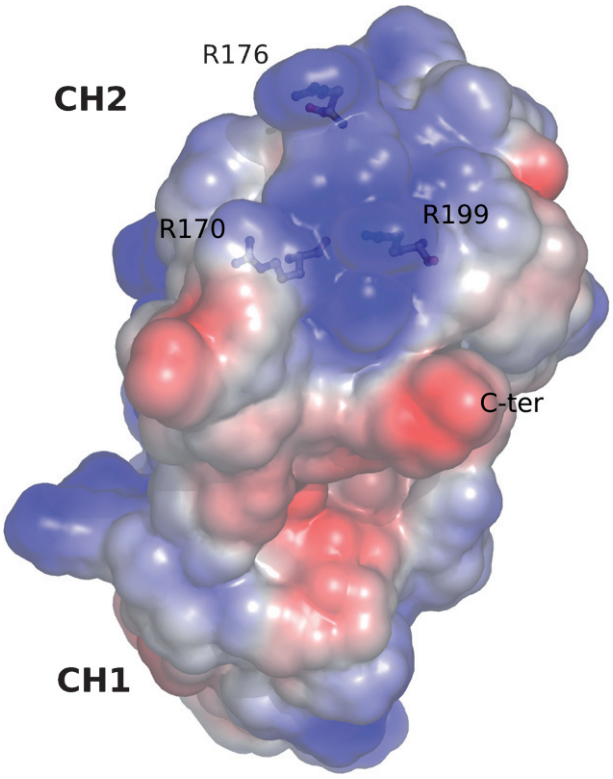

Figure 7. Putative PiP2 binding site on ABD of α-actinin. Solvent accessible surface of ABD colored by electrostatic potential. Residues identified as putative PiP2 ligands (R170, R176 and R199) are highlighted.

identified: processing by proteases and phosphorylation by tyrosine kinases (reviewed in [16]). The proteolytic process is carried out by calpain, which is believed to cleave proteins involved in integrin-mediated adhesions and actin-based membrane protrusions during cell migration (reviewed in [133]). Calpain activity is regulated by calcium, and depends on the protease isoform, but the calcium concentrations within a cell are not high enough for calpain activation [134]. Phosphoinositides PiP2 and PiP3 have been shown to modulate autolysis of calpain and proteolysis of α-actinin and brain spectrin isoform by calpain [135]. Sprague et al. [136] have shown that the susceptibility of α-actinin to calpain 1 cleavage is decreased by PiP2 and increased by PiP3, while the calpain 2 isoform is not influenced by PiP2. The same group also mapped the calpain 2 cleavage site in presence of PiP3 to the final helix of the CH2 domain of α-actinin (after residue Tyr246 in chicken gizzard α-actinin).

Regarding tyrosine phosphorylation regulation, integrin-activated tyrosine kinase focal adhesion kinase (FAK), a regulator of adhesion plaques and cell motility, phosphorylates the ABD domain of α-actinin on Tyr12 of the non-muscle human isoform, reducing its affinity to actin [137], suggesting that α-actinin is a target for signaling pathways that regulate cell adhesion. Decrease of affinity for actin filaments could also change the mechanical properties of the cytoskeleton leading to enhanced cell motility [137].

EM model of full-length α-actinin

Electron microscopy has been used to study two-dimensional crystals of α-actinin grown under a lipid monolayer. By docking high-resolution models obtained by X-ray crystallography and NMR of the single domains into a 20 Å electron density map, hybrid models of full-length actinin from rabbit skeletal muscle [104] and chicken gizzards [138] were built (Fig. 8). It was not possible to distinguish CH1 from CH2 of the ABD and EF12 from EF34 of the CaM-like domain, leading to ambiguity in the orientation of these domains. In the model of rabbit skeletal muscle α-actinin, the ABDs of both monomers are found in the open conformation, and form a closed ABD structure *via* domain swapping with a neighboring molecule. The CaM-like domain was found in between the two CH domains and close to the connecting neck. In the chicken gizzard model, the ABD structure at one end of the dimer is similar to the previously described open, domain-swapped conformation, while at the other end the ABD is in the closed conformation. The position of the CaM-like domain is different in the two ends of the molecule but in none of them it is close to either the linker between the CH domains or the neck between the ABD to the rod domain. These models do not sustain the idea that the CaM-like domain would interact with the linker between ABD and the rod domain to regulate binding to actin and titin [117].

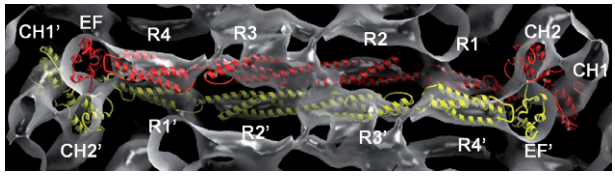

Figure 8. A complete structure of α-actinin (after Fig. 5 of [104]) as generated by modeling the rod, ABD and CaM-like domain into electron density map obtained by electron microscopy. Two α-actinin subunits on the dimer are marked in red and yellow, respectively. Individual domains of both dimers are labeled. The gray shading represents the contour of the original electron density used in the reconstruction.

Using the same lipid-monolayer system, a study on the interaction between actin rafts (2D bundles) and α-actinin has also been performed [64]. It was observed

that the distribution of the angles measured between α-actinin and actin filament clusters in five ranges around 0, 60, 90, 120 and 180° and that the length of the bound α-actinin can vary by more than 55 Å. The Authors suggest that α-actinin could therefore be involved in tension sensing by acting as a platform for mechano-sensing signaling molecules [64]. α-Actinin was additionally observed to bind with both ends to the same actin filament. This type of monofilament binding might be involved in regulating accessibility of binding sites on actin for other proteins and/or linking single filaments to integrins.

α-actinin as a versatile protein interaction platform

Aside from its interactions with actin filaments, α-actinin has emerged as a major multivalent platform for a number of protein-protein interactions with many cytoskeletal and regulatory proteins (reviewed in [16, 139, 140]). The complete directory of binding partners is beyond the scope of this review, but a comprehensive overview of the functional categories illustrate the versatility of the molecule engaged in structural, signaling and metabolic roles.

At adhesion sites, including focal adhesions, adherent junctions and hemidesmosomes, the first binding partners of α-actinin to be discovered were cytoplasmic tails of the beta-subunit of integrin and the intracellular adhesion molecule-1 (ICAM-1) [49, 51, 141]. Many more interactions with transmembrane proteins, most of them adhesion proteins, have been identified since then [16, 50–52, 54–62, 142, 143], such as receptors of NMDA [55], adenosine A2A [58], glutamate [62], vinculin [144–146] and inducible nitric oxide synthase in macrophages [147]. The interactions are typically formed between the negatively charged rod domain and positively charged cytoplasmic peptides, and serve multiple functions, from linking transmembrane proteins to actin cytoskeleton, acting as a scaffold for recruitment of signaling molecules, clustering the adhesion molecules at specific sites, and regulation of the receptor activity. α-Actinin was identified as a component in dense regions (dense bodies), *i.e.*, periodic structures found in stress fibers that are considered to be structural and functional analogues of the sarcomere Z-disk [148]. Several PDZ and LIM domain proteins [149], commonly found in the dense regions, have been found to interact with α-actinin: zyxin, cysteine-rich protein (CRP) [150, 151] and other members of the CRP family. α-Actinin was found to directly bind to zyxin and CRP, acting therefore as a scaffold for interactions and subcellular distribution of these proteins [152–154]. α-Actinin also binds to the enigma/cypher family of proteins, which typically possess an N-terminal PDZ domain binding to the cytoskeletal proteins and a C-terminal LIM domain that bind to kinases: CLP-36 binds to α-actinin with its PDZ domain, and to a kinase Clik1 *via* its LIM domain [155–157].

In muscle, in addition to some of the above proteins, α-actinin interacts with different classes of proteins: contractile machinery and associated adaptor or signaling proteins, transmembrane receptors and channels, and metabolic proteins (reviewed in [158–160]). Proteins of the contractile machinery that bind to α-actinin are the molecular rulers titin [122] and nebulin [161], actin filament capping protein CapZ [162], as well as paladin/myotilin/myopalladin family of Z-disk adaptor proteins [163, 164], enigma/cypher family proteins hCLIM1 [165], Z-disk-associated protein (ZASP/cypher/oracle) [127,166], and actinin-associated LIM protein (ALP) [166, 167], muscle LIM protein MLP (a member of the CRP family) [168], LIM and SH3 domain protein-2 (Lasp-2) [169], smithin [170], and the calsarcin family of proteins (filamin-, actinin-, and telethonin-binding protein of the Z-disk-FATZ/calsarcin/myozenin) [171–174], which localize to the Z-disk in striated muscle and bind to the Ca^{2+} CaM-dependent protein phosphatase calcineurin. Calcineurin is an important signaling molecule in the skeletal muscle, playing an important role in determination of muscle fiber type [175] and hypertrophy [173, 176].

A number of transmembrane receptors and ion channels have also been found to bind to α-actinin: NR1 and NR2B subunits of the NMDA glutamate receptor [177], adenosine A_{2a} receptor [58], L-type calcium channel [178], policystin-2 [179] as well as Kv1.4 and Kv1.5 potassium channels [180].

Sarcomeric α-actinins also interact with metabolic enzymes including phosphorylase involved in glycogenolysis [181] as well as with fructose-1-6-biphosphatase and aldolase (in a ternary complex) [182]. Binding of metabolic enzymes to cytoskeletal proteins is a recognized mechanism of enzyme regulation [183], and tethering the metabolic enzymes at the sarcomeric Z-disk contributes to the local availability of the metabolites required for energy generation [140].

Most of the interactions involve the rod region of α-actinin (receptors and channels, FATZ, myotilin), but the CaM-like domain and lately also ABD are also emerging as interacting domains with various proteins, like ZASP, hCLIM1 and titin for CaM, while parvin/actopaxin/affixin and a multi-domain scaffolding protein ArgBP2 have been found to interact with ABD [184, 185].

Conclusions

α-Actinin has emerged as a multitasking protein, its roles ranging from bundling actin filaments to acting as a versatile protein interaction platform for structural, membrane and signaling proteins. A body of structural information is already available on ABD, rod, EF34-hands, providing molecular details on individual domains. Additionally, a hybrid structural biology approach, a combination of electron microscopy on the α-actinin and high-resolution structures of the domain building blocks lead to a generation of a low-resolution model of the full-length molecule. Nevertheless, detailed three-dimensional information of the interaction of the functional domains (ABD, CaM) in the context of the full-length molecule, and conformational transitions associated with its regulation, are still awaiting structural elucidation.

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