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Review

A new twist to coiled coil

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ABSTRACT

Spectrin repeats have been largely considered as passive linkers or spacers with little functional role other than to convey flexibility to a protein. Whilst this is undoubtedly part of their function, it is by no means all. Whilst the overt structure of all spectrin repeats is a simple triple-helical coiled coil, the linkages between repeats and the surface properties of repeats vary widely. Spectrin repeats in different proteins can act as dimerisation interfaces, platforms for the recruitment of signalling molecules, and as a site for the interaction with cytoskeletal elements and even direct association with membrane lipids. In the case of dystrophin several of these functions overlap in the space of a few repeats.

1. Introduction

The presence of multiple coiled coil modules, and in particular spectrin repeats is a common feature of cytoskeletal linking proteins, or cytolinkers. Cytolinker was a term originally coined to describe plectin [1] but has now been adopted to describe a broader group of proteins including plakins, nesprins and spectrin family proteins, all of which contain multiple spectrin repeats. The presence of spectrin repeats in these cytolinkers can mediate self association and permits flexible and perhaps extensible linkages so the proteins can connect between different cytoskeletal filament systems, or between cytoskeletal systems and cellular membranes. However in recent years evidence has emerged of a role for the spectrin repeat as a binding interface in its own right, making direct protein–protein interactions and in some cases protein-lipid interactions.

2. Overview of the family of spectrin repeat containing proteins

More than 97% of known spectrin repeat containing proteins are found in metazoans with over two thirds of those in chordates [2]. Despite scattered examples of spectrin repeats in all other kingdoms, this would tend to suggest that the spectrin repeat arose with the evolution of the animal kingdom. With the exception of one or two outliers, as mentioned above, most proteins are considered as cytolinkers and can be broadly grouped into 2 or 3 families depending on ones perspective. The eponymous family from which the repeat derives its name includes the proteins α-actinin, spectrins themselves and dystrophin and utrophin. These proteins share a variable number of spectrin-like repeats, from 4 in α-actinin to 24 in dystrophin, and depending on the protein also have an amino-terminal actin binding domain comprising tandem CH domains and carboxy-terminal calcium binding EF hands. In addition different family members have acquired additional domains specific to their cellular functions, including PH, SH3, WW and ZnF (Fig. 1A). Full listings and domain compositions can be found in several online databases for example SMART, PFAM and Domain Club (http://smart.embl-heidelberg.de/, http://pfam.

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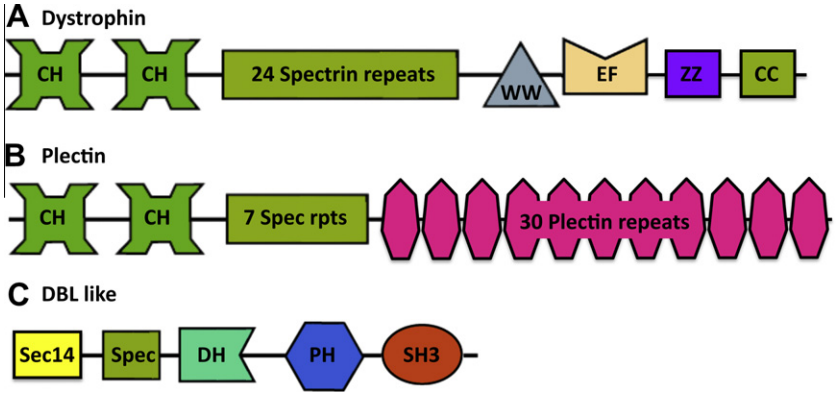

Fig. 1. Schematic representation of selected members of spectrin repeat containing proteins from the three main families. (A) Dystrophin; (B) Plectin and (C) DBL-like. Modules are coded according to the style and nomenclature of Pawson and Nash [53] with the addition of the Sec14 domain [54] (yellow box) and ZZ domain [55] (purple box) and plectin repeats (magenta heptagons). Definitive publications to the modules shown above are: CC [56] CH [57] DH [58] EF [59] PH [60,61] Plec [62] SH3 [63,64] Spec [7] WW [65].

sanger.ac.uk/, http://pawsonlab.mshri.on.ca/DomainClub/domainClub.php). For the purposes of this review we will discuss in more detail new functions and properties of the spectrin repeats of the spectrin family member dystrophin.

The plakin family of proteins is characterised by the presence of plectin repeats and spectrin repeats often interspersed with other sequences with a propensity to form dimeric coiled coils. Other modules found in plakins include tandem CH domains, EF hands, SH3 and KASH again dependent on cellular function (Fig. 1B). Plakin family proteins function to interconnect different cytoskeletal filament networks with each other and directly to membranes or membrane associated structures. Depending on their domain composition they variously connect intermediate filaments via their plectin repeats (e.g. desmoplakin, plectin and some nesprin isoforms), actin filaments via their CH domains (plectin, MACF1 and some nesprin isoforms) and microtubules (plectin, MACF1). In turn they associate with other membrane anchored proteins in the plasma membrane at adhesion sites such as costameres, desmosomes and hemidesmosomes. The plakins also have roles in organelle positioning including mitochondria and Golgi, and in the maintenance of nuclear membrane connectivity to the cytoskeleton as well as the structure of the nuclear lamina. Readers are referred to more authoritative reviews for details of these functions [3,4].

In addition to multiple repeated copies of spectrin repeats in the cytolinker proteins mentioned above, spectrin repeats also occur sparsely in some Rho family guanine nucleotide exchange factors (RhoGEFs) including the RhoGEF DBL, its big sister MCF2L and more distant relatives such as trio and kalirin. With the exception of DBL itself, these all contain an amino terminal SEC14 domain, followed by one or more spectrin repeats followed by one or more copies of the DH and PH domains characteristic of GEFs also with SH3 and S/T kinase domains (Fig. 1C). Loss of the spectrin repeat in kalirin alters is effects on actin based structures such as dendritic spines [5]. In a similar manner deletion of the spectrin repeat from Dbl contributes to its oncogenic potential by removing binding sites for HSc70 and a ubiquitin ligase that serve to maintain low steady state levels of the protein [6]. Thus the functions of the spectrin repeats in kalirin and Dbl appear to control GEF function and/or targeting of the GEF activity.

3. Spectrin family repeat structure

The core elements of the spectrin repeat are a triple-helical coiled-coil bundle, with the 3 helices forming the domain gently curving and wrapping around each other in a left-handed supercoil (Fig. 2). The archetypal spectrin repeat structure obtained from the direct protein sequencing of spectrin in the early nineteen eighties revealed a repeating 106 amino acid sequence with conserved periodic hydrophobic and charged residues [7]. Predicted sequences for dystrophin and α-actinin obtained slightly later by DNA sequencing also revealed similarities to the repeating regions of spectrin [8–10] but with slightly different average repeat lengths of 122 and 109 residues for α-actinin and dystrophin, respectively. An evolutionary relationship has also been proposed for this protein family from a likely α-actinin ancestor and subsequent diversification to spectrins and then dystrophin/utrophin [11–13]. The repeats of α-actinin and spectrin are known to form dimers, indeed, the regular repeat length and conserved surface charge particularly in the e and g positions in the heptad lends itself to dimerisation. By convention the amino acids in helices are lettered from a to g to represent the 7 residues per two turns of the helix, i.e. the heptad. Whilst hydrophobic residues at the a and d positions in the heptad, a hallmark of a triple-helical coiled coil, are conserved in dystrophin and its autosomal homologue utrophin, they both lack the conservation of repeat length and charged residues at the e and g positions in the heptad to form stable dimers [14–16] (Fig. 2).

The first structures of single spectrin repeats as predicted [17] revealed tight triple α-helical coiled-coils [18,19]. However these single repeat structures did not reveal the true spectrin coiled coil structure due to either the long helix folding back on itself or the repeat dimerising. It was only later when multiple repeats were solved that the continuous relationship between the helices in the repeat junction was elucidated [20–22] (Fig. 2). Furthermore the crystal structures of a repeat pair from α-spectrin in multiple crystal forms revealed the potential flexibility of spectrin repeats [21] whereas structures of the four spectrin repeats from α-actinin yielded a rather rigid dimerised structure [20,22]. As noted above, dystrophin repeats are more variable in length and have more frequent insertions in the helices [14] (Fig. 2). In addition, and in contrast to spectrin molecules, four predicted hinges separating the rod region into three sub-regions were speculated to confer additional flexibility to the molecule (Fig. 3) [9]. The alpha-helical nature of the dystrophin spectrin-like repeats was confirmed, however additional residues were required to extend the helices into the adjoining helices in order to produce a stable fold [23–25]. These studies suggested that the dystrophin repeats may fold in an overlapping or nested manner with the structural integrity of each repeat being reliant in part on its neighbours [16,26,27]. This