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Function and Interactions of the Ysc84/SH3yl1 family of actin and lipid binding proteins

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Abstract

Understanding how actin filaments are nucleated, polymerized and disassembled in close proximity to cell membranes is an area of growing interest. Protrusion of the plasma membrane is required for cell motility, while inward curvature, or invagination, is required for endocytic events. These morphological changes in membrane are often associated with rearrangements of actin, but how the many actin-binding proteins of eukaryotes function in a co-ordinated way to generate the required responses is still not well understood. Identification and analysis of proteins that function at the interface between the membrane and actin regulatory networks is central to increasing our knowledge of the mechanisms required to transduce the force of actin polymerization to changes in membrane morphology. The Ysc84/SH3yl1 proteins have not been extensively studied, but work in both yeast and mammalian cells indicate that these proteins function at the hub of networks integrating regulation of F-actin with changes in membrane morphology.

Introduction

The actin filament network plays a central role in many cellular processes from the generation of cell morphology and intracellular trafficking, to contractility, motility and cell division [1]. Within cells the polymerization and depolymerization of actin filaments, as well as their organization into higher order structures are controlled by the association of actin with a large number of actin binding proteins [1].

Actin monomers are nucleated and assembled into polarized actin filaments, which may be linear or branched. Filaments can be loosely cross-linked or associated more tightly into bundles. The filaments within these organizations may be regulated by capping proteins; stabilized by co-filamentous binding proteins, and may also serve as tracks for movement of protein complexes and organelles by myosins. An increasingly recognized site of actin function is at membrane surfaces. Actin filaments can bind proteins at the plasma membrane and have been shown to be involved in the formation of structures associated with cell invasion and motility including, filopodia, lamellipodia, dorsal ruffles, invadosomes and focal adhesions. Importantly, specific lipids within the membrane are able to regulate the activity of certain actin binding proteins that can either activate assembly or disassembly of actin filaments thus ensuring tight control of actin structures at these key interface locations.

This review focuses on a highly conserved protein family Ysc84/SH3yl1, that may facilitate localized regulation of newly formed actin filaments at the plasma membrane.

Identification and interactions of Ysc84, Lsb3 and SH3yl1

Ysc84 was identified in both candidate-based and high-throughput yeast two-hybrid screens as interacting with a number of proteins associated with the actin cytoskeleton in the model organism, *Saccharomyces cerevisiae* [2-5]. Among interacting partners were the yeast homologue of the actin nucleation-promoting factor WASP (called Las17); an endocytic cargo binding protein Sla1 (homologue of CIN85/CD2AP) and an actin binding protein Abp1 (mammalian homologue mAbp1, also similar to drebrin). A highly related gene/protein, Lsb3, which interacted with a similar subset of proteins, was also identified [2, 4]. Ysc84 and Lsb3 are considered to have arisen from the whole genome duplication that occurred in the *Saccharomyces cerevisiae* ancestral genome. A STRING (Search Tool for the Retrieval of Interacting Genes/Proteins*)* diagram depicting experimental and predicted interactions for Ysc84 is shown in figure 1A. These compiled data reflect the likely actin-based function for this protein

SH3-yl1 was first identified in mouse skin where it was found to have increased expression in the anagen phase of the hair cycle. This is the phase during which the hair follicle regenerates, and the new hair grows [6]. A second study demonstrated that SH3yl1 is widely expressed in other mouse tissues, predominantly in kidney, but also in the small intestine, colon and liver [7]. Screens for binding partners for SH3yl1 have revealed interactions with SHIP2, DOCK4, N-WASP and dynamin 2 [8, 9], and a STRING diagram for SH3yl1 also places this protein in a hub of actin-based functions (Figure 1B).

Domain structure and conservation of Ysc84/SH3yl1 proteins

Ysc84 and SH3yl1 show a highly related domain structure and within these domains there is a high level of homology. At the N-terminus is a domain which has been called both the Ysc84 actin binding (YAB) domain [10] and the SH3yl1, Ysc84, Lsb3, and plant FYVE (SYLF) domain [8]. At the C-terminus there is a Src homology-3 (SH3) domain (Figure 2A). The region between the two domains is variable in length (<100 residues in human SH3yl1 and about 200 residues in yeast Ysc84) and does not contain any clear homology or recognized sequence motifs.

The YAB/SYLF domain is found in all vertebrates and fungi but surprisingly not in classes of invertebrates including, insecta, mollusca and echinodermata. This domain is also found in plants (e.g *Arabidopsis thaliana* and *Oryza sativa*) but in this case it is found most often at the C-terminus of proteins, while a putative lipid binding FYVE domain is most often found at the N-terminus of these proteins. A single member of this protein family appears to be present in each genome with the exception of those yeast species that have undergone genome duplication. The full YAB/SYLF domain has a high level of homology across eukaryotes, (43% identity between yeast and human; amino acid residues 1-180; Figure 2B,C) strongly suggesting a conserved function. Intriguingly, many bacteria also encode a YAB/SYLF domain-containing protein. This includes species of Rhodobacter, Pseudomonas, Campylobacter, Bordatella and Burkholderia, though no functional data for the protein has been reported.

In vivo functions of Ysc84/SH3yl1 family of proteins

Ysc84 and its homologue Lsb3 were shown to co-localize with cortical actin patches, and F-actin is required for Ysc84 localization at the plasma membrane [2]. During endocytosis in *S. cerevisiae*, the growth of actin filaments by polymerization is

considered central to generating the force required to drive inward curvature of the plasma membrane against the outward force of cell turgor pressure [11]. Deletion of *YSC84* reduced the rate of endocytic invagination and the number of failed invaginations was found to increase supporting a role for Ysc84 in establishing conditions to facilitate invagination [10]. Furthermore, live cell imaging revealed that Ysc84 arrives at the endocytic site after coat protein recruitment and cargo binding but before the majority of actin binding proteins including the major actin nucleator, Arp2/3, indicating a possible role at onset of actin function.

Following PDGF induction of NIH3T3 cells transfected with HA tagged SH3yl1, SH3yl1 was found to localize at early stage circular dorsal ruffles (CDRs). These are actin-rich circular ruffles of membrane that are implicated in uptake of cellular receptors and extracellular material [8, 12]. SH3yl1 targeting siRNAs were used to reduce levels of SH3yl by >90% in NIH3T3 cells and this caused a significant reduction (55% to 18%) in the ability of cells to form CDRs in response to PDGF [8]. Most recently, targeted depletion of SH3yl1 in the MDA-MB-231 breast cancer cell line was shown to suppress cell migration; this could be rescued by wild type SH3yl1 but not by a form with a mutation blocking binding of its SH3 domain to DOCK4 [13]. Together, these results support a function for SH3yl1 in the formation and/or regulation of actin-based structures associated with the plasma membrane.
Finally, support for conserved interactions and function of Ysc84 and SH3yl1 also comes from complementation studies in yeast. A yeast strain was generated which had a severe growth phenotype (*ysc84*Δ, *lsb5*(*1-151*). These cells are temperature sensitive with no growth at 37°C. The temperature sensitivity phenotype was rescued by addition of wild type *YSC84* to cells. Importantly, expression of human SH3yl1 also restored growth, albeit not to the same extent as the endogenous protein indicating at least partial conservation of function. In addition SH3yl1 expressed in otherwise wild type yeast cells caused a disruption of actin organization, supporting the possibility that both proteins affect actin function [2].

Mechanism of Ysc84/SH3yl1 function from biochemical studies

Recombinantly produced Ysc84 YAB domain is able to bind actin directly and organize it into loose bundles. Unlike the majority of actin bundling proteins however, the YAB domain does not bind to pre-formed actin filaments. Rather, it can only bind if present

throughout polymerization indicating that it may be loaded onto filaments during the nucleation step and that a key interaction site may only be accessible at this stage. A second feature of Ysc84 actin binding is that the full length protein does not bind to actin unless its SH3 domain has been bound by an interacting partner such as Las17/WASP. This would ensure that the actin binding activity of Ysc84 would be limited to sites where Las17 is localized. Recent work has indicated that Las17 is able to nucleate actin filaments de novo, and also independently of Arp2/3 [14]. Given that both Las17 and Ysc84 arrive before Arp2/3 and other actin binding proteins at endocytic sites, it is tempting to speculate that one function of Ysc84 might be to regulate or organize these nascent actin filaments.

Work by Hasegawa and colleagues [8] indicated that unlike yeast Ysc84, neither full length, nor the N-terminal domain of SH3yl1 interact with F-actin. Given the high level of conservation between the proteins, and their other interaction partners this lack of actin binding seems surprising but awaits more detailed analysis. In preliminary experiments we have observed clear binding of the GST-SH3yl1 YAB/SYLF domain with F-actin when incubated during polymerization (AU, RC data not shown) and differences between outcomes may reflect experimental conditions. An important finding reported by Hasegawa and colleagues was a previously unknown interaction of the YAB/SYLF domain of SH3yl1, as well as yeast Ysc84 and Lsb3 YAB domains with liposomes [8]. For SH3yl1, this binding was shown to be preferential for liposomes containing. $PI(3,5)P_2$, $PI(4,5)P_2$ or $PI(3,4,5)P_3$. Mutations in an N-terminal amphipathic helix (KK14,15) led to partial inhibition of liposome binding indicating that this region forms part of a motif that facilitates localization of SH3yl1 to the plasma membrane. When expressed in cells, the same KK mutation also reduced localization to ruffles following PDGF stimulation supporting the importance of this motif for SH3yl1 function [8].

Perspectives

While the common domain features and interaction partners of Ysc84 and SH3yl1 demonstrate that these proteins share strong conservation at the level of the cellular processes in which they function, there are still many questions surrounding their mechanism of action.

In one scenario, the YAB/SYLF domain could be viewed as a solely lipid binding domain localizing SH3yl-1 to regions of the plasma membrane with high levels of phosphatidyl bis- or tri- phosphates. In this case its C-terminal SH3 domain would then act as a binding scaffold to recruit various binding partners such as N-WASP, dynamin and DOCK4 to the membrane; these proteins would then effect changes in actin organization (figure 3A). In this model, it might be expected that changes in levels of PIP lipids at the membrane would affect localization of SH3yl-1/Ysc84 and that mutations in SH3 would affect localization of binding partners but not of SH3yl1 itself. Given that the only functional part of the YAB/SYLF domain thus far shown to be involved in lipid binding is a helix at the extreme N-terminus, the function of the rest of this 180-200 amino acid domain remains unclear.

In a second scenario, the N-terminal domain could bind actin and this binding would then be regulated by interaction with plasma membrane lipids. Such regulation is observed with a number of actin binding proteins such as capping protein and profilin. In this model the SH3 domain would then serve to localize the protein at relevant sites, and possibly facilitate conformational change to allow actin binding and bundling. In support of this part of the model, deletion of the SH3 domain of Ysc84 does indeed prevent localization to any cell structure. In addition, disruption of F-actin by addition of latrunculin-A to yeast cells also leads to loss of Ysc84 localization to cortical puncta, demonstrating the importance of actin rather than lipids for localization per se [2]. Further support for this model would require greater analysis of actin binding activity and mapping of interaction sites. Possibly because of their lipid binding capacity, expression of these proteins is toxic in bacteria and it is possible that the proteins are not sufficiently well folded to allow full protein binding capacity to be supported. Purification from mammalian cells or from an insect protein expression system may allow the remaining question of actin binding of SH3yl-1 to be addressed more fully.

Future work in plants may provide a useful alternative experimental system to understand YAB/SYLF mechanism and function. Given that in the plant proteins containing thee domain, there is also a PI3P binding motif (FYVE), it is of interest whether YAB/SYLF acts as a second lipid binding domain, and also whether the lipid binding preferences are similar to those found for SH3yl1. The presence of a clear YAB/SYLF homology domain in bacteria is also of interest but there is no functional

information for these proteins. However, given the presence of ancestral actin related proteins in many bacteria, the conservation of this binding function will be worthy of investigation.

Irrespective of mechanistic details, the Ysc84/SH3yl-1 family of proteins show a high level of conservation throughout evolution. Within eukaryotes the protein appears to function at the hub of a network of actin based activities regulating motility in mammalian cells and membrane curvature during endocytosis in budding yeast.

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Figure legends

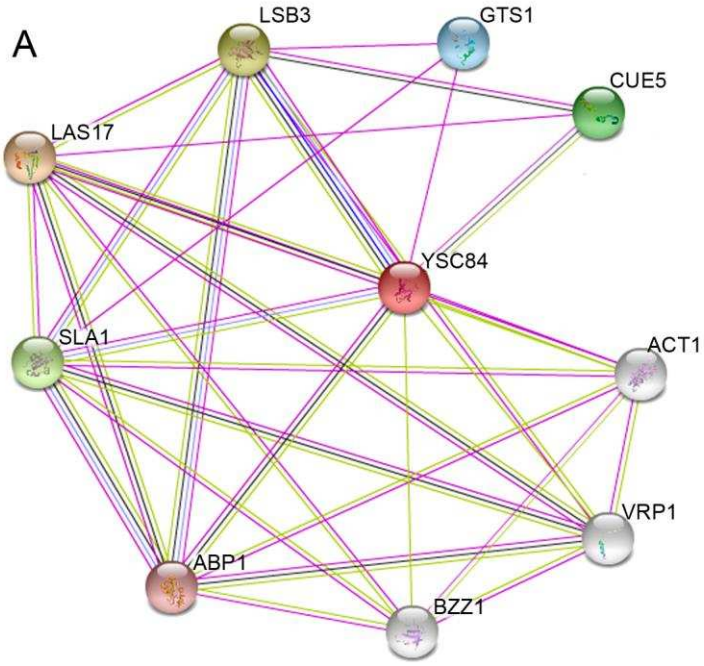
Figure 1 STRING diagrams illustrating reported interactions of Ysc84 and SH3yl1.
(A) Proteins interacting with Ysc84: Las17 (WAS protein homologue), Sla1 (protein with multiple SH3 domains similar to CDSAP/CIN85); Abp1 (contains ADH homology domain and SH3 domain similar to Drebrin); Bzz1 (syndapin homologue); Vrp1/verprolin (WASP Interacting protein, WIP homologue); ACT1 (actin); Cue5 (ubiquitin binding protein); Gts1 (ArfGAP protein); Lsb3 (Ysc84 homologue). (B) Proteins interacting with SH3yl1: WAS (Wiskott Aldrich syndome protein); WASL (WAS like); SH3D19 (protein with multiple SH3 domains; DBNL (Drebrin like); NCKIPSD (Nck interacting protein with SH3 domain); Myo1F (myosin 1F); DOCK4 (Dedicator of cytokinesis-4), SHIP2 (Inositol polyphosphate phosphatase like protein-2, IPPLP2); DNM2 (dynamin-2); PEX14 (peroxisomal membrane anchor protein)

Figure 2 Schematic of Ysc84/SH3yl1 domains and phylogenetic tree
(A) Domain structure of yeast Ysc84 and human SH3yl1 depicting N-terminal YAB/SYLF domain and C-terminal SH3 domain. (B) Alignment of N-terminal domains of a number of Ysc84 homologues: A.thaliana (NP_189909); O.sativa (NP_001060279); D.rerio (XP_694886.2); X.laevis(NP_001086532.1); M.musculus (CAG33642); H.sapiens (AAH08375); G.gallus (XP_419926); S.cerevisiae Ysc84 (NP_011880); S.cerevisiae Lsb3 (NP_219497); S.pombe (NP_593048); N.crassa (XP_323207); G.zeae (XP_389673.1); A.nidulans (XP_408305.1). Pink arrows indicate residues changed in human SH3yl1 that alter lipid binding (KK 14, 15).(C) Unrooted phylogenetic tree of the

N-terminal YAB/SYLF domains shown in the alignment generated using Treeview software.

Figure 3 Models of Ysc84/SH3yl1 mechanism of action

(A) The YAB/SYLF domain of SH3yl1 binds to specific phosphoinositol phosphate lipids in the plasma membrane thus recruiting the protein to discrete sites. The SH3 domain is then able to interact with various partners including DOCK4 and N-WASP to drive reorganization of actin cytoskeleton to the region. (B) In an alternative model, the SH3 domain of Ysc84/SH3yl1 may interact with key protein partners at the plasma membrane such as WASP/Las17. Binding then causes a conformational change allowing the YAB/SYLF domain to bind and bundle F-actin. The lipid binding property of the YAB/SYLF domain may regulate this activity towards actin or it may help further anchor actin filaments in close proximity to the plasma membrane.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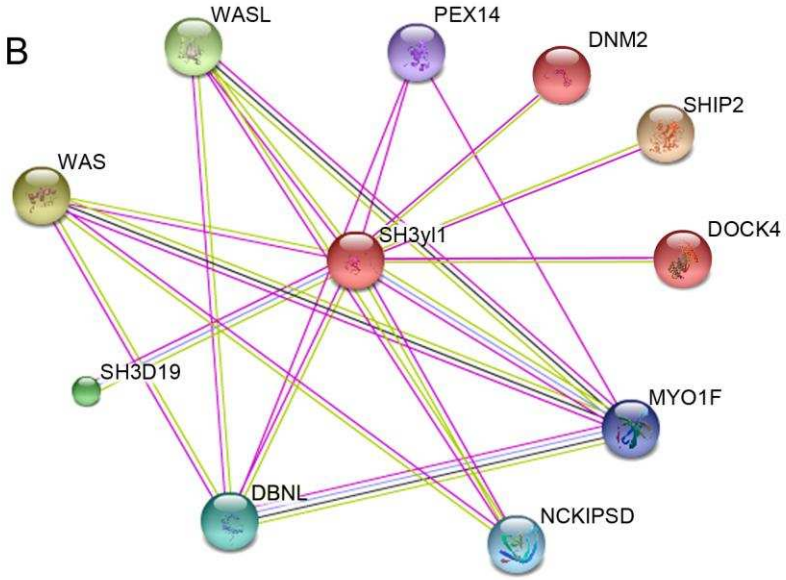
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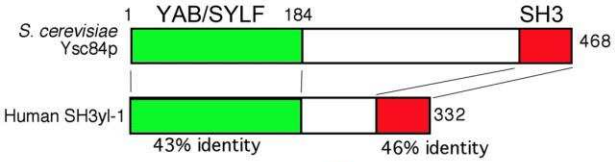
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Ysc84p
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Human SH3yl-1
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43% identity
46% identity

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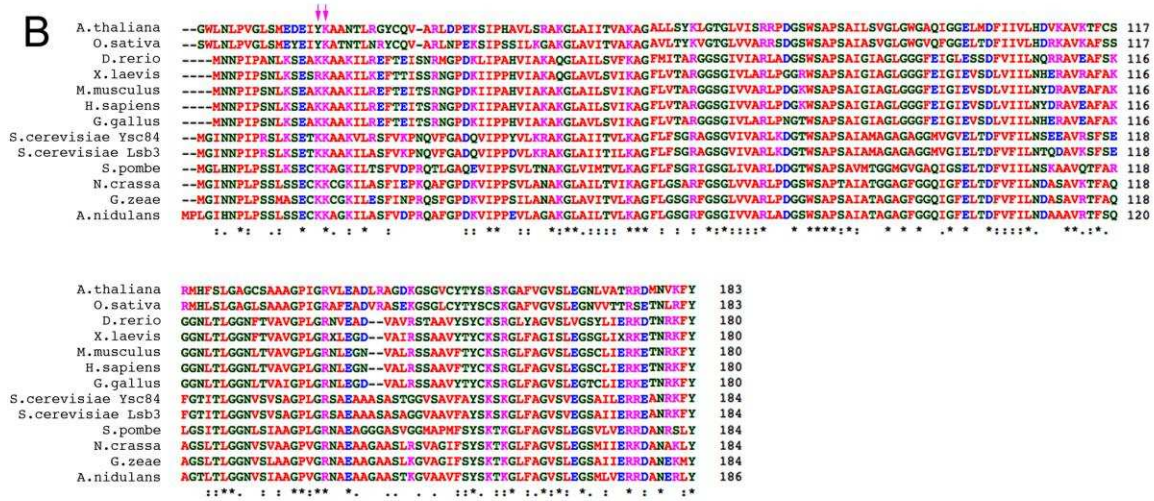
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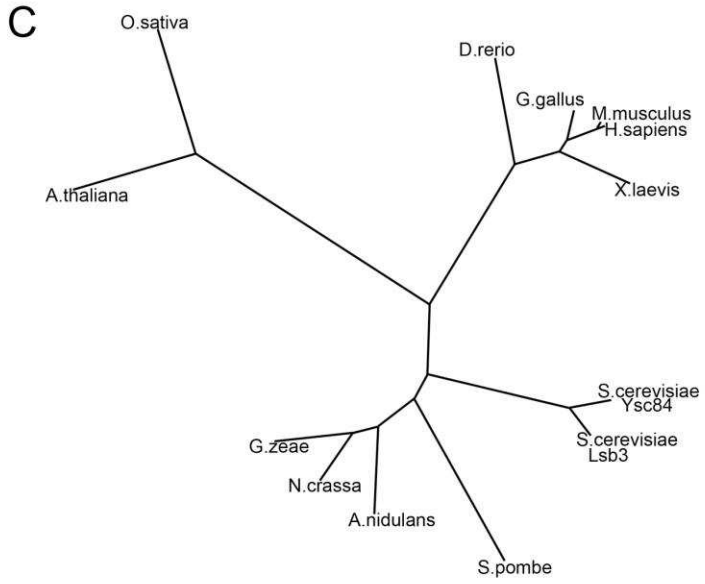
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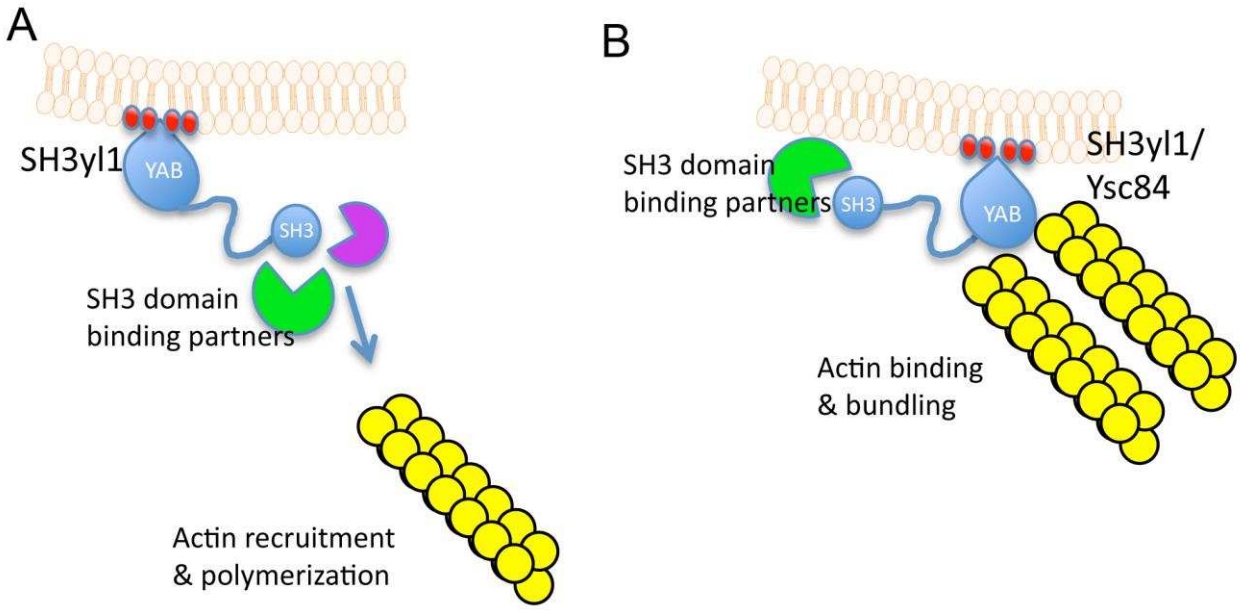
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