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A spectrin membrane skeleton of the Golgi complex

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Abstract

The existence of a Golgi-localized membrane cytoskeleton has been revealed by the identification of two major components of the spectrin membrane skeleton, spectrin and ankyrin, that associate with the Golgi complex. Golgi spectrin was identified with an antibody specific for the β-subunit of the erythroid isoform of spectrin (β1Σ1). This antibody recognizes a 220 kDa polypeptide that localizes to discrete regions of the Golgi complex and associates with Golgi membranes in a Brefeldin A sensitive manner. Two isoforms of Golgi ankyrin have been identified: a 119 kDa form (Ank_{G119}) which represents a truncated, alternatively spliced isoform of a recently cloned novel ankyrin of the nervous system Ank_G, and a larger 195 kDa ankyrin (Ank_{195}) that cross-reacts with antibodies to erythrocyte ankyrin. A Golgi localized membrane skeleton composed of these unique membrane skeleton isoforms could serve a variety of important functions, including the maintenance of Golgi structural organization and the formation of discrete membrane domains within Golgi compartments.

Keywords: Spectrin; Cytoskeleton; Protein sorting; Golgi; Membrane

1. Introduction

A role for cytoskeletal structures in the maintenance of Golgi structure and function is evident in a number of the properties of this complex organelle. For example, whereas Golgi membranes require structural stability to maintain a precise structural organization that correlates with Golgi function, membrane instability is necessary for extensive membrane trafficking that occurs between Golgi compartments; the latter process is likely to employ structural elements with dynamic assembly properties. The Golgi also maintains a fixed localization within the cytoplasm and communicates with other organelles through directed vesicular trafficking. In addition, integral membrane proteins residing either transiently or permanently in the Golgi complex are restricted to various degrees in their distribution within the organelle, illustrating a requirement for membrane domain formation. While it is well established that microtubules and microtubule-associated motor proteins are involved in maintaining the cytoplasmic localization of the Golgi [1] and that various Golgi-associated coat structures (COP I, COP II and clathrin; [2,3]) facilitate vesicular transport to and from this organelle, much less is known about regulatory mechanisms governing these other properties of the Golgi.

A recently identified Golgi-localized, spectrin membrane skeleton is a good candidate for regulating these additional, critical properties of the Golgi.

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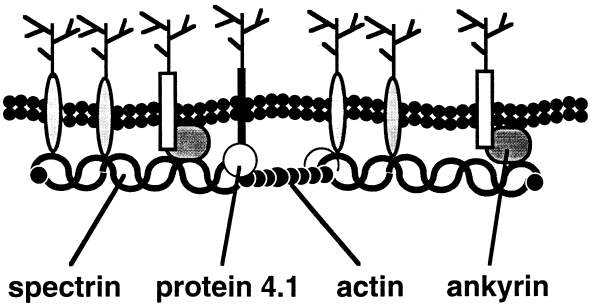

Fig. 1. The spectrin membrane skeleton. The classical spectrin membrane skeleton of the erythrocyte is composed of linear spectrin oligomers cross-linked by short actin filaments to form a two-dimensional meshwork. This meshwork is coupled to the cytoplasmic surface of the plasma membrane through a variety of interactions: (1) direct interactions of membrane proteins with the β-subunit of spectrin; (2) binding to the membrane skeleton protein ankyrin; and (3) binding to the membrane skeleton protein 4.1, a protein which also serves to mediate spectrin–actin interactions.

The spectrin membrane skeleton exists in cells as an extensive, two-dimensional lattice of filaments that underlies the cytoplasmic surfaces of membranes (for review, see [4]). The lattice (Fig. 1) is composed of linear filaments of spectrin cross-linked by short actin polymers. Close membrane association of the lattice is mediated by direct interactions between integral membrane proteins and spectrin, or the membrane skeleton protein ankyrin. Until recently, the spectrin membrane skeleton was thought to function primarily at the plasma membrane where it serves two critical functions: the maintenance of membrane structural stability and membrane domain organization. In this report we will review recent studies that indicate the existence of a spectrin membrane skeleton associated with the Golgi complex and speculate on its potential roles in Golgi function.

2. Golgi membrane skeleton proteins

2.1. Golgi spectrin

The first membrane skeleton protein found associated with the Golgi complex was spectrin. Functioning as the major structural protein of the plasma membrane skeleton, spectrin exist as a dimer of homologous but non-identical subunits, termed α and β, arranged in a head to tail orientation. Spectrin dimers are flexible rod-shaped molecules that can self-associate end to end to form linear spectrin oligomers which serve as the basic structural unit of the membrane skeleton [5].

Spectrins have been found in a variety of organisms and are ubiquitous among vertebrate tissues, implying that they play a fundamental role in all cells. Coincident with the broad species and tissue distributions of spectrins is the existence of multiple isoforms of spectrin subunits. To date, about a dozen distinct isoforms of spectrin have been discovered, and many of these have been shown to have unique tissue and sub-cellular distributions. In some cases, distinct isoforms have been found to co-exist within a single cell, implying multiple functions of the membrane skeleton. In fact, spectrin is a member of a large gene family including other cytoskeletal proteins such as dystrophin and α-actinin, indicating a common cytoskeletal structure that is that can be adapted to a variety of different functions [6,7].

The existence of a specific Golgi localized form of spectrin was first revealed with an antibody specific for the β-subunit of erythrocyte spectrin [8]. Immunofluorescence staining of non-erythroid cells showed β-spectrin localization to peri-nuclear reticular structures that were morphologically reminiscent of the Golgi complex [8] (Fig. 2). This localization was distinct from that of non-erythroid spectrins examined in the same cell types, all of which localized exclusively to the plasma membrane [9]. Golgi localization of the erythroid β-spectrin homolog was confirmed by co-staining with specific Golgi markers, including mannosidase II and β-COP [8]. The erythroid β-spectrin antiserum stained the Golgi complex many cell types (MDCK, MDBK, NRK, 293, C2C12 and L cell fibroblasts) implying a ubiquitous distribution, and hence function, in the Golgi of mammalian cells [8]. Importantly, Golgi spectrin does not appear to be uniformly distributed throughout the Golgi complex, since only partial overlap with other Golgi proteins was observed by indirect immunofluorescence, suggesting that membrane skeleton distribution and function is limited to a particular Golgi compartment [8].

While the precise structure of Golgi spectrin must await its molecular cloning, the available evidence suggests that it is a structural homolog of erythroid

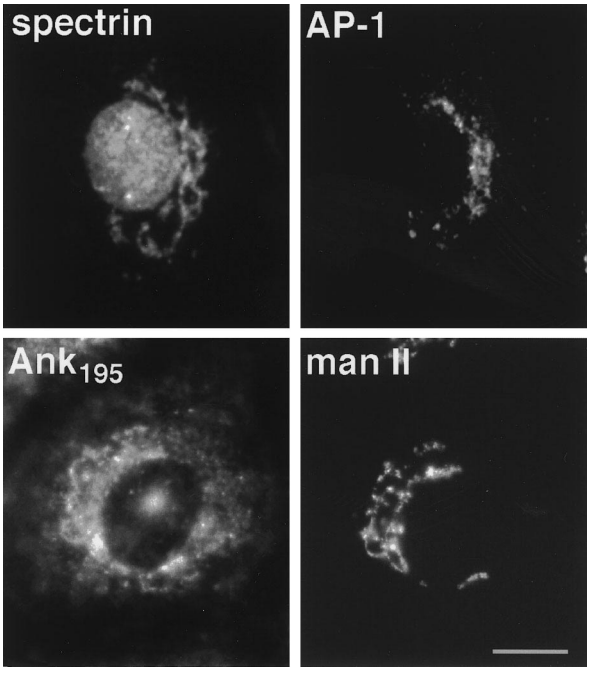

Fig. 2. Golgi membrane skeleton proteins. Golgi spectrin is observed by staining of a Madin–Darby bovine kidney epithelial cell with an antibody raised against the β-subunit of erythrocyte spectrin (β1Σ*). Double staining with an antibody to the Golgi-localized clathrin adaptor protein AP-1 demonstrates localization of the erythroid β-spectrin homolog (spectrin) to the Golgi. A normal rat kidney (NRK) epithelial cell double stained with antibodies to erythrocyte ankyrin (Ank_{195}) and the medial Golgi marker mannosidase II (man II) demonstrates Golgi-localization of the 195 kDa ankyrin isoform identified with the erythroid ankyrin antibody in these cells. Scale bar: 10 μm.

β-spectrin: (1) Golgi spectrin was identified with an erythroid β-spectrin specific antibody; (2) this antibody recognized a single polypeptide in purified rat liver Golgi membranes with a molecular mass comparable to that of erythroid β-spectrin, 220 kDa; and (3) when microinjected into living cells, purified erthyroid spectrin [8] readily localizes to the Golgi. Surprisingly, all of our attempts so far to identify a partner subunit for Golgi spectrin akin to the α/β herterodimer of plasma membrane spectrin have been unsuccessful. Perhaps Golgi spectrin functions without an associated α-spectrin, analogous to a unique β-spectrin isoform of the neuromuscular junction [10].

Golgi spectrin exhibits a dynamic association with Golgi membranes. In mitotic cells, where the Golgi is extensively fragmented and distributed throughout the cytoplasm, Golgi spectrin displays a diffuse cytoplasmic distribution consistent with its dissociation from Golgi membranes [8]. Similarly, in cells treated with the fungal metabolite Brefeldin A (BFA), Golgi spectrin dissociates within minutes from Golgi membranes [8]. This rapid dissociation of Golgi spectrin in BFA-treated cells is similar to the behavior of other peripherally associated, macromolecular assemblies, such as clathrin [11] and coatamer (COP I) coats [12], and is consistent with a constitutive assembly cycle for the Golgi membrane skeleton. Such a dynamic assembly state for a Golgi localized membrane skeleton is consistent with the highly dynamic functions of the Golgi complex.

2.2. Golgi ankyrin

Ankyrin is a critical membrane skeleton component which serves to link the spectrin lattice to the cytoplasmic surface of cellular membranes [13]. The great diversity of spectrins is mirrored by a complementary variety of plasma membrane ankyrins. There are three types of ankyrin isoforms, designated Ank1, Ank2 and Ank3. Ank1 corresponds to the erythroid form [14] whereas Ank2 is the major brain ankyrin isoform [15] and Ank3 designates a distinct and variable group of ankyrins expressed in neurons [16], epithelia [17], and macrophages [18]. All ankyrins share highly conserved structural features: a globular amino terminal domain of 90 kDa that is composed in part of 24 copies of a 33 amino acid repeat which serves to bind to the cytoplasmic domains of a variety of membrane proteins; a central 60 kDa domain which binds the β-subunit of spectrin; and a 30 kDa carboxy terminal domain which represents the least conserved region. As with the multiple isoforms of spectrin, the existence of multiple forms of ankyrin indicates diversity of potential functions of the membrane skeleton.

Two isoforms of Golgi ankyrin have been identified: a small 119 kDa form (Ank_{G119}, [19]) and a 195 kDa ankyrin (Ank_{195}, [20]) that cross-reacts with an antibody specific for the erythroid (Ank1) isoform. Ank_{G119} represents a truncated form of a larger ankyrin molecule recently cloned from brain, Ank_G, which localizes to nodes of Ranvier and initial segments of axons [15]. Compared to Ank_G, Ank_{G119} has a truncated amino terminal domain (47 kDa) comprising only the last 13 of 24 ankyrin repeats, a

complete 67 kDa spectrin binding domain, and a truncated (5 kDa) carboxy terminal domain [19]. Antibodies to Ank_{G119} stain the Golgi complex in subconfluent MDCK cells and punctate endosomal and cytoplasmic structures in confluent monolayers [19]. Recombinant peptides bind to purified erythrocyte spectrin in vitro with high affinity ($K_d = 4.2$ nM) and to Golgi spectrin (βIΣ*) from MDCK cell extracts [19].

The Golgi localized ankyrin, Ank_{195}, was initially identified with antibodies specific for canine erythrocyte ankyrin [20]. Since the gene coding for this protein has not been cloned, we know nothing about its primary structure. An antibody that recognizes Ank_{195} in MDCK cells prominently stains the Golgi complex (Fig. 2, [20]). This antibody did not react with Ank_{G119}, thereby identifying Ank_{195} as a Golgi ankyrin distinct from Ank_{G119} [20]. Immunolocalization studies performed with tissue culture cells extracted with detergent prior to fixation demonstrate that both Ank_{195} and Golgi spectrin localize to detergent insoluble structures. These structures maintain the overall morphology of the Golgi complex, indicating that Golgi spectrin and Ank_{195} form a high order oligomeric structure on Golgi membranes [20]. Like Golgi spectrin, Ank_{195} also rapidly dissociates from Golgi membranes following treatment with BFA, suggesting that it too possesses a rapid and constitutive assembly state [20]. Ultrastructural localization studies [20] performed with Ank_{195} specific antibodies reveal staining of non-clathrin coated vesicles that are closely associated with Golgi stacks and fenestrated tubular networks characteristic of the trans Golgi network (TGN). Both Ank_{195} and Ank_{G119} have been shown to be expressed in MDCK cells, indicating that the Golgi complex possesses at least two distinct forms of ankyrin and perhaps membrane skeleton. This diversity of Golgi ankyrins in a single cell implies multiple functions of the Golgi membrane skeleton.

2.3. Other membrane skeleton proteins

The linear spectrin oligomers of the red blood cell membrane skeleton are cross-linked by short actin filaments to generate the characteristic two-dimensional lattice of the membrane skeleton. Spectrin-actin interactions are, in turn, facilitated by two additional membrane skeleton proteins: protein 4.1 and adducin [4]. We expect that Golgi localized forms of these proteins also exist. Unfortunately, all of our attempts so far to demonstrate the existence of a Golgi localized actin which could serve to cross-link Golgi spectrin filaments have failed. However, an actin related protein centractin (Arp1, [21]) may provide an alternative mechanism for cross-linking Golgi spectrin. Centractin was identified as a component of the dynactin complex [22], which binds to and co-functions with the minus end directed microtubule motor protein dynein [23]. Centractin associates with the dynactin complex as short (37 nm) filamentous polymers of 8–13 monomers [24], comparable to the short (30–50 nm) actin filaments of the red cell membrane skeleton [25]. Antibodies to centractin faintly co-localize centractin with Golgi spectrin, although this affect is most notable upon over expression of ectopic centractin, which additionally causes gross perturbations in Golgi morphology [26]. Centractin co-immunoprecipitates with Golgi spectrin as well as with an additional membrane skeleton protein, adducin, which regulates actin-spectrin interactions in the erythrocyte membrane skeleton [26]. These observations suggest that centractin may substitute for actin as a spectrin cross-linking protein for the Golgi membrane skeleton.

The co-immunoprecipitation of adducin with centractin and Golgi spectrin [26] implicates this protein as a likely candidate for regulating of Golgi membrane skeleton assembly, although no direct demonstration of a Golgi localized adducin has yet been observed. While evidence for a Golgi-specific protein 4.1 is also lacking, the enormous variety of alternatively spliced protein 4.1 transcripts that can potentially exist [27] indicates that it may only be a matter of time before a Golgi localized isoform is discovered.

3. Possible functions of the Golgi membrane skeleton

The presence of two major components of the spectrin membrane skeleton at the Golgi complex, spectrin and ankyrin, implies the existence of a Golgi localized spectrin membrane skeleton analogous to the one found at the plasma membrane. That these two proteins are present as an assembled complex is

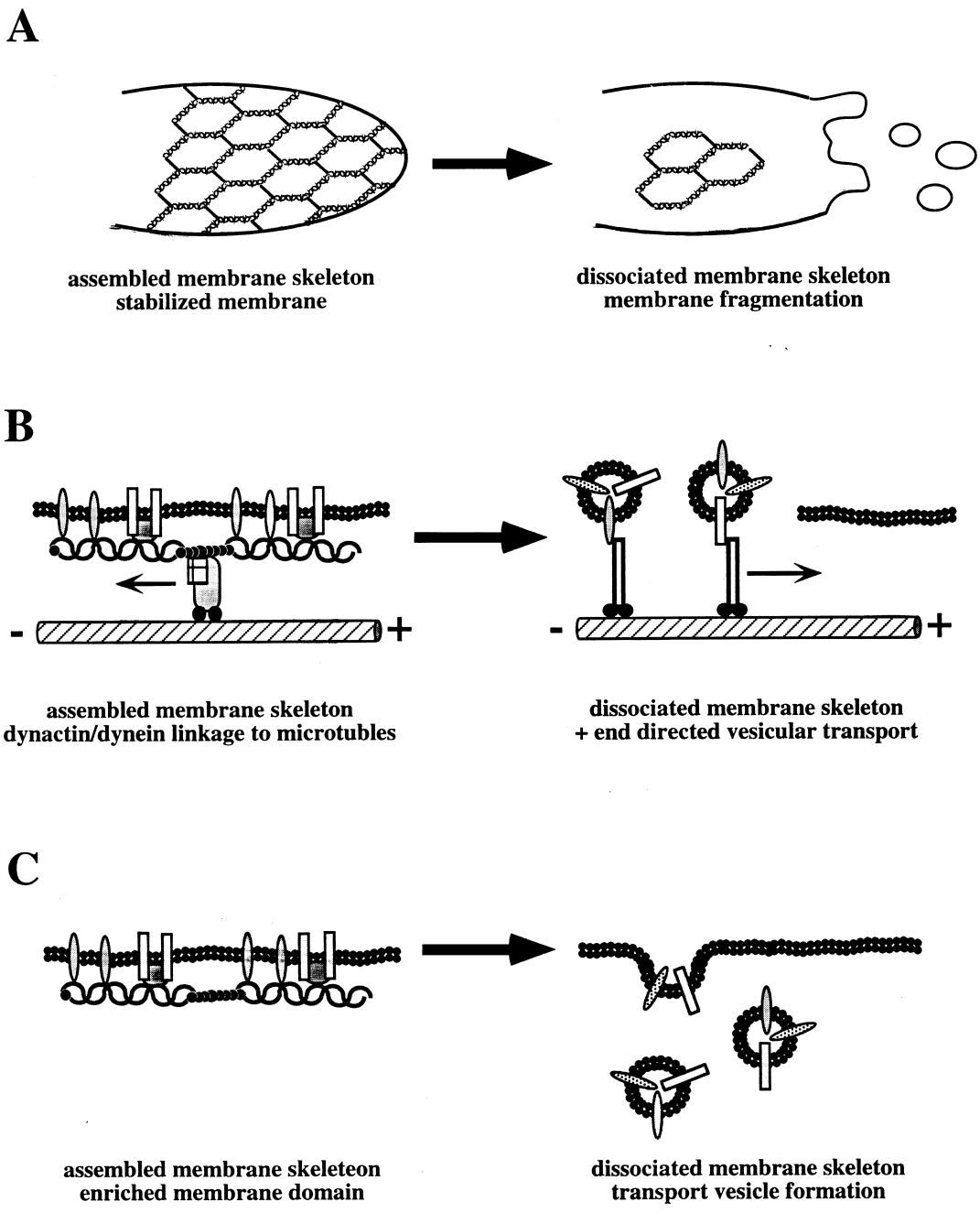

Fig. 3. Possible functions of the Golgi membrane skeleton. (A) The Golgi membrane skeleton could function to stabilize Golgi membranes. Regulated dissociation of the Golgi membrane skeleton could result in a destabilization and fragmentation of uncoated portions of the Golgi membrane. (B) The Golgi membrane skeleton could serve to indirectly link the Golgi complex to microtubules through interactions with dynactin/dynein. A dynein-dependent microtubule interaction would direct a centrosomal localization of the Golgi complex. Dissociation of the spectrin membrane skeleton could result in a disruption of dynein dependent microtubule interactions thereby allowing alternate (anterograde) microtubule interactions of Golgi membrane fragments/vesicles. (C) An assembled membrane skeleton having a discrete distribution within the Golgi complex could serve to restrict the lateral distribution of bound membrane proteins, giving rise to a discrete Golgi membrane domain. Localized dissociation of the membrane skeleton could result in local membrane destabilization and the formation of vesicular structures enriched in membrane proteins previously bound to the membrane skeleton.

indicated by the observations that Golgi ankyrins bind Golgi spectrin in vitro [19], both proteins can be isolated as a complex from cell extracts [19], and both spectrin and ankyrin localize to a detergent insoluble Golgi structure in Triton X-100 extracted cells and Golgi membranes [20,28]. Although no direct functional data presently exists, we can speculate on potential functions of the Golgi membrane skeleton based on known functions of the plasma membrane version.

In the red blood cell, the spectrin membrane skeleton provides structural support to the plasma membrane. Genetic defects and deficiencies in membrane skeleton proteins give rise to red cells with altered morphology and reduced half life in the circulation, ultimately leading to clinical hemolytic anemias [29]. A hallmark characteristic of spectrin deficient erythrocytes is the extensive blebing and fragmentation of the cell surface, indicating an extensive destabilization of the plasma membrane [29].

The Golgi complex has a well characterized structural organization, vividly revealed by the electron microscope [30], consisting of stacks of Golgi cisternae with associated tubulo-vesicular complexes at the *cis*- and *trans*-faces. It is possible that the spectrin membrane skeleton could serve to stabilize this complex structure, or some portions of it. However, the Golgi is known to be a highly dynamic organelle that engages in extensive membrane turnover. Hence, structural stabilization must be counterbalanced by membrane destabilization. The dynamic assembly state of the Golgi membrane skeleton shown by the rapid dissociation of both spectrin and ankyrin from Golgi membranes (BFA treatment, mitotic cells; [8,20]) indicate that the spectrin membrane skeleton may be particularly well suited for counterbalancing membrane stabilization and de-stabilization (Fig. 3A). A localized, assembled membrane skeleton could transiently stabilize a domain within the Golgi complex, allowing the accumulation of proteins and enzymatic activity to take place. Subsequently, regulated disassembly of the membrane skeleton could lead to destabilization of the membrane followed by release of modified cargo by vesicle formation. We note that recent studies have introduced into cells mutant forms (dominant negative) of β-spectrin that disrupt Golgi organization and protein trafficking [31]. However, it is not clear whether this is a consequence of disrupting the Golgi or plasma membrane skeleton as the mutant forms were derived from plasma membrane β-spectrin. This approach will be particularly useful when applied in the future to studies employing Golgi-specific isoforms of spectrin.

The Golgi membrane skeleton could also contribute to the structural organization of the Golgi through mediating the linkage of Golgi membranes to microtubules [1]. The Golgi is positionally fixed within the cytoplasm to a region in close proximity to microtubule organizing centers. This positional localization is mediated by microtubules since disruption of microtubule assembly leads to fragmentation and dispersion of the Golgi. In detergent extracted cells, insoluble structures containing both Golgi spectrin and ankyrin were colinear with individual microtubules [20], indicating a stable interaction between the two cytoskeletal systems.

A role for the membrane skeleton in linking the Golgi to microtubules is also supported by the observation that centractin, a component of the dynactin complex, interacts with Golgi spectrin [26]. Dynacin associates and co-functions with the minus end directed microtubule motor protein dynein [23], thereby providing a possible link between the spectrin membrane skeleton and microtubules. In fact, dynein has been implicated in the centrosomal localization of the Golgi complex [32]. Again the dynamic assembly state of the Golgi membrane skeleton could impart important functional significance to this interaction (Fig. 3B). Regulated disassembly of a portion of the membrane skeleton that is anchored to microtubules through a dynactin/dynein linkage could lead to a release of that portion of membrane from minus-end directed movement, and allow it to dissociate from the Golgi either by diffusion or by association with plus-end directed (kinesin) motor proteins [33]. It should be noted, however, that in vitro binding studies have indicated that functional dynein can interact with Golgi membranes independent of spectrin and ankyrin [28], indicating that the Golgi membrane skeleton is not the only Golgi binding site for dynein.

The second major function proposed for the plasma membrane skeleton is the formation membrane domains. The plasma membrane skeleton associates with the cytoplasmic surface of the membrane

through direct interactions with the cytoplasmic domains of specific membrane proteins, an interaction that results in a restriction of the lateral mobility of bound membrane proteins [34,35]. Thus, if the membrane skeleton is restricted in its distribution within the cell, it can create a membrane domain enriched in classes of membrane skeleton-bound membrane proteins. This has been observed in polarized cells such as neurons [36], epithelia [9,37,39], and muscle [10]. For example, in cultured canine kidney epithelial cells (MDCK), it has been found that the membrane skeleton is localized exclusively to the basal-lateral plasma membrane where it interacts with basal-lateral-specific membrane proteins and retains them in that domain by sequestering them away from endocytosis and degradation in lysosomes [40].

The Golgi is an organelle that clearly has a requirement for machinery that serves to establish and maintain membrane domains. It is a multi-compartment organelle, and many resident Golgi membrane proteins are restricted in their distributions within these compartments [41]. A Golgi-localized membrane skeleton could serve to facilitate the differential distribution of Golgi membrane proteins in a manner similar to that proposed for the plasma membrane form. This role for the Golgi membrane skeleton, however, is in contrast to the observed high diffusional mobility of some Golgi resident proteins [42].

The Golgi is also the site in the secretory pathway where a variety of classes of newly synthesized membrane proteins are sorted from each other prior to their targeting to different intracellular membranes and plasma membrane domains. This process also requires formation of membrane domains that are enriched in classes of membrane proteins. A Golgi membrane skeleton serving this function can be viewed as a membrane protein sorting machine (Fig. 3C, [43]). In this regard it is notable that the Golgi ankyrin isoform Ank_{195} has been localized to the trans Golgi network, a region of the Golgi complex where numerous membrane protein sorting events are known to occur [44].

Studies from several laboratories have recently identified homologs of components of the plasma membrane skeleton on Golgi membranes. Tentative linkages have been shown between ankyrin, spectrin, dynactin and microtubules. Although analogies to function of the plasma membrane skeleton provide interesting speculation, molecular cloning of Golgi spectrin, reconstitution of its binding to other membrane skeleton proteins and identification of membrane proteins that bind Golgi spectrin/ankyrin will be needed to definitively demonstrate the role of this novel cytoskeletal structure.

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