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Review

The dystroglycan: Nestled in an adhesome during embryonic development

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ABSTRACT

Invertebrate and vertebrate development relies on complex processes that require many coordinated cell functions including cell adhesion, migration, proliferation and polarization. These processes depend on tissues and are spatio-temporally regulated by specific interactions between cells and between cells and the extracellular matrices. The dystroglycan, a transmembrane receptor that binds multiple extracellular matrix proteins, is expressed from oogenesis to organogenesis. There are increasing data suggesting that the axis, consisting of extracellular component–dystroglycan–cytoplasmic proteins, controls both the adhesion of cells to matrices as well as the transduction of signals coming from or directed to matrices. In this article, we review current advances leading to consider that the dystroglycan is a key protein nestled in an adhesome involved in mechanisms of cell adhesion during embryonic development.
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Introduction

Embryogenesis depends largely on coordinated cell–cell and cell–extracellular matrix adhesions. For a long time, extracellular matrices (ECMs) were seen as stable structures to support the morphogenesis of tissues and organs. It now seems clear that ECMs are surprisingly dynamic and versatile and that they influence, through direct or indirect means, all steps of embryonic and adult life. ECMs are evolutionarily ancient structures, which probably appeared when the first communities of cells have emerged (for a review, Adams, 2013). ECMs are composed of heterogeneous networks of fibrillar and non-fibrillar components including collagens, laminins, fibronectin, nidogen, elastin, fibrilins, tenascin, proteoglycans and non-proteoglycan polysaccharides. These ECM components are secreted and assembled locally into organized networks that are present in invertebrate and vertebrate embryos. ECMs are dynamic structures of the cell environment, whose composition and spatial organization differ between species, developmental steps and tissues. In most species, ECM components act as a reservoir and a scaffold for growth factors, hormones and extracellular miRNAs (Edeleva and Shcherbata, 2013; Piccinini and Midwood, 2014). They also act to present growth factors to their receptors, to sense and transduce mechanical signals (Schiller and Fässler, 2013).

Conventionally, ECMs have been defined as including basement membranes (*basal laminae*) and interstitial matrices, which are less compact and more porous than basement membranes. Interstitial matrices are present between cells, are made by stromal cells, and are fibrillar. The structure of interstitial matrices depends on the nature of fibrils, the type and amount of proteoglycans. Interstitial matrices are found in loose and dense connective tissues such as cartilage, bone, and embryonic connective tissues. Basement membranes are sheet-like cell-adherent extracellular matrices that surround or underlie cells, tissues and organs. They are composed of independent networks of laminins and collagens that are tethered to nidogens and proteoglycans (Yurchenco and Patton, 2009). Basement membranes represent barriers limiting bacterial and viral offensive or infiltration of malignant cells between tissues. Alterations of basement membranes and interstitial matrices deregulate the behavior of cells and are often responsible for developmental disorders and various diseases (Lu et al., 2012).

ECMs components bind to cell surface receptors that are mainly transmembrane glycoproteins connecting them to cytoskeleton networks directly to actin or via cytoskeletal linkers. They provide links

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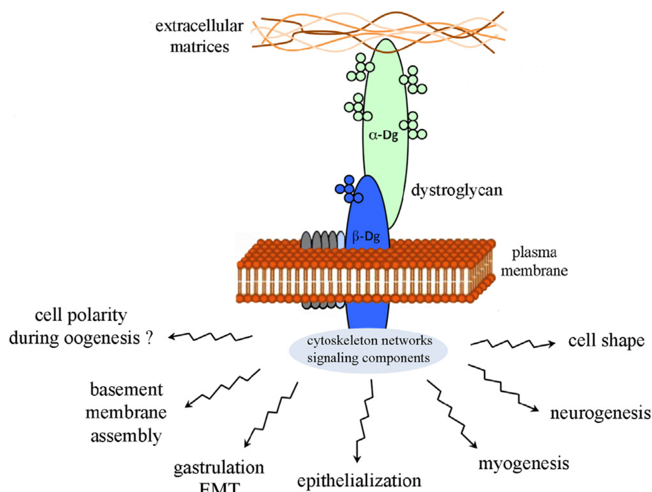

Fig. 1. The main functions of the dystroglycan adhesome during development. The components of extracellular matrices bind to α-Dg. This interaction results in the binding of the intracellular domain of β-Dg to cytoskeleton networks or signaling components. This consequently leads to several functions for the Dg adhesome according to species, tissues, organs and stages of embryonic development. EMT: epithelial-to-mesenchymal transition.

between ECMs and the underlying cytoskeleton leading to solid anchorages of cells, cytoskeletal rearrangements, co-regulations of growth factor activities and activations of signal transduction. They also provide direct or indirect controls of cellular activities such as adhesion, migration, differentiation, proliferation, and apoptosis. Furthermore, they are crucial for biochemical signals, which transit from the cell surface through the cytoplasm to the nucleus to activate or repress the transcription of genes. In turn, cells could modify and remodel ECMs by feedback-regulations and thereby control their extracellular environments. Although researches on the role of ECM receptors have been mainly focused on the α/β-heterodimeric transmembrane integrin proteins, the role of other receptors cannot be excluded as shown by more and more studies. It is in particular the case for the dystroglycan (Dg), a cell surface receptor for ECM components. For several years, various model organisms have been used to study ECM/Dg interactions in particular during adhesion processes. These include nematode worm, fruit fly, zebrafish, frog, chicken and mouse. They all contributed in various ways and significantly to our understanding of the functions of Dg as part of an adhesome during embryogenesis. This particular structure is a multi-molecular complex bringing together membrane receptors, adapter proteins, actin-associated proteins, kinases, phosphatases, G-proteins, Guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). An adhesome provides interactive interfaces between ECMs, cellular scaffoldings and signaling machineries (Geiger and Yamada, 2011).

In this review, we will describe the Dg structure and its ligands and focus on Dg adhesive functions during embryonic development using data provided by genetic experiments, gain or loss-of-function and mutations (Fig. 1). However, the Dg is also involved in other processes outside of embryonic development, which will not be discussed here, such as hematopoiesis, virus particle entry and cancers. The latter are apparently associated with a loss of Dg affecting both cell adhesion and migration (Sgambato and Brancaccio, 2005).

Dystroglycan discovery, characterization and ligands

In 1987, biochemical studies from brains of embryonic chickens had led to the identification of a laminin-binding protein with a molecular mass of 120 kDa, called cranin (or LBP120) (Smalheiser and Schwartz, 1987). Later, searches for membrane molecules associated with dystrophin, the cytoskeletal protein that is defective in Duchenne's muscular dystrophy, resulted in the discovery of a novel complex of glycoproteins, labeled as the "dystrophin-glycoprotein complex (DGC)" (Ervasti et al., 1990). Subsequent cloning of these molecules revealed the complex to consist of multiple transmembrane molecules. The Dg has been identified as a glycan component of the complex and surprisingly, amino acid sequencing of the purified cranin demonstrated that it was identical to the Dg (Gee et al., 1993). Other members of the DGC include transmembrane proteins, sarcoglycans and sarcospan (Fig. 2). This complex, in turn, interacts with multiple cytoplasmic proteins, including dystrobrevin, syntrophin, utrophin, the latter two linking to F-actin.

The Dg gene is highly conserved between invertebrates and vertebrates. Protein sequence comparisons reveal that the Dg is a structurally distinct molecule, which belongs to none of previously identified families of cell adhesion molecules. It lacks strong homology with other proteins, although some similarity has been noted with immunoglobulin and cadherin-like domains (De Rosa et al., 2011). The Dg is a large glycoprotein generated by the translation from a single transcript. The precursor protein is subject to extensive co- and post-translational modification including proteolysis and extensive glycosylation resulting in two subunits, α and β, that interact noncovalently (Ibraghimov-Beskrovnaya et al., 1992). Interestingly, the *Caenorhabditis elegans* Dg appears not to be processed into separate α and β subunits upon maturation (Johnson et al., 2006). Also, the *Drosophila* Dg is encoded by a single gene, exists in differentially expressed splice versions, that lack the mucin-like domain and seems not to be cleaved (Deng et al., 2003; Schneider and Baumgartner, 2008).

The α-Dg subunit possesses two globular regions separated by a serine-threonine-rich mucin domain. The globular domains include potential sites for N-glycosylation, and the mucin region includes multiple consensus sites for O-linked glycosylation. This glycosylation is species specific, developmentally regulated and tissue specific leading to molecular mass of α-Dg varying between 120 and 200 kDa. The pattern of glycosylation dictates the specificity of ligand binding. The glycosylations of α-Dg allow binding to its ligands in a calcium-dependent manner through their "laminin G-like" (LG) modules, a protein motif present in many ECM proteins. The α-Dg has a complex and still not fully characterized pattern of glycosylation in its central mucin-type domain that is crucial since aberrant glycosylation of α-Dg is linked to diseases named dystroglycanopathies and to tumors (Muntoni et al., 2011; Moore and Winder, 2012). The α-Dg is known to bind laminins, agrin, neurexins, perlecan, pikachurin and biglycan (Fig. 2A; for a review: Sciandra et al., 2013). The major extracellular ligands for the Dg are members of the laminin family, which are major constituents of ECMs (for a review: Aumailley, 2013).

The β-Dg has a single domain spanning the plasma membrane and an amino-terminal extracellular domain that binds to the carboxy-terminal globular domain of α-Dg. The transmembrane domain of the β-Dg subunit is known to interact with sarcoglycans (α, β, γ and δ) and sarcospan. Their function is not fully understood. They form a sarcoglycan–sarcospan subcomplex that stabilizes the α-Dg association with β-Dg at the cell surface (for a review: Marshall et al., 2013). The cytoplasmic tail of β-Dg interacts with the proteins dystrophin, utrophin, syntrophins and α-dystrobrevin, thereby to F-actin (for a review: Cohn and Campbell, 2000). By co-immunoprecipitation and gel overlay assays, the dystrophin containing the WW domain and two putative Ca^{++}-binding EF-hand motifs were shown to interact with the β-Dg cytoplasmic domain (Rentschler et al., 1999). Thus, the Dg-dystrophin and Dg-utrophin complexes form cell adhesion

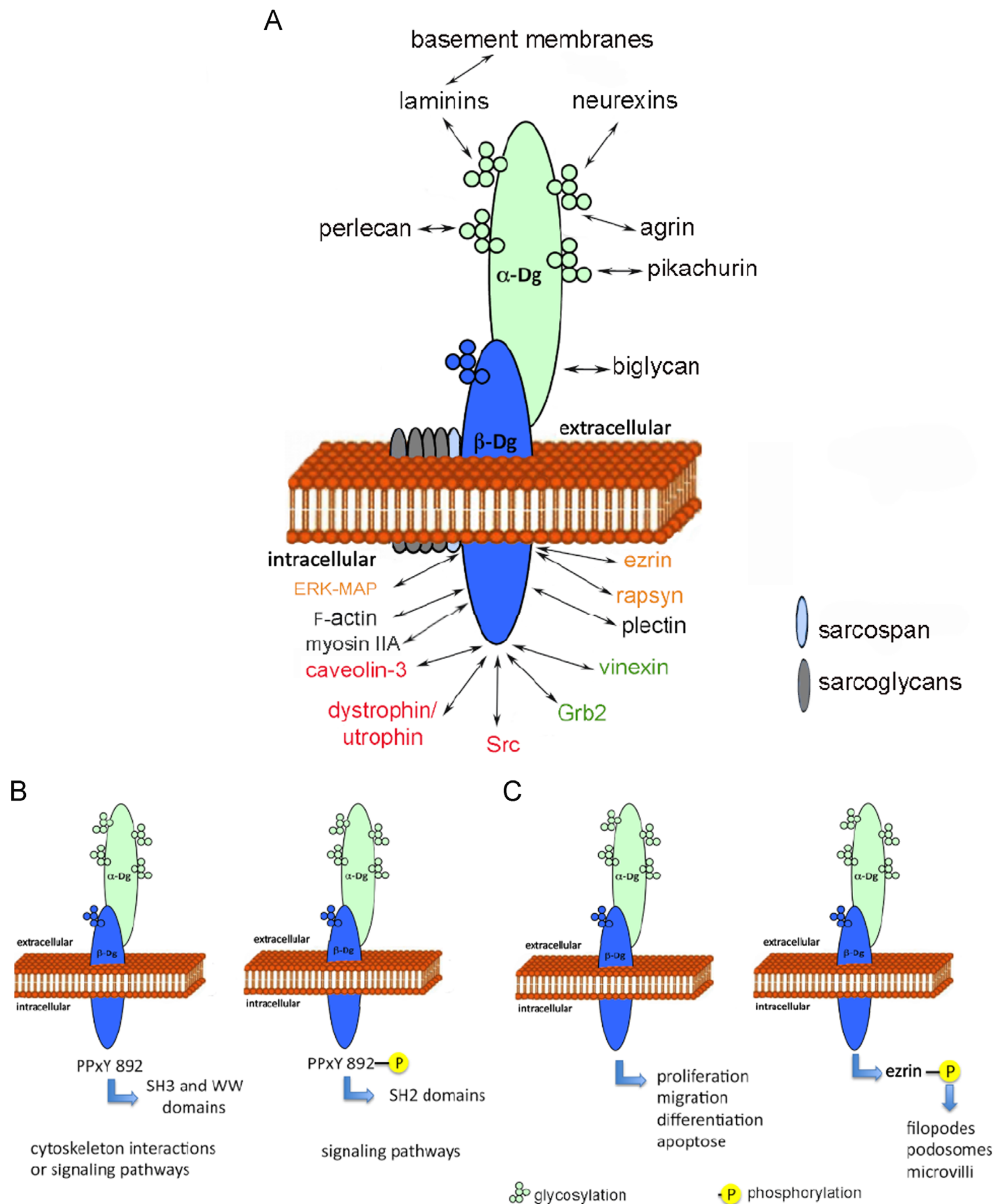

Fig. 2. The extracellular and intracellular binding partners of the dystroglycan. (A) Schematic representation of the organization of the α- and β-Dg at the cell membrane showing topology and major interactions. In the extracellular region, the α-Dg is able to interact with several ligands: laminins, perlecan, agrin, neurexins and pikachurin at the mucin-like domain, and biglycan in its C-terminal domain. The transmembrane region of β-Dg interacts with the transmembrane proteins sarcoglycans and sarcospan. The cytoplasmic domain of β-Dg binds to WW domains of cytoplasmic ligands by the PPxY sequence in the C-terminal domain. These ligands are shown in red. The C-terminal domain of β-Dg interacts with SH2/SH3 domains of proteins that are shown in green. The juxtamembrane cytoplasmic domain binds to proteins (shown in orange) by the RKKRK sequence. The β-Dg cytoplasmic domain also interacts with F-actin, myosin IIA and plectin (shown in black) in unknown sites. (B–C) The state of tyrosine phosphorylation regulates the dynamics of Dg. (B) The tyrosine residue 892 is part of PPxY motif that interacts with WW domains of dystrophin or utrophin or the SH3 domain of Grb2 protein (growth factor receptor-bound protein 2). This motif can be phosphorylated (P) by the tyrosine kinase c-Src. This phosphorylation allows interaction with the SH2 domain of Grb2, which prevents the interaction of Dg with the cytoskeleton. The phosphorylation of β-Dg helps to modulate its interactions with cytosolic proteins, functioning as a molecular switch between SH3, WW and SH2 domains, cytoskeletal *versus* signaling proteins. (C) The Dg is involved in various signaling pathways controlling cell proliferation, cell migration, differentiation and apoptosis. The Dg is also involved in cell shape. It is able to interact with ezrin and thereby controls the formation of filopodia, podosome or actin rich microvilli. (Adapted from Bozzi et al. (2009)).

structures that link ECMs to the F-actin cytoskeleton. *In vitro* studies have suggested that the β-Dg interacts with growth factor receptor bound protein 2 (Grb2), which is an adapter protein, composed of one Src homology 2 domain (SH2) surrounded by two Src homology 3 domains (SH3) (Yang et al., 1995). This association is mediated through β-Dg proline-rich domains and Grb2 SH3 domains.

ECM–Dg interactions induce phosphorylation of a tyrosine within the cytoplasmic domain of β-Dg, Tyr 892 in human and Tyr 890 in mouse. It was shown that the tyrosine kinase involved

Table 1
The dystroglycan and its associated proteins.

Dystroglycan	Ligands	Sites of interaction	Roles	References
	Agrin	O-mannosylglycan protruding from the mucin-like region	Aggregation of acetylcholine receptors on skeletal muscle fibers	Gee et al. (1994)
α-Dystroglycan	Biglycan	The protein core of the COOH-terminal third of α-dystroglycan	Muscle integrity, and synapse stability at the neuromuscular junction	Bowe et al. (2000)
	Laminins	O-mannosylglycan protruding from the mucin-like region	Connect laminin to actin	Ervasti and Campbell (1993)
	Neurexins	O-mannosylglycan protruding from the mucin-like region	Intercellular adhesion of brain cells	Sugita et al. (2001)
	Perlecan	Mucin-like region	Integrity of ECMs	Costell et al. (1999)
	Pikachurin	O-mannosylglycan protruding from the mucin-like region	Connection between retinal photoreceptors and bipolar cells	Sato et al. (2008)
β-Dystroglycan	Caveolin-3	Phosphorylated Y in the C-terminal WW domain binding motif: $PPxY^{892}$	Regulation of membrane cytoskeletal connections	Sotgia et al. (2000)
	Dystrophin/ utrophin	Non- phosphorylated Y in the C-terminal WW domain binding motif: $PPxY^{892}$	Regulation of membrane cytoskeletal connections	James et al. (2000)
	ERK-MAP	The juxtamembrane portion of the cytoplasmic domain	Signaling	Ferletta et al. (2003)
	Ezrin	The juxtamembrane portion of the cytoplasmic domain RKKRK	Regulation and organization of the actin cytoskeleton and cellular morphology.	Spence et al. (2004b)
	F-actin	Cytoplasmic tail	Organization of the actin cytoskeleton in fibroblasts	Chen et al. (2003)
	Grb2	The C-terminal SH3 binding domain: PxxP	Signal transduction and cytoskeleton organization	Yang et al. (1995)
	Myosin IIA	Cytoplasmic tail	Organization of the actin cytoskeleton in notochord cells	Buisson et al. (in preparation)
	Plectin	The C-terminal binding domain	Desmin intermediate filament anchorage at the sarcolemma	Rezniczek et al. (2007)
	Rapsyn	The juxtamembrane portion of the cytoplasmic domain RKKRK	Clustering acetylcholine receptors during neuromuscular synapse formation	Cartaud et al. (1998)
	Src family kinases	Phosphorylated Y in the C-terminal WW domain binding motif: $PPxY^{892}$	Regulation of podosome formation in myoblasts.	Thompson et al. (2008)
	Vinexin	The C-terminal SH3 binding domain: PxxP	Cell adhesion and spreading.	Thompson et al. (2010)

ERK: extracellular signal-regulated kinase; Grb2: growth factor receptor-bound protein 2.

in this phosphorylation is the SH2 domain containing protein c-Src (Sotgia et al., 2001). The Tyr 892 residue is part of the PPxY motif that interacts with the WW domain of dystrophin/utrophin or with the SH3 domain of Grb2. Once tyrosine is phosphorylated, the β-Dg is no longer able to interact with SH3 and WW domains leading to a loss of interaction with dystrophin/utrophin and thus with the cytoskeleton. In general, the phosphorylation of β-Dg helps to regulate its cytoplasmic interactions, functioning as a balance between interaction with SH3 or WW domains when the β-Dg is not phosphorylated, and with the SH2 domain when the β-Dg is phosphorylated (Fig. 2B).

The cytoplasmic domain of β-Dg was also found to interact with several components of the Extracellular signal-Regulated Kinase/Mitogen-Activated Protein Kinase (ERK-MAP) cascade and indirectly with the Focal-Adhesion Kinase (FAK) (Yang et al., 1995; Spence et al., 2004a). The cytoplasmic domain of β-Dg also binds to different ligands according to species, stages of development, tissues and organs. It interacts with caveolin-3, a muscle-integral membrane protein of the sarcolemma; with rapsyn, a protein located at the post-synaptic membrane in neuromuscular junctions; with dynamin, a GTPase implicated in endocytosis. It also interacts with plectin, a widely expressed cytolinker protein at Z-disks and the sarcolemma, where it acts as a mediator of desmin intermediate filament anchorage (Sotgia et al., 2000; Bartoli et al., 2001; Zhan et al., 2005; Rezniczek et al., 2007). Finally, the Dg binds to the cytoskeletal adapter protein ezrin (Fig. 2C; Spence et al., 2004b) and forms a complex with a Rho-specific guanine nucleotide exchange factor (Dbl). The complex is targeted to the membrane by the Dg where it drives the local activation of the cell division control protein 42 (Cdc42) and the formation of filopodia (Batchelor et al., 2007).

Thus, all these data suggest that the glycosylation of α-Dg is crucial for its link to laminin and that the phosphorylation of β-Dg on tyrosine regulates its association with intracellular binding partners. These interactions between ECM components, the Dg and cytoplasmic proteins (Table 1) may be of biological importance in transducing signals arising from the binding of Dg to ECM proteins or in transferring information between the Dg complex and several signaling pathways that control mechanisms of adhesion during embryonic development.

Dystroglycan expression

In humans, Dg transcripts were detected in cardiac and skeletal muscles, brain, kidney, liver, lung, diaphragm, placenta, pancreas and stomach (Ibraghimov-Beskrovnaya et al., 1992). The highest level of expression is in heart and skeletal muscles. In adult mice, the Dg exhibits essentially the same expression profile, *i.e.* in skeletal muscles, gastrointestinal tract (salivary glands, pancreas, intestine, liver), trachea, kidney, mammary gland, testis and the uterus (Durbeej et al., 1998). In early mouse development (E5-E6), transcripts are detected in cells around the Reichert's membrane, which is a thick basement membrane between the parietal endoderm and the trophectoderm (Williamson et al., 1997). Later during development, the protein expression correlates with basement membranes of notochord, neural tube, myotomes, myocardium, spinal cord, lung buds, sex cords, promesonephros, mesonephric duct and tubules (Anderson et al., 2007). In *Xenopus laevis*, Dg-maternal mRNAs are detected from the 4-cell stage. Then, they are detected throughout the development of embryos in different tissues. The protein is present in notochord cells and

remains expressed throughout its differentiation processes. It is also present in cells of hypochord, brain, otic vesicles, eyes, visceral arches, somites, pronephros and pronephric canal, skin and heart (Lunardi and Dente, 2002; Moreau et al., 2003). In *Danio rerio*, Dg-maternal mRNAs are detected at the 128-cell stage, before the onset of zygotic transcription and ubiquitously expressed throughout gastrulation. By the tailbud stage, transcripts are present in adaxial cells, the developing neural tube, throughout the paraxial mesoderm, in the notochord and hypochord (Parsons et al., 2002). During *Drosophila* development, the Dg is expressed in oocytes, at the basal side of follicular epithelium, in imaginal discs of wings, on muscle, glia, neurons and also on the apical surface of photoreceptor cells (Schneider et al., 2006). In *Caenorhabditis elegans*, the Dg is not expressed in muscle but in gonads, epithelial cells and neurons (Johnson et al., 2006).

The ubiquitous expression of Dg in all these species and in a variety of cell types from early development to adulthood indicates that it might have critical roles in a variety of processes essential to organ formation and where cell adhesions with ECMs are required.

Dystroglycan promotes cell polarity during oogenesis

During *Drosophila melanogaster* oogenesis, the establishment of the anteroposterior polarity in oocyte is essential for the establishment of the anteroposterior axis of the future embryo. This process involves cytoskeletal rearrangements that translocate the microtubule-organizing center from the anterior region of early oocyte to the posterior region of developing oocyte (for a review: Riechmann and Ephrussi, 2001). Then, following a signal from posterior follicle cells, the posterior microtubule-organizing center disappears and a new one forms in the anterior pole of oocyte. Clonal analyses of homozygous *Dg* mutation in the germline show the lack of actin enrichment at the oocyte cortex and the lack of displacement of the microtubule organizing center to the posterior region of oocyte. This results in the loss of the early polarization of oocyte (Deng et al., 2003).

The Dg function has also been investigated in the ovarian follicular epithelium. This epithelium renews constantly from two somatic stem cells per ovariole. These stem cells give rise to follicle cells that proliferate and form through a mesenchymal–epithelial transition a columnar epithelium over the growing oocyte. In the epithelium, follicle cells are in contact with a basement membrane and with germline cells leading to distinct basal, apical and lateral cell-membrane domains. Each domain accumulates specific protein complexes that are actively involved in the cell-membrane polarity. The Dg is localized at basal-cellular domains of plasma membranes, where it interacts with perlecan, a large multidomain heparan sulfate proteoglycan of the ECMs. The Dg function in follicle cells has been studied with lethal *Dg* alleles that have been generated by the excision of a P-element inserted into the first non-coding exon of *Dg* to produce deletions around the Dg promoter (Deng et al., 2003). Inactivation of the gene encoding Dg causes loss of lateral cell markers and an expansion of apical markers to the basal pole of follicle cells. Overexpression of Dg results in a reduced apical localization of these markers. Mutant cells lose their epithelial shape, form multiple layers and often die (Deng et al., 2003). Interestingly, clonal analyses of Dg mutant follicle cells, which allow comparing wild-type and mutant cells in the same tissue, show an abnormal orientation of basal actin fibers in adjacent non-mutant follicle cells as well as disruption of its laminin network. Basal-actin fibers lose their orientation at a direction perpendicular to the anteroposterior axis of the egg chamber. This suggests that the Dg has a non-cell-autonomous effect on the planar polarity of the basal actin in follicle cells that is to say that the Dg directs the orientation of laminin networks that transmit information into a neighboring cell to coordinate the orientation of actin fibers (Deng et al., 2003). Interestingly, when follicle cells lack perlecan, they develop polarity defects similar to those of Dg mutant cells (Schneider et al., 2006). These data suggest that the perlecan and the Dg provide a basal 'polarizing cue' required for differentiation of basal membranes and maintenance of epithelial cell polarity in follicle cells (Schneider et al., 2006). Therefore, it has been proposed that the binding of perlecan to the Dg, stabilizes the Dg in basal membranes and that the Dg is required for stabilizing specific protein complexes at lateral membranes, which in turn prevents apical components from invading basolateral-membrane domains (Schneider et al., 2006). Today, these conclusions seem to be questioned as a result of the discovery of Dg nonsense mutations that are homozygous viable and fertile (Christoforou et al., 2008). The effects of these null mutations on cell polarity in the ovary have been studied (Mirouse et al., 2009). They show that apical, lateral, and basal plasma membrane domains of follicle cells form normally but cells lose the planar polarity of their basal actin stress fibers. The oocyte grows in all directions and exhibits a short, round-egg phenotype (Mirouse et al., 2009).

The differences in results provided by these studies could be explained by the fact that studies of Deng et al. (2003) use deletions in the Dg locus that also remove the *mRpL34* gene that encodes a mitochondrial ribosomal protein (*mRpL34* gene), whereas studies of Mirouse et al. (2009) use null alleles of Dg. It is interesting to note that phenotypes obtained by *Dg*-deletion alleles can be rescued by transgenes expressing either mRpL34 or Dg proteins suggesting that the loss of both genes causes polarity defects (Mirouse et al., 2009). This also suggests that the energetic stress caused by disruption of mRpL34 can explain by itself the epithelial polarity phenotypes of *Dg*-deletion alleles. Surprisingly, an identical polarity phenotype, to those observed for *Dg*-deletion alleles, is obtained when flies carrying nonsense alleles of *Dg* are cultured on food without glucose (Mirouse et al., 2009). Thus, it has been proposed that the polarity phenotype observed, under normal conditions with *Dg*-deletion alleles, results from the loss of mRpL34 proteins that disrupts mitochondrial function leading to reduce cellular energy. Consequently, the Dg seems to be required for follicle-cell polarity only under conditions of energetic stress (Mirouse et al., 2009). Furthermore, it has been shown that a null mutant of the *Drosophila* homolog of dystrophin has no consequence on follicle cell epithelialisation under low-energy conditions, that the Dg that lacks the SH3-binding domain disrupts follicle-cell polarity and that the Dg with a mutated dystrophin-binding site does not (Deng et al., 2003; Yatsenko et al., 2007). Thus, from all these data, it seems likely that interaction between the Dg and its ligand perlecan controls epithelial polarity under low-energy conditions by signaling through the SH3-binding domain. These results should be interpreted with caution because Haack et al. (2013) have nicely showed that the phenotype of Dg mutants resulted of an artefact due to the increased damage caused by dissecting ovaries of starved flies. They suggest that the Dg is not required for apical–basal polarity under starvation conditions in the follicle-cell epithelium. Further investigations will be required to understand the exact molecular mechanisms underlying the role of Dg in germline and follicle-cell polarization due to the signaling cascade it activates in these processes.

Dystroglycan promotes basement membrane assembly in early development

During early development, basement membranes appear generally beneath cells that secrete their components, but in some

cases, they are assembled on cell surfaces that do not synthetize basement membrane proteins. These two points argue that assembly of proteins in basement membranes might be mediated by cell-surface receptors. As Dg is a receptor of laminins, a main component of basement membranes, efforts have been devoted to determine if it initiates and promotes the matrix assembly.

In 1997, the knockout of Dg in mice showed that the Dg depletion is lethal for mice embryos, which die at embryonic day 6.5 because of the disorganization of Reichert's membrane, a specialized basement membrane appearing around the implantation of embryos that lies between parietal endoderm and trophoblast cells (Williamson et al., 1997). The Dg depletion causes a patchy distribution of laminin and collagen instead of a continuous layer, in addition embryos showed gastrulation and mesoderm defects. The authors have concluded that the Dg may be necessary for the assembly of ECM proteins that comprise Reichert's membrane. Interestingly, mouse embryos that lack the laminin γ1 chain did not survive beyond day 5.5. Basement membranes did not develop and primitive endoderm cells remained in the inner cell mass (Smyth et al., 1999). On the other hand, crucial events of the basement membrane formation during early gastrulation in mice can be recapitulated using embryoid bodies (EBs). EBs arise from suspended aggregates of mouse embryonic stem cells. Following two days of culture, EBs provide an *in vitro* model of blastocyst development in which the inner cell mass differentiates to form visceral endoderm, basement membrane, polarized epiblast and proamniotic-like cavity. The endoderm synthesizes and secretes laminins and most of the type IV collagen. The basement membrane in turn is required for polarization of the epiblast and cavitation. In 1998, using the strategy of Dg-null EBs, it was demonstrated that the Dg is crucial to bind soluble laminins, to organize it at cell surfaces which constitutes the initial step in the formation of a basement membrane (Henry and Campbell, 1998). Later, it has been shown that EBs, formed from laminin-null or integrin-null embryonic stem cells, were unable to form a basement membrane, to convert the inner cell mass into polarized epiblast and to form a proamniotic cavity (Li et al., 2002). Conversely, when the Dg lacks in EBs, a basement membrane forms followed by epiblast differentiation and cavitation. This result is corroborated by a study on zebrafish embryos using antisense-morpholino oligonucleotides to inhibit the expression of Dg (Parsons et al., 2002). The loss of Dg expression is not lethal and laminin-matrix assembly is not affected during early development suggesting that the Dg is dispensable for basement membrane formation.

Other studies performed *in vitro* have implicated the Dg in basement membrane assembly. In cultures of muscle cells derived from Xenopus embryos, clusters of Dg are induced by laminin–laminin binding (Cohen et al., 1997). In cultures of C2C12 myoblasts, the COOH-terminal long arm of laminin mediates receptor binding that facilitates interactions between the three NH_2-terminal short arms leading to the basement membrane assembly (Colognato et al., 1999). Also, the binding of the α-Dg subunit to laminin is a crucial step in the formation of laminin matrices of embryonic-stem cells, in deposition of laminin on the surface of Schwann cells, and in polymerization of laminin in mammary epithelial cells (Tsiper and Yurchenco, 2002; Weir et al., 2006). Interestingly, *in vitro* molecular genetic analyses in mammary epithelial cells and *in vivo* in Xenopus kidney, skin and notochord have demonstrated that the Dg can mediate laminin deposition (Weir et al., 2006; Bello et al., 2008; Sirour et al., 2011; Buisson et al., in preparation).

Both the genetic and the EBs data reveal that the Dg is not generally essential for basement membrane assembly and that its genetic loss does not result in the disruption of most basement membranes. Thus, it is conceivable that the involvement of Dg in the formation of basement membranes may vary depending on species, cell types, embryonic regions and/or states of embryonic development. Early in development, the Dg is required for the formation of the extra-embryonic basement membrane (Reichert's membrane) but not for the embryonic basement membrane adjacent to epiblast later in development. It is conceivable that deposition and/or formation of laminin matrices is regulated by synergistic function of Dg, integrins and syndecans, and that other matrix components stabilize laminin incorporation into ECMs. It is also conceivable that differences between early and late requirements for Dg in basement-membrane formation may be explained by the action of other laminin receptors differentially expressed in the space, time and tissues during embryonic development. However, most data support a model whereby the Dg ensures the initial binding of laminin to cell surfaces, whereas integrins and perlecan are required for the assembly of laminin into matrices after its binding to cells. Thus, the Dg plays a key role in nucleating the assembly of a primary laminin matrix, which then will serve as scaffolding for the assembly of other components of embryonic-basal membranes. Following matrix assembly on the cell surface, the laminin/Dg interaction is required to promote cell adhesion mechanisms involved later during development.

Gastrulation requires the disengagement of the dystroglycan adhesome

In birds and mammals, at the level of the primitive streak, a transient embryonic structure where gastrulation takes place, the epithelial-to-mesenchymal transition (EMT) generates the mesoderm layer. EMT is a multistep process in which cells change their epithelial shape to adopt an invasive-mesenchymal phenotype. It includes local loss of cell polarity, tight junctions, disruption of ECM, which favours the ingression of cells. Using gastrulation of chick embryos as a model of EMT, it has been shown that integrins and the Dg are two major groups of basal membrane proteins involved in epiblast-cell adhesion to ECMs. The Dg gene expression is restricted to the epiblast during early development and the protein is localized to basolateral membranes (Nakaya et al., 2011). In epiblast cells, the Dg mediates adhesive links between intracellular-cortical microtubules and ECMs, by interaction of its β-subunit with the cortical CLIP-associated protein (CLASP), a microtubule plus-end tracking protein (Nakaya et al., 2013). The adhesome ECM/Dg/CLASP/microtubules maintains interactions between epiblast cells and ECMs, thereby their polarity. The disruption of microtubules and the expression of CLASP mutants lead to the loss of Dg at cell surfaces in front of the ECM and of epiblast-cell adhesion to the ECM. It was shown that the removal of Dg from the complex promotes ECM breakdown and thus cells are able to initiate their EMT (Nakaya et al., 2013). These data suggest that the disengagement of this complex promotes ECM breakdown, thereby promoting the loss of adhesion to the matrix and therefore the ingression of cells during gastrulation. They also suggest that the stability of the adhesome ECM/Dg/CLASP/microtubules promotes cell adhesion to ECMs and cell epithelialization.

Dystroglycan controls cell epithelialization

During morphogenesis, epithelia undergo rearrangements in response to extracellular signals. This requires the coordinated regulation of cell–cell and cell–matrix adhesion. This last broadly relies on integrin-mediated cell-matrix adhesion on the basal side of cells. However, there are more and more data to suggest the involvement of Dg in these processes. In mouse, the Dg is enriched

towards the basal side of epithelial cells that are in close contact with ECM in developing and adult tissues, such as kidney, liver, intestine, trachea, salivary gland and skin (Ibraghimov-Beskrovnaya et al., 1993; Durbeej et al., 1998). Most studies, to address its role, were performed *in vitro* using organotypic cultures and blocking antibodies against the Dg or laminins. They suggest a key role of Dg in promoting the cell adhesion for epithelialization, survival and differentiation of many tissues. It is necessary for the cell adhesion during branching of tubular epithelia as lung, and salivary glands (Streuli, 1999). Also, it is required for the cell adhesion leading to the differentiation of mammary gland cells, pancreas β-cells, thymocytes and oligodendrocytes (Jiang et al., 2001; Galvin et al., 2010; Liou et al., 2010).

In the skin of *Xenopus laevis*, the Dg is expressed in the more internal sensorial layer. *In vivo*, morpholino knockdowns of Dg affect cell–cell adhesion, as shown by the reduction of E-cadherin expression at intercellular contacts. The depletion of Dg also affects the laminin deposition, the ECM organization and the intercalation of multiciliated cells suggesting a non-autonomous role in skin epithelialization (Sirour et al., 2011).

The notochord, a tubular epithelial tissue, develops from the mesoderm during gastrulation in the midline of embryos. Its formation required the segregation from paraxial-mesodermal cells, the mediolateral intercalation of cells, the secretion of an ECM and the differentiation of a vacuole. Interestingly, the Dg expression in notochord is dynamic during early development, to the end of gastrulation and during neurulation (Moreau et al., 2003). This expression coincides with the segregation and anteroposterior differentiation of the notochord. Dg-depleted cells are properly specified, exhibit defects in ECM formation, intercellular adhesion and cell polarity, leading to defects in morphogenesis and differentiation. Data show that the Dg is required for the notochord ECM assembly, the notochord-cell recruitment within the tissue and the mediolateral-cell intercalation. Moreover, myosin IIA was identified as a new Dg ligand in notochord cells. In particular, the laminin-Dg-myosin IIA adhesome is involved in maintaining cytoskeleton integrity and polarity during the differentiation of cells, *i.e.* the formation of vacuoles (Buisson et al., in preparation).

Dystroglycan as an adhesion receptor during myogenesis

In human, the importance of Dg for adult muscle function is well established, in particular due to severe phenotypes of muscular dystrophies (Carmignac and Durbeej, 2012). Muscular dystrophies comprise a heterogeneous group of disorders that produce progressive skeletal muscle weakness and wasting in patients with mutations disrupting the adhesion of muscle cells to ECMs. The Dg is a component of the dystrophin-glycoprotein complex in muscle, where it constitutes a key element to anchor the ECM to intracellular actin filaments. The lack or mutation of one or more components of this complex results in debilitating muscular and neuromuscular diseases (Barresi and Campbell, 2006). The Dg thus ensures the structural stability of the muscle cell membrane, thereby protecting muscle cells against membrane damage induced by muscle contractions and relaxations. While the role of Dg is well established in adult muscles, it remains poorly understood in early muscle development.

In mouse embryos, the Dg is expressed in somites during their differentiation. It colocalizes with components of ECMs around somites (Anderson et al., 2007). During the segregation of myotomes, the Dg is uniformly distributed at the surface of myotomal cells that express Myf5, a transcription factor of the family of Myogenic Regulatory Factors (MRF), as well as in migratory myoblasts (Anderson et al., 2007). Consequently, the Dg could play a role in myoblast adhesion and migration. However, this possibility is difficult to analyze during myogenesis because of the early embryonic lethality of mice lacking the Dg (Williamson et al., 1997). Furthermore, in chimeric mice with Dg deficiency in skeletal muscles, or in mice with a knockout of Dg in myoblasts, both adhesion and migration seem to be unaffected during early development. Also, the deposition of laminin and the formation of basement membranes appear unaffected in muscles (Cohn et al., 2002; Côté et al., 1999). The latter reinforces the view that the Dg is necessary for some but not all basement membrane formation during embryonic development.

Interestingly, *in vitro*, it has been demonstrated that the Dg is a component of myoblast podosome, an actin-rich structure surrounded by adhesion and scaffolding proteins (Thompson et al., 2008). By immunoprecipitation, GST-pulldown and immunofluorescence, a complex comprising Dg, Src and Tks5 has been identified in podosomes. The adapter protein Tks5 is a scaffolding protein containing five SH3 domains known to be required for podosome formation. The Dg overexpression and mutation of the Dg tyrosine 890 (tyrosine 892 in human) led to propose that Src-dependent phosphorylation of Dg results in the formation of a Dg/Src complex that drives the interaction between the Dg and Tks5. In turn, this complex regulates the podosome formation in myoblasts (Thompson et al., 2008). Furthermore, decreasing levels of Dg by RNAi knockdown increased myoblast adhesion and spreading on fibronectin substrates, whereas overexpressing Dg reduced adhesion and spreading (Thompson et al., 2010). Thus, it seems that the ECM/Dg/Src/Tks5 adhesome actively regulates myoblast behaviors. It remains to show whether or not this is the same in adhesion and migration mechanisms that govern myogenesis *in vivo*. A possible answer comes from studies in Xenopus.

In Xenopus embryos, the Dg is expressed at the border between somites and the notochord, as well as at intersomitic junctions. The Dg depletion by morpholinos or overexpression of a Dg deleted of its cytoplasmic domain has highlighted its fundamental role during somitogenesis (Hidalgo et al., 2009). In these contexts, the Dg disruption results in normal segmentation of the presomitic mesoderm but affects the number, the size, and the integrity of somites. The adhesion of myoblasts to ECMs, required for their alignment in somites, is also affected without disrupting the expression of differentiation markers MyoD and MRF4. Thus, the results show that laminin/Dg interactions are necessary for myoblast adhesion required to form myotome fibers in parallel alignment with the notochord. In zebrafish, the knockdown of Dg by antisense morpholinos leads to disorganized muscles and apoptotic as well as necrotic cells (Parsons et al., 2002). In a forward genetic approach, a zebrafish mutant (*patchytail*) has been identified (Gupta et al., 2011). It corresponds to a point mutation identified in the Dg gene that results in a missense amino acid change of valine to aspartic acid. This change is present in the C-terminal domain of α-Dg leading to reduce transcripts and to the complete absence of Dg. Mutants show that the Dg is dispensable for the basement-membrane formation during early zebrafish development. At later stages, however, the loss of Dg leads to impaired locomotion and dystrophic muscles due to extensive tearing of ECMs at the myosepta, thus destabilizing myofiber attachments at somite boundaries. These data suggest that the zebrafish-Dg adhesome seems to be required for long-term survival of muscle cells, but is dispensable for muscle formation during early embryonic development (Gupta et al., 2011). Again, this suggests that the Dg-adhesome function may be species and tissue specific.

The Dg is also important for the development and function of myotendinous junctions (MTJs). MTJs are highly specialized and architecturally complex structures at the interface between muscle

and tendon. The development of MTJs is a complex process involving cell–ECM interactions as well as cell–cell interactions between muscle and tendon. An important first step is the deposition of a basement membrane at the interface between tendon and muscle cells. Much of our knowledge of this process comes from studies in *Drosophila*. In this model, tendon cells connect muscle cells to the chitinous exoskeleton and are similar to tendon cells that link muscles of vertebrates to bone. At the interface between tendon and muscle cells, precise spatiotemporal expressions of Dg are required for the MTJ formation. At earlier stages, the Dg is first uniformly present at epidermal cell surfaces then according to a striped pattern. It is excluded from epidermal cells that will give rise to tendon cells. Then, the Dg is enriched at the termini of growing muscles facing the tendon matrix emphasizing its role as an adhesive molecule (Schneider and Baumgartner, 2008). When the Dg is abnormally expressed in tendon cells, the composition of the tendon matrix is affected, resulting in aberrant muscle attachments and embryonic death (Yatsenko and Shcherbata, 2014). Interestingly, the dynamic expression of Dg is posttranscriptionally regulated by miRNA. Both the miRNA (miR-9a) and the Dg have expression patterns that are mutually exclusive. The Dg is present in ectodermal cells, while tendon cells express the miR-9a (Yatsenko and Shcherbata, 2014). Upon miR-9a deficiency, the Dg is detected not only in muscles but also on the membrane of tendon cells. This expression of Dg in tendon results in alteration of contacts between muscle and tendon cells and disorganization of musculature assembly (Yatsenko and Shcherbata, 2014). These data suggest that the Dg adhesome is required at the MTJ and that the miR-9a acts as a factor that regulates the expression of Dg in tendon cells, and thereby the function of the adhesome.

The functions of dystroglycan during neurogenesis

In mouse, the Dg is expressed in the floor plate of the neural tube and in cells facing the basement membrane delineating the neuroepithelium of forebrain and hindbrain. It is also expressed at the level of spinal cord, otic and optic vesicles. Interestingly, the Dg is also found in motoneuron axons suggesting that it plays a role in cell adhesions required for the axonal guidance and growth (Anderson et al., 2007). This hypothesis is consistent with work done in *Caenorhabditis elegans*, where a mutation in the gene, which leads to depletion of Dg, causes defects in guiding the growth of neurons (Johnson et al., 2006). It is also consistent with new findings on the developing nervous system of mice and in particular on the axonal guidance that requires precise patterning of guidance cues (Wright et al., 2012). These cues include members of the Slit, Netrin, Semaphorin, and Ephrin families of ligands. They function as attractants or repellants by binding to cell-surface receptors that transduce guidance informations through signaling cascades that reorganize the cytoskeleton within growth cones of axons (for a review, Vitriol and Zheng, 2012). Mice, in which the Dg was deleted from the epiblast to circumvent the early embryonic lethality, have been generated (Wright et al., 2012). Using this model, it was found that the Dg is required for the development of major axonal tracts that grow along basement membranes of spinal cord ventrolateral funiculus, dorsal funiculus, and descending hindbrain projections. It was also found that the Dg binds directly to the laminin G domain of Slit leading to organize its distribution in both the basement membrane and the floor plate of spinal cord *in vivo* (Wright et al., 2012). Therefore, it can be proposed that Dg functions in an adhesome that controls axon guidance by organizing the availability of axonal tracts and guidance cues.

During mouse brain development, the precise synapse formation is crucial for the central nervous system to function normally. It requires the precise adhesion, migration and targeting of axons, the apposition of presynaptic and postsynaptic termini and finally the proper differentiation and maturation of neurons and synaptic termini. The Dg was found in neurons of the cerebral cortex, hippocampus, olfactory bulb, basal ganglia, thalamus, hypothalamus, brainstem and cerebellum. Electron microscopy revealed that the Dg was preferentially associated with postsynaptic specializations. The Dg was also detected in astrocytes around vessels, in those facing the pia mater and in endothelial cells at the blood–brain barrier (Zaccaria et al., 2001). Laminin, agrin, and perlecan are not abundant in brain except in the perivascular space in contact with astrocytes but not with neurons. The Dg has been identified as a receptor for neurexins, specific proteins of the neuron-specific cell surface proteins (Sugita et al., 2001).

The works of Anderson et al. (2007) have demonstrated the expression of Dg in the brain neuroepithelium of embryos at the level of cell contacts with the basal lamina surrounding optic vesicles and neural tube. The depletion of Dg specifically in the central nervous system of mice with the Cre-loxP system, results in brain malformations similar to human syndromes associated with defects such as dystrophy syndromes (Moore et al., 2002). The Dg-null brain phenotypes include a fusion of left and right hemispheres and cerebellar folia, a training defect of the different cortical layers and aberrant migration of granule cells (Moore et al., 2002). The brain-specific knockout of Dg shows discontinuities in the pial surface basal lamina (glia limitans) and cortical neuron migration defects (Moore et al., 2002; Michele and Campbell, 2003). Moreover, the brain-specific deletion of Dg shows distinct functions for neuronal and glial Dg. Neuronal Dg plays a role in synaptic plasticity and glial Dg is involved in adhesion processes during forebrain development. Specific differences in the Dg glycosylation in these cells may modulate the diversity of its ligands and binding affinities leading to the diversity of Dg adhesive functions in the brain (Satz et al., 2010). All these studies show that the Dg has an important role in the formation of the central nervous system and especially on cell adhesion required for growth and guidance of neurons during embryonic development.

The vertebrate retina is part of the central nervous system. In retina, photoreceptors form specialized synapses with bipolar and horizontal cells, the ribbon synapse. In mouse, a novel protein of the retinal ECM, pikachurin, has been identified, and observed in the synaptic cleft of the ribbon synapse (Sato et al., 2008). The pikachurin is expressed in photoreceptors of the neuroblast layer at mouse embryonic day 14.5, which corresponds to early cone and rod development. In the adult retina, the pikachurin is restricted to the synaptic cleft of the ribbon synapse, near the postsynaptic termini of bipolar cells and colocalized with both the dystrophin and Dg. The pikachurin contains domains similar to the laminin G-like domains known to interact with Dg. Immunohistochemistry and pull-down assay have established that the pikachurin is a novel ligand of α-Dg (Sato et al., 2008; Kanagawa et al., 2010). In order to investigate its biological functions, a pikachurin-knockout mouse was generated. Whereas dendrites of horizontal cells in the ribbon synapses were normal, dendrites of both rod and cone photoreceptors were absent in these mice affecting synaptic signal transmission and both the timing and the amplitude of the bipolar cell response to scotopic and photopic conditions (Sato et al., 2008). The authors propose that interactions between dystrophin and pikachurin–Dg complex regulate the adhesion required for apposition of bipolar cell dendritic tips to the photoreceptor ribbon synapses by inducing a structural change in the photoreceptor terminus or by attracting the postsynaptic terminus through an unknown factor. More recently, using retinal

photoreceptor-specific Dg knockout in mice, it was found that the loss of Dg prevents the pikachurin accumulation on tips of photoreceptor synapses. Furthermore, the overexpression of pikachurin in cell cultures (HEK293 cells) induces the clustering of α-Dg–pikachurin complex on the cell surface. These data suggest that the pikachurin is required for the presynaptic accumulation of Dg on the photoreceptor synaptic surface of retina, and conversely that the Dg is required for pikachurin accumulation. They also suggest that interactions of pikachurin with the Dg at photoreceptor cell surfaces are required for the formation of proper photoreceptor ribbon synaptic structures (Omori et al., 2012). It will be of interest now to determine whether the binding between pikachurin and Dg is required for the pikachurin function and to determine mechanisms by which the pikachurin regulates the apposition of bipolar cell dendritic tips to photoreceptor-ribbon synapses. This will provide clues to understand adhesive interactions between ECM and Dg that are required for the formation and function of synaptic structures underlying the retinal abnormalities observed in muscular dystrophy patients.

In avian and Xenopus retina, the Dg protein is detectable on lens vesicle, vitreal border of retina in the endfeet of neuroepithelial progenitors and on cells fated to form the pigmented epithelial layer. In Xenopus, morpholino-mediated loss of Dg function causes the disruption of basal lamina layers and increases apoptosis at early stages. Later in development, it display ocular malformations, such as microphtalmia and retinal delayering with photoreceptors and ganglion cells scattered throughout the retina or aggregated in rosette-like structures (Lunardi et al., 2006). In Dg-deficient Zebrafish embryos, cells within ganglion cell layers are loosely packed with gaps therebetween. Also, the lens contains cells with several inclusion bodies and the cornea is absent (Gupta et al., 2011).

In the adult *Drosophila* brain, the Dg is detected in the medulla and lamina. The Dg is also present in the retina. In the larval brain, the Dg is expressed in neurons and glial cells. A high level of Dg is detected in axons of photoreceptor sensory neurons, in the optic stalk, and in glial cells in optic lobes (Shcherbata et al., 2007). The overexpression of Dg in photoreceptors results in a small but significant increase in their size. Genetic and RNAi-induced perturbations of Dg cause abortive photoreceptor elongation during differentiation that results in stunted photoreceptors in the adult. The Dg does not affect neuronal commitment but is necessary to regulate neuronal adhesion required for proper photoreceptor axon adhesion and migration during differentiation (Shcherbata et al., 2007; Zhan et al., 2010).

Together, these data show that Dg–ligand interactions are required for the integrity of basement membranes in the brain, cornea and retina and that disruption of this function results in abnormal cell adhesion required for the proper embryonic development of these tissues. They also show that the Dg is nestled in an adhesome required for cell adhesion mechanisms leading to neuroblast migration, axon guidance and ribbon synapse formation.

Dystroglycan in cell signaling and shape

In addition to the above crucial roles at the plasma membrane, the Dg also functions as a signal-transducing molecule. The α-Dg receives inputs from extracellular laminins or other LG domain containing ligands, which are transduced via the β-Dg to generate signals inside cells. *In vitro*, cellular adhesion to fibronectin, agrin or laminin was shown to trigger the phosphorylation of the tyrosine residue (Y892) within the β-Dg cytoplasmic domain that is one of the residues involved in interactions with the WW domain of dystrophin or utrophin (Sotgia et al., 2003). This tyrosine is also involved in the binding of the SH3 domain of Grb2, an adapter protein involved in signal transduction and cytoskeleton organization, both in skeletal muscle and brain (Moore and Winder, 2010). In bovine brain synaptosomes, the β-Dg binds the FAK through the SH2 domain of Grb2 (Cavaldesi et al., 1999). As a general mechanism, the phosphorylation of β-Dg might modulate its interaction with dystrophin or utrophin, functioning as a molecular switch between WW or SH3, and SH2 domains. The Dg was also thought to modulate the Mitogen-activated-protein-kinase-Kinase/Extracellular signal-Regulated Kinases (MEK/ERK) pathway according to two mechanisms. First, α-Dg competes with α6β1 integrins for the binding with laminin, reducing the ERK activity (Ferletta et al., 2003). Second, the Dg sequesters specific components of the signaling cascade and thereby limits their activity to define cellular compartment. Then, in Cos-7 cells, the β-Dg interacts with MEK within membrane ruffles, capturing it and preventing the phosphorylation of ERK catalyzed by MEK (Spence et al., 2004a, 2004b). It has been also shown that blocking the interaction of α-Dg with laminins results in an increased activity of caspase-3, a known hallmark of apoptosis, and an inhibition of the PI3K/Akt signaling pathway that promotes cell survival (Datta et al., 1999).

An outside-in signaling is also highlighted in Xenopus pronephros, skin and notochord because the deletion of the Dg-cytoplasmic domain does not prevent interactions between laminin and cells that express the mutant protein, but abolishes the downstream morphogenesis of these tissues (Bello et al., 2008; Sirour et al., 2011; Buisson et al., in preparation). Furthermore, point mutations in the Dg-cytoplasmic domain do not prevent laminin/Dg bindings but lead to the disruption of the mediolateral intercalation of cells required for notochord formation and/or affect the cytoskeleton integrity required for the differentiation of notochord cells (Buisson et al., in preparation).

Dg is also involved in the formation of actin-rich membrane surface protrusions, such as microvilli-like structures of epithelial cells. The β-Dg has been shown to bind the cytoskeletal adapter protein, ezrin, and forms a complex with a RhoGEF (guanine nucleotide-exchange factor), which may be responsible for activating Cdc42 in a localized manner and thus causes the filopodia phenotype in fibroblasts (Batchelor et al., 2007). Moreover, it has been shown that the Dg interacts with vinculin by binding to the vinculin-binding protein, vinexin. By this interaction, the Dg controls cell adhesion and spreading in myoblast focal adhesion (Thompson et al., 2010).

Another argument, which suggests that laminin/Dg interactions generate intracellular signaling *in vivo*, comes from the analysis of skin development in Xenopus embryos. The Dg depletion leads to the down regulation of the transcription factor P63, a marker of differentiated epidermis. In addition, the inhibition or activation of the Notch pathway prevents and promotes transcription of *X-dg* suggesting that Dg acts as a key-signaling component in the Notch pathway (Sirour et al., 2011).

All these data highlight the fact that following cell adhesion to the laminin rich ECM via the Dg, the cytoplasmic domain of Dg may assembles multiprotein complexes that relay signals coming from ECM–cell interactions to regulate cytoskeletal assembly, cell shape and intracellular signaling pathways.

Conclusions

In conclusion, there are many experimental arguments that strengthen the idea that Dg and its extra- and intracellular partners have all the functional characteristics of an adhesome providing interactive interfaces between ECMs, the cellular scaffoldings and signaling machineries. Throughout the embryonic development, it acts to ensure both the adhesion of cells to matrices as well as the

transduction of signals. It results that this adhesome is involved in mechanisms of cell adhesion required for matrix organization, cell polarity, cell shape, cell signaling and mechanical stability of tissues at any time during embryonic development (Fig. 1). Interestingly, functions of this adhesome seem to vary according to species, tissues, organs, and especially during embryonic development. Although substantial progress has been made toward dissecting the adhesive function of Dg adhesome, many questions remain for the future. In particular, how the integrin and Dg adhesomes work synergistically or independently to regulate efficiently cell adhesive interactions with ECMs during development? In addition to identifying new cytoplasmic ligands, another major challenge is to elucidate how the Dg is linked to pathways of cell communication, signal transduction and gene transcription that contribute to each step of development. Answering this question will certainly improve our understanding of how the Dg-adhesome regulates the adhesion between cells and ECMs required for embryonic developmental processes. The role of miRNAs is also a significant open question. The searches of miRNAs that targeted Dg might reveal important information about the regulation of complex molecular events involved in the patterning, maintenance, and turnover of this adhesome. This will be extremely important for a better understanding of the Dg-adhesome function that contributes to cell-matrix adhesion during development and its dysfunction that leads to disorders of embryonic development.

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