Chapter 6

Dystrophin–Glycoprotein Complex in Blood Cells

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Additional information is available at the end of the chapter

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Abstract

The Dystrophin-Associated Protein Complex (DAPC), known as the Dystrophin–Glycoprotein Complex (DGC), comprises an array of glycoproteins that are essential for the normal function of striated muscle, in which they were first described, and for many other tissues, including blood. Understanding the role that these molecules play in muscle function has increased over the last decade, and some of the knowledge derived can be applied to other biological systems. However, there is no doubt that to date, some progress has been achieved in blood cells.

Multiple interactions have been described among the proteins comprising the DGC, it is now well established that the DGC possesses a crucial role for numerous signaling pathways, recruiting and regulating various signaling proteins into a macromolecular complex. The aim of this chapter is to summarize the current state of knowledge regarding DGC processing and assembly, mainly in muscle tissue and in blood cells, with a primary focus on the dystroglycan heterodimer and associated proteins, including ion channels and membrane lipids. In addition, and due to increasing evidence involving dystroglycan proteins in the pathophysiology of solid tissue cancer, Duchenne muscular dystrophy, and leukemia, current information on these topics will be included.

Keywords: DGC, dystroglycan, intermediate filaments, leukemia cells, adhered platelets

1. Introduction

Dystrophin-associated glycoprotein complex, known as the DGC, is a multimeric and multifaceted protein complex located in the plasma membrane and mediates interactions among the cytoskeleton, cell membrane, and extracellular matrix (ECM) of the muscle and nonmuscle tissues. Therefore, the DGC is involved in signaling pathways that regulate the structural organization of specialized membrane-contact zones, and on the basis of its different biochemical characteristics and localization, the DGC can be divided into the following three

subcomplexes: the dystroglycan (Dg), the sarcoglycan, and the cytoplasmic, dystrophin-containing complex.

The dystroglycan subcomplex comprises α- and β-dystroglycan. α-Dystroglycan is the extracellular component that binds to α-laminin and to other components of the basal lamina (ECM), while β-dystroglycan is the transmembrane component. Both attach the intracellular cytoskeleton to the ECM, a task that is widespread in all human tissues and cells [1].

The sarcoglycan subcomplex is a multimember complex that, in association with dystroglycan, stabilizes interactions with the extracellular and transmembrane components of the DGC, as well as with dystrophin and its associated proteins. To date, six sarcoglycan genes have been identified that give rise to their respective proteins α-, β-, γ-, δ-, ε-, and ζ-sarcoglycan, which are organized in a tetrameric arrangement; however, it has been hypothesized that the six sarcoglycans can be arranged in an exameric structure [2].

The dystrophin subcomplex can form a mechanically strong bond with any costameric protein, forming a mechanically strong link between the sarcolemma and the costameric cytoskeleton through interaction with γ-actin filaments. Additionally, based on its structure, protein interactions, and the membrane defects associated with its absence or abnormality in dystrophic muscle, the dystrophin complex provides mechanical stabilization of the sarcolemmal membrane against the stresses imposed upon it during muscle contraction or stretch [3].

Therefore, the DGC appears to play both mechanical and nonmechanical roles in skeletal muscle and in nonmuscle cells, although neither the DGC structure nor the functions are completely understood at present.

This chapter focuses on recent insights into the specific roles of the DGC in different tissue cells, including blood cells, with special focus on dystroglycan biology and its feasible pathophysiologic implications in human leukemia cells and dystrophies.

2. Dystrophin–glycoprotein complex

Dystrophin is the protein that plays a central role in trans-sarcolemmal linkage between the basement membrane and the intracellular actin cytoskeleton, and is the product of the largest identified gene in the human genome [4].

The complexity of Duchenne muscular dystrophy (*DMD*) gene expression, which results in multiple transcripts and protein isoforms, has hampered understanding of the functions of individual dystrophin protein isoforms. The transcription of human DMD is controlled by the following three independent promoters, brain (B), muscle (M), and Purkinje (P) promoters, which indicate the tissue distribution of dystrophin expression, as well as four internal promoters (R for retinal, B for brain, S for Schwann cells, and G for general), which give rise to shorter transcripts encoding for the truncated COOH-terminal isoforms formed from the alternative splicing that generates dystrophin isoforms of 260 kDa (Dp260), 140 kDa (Dp140) [5], 116 kDa (Dp116) [6], and 71 kDa (Dp71) [7, 8]. When

these COOH-terminal dystrophin submembrane cytoskeletal proteins interact with a large macromolecular protein complex, they constitute the dystrophin-associated protein complex (DAPC). The crucial structural role of this complex is based on its strategic localization, spanning the plasma membrane and linking with the ECM and the actin cytoskeleton. Since the original discovery of the dystrophin-glycoprotein complex (DGC) [9], a large number of studies have characterized the various components involved in dystrophin [10]. Dystrophin-associated proteins can be divided into sarcolemmal proteins (β-dystroglycan, α-sarcoglycan, β-sarcoglycan, γ-sarcoglycan, and δ-sarcoglycan, sarcospan), cytosolic proteins (dystrobrevins, syntrophins, neuronal nitric-oxide synthase [nNOS]), and extracellular proteins (α-dystroglycan and laminin) [11]. Several DGC components are also found in two or more isoforms, which are either generated by alternative splicing of a single gene or originate from distinct genes [12, 13].

The large, multi-subunit DGC is found in the sarcolemma of striated muscle fibers, and this is essential for maintaining the structural integrity of these fibers during contraction; therefore, the generally accepted role for the DGC is its acting as a molecular shock absorber and stabilizing the plasma membrane during muscle contraction. However, its role goes beyond that solely of a passive scaffold among the elements of the complex, anchoring these near sites-of-action or important partners, since genetic disruption of any of the DGC elements causes mislocalization, destabilization, and the loss-of-function of the cell [14].

As evidence of DGC signaling capacity, it has been reported that nNOS is associated with the DGC via α-dystrobrevin, and that there is a loss of nNOS from the sarcolemma in Duchenne muscular dystrophy (DMD) [15]. Additionally, the DGC promotes the mechanical activation of cardiac nNOS by acting as a mechanosensor in the regulation of AMP-activated protein kinase AMPK activity [16].

The complex also constitutes a scaffold for signaling molecules based on its association with several signaling proteins, including Grb2-Sos1 [17], MEK and ERK [18], heterotrimeric G protein subunits [19], archvillin [20], and nNOS [21].

3. Dystrophin-related proteins

Dystrophins share structural homology with a range of paralog proteins denominated the dystrophin-related proteins (DRP), such as utrophin, DRP2, dystrobrevin, and dystrotelin [22].

The utrophin gene possesses internal promoters and shorter protein products and is also modulated by alternative splicing [23]. Transcription of full-length utrophin (Up395) is driven by two independent promoters: Utrn-A and Utrn-B. The Utrn-A protein is the main isoform in adult skeletal muscles, in contrast with Utrn-B, which is found in the vascular muscle endothelium [24].

G-utrophin, or Up113, was the first short product identified as a structural homolog of Dp116, while Up140 and Up71 are homologous to the short dystrophins Dp140 and Dp71, respectively;

these short utrophins do not possess actin-binding sites in the N-terminal domain of the molecule [25]. Up71 is detected in nonmuscle tissues such as lung, kidney, thymus, liver, and brain, while Up140 is found in lung, muscle, kidney, thymus, liver, testes, and brain. Full-length utrophins are also detected in nonmuscle tissues, such ass those of the central nervous system (CNS), peripheral nerves, testes, kidney, spleen, liver, and lung, and in small arteries and veins [26, 27]. In 1995, utrophin was described as a component of the platelet cytoskeleton, participating in its reorganization [28], while in hematopoietic stem/progenitor cells, Up400 and Up140 comprised the main gene products [29]. In addition, Up71 has been described in platelets [30], as well as in neutrophils [31].

It has long been considered that utrophin and dystrophin share comparable functions during fetal development and adulthood, maintaining utrophin expression in adult dystrophic tissues, compensating for dystrophin loss, as has been observed in mdx skeletal and cardiac muscles [24, 32]. However, spontaneous upregulations also occur in nonmuscle tissues, such as in Dp71-deficient platelets [33] and, most importantly, in the brains of DMD mouse models [34]. However, their expression in distinct structures, as compared with dystrophin, may not reflect functional compensation [24].

4. Dual role of the Dp71 isoform

Dp71 (70–75 kDa) is the first product of the *DMD* gene detectable in pluripotent embryonic stem cells (ESC) during development. It decreases in differentiated ESC cultures and tumors [35] and is the major dystrophin expressed in nonmuscle cells, such as neural tissue [36], glia [37], spermatozoa [38], and astrocytoma cells [39]; in platelets, its participation has been suggested in cytoskeletal reorganization and/or signaling, and in thrombin-mediated platelet adhesion [28].

The variation in the molecular mass of Dp71 transcripts is consistent with the expression of Dp71 isoforms derived from transcripts alternatively spliced for exons 71 and/or 78 [40]. The splicing product of exon 78 produces the isoform known as Dp71d, which preserves the C-terminal, while Dp71f is the product of the absence of exon 78. Two other gene products resulting from an alternative splicing at exons 71–74 and/or 78 transcripts, Dp71Δ110^{a} and Dp71Δ110^{m}, respectively, with a relative mass of 55 kDa, have been recently characterized [40, 41].

In 2005, Dp71d/Dp71Δ110^{m}~DGC and Up400/Up71~DGC were described as participating with structural roles associated with the actin cytoskeleton in the formation of membrane scaffolds. They were probably involved in defining platelet shape, substrate adhesion, and granule migration, as well as possessing a signaling role, participating in signaling triggered by adhesion to glass and by interaction with agonists such as thrombin [30].

The presence of Dp71 and some DGC elements that form a nuclear complex at the plasma membrane and in the nucleus of muscle cells suggested their participation in nuclear structure and in the modulation of nuclear processes [42].

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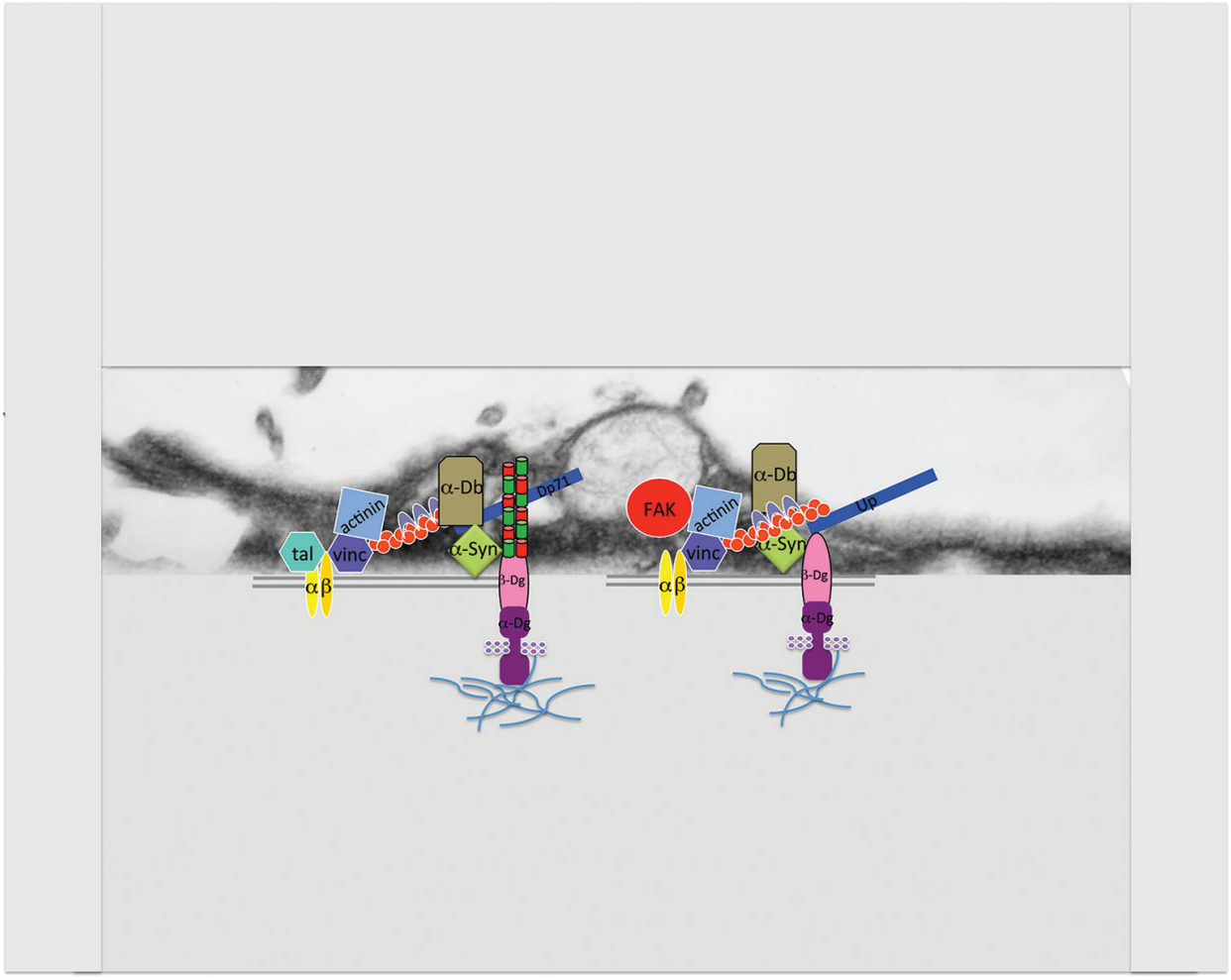

Figure 1. Schematic diagram of the dystrophin–glycoprotein complex (DGC) composed of Dp71 (left) and utrophin (right) in adhered platelets. Dystrophin is a linker between the cytoskeleton and the extracellular matrix (ECM). Dp71 and utrophin are associated with the dystroglycan complex and the dystrobrevin/syntrophin complex (α-Db/α-Syn). α-Dystroglycan (α-Dg) binds to ECM proteins and β-dystroglycan (β-Dg); β-Dg binds to the dystrophin, completing the link between the actin cytoskeleton and the ECM. Focal adhesion (magnified at the bottom of the figure) clusters the α- and β-integrin receptors and induces recruitment of focal adhesion proteins vinculin (Vin), talin (Tal), and α-actinin (α-Act), which connect directly with microfilaments and short dystrophins (Dp71) and indirectly with microtubules and intermediate filaments. The adhesion complex activates integrin-associated signaling cascades, including focal adhesion kinase (FAK). Dystroglycan plays a scaffold role, modulating the cytoplasmic protein kinases, and is in close association with integrin β1.

The neuronal cell line PC12 expresses at least two different Dp71 protein isoforms generated by the alternative splicing of exon 78 [43, 44]. The splicing isoform of Dp71 (Dp71d) contains ^{13}C-terminal amino acids encoded by exon 78, which are replaced by 31 new amino acids encoded by exon 79 in the Dp71f isoform upon removal of exon 78 [40]. Depletion of total Dp71 protein levels gives rise to impairment in nerve growth factor (NGF)-induced neurite outgrowth [45] and in the cell adhesion activity of PC12 cells [46], indicating that Dp71 is required for these neuronal functions. Dp71f assembles an adhesion complex comprising talin, α-actinin, paxillin, focal adhesion kinase (FAK), and actin, but not vinculin, contributing to cell stability [47].

During the platelet adhesion process, short dystrophins (Dp71d/Dp71Δ110^{m}) and utrophins (Up400/Up71) have demonstrated potential association with the integrin β-1 fraction and with focal adhesion system that includes α-actinin, vinculin, and talin. Apparently, in order to fulfill this hemosatic role, the coexistence of the DGC composed of short dystrophins or utrophins plays both a structural role in participation in stress-fiber assembly and in the centralization of cytoplasmic granules, and a regulatory role, incorporating FAK into the complex. The coexistence of dystrophin and utrophin complexes indicates structural and signaling mechanisms that are complementary to the actin network during the adhesion process [48] (**Figure 1**).

5. DGC components

The findings described in systematic proteomic studies indicate that dystrophin interacts closely with core members of the dystrophin-associated glycoprotein complex, such as dystroglycans, sarcoglycans, syntrophins, dystrobrevins, and sarcospan, but that it also forms indirect linkages with a large variety of other protein species, including tubulin, vimentin, desmin, annexin, and collagens [49].

5.1. Dystrobrevins

Dystrobrevins are proteins among dystrophin-related proteins that are encoded by two different genes, *α* and *β* and that possess significant homology to dystrophin. *α-Dystrobrevin* is expressed predominantly in muscle and brain, whereas *β-dystrobrevin* is expressed in nonmuscle tissues, which is abundant in brain, kidney, lung, and liver. Dystrobrevins have also been involved in intracellular signaling in muscle and nonmuscle tissues, either directly or through interaction with syntrophin, another element of the DGC. In humans, Sadoulet-Puccio et al. [50] found six isoforms of dystrobrevin (designated α-, β-, γ-, δ-, ε-, and ζ-dystrobrevin), which ranged in size from 22 to 80 kDa.

Human α-dystrobrevin and its few isoforms are expressed in the cytosol and the nucleus of the promyelocytic HL-60 cell line. A distinct distribution pattern of α-dystrobrevin, including colocalization with actin, was described in HL-60 promyelocytes, differentiated mature granulocytes, and in human neutrophils, supporting a signaling role [51]. In adhered platelets, it was suggested that actin filaments and microtubules contribute to α-granule and dense granule mobilization in adhered platelets, identifying α-dystrobrevins as part of the platelet transport machinery that is closely associated with the ubiquitous kinesin heavy chain (UKHC), this system is depicted in **Figure 2** [52].

5.2. Sarcoglycans

The sarcoglycan complex (SGC) is composed of α-, β-, γ-, and δ-sarcoglycan isoforms encoded by separate genes, and of sarcospan. Sarcoglycans are single transmembrane glycoproteins with the N-terminus oriented extracellularly for α-sarcoglycan and intracellularly for β-,

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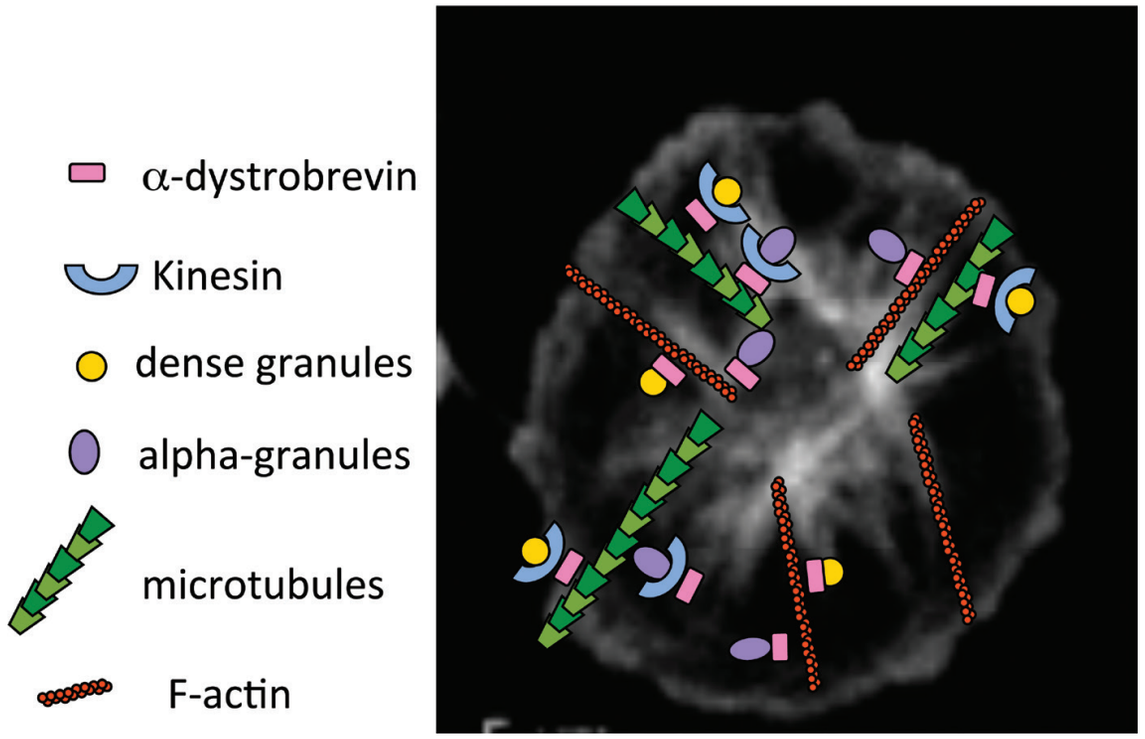

Figure 2. Platelet distribution of cytoskeleton elements. Schematic diagram of actin filaments, microtubules, and intermediate filaments in adhered platelets. Plectin is the protein that acts as a link among the three main components of the cytoskeleton.

γ-, and δ-sarcoglycans [53]. Contrariwise, sarcospan is composed of four transmembrane-spanning segments that are homologous to the tetraspanin family. The function of the SGC is not fully understood, but it appears to strengthen the interaction of β-dystroglycan with α-dystroglycan and dystrophin, as well as to play a role in intracellular signal transduction for sarcoglycan [54]. Sarcospan, a 25-kDa transmembrane protein, improves the cell-surface expression of the three major laminin-binding complexes, i.e., the dystrophin– and utrophin–glycoprotein complexes, as well as of an α7β1 integrin [55].

5.3. Syntrophins

Syntrophins are a multigene family of intracellular membrane-associated adaptor proteins and consist of five homologous isoforms: α1-syntrophin, β1-syntrophin, β2-syntrophin, γ1-syntrophin, and γ2-syntrophin; they possess a different cellular and subcellular localization, suggesting a distinct functional role [56]. In human platelets, a 54-kDa band corresponding to α-syntrophin is well expressed [30].

The pleckstrin homology (PH) and PDZ domains of syntrophins were shown to bind various proteins, including nitric oxide synthase (NOS), and have been implicated in the regulation of various plasma membrane ion channels, such as voltage-operated sodium channels and other nonvoltage gated channels, such as mechanosensitive Na^+ channels [57].

5.4. Dystrolglycans

The single dystroglycan gene encodes for a precursor protein that undergoes posttranslational proteolytic cleavage, which in turn produces two noncovalant DGC subunits: α- and β-dystroglycan. α-Dystroglycan is a dumbbell-shaped protein that binds to the laminin G domain in ECM components such as laminins, agrin, and perlecan. β-Dystroglycan (β-Dg) possesses a single transmembrane domain spanning the plasma membrane and an extracellular amino-terminal extracellular domain binding to the carboxy-terminal globular domain of α-Dg [58].

5.4.1. Dg involved in the signaling process

The β-Dg dual role (structural and signaling) has been demonstrated in various cell types and tissues. Examples of the former role are represented by the participation of β-Dg in cytoskeleton remodeling, where it is associated with actin [59, 60], while its signaling role is represented by its association with the extracellular signal-related kinase-mitogen-activated protein (ERK-MAP) kinase cascade [18], or with integrins modulates myoblast anchorage and migration [61]; this latter process is critically regulated by Src-mediated phosphorylation of β-Dg at tyrosine 890 [62].

Grb2–β-Dg interaction could facilitate the transduction of signals between the DGC and extracellular proteins and other signaling pathways [62]. However, when Dg is localized at the tips of dynamic filopodia, it directs local Cdc42 activation and recruits the guanine nucleotide exchange factor (GEF) Dbl to generate actin protrusions [60].

Dystroglycan is also a multifunctional adaptor or scaffold capable of interacting with components of the ERK-MAP kinase cascade, including MEK and ERK [18]. However, it has been established that integrin α6Aβ1 and dystroglycan play antagonistic roles in signaling to the Ras-Raf-MEK-ERK pathway in response to laminin [63].

5.4.2. Dg promoter of the adhesion process

Since 1995, dystroglycan-associated proteins, such as utrophin, have been considered residents of focal adhesions in nonmuscle cells [59, 64, 65] and, after direct interaction of the cytoplasmic tail of β-Dg with F-actin was described [66], Dg has been implicated in cell adhesion and spreading.

Dg was identified in podosomes at the early stages of myoblast spreading; these structures contain a regulatory complex comprising dystroglycan, Tks5, and Src [67]. Myoblast spreading occurred in relation to dystroglycan expression levels, which in turn altered the size and number of focal contacts, focal adhesions, and fibrillar adhesions. Dystroglycan-mediated cell adhesion and spreading took place through indirect interaction with vinculin by binding to the vinculin-binding protein vinexin [61], while an adhesome was made up of by laminin-Dg-myosin IIA, crucial for maintaining the shape of notochordal cells [65].

In addition to a specific role in the maintenance of muscle integrity, Dg plays a more ubiquitous role in cell adhesion, signaling, and polarity. During embryogenesis, the follicle-cell

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epithelium (FCE) maintains the cell polarity promoted by the association between perlecan and Dg [68], while in astrocytes, end-feet in brain laminin induced a dramatic, polarized redistribution of cell-surface clusters or macrodomains, which colocalized extensively with β-Dg and AQP4 [69].

The cytoskeletal polymers—actin, microtubules, and intermediate filaments—are interlinked by coordinated protein interactions to form a complex three-dimensional (3D) cytoskeletal network; these components are depicted in **Figure 3**. Although these systems are composed of distinctly different proteins, they are in constant and intimate communication with each another and with intermediate filaments, and their associated proteins are important components in mediating this crosstalk [70].

In platelets, two members of type-III intermediate filament (IF) proteins, desmin and vimentin, maintain a close relationship with DGC components, such as β-dystroglycan [β-dg], α-syntrophin [α-syn], and α-dystrobrevin [α-db], and are codistributed at the granulomere zone, participating in α-granule distribution [71].

The epithelial sodium channel (ENaC) is associated with IF and with dystrophin-associated proteins (DAP) via α-syntrophin and β-dystroglycan. ENaC is apparently dispensable for

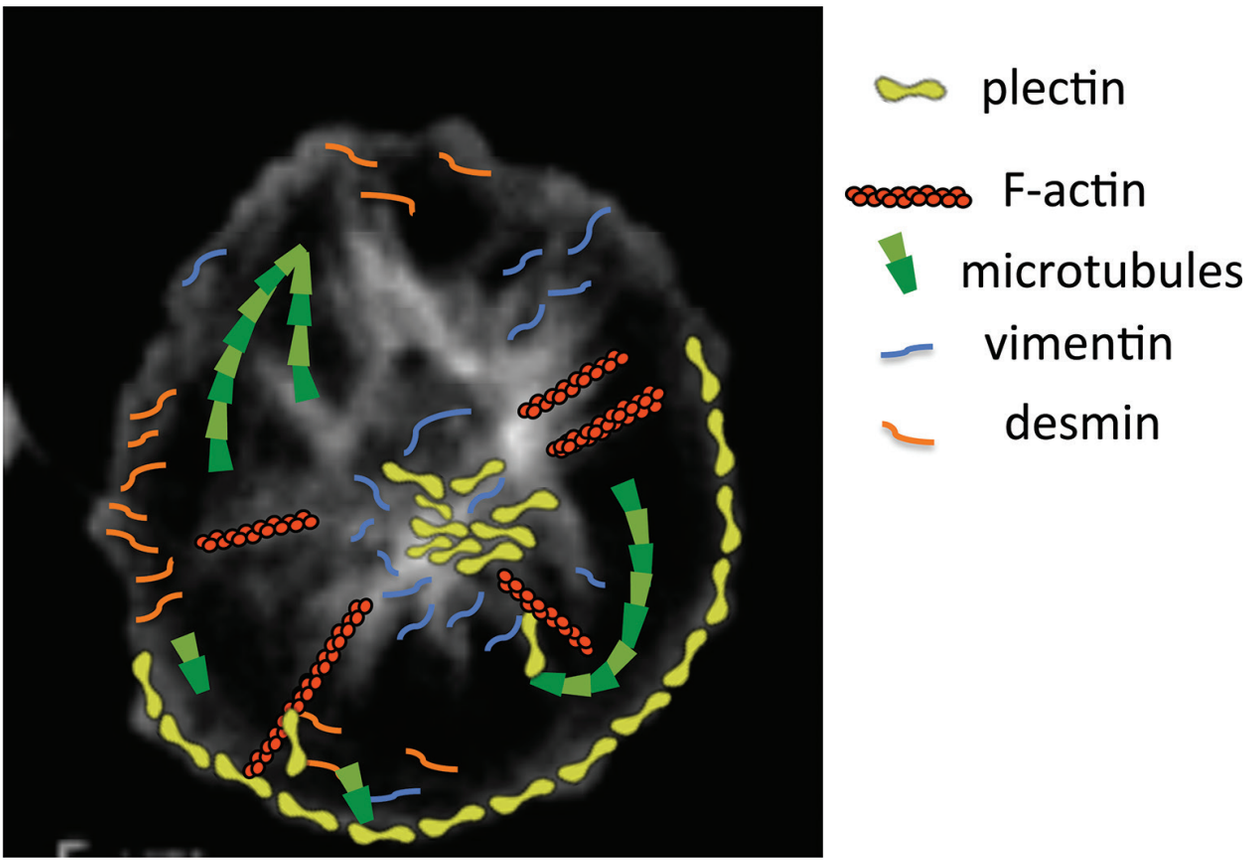

Figure 3. Schematic diagram of microtubules and actin filaments participating in the transport of alpha and dense granules in the platelet adhesion process, during which α-dystrobrevins are the regulatory and adaptor proteins for governing trafficking events.

migration and alpha- and dense-granule secretion, whereas Na^+ influx through this channel is fundamental for platelet collagen activation [72]. This channel is overexpressed in platelets from hypertensive subjects in relation with control subjects, and β-Dg is a scaffold for the organization of ENaC and associated proteins [73].

5.4.3. Dg and its posttranscriptional modifications

Posttranscriptional modifications in the Dg protein possess important implications in cellular functions. The transmembrane β-subunit, which interacts with α-Dg extracellularly and which also connects with several different cytolinker proteins intracellularly, is additionally subject to altered N-linked glycosylation [74]. Additional modifications to β-Dg, however, include phosphorylation on tyrosine [75, 76] and specific proteolytic cleavage events. Tyrosine phosphorylation of β-Dg serves as a molecular switch to regulate the binding of different cellular-binding partners [77], but it is also a signal of the internalization of Dg from the plasma membrane [78, 79] and may mediate some proteolytic events and nuclear translocation [80, 81].

β-Dg is subject to proteolysis at several key sites: matrix metalloproteinase (MMP)-mediated cleavage liberates the extracellular portion of β-Dg, MMP-9-mediated proteolytic cleavage of the β-Dg, and it has been implicated in dendritic outgrowth and arborization in primary hippocampal neurons [82]. The remaining 31 kDa transmembrane stub and cytoplasmic domain can be detected with antibodies at the carboxy terminus of the cytoplasmic domain. As yet unknown proteases generate smaller fragments corresponding to the cytoplasmic region of β-Dg [83, 84], most typically observed as a 26-kDa fragment, but occasionally as a 17-kDa fragment.

In hematopoietic stem/progenitor cells, a 50-kDa β-Dg is the main product, while in differentiated cells, such as neutrophils and platelets, the characteristic glycosylated 43 kDa band is present [29, 31]. A 65-kDa band was also observed in neutrophils; perhaps this molecular weight (MW) is due to a posttranscriptional modification such as SUMOylation.

Ezrin is able to interact with dystroglycan through a cluster of basic residues in the juxtamembrane region, and appears to be responsible for dystroglycan-mediated formation of filopodia [18]. Colocalization of endogenous dystroglycan with ezrin at the cleavage furrow and midbody during cytokinesis not only affords dystroglycan a role in organizing the contractile ring through direct or indirect associations with actin, but also can modulate the cell cycle by affecting extracellular signal-regulated kinase levels [85]. Recent experiments have demonstrated β-Dg trafficking from the cytoplasm to the nucleus by ezrin-mediated cytoskeleton reorganization, the latter dependent on IMPα2/β1 [86].

Due to the presence of a conventional nuclear localization sequence (NLS)-/Imp-dependent nuclear import pathway in the cytoplasmic juxtamembrane region of β-Dg [87], β-Dg and proteolytic fragments containing the nuclear localization signal can be targeted to the nucleus via an importin-dependent pathway [88], where it can exert effects on nuclear architecture [89].

5.4.4. Dg in the differentiation process

The expression has been described as the major components of DAPC visceral and subcutaneous rat adipose depots that are regulated during adipogenesis and by ECM components, suggesting an important role in adipocyte differentiation [90].

The human myeloid leukemia cell line HL-60 achieves increasing cessation after its exposure to all-trans-retinoic acid (ATRA) and dimethyl sulfoxide (DMSO) and becomes differentiated into granulocytes, evoking the biology of the disease *in vitro* [91, 92]. Recently, it was demonstrated that dystroglycans actively participate in the differentiation process, in that the expression levels of α-Dg (160 kDa), β-Dg (42kDa), and β-DgpY892 (42 kDa) were increased in differentiated compared with nondifferentiated cells. Additionally, low levels of β-Dg in differentiated HL-60 cells are accompanied by reducing actin-based protrusions, such as in filopodia and lamellipodia extrusion, avoiding motility or phagocytic capabilities, respectively [93]. Similar changes were also observed when HL-60 cells were transfected with a shRNA directed to dystroglycan; therefore, a direct consequence of the reduction in dystroglycan exerted a direct effect on actin cytoskeletal dynamics, either on its direct or indirect interaction with actin, but also interfering with actin regulatory pathways [66].

The Kasumi-1 cell line is a model system of acute myeloid leukemia (AML) with *t*(8;21) translocation and the corresponding functional consequences of the AML1–ETO fusion oncogene on myeloid differentiation [94]. *In vitro*, macrophages differentiated from myelomonocytic cell lines exhibited downregulation of adhesion molecules after tissue plasminogen activator (TPA) treatment [95]. The biochemical analysis of cytoplasmic or nuclear Kasumi-1 cell extracts revealed bands of 50, 38, and 30 kDa present in the nucleus of the cells, while the majority of 43 kDa β-Dg was found mainly in the cytoplasmic compartment, with the 38-kDa band also abundant in the cytoplasm of nondifferentiated Kasumi-1 and differentiated Kasumi-1 cells. The phosphorylated 31-kDa fragment of dystroglycan is the species that is most translocated to the nucleus of nondifferentiated cells, while the 50-kDa fragment comprised the most abundant species at the nucleus of differentiated cells. The diminished expression levels of Dg in differentiated Kasumi-1 cells compared with nondifferentiated cells could facilitate cell recruitment in solid tissues; apparently, the phosphorylated species may be ubiquitinated and processed by the proteasome. However, a direct consequence of a reduction in dystroglycan exerts an effect on actin cytoskeletal dynamics, but does not impair the differentiation process [96].

5.4.5. Dg in cell membrane organization

Several structures of the cell membrane play major roles in physiological functions through signaling and adhesion to neighbor cells and to ECM. Generic features, such as the cytoskeleton meshwork, rafts, and protein complexes, which are subjected to thermal motion, contribute to building membrane structures such as focal adhesions (FA) [97] and immune [98] and neuronal [99] synapses. The rapid and transient association of the partners of a given signaling pathway, localized in close proximity within narrow structures/domains, is a requirement for rapid and reliable signal transmission [100].

The existence of "rafts" supposes that membrane lipids and proteins associate with each other according to their affinities, due to their hydrophobicity and geometry [101]. Rafts were initially proposed as contributing to protein sorting along the synthesis pathway, and have also been associated with several membrane features, including signaling platforms and adhesion structures. Caveolae are cholesterol- and sphingolipid-enriched membrane invaginations [102], and caveolin-1 is the primary caveolae structural protein in several cells [103]. Therefore, caveolae and caveolin-1 play a key role in orchestrating the activation of pathways that underpin cell proliferation, migration, and contraction [104]. For example, direct interaction between caveolin-1 and β-Dg was demonstrated in contractile smooth muscle, where the distribution of caveolae is determined by their tethering to the actin cytoskeleton via caveolin-1 and the DGC [105].

In this regard, cholesterol demonstrated to be essential to modulate platelet cytoskeleton reorganization, while the association of caveolin-1 PY14 with intermediate filaments, as well as with focal adhesion proteins via vinculin, was a determinant in adhered platelets, where β-Dg participation was a key scaffold component for caveolin-1 and FAK [106].

In general, diseases of the DGC are incurable, in part because the majority of these give rise to great damage resulting from the loss of these proteins. However, there is increasing evidence that proteins in the DGC may play a significant role in the pathophysiology of more common diseases such as cancer, in which the DGC has been implicated.

Throughout these years of basic research, it has been observed that dystroglycan functional changes, either for posttranscriptional modifications or for deregulation of the protein, simultaneously affect both scaffolding and signaling roles. These changes modify cell adhesion and motility, MAPK signaling, or its translocation to the nuclei that, in the prostate, is associated with the ETV1 transcription factor, acting directly on cancer progression and the pathophysiology of the disease [81]. Therefore, a complete understanding of the role of DGC elements in the pathophysiology of a disease would allow the identification of strategies for the development of specific therapeutics.

Previous studies demonstrated that preventing tyrosine phosphorylation of β-Dg in mdx mouse alleviated the dystrophic phenotype in a genetic mouse model, ameliorating many of the main pathological symptoms associated with dystrophin deficiency [78]. The use of dasatinib was found to decrease β-Dg phosphorylation levels in tyrosine and to increase the relative levels of nonphosphorylated β-Dg in the sapje zebrafish, improving its physical condition [79].

6. Conclusion

Since 1980, the dystrophin–glycoprotein complex has been considered only as a group of multiproteins working together to ensure the function of muscle tissue; however, along these years and according to basic research, dystrophin has acquired prime status and has become the central component of a scaffold of proteins expressed in a variety of tissues including blood. Within the complex elements, dystroglycan has received the majority of our attention

and has been identified as participating in the clustering of membrane receptors, integrins, and ion channels, modulating cellular signal integration, such as in the differentiation process.

Despite all of these advances, it remains difficult to dissect the specific function of a particular protein and, given the close association and interdependence of the different elements of the complex, it should be difficult to define the specific contribution of each of the complex's protein elements. However, the improvement and development of biochemical and molecular tolls will undoubtedly aid in elucidating novel therapies to counteract common diseases such as cancer.

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